Ablative Fractional Resurfacing for Burn Scars & the Impact on Adult Reconstructive Burn Surgery: Exploring the Effects of a Novel Treatment Paradigm

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A thesis in fulfilment of the requirements for the degree of
Doctor of Philosophy

September 2021

“Never be ashamed of a scar. It simply means you were stronger than whatever tried to hurt you.”

— Unknown source

Acknowledgments

Working on this thesis over the past years has undoubtedly been one of the most formative times of my life not only as a surgeon but also as an individual. During these past personally impactful years, many friendships have arisen resulting in interactions that have enriched and help shape my professional and personal life. Many people were pivotal for the success and fun of the last years, and I am tremendously grateful for all that they have done to help contribute to the conclusion of this thesis.

First and foremost, I would like to thank my supervisor, Professor Peter Maitz for being such a formative mentor, leader, and friend throughout my PhD, professional career as well as personal life. You have empowered me with responsibility, support, trust, guidance, confidence, and have continuously pushed me to do more. By doing so you have facilitated all the traits required in order to make me stronger and more confident to achieve both professional and personal goals. Equally, you have provided important direction when required. Over the past 8 years you have been my academic leader and mentor, taught me a logical way of approaching a surgical problem, dexterity, and encouraged my creative surgical thinking. I am also very thankful that you encouraged me to write this PhD as a full thesis instead of a thesis by publication, because whilst writing, I realised that it would not have been possible to document all my thoughts and conclusions in any other form. Thank you for everything.

To Zhe Li, my co-supervisor, senior scientist and leader of our skin laboratory. I would like to thank you for your support and basic scientific expertise. Our various scientific and academic discussions in between operating cases or after theatre lists, have helped me form my thoughts and sparked new ideas.

To Associate Professor Peter Haertsch, for your unconditional support, help, leadership, and respect. It is an absolute privilege to be able to work with and learn from one of the surgeons who has been involved and working in various countries, when plastic surgery became popular as an own specialty. You have been pivotal in my career, have taught me that there are many different ways of achieving a successful result, that less is more, and have inspired my creative surgical thinking. It is rare these days to find surgeons like you, with such tremendous experience, who do not flinch from any surgical challenge with an overall altruistic approach to medicine. I would also like to thank you for the confidence and support you have given me over the past few months in my new clinical role. It was comforting to know, that I can always ask you for direction and guidance if needed.

To the chief secretary Ana Rodriguez, our burns theatre coordinator Monica Ditu, our burns speech pathologist Dr Nicola Clayton, and all the nursing and allied health staff of the Concord Burns Unit. I would like to thank all of you for your unconditional support and tireless efforts in helping me pursue my research ideas and projects during a busy and hectic clinical working day. You are the backbone of our unit and the true reason for a successful outcome of our patients' care.

To my dear parents, for your support and belief in me, for your guidance and comfort throughout this time and my entire life. You have taught me to never give up. You have stood by my side in good times as well as bad and helped me find the right path, when I was in doubt. Without your help, I would never have achieved any of the things that I have accomplished, and I will forever be grateful for all that you have sacrificed for our family. To my mother, Ursula Issler, who is an exceptionally talented, and successful physiotherapist and who developed a manual redressing therapy for clubfeet. I am incredibly proud of your achievement to capture your life's work in a 3-dimensional e-book, and I would like to thank you for our discussions about functional kinetics and kinematics which have made me aware how important this aspect also is in scar formation and accurate planning of surgical tissue rearrangement/release across entire functional units as described in Chapter 6. To my dear father, Christian Issler, who is a retired pediatrician and chess grand master. You have taught me strength, durability, and that with a will there is a way. Your unconditional love, support, and belief in me have always empowered me and helped me to overcome any hurdle.

To Oliver Fisher, my husband, my love, my best friend, and my life. As an academic upper gastrointestinal tract surgeon with a PhD in Barrett's disease, you have been a tremendous help with this thesis. After long shifts at the hospital, utterly exhausted, there were uncountable nights where you have helped me with statistics and finding ways of how to express my research goals. Despite your workload and related absence over the past years, you have managed to be a great father for our children, were always there for me, giving me stability, guidance, comforting me and supporting me when needed. I want to thank you for always helping me pursue my dreams. You and our beloved children Aliya and Luca are the true reason I was able to achieve all of these milestones over the past three years.

Finally, to the patients who agreed to participate in the included studies. To accompany you as burn survivors through your journeys of recovery and witnessing your progress and improvement is tremendously rewarding. Your spirit, thankfulness and positive attitude is a true inspiration and the reason why I am so passionate to continue to research on burn scar development and treatment.

To conclude, this profound exposure to the nature of a burn scars has made me aware of the true challenges of burn surgery and are helping me become the academic burn surgeon I aspire to be. I am thankful that I was able to have this experience.

Andrea

Statement of Originality

‘I hereby certify that to the best of my knowledge the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.
I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.’

Andrea C. Issler-Fisher

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  I was the first author of this article.
- *Lasers in Surgery & Medicine 2020. Issler-Fisher AC et al. Ablative fractional resurfacing with laser-facilitated steroid delivery for burn scar management: Does the depth of laser penetration matter? (see Appendix C)*
  I was the first author of this article.
- *Burns 2020. Issler-Fisher AC et al. “Ablative fractional resurfacing for burn scar management affects the number and type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay.” (see Appendix D)*
  I was the first author of this article.
- *Journal of Burn Care & Research 2019. Clayton N et al. “Ablative fractional resurfacing in acute care management of facial burns: a new approach to minimise the need for acute surgical reconstruction”*
  I was the senior/last author of this article. (see Appendix E)

Dr Andrea C. Issler-Fisher

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‘As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.’

Prof Peter K.M. Maitz

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Publications and awards arising from work relating to this thesis

Peer Reviewed Journal Articles

1. **Letter to the Editor: Fractional CO2 laser ablation of porcine burn scars after grafting.** Issler-Fisher AC, Li Z, Maitz PKM. Burns. 2020 Aug 29;S0305-4179(20)30510-6. doi: 10.1016/j.burns.2020.07.029.
2. **Effectiveness and safety of ablative fractional CO_2 laser for the treatment of burn scars: A case-control study.**

   Issler-Fisher AC, Fisher OM, Haertsch PA, Li Z, Maitz PKM. Burns. 2020 Oct 17:S0305-4179(20)30549-0. doi: 10.1016/j.burns.2020.10.002.
3. **Ablative fractional resurfacing for burn scar management affects the number and type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay.**

   Issler-Fisher AC, Fisher OM, Aggarwala S, Haertsch P, Maitz PK. Burns. 2020 Feb;46(1):65-74. doi: 10.1016/j.burns.2019.01.004.
4. **Ablative fractional resurfacing with laser-facilitated steroid delivery for burn scar management: Does the depth of laser penetration matter?**

   Issler-Fisher AC, Fisher OM, Haertsch P, Li Z, Maitz PKM.Lasers Surg Med. 2020 Feb;52(2):149-158. doi: 10.1002/lsm.23166.
5. **Ablative fractional resurfacing in acute care management of facial burns: a new approach to minimise the need for acute surgical reconstruction.**

   Clayton NA, Haertsch PA, Maitz PK, Issler-Fisher AC. J Burn Care & Research. 2019. Apr 26;40(3):368-372. doi: 10.1093/jbcr/irz030.
6. **Ablative fractional CO2 laser for burn scar reconstruction: An extensive subjective and objective short-term outcome analysis of a prospective treatment cohort.** Issler-Fisher AC, Fisher OM, Smialkowski AO, Li F, van Schalkwyk CP, Haertsch P, Maitz PK. Burns. 2017 May;43(3):573-582.doi:10.1016/j.burns.2016.09.01 4.

Awards

1. **October 2018:** Extraordinary Conference Contribution Medal awarded at ANZBA 2018 meeting
2. **October 2018:** Finalist CRGH Research Prize (Student Category (postgraduate)): ‘The Biological Effects and Clinical Outcomes of Novel Laser Based Treatment Approaches for Burn Scar Management’
3. **November 2017:** NSW Premier’s Awards for Improving Service Levels in Hospitals
4. **November 2017:** NSW Premier’s Awards: Anthea Kerr Award for Individual Excellence

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List of Abbreviations

CRGH	Concord Repatriation General Hospital
HTS	Hypertrophic scar
ECM	Extracellular matrix
TBSA	total body surface area
AFL-CO_2	ablative fractional CO_2 laser
AFR	ablative fractional resurfacing
FST	Fitzpatrick Skin Type
PIH	Post-inflammatory hyperpigmentation
VSS	Vancouver Scar Scale
POSAS	Patient and Observer Scar Assessment Scale
POSAS-O	POSAS Observer Scale
POSAS-P	POSAS Patient Scale
QoL	Quality of life
BSHS-B	Burns Specific Health Scale – Brief
LADD	Laser assisted delivery of drugs
DOI	Date of injury
CEA	Cultured epithelial autograft
STSG	Split-thickness skin graft
FTSG	Full-thickness skin graft
ROM	Range of motion
MAZ	Microscopic ablative zones
LOS	Length of stay
ICU	Intensive care unit
ROM	Range of motion
MCPJ	Metacarpophalangeal joint

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Preface

I have dedicated the past 9 years almost exclusively to burns and reconstructive surgery. The work both related to this PhD but also leading up to it encompassed the introduction of a novel treatment modality into the routine burn scar management program at Concord Repatriation General Hospital in Sydney. Associated with this we established a prospective data management system for quality control and auditing purposes. Our work surrounding this novel treatment has led to a change in the standard reconstructive care not only in our unit, but also in other burn units in Australia.

My clinical work has encompassed the systematic and extensive assessment of hundreds of burn scars and burn victims over several years. Added to that, my work includes the acute surgical management of these patients. Thus, I have had the privilege of treating burn victims from the time they present with their initial injury, subsequently managing and operating on them both during their acute as well as subsequent reconstructive phases and then guiding them through their recovery often for several years after their injury. Because of my research on burn scarring, I have been required to systematically document all features related to these victims' injuries. This process and the resulting conclusions I have come to by observing these patients over years, has allowed me to develop an understanding for burn scar development, the natural history of burn scars, as well as identify some of the many of the underlying problems that affect these patients. This process has not only shaped my understanding of how to tailor a reconstructive approach to the essential needs of each individual patient, but also impacted clinical decisions regarding patient care in the acute stage of a burn injury. Added to this, I have had the opportunity to be in close contact with research collaborators, teachers and mentors across the world who have tremendously helped shape and mature my surgical thinking when dealing with these complex and challenging patients.

With this thesis, I hoped to document some of the seminal aspects of this journey. Whilst I appreciate that it is impossible to grasp the full complexity that is involved in reconstructive burn care as well as what impacts the choice of a reconstructive treatment modality, this thesis may serve as a document to assist understanding why there are other surgical options of treating burn scars than simply excising them.

Thesis Synopsis & Outline

Burn scars are a major clinical sequelae of severe burn wound healing. The understanding of the development and management of burn scarring has become even more important with the increased survival rates of major burn injuries seen due to modern advances in medical care. Despite sedulous efforts in traditional scar management, severe scars often remain and can significantly diminish quality of life of patients through disfigurement, pain, itchiness, and contractures restraining the range of motion of the affected body and joint. Aside from non-surgical therapeutic options for improving scars, such as physical therapy, compression, local medical therapy and different types of laser treatments, surgical revision remains the main therapeutic approach for contracted scars to ultimately release tension and improve the range of motion of impacted areas. Nevertheless, although highly effective, these procedures are often associated with considerable morbidity, the efficacy is limited to the surgical site, and scar symptoms adjacent to the surgical site often persist, with some symptoms such as pruritus, rarely being specifically addressed.

Over the past decades, photo-medicine has evolved and become an increasingly popular treatment modality for severe burn scars, particularly the use of ablative fractional resurfacing techniques such as the ablative fractional CO_2 laser (AFL-CO_2). Fractional ablative lasers produce light, which is absorbed by water in the tissue. The laser energy heats up the tissue causing evaporation of water in the affected area. This thermal stimulation is thought to induce new fibroblasts and the formation of new collagen thus leading to a modulation of the scar composition.

The overall aim of this thesis is to describes the efficacy and safety of this novel treatment approach, explain why this treatment modality has led to a different understanding of burn scar remodelling and why a coordinated approach can treat some of the underlying problems much more efficiently than conventional reconstructive burn scar management.

The thesis is presented in 6 chapters.

Chapter 1 provides an overall background on the epidemiology of burns, the disease background of burn scars as well as a historical contextualization of burn scar reconstruction and conventional burn scar management techniques.

Chapter 2 provides an overview on light-based therapies in general as well as specifically for the treatment of burn scars.

Chapter 3 includes the methodology regarding how data on patients treated with AFL-CO_2 was prospectively collected which was subsequently utilized for the projects described in Chapter 4. It also includes the CRGH Burn Scar treatment protocol which underpins the way all patients included in this study were treated.

Chapter 4 involves the results of the following outcome analyses on the efficacy and safety of ablative fractional resurfacing (AFR) for burn scars:

- A summary of the first interim analysis on subjective and objective outcomes following one treatment with the AFL-CO_2, which was published just a few months before my PhD enrolment and served as the basis of all the future projects.
- A case control study on the effectiveness and safety of AFL-CO_2 for burn scars.
- A study on laser settings, evaluating various penetration depths and the effect of this on the overall outcome.
- An analysis of the effect of AFL-CO_2 on the number and type of elective reconstructive procedures, hospital admission patterns and length of stay of burn victims undergoing reconstructive procedures.
- And lastly a case report illustrating the prophylactic potential of AFL-CO_2 in the acute management of facial burn injuries.

Chapter 5 includes the discussion of each of the presented projects in Chapter 4

Chapter 6 provides an overview of the lessons learnt during the projects described in Chapter 4 and conclusions drawn. It illustrates and highlights the importance of a fundamental understanding of burn scar development, the nature of burn scars, their underlying problems, as well as the need to tailor a reconstructive approach to each individual burn patient. Further, illustrative cases are presented supporting the underlying hypotheses and how to effectively combine AFL-CO_2 with surgery.

Appendix A includes the initial outcome analyses (pilot project, before enrollment in this PhD) upon which this thesis is based on as supplementary material.

Appendices B – E include the published projects presented in Chapter 3 during the course of this PhD.

Appendices F – N include patient information forms, as well as assessment forms used for the prospective data collection.

https://esprit-kintsugi.com

Kintsukuroi: The Japanese art of mending broken objects and aggrandize the damage by filling the cracks with gold in the believe that when something's suffered damage and has history it becomes even more beautiful.

"How good it would be to have every memory of the moments we erred marked in gold;
Like a precious lesson or remembrance
But never regret, because battle scars are somehow beautiful;
Somehow, they last, etched onto our conscience
In a freehand aurulent:
Kintsukuroi"

The Crimson Solioquies

Chapter 1. Introduction

Chapter 1: Introduction

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1.1. Epidemiological background

Burn injuries are a global public health problem and present as one of the broadest forms of trauma with a large range of severity and morbidity [1]. Severe burn injuries belong to one of the most traumatic and debilitating injuries affecting nearly every organ system and leading to significant morbidity and mortality [2]. The prevalence and mortality of burn injuries varies greatly between low-, middle- and high-income countries [3]. Whilst in India over 1 million people are moderately to severely burnt every year, the United States of America reported over 410’000 burn injuries in 2008 with approximately 40’000 requiring hospitalization [3]. In Australia and New Zealand, it is estimated that 1% of the population sustains a burn injury annually, of which 10% need hospitalization, and 10% of which will suffered a life-threatening injury [4].

According to the World Health Organisation (WHO), globally, burn injuries account for an estimated 180’000 death annually, of which the vast majority occur in low- and middle-income countries [3]. With the advances in modern medicine, the mortality rates have decreased significantly, particularly in higher income countries [5]. However, non-fatal burn injuries are the leading cause of morbidity with long hospitalization, disability and disfigurement [3]. Worldwide, in 2004, almost 11 million people required medical attention due to their burn injuries and in low- and middle-income countries, burns are the leading cause of disability-adjusted life-years (DALYs) lost [3].

Thus, the advances in medical care with its associated unprecedented survival rates after significant burn injuries pose a significant challenge for modern healthcare systems [5]. Scarring as the rule and lasting reminder of the insulting injury is sadly the consequence [6].

Due to the inflammatory nature of the burn wound, pathologic scarring appears to be more prevalent following burn injuries than after surgical procedures or other traumata [6]. The prevalence of pathological scarring varies greatly in the literature, ranging from 26% to 77% [6-9]. Equally, the prevalence of burn scar contractures varies considerably between studies ranging from 38-54% of patients at the time of patient discharge [10]. These variations in the prevalence of pathological scarring are probably multifactorial as a significant component of scarring is natural scar maturation, scar management, ethnicity, body location, etc. Furthermore, other disabling factors of burn scars such as scar related pruritus, neuropathic pain and heat intolerance would need to be factored in as well, which is often not the case in these studies as for example a scar does not necessarily need to be hypertrophic to be itchy.

To summarize, burn injuries are a very common injuries and the reduction of mortality rates associated with severe burns leads to a shift of burn wound care towards the prevention and management of burn scars. Severe scarring as an inevitable consequence of the insult, as well as personal, social and economic expectations of modern society, pose a new level of complexity to modern burn care.

1.2. Burn scars: disease background

1.2.1. Definitions

Each burn scar undergoes a natural maturation process, which usually progresses over 12-24 months following initial trauma depending on patient- and scar-characteristics. The immature scar develops and peaks around 3 to 6 months post injury (proliferative/remodelling phase), before natural improvement in quality and size occurs over the subsequent 9-18 months (maturation/regenerative phase).

Burn scars display various characteristics, including changes in vascularisation, dyschromia, structural changes, tension, and contour abnormalities [5]. These properties can occur as the single feature of a scar or, more frequently, combined. A multitude of factors determine the severity and type of a burn scar, such as wound depth, mechanism of injury, patient age, ethnicity, Fitzpatrick skin type [11], co-morbidities, smoking, anatomical location and type of treatment. As such, a mature scar may be altered in vascularisation, flat and smooth in a Caucasian patient with a Fitzpatrick skin type 1-2, but be hypertrophic, yielding to firm, and dyschromic in an Asian patient with Fitzpatrick skin type 3-4. The question thus arises, which one of these scars is a pathological scar?

Pathological or abnormal scarring is a frequently used terminology, however there is a lack of clear definitions. Due to this, the prevalence for pathological scarring is also unknown and varies greatly in published reports. Scars are the natural consequence of a traumatic insult to the integument. The term scar defined as per Oxford dictionary has three definitions:

1. *“Scar of a wound: to leave a mark on the skin after it has got better”*

2. *"Scar of an unpleasant experience: to leave somebody with a feeling of being very sad or with mental pain*"
3. *"Scar to damage the appearance of something"*

Thus, it appears to be confusing what defines a pathological from a non-pathological scar. Without agreement of their actual meaning, the terms "scar", "fibrosis", "cicatrix" and "contracture" are often used interchangeably [12]. Differentiating a pathologic from non-pathologic scar remains a matter of debate [13]. However, it is important to define these terms in order to better understand the two different cellular and biochemical mechanisms which result in scarring [13]. "Disease" is defined as *"any impairment of normal physiological function affecting all or part of an organism, or a pathology which causes significant pain or suffering that interferes with daily living"*[14]. Consequently, if pathological scarring were to be seen as a disease and non-pathological scarring as normal wound healing, it has been suggested that pathological scarring should be defined as "*scarring that causes significant pain, pruritus and/or functional impairment of an organ"*[14]. Fearmonti et al. define significant pain and pruritus to be interfering with activities of daily living, and as such, deem that not all hypertrophic scars are pathologic [14]. Accordingly, a more appropriate definition of a pathological scar may be "*a scar affecting and/or interfering with daily living, physically or psychologically*". This may be in relation to stigma, significant symptoms (including pruritus, pain, and heat intolerance), impaired function or just "tightness", which may not necessarily result in actual reduced range of motion but may cause discomfort and restrictions for daily activities. For example, a firm, tight, but relatively thin scar plate on the torso may not be symptomatic other than feeling "tight", but it may cause painful postural changes affecting the spine or other body parts, which fall into the category of a pathological scar. Equally a perfectly thin, but naturally contracted scar on a cheek may cause an extrinsic contracture and pull on the lower eyelid leading to an ectropion. This means that a "pathological scar" does not necessarily need to be an "abnormal scar" and vice versa.

Hypertrophic scars (HTS) and keloid scars are often referred to as sequelae of wounds with abnormal wound responses in predisposed individuals [15]. HTS and keloid scars are considered to be a dermal form of fibroproliferative disorders, originating from altered wound healing mechanisms due to injuries to the deep dermis [16]. The abnormal wound healing with more extracellular matrix (ECM) deposition than degradation, results in altered consistency ranging from soft and doughy, to rubbery and firm, raised, red, and potentially itchy or painful scars. In contrast to keloid scars, HTS occur soon after trauma, remain within the borders of the original injury, often develop across joints, and can regress to a certain extent over the natural course of scar maturation [15]. Keloid scars spread beyond the original scar margin, infiltrate into the adjacent normal dermis, but rarely invade into subcutaneous tissue and seldom occur across joints [15, 17]. They tend to continue to grow slowly over time without a quiescent or regressive phase [18, 19]. However, differentiation between two types of keloid scars, a keloid-like scar and a real keloid scar is essential to understand the patient's individual disease burden. The keloid-like scar is a scar excessively growing and spreading beyond the original borders of the scar, but the same patient may have a completely normal scar (flat/smooth/within borders of initial insult) on another part of the body (e.g. inconspicuous donor-site scar from a split-thickness skin graft or a nicely faded surgical scar from a previous surgery). These type of keloid scars usually develop due to the inflammatory nature or prolonged/complicated wound healing following a burn injury in a patient with a certain predisposition/ethnicity/skin type and should be referred to as "keloid-**like**" scars rather than a true "keloid" scar, as the response to treatments/insults is usually very similar to HTS. Because real keloid scars are scars with tumorous growth from any type of trauma. These patients develop keloid scars following any insult to dermal structures (e.g. acne, surgical scars, burn injuries, etc.). Treatment is extremely challenging and the response to any type of intervention is often poor and recurrence rates are high. Thus, in contrast to keloid-like scars which are very amenable to the principles described in this thesis, real keloid scars may also benefit from the treatments described herein, but there are no cases of this rare condition included in this thesis and the optimal treatment of these challenging patients remains yet to be determined.

1.2.2. Pathophysiological background & scar characteristics

1.2.2.1. Pathophysiological basics of wound healing in burn injuries

The four phases of wound healing are haemostasis, inflammation, proliferation (development of granulation tissue), and remodelling/regeneration (scar maturation) [20]. Their modulation and balance can determine if excessive scarring occurs [21].

Cytokines and chemokines are released to recruit mast cells, fibroblasts and macrophages in order for the skin to heal [22]. In a deep burn injury, fibroblasts from the deep dermal layer are activated synthesising extracellular matrix (ECM), and produce large quantities of collagen and inflammatory cytokines (including TGF-ß) [22]. However, these deep dermal fibroblasts have reduced collagenase activity, thus decreasing collagen degradation [22], resulting in an imbalance of the tissue homeostasis with excessive collagen deposition, the basis of a hypertrophic scar. Added to the regional fibroblasts, fibrocytes from the bone marrow migrate to the wound, into the ECM which serves as scaffold for cell movement and vascularization [23]. These fibrocytes then turn into fibroblasts and increase local TGF-ß production [21]. In burn patients in particular, significantly higher percentages of type I collagen positive fibrocytes can be identified compared to control individuals [24, 25], correlating with high serum levels of TGF-ß [25, 26]. Together with various other important growth factors and cytokines involved in the wound healing process, TGF-ß plays a critical role in fibroblast proliferation and collagen production and is poorly regulated and overproduced in pathological scars. TGF-ß appears to stimulate fibroblasts to develop into myofibroblasts, which strongly correlates with the severity of size of the burn injury [22]. The newly differentiated myofibroblast contract in order to decrease the wound size, which can be clinically visualized during the proliferative and remodelling phase [18]. In normal wound healing the presence of these myofibroblasts is transient, however at sites of pathogenic scarring, myofibroblasts persist and exuberant deposition and contraction of extracellular matrix (ECM) occurs [27]. Further, increased numbers of myofibroblasts are a persistent component of abnormal/hypertrophic scars [28].

The ideal wound healing involves degradation of ECM and modification of the immature type III collagen in early wounds into the mature type I collagen to provide the new wound with more strength [18]. In hypertrophic and keloid scarring there is a dysregulation of collagen production and degradation, resulting in an overproduction of type III collagen bundles with a deranged ratio of type III to type I collagen [29]. The pliability and height of the scar is further affected by the changes in the ECM including up-regulation of fibronectin and hyaluronic acid, down-regulation of decorin and absent elastin [21].

Another important aspect of “abnormal” scarring is the role of the T-helper (Th) cells, which can either produce an anti-fibrotic or a pro-fibrotic environment [22]. In burn injuries, it appears as if there is an imbalance between T-helper 1 cells (creating an anti-fibrotic environment) and T-helper 2 cells (creating a fibrotic environment) polarised to Th 2 cell response which supports fibrosis. Th2 cells express increased cytokines (such as IL-4, IL-5, IL-

10), which can support the development of TGF-ß producing T-helper 3 cells, reduce fibroblast collagenase activity, and induce fibrocyte differentiation.

To summarize, if control mechanisms which regulate the balance of tissue repair and regeneration are lost, abnormal scarring occurs [5].

1.2.2.2. Predisposing factors for abnormal/pathological scarring

Various risk factors have been associated with HTS and keloid scars. In general, predisposing factors can be divided into individual and environmental factors. Individual causes include age, co-morbidities, ethnicity, genetic and endocrine factors, body location, as well as predisposed wounds. Environmental factors include the variability of the injuring agent, mode of wound-care, nutrition, presence of infection, and access to early scar management.

Scarring is further affected by age-related differences in tissue repair. Young children and older patients heal, and scar differently compared to middle-aged adults. In the late 19th century fetal “scarless healing” was discovered and various contributing factors were identified such as lacking TGF-ß, a paucity of inflammatory cells, and higher concentrations of hyaluronic acid [30, 31]. In contrast to adults, children have thinner skin, higher skin elasticity, greater healing capacities, and are growing (thus the scar is exposed to hormonal changes, as well as a natural growth related “scar stretch”). Children may develop severe hypertrophic scarring at the beginning of the remodeling phase of wound healing, but due to their strong healing capacity and growing bodies, their scars often experience a positive change over the subsequent years with overall superior scarring tendencies compared to adults. Older people, on the other hand, have a reduced immune response, thinner dermis, decreased vascularity, decreased hair and other skin adnexa which may lead to prolonged wound healing, but the looser skin/increased elasticity allows for contraction of larger wounds with overall less tension. Thus, scars are less likely to become hypertrophic in the elderly population [32].

As can be observed in older patients, other factors may contribute to a thinner scar dermis and subsequent “better” scarring, such as widely meshed split-thickness skin graft or poor vascularization due to certain co-morbidities, smoking and poor nutrition. In wounds/scars with a thin dermis, poor blood supply and/or immunosuppression, there are less modulating molecular factors contributing to hypertrophic scarring, which may be the underlying cause of the paradox better scarring often observed in these patient groups. This may also explain why patients who survive a very extensive burn injury with a prolonged hypermetabolic state often scar with thinner scars under tension (resulting in tightness) but with less hypertrophic/thick areas compared to patients with a stronger immune system.

Endocrine factors have also been associated with pathological scarring, as worsening of scars (particularly keloid scars) is often observed in puberty and pregnancy, whilst menopause may prompt a regression [15, 33].

Multiple genetic factors, in particularly race and complexion, have been identified to contribute to HST and keloid scars [34]. Ethnicity, such as African, Hispanic and Asian extraction tend to be more likely affected by pathological scarring [35]. Aside of ethnic predisposition, there also appears to be a relationship between pathological scar formation and skin colour as supported by the phenomenon, that HTS and keloids occur up to 15 times more frequently in darker skinned individuals and predominantly occur in parts of the body with higher concentrations of melanocytes [15]. Seeing that pathological scarring is very frequently seen in black people, but extremely rare in people with albinism, a higher incidence of pathological scarring in more pigmented skin, compared to e.g. palms and soles, there appears to be a close relationship between pathological scarring and melanin pigmentation [36]. Under normal conditions, melanocytes sitting in the basal layer of the epidermis do not proliferate and do not express cytokines related with themselves. In a wound, the microenvironment of the local skin changes and induces melanocytes to proliferate and produce melanin. Cytokines induce a migration of these melanocytes to the area of injury where the basal membrane is broken, and get in contact with proliferative fibroblasts from the dermal layers [36]. Gao et al. demonstrated in an in vitro study that melanocytes can stimulate development of pathological scarring (by stimulating the growth and proliferation of fibroblasts, increase collagen synthesis and extracellular matrix deposition, activate the TGF-ß signaling pathway), dependent on the melanocyte number, distribution in the skin, activation status, and other factors [36]. Thus, during wound healing melanocytes from the stratum basale interact with fibroblasts from the dermal layers due to the damaged basal membrane, which in turn facilitates fibroblast proliferation and collagen deposition. It is assumed that the contact between melanocytes from the epidermis and fibroblasts from the dermis play a significant role in formation of abnormal scars [36].

Lastly, familial predisposition appears to be an additional genetic factor. A positive family history is not unusual for abnormal/pathological scarring and certain factors from the immune system appear to favor pathological scars such as certain HLA types (HLA-B14/-B21/-BW16/-BW35/-DR5/-DQW3; Blood Group A) [17, 37].

Predisposed areas for abnormal/pathological scarring include body areas which are frequently subjected to increased skin tension [38]. Pathological scarring often occurs when scars cross joints or skin creases at a right angle. Further, predisposed areas include chest, shoulders, flexor surfaces of extremities, anterior neck and, and areas with a high concentration of melanocytes [15, 17]. Ear lobes, shoulders, and the sternal notch are particularly prone for keloid scars [15].

Aside from the genetic, ethnic, and anatomical components, it is the inflammatory nature of the burn injury, the prolonged course of wound healing, as well as frequent wound infections, which make the burn wound particularly prone for hypertrophic scarring [5, 39].

1.2.2.3. Histopathological basics of different scar characteristics

Burn scars are complex and have several scar characteristics including altered colour, tension, structural changes, and surface irregularities. The optimal treatment approach for a burn scar ideally addresses all these different aspects holistically [40].

The altered colour of a burn scar is the result of changes in vascularisation as well as pigmentation. Haemoglobin in erythrocytes is responsible for the red shades within the scars. In immature scars or scars exposed to high tension, there are excessively proliferating, dilated micro-vessels, which are responsible for the stronger degrees of erythema, whereas in a mature scar, the number of blood vessels is reduced and provides a pale appearance of the scar [41, 42]. The melanin produced by melanocytes in the epidermis is responsible for the different shades of brown/blue colour/pigmentation [41]. Dyschromia is an important characteristic of a burn scar, which affects in particular darker skin types and patients of certain ethnicities. Post inflammatory hyperpigmentation with excessive melanin production is a frequent sequela of the inflammatory insult in a burn injury. Similarly, hypopigmentation is very common and most likely reflective of a post-inflammatory “dormant state” of the melanocytes with a lack of melanin production [43].

The structural changes in the scar are the result of an imbalance in biosynthesis and tissue degradation during the wound healing process [5]. The loss of control mechanisms of tissue repair and regeneration leads to excessive collagen production and fibroblast proliferation. Additionally, the highly mechanoresponsive nature of fibroblasts have shown to play an integral part in scar hypertrophy and contracture [40]. Mechanical strain has two consequences: matrix remodelling genes are up-regulated and normal cell apoptosis is down-regulated. Both of these effects result in additional tissue production and the scars become firm and raised [40, 44, 45]. The additional component of contracture, which is always part of the regular wound healing process, adds to that mechanical strain and results in further scar contracture, surface irregularities, and contour abnormalities within a burn scar.

1.2.3. The “Scar Burden”

Scars remain as a permanent reminder of the damage that occurred. The psychological impact of the injury itself or its consequences may have detrimental physical, aesthetic, and social effects, impacting social and workplace reintegration, which is in turn associated with a significant financial burden for modern health-care systems and society.

Burn scars remain as a major clinical outcome of severe burn injuries and often persist to significantly diminish quality of life by disfigurement, pain, itch, heat intolerance, and contractures restraining the motion of body and joints [40, 46]. Most of these symptoms co-exist and patients seeking burn scar management often report several of these aspects.

A previous report stated that the most common and distressful complication of burn patients is abnormal appearance (75.2%), itching (73.3%), and pain (67.6%) [47]. However, aside from these common features, for which patients often seek reconstructive care, patients often seem to name scar thickness and a decrease in pliability above the burden of the aesthetic stigma. Large burn scars are often referred to as a tight armour restricting movement without necessarily leading to a functional impairment. These disturbances in body flow during daily tasks may cause secondary problems, such as postural changes or pain in areas other than the skin. Additionally, in particular in countries with a warm climate heat intolerance as well as impaired ability to sweat can severely affect patients and substantially impact their way of living. These burn scar related issues are very poorly described in the literature as they are difficult to capture and therapeutic interventions are limited.

As burn scar pruritus, pain, as well as functional impairment are frequently referred to in reports about burn scars, the following sub-chapters provide an overview of the current understanding of these symptoms.

1.2.3.1. Burn scar pruritus

Pruritus can be a debilitating sequelae of burn injuries and is reported to severely affect 87% in adult and 100% in paediatric burn patients [48-50]. Prevalence of burn scar related itch varies in the literature form 30% up to 68% with up to 97% of sensory impairment [51-53]. Pruritus severely impacts patients’ quality of life (QoL), resulting in anxiety, depression, and sleeplessness [54, 55]. The impact of psychosocial wellbeing of patients may exaggerate the itch causing a vicious cycle [49, 52].

The itch begins at the time of wound healing (within several days of injury) and peaks 3 to 12 months post burn injury [47]. It was found that in immature scars histamine levels are high and return to normal during the scar maturation process [56, 57]. However, itch can persist well beyond scar maturation and cause distress even years after the injury. Acute pruritus has been described as less than 6 months, and chronic pruritus as greater than 6 months post burn injury [58]. Generally, severity and frequency reduce over time, however, itchiness often continues well past 2 years post wound healing and up to 67% of patients still report mild to moderate pruritus 2 years post burn injury [49, 59].

Pruritus can affect the rehabilitative phase of all types of burn wounds, including wounds which healed with conservative management, grafted areas or donor-sites [58]. Several risk factors have been described to contribute to post burn pruritus including female gender, younger age, greater TBSA, deeper burn, psychological characters, HTS, and shorter time since injury [49, 60-62]. Additionally, some histopathological risk factors were identified, such as thin collagen bundles, abnormal ratio of type I and type II collagen, reduced number of elastic fibres, thicker burn scars, and prominent mast cell depositions [63]. On a cellular level histamine, neurokinin, tachykinin, bradykinin and neuropeptides all have a role in pruritus [63, 64]. Mast cell degeneration with release of mediators (such as histamine, leukotriens, etc.) can result in a neuroinflammation which in turn leads to itch and pain [56, 57].

There is a variety of possible mechanisms for post burn pruritus, possibly differing if in the acute or the chronic healing phase, however specific mechanism leading to burn scar pruritus are still not entirely understood.

Pruritus has been classified into four categories: pruritogenic (arising in skin due to inflammation, dryness or other skin damage), neuropathic (disease at any point along the afferent neurologic pathway), neurogenic (originating centrally but without evidence of neurologic pathology), and psychogenic (associated with psychiatric conditions) [65].

However, regardless of the current theories, there is a consensus that it is most likely a combination of neuropathic, neurogenic, pruritogenic, and psychogenic involvement in the pathophysiology of burn scar pruritus with a predominance of pruritogenic and neuropathic components [58].

Basic interactions of itch and pain have been debated for some time and both sensations seem to be interconnected in several ways [66, 67]. However, there is a clear difference between the involved neurons, particularly in the peripheral regions [68]. The subjective sensation, inducing stimuli and reflex patterns (withdrawal from pain, scratching from itch) are clearly distinct [69]. Further, both sensations are elicited by signals traveling along unmyelinated afferent C-fibres, however depending on the strength of the stimulus perceived as pain (strong, dermal fibres) or pruritus (weak, epidermal fibres) [70].

1.2.3.2. Burn scar pain

Pain induced by a burn injury is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such a damage"[71]. Burn pain is associated with three mechanisms: nociceptive, neuropathic, and inflammatory [2]. Nociceptive pain levels decline as the burn scar matures, whilst neuropathic type pain increases with scar maturation [2].

Painful scars are considered to be of multifactorial aetiology [53]. It is reported that burn size (%TBSA) and depth predicts painful scars, but length of time following a burn injury does not reduce pain [52, 72, 73]. Traumatic memories associated with the scar appear to be connected with burn scar pain, as both anxiety and stress seem to correlate with pain perception post injury [53, 55]. Equally, specific conditions like post-traumatic stress disorder, substance abuse and depression were found to be associated with neuropathic post-burn pain [74]. Pain is transmitted via free nerve fibres (consisting of both myelinized and unmyelinized C-fibres), which are present all over the skin [53]. Even though a correlation between the number of nociceptor-fibres and pain sensation would make sense, various groups question this hypothesis as fibre densities found in painful scars appears to vary greatly [75-77]. However, a disbalance between non-peptidergic unmyelinated and peptidergic fibres was found in painful scars and neuropathic pain may also appear when the burn has directly damaged the epidermal fibres or as a consequence of the neuroinflammatory response [53].

Burn scar related pain is still not entirely understood and further research in particular investigating nerve fibre density and balance in correlation with burn scar pain is necessary to optimize therapy and prevention.

1.2.3.3. Functional impairment

Contractures arising from scar bands or scar plates, resulting in restriction in range of motion with functional impairment may have a dramatic impact on a patient's quality of life due to restricted activities of daily living, social anxieties and chronic pain [13]. Contractures over joints are probably the most frequently described sequelae of burn scars. In the upper extremities fine motor tasks involving essential activities including grooming and feeding oneself is often affected, whilst the lower limb contractures limit the ability to ambulate [78]. Fearmonti et al. described the significance of disease to be determined by the location of the scar and the degree of contracture [13]. The degree of functional impairment can be objectively captured by a goniometer, scores and questionnaires limitation of daily living. It appears that the combination of the objective (goniometer) as well as subjective assessment tools are important to capture the severity of a contracture as the goniometer assessment only allows for the measurement of one joint in one direction, which does not necessarily reflect if a contracture results in functional impairment.

The incidence and severity of impaired function is poorly reported [13]. Additionally, most studies in the literature focus on specific joints or address the overall impact of a burn injury on quality of life amongst which a limited function may be part of. Schneider et al. has published one of the most extensive prospective data collections on burn contractures [78]. 985 patients were evaluated, of which 38.7% developed at least one contracture at hospital discharge. Only four joints were included in this analysis (shoulders, elbows, hips and knees), with shoulders being the most frequently affected, followed by elbows, knees and hips. The demonstration that over a third of patients are discharged with an already forming contractures, highlights the need for intensive occupational therapy/physiotherapy and early intervention.

Functional impairment is however more than a restricted range of motion of a joint. The principles of functional kinematics are of utmost importance in the development of burn scar contracture. Functional kinematics is referred to as the "geometry of motion". The actual limitation of a physical activity is not always an impairment of one or two joints, but rather as a consequence of a chain of motion of points/joints leading to a contraction band/plate when the whole chain is moving in one direction. This chain of motion may affect/limit certain movements but there may not be a visible obvious contracture band when assessing the scar in neutral position or by moving one single joint in one direction. Therefore, the measurement of a single joint with a goniometer never reflects the true functional impairment of a scar contracture. The acknowledgment of this phenomenon is particularly important when planning the reconstructive intervention. This is explained in more depth in Chapter 6.

1.2.3.4. The importance to identify different aspects of the "scar burden"

The impact a burn injury has on quality of life is significant. Anxiety, social avoidance, impairment of activities of daily living as well as significant symptoms make a return to normal life very challenging [6]. Burn scars are complex and it is essential to be able to appreciate this complexity. When assessing burn patients, it is important to acknowledge and individually identify the different burn scar characteristic (erythema, altered pigmentation, structural changes, tension) and symptoms (pruritus, neuropathic pain, heat intolerance, inability to sweat, limited range of motion). The same scar can be experienced very differently by different individuals and some characteristics/symptoms may be more accentuated in one individual and less in another. It is only by identifying each of these aspects, as well as their relevance to the patient, that a treatment can be tailored to address these issues holistically thus leading to a satisfied patient instead of simply wanting to make the scar more aesthetically pleasing.

1.3. Historical background on burn scar therapies

Before the 18th century, reconstructive burn surgery was mostly anecdotal, as surgery remained a treatment of last resort due to the associated pain and limited anaesthetic possibilities [79, 80]. During the late 18th and 19th century the germ theory of disease has led to the development of antiseptic surgical techniques, as well as the development of general anaesthesia with significant advances to be able to perform surgical reconstructions [81, 82]. During the early 20th century the value of local tissue rearrangements such as the Z-type incision to relax burn scar contractures was more and more acknowledged [83].

Following the efforts of great teachers and surgeons like Hippolyte Morestin and Harold Gillies, scar excision and replacement became more popular after World War I [84-86]. In particular during and after World War II reconstructive burn care evolved, anaesthesia advanced, and larger scar excisions with better options for defect coverage and improved microsurgical techniques became available [86]. Additionally, burn care changed dramatically following the pioneering work of Zora Janzekovic of early tangential burn wound excision and skin grafting [87], as well as an increasing understanding of the burn pathophysiology and improved pain management [88]. Morbidity and mortality could be markedly reduced which has led to a substantial increase in post burn rehabilitation and need for burn scar reconstruction. With the evolvement of burn care, increased understanding of wound healing mechanisms, burn scar development, regeneration and rehabilitation, modern burn surgery is now at the point where newer technologies such as photo-medicine combined with simple reconstructive surgeries allow to preserve original tissues by taking advantage of the patient's own healing abilities, providing great benefit to patients with less morbidity.

1.4. The conventional burn scar management

Once the acute treatment phase of a burn survivor is over, the lengthy and often challenging rehabilitation process starts. Burn rehabilitation following a large burn injury is often prolonged and dominated by management of pain, pruritus, heat intolerance, cosmetic stigma and psychological adjustment, which often prevents early return to work and school [89, 90].

There are an armamentarium of burn scar treatment approaches available ranging from non-surgical therapies including compression garments, silicone products, physiotherapy, intralesional injections of immunomodulating drugs and laser therapies [40]. Most of these therapies are part of the standard care in burn scar rehabilitation and widely accepted despite the lack of scientific evidence [40, 91, 92]. The extensive range of reconstructive surgical approaches all have in common to ultimately release the tension in contracted scars and increase limited range of motion of a restricted body part [40, 91, 93]. A successful outcome of any of these surgical reconstructive procedures is obviously subject to various factors (design, type of procedure, surgical skills, patient related factors). Thus, it is not surprising that for most surgical reconstructive approaches, the evidence base is more historical than scientific. The limitation of almost all surgical reconstructive releases/excisions include:

- High morbidity (often long anaesthetic times, lengthy recovery, additional wounds/donor-sites, additional occupational/physiotherapy/splints, etc.)
- Relatively high recurrence rates as surgeries are limited to one site. If the surgery only addresses one contracture within a complex scar, a shift of tension occurs and if tension persists or recurs, symptoms (pruritus, pain, etc.), alterations in pigmentation and structural changes and tension remain and potentially lead to an additional contracture.

Standard of care generally involves daily massaging of the scars with moisturisers, ointments or oils as well as fitted pressure garments and silicone therapy following immediate wound closure or if early signs of scar hypertrophy appear. In various burn units it is standard of care to intralesionally inject small, nodular, hypertrophic scars with anti-mitotic drugs such as corticosteroids or 5-fluorouracil with relatively good success [94, 95]. However, side effects including subcutaneous atrophy, telangiectasia, ulceration and hypopigmentation can occur, particularly in inexperienced hands [86, 87].

During the scar maturation phase, which generally takes 1 to 2 years, it is not recommended to proceed with any surgical scar reconstruction except the above-mentioned conservative measures unless an organ (e.g. cornea in eyelid ectropion) or a joint is at risk due to the contracture. Once scar maturation is achieved, surgical scar reconstruction is usually initiated, very much depending on patient's need, surgical abilities, familiarities of techniques and logistical aspects of the medical facilities. There is no consensus of which surgical approach is best applied for a specific scar. Due to the multifactorial nature of scars and choice of surgical reconstructive options, the variety of treatment approaches is huge ranging from simple local tissue rearrangements, to cultured epithelial autografts, skin grafts, expander surgery, local regional flaps or more complex microsurgery. However, generally much of burn reconstruction still focusses on removing the scar and replacing it with tissue from another region of the body [22]. The efficacy and success of the treatment depends on the correct choice of surgical modality for an individual patient and the surgeon's experience.

However, pain and pruritus often remain a debilitating problem, in particular in patients who suffered a large %TBSA burn injury as the surgical treatment is limited to one site. Thus, there are additional therapies which are often combined. Due to the many complex mechanisms involved in pruritus and neuropathic pain, there is an armamentarium of treatment modalities available with mixed efficacy [13]. Attempts were made involving thermal, mechanical, or chemical stimuli, which are assumed to elicit the pain pathway and simultaneously attenuate the pruritus pathway [96]. First line treatments involve antihistamines and topical emollients with very limited proven effectiveness [60, 97, 98]. Other approaches include cooling, transcutaneous electrical nerve stimulation (TENS), scrambler therapy (mixes C-fibre transmission signals), massaging, and silicone gel sheeting with varying efficacy [54, 59, 98-100]. For the treatment of refractory/chronic pruritus, antihistamines become much less effective as pruritus appears to change into more similar mechanisms like neuropathic pain [58]. This type of pruritus is much more susceptible to gabapentin rather than antihistamines [97, 101]. Anticonvulsants such as pregabalin and gabapentin are often used in the treatment of neuropathic pain and itch with relatively good efficacy [2]. Anecdotally intralesional injections of botulinum toxin injections were described as an effective treatment option for reducing resistant itch [102]. Laser therapies are an emerging technology in the treatment of burn scar pruritus and gains more and more interest, in particular pulsed dye laser (PDL), pulsed Nd:YAG laser as well as fractional CO_2 laser [40, 103, 104]. However, the exact mechanisms of specific burn scar pruritus and neuropathic pain are not well understood, and many approaches are adopted by professionals reflecting empirical approaches with limited evidence to support their efficacy [58]. Larger scale studies are lacking, and therapies are most likely best used in combinations.

Light based therapies, in particular the newer fractional ablative laser devices have emerged as a promising new treatment modality. As such improving the understanding of the underlying mechanisms of laser therapies is essential for modern burn surgeons who aim to offer holistic care for their patients.

Chapter 2. Light based therapies for burn scars

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2.1. Background on light-based therapies in medicine

2.1.1. History

Back in ancient Egypt, 4000 BC, first documentations about the use of light for medical purposes can be found [105]. Topical natural photosensitizer were applied and coupled with sunlight to help re-pigment skin of patients suffering from vitiligo [105]. In 1878 it was discovered that short-wavelength UV light has an effect on bacteria and was subsequently used for sterilization, but first reports on UV light on a biological system was documented in 1903 when light was used to treat Lupus in humans [106, 107]. In Europe sunlight was utilized throughout the 19th century as a cure for cutaneous tuberculosis [105]. Whilst these early reports on the use of light for medical purposes exist, the theoretic underpinnings of lasers with the essential formulas and theoretic concepts of laser light were first described by Albert Einstein in 1917 in his treatise called “The Quantum Theory of Radiation” [108]. In the 1950s Townes, Gennadiyevich, and Mikhailovich have further elaborated Einstein’s fundamental work and were collectively awarded the Nobel Prize in Physics in 1964 for their work in quantum physics [109]. However, it was not until 1960 when the first true laser was developed and successfully operated by Dr Theodore Maiman [110-112]. Soon thereafter, the potential of lasers as a highly targeted, therapeutic treatment modality was recognized and several additional lasers for medical purposes were developed [105, 109].

2.1.2. General laser basics

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation [112]. A laser device creates energy in the form of a light beam which is absorbed by specific targets in tissues and transformed into heat with a subsequent specific effect in the tissue [105, 109].

All lasers are composed of the same four components: [105, 109, 113]

- The **laser medium**, which can be solid, liquid, or a gas containing the atoms that will release photons when stimulated by an external energy source. The laser medium determines the wavelength and identification (name) of the laser (e.g. in a CO_2 laser, the medium is the gas CO_2).
- The **optical cavity/resonator**, which surrounds the laser medium and in which the amplification process of the photons occurs.

- The **power supply/energy source** which excites all the electrons in the atoms of the laser medium and creates population inversion (= more atoms are in a higher, excited state than in a lower, unexcited energy state). When the electrons return into their resting position, photons are emitted and amplified in the optical cavity.
- The **delivery system** delivers the light to the target, usually in form of a fibre optic or articulating arm with mirrored joints.

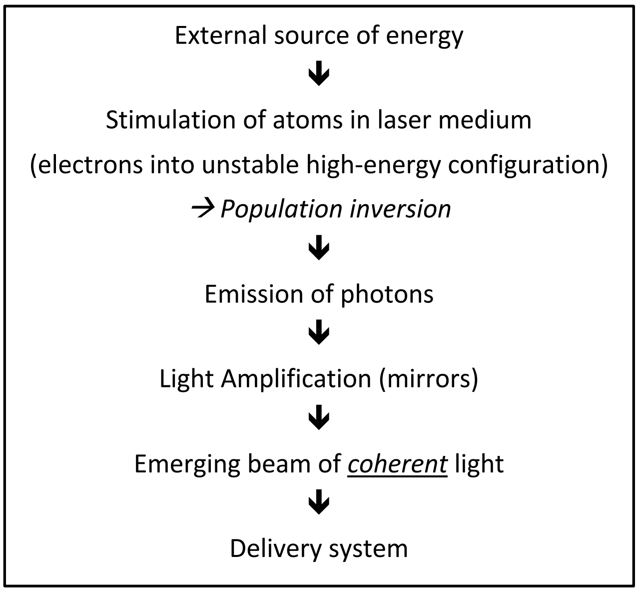

Figure 1. The concept of a laser device
External energy supplies the laser cavity containing the laser medium where the resting atoms get excited. When more atoms are in an unstable high-energy configuration, population inversion is created, and photons are released for light amplification within the optical cavity/resonator. When sufficient intensity has been developed for complete amplification to occur, the photons are then allowed to escape through a partially reflective mirror and the emerging beam of light gets delivered to the appropriate target.

The emerging beam of laser light has three distinct properties which distinguish it from a standard flashlight or lamp [40, 105, 109, 112]:

- It is **monochromatic**: because the wavelength of laser light approaches unity, which means that the beam is composed of photons of the same and single wavelength.
- It is **coherent**: because all the waves of light move spatially and temporally in phase.
- It is **collimated**: because the transmission of light waves is parallel without significant divergence of the beam. As a result, the emerging laser beam has a very high energy density as the energy gets densely packed into small volume.

2.1.3. Laser-tissue interactions

The interaction of laser light with living tissue depends on the wavelength of the emitted photons of a particular laser device [105]. In order to achieve a particular biologic effect with minimal collateral damage, the emerging laser light must be absorbed by a specific component in the skin [40]. That specific absorption is generally a function of the wavelength and the pulse duration of a device and can be described as the conversion of light into heat when the photons hit a specific target in the skin called chromophore [109, 114]. If the light is reflected from the surface or if the light is imprecisely absorbed by any chromophore, there will be no or an inaccurate effect in the skin [105].

The transfer of energy of the photon to the chromophore can lead so several laser tissue interactions: chemical (photochemical), mechanical (photoacoustic or photodisruptive) or thermal (photothermal). The latter is the most common effect of lasers used for resurfacing purposes in plastic and burn surgery [109].

There are three main chromophores in the skin: melanin, haemoglobin, and water (intracellular or extracellular), which are selectively targeted by laser devices of specific wavelengths [5, 105]. Laser beams with different wavelengths pass different depths of tissues and get absorbed by different chromophores in the tissue [5]. In general, the increase of the external power supply can increase the penetration depth of the laser beam [5].

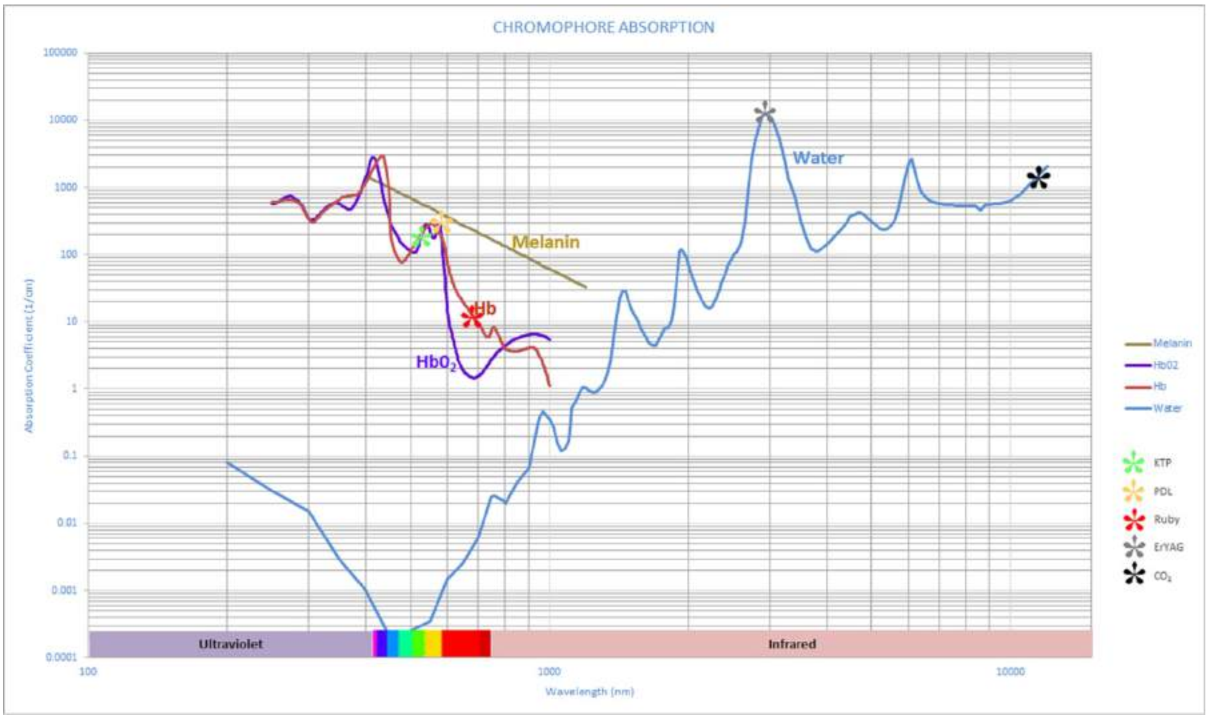

Figure 2. Chromophore absorption chart.

Figure from Issler-Fisher AC et al. “Laser Modulation of Hypertrophic Scars”. Clinics in Plastic Surgery 44 (2017) 757–766 [5].

2.2. Laser modulation for burn scars

2.2.1. Background

Following the first description of selective photothermolysis in 1983 by Drs Anderson and Parrish, the concept has evolved dramatically and subsequently lasers of various specific wavelengths were introduced [114, 115]. During the same time Apfelbeg et al. [116] and Castro et al. [117] reported for the first time that lasers may be an effective treatment modality for hypertrophic and keloid scars. Argon lasers (488nm), Nd:YAG lasers (1064nm), and common CO_2 lasers (10’600nm) have been described for the treatment of hypertrophic scarring, but all associated with relatively high recurrence rates [115, 118-122]. In 1994, however, vascular-specific flashlamp-pump pulsed dye laser (PDL) was reported to be effective for improving erythematous and hypertrophic scars with lower recurrence rates [40]. Over the subsequent years, the PDL (585nm or 595nm) has been one of the best researched lasers for hypertrophic scarring with substantial long-term improvements and reduced need for surgical scar excision [44, 115, 123-125].

In 2004, Manstein et al. have intro introduced the concept of fractional photothermolysis which has revolutionised the clinical use of lasers [40, 126]. The conventional ablative skin resurfacing as well as non-ablative dermal remodelling techniques, both lead to homogeneous thermal damage within the skin in a 2-D layer [126]. In contrast, fractional lasers create microscopic thermal injuries to the skin in 3-D patterns, by using a technology that splits the laser beam into a pixelated pattern of microbeams and specifically spares tissue surrounding each microscopic wound [126]. A rapid wound healing response is initiated in these hundreds of microscopic lesions, as the viable dermal islands of uninjured tissue serve as a reservoir to promote neocollagenesis and tissue remodelling [5, 91, 126].

Due to the limited collateral thermal damage, fractional photothermolysis appears to be much safer compared to traditional resurfacing techniques and has gained more and more interest over the past decade [5].

The microscopic treatment lesions of fractional photothermolysis can be non-ablative or ablative. Non-ablative fractional laser resurfacing devices were introduced in 2004, where the dermis is heated up to between 50°C to 70°C inducing an irreversible coagulation of tissue (collagen). Whilst non-ablative fractional lasers became very popular in aesthetic surgery and dermatology, their efficacy for thick, dense hypertrophic scars is rather limited. This has dramatically changed when, ablative fractional lasers were introduced in 2007, heating up the dermis to greater than 100°C, inducing tissue vaporization with a thermal coagulation zone around the ablated columns. [5]

2.2.2. Ablative fractional resurfacing for burn scars

Ablative fractional CO_2 laser (AFL-CO_2) allows for an overall change in burn scar management. It facilitates to treat the cause for bad scarring by using the body's own capacity to heal itself rather than replacing a scar with another scar. AFL-CO_2 is not a silver bullet for every scar but, it allows to rethink how to holistically approach burn scars.

AFR releases scar tension twofold. Firstly, the simple creation of little holes into the scar releases the scar mechanically, which is often described by patients as a feeling of release immediately following treatment of a larger contracted area.

In a second step, these microscopic thermal lesions contract again, and a rapid mini-wound healing reaction with a molecular cascade is prompted from the islands of undamaged surrounding tissue, serving as a reservoir for scar remodelling. Histologic analyses have shown that heat shock proteins, matrix metalloproteinases and inflammatory cascades contribute to that healing response with prolonged neocollagenesis and subsequent collagen remodelling [5, 127-130]. Ozog et al. [127] demonstrated that there was a significant decrease in type I collagen, and significant increase in type III collagen along with a significant improvement in the collagen arrangement/configuration. The remodelling process leads to a release in scar tension through a change of the dermal architecture and composition, which ultimately results in increased pliability, scar flattening, and promotes healing of chronic wounds in unstable scars [5, 103, 127, 131-135].

There are several fractional ablative laser devices on the market with distinct technical characteristics to amplify safety and efficacy [5]. However, the most commonly used device for pathological burn scars is the ablative fractional 10,600-nm wavelength CO2 Ultrapulse® laser (by Lumenis®) including ActiveFX™ and DeepFX™ hand pieces and the SCAAR FX™ mode. The energy is delivered in a tiny grid with a short pulse duration for a controlled ablation/coagulation ration to minimise harm to the surrounding area. The high power and ablation at precise depth allows for penetration ranging up to 4.0 mm penetration depth. The distinctive pattern of fractional laser injury achieved by a combination of short pulse duration and high energy enables precise and effective treatment [5].

2.2.3. Laser facilitated drug delivery

Laser assisted delivery of drugs (LADD) is an evolving technique, enhancing the bioavailability of topically applied medications [136, 137]. Traversing the stratum corneum of the epidermis is key for optimal delivery of topically applied drugs. Fractional laser therapy creates precise, uniform columns of tissue vaporization, which facilitates drug delivery past the epidermal barrier and evenly distributes the applied topical agent within the dermal layer.

Small nodular hypertrophic burn scars are commonly injected with anti-mitotic drugs such as corticosteroids and 5-fluorouracil [94, 95]. Intralesional injection of corticosteroids is even considered as the treatment of choice for small and younger keloid scars, as well as small nodular hypertrophic scars [138]. In order to achieve the desired effects of the injected drugs, corticosteroids for example should be injected into the papillary dermis where the collagenase production takes place. Corticosteroids lead to a decreased synthesis of collagen and gycosaminoglycanes, decreased fibroblast proliferation, suppress pro-inflammatory mediators and decrease mucinous ground substance [139, 140]. The inhibition of collagenase inhibitors that prevent the degradation of collagen leads to the aspired result of a decrease in dermal thickening and subsequent flattening of the scar. However, these drugs are usually injected with a 25- to 27-gauge needle into the very dense structure of the scar, which often leads to a local accumulation of the medication or to an injection at a too deep layer. Thus, if intralesional corticosteroids are not delivered in a controlled manner, atrophy (of epidermis, dermis or subcutaneous fat), ulceration/necrosis, white flecks (visible deposition of steroids), telangiectasia, and hypopigmentation can be the consequence [40]. Whilst some of these side-effects are a desired outcome, they are only beneficial if achieved in a controlled manner. Another limitation of injecting antimitotic drugs with a needle is, that scars involving larger surface areas cannot be injected by this technique [40]. Accordingly, LADD of medications like corticosteroids is a very promising technique to safely apply and evenly distribute the medication to scars of various sizes [40].

Several animal studies have been published about the enhanced bioavailability of drugs administered via LADD [141-143], and a few clinical case series exist looking at the outcome of LADD of antimitotic drugs in the treatment of hypertrophic scars [137, 144-146].

Nevertheless, burn centres using AFL-CO_2 use LADD of corticosteroids in most cases when treating hypertrophic scars. Thus, further investigation is warranted if the positive effects on burn scars are due to appropriately delivered and evenly distributed corticosteroids, due to the laser modulation of the scar tissue, or due to the combination of the two.

If used immediately postoperatively, AFL-CO_2 is an excellent tool to facilitate the delivery of drugs past the epidermal barrier, as the precise and uniform ablative channels resulting from the induced tissue vaporization, serve for an even distribution of drugs in the dermal layer [40].

LADD in burn scars is commonly associated with the use of antimitotic drugs such as corticosteroids and 5-fluorouracil for hypertrophic scars. However, there are anecdotal reports of the use of laser assisted delivery of dermal fillers (poly-L-lactic acid) for atrophic scars. Additionally, laser assisted delivery of bimathoprost 0.03% ophthalmic solution (prostaglandin analog) for the treatment of hypopigmented scars (not TGA approved) is another innovative approach. The mechanism behind depigmentation in burn scars is not entirely understood. Theories include the loss of melanocytes or damage to the cells resulting in a decrease of their function. The latter is probably far more common, and the melanocytes often remain present, but are found in a type of “dormant” state. The induction of a wound healing reaction with tissue modulation may re-stimulate these dormant melanocytes, in addition to the stimulating effect of bimathoprost 0.03% inducing the synthesis of melanin. Thus, LADD is an under-researched treatment adjunct, with very promising potential to address various scar characteristics.

2.3. Thesis rationale

Given the promising results of light-based scar modulation and published reports, the CRGH burns unit acquired an AFL-CO_2 device in 2014 and began treating burn survivors. Patients were prospectively audited with very promising preliminary results and a report on the Unit’s series was successfully published in Burns in 2017. Overall, this first series served as “the pilot project” for this thesis during which initial experience could be gathered, and areas identified that warranted improvement but also further research. An overview of this published report is provided in Chapter 4.1. Given these encouraging results as well as the profound impact the AFL-CO_2 had on patients treated for severe scarring within our service, several main questions arose that required addressing. For the purpose of this thesis, the general aim was to explore the outcomes of utilizing the AFL-CO2 by addressing four broad domains:

1. To understand to what extent does a treatment with the AFL-CO_2 impacts severe burn scarring compared to an untreated control-group?
2. Considering AFL-CO_2 is effective but widely divergent treatment settings seem to be used, do the settings and resulting penetration depths impact outcomes?
3. Because of the profound impact the laser had on patient management, how does this affect overall patient treatment algorithms, case-mix etc. of a burn service?
4. Is there any potential for the laser to exert prophylactic benefits?

To address these research domains the existing framework for data capture as well as treatment algorithms were refined and a research methodology, as outlined in Chapter 3, was applied. The results of these research efforts are presented in Chapter 4.

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3.1. Establishing a prospective database at the CRGH Burns Unit

3.1.1. Rationale for data collection

AFR has been described as a promising adjunct to traditional burn scar management over the past decade [91, 103, 127]. The Concord Repatriation General Hospital (CRGH) Burns Unit was the first adult burn centre on the Australian East Coast to establish an AFR program burn scar management. At the time when a first prospective data collection was initiated in our unit, well-established guidelines on the use of AFR for burn scars was limited to a consensus paper published by Anderson et al. in 2013 [91]. As such, we aimed to establish a prospective database and tissue bank of burn patients before and after treatment with the AFL-CO_2, to document their outcomes for quality outcome analyses, and to potentially establish best practice guidelines for future treatment algorithms in Australia.

A first analysis of our data was published in the BURNS Journal in 2017, revealing promising results with a significant improvement in scar thickness, colour, texture, pliability, pruritus, pain, and most importantly in burn specific quality of life after only one laser treatment [147] (see Chapter 4.1.). This first experience helped further define what variables we were interested in collecting and resulted in an extensive, systematic and continuous documentation of all patients treated with AFR at CRGH in a prospectively maintained (by the candidate herself) database. Because of the granularity and extensiveness of the collected data, we were able to explore many more aspects relating to AFR thus providing the underlying rationale for this PhD thesis. The aim was to prospectively collect and analyse all relevant data of burn patients treated with the AFL-CO_2 for severe scarring, including patient demographics, information regarding the burn injury, scar information, laser-settings, intervals between treatment sessions, combined treatment-modalities, and various outcome parameters mentioned below. The resulting dataset was set up to facilitate future subgroup analyses as well as to audit outcomes with the ultimate aim of helping to develop best practice guidelines for the use of AFL-CO2 for burn scars.

3.1.2. Hospital setting & patient population

The CRGH Burns Unit in Sydney, Australia, is a quaternary referral facility for burn patients within a teaching hospital of the University of Sydney. The unit is a state-wide referral centre for burn patients and includes a high-volume Burns Outpatient Clinic reviewing up to 1000 patients per month.

In December 2014 treatment with the ablative fractional laser (AFL) was introduced for scar management at the CRGH Burns Unit and with it a prospective data collection of every burn scar patient treated with the AFL-CO_2 was initiated and after the initial experiences and analysis, later extended for quality outcome analysis. Due to the high demand and increasing referral base of patients requiring burn scar management, a dedicated Burn Scar Clinic was developed in early 2015. Burn victims suffering from the sequelae of their injury are referred to the Burn Scar Clinic, where their scars are systematically evaluated, and a treatment plan tailored to each individual patient including non-invasive therapies, laser treatments, and reconstructive surgical procedures.

3.1.3. Data collection & follow-up protocol

Following a systematic assessment of all burn scars a treatment plan was established customized to each patient’s individual needs and scar characteristics. Patients with pathological scars scheduled for treatment with the AFL-CO_2, were assessed for suitability of enrolment in the project. Inclusion criteria included the ability to provide informed consent and patients with burn scars comprising structural changes (atrophic, hypertrophic, keloid scars). Exclusion criteria included: symptomatic scars with no structural changes (i.e. no hypertrophy, atrophy or keloid-characteristics), scars with altered colour but with no structural changes, and impairing psychiatric or medical co-morbidity prohibiting the provision of informed consent.

Patients fulfilling the inclusion criteria were offered participation in the project. Patients who refused to participate were treated without detailed data-collection. If inclusion criteria were met, the Participant Information Sheet (Appendix F) was handed out to the patient and explained by the principal investigator. If the patient agreed to participate, written consent was obtained (Appendix G). A separate signature (written consent) for the collection of tissue specimens was required. If the patient did not wish to have any tissue collected, but consented to the primary procedure, these patients were treated in accordance with the rest of the study protocol.

3.1.3.1. Demographics & information about burn injury/burn scar

At the date of enrolment information on the patients and their scars were captured. Table 1. (Appendix H). This included patient's demographics including age, gender, smoking-status, and co-morbidities. The ethnical background of the patient was noted as well as the skin type according to Fitzpatrick [11, 148].

The Fitzpatrick skin type (FST) is the gold standard for describing sensitivity to UV exposure and a widely accepted classification system to describe the constitutive skin colour [149, 150]. It is further an independent predictor of skin cancer risk [150]. In 1975 by Thomas B. Fitzpatrick developed a numerical classification for human skin colour in an attempt to estimate the response of different types of skin to ultraviolet (UV) radiation exposure [127]. The original classification included skin types I to IV, which was extended a few years later to include brown and black skinned people [151]. A lower FST corresponds to skin that burns easily and tans minimally, and a higher FST indicates skin that burns rarely and tans copiously. The FST is originally defined as patient-self reported response to moderate UV exposure [151]. However, clinician often predict the FST based on ethnicity and pigmentary phenotypes [150]. Studies have shown that the FST correlates poorly to race and that there is a phenotypically unmeasurable component of race that influences the FST beyond its relationship with pigmentary phenotypes [150, 152].

The "real" skin type reflecting an individual's predisposition for abnormal scarring and susceptibility to treatment, is probably a combination of the skin constitution according to FST as well as the genetic predisposition of race. Thus, it is important to capture both variables for a complete scar risk assessment. For example, the skin of a Chinese person, with FST 2, is definitely not responding equally to phototherapy as compared to a patient of Anglo-Saxon extraction with the same FST. Thus, as ethnicity is highly correlating with scarring potential after an injury, it seemed to be prudent to include FST as well as ethnicity (Table 1) into this data collection.

Further, information on the initial burn injury resulting in the assessed scar was documented as listed in Table 1. These variables were captured on the date of the initial assessment.

Table 1: Data collection: information on demographics and information about the burn injury and scar

Demographics	**Age & gender** **Smoking status** **Co-morbidities:** - Pulmonary disease - Cardiac disease - Vascular disease - Diabetes mellitus - Renal disease - Neurological disease - Psychiatric disease - Substance abuse - Other co-morbidity - No co-morbidity **Ethnical background:** - Australian Aboriginal - Anglo-Saxon/Celtic - Torres Strait Islander - Maori Pacific Islander - North West European - South East European - North East Asian - South East Asian - South / Central Asian - North African/Middle East - Sub-Saharan African - South American - Not stated **Fitzpatrick skin type** - Type 1: Pale white skin; blond/red hair; blue eyes; freckles → Always burns, never tans - Type 2: White skin; fair; blond/red hair; blue/green/hazel eyes → Usually burns, tans minimally - Type 3: Cream white/light brown skin; fair with any hair/eye colour → Sometimes mild burn, tans uniformly - Type 4: Moderate brown skin; typical Mediterranean skin tone → Rarely burns, always tans well - Type 5: Dark brown skin; Middle Eastern skin types → Very rarely burns, tans very easily - Type 6: Deeply pigmented dark brown to black skin → Never burns, tans very easily

Information on burn injury & scar	**Date of injury (DOI)** **Burn mechanism** - Flame - Scald - Contact - Chemical - Electrical - Explosion - Hot oil - Friction - Cold **% TBSA burnt at initial injury** **Localisation (General)** - Face - Neck - Back - Chest - Abdomen - Flank - Buttocks - Axilla - Upper limb - Lower limb **Location (specific)** **Type of scar** - Healed by secondary intention (conservative treatment) - Grafted - Re-grafted - Cultured epithelial autograft (CEA) - Full-thickness skin graft - Flap - Excision of scar/burn wound scar **Prolonged wound healing (>3 weeks)** (yes/no) **Wound infection (requiring antibiotic treatment) (yes/no)** **Date of operation / Time since operation** **Pervious steroid injection**

3.1.3.2. Scar characteristics, objective & subjective outcome parameters

As a prospective study, evolving scar characteristics as well as various subjective and objective outcomes were collected at the date of enrolment to assess patients' baseline status, at follow-up 4-6weeks after each treatment cycle, and at 12 months after final laser therapy. (Appendix H & I).

In the majority of cases, one scar was selected to serve for reference purposes throughout the course of data collection and the thickest area of that scar chosen as a reference point. The scar was photo documented in the patients file, mapped out, marked with an X, and the selected area chosen as the reference point which was the area assessed for each scar assessment score as well as the ultrasound measurement for scar thickness. The same applied to patients who sustained large %TBSA injuries, where a specific area of the scar, which was deemed particularly thick/symptomatic was chosen to serve as the referencing area. The adjacent thickness of the uninjured skin was also measured, so that the thickness of each scar could be normalized to each patient. The evaluated outcomes are listed in Table 2.

Scar assessment scores reflect the impression of an expert and or the patient about the scar appearance and scar qualities and are an important tool to evaluate the effectiveness of scar therapies. If a scar assessment scale is tested to be reliable, feasible, consistent and valid, it is considered suitable for the comparison of clinical results [153]. The Vancouver Scar Scale (VSS) was introduced in 1990 and adopted extensively into clinical practice as the first validated scar scale [154, 155]. To date it probably remains one of the most frequently used tools to evaluate burn scars [155]. The VSS comprises 4 domains: vascularity (0-3points), pliability (0-5points), pigmentation (0-2points), and height (0-3points) with a maximal score of 13, assessed by an observer/scar expert [154]. By using a semiquantitative approach to organize a list of subjective assessments, the VSS sets a precedent for the systematic assessment of burn scars [155]. However, there are limitations to the VSS as studies have shown that the VSS has only intermediate evidence for validity and reliability, and it does not incorporate burn scar symptoms, functional restrictions and psychological aspects of the scar [155]. Various modifications as well as new scar assessment scores have been described, but the introduction of the Patients and Observer Scar Assessment Scale (POSAS) in 2004 seemed to have been a turning point in the assessments of scars via scores [153]. The POSAS is the first scar assessment score including both the patient’s and the assessor’s perspective, consisting of two parts: a Patient Scale (POSAS-P) and an Observer Scale (POSAS-O) [155]. Additionally, to evaluate the physical characteristics of a scar, it also asks patients to rate any pain and pruritus associated with their scar. Both, the POSAS-P and the POSAS-O scores contain six items, scored numerically on a ten-step scale. The total score of the Patient and Observer Scale results from tallying the scores of each of the six items, and thus ranges from 6 to 60, respectively. Added to that, patients and observers rate their general overall opinion of the scar quality ranging from 1 (normal skin) to 10 (worst imaginable scar) (www.posas.org & [153]).

To provide a more complete picture of the scars the scar assessment scores VSS (Appendix K) as well as the POSAS (Appendix L) were evaluated and documented in the prospective database. Table 2.

As scar thickness is a crucial component of hypertrophic scarring, the scar thickness was measured with an ultrasound for this prospective data collection as an objectively assessed outcome parameter. The scar(s) were photographed at the initial assessment, mapped out and the thickest point marked on the photo with an X, so that the scar(s) was always measured at the same position of the thickest area of the scar. The adjacent thickness of the uninjured skin was also measured, so that the thickness of each scar could be normalised to each patient.

As burn scar pain and pruritus is an extremely limiting factor for a burn survivor and contributes substantially to post burn quality of life (QoL), questionnaires focussing on these aspects served as a subjective assessment tool of this prospective data collection.

These subjective outcome parameters included questionnaires about pain using the Douleur Neuropathique 4 Questions (DN4) (Appendix M) [156], pruritus using a modified 5-D itch scale (4-D Pruritus Scale) (Appendix N) [157], and QOL using the Burns Specific Health Scale – Brief (BSHS-B) (Appendix O) [158].

As described in paragraph 1.2.3., neuropathic pain plays a significant role in burn scars, particularly as the scar matures, the nociceptive pain levels decline, whilst the neuropathic type increases [2]. Sensations such as “pins and needles”, “painful cold”, “burning” or “electric shock” are frequently reported by patients as the main type of pain in burn scars. There is still no consensus on diagnostic criteria of neuropathic pain [159-161]. However, the French Neuropathic Pain Group consists of a panel of experts who addressed questions around neuropathic pain and developed a questionnaire based on clinical experience and analysis of the literature [156]. The questionnaire derived from a list called the DN4, which stands for “douleur neuropathic 4 questions” (i.e. neuropathic pain four questions in French)[156]. The DN4 list includes a series of four questions to explore both sensory descriptors as well as signs related to a bedside examination. The total score is the tally of 10 items, with a cut-off value of 4/10 required for the diagnosis of neuropathic pain [156]. The DN4 is frequently used to assess neuropathic pain in several diseases/traumas associated with neuropathic pain and is considered as an easily applied and effective tool to evaluate the presence and extent of neuropathic pain [162-164]. Thus, this questionnaire was included as the assessment tool for neuropathic pain as an outcome parameter for this prospective data collection.

Despite itch being a very common and debilitating symptom, there are limited questionnaires and evaluation tools available for its quantification [165]. Visual analogue scales (VAS) are often used to rate pruritus, however, whilst it is adequate to assess the severity of itch, it does not include the impact of the symptom on the daily life and overall QoL [157]. Further, it has never been validated if the VAS detects changes over time and was criticized to fail to detect some changes in pruritus severity [157]. Other questionnaires, amongst others the “Eppendorf Itch Questionnaire” (EIQ) by Darsow et al., the “Questionnaire for the Assessment of Pruritus” by Yosipovitch et al. which was modified from the McGill Pain Questionnaire, were developed to assess pruritus [166-168]. However, despite collecting valuable information, they are time consuming, do not provide a quantifiable measure of itch, and none of these scales demonstrated to be sensitive to capture change over time [157]. The 5-D Pruritus Scale is a multidimensional questionnaire that was designed to capture outcomes in clinical trials. It was specifically developed to be able to measure pruritus in a brief manner, which is easy to complete, easy to score, sensitive to the multidimensional nature of pruritus and its effect on QoL, and is able to detect change over time [157]. This questionnaire was chosen to assess itch, as it has a very high test-retest reliability, has been validated, and most importantly, is sensitive to change over time [157]. The original description of the score includes duration, degree, direction, disability and distribution. The latter aspect was excluded in this prospective data collection as the location of pruritus was given by the site of the scar. Thus, the modified 4D Pruritus Score (containing duration, degree, direction and disability) used in this data collection, ranges from a minimum score of 7 (no itch) to 35 (worst itch).

Once the acute treatment is completed following a burn injury, the scar related stigma, symptoms, function, and psychological outcome determines the post injury QoL, which effectively is the ultimate outcome parameter of a burn survivor. To capture all the important dimensions of health in a burns patient, a well-functioning outcome scale is needed [158].

WHO defines QoL as: “An individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment.” (https://www.who.int).

In 1982 the Burn Specific Health Scale (BSHS) was described as an assessment tool to capture the QoL of a burn survivor [169], which was subsequently validated and abbreviated to the BSHS-A (Abbreviated Burn Specific Health Scale) with 80 items [170], and later revised and shortened in the BSHS-R (Revised Burn Specific Health Scale) [171]. The questionnaire was further improved in 2000 by Kildal et al. who published the BSHS-B (Brief Version of the Burn Specific Health Scale) [158]. The BSHS-B was chosen as the QoL assessment tool, as it appears to summarize well burn specific QoL in a relatively short and concise questionnaire, and it emerges to be sensitive to capture change over time. Further, in a systematic review published in April 2020, where 15 health related quality of life instruments were included, the BSHS-B as well as the Brisbane Burn Scar Impact Profile instruments were rated to have the best measurement properties [172]. The BSHS-B is an outcome scale designed for burn patients, containing important aspects of post burn distress. It includes 40 questions within 9 well defined fields (simple abilities, hand function, affect, body image, interpersonal relationship, sexuality, heat sensitivity, treatment regimens, and work). The maximal number of points is 160, which is equal to a normal QoL. This means the higher the number, the better the QoL [158] (Table 2).

As a summary subjective assessment, at each follow-up, patients rate their overall improvement/experience since their last treatment as: “worse”, “unchanged”, “improved a little bit”, “improved quite a bit,” and “improved extremely” (Appendix I). Further, after each treatment patients are asked about the common adverse effects such as erythema, pain and itch, how long these events have lasted for, and if they have experienced any complications (infections, wound breakdown, burn injury, etc.). The treatment is considered as finalized if the treatment goal has been achieved, or if the scar has reached a plateau of improvement.

If the treatment has been marked as finalized, it is further noted if the patient is satisfied with the outcome or not. Table 2.

Table 2. Data collection: scar characteristics (parameters which change over time), complications/adverse effects, subjective impression

Scar Characteristics	**Concomitant conservative scar treatments: (standard scar therapy for immature scars)** - Silicone (yes/no) - Massage (yes/no) - Pressure garments (yes/no) - Physiotherapy (yes/no) **Limited range of motion (ROM)** (yes/no) - Location (neck, axilla, etc.) - Degree (°) of active ROM - Direction (extension/flexion, abduction/adduction, etc.) **Need for simultaneous reconstructive surgery** (yes/no) - Type of procedure **Need for simultaneous reconstructive surgery (yes/no)** - Type of procedure **Scar thickness** (mm) - Normal skin thickness - Thickness of assessed point (usually visually thickest area) **VSS** (0 – 13) **POSAS** - POSAS-P (6 – 60) - POSAS P total (1 – 10) - POSAS-O (6 – 60) - POSAS-O total (1 – 10) **Wound breakdown** (yes/no) **Douleur Neuropathique 4 Questions (D4 Pain Score)** (0 – 10) **4D Pruritus Scale** (7 – 35) **Burns Specific Health Scale – Brief (BSHS-B)** (0 – 160) - Simple abilities (0 – 12) - Hand function (0 – 20) - Affect (0-28) - Body image (0 – 16) - Interpersonal relationship (0 – 16) - Sexuality (0 – 12) - Heat Sensitivity (0 – 20) - Treatment regimens (0 – 20) - Work (0 – 16)
Subjective impression post-treatment	- Worse, - Unchanged - Improved a little bit - Improved quite a bit - Improved extremely

Adverse effects	**Complication** (yes/no) - Type of complication **Expected Adverse Effects:** yes/no, length (days) - Erythema - Pain - Other (type)
Final follow-up	- yes/no - Satisfied with treatment outcome: yes/no - Lost to follow-up: yes/no

3.1.3.3. Treatment settings

For each treatment with the AFL-CO_2, the location to which the treatment was provided, how much %TBSA scar was treated, if the procedure was performed under local or general anaesthesia, specifics regarding the laser settings, and immediate common treatment effects and adverse effects were documented of the specific area marked as the reference point. Table 3. (Appendix J).

Table 3. Data collection: treatment settings

Procedure	**Combined operation:** Simultaneously performed reconstructive surgical procedure - yes/no - type **Location** (location of treated scar) **% TBSA scar treated** **Anaesthesia** - Local anaesthesia - General anaesthesia
AFL-CO_2 settings	**Handpieces** - Number of handpieces - Type of handpieces - Same handpiece with different settings (yes/no) - Total FX (yes/no) **Settings** - DeepFX/SCAAR-FX: highest energy (mJ) & highest density (%) - Active FX: highest energy (mJ) & highest density (%) - Double pulse (yes/no), double pulse energy (mJ) & density (%) - Specific settings used for entire scar at that particular body location: shape, size, energy (mJ), density (%), rate (Hz) **Laser facilitated steroid infiltration** - yes/no - Type (Kenacort A10 or Kenacort A40)
Treatment effects	**Treatment effects:** yes/no - Pinpoint bleeding - Erythema - Oedema - Exudate - Pain - Epidermal loss - Pruritus

3.1.3.4. Final follow-up

At the final follow-up all treated scars were assessed and rated as mentioned above and the clinical data collection completed. Additionally, patients were asked by the clinician assessing all the scar assessment socres, if they were: unsatisfied or satisfied (if the expectations or needs of the treatment were fulfilled) with the achieved end-result. The treatment was regarded as finalized if the scar had reached a plateau (meaning the scar has improved to an extend where it does not improve anymore) or if the patient decided to finalize the treatment if there were no more functional limitations. If patients did not present for follow-up after >12mt they were deemed lost to follow-up (Table 2).

3.1.3.5. Forms, Patient Information & Consent

Appendix F includes the patient information form which was handed out to each participant of the data collection. For each patient at consent form (Appendix G) was filled out. Appendix H-O include the data collection forms, assessment scales and questionnaires used for this data collection.

3.1.3.6. Specific methods for subgroup analyses

To facilitate readability of the thesis, some project-specific methodology is presented in Chapter 4 with the respective study designs briefly being outlined in each chapter.

3.2. Ethics approval

The initial application of the Low and Negligible Risk (LNR) application for the clinical data collection: *Ablative fractional CO_2 laser for the treatment of severe burn scars: Establishment of a prospective registry and outcome analysis* for the purpose of quality outcome analyses, was reviewed by the Sydney Local Health District (SLDH) Human Research Ethics Committee – Concord Repatriation General Hospital (CRGH) and approved on 13 March 2015: LNR/14/CRGH/257, CH62/6/2014-187.

The project was further extended and resubmitted in form of a National Ethics Application Form (NEAF) with the additional inclusion of collection of tissue samples for histopathological, immunohistochemistry, and molecular analysis, and approved on 18 May 2017 by the SLDH Human Research Committee – CRGH: HREC/17/CRGH/16, CH62/6/2017-008.

3.3. Statistical analysis

3.3.1. Description of general statistical methods

Only patients with complete follow-up data were analysed, meaning that in certain instances the number of patients and scars analysed may be different from the total cohort. Therefore, the total number of patients and scars contributing to the results of subjective/objective outcomes is clearly denoted. Continuous variables were compared using Student's t-test, Wilcoxon rank sum test, one-way analysis of variance (ANOVA) and the Kruskal-Wallis test where appropriate. Where necessary, log2 transformation of continuous data was performed to achieve normal distribution for these analyses. Differences between proportions derived from categorical data were analysed using Pearson's chi-squared test or Fisher's exact test where appropriate. Data are presented as median with interquartile range (IQR) unless denoted otherwise. Uni- and multivariable linear and logistic regression analyses were performed where appropriate. All p-values ≤0.05 were regarded as statistically significant and all statistical analyses were performed using R Statistical Packages [173].

3.3.2. Project specific statistical considerations

3.3.2.1. Effectiveness & safety of AFL-CO_2 for the treatment of burn scars: a case-control study

Statistical analyses were performed within patient groups (treatment group pre vs. post AFL-CO_2 and after initial and subsequent assessment for the control group) as well as between treatment groups (treatment vs. control groups). Where within group analyses were performed, these were performed as paired tests.

3.3.2.2. AFR with laser-facilitated steroid delivery for burn scar management: Laser penetration depth study

Laser handpiece energy settings directly correlate with penetration depth. As such to assess the depth of scar penetration the maximum penetration depth was divided by the scar thickness at the thickest point of each scar to calculate the percentage of tissue penetration. Patients were subsequently divided into 5 groups depending on minimal scar penetration depth: 0-25%, 26-50%, 51-75%, 76-100% & >100% penetration of scars.

3.3.2.3. AFR for burn scar management affects the number & type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay study

Analyses were stratified both according to the treatment "era" (i.e. pre- vs. post-laser introduction) as well as according to whether AFL-CO_2 was included in the patient's reconstructive surgical procedure or not.

3.4. Treatment protocol

3.4.1. Scar algorithm

Burn survivors suffering from the sequelae of their injury, requiring burn scar management are referred to the outpatient Burn Scar Clinic. The scars are systematically evaluated and a treatment plan for each individual patient tailored towards their needs, including non-invasive therapies, laser treatment and reconstructive surgical procedures. Figure 3 illustrates the treatment algorithm for burn scars at the CRGH Burns Unit.

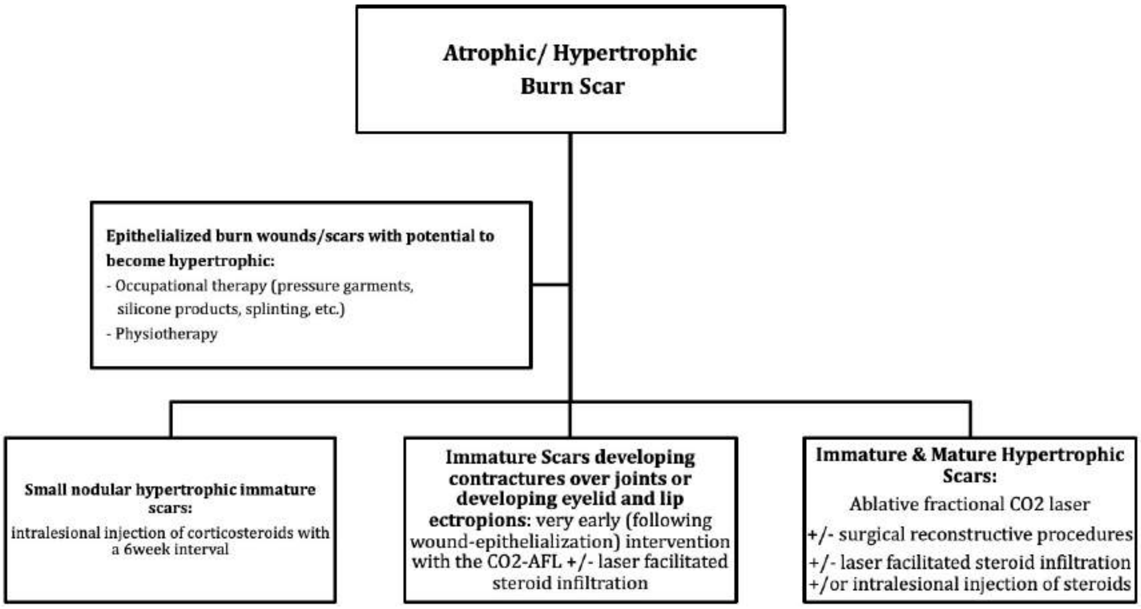

Figure 3. Treatment algorithm for burn scars, Burns Unit, CRGH

Various aspects of hypertrophic scars can be specifically addressed by different functions of AFL devices. The AFL-CO_2 has different modalities (superficial, deep, or combined), by which tissue can be ablated superficially or deep. Superficial ablation can be used to correct surface irregularities and lead to a smoother overall appearance of the scar (e.g. flattening of the typical cobble stone appearance of a meshed skin graft). Deeper ablation is generally used to release tension and stimulate dermal remodelling as described in Chapter 2. Depending on scar qualities and patient's needs the selection of the AFL-CO_2 modality, as well as the choice of treatment settings allow the surgeon to modify and tailor the treatment accordingly. [40]

Conventionally, it is recommended to await full scar maturation before reconstructive intervention, unless there is an acute indication to prevent secondary impairment of organ or joints (e.g. ectropion, contracture over a joint) [40, 93]. The ideal timing of AFR intervention is undetermined, however, it is suggested that treatment can be initiated soon after epithelialization of the wound occurred (see Chapter 4.4. & 4.5.), which may reduce contracture formation, enhances range of motion and hereby mitigating and accelerating the rehabilitative process [40, 91, 134]. Further, it is very important that the choice of modality and aggressiveness of treatment settings has to be adjusted to scar location, scar maturation, skin type and ethnicity of the patient.

For an optimal outcome, AFL-CO_2 will need to be repeated multiple times. Depending on the patient's response, skin type, ethnicity, age, general health, scar type and location, the number of laser treatments can range from as little as one up to 8 or 9 laser sessions. Equally, the treatment interval can range from a minimal treatment interval of 6 weeks up to >6 months. Immature scars of patients with a lighter Fitzpatrick skin type may need a longer treatment interval than mature scars of patients with a darker Fitzpatrick skin type due to the prolonged remodelling phase reflected by longer persisting post-procedural erythema.

3.4.2. Perioperative considerations

AFL-CO_2 is generally very well tolerated, however, as the procedure of resurfacing with AFL-CO_2 is relatively painful, pain management during the treatment with AFL-CO_2 is very important, in particular as burn survivors often have a different pain perception compared to other patient cohorts. Burn patients often suffer from posttraumatic stress disorder, have a pre-set mindset towards procedural pain, suffer from neuropathic pain, and are frequently on chronic pain medication complicating pain control [40]. Thus, the pain management can range from applying ice to the area of treatment shortly before the procedure, topical anaesthetic creams, sedation, to full general anaesthesia.

3.4.2.1. Expected immediate side effects & adverse effects

Erythema, pinpoint bleeding, oedema and discharge of serous fluid are expected effects immediately following treatment with AFL-CO_2 and by some experts even considered to be an aspired endpoint for successful treatment settings. These effects may last for a few days after the intervention. If scars are very fragile or if treatment settings are too strong, small areas of epidermal loss can be noted. As long as the loss involves the epithelium only, these areas will re-epithelialize quickly. However, if areas show a deeper abrasion of skin, it may be an indication of too strong settings for that scar which may result in a thermal insult with subsequent worse scarring.

Crusting with exfoliation over approximately 14 days is another expected outcome, particularly for patients treated with superficial fractional ablative lasers/modes. Post-procedural pain often persists only over about 1-2 hours after the treatment and is described by a feeling of heat by the patients [40]. Mild pain can persist over the subsequent 1 to 2 days. Post-procedural pruritus is less frequently seen, however, if present often lasts for several days or weeks following treatment. Particularly mature, old scars (>5-10 years post injury) tend to be more prone to pruritus, which may indicate that the remodelling process may be experienced more pronounced in patients who have lived with their scars for long time.

Transient post-inflammatory hyperpigmentation (PIH) is another side/adverse effect which often occurs, in particular in patients with darker skin types of Middle Eastern, Indian or Asian descent. However, PIH can often be anticipated if a patient is assessed during their initial consultation (assessing the donor sites, looking at the actual scar and considering the patient's skin type and ethnicity). In these cases, a prophylactic dose adjustment (particularly if using the superficial ablative modality) as well as post-procedural prescription of compound cream (including corticosteroids, hydroquinone, and retinoids) may prevent post-procedural PIH. At CRGH if a patient at risk of PIH is identified, patients receive a course of compound cream (0.01% fluocinolone, 4% hydroquinone, 0.05% tretinoin) topically at night for 6 – 8 weeks, commencing approximately 3 weeks after the laser treatment.

Post-procedural hypopigmentation is less frequently seen, however, can occur in particular in lighter Fitzpatrick skin types of Anglo-Saxon descent. It is generally transient as well and re-pigmentation generally occurs within a few weeks/months.

The actual rate of adverse effects/complications is relatively low [174, 175]. The rate of infections is reported to be <1%, in spite of the increased receptiveness of burn victims [40, 91, 174]. Burn patients undergoing treatment with the AFL-CO_2 at CRGH, do not receive prophylactic antibiotics, with a few exceptions as described in Chapter 3.4.3.

Lastly, the power of AFL devices makes them attractive to achieve great outcomes, however, if used incorrectly, they can cause substantial harm [40]. Energy-based light devices transform light into heat, which indicates that if too strong settings are used, in particular with the distinct nature of a burn scar, an iatrogenic burn injury can occur. Thus, it is strongly recommended that treatment of burn scars with AFL devices should remain in the hands of a specialist familiar with the nature of burn scars as well as knowledge in light-based therapies. [40]

3.4.3. Treatment setting

All procedures (laser and surgical reconstructive treatments) were performed under local or general anaesthesia in the dedicated burns theatre within the CRGH Burns Unit**,** approved by the local laser safety committee.

Scars suitable for AFR were treated with the ablative fractional 10,600-nm wavelength CO2 Ultrapulse® laser (by Lumenis®) including ActiveFX™ and DeepFX™ hand pieces and the SCAAR FX™ mode. Treatment settings were chosen according to clinical judgement which incorporates a variety of factors to help guide laser setting selections (see Chapter 4.3.). These include patient factors such as specific scar locations, thickness (as measured by ultrasound at the thickest area), scar maturity, type of scar, Fitzpatrick skin type, ethnicity etc. Typically, the laser treatment was started at thickest point of the scar with the maximum energy levels and subsequently these were adapted whilst passing across the thinner areas of the scar. For energies up to 35mJ, densities of 5-10% were chosen. Energies between 40-60mJ were usually combined with a density of 5%, 70-80mJ with a density of 3-5%, and 90-150mJ with a density of 1% (with the DeepFX™ hand piece). Laser facilitated drug delivery of corticosteroids (Kenacort A40, Kenalog 40mg/ml) topically and/or by intralesional injection (of hypertrophic/nodular areas) following treatment of hypertrophic burn scars with the AFL-CO_2 Ultrapulse® was part of the standard treatment protocol.

All problematic areas/scars of a burn victim were aimed to be treated in one treatment session with the AFL-CO_2, however the treatment area was usually kept under 30% TBSA (total body surface area) based on clinical experience on what was well tolerated by patients and due to time restriction in operating theatres.

Postoperative wound care included double layer bactigras for 48hours, followed by topical paraffin twice daily for 7days. Pressure garments were generally worn again after 3days when the scar was fully epithelialized. After the procedure, patients were not to be exposed to a dirty or dusty environment or extreme temperatures for about 7 days. Photoprotection was advocated and application of sunblock recommended once the scar was fully epithelialized.

Patients routinely received valacyclovir orally for 5days if a scar adjacent to the perioral area was treated with the AFL-CO_2. Patients with hypertrophic scars in areas of facial hair with recurrent acute on chronic folliculitis episodes received one single dose of pre-operative intravenous Cefazoline 2g. No other routine prophylactic antibiotics or antiviral medication were used.

Chapter 4. Outcome analysis of burn scars treated with AFL-CO_2

Chapter 4: Outcome analysis of burn scars treated with AFL-CO_2

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4.1. Subjective & objective outcome analysis following one treatment with the AFL-CO_2

A first analysis of the CRGH prospective scar data collection looking at the effect of one treatment with the AFL-CO_2 was published in 2017 (Appendix A). In an attempt to provide a holistic picture of burn patient outcomes following treatment with AFL-CO_2, various subjective and objective collected outcome parameters were assessed.

To be included in the quantitative analysis, patients had to have completed one first treatment with the AFL-CO_2 and at least one first follow-up. To evaluate the impact of natural scar maturation on outcome parameters, the patient cohort was further split into two groups. One group consisted of patients with young, immature scars, who presented for their first treatment less than 2 years following the burn injury/last operation. The second group included patients with mature scars having their initial treatment more than 2 years after the burn injury/last operation.

47 patients with 118 scars who have completed one treatment and one first follow-up with the AFL-CO_2 were analysed for this preliminary analysis. AFL-CO_2 treatment was initiated after a median of 17.9 months (IQR 10.9–43.1 months) following the burn injury and a median of 14.8 months (IQR 8.8–19.0 months) following the last operation (debridement and skin graft or xenograft), respectively. Outcome parameters were assessed at a median of 55 days (IQR 32–74), which all showed statistically significant improvement.

The intra-patient normalized scar thickness decreased from a median of 2.4mm (IQR 1.8–3.1) to 1.9mm (IQR 1.4–2.8; $p < 0.001$), with a concomitant drop of the VSS from a median of 7.0 (IQR 6.3–8.8) to 6.0 (IQR 4.3–7.0; $p < 0.001$). The Observer Scar Assessment Score of the POSAS (POSAS-O) decreased from a median of 29.0 (IQR 24.0–33.0) to 21.0 (IQR 18.0–25.0; $p < 0.001$), and the overall POSAS-O showed a drop by 1 point ($p < 0.001$). The Patient Score of the POSAS (POSAS-P) decreased from a median of 36.0 (IQR 27.0–42.0) to a median of 23.0 (IQR 17.0–32.0; $p < 0.001$) following one treatment with AFL-CO_2 and the overall POSAS-P score improved by 4 points from 9.0 (IRQ 8.0–10.0) to 5.0 (IRQ 4.0–8.0; $p < 0.001$). Neuropathic pain (DN4 Pain Questionnaire) decreased from a median of 3.0 (IQR 1.0–6.0) to 2.0 (IQR 0.0–5.0; $p < 0.001$). And the modified 4D Pruritus Score dropped by 2.5 points from 16.0 (IQR 9.8–20.0) to 13.5 (IQR 7.0–18.0; $p < 0.001$). Lastly, the overall burn specific quality

of life measured with the BSHS-B, increased by 16 points from a median of 120 (IQR 110–139) at baseline to a median of 136 (IQR 104–149; $p < 0.001$).
These results remained significant even when stratified according to scar maturation (<2 years after injury, >2years after injury).

This preliminary analysis together with the increasing clinical demand for this treatment modality with extremely high patient satisfaction, led to the continuation and further extension of the prospective database, ongoing analysis and various side projects to further investigate the potential of this novel treatment algorithm. It has further provided the foundation to develop treatment protocols and algorithms as described in Chapter 3.

4.2. Effectiveness & safety of ablative fractional CO_2 laser for the treatment of burn scars: a case-control study

As it was noticed during the pilot project in Chapter 4.1., the introduction of AFL-CO_2 has led to a change in choices of surgical burn scar reconstruction with a shift towards simpler local tissue rearrangements combined with the laser treatment, with reduced length of stays, quicker rehabilitation times, which positively influence the psychosocial rehabilitation of burn survivors [176]. However, there is a paucity of higher-level data on the use of AFL-CO_2 for burn scars and control groups usually involved the same scar of the treated patients in a so-called "split scar" approach [177, 178]. There is an increased understanding that the effects induced by AFL-CO_2 may have a positive effect on adjacent zones. Equally, if one side of the scar is treated and tension is released, it will subsequently influence the neighbouring area of the untreated scar [177]. Some experts believe that it is possible, that the treatment of a larger body surface area with AFL-CO_2, may have systematic effects and potentially positively influences scars located at other sites. Further, the impact of natural scar maturation on many of the aspects impairing burn patients has not been studied nor compared to AFL-CO_2.
Accordingly, a nested case-control study was performed to evaluate the effect of AFL-CO_2 on various objective and subjective outcome parameters, in particular analysing the effect on burn specific quality of life (QoL).

For the present analysis, a nested case control study was performed. Twenty patients were assessed in the scar clinic, but their actual treatment was deferred due to lacking theatre time or patient related factors. These 20 patients were then subsequently re-assessed immediately before their treatment with AFL-CO_2 and served as a control group. To be included in the quantitative analysis for the case-control study, patients in the treatment group had to have completed one first treatment with the AFL-CO_2 and at least one first follow-up (patients generally require 3-6 treatment cycles with the AFL-CO_2 for an optimal outcome). To account for the impact of normal scar maturation, patients were further stratified into immature and mature scar groups and the differences in case and control cohorts were analysed according to their scar maturation. Data was analysed according to the statistics section (Chapter 3.3.2.1.). Appendix B.

4.2.1. Demographics

187 patients were included in the analysis with 167 in the AFL-CO_2 treatment and 20 patients in the control group.

Age, gender, ethnicity, Fitzpatrick skin type, smoking status, co-morbidities, and prolonged wound healing showed no significant differences between the two groups (Table 4). The same applied to data relating to the burn mechanism and %TBSA. The median time since injury was 17 months (IQR 9 – 51.5) in the AFL-CO_2 group and 11.5 months (IQR 8 – 25.8) in the control group ($p = 0.34$). Equally, the duration between the initial assessment and the follow-up was comparable with 154 days (IQR 84 – 224) in the AFL-CO_2 cohort and 148 days (IQR 123 – 259) in the control group ($p = 0.28$, Table 4).

Data on scar characteristics and associated previous management was also similar between groups. Accordingly, it was deemed that the case and the control cohorts were comparable for further comparative outcome analyses (Table 4).

Table 4. Comparison case versus control: demographics & burn mechanism

Demographics	Total (n pt = 187)	Case (n pt = 167)	Control (n pt = 20)	p-value
Age (years) *median*	39 (IQR 27 – 49)	37 (IQR 27 – 50.5)	43 (IQR 25.5 – 47.3)	0.98
Gender:				0.64
- female	112 (59.9%)	101 (60.5%)	11 (55%)	
- male	75 (40.1%)	66 (39.5%)	9 (45%)	
Ethnicity:				0.89
- Anglo-Saxon	87 (46.5%)	79 (47.3%)	8 (40%)	
- East European	16 (8.6%)	14 (8.4%)	2 (10%)	
- Middle Eastern	15 (8%)	13 (7.8%)	2 (10%)	
- African	1 (0.5%)	1 (0.6%)	0	
- Asian	59 (31.6%)	51 (30.5%)	8 (40%)	
- Indigenous Australian, Maori, Pacific Islanders	7 (3.7%)	7 (4.2%)	0	
- South American	2 (1.1%)	2 (1.2%)	0	
Fitzpatrick skin type:				0.68
- 1	5 (2.7%)	5 (3%)	0	
- 2	39 (20.9%)	35 (21%)	4 (20%)	
- 3	86 (46%)	76 (45.5%)	10 (50%)	
- 4	38 (20.3%)	32 (19.2%)	6 (30%)	
- 5	16 (8.6%)	16 (9.6%)	0	
- 6	3 (1.6%)	3 (1.8%)	0	
Smoker	19 (10.2%)	19 (11.4%)	0	0.23
Co-morbidities:				
- Cardiac	21 (11.2%)	18 (10.8%)	3 (15%)	0.45
- Vascular	4 (2.1%)	3 (1.8%)	1 (5%)	0.37
- Pulmonal	4 (2.1%)	4 (2.4%)	0	1
- Diabetes mellitus	11 (5.9%)	9 (5.4%)	2 (10%)	0.33
- Neurological	6 (3.2%)	5 (3%)	1 (5%)	0.50
- Psychiatric	21 (11.2%)	19 (11.4%)	2 (10%)	1
- Other	39 (20.9%)	37 (22.2%)	2 (10%)	0.26
Prolonged wound healing (>21 days to epithelialization)	74 (39.6%)	62 (37.1%)	12 (60%)	0.08
Burn Information	Total (n pt = 187)	Case (n pt = 167)	Control (n pt = 20)	p-value
% TBSA, *median*	10 (IQR 3 – 30)	10 (IQR 3 – 35)	4 (IQR 1.5 – 19)	0.43
Burn Mechanism:				0.16
- Flame	78 (41.7%)	74 (44.3%)	4 (20%)	
- Scald	40 (21.4%)	34 (20.4%)	6 (30%)	
- Contact	18 (9.6%)	14 (8.4%)	4 (20%)	
- Hot oil	20 (10.7%)	17 (10.2%)	3 (15%)	
- Explosion	11 (5.9%)	10 (6%)	1 (5%)	
- Chemical	5 (2.7%)	4 (2.4%)	1 (5%)	
- Electrical	2 (1.1%)	2 (1.2%)	0	
- Other (Friction, etc.)	13 (6.9%)	12 (7.2%)	1 (5%)	
Time since injury (months), *median*	16 (IQR 9 – 47)	17 (9 – 51.5)	11.5 (8 – 25.8)	0.34
Duration 1st treatment to follow-up (months), *median*	5.1 (IQR	5.1 (IQR 2.8 – 7.5)	4.9 (IQR 4.1 – 8.6)	0.11
Scar Information	Total (n scar = 337)	Case (n scar = 305)	Control (n scar = 32)	p-value
Scar per patient, *median*	2 (Range 1 – 8)	2 (IQR 1 – 2)	2 (IQR 1 – 2)	0.69
Maturity				
- Immature (<2years)	209 (62%)	186 (61%)	23 (71.9%)	0.23
- Mature (>2years)	128 (38%)	119 (39%)	9 (28.1%)	
Scar thickness (µm)				
median	3.2 (IQR 2.2 – 4.5)	3.2 (IQR 2.2 – 4.5)	3.1 (2.35 – 3.95)	0.89
mean (SD)	3.48 (1.61)	3.48 (1.64)	3.48 (1.32)	

Type of scar:				0.95
- Conservative	54 (16%)	48 (15.7%)	6 (20%)	
- Grafted	180 (53.4%)	165 (54.1%)	15 (50%)	
- Re-grafted	36 (10.7%)	32 (10.5%)	4 (13.3%)	
- Xenograft	47 (13.9%)	42 (13.8%)	5 (16.7%)	
- Donor-site	5 (1.5%)	5 (1.6%)	0	
- Other[i]	13 (3.9%)	13 (4.3%)	0	
Concomitant conservative scar management:				
- Silicone	69 (20.5%)	60 (35.9%)	9 (47.4%)	0.33
- Massage	121 (35.9%)	107 (64.1%)	14 (73.7%)	0.46
- Garments	81 (24%)	69 (41.3%)	12 (63.2%)	0.09
- Physiotherapy	23 (6.8%)	19 (11.4%)	4 (21.1%)	0.26
Localization:				
- Face	42 (12.5%)	39 (12.8%)	3 (9.4%)	0.99
- Neck	19 (5.6%)	18 (5.9%)	1 (3.1%)	
- Chest	32 (9.5%)	29 (9.5%)	3 (9.4%)	
- Abdomen/Flank	15 (4.5%)	14 (4.6%)	1 (3.1%)	
- Back/Buttock	13 (3.6%)	12 (3.9%)	1 (3.1%)	
- Upper limb	144 (42.7%)	129 (42.3%)	15 (46.9%)	
- Lower limb	72 (21.4%)	64 (21%)	8 (25%)	
Laser combined with surgical procedure	32 (9.5%)	30 (10.1%)	2 (7.1%)	0.69

[i] Other = excision of scar, full-thickness skin graft, cultured epithelial autograft, flap, etc.

4.2.2. Comparison of scar-related outcomes – ultrasound measured scar thickness

Scar thickness showed a significant reduction in the AFL-CO_2 treatment group (3.2 µm (IQR 2.3 – 4.5) → 2.6 µm (IQR 1.9 – 3.4), $p < 0.001$), and a non-significant decrease in the control group (3.1 µm(IQR2.4–4.0) → 2.3µm (IQR 1.9 – 3.8), $p = 0.47$). However, there was no difference in scar thickness between the AFL-CO_2 case vs control group (Table 5, Figure 4).

4.2.3. Comparison of scar-related outcomes – Vancouver scar scale (VSS)

The VSS reduced by two points (8 (IQR 7 – 9) → 6 (IQR 5 – 7), $p < 0.001$) in the treatment group and by one point (9 (IQR 8 – 0.9) → 8 (IQR 7 – 9), $p = 0.03$)) in the control group. This improvement was significantly higher when compared between the treatment and control group (Figure 5).

4.2.4. Comparison of scar-related outcomes – observer scores of the patient & observer scar assessment score (POSAS-O)

The POSAS-O showed a difference in both cohorts which appeared to be significant when both groups were compared, but not significant for the POSAS-O overall score (Table 5, Figure 6).

Table 5. Comparison case versus control: outcome parameters

Variables	**Case** (n pt=167)	**p-value**	**Control** (n pt=20)	**p-value**	**p-value for case vs control**
Scar thickness (US), µm					
Median (IQR)	3.2 (2.3 – 4.5) → 2.6 (1.9 – 3.4)	**<0.001**	3.1 (2.4 – 4.0) → 2.3 (1.9 – 3.8)	0.47	0.59
Mean (SD)	3.6 (1.6) → 2.9 (1.4)		3.4 (1.4) → 3.1 (1.8)		
VSS (0-13)					
Median (IQR)	8 (7 – 9) → 6 (5 – 7)	**<0.001**	9 (8 – 9.8) → 8 (7 – 9)	0.03	**<0.001**
Mean (SD)	7.7 (1.8) → 6.0 (1.9)		8.6 (1.8) → 8.1 (1.6)		
POSAS-O (6-60)					
Median (IQR)	26 (22 – 32.5) → 20 (16 – 24)	**<0.001**	27 (24 – 31) → 22 (20.5 – 27)	**<0.001**	**<0.001**
Mean (SD)	27.5 (7.5) → 20.4 (5.9)		27.3 (6.3) → 23.7 (6.2)		
POSAS-O overall (1-10)					
Median (IQR)	5 (4 – 6)→ 3 (3 – 4)	**<0.001**	5 (4 – 6) → 4 (3 – 5)	**<0.001**	0.01
Mean (SD)	5.0 (1.72) → 3.7 (1.38)		5.1 (1.4) → 4.4 (1.5)		
POSAS-P (6-60)					
Median (IQR)	35 (28 – 40) → 24 (19 – 32)	**<0.001**	32 (27 – 39) → 33 (27.5 – 38)	0.99	**<0.001**
Mean (SD)	34.6 (10.2) → 25.1 (9.8)		32.7 (9.3) → 33 (8.1)		
POSAS-P overall (1-10)					
Median (IQR)	8 (7 – 10) → 5 (4 – 8)	**<0.001**	7 (5 – 9) → 7 (5 – 8)	1	**0.009**
Mean (SD)	8.0 (2.1) → 5.8 (2.4)		7.1 (2.3) → 6.4 (2.0)		
DN4-Pain Score (0-10)					
Median (IQR)	4 (1 – 6) → 3 (0 – 3)	**<0.001**	4 (3 – 5.3)→ 4 (2 – 5)	0.11	**0.03**
Mean (SD)	3.9 (2.8) → 2.9 (2.5)		4.2 (2.5) → 3.7 (2.0)		
Modified D4 Pruritus Questionnaire (7-35)					
Median (IQR)	16 (10 – 20) → 12 (7 – 17)	**<0.001**	17 (10.5 – 19.5) → 17 (12 – 19)	0.23	0.04
Mean (SD)	15.6 (6.1) → 13.3 (5.7)		16.8 (6.5) → 15.7 (5.8)		
BSHS-B (total Score: 0-160)					
Median (IQR)	119 (101 – 143) → 133 (106.5 – 147.5)	**<0.001**	130.5 (124–141)→120 (101–143.8)	0.1	0.01
Mean (SD)	116.8 (29.2) → 126.1 (27.4)		126.3 (24.5) → 113 (38.0)		
Global Impression					
➢ **unchanged**	21 (9.8%)		15 (53.6%)		**<0.001**
➢ **a little bit**	99 (46.4%)		13 (46.4%)		
➢ **quite a bit**	61 (28.5%)		0		
➢ **extremely**	33 (15.4%)		0		

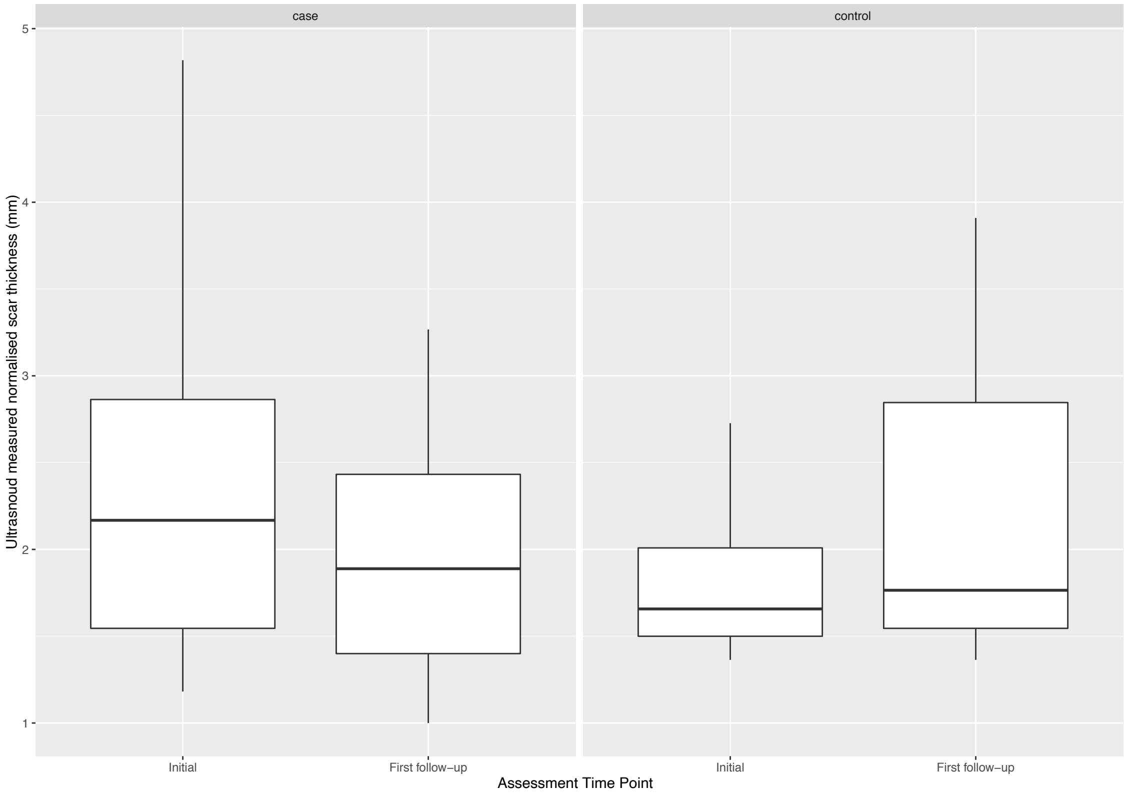

Figure 4. Boxplot demonstrating the effect of one treatment with the AFL-CO_2 laser vs the control group on normalised scar thickness.

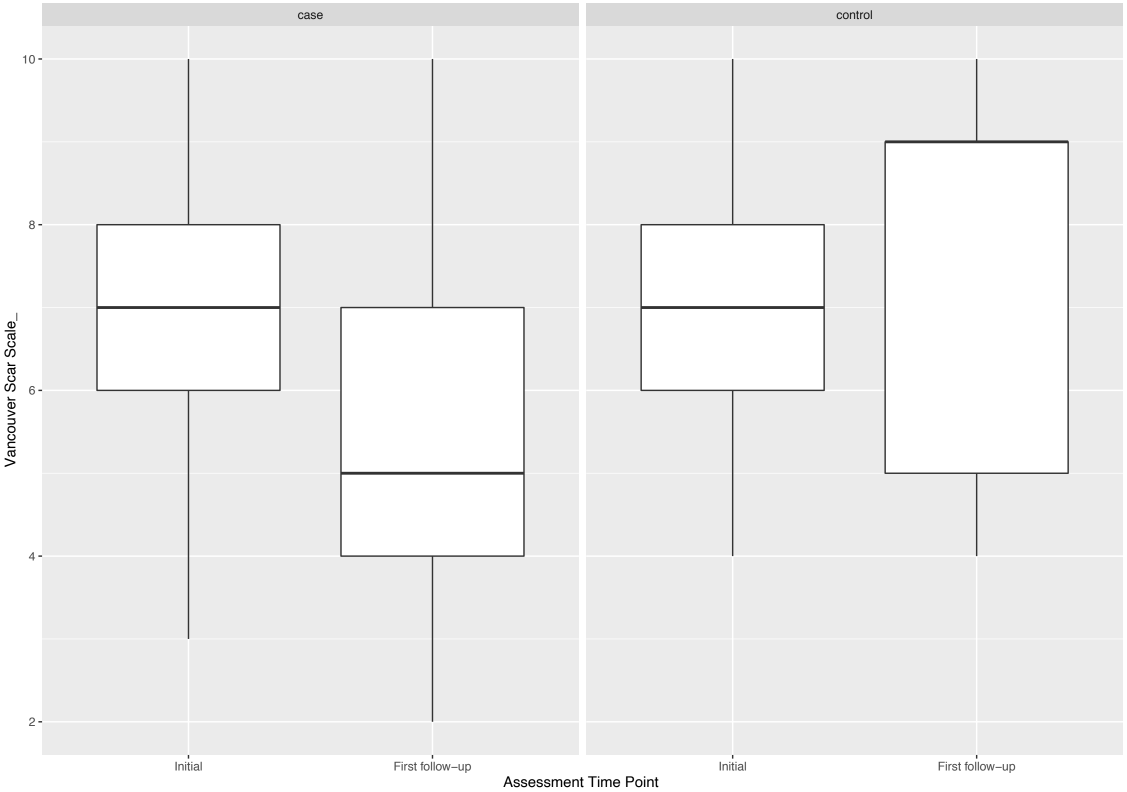

Figure 5. Boxplot demonstrating the effect of one treatment with the AFL-CO_2 laser vs the control group on the VSS.

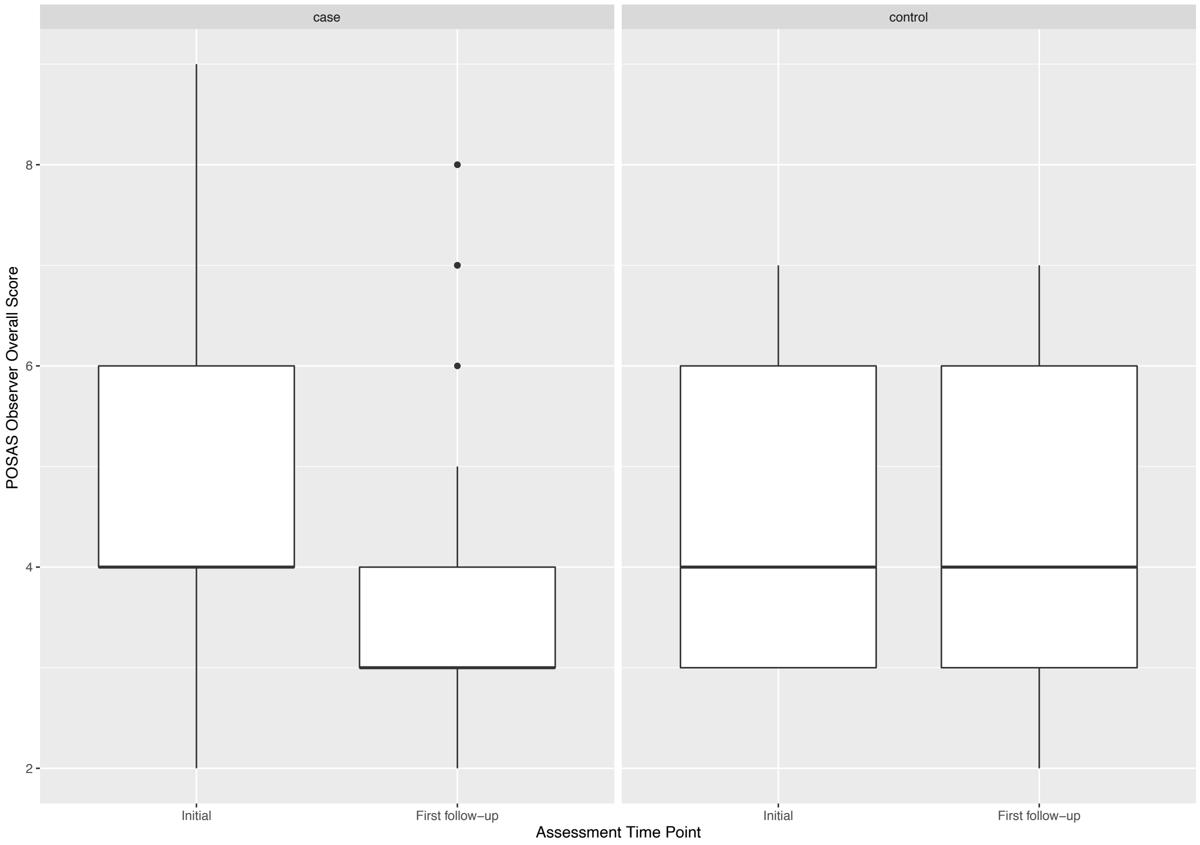

Figure 6. Boxplot demonstrating the effect of one treatment with the AFL-CO_2 laser vs the control group on the overall Observer Score of the POSAS.

4.2.5. Comparison of subjectively assessed outcomes - patient reported scores of the patient & observer scar assessment score (POSAS-P)

The POSAS-P as well as the POSAS-P overall scores showed statistically significant differences between the case and the control cohorts respectively, with the treatment group reporting a reduction of 11 points ($p < 0.001$), whereas in the control group there was an increase of the score by 1 point ($p = 0.99$). Similarly, the POSAS-P overall score in the treatment group decreased by 3 points ($p < 0.001$), whereas in the control group it remained the same ($p = 0.23$, Table 5.)

4.2.6. Comparison of subjectively assessed outcomes – neuropathic pain scores

Looking at pain scores, there was a significant improvement in the treatment group whereas the control group described the same scores in their initial assessments and follow-ups (Table 5). If only patients with previous neuropathic pain scores were included in the analysis (scores ≥ 4), results remained the same regardless of maturation status of the scars (Table 6).

Pruritus scores dropped by 4 points in the treatment cohort ($p < 0.001$), whereas the control group remained unchanged (Table 5).

4.2.7. Comparison of subjectively assessed outcomes – burn specific quality of life

Patients rated their burn specific QoL being improved by 14 points after just one AFL-CO_2 treatment (119 (IQR 101 – 143) before treatment to 133 (IQR 106.5 – 147.5) post-treatment, $p < 0.001$). In the control group scores got worse from 131 (IQR 124 – 141) to 120 (IQR 101 – 143.8, $p = 0.1$). When QoL subdomain-analyses were performed, the biggest differences in Affect, Body image, Heat Sensitivity, Treatment and Work were observed. Body image significantly improved in the treated group, whereas it was rated worse in the control group. Heat sensitivity overall also significantly improved in the treatment group by 4 points ($p < 0.001$). The subdomain "Treatment" (i.e. QoL associated with treatment regiments required for burn scars) generally improved in the treated cohort but worsened or remained unchanged in the control group. An overview of the QoL outcome analysis is provided in (Table 7). Figure 7 illustrates regularly observed improvement of facial scarring following AFL-CO_2, simultaneously enhancing the patients QoL by relieving symptoms of painful chronic folliculitis.

Table 6. Comparison case versus control: patients with neuropathic pain only (defined as DN4 Pain scores of 4 or more)

Variables *medians (IQR)*	Case (n pt=52)	p-value	Control (n pt=9)	p-value	p-value for case vs control
DN4-Pain Score (4-10)	6 (4 – 8) → 4 (1 – 6)	**<0.001**	5 (4 – 7.5) → 4.5 (3.25 – 5)	**0.006**	0.4
DN4-Pain Score (4-10): Immature Scars only (<2years post injury)	6 (5 – 8) → 4 (4 – 6)	**<0.001**	6 (5 – 8) → 4 (4 – 6)	0.02	0.3
DN4-Pain Score (4-10): Mature Scars only (>2years post injury)	5 (5 – 7) → 4 (2 – 5)	**0.001**	9 (7 – 9) → 5 (4.5 – 5)	0.10	0.10

Table 7. Comparison case versus control: domains of BSHS-B

BSHS-B *medians (IQR)*	**Case** (n pt=167)	p-value	**Control** (n pt=20)	p-value	p-value case vs control
Simple abilities	12 (10 – 12) → 12 (11 – 12)	**<0.001**	12 (12 – 12) → 12 (11.5 – 12)	1	0.02
- immature	12 (10 – 12) → 12 (11-12)	**<0.001**	12 (12 – 12) → 12 (10 – 12)	1	**<0.001**
- mature	12 (12 – 12) → 12 (12-12)	0.01	12 (12 – 12) → 12 (12 – 12)	NA	0.35
Hand function	20 (16 – 20) → 18 (18 – 20)	**<0.001**	20 (18.3 – 20) → 20 (17.8 – 20)	0.71	0.3
- immature	20 (16 – 20) → 20 (18 – 20)	**0.001**	20 (18.8 – 20) → 20 (18 – 20)	0.4	0.04
- mature	20 (14 – 20) → 20 (18 – 20)	**0.003**	20 (17.8 – 20) → 20 (17.8 – 20)	NA	0.44
Affect	25 (20.8 – 28) → 26 (21 – 28)	0.01	26 (19 – 27.8) → 21 (16.8 – 27)	0.08	**<0.001**
- immature	25 (21 – 28) → 26 (21 – 28)	0.7	26.5 (25.3 – 28) → 22.5 (17 – 26.3)	0.02	**0.003**
- mature	26 (15 – 27) → 27 (19.5 – 28)	**<0.001**	17 (11 – 24.5) → 21 (12 – 26.3)	0.1	0.20
Body image	8 (4 – 12) → 9.5 (4 – 13)	**<0.001**	7.5 (3.5 – 10) → 6 (3.8 – 13)	0.09	0.05
- immature	8 (4 – 13) → 10 (4 – 14)	**<0.001**	8.5 (6.5 – 10) → 7 (4 – 12)	0.5	0.08
- mature	8 (4 – 11) → 9 (4.5 – 12,5)	**<0.001**	3 (0.8 – 5.3) → 4 (1 – 12.3)	0.2	0.31
Interpersonal relationships	16 (16 – 16) → 16 (16 – 16)	0.16	16 (14 – 16) → 15.5 (13.8 – 16)	0.8	**<0.001**
- immature	16 (16 – 16) → 16 (16 – 16)	0.8	16 (14 – 16) → 14 (14 – 16)	0.3	**<0.001**
- mature	16 (15 – 16) → 15 (16 – 16)	0.10	13 (10.8 – 15.3) → 14.5 (11 – 15)	0.61	0.12
Sexuality	12 (10 – 12) → 12 (10 – 12)	0.05	12 (12 – 12) → 11.5 (7.8 – 12)	0.02	0.09
- immature	12 (10 – 12) → 12 (10 – 12)	0.3	12 (12 – 12) → 12 (8.5 – 12)	0.03	0.05
- mature	12 (8.5 – 12) → 12 (9.8 – 12)	0.03	12 (8.3 – 12) → 11 (8 – 11.8)	0.2	0.89
Heat Sensitivity	8 (3 – 16) → 12 (5– 17)	**<0.001**	13.5 (11 – 14.8) to 10 (3 – 16.5)	0.5	0.6
- immature	6 (3 – 14) → 12 (5– 16)	**<0.001**	13 (11 – 14) to 13.5 (5 – 15.8)	0.7	0.9
- mature	9 (4 – 16) → 12 (4– 19.5)	0.03	16.5 (3.8 – 19.5) to 13 (0.8 – 14.3)	0.5	0.27
Treatment	15 (11 – 18) → 17 (13 – 20)	**<0.001**	18 (12 – 19.8) to 16 (9.8 – 18.3)	0.05	0.2
- immature	14 (11 – 17) → 16 (13 – 19)	**<0.001**	17.5 (12 – 19.3) to 13 (10 – 18.8)	0.07	0.1
- mature	16 (10.5 – 18) → 18 (13 – 20)	0.10	18 (11.3 – 19.5) to 18 (11.3 – 18)	0.36	0.94
Work	11 (8 – 15) to 14 (10 – 16)	**<0.001**	12.5 (4.5 – 16) → 10 (4 – 16)	0.9	0.07
- immature	12 (8 – 15) to 14 (11 – 16)	**<0.001**	13.5 (5.5 – 16) → 9.5 (4 – 16)	0.7	0.07
- mature	11 (4 – 16) to 14 (9 – 16)	**<0.001**	10.5 (2 – 13) → 16 (4 – 16)	0.13	0.62
Total score (0-160) Median (IQR) Mean (SD)	119 (101 – 143) → 133 (106.5 – 147.5) 116.8 (29.2) → 126.1 (27.4)	**<0.001**	130.5 (124 – 141) → 120 (101 -143.8) 126.3 (24.5) → 113 (38.0)	0.09	0.01
immature Median (IQR) Mean (SD)	120 (105 – 139.5) → 130 (109 – 147) 116.8 (29.2) → 133.0 (27.4)	**<0.001**	133.5 (124 – 140.8) → 119.5 (102 – 140.5) 126.3 (24.5) → 113.0 (38.0)	**0.04**	**0.006**
mature Median (IQR) Mean (SD)	117 (87 – 144) → 134 (105 – 149.5) 112.7 (36.5) → 123.3 (34.0)	**<0.001**	130 (80.5 – 139) → 120 (78 – 145.5) 112.8 (38.4) → 113.3 (41.4)	0.9	0.5

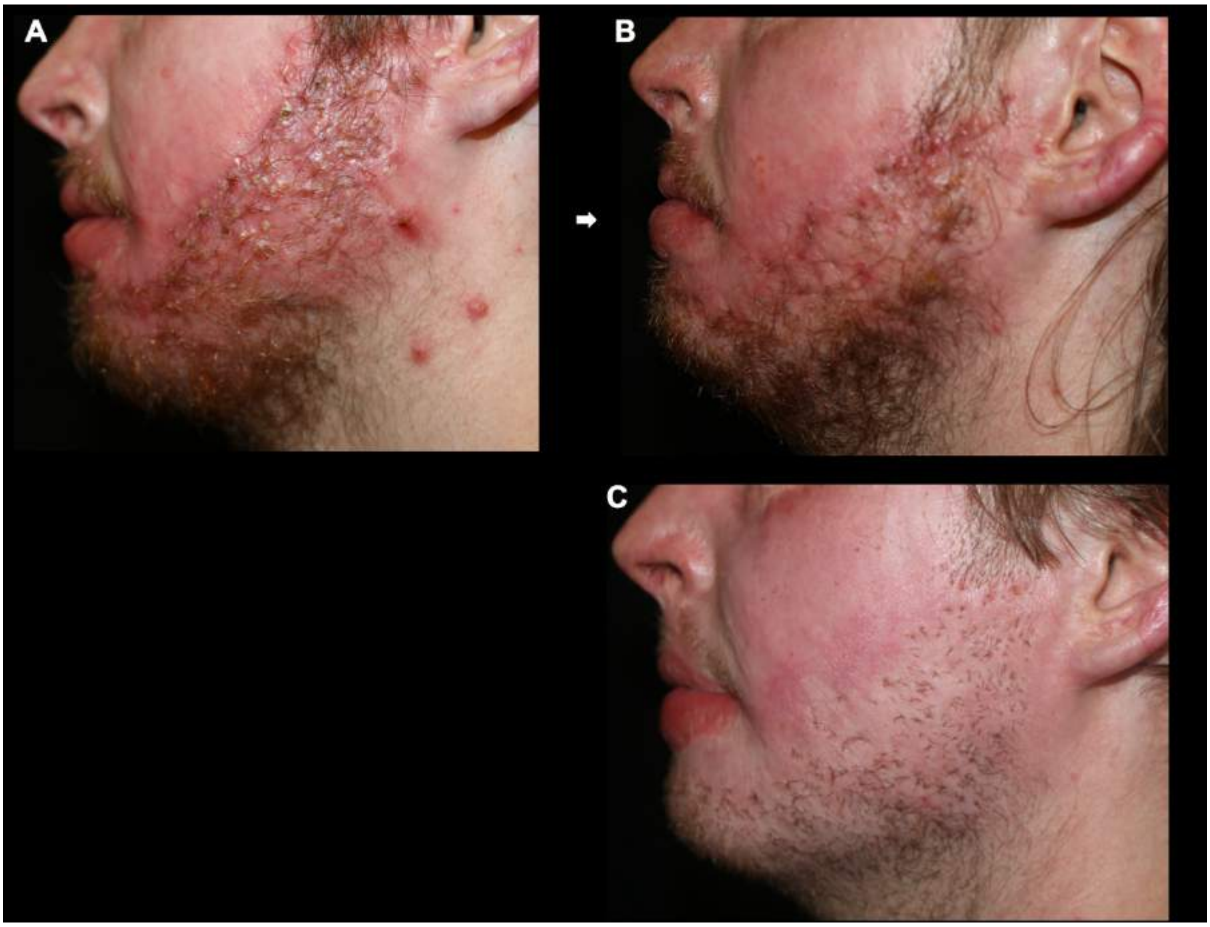

Figure 7. Facial hypertrophic scars with chronic folliculitis before and AFL-CO_2 treatment.
A. Nineteen-year-old Caucasian male patient with Fitzpatrick skin type 2, 10.5 months following a 67% TBSA burn injury by an explosion with hypertrophic scarring and chronic folliculitis. **B.** Same patient 6 months later (9 weeks following his first treatment cycle with AFL-CO_2. DeepFX handpiece with settings DeepFx 50mJ Energy, 3% Density, 300-Hz) plus laser facilitated delivery of Kenacort A40. **C.** One and half years following 3 treatment cycles with AFL-CO_2 and laser facilitated infiltration of corticosteroids.

4.2.8. Comparison of treatment & control cohorts stratified by scar maturation status

All of the assessed domains showed a statistically significant improvement in the AFL-CO_2 treatment cohort in the immature as well as the mature scar groups. The control cohort only showed significant improvement in the immature scar group in the domains VSS, POSAS-O, POSAS-O overall and BSHS-B, but revealed no significant changes in the other assessed domains. In the mature control group, there were no significant changes reported in any of the evaluated outcomes (Tables 8 & 9). Figure 8 illustrates a relatively mature hypertrophic scar following treatment with AFL-CO_2 and laser facilitated steroid infiltration.

Table 8. Comparison case versus control outcome parameters: immature scars only

Variables *medians (IQR)*	**Case** (n pt=104)	p-value	**Control** (n pt=14)	p-value	p-value for case vs control
Scar thickness (US), µm	3.6 (2.5 – 4.7) → 2.8 (2.1 – 3.8)	**<0.001**	3.3 (2.5 – 4) → 2.5 (2.0 – 4.3)	0.46	0.83
VSS (0-13)	8 (7 – 9)→ 6 (5 – 8)	**<0.001**	9 (8 – 10) → 8 (7 – 9)	**<0.001**	**<0.001**
POSAS-O (6-60)	26 (22 – 34) → 20 (17 – 25)	**<0.001**	28.5 (26 – 32.3) → 22.5 (21 – 27)	**0.005**	0.02
POSAS-O overall (0-10)	5 → 4	**<0.001**	5 (4.8 – 6.3) → 4 (3.3 – 5)	**0.006**	0.04
POSAS-P (6-60)	37 (30 – 44) → 26 (19 – 34)	**<0.001**	31 (29.3 – 36) → 31 (27.3 – 34)	0.22	**0.01**
POSAS-P overall (0-10)	9 (7 – 10)→ 6 (4 – 8)	**<0.001**	7.5 (5 – 8.3) → 7 (5.3 – 7.8)	0.97	0.05
DN4-Pain Score (0-10)	5 (3 – 6) → 4 (1 – 5)	**<0.001**	4 (3 – 5.3) → 4.5 (3.3 – 6)	0.39	0.09
Modified D4 Pruritus Questionnaire (7-35)	17 (14 – 21) → 14 (11 – 18.8)	**<0.001**	17 (12 – 19) → 18 (12.3 – 19)	0.89	0.14
BSHS-B (total Score: 0-160)	120 (105 – 139.5) → 130 (109 – 147)	**<0.001**	133.5 (124 – 140.8) → 119.5 (102 – 140.5)	**0.04**	**0.006**
Global Impression					
➢unchanged	14 (9.7%)		9 (47.4%)		
➢a little bit	67 (46.2%)		10 (52.6%)		**<0.001**
➢quite a bit	50 (34.5%)		0		
➢extremely	14 (9.7%)		0		

Table 9. Comparison case versus control outcome parameters: mature scars only

Variables *medians (IQR)*	**Case** (n pt=63)	**p-value**	**Control** (n pt=6)	**p-value**	**p-value for case vs control**
Scar thickness (US), µm	2.5 (1.9 – 3.4) → 2.2 (1.7 – 2.8)	**0.003**	2 (1.65 – 2.48) → 2 (1.65 – 2.53)	0.39	0.39
VSS (0-13)	7 (6 – 8) → 5 (4 – 7)	**<0.001**	7 (6 – 8) → 9 (5 – 9)	0.27	**0.003**
POSAS-O (6-60)	26 (23 – 30.8) → 19.5 (16 – 23.8)	**<0.001**	23 (18 – 30) → 22 (15 – 27)	0.24	0.18
POSAS-O overall (0-10)	4 (4 – 6) → 3 (3 – 4)	**<0.001**	4 (3 – 6) → 4 (3 – 6)	0.05	0.12
POSAS-P (6-60)	32 (24.8 – 38) → 22 (18.3 – 27.3)	**<0.001**	37 (16 – 44) → 43 (35 – 44)	0.03	**<0.001**
POSAS-P overall (0-10)	8 (6.8 – 10) → 5 (5 – 7)	**<0.001**	7 (4 – 10) → 9 (4 – 9)	0.73	0.06
DN4-Pain Score (0-10)	1 (0 – 5) → 0 (0 – 3)	**<0.01**	2 (1.5 – 6) → 2 (1.5 – 4.3)	0.12	0.22
Modified D4 Pruritus Questionnaire (7-35)	11 (7 – 16) → 7 (7 – 11)	**<0.001**	20 (7 – 23.5) → 13 (7.5 – 16.5)	0.23	0.21
BSHS-B (total Score: 0-160)	117 (87 – 144) → 134 (105 – 149.5)	**<0.001**	130 (80.5 – 139) → 120 (78 – 145.5)	0.90	0.49
Global Impression					
➢unchanged	7 (10.1%)		6 (66.7%)		
➢a little bit	32 (46.4%)		3 (33.3%)		**<0.001**
➢quite a bit	11(15.9%)		0		
➢extremely	19 (27.5%)		0		

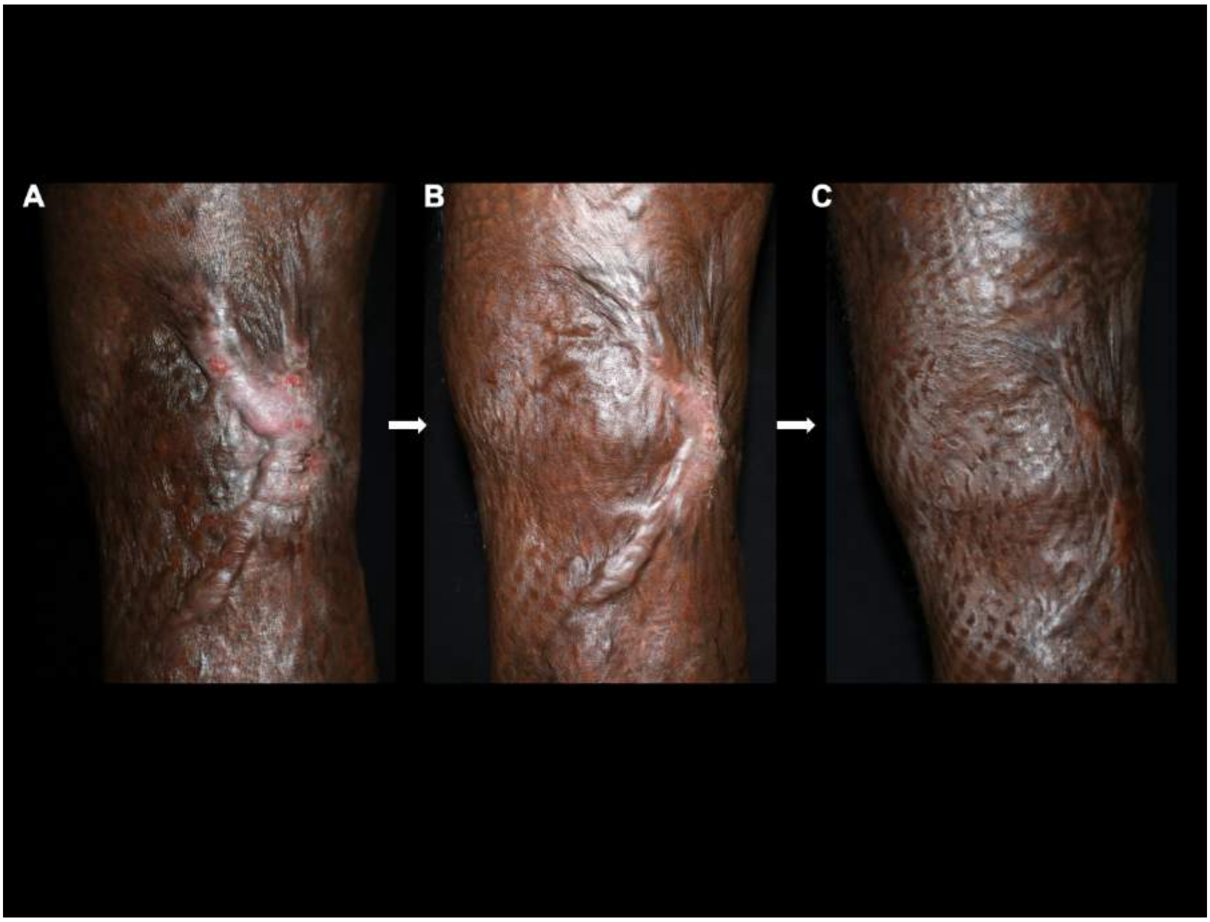

Figure 8. Relatively mature hypertrophic scar before and after AFL-CO_2 treatment

A. 32year old Sri-Lankan male patient with Fitzpatrick skin type 6, 22 months following a 41% TBSA flame burn injury with hypertrophic scarring. **B.** Same patient 6months later (11 weeks following his first treatment cycle with AFL-CO_2 laser. DeepFX handpiece with settings ScarFX 80mJ Energy, 3%, 250-Hz & DeepFx 30mJ Energy, 10% Density, 300-Hz) plus laser facilitated delivery of Kenacort A40. **C**. 2.5 years following 3 treatment cycles with AFL-CO_2 laser and laser facilitated infiltration of corticosteroids.

4.2.9. Complications & side effects of AFL-CO2 treatment

Five of 167 patients (2.99%) had complications following the laser treatment. One patient (0.60%) developed a wound infection at the treated site, one patient who had simultaneous fat-grafting developed an infection of the fat graft (0.60%), and two patients (1.20%) had a wound-break down (of which one was due to a blunt trauma to the site during a sporting injury). One patient (0.60%) reported persistent itchiness. Equally, three patients (1.80%) reported persistent erythema in the treated areas. All complications were successfully treated conservatively. No outbreak of Herpes simplex was recorded.

4.3. Ablative fractional resurfacing with laser-facilitated steroid delivery for burn scar management: does the depth of laser penetration matter?

Ablative fractional laser devices, such as the AFL-CO_2, apply the laser beam to fractions of skin surface. Based on water absorption and bulk heating, epidermal and dermal structures are removed, resulting in microscopic ablative zones (MAZ) [179]. High energy and a short pulse duration in AFL-CO_2 facilitate precise effects with minimal side effects, so that islands of undamaged skin can serve as reservoirs to trigger small wound healing reactions and subsequent scar remodelling [5]. AFL-CO_2 devices ablate micro-columns vertically through epidermis and dermis [179]. The effective depth of these MAZs depends on the amount of energy applied and skin conditions, such as hydration and surface temperature [179]. The SCAAR ™ mode of the ablative fractional 10,600-nm wavelength CO2 Ultrapulse® laser (by Lumenis®), for example, can penetrate to reach a depth of up to 4.0 millimetres (mm) with a narrow zone of coagulation and minimal collateral damage. However, laser density plays a crucial role as well, because if too high densities are used, it may result in bulk heating and total scar ablation [179, 180].

Data in Chapter 4.2. supports the positive clinical efficacy of AFL-CO_2 for burn scar management, however, the importance of the individual laser settings for laser-tissue interactions and patient outcomes is not entirely understood. Thus, a retrospective audit of the CRGH practice was performed to investigate whether the maximum depth of AFL-CO_2 penetration in pathological burn scars influences burn scars and patient outcomes.

The primary aim of this retrospective study was to determine the influence of the depth of laser penetration on the scar thickness measured by ultrasound. To evaluate the impact of natural scar maturation, the patient cohort was split into two groups according their scar maturation: the first group consisted of patients with young, immature scars, who presented for their first treatment less than 2 years following the burn injury/last operation, and the second group included patients with mature scars, who had their initial treatment more than 2 years after the burn injury/last operation. Secondary outcomes included the effect of penetration depth on the above-mentioned objective and subjective outcome parameters.

Laser handpiece energy settings directly correlate with penetration depth. As such to assess the depth of scar penetration the maximum penetration depth was divided by the scar thickness at the thickest point of each scar to calculate the percentage of tissue penetration. Patients were subsequently divided into 5 groups depending on minimal scar penetration depth: 0-25%, 26-50%, 51-75%, 76-100% & >100% penetration of scars. Subsequent data was analysed according to the statistics section (Chapter 3.3.2.2.). Appendix C.

4.3.1. Demographics & burn mechanism

A summary of patient demographics is provided in Table 10. 78 patients with 158 scars had complete data allowing for analysis of which 59.0% (n = 46) were female and 41.0% (n = 32) were male with a median age of 40 years (IQR, 29.0–51.8). Most patients were Anglo-Saxon/Celtic with a Fitzpatrick skin type 3 (n = 42, 54%). The median total burn surface area (TBSA) resulting in scarring was 7.5% and most scars were caused by flame injuries. 66.7% of scars were regarded as immature (<2years post-injury) and most hypertrophic scars resulted from grafted wounds (n = 75, 47.5%).

Table 10. Patient demographics and information on burn mechanism

Demographics	n = 78 patients
Gender: female /male (%)	46 (59%), 32 (41%)
Age (years), *median*	40 (IQR 29 – 51.8)
Ethnical Background: (%)	
➢ Anglo-Saxon/Celtic	45 (57.7%)
➢ South East Asian	13 (16.7%)
➢ North East Asian	5 (6.4%)
➢ South & Central Asian	6 (7.7%)
➢ South East European	2 (2.6%)
➢ North African/Middle Eastern	4 (5.1%)
➢ Maori/Pacific Islander	2 (2.6%)
➢ South American	1 (1.3%)
Fitzpatrick Skin Type: (%)	
➢ Type 1	3 (3.9%)
➢ Type 2	18 (23.1%)
➢ Type 3	42 (53.9%)
➢ Type 4	8 (10.3%)
➢ Type 5	6 (7.7%)
➢ Type 6	1 (1.3%)
Smokers (%)	4 (5.1%)
% TBSA burnt, *median*	7.5 (IQR 3 – 80)
Burn mechanism: (%)	
➢ Flame	39 (50%)
➢ Scald	15 (19.2%)
➢ Hot Oil	7 (9.0%)
➢ Contact	6 (7.7%)
➢ Other (chemical, electrical, friction, etc.)	11 (14.1%)
Scar Information:	**n = 158 scars**
Scar maturation: (%)	
➢ Immature Scars (<2y post injury)	108 (63.4%)
➢ Mature Scars (>2y post injury)	50 (31.6%)

Type of scar: (%)	
➢ Conservative treatment	24 (15.2%)
➢ Grafted	75 (47.5%)
➢ Re-Grafted	25 (15.8%)
➢ Biobrane® xenograft	25 (15.8%)
➢ Other (e/o graft, FTSG, donor-site, etc.)	9 (5.7%)
Scar location	
➢ Abdomen	3 (1.9%)
➢ Back	5 (3.2%)
➢ Buttock	3 (1.9%)
➢ Chest	14 (8.9%)
➢ Face	17 (10.8%)
➢ Flank	4 (2.5%)
➢ Lower limb	34 (21.5%)
➢ Neck	8 (5.1%)
➢ Shoulder	6 (3.8%)
➢ Upper limb	64 (40.5%)
Scar per patient, *median*	2 (range 1-5)
Scar thickness (μm), *median*	3400 (IQR 2500 – 4500)
Scar penetration with AFL-CO2 (μm), *median*	900 (IQR 900 – 1800)
Concomitant Scar management: (%)	
➢ Silicone	41 (25.9%)
➢ Massage	58 (36.7%)
➢ Garments	44 (27.8%)
➢ Physiotherapy	14 (8.9%)

4.3.2. Effects of laser penetration depth on burn scar thickness

Of the 158 analysed scars, the median scar thickness measured at the thickest point was 3400μm (IQR 2500 – 4500) and the median laser scar penetration depth was 900μm (IQR 900 – 1800). Scar penetration categories were as follows: 0 – 25% (n=40), 25 – 50% (n=76), 50 – 75% (n=31), 75 – 100% (n=8), >100% (n=3). Median reduction in maximum scar thickness was 800μm following one treatment ($p<0.001$; Table 11). However, this effect depended on the depth of scar penetration, whereby scars penetrated ≥75% showed no significant improvement in scar thickness and those penetrated >100% showed a tendency to become worse (Figure 9). Similar results we found when the analysis was stratified according scar maturation status. Immature (<2years post injury) and mature (>2years post injury) scars decreased significantly by a median of 800μm and 600μm, respectively (Table 12). In the immature scar group, the biggest effect was achieved when the maximum penetration reached 51-75% of the scar thickness, resulting in a drop of 1400μm following one treatment ($p = 0.011$). If 76-100% was penetrated, the difference was not statistically significant anymore and if >100% was penetrated the scar became thicker, although these groups only included 5 and 1 patients, respectively. Similar results could be observed in the mature scar group, with the only difference being that the largest improvement in ultrasound measured scar thickness was achieved in the 26-50% penetration depth group (Table 12).

Table 11. Outcomes stratified according to scar penetration depth

Outcome parameter *median (IQR)*	Penetration depth	Before 1st treatment	After 1st treatment	p – value
Scar thickness (µm)	**All** (n=158)	3400 *(2500 – 4500)*	2600 *(2025 – 3575)*	<0.001
	0 – 25% (n=40)	3850 *(3400 – 6000)*	3100 *(2275 – 4050)*	<0.001
	26 – 50% (n=76)	3200 *(2175 – 4400)*	2600 *(1900 – 3400)*	<0.001
	51 – 75% (n=31)	3400 *(2250 – 4550)*	2300 *(1900 – 3300)*	0.002
	76 – 100% (n=8)	2650 *(1650 – 3100)*	2400 *(2000 – 2850)*	0.800
	>100% (n=3)	2800 *(2650 – 3400)*	3700 *(3350 – 4750)*	0.250
VSS (0-13)	**All** (n=158)	8.0 *(7.0 – 9.0)*	6.0 *(5.0 – 8.0)*	<0.001
	0 – 25% (n=40)	8.0 *(7.0 – 9.0)*	6.0 *(5.0 – 7.0)*	<0.001
	26 – 50% (n=76)	8.0 *(6.8 – 9.0)*	6.0 *(4.0 – 8.0)*	<0.001
	51 – 75% (n=31)	9.0 *(7.0 – 10.0)*	7.0 *(6.0 – 8.0)*	<0.001
	76 – 100% (n=8)	8.5 *(8.0 – 9.0)*	7.0 *(6.0 – 7.0)*	0.002
	>100% (n=3)	10.0 *(9.0 – 10.5)*	8.0 *(7.5 – 8.0)*	0.1
POSAS O (0-60) **POSAS O overall** (0-10)	**All** (n=158)	27.0 *(23.0 – 33.8)* 5.0 *(4.0 – 7.0)*	20.0 *(17.0 – 25.0)* 4.0 *(3.0 – 4.75)*	<0.001 <0.001
	0 – 25% (n=40)	30.0 *(24.0 – 36.5)* 6.0 *(4.0 – 7.0)*	21.5 *(17.75 – 27.25)* 4.0 *(3.0 – 5.0)*	<0.001 <0.001
	26 – 50% (n=76)	26.5 *(21.75 – 32.25)* 5.0 *(4.0 – 6.25)*	19.5 *(16.0 – 24.0)* 3.0 *(3.0 – 4.0)*	<0.001 <0.001
	51 – 75% (n=31)	28.0 *(23.0 – 33.5)* 5.0 *(4.0 – 6.0)*	21.0 *(17.0 – 25.0)* 4.0 *(3.0 – 5.0)*	<0.001 <0.001
	76 – 100% (n=8)	27.0 *(22.25 – 29.25)* 5.0 *(4.0 – 5.0)*	19.0 *(17.0 – 19.25)* 3.0 *(3.0 – 3.25)*	0.014 0.018
	>100% (n=3)	27.0 *(23.0 – 30.00)* 5.0 *(4.0 – 6.0)*	25.0 *(22.0 – 25.0)* 5.0 *(4.0 – 5.0)*	0.371 1
POSAS P (0-60) **POSAS P overall** (0-10)	**All** (n=153)	33.0 *(27.0 – 40.0)* 8.0 *(7.0 – 10.0)*	24.0 *(20.0 – 32.0)* 5.0 *(4.0 – 8.0)*	<0.001 <0.001
	0 – 25% (n=35)	38.0 *(33.0 – 44.0)* 9.0 *(8.0 – 10.0)*	28.0 *(21.0 – 37.0)* 6.0 *(5.0 – 8.0)*	<0.001 <0.001
	26 – 50% (n=76)	30.0 *(22.75 – 39.25)* 8.0 *(6.0 – 9.25)*	22.5 *(16.0 – 29.0)* 5.0 *(4.0 – 7.0)*	<0.001 <0.001
	51 – 75% (n=31)	33.0 *(31.0 – 38.0)* 8.0 *(7.0 – 9.0)*	26.0 *(23.0 – 34.0)* 7.0 *(5.0 – 7.0)*	<0.001 <0.001
	76 – 100% (n=8)	31.0 *(27.75 – 38.0)* 7.5 *(5.0 – 8.5)*	22.5 *(21.0 – 24.25)* 5.0 *(4.0 – 6.25)*	0.008 0.198
	>100% (n=3)	34.0 *(33.0 – 35.0)* *7.0 (7.0 – 7.5)*	30.0 *(30.0 – 33.0)* 8.0 *(7.5 – 8.0)*	0.371 0.773
DN4-Pain (0-10)	**All** (n=151)	5.0 *(2.0 – 6.0)*	4.0 *(1.0 – 5.0)*	<0.001
	0 – 25% (n=35)	5.0 *(4.0 – 7.0)*	4.0 *(2.0 – 6.0)*	<0.001
	26 – 50% (n=76)	3.0 *(1.0 – 6.0)*	2.5 *(0.0 – 4.0)*	<0.001
	51 – 75% (n=31)	5.0 *(3.5 – 6.0)*	4.0 *(2.5 – 5.0)*	<0.001
	76 – 100% (n=8)	3.0 *(1.5 – 4.25)*	3.5 *(0.75 – 4.25)*	1
	>100% (n=1)	–	–	–
Modified D4 Pruritus (7-35)	**All** (n=144)	17.0 *(11.0 – 21.0)*	14.0 *(9.0 – 18.25)*	<0.001
	0 – 25% (n=33)	20.0 *(19.0 – 24.0)*	17.0 *(14.0 – 22.0)*	0.005
	26 – 50% (n=71)	15.0 *(8.0 – 18.0)*	10.0 *(7.0 – 17.0)*	<0.001
	51 – 75% (n=31)	15.0 *(13.0 – 21.0)*	13.0 *(11.0 – 18.5)*	0.003
	76 – 100% (n=8)	17.5 *(8.3 – 19.0)*	14.5 *(8.3 – 20.0)*	0.784
	>100% (n=1)	-	-	
Global impression	**All** (n=158)			
➢ unchanged			16 (10.1%)	
➢ a little bit			67 (42.4%)	
➢ quite a bit			44 (27.8%)	
➢ extremely			21 (13.3%)	

IQR, inter-quartile range; POSAS, Patient and Observer Scar Assessment Score; VSS, Vancouver Scar Scale.

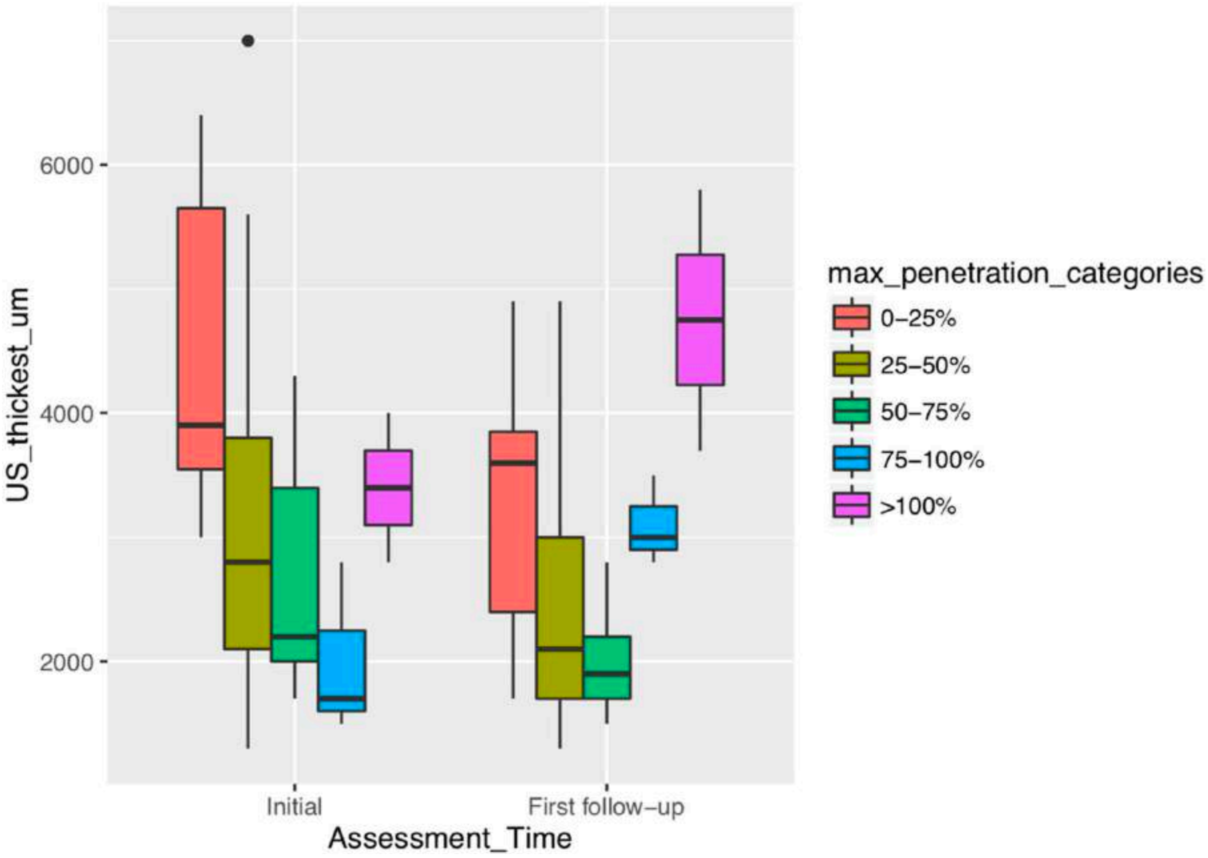

Figure 9. Boxplot demonstrating the effect of different penetration categories on scar thickness before and after one treatment with the AFL-CO_2.

Table 12. Change of outcomes stratified according scar penetration depth and maturation status

Scar thickness (μm)	Penetration depth	Before 1st treatment	After 1st treatment	p – value
Immature Scars	**All** (n=108)	3600 *(2575 – 4700)*	2800 *(2100 – 3850)*	<0.001
	0 – 25% (n=29)	3800 *(3200 – 6000)*	3000 *(2100 – 4200)*	<0.001
	26 – 50% (n=51)	3200 *(2400 – 4450)*	3000 *(2100 – 3900)*	0.019
	51 – 75% (n=22)	4100 *(2850 – 4700)*	2700 *(2100 – 3750)*	0.011
	76 – 100% (n=5)	3000 *(2500 – 3400)*	2100 *(1700 – 2200)*	0.100
	>100% (n=1)	2500 *(2500 – 2500)*	3000 *(3000 – 3000)*	-
Mature Scars	**All** (n=50)	3000 *(2100 – 3875)*	2400 *(1900 – 3200)*	<0.001
	0 – 25% (n=11)	3900 *(3550 – 5650)*	3600 *(2400 – 3850)*	0.002
	26 – 50% (n=25)	2800 *(2100 – 3800)*	2100 *(1700 – 3000)*	0.002
	51 – 75% (n=9)	2200 *(2000 – 3400)*	1900 *(1700 – 2200)*	0.022
	76 – 100% (n=3)	1700 *(1600 – 2250)*	3000 *(2900 – 3250)*	0.25
	>100% (n=2)	3400 *(3100 – 3700)*	4750 *(4225 – 5275)*	0.5
VSS (0 – 13)	No of patient	Before 1st treatment	After 1st treatment	p – value
Immature Scars	**All** (n=108)	8 *(7.0 – 9.0)*	6 *(5.0 – 7.0)*	<0.001
	0 – 25% (n=29)	8 *(7.0 – 9.0)*	6 *(5.0 – 7.0)*	<0.001
	26 – 50% (n=51)	8 *(6.5 – 9.0)*	6 *(4.0 – 8.0)*	<0.001
	51 – 75% (n=22)	9 *(8.0 – 10.0)*	7 *(6.0 – 8.8)*	0.007
	76 – 100% (n=5)	9 *(9.0 – 9.0)*	7 *(6.0 – 7.0)*	0.001
	>100% (n=1)	-	-	-
Mature Scars	**All** (n=50)	8 *(7.0 – 9.0)*	6 *(4.25 – 7.0)*	<0.001
	0 – 25% (n=11)	8 *(7.0 – 8.5)*	6 *(4. 5 – 6.0)*	0.002
	26 – 50% (n=25)	7 *(7.0 – 9.0)*	5 *(4.0 – 7.0)*	<0.001
	51 – 75% (n=9)	7 *(7.0 – 9.0)*	6 *(5.0 – 7.0)*	0.05
	76 – 100% (n=3)	8 *(7.5 – 8.0)*	7 *(6.5 – 7.5)*	0.38
	>100% (n=2)	10.5 *(10.3 – 10.8)*	8 *(8.0 – 8.0)*	0.04

POSAS-O	No of patient	Before 1st treatment	After 1st treatment	p – value
Immature Scars score (0 – 60) overall (0 – 10)	**All** (n=108)	27.0 *(22.0 – 35.0)* 5.0 *(4.0 – 7.0)*	20.0 *(17.0 – 25.0)* 3.5 *(3.0 – 5.0)*	<0.001
	0 – 25% (n=29)	30.0 *(23.0 – 38.0)* 6.0 *(4.0 – 7.0)*	20.0 *(17.0 – 27.0)* 4.0 *(3.0 – 5.0)*	<0.001
	26 – 50% (n=51)	25.0 *(21.0 – 31.0)* 5.0 *(3.5– 6.0)*	19.0 *(16.5 – 23.5)* 3.0 *(3.0 – 4.0)*	<0.001
	51 – 75% (n=22)	29.0 *(23.3 – 35.0)* 5.0 *(4.0 – 7.0)*	22.0 *(19.3 – 25.8)* 3.0 *(3.0 – 5.0)*	<0.001
	76 – 100% (n=5)	29.0 *(25.0 – 29.0)* 5.0 *(5.0 – 5.0)*	19.0 *(19.0 – 20.0)* 3.0 *(3.0 – 4.0)*	<0.001 0.006
	>100% (n=1)	-	-	-
Mature Scars score (0 – 60) overall (0 – 10)	**All** (n=50)	28.5 *(23.0 – 32.0)* 5.0 *(4.0 – 7.0)*	21.0 *(17.0 – 25.0)* 4.0 *(3.0 – 4.0)*	<0.001 <0.001
	0 – 25% (n=11)	31.0 *(24.5 – 34.0)* 5.0 *(4.0 – 7.0)*	22.0 *(21.0 – 28.0)* 4.0 *(4.0 – 4.5)*	0.006 0.06
	26 – 50% (n=25)	29.0 *(26.0 – 33.0)* 5.0 *(4.0 – 7.0)*	21.0 *(15.0 – 25.0)* 4.0 *(3.0 – 4.0)*	<0.001 <0.001
	51 – 75% (n=9)	23.0 *(23.0 – 26.0)* 4.0 *(4.0 – 5.0)*	17.0 *(17.0 – 18.0)* 3.0 *(3.0 – 3.0)*	0.01 0.02
	76 – 100% (n=3)	20.0 *(20.0 – 25.0)* 4.0 *(3.5 – 4.5)*	17.0 *(17.0 – 18.0)* 3.0 *(3.0 – 3.0)*	0.17 0.16
	>100% (n=2)	30.0 *(28.5 – 31.5)* 6.0 *(5.5 – 6.5)*	25.0 *(25.0 – 25.0)* 5.0 *(5.0 – 5.0)*	0.5 1
PSOSAS-P	No of patient	Before 1st treatment	After 1st treatment	p – value
Immature Scars score (0 – 60) overall (0 – 10)	All (n=103)	35 *(30.0 – 44.0)* 8.0 *(7.0 – 10.0)*	26 *(21.0 – 35.0)* 6.0 *(4.0 – 8.0)*	<0.001 0.001
	0 – 25% (n=24)	38 *(33 – 51)* 9.5 *(8 – 10)*	30 *(23 –36.3)* 7 *(4 – 8)*	<0.001
	26 – 50% (n=51)	34 *(24.5 – 43.5)* 8.0 *(6.5 – 10.0)*	25 *(17.0 – 32.0)* 5.0 *(4.0 – 7.5)*	<0.001
	51 – 75% (n=22)	32.5 *(31.0 – 38.8)* 8.0 *(7.0 – 9.0)*	26 *(23.3 – 35.0)* 7.0 *(5.0 – 7.0)*	<0.001 0.001
	76 – 100% (n=5)	32 *(30.0 –38.0)* 7.0 *(5.0 – 8.0)*	24 *(23.0 – 25.0)* 4.0 *(4.0 – 5.0)*	0.04 0.1
	>100% (n=1)	-	-	-
Mature Scars score (0 – 60) overall (0 – 10)	**All** (n=50)	32.0 *(22.0 – 35.0)* 8.0 *(6.0 – 9.75)*	22.0 *(20.0 – 28.0)* 5.0 *(5.0 – 7.0)*	<0.001 0.003
	0 – 25% (n=11)	38.0 *(33.0 – 40.0)* 8.0 *(6.0 – 9.0)*	23.0 *(20.0 – 41.0)* 5.0 *(5.0 – 7.5)*	0.45 0.40
	26 – 50% (n=25)	27.0 *(21.0 – 32.0)* 7.0 *(3.0 – 8.0)*	21 *(16.0 – 23.0)* 5.0 *(4.0 – 7.0)*	0.006 0.03
	51 – 75% (n=9)	34 *(32.0 – 36.0)* 9.0 *(8.0 – 10.0)*	28 *(23.0 – 30.0)* 7.0 *(6.0 – 8.0)*	0.02 0.06
	76 – 100% (n=3)	29.0 *(25.5 – 33.5)* 10.0 *(7.5 – 10.0)*	21.0 *(21.0 – 21.5)* 10.0 *(7.5 – 10.0)*	0.14 1
	>100% (n=2)	33.0 *(32.5 – 33.5)* 7.0 *(7.0 – 7.0)*	30.0 *(30.0 – 30.0)* 8.0 *(8.0 – 8.0)*	0.5 0.35
DN4 Pain Score	Penetration depth	Before 1st treatment	After 1st treatment	p – value
Immature Scars	**All** (n=98)	5.0 *(3.0 – 8.0)*	4.0 *(2.0 – 5.0)*	<0.001
	0 – 25% (n=29)	6.0 *(2.0 – 8.0)*	4.0 *(1.0 – 6.0)*	<0.001
	26 – 50% (n=41)	6.0 *(3.0 – 8.0)*	4.0 *(2.0 – 6.0)*	<0.001
	51 – 75% (n=22)	5.0 *(3.0 – 6.0)*	3.5 *(3.0 – 4.0)*	<0.001
	76 – 100% (n=5)	4.0 *(3.0 – 5.0)*	4.0 *(4.0 – 5.0)*	0.58
	>100% (n=1)	-	-	-
Mature Scars	**All** (n=45)	2.0 *(0.0 – 4.5)*	0.0 *(0.0 – 4.0)*	0.005
	0 – 25% (n=6)	4.5 *(4.0 – 5.0)*	5.0 *(5.0 – 7.3)*	0.4
	26 – 50% (n=25)	1.0 *(0.0 – 2.0)*	0.0 *(0.0 – 0.0)*	0.02
	51 – 75% (n=9)	2.0 *(0.0 – 4.5)*	0.0 *(0.0 – 4.0)*	0.2
	76 – 100% (n=3)	0.0 *(0.0 –1.0)*	0.0 (*0.0 – 1.5)*	0.8
	>100% (n=2)	-	-	-
4D Pruritus Score	Penetration depth	Before 1st treatment	After 1st treatment	p – value
Immature Scars	**All** (n=103)	18.5 *(14.0 – 21.0)*	15.5 *(12.0 – 21.0)*	<0.001
	0 – 25% (n=27)	20.0 *(19.0 – 25.0)*	21.0 *(14.0 – 22.0)*	0.06
	26 – 50% (n=49)	17.0 *(14.0 – 19.0)*	14.0 *(9.0 – 17.0)*	<0.001
	51 – 75% (n=22)	15.0 *(14.0 – 21.0)*	17 *(13.0 – 19.0)*	0.13
	76 – 100% (n=5)	19.0 *(19.0 – 19.0)*)	20.0 *(17.0 – 20.0)*	0.85
	>100% (n=1)	-	-	-
Mature Scars	**All** (n=)	8.0 *(7.0 – 16.25)*	7.0 *(7.0 – 12.0)*	<0.001
	0 – 25% (n=6)	19.5 *(17.0 – 22.0)*	17.0 *(16.3 – 17.8)*	0.10

	26 – 50% (n=22)	7.0 *(7.0 – 8.0)*	7.0 *(7.0– 7.0)*	0.01
	51 – 75% (n=9)	13.0 *(11.0 – 19.0)*	7.0 *(7.0 – 12.0)*	0.01
	76 – 100% (n=3)	0.0 *(0.0 – 8.0)*	0.0 *(0.0 – 6.0)*	0.85
	>100% (n=0)	-	-	-

Median is reported unless denoted otherwise. Immature Scars: <2 years following initial burn injury; Mature Scars: >2 years following initial burn injury. IQR, inter-quartile range; POSAS, Patient and Observer Scar Assessment Score; VSS, Vancouver Scar Scale.

4.3.3. Objective & subjective outcomes stratified according to penetration depth

All evaluated objective and subjective outcome parameters improved significantly in all penetration depth groups up to 75% scar penetration depth (Table 11). If penetrated 76–100% and >100%, the VSS, the POSAS-O and POSAS-O overall, as well as the POSAS-P still improved, however, without statistical significance. The POSAS-P overall even deteriorated if scars were penetrated >100%, albeit only three patients were in this group. The VSS and the POSAS-O and P showed significant improvement after one treatment throughout all penetration depths in immature scars. In mature scars, however, the improvements were only significant up to 75% penetration depth (Table 12).

Neuropathic pain assessed with the DN4 Pain questionnaire showed significant improvement across all penetration categories, except for those penetrated >75%, where a trend to worsening symptoms was observed (Table 11). If only patients with neuropathic pain before treatment were assessed—defined by a DN4 pain score of ≥4 (n = 31)—the scores dropped significantly from 6.0 (IQR, 5.0–8.0) to 4.0 (IQR, 4.0–6.0; P < 0.001) following one treatment. This effect was consistent across all penetration categories (0–100%) and in immature (<2 years) scars, whereas in patients with mature scars (>2 years) there was a slight worsening of pain scores by 0.5 points in those penetrated 0–25%, but improvements in those with higher penetration categories (Table 12).

Itch, measured with the modified D4 Pruritus Scale, showed significant improvement across all penetration categories up to 75% and overall if stratified according to scar maturation (Tables 11 and 12).

4.4. Ablative fractional resurfacing for burn scar management affects the number & type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay

As discussed in Chapter 1, approaches for burn scar treatment range from non-surgical options (such as silicone products and pressure garments), laser treatments, to injecting small hypertrophic scars with corticosteroids as well as radiotherapy for keloid scars, and surgical reconstruction. The surgical reconstructive options for burn scar management comprise of dermabrasion and cultured epithelial autografting (CEA), contracture release and grafting, excisional grafting, the use of tissue expanders and different tissue flaps [181, 182]. However, most of these surgical reconstructive options are associated with considerable morbidity, involving a lengthy, painful process, donor-sites, time off work and admissions to the hospital [44, 181].

This retrospective study analysed all elective burn reconstructive procedures performed at the CRGH Burns from September 2013 to June 2017 stratified by pre- versus post laser introduction. By analysing the number and pattern of laser cases performed in that time frame, it was intended to determine if AFL-CO_2 has led to a replacement of conventional reconstructive procedures, impacted the elective reconstructive case mix, and how it has affected patient operating times, admission patterns as well as hospital length of stay (LOS). Appendix D.

4.4.1. Data collection to analyse how AFL-CO_2 affects the number & type of elective surgical reconstructive procedures for burn scars, hospital admission patterns as well as length of stay

Burn scar treatment with the AFL-CO_2 was introduced in our facility during the fourth quarter of 2014. Hospital's data was collected through CRGH administrative and electronic medical records from September 2013 until June 2017. Information on patient demographics and details on the initial burn injury (where available) was collected through the database of the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service as well as from our prospective database of all patients who are treated with the AFL-CO_2 as described in Chapter 3.1. Firstly, the number and types of elective reconstructive procedures performed pre- and post-laser introduction as well as changes in the number of cases over time (stratified by annual quarter) was analysed and compared. Subsequently, the effect of the change in practice on operating/anaesthetic times as well as the overall hospital LOS was evaluated and compared before and after the introduction of the AFL-CO_2. Anaesthetic time was chosen as a more accurate indicator for total procedural (operating theatre) time, as for example the treatment of multiple areas during one anaesthetic may require repositioning and re-draping of patients. Lastly, to evaluate the efficacy of treatment with the AFL-CO_2 treatment a prospective analysis of 41 patients with 93 scars who have completed their full treatment with the AFL-CO_2 was carried out, analysing various subjective and objective outcome measures (VSS, POSAS, DN4 questionnaire, 4-D Pruritus Scale, BSHS-B as described earlier). These outcome measures were further stratified according to the maturation status of the scar (immature=<2years post injury, mature=>2years post injury). Data was analysed according to the statistics section (Chapter 3.3.2.4. Statistical analysis).

4.4.2. Number of elective reconstructive procedures before & after AFL-CO_2

In total 412 elective burns scar cases (including 82 prior AFL-CO_2 and 330 post AFL-CO_2) were treated during September 2013 to June 2017. While all 100% (82/82) patients received conventional reconstructive procedures prior to AFL-CO_2 introduction, only 23.9% (79 out of 330) had conventional reconstructive procedures post AFL-CO_2 introduction. AFL-CO_2 treatment accounted for 60.9% (251/412) of total procedures (pre- and post-laser introduction) and 76.1% (251/330) procedures post AFL-CO_2 introduction. Significantly more female patients received laser procedures compared to male patients (67% vs. 46%, $p<0.001$) and patient median age was 37 years (36 non-laser, 38 laser-based procedures, $p=0.58$). Information regarding the burn mechanism, including % TBSA burnt, type of burn injury, type of scar, and scar maturation, were not statistically significant between the pre- and post-laser era (Table 13). However, the time interval from initial burn injury to first scar intervention appeared a bit longer in the laser cases compared to the non-laser cases (Table 13).

Table 13. Demographic data of patients undergoing elective reconstructive procedures performed at CRGH from September 2013 to June 2017.

	All procedures	Pre – Laser Era	Post – Laser Era	p – value	Non - Laser Cases	Laser Cases	p – value
Number of cases	412 (100%)	82 (100%)	330 (100%)	-	161 (39.0%)	251 (60.9%)	-
Gender: Female	242 (58.7%)	47 (57.3%)	195 (59.1%)	0.77	74 (46.0%)	168 (66.9%)	
Male	170 (41.3%)	35 (42.7%)	135 (40.9%)		87 (54.0%)	83 (33.1%)	<0.001
Age (years) *median*	37 (27.0 – 49.0)	36 (27.0 – 47.3)	38 (27.3 – 49.0)	0.43	36 (28.0 – 38.8)	38 (27.0 – 39.7)	0.58
% TBSA[i] burnt *median*	15 (5.6 – 38.0)	18.25 (3.0 – 30.8)	15 (6.0 – 38.0)	0.43	23 (4.9 – 38.0)	15 (6.6 – 36.8)	0.85
% TBSA[i] grafted *median*	5 (2.0 – 25.8)	15 (2.0 – 30.0)	5 (2.0 – 25.0)	0.48	6 (2.0 – 30.0)	5 (3.0 – 25.0)	0.53
Type of burn injury:	238	56	182	0.02	104	134	0.01
- Flame	153 (64.3%)	29 (51.8%)	124 (68.1%)		59 (56.7%)	94 (70.1%)	
- Scald	35 (14.7%)	7 (12.5%)	28 (15.4%)		13 (12.5%)	22 (16.4%)	
- Contact	17 (7.1%)	6 (10.7%)	11 (6.0%)		11 (10.6%)	6 (4.5%)	
- Other	33 (13.9%)	14 (25.0%)	19 (10.4%)		21 (20.2%)	12 (9.0%)	
Time since burn injury (months): *median*	19 (10.3 – 34.0)	15.5 (9.0 – 31.3)	19.5 (11.0 – 34.0)	0.22	15 (6.8 – 29.5)	21.5 (14 – 36.5)	<0.001
- Immature scars (<2 y)	143 (60.1%)	34 (60.7%)	109 (59.9%)	0.91	67 (64.4%)	76 (56.7%)	
- Mature scars (>2y)	95 (39.9%)	22 (39.3%)	73 (40.1%)		37 (35.6%)	58 (43.3%)	0.22
Type of Scar:	474[ii]	118[ii]	356[ii]		210	264	
- Conservative	30 (6.3%)	7 (5.9%)	23 (6.5%)	0.83	10 (4.8%)	20 (7.7%)	0.15
- Skin Graft	208 (43.9%)	49 (41.5%)	159 (44.7%)	0.98	94 (44.8%)	114 (54.3%)	0.22
- Re-Graft	82 (17.3%)	24 (20.3%)	58 (16.3%)	0.13	41 (19.5%)	41 (19.5%)	0.16
- Biobrane® xenograft	154 (32.5%)	38 (32.2%)	116 (32.6%)	0.57	65 (31%)	89 (42.4%)	0.53

The information in Table 13 could only be collected from patients who sustained their burn injury after 2013, who were initially treated at Concord Hospital for their acute burn injury or received treatment with the CO_2-AFL.

[i] TBSA = total body surface area

[ii] Total sums of previous scar treatments are greater than the number of cases as some patients received multiple treatments to their injuries before being referred for scar reconstruction.

4.4.3. Type of elective reconstructive procedures & the change in procedural case-mix following AFL-CO_2 introduction

A detailed summary of the types of procedures performed during the analysed timeframe is provided in Table 14. Interestingly, more than half of the elective cases prior to laser introduction were combined surgeries, which means that more than one type of reconstructive procedure was per-formed. However, following AFL-CO_2 introduction only 13% of the non-laser cases included more than one surgical procedure. Equally, the treatment of multiple scars during one anaesthetic was more evident, with 55.7% of all laser cases received the treatment to multiple scars (median of 2 scars/per procedure in the range 1-6). Comparing the non-laser cases, pre- vs. post-laser introduction, a clear change of reconstructive surgical procedures was seen. For example, prior to laser introduction, the procedures performed were predominantly scar excisions (48.8%), release and split thickness skin grafts (36.4%), and Z-plasties (31.7%), whereas after laser introduction, scar excisions decreased substantially to only 10%, Z-plasties accounted for only 19.7% of all surgical procedures and no releases with STSG or dermal templates were performed. Additionally, dermabrasion as well as eyelid and ectropion releases were much less frequently performed after laser introduction. There were no regional flaps, free flaps or tissue expanders performed following AFL-CO$_2$ introduction. Finally, when analysing the cases performed after laser introduction, 12.1% of all laser cases were combined with other reconstructive surgical techniques, 82.5% of which were Z-plasties (Table 15). The indications for post burn reconstruction were summarized into three broad categories: Resurface (removal and resurfacing of unsightly or symptomatic burn scar by excision and closure either directly, serially, with a graft, substitute or flap), release (release of contracture and graft, skin substitute or flap) and/or replace (Reconstruction of lost complex tissue — nose, ears, digits, etc.). As demonstrated in Table 16, one could observe a significant shift in the resurface group with the laser being used to improve the appearance and symptoms of the scar. We also found a significant reduction in releasing procedures alone comparing pre- vs post laser introduction. As such, a substantial reduction in the numbers of conventional reconstructive procedures as well as the associated procedural complexity following laser introduction could be observed (Figure 10).

Table 14. Numbers and types of elective reconstructive procedures performed at CRGH from September 2013 to June 2017.

	All procedures	Pre – Laser Era Sept 2013 – Dec 2015	Post – Laser Era Dec 2015 – June 2017
Number of cases	412 (100%)	82 (100%)	330 (100%)
Laser (alone or combined)	251 (60.9%)	-	251 (76.1%)
Laser to multiple scars	184 (44.7%)	-	184 (55.7%)
1x laser	-	-	95 (37.8%)
2x laser	-	-	73 (29.1%)
3x laser	-	-	42 (16.7%)
4x laser	-	-	24 (9.6%)
5x laser	-	-	9 (3.6%)
6x laser	-	-	3 (1.2%)
7x laser	-	-	3 (1.2%)
8x laser	-	-	2 (0.8%)
Non-Laser	161 (39.0%)	82 (100%)	79 (23.9%)
Combined procedures:	126 (30.6%)		
Non-Laser combined:	86 (20.9%)	43 (52.4%)	43 (13.0%)
Laser combined:	40 (9.7%)	-	40 (12.1%)
E/O[i] Scar	73 (17.7%)	40 (48.8%)	33 (10%)
Serial E/O[i] Scar	6 (1.5%)	4 (4.9%)	2 (0.6%)
Z-Plasties	91 (22.1%)	26 (31.7%)	65 (19.7%)
Release & STSG[ii]	29 (7.0%)	29 (36.4%)	0
Release & Dermal Template	2 (0.5%)	2 (0.5%)	0

Dermabrasion & CEA[iii] or STSG[ii]	8 (1.9%)	5 (6.1%)	3 (0.9%)
Eyelid Ectropion Release/ Canthoplasty	7 (1.7%)	5 (6.1%)	2 (0.6%)
Lip Ectropion / Mouth Angle Release	12 (2.9%)	7 (8.5%)	5 (1.5%)
Local (except Z-plasties)	13 (3.2%)	6 (7.3%)	8 (2.4%)
Regional/Free Flaps	3 (0.7%)	3 (0.7%)	0
Expander	4 (1%)	4 (1%)	0
Other[iv]	34 (8.3%)	8 (9.8%)	26 (7.9%)

[i] E/O = excision of, [ii] STSG = split thickness skin graft, [iii] CEA = cultured epithelial autograft, [iv] Other = resection-arthrodesis, stump revision, fat grafting, removal of heterotopic ossification, etc.

Table 15. Numbers and types of elective reconstructive procedures performed in the Post – Laser Era at CRGH (December 2015 to June 2017).

Total Number of Cases: 330	**No Laser**	**Laser** (n = 251)	
		Laser alone	**Laser combined**
Number of cases	79 (23.9%)	211 (63.9%)	40 (12.1%)
E/O[i] Scar	27 (8.2%)	-	6 (1.8%; *15%*)
Serial E/O[i] Scar	2 (0.6%)	-	0
Z-plasties	32 (9.7%)	-	33 (10%; *82.5%*)
Dermal Template & STSG[ii]	0	-	0
Dermabrasion & CEA[iii] or STSG[ii]	3 (0.9%)	-	0
Eyelid Ectropion Release / Canthoplasty	2 (0.6%)	-	0
Lip Ectropion / Mouth Angle Release	5 (1.5%)	-	0
Local flaps (except Z-plasties)	7 (2.1%)	-	1
Regional / Free Flaps	0	-	0
Expander	0	-	0
Other[iv]	20 (6.1%)	-	6 (1.8%; *15%*)

[i] E/O = excision of, [ii] STSG = split thickness skin graft, [iii] CEA = cultured epithelial autograft, [iv] Other = fat grafting, nasal reconstruction, Donelan-plasty, etc.

Table 16. Changes in post burn reconstruction procedure group types, when grouped by scar resurfacing, releasing and replacement.

Indication	**Pre-Laser (n=82)***	**Post-Laser (n=329)**	**p-value**	**Non-Laser (n=160)**	**Laser (n=251)**	**p-value**
Resurface	41 (50%)	204 (62%)	<0.001	68 (42.5%)	177 (70.5%)	<0.001
Release	35 (42.6%)	62 (18.8%)		68 (42.5%)	29 (11.6%)	
Resurface & Release	3 (3.7%)	43 (13.1%)		7 (4.4%)	39 (15.5%)	
Replace	3 (3.7%)	16 (4.9%)		13 (8.1%)	6 (2.4%)	

**for the total number of procedures pre & non–laser, there were 4 other reconstructive procedures which did not allow for clear classification as per the groups above and thus were excluded for the statistical analysis.*

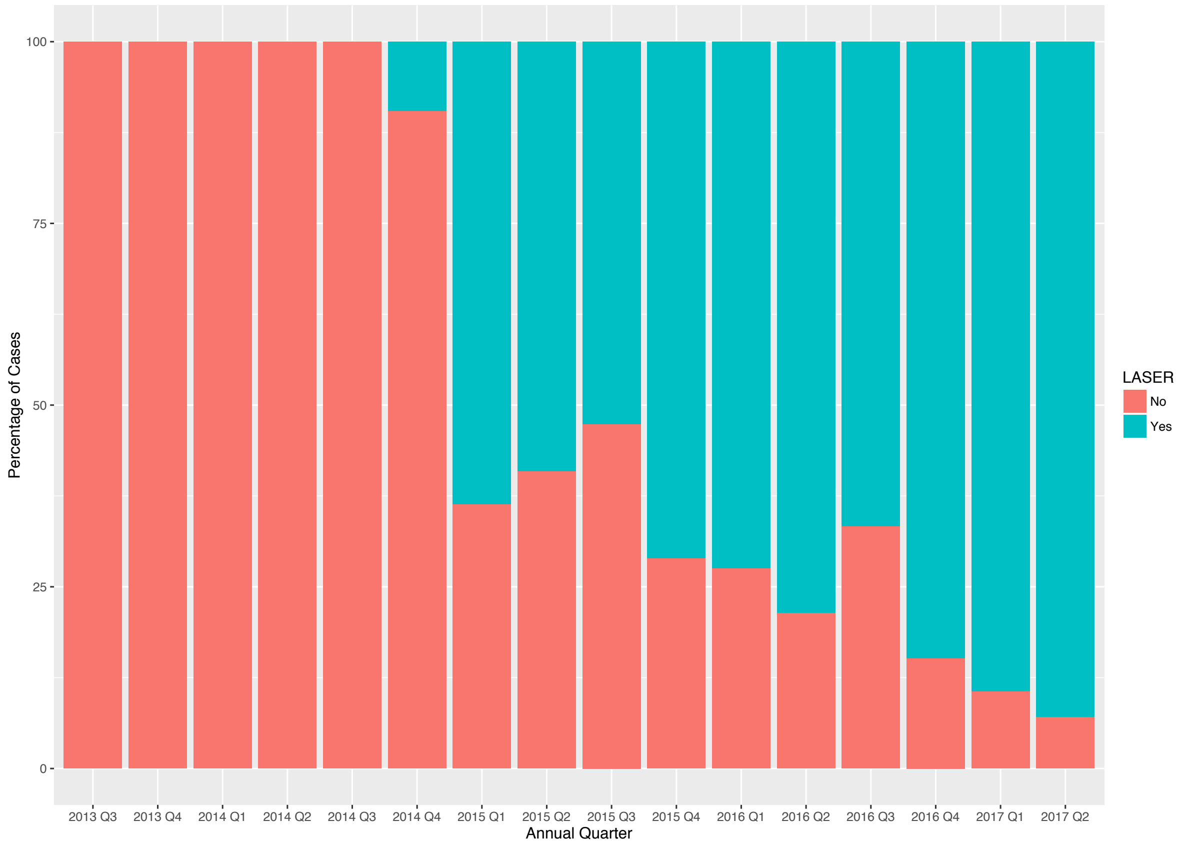

Figure 10. Change in proportion of laser cases for elective burn scar reconstruction since introduction of the AFL-CO_2 at CRGH.

4.4.4. Increase in number of treatments per patients following AFL-CO_2 introduction

AFR may result in multiple treatments being required to achieve the final results [91]. However, some data indicate that the number of reconstructive procedures per burn patient lifetime may be as a high as 3.6 [183]. Thus, it was assessed how many treatments patients underwent on average pre- vs. post-laser introduction. It was found that the median number of treatments pre laser were 1 (range 1-4), whereas post laser introduction it increased to 2 (range 1-6, $p<0.001$). Equally, when stratified by laser vs. non-laser cases, the median number of treatments in the laser group was higher (2 [range 1-8] vs. 1 [range 1-6], $p<0.001$).

4.4.5. Effect of AFL-CO_2 introduction on operating / anaesthetic times

The median anaesthetic time for all reconstructive procedures performed for the entire study duration was 70min (IQR 45-103). The median anaesthetic time prior to laser introduction was 90min (IQR 61.5-109.8) and dropped significantly to 64min (IQR 44 -100.50) following AFL-CO_2 introduction ($p<0.001$). Examining the type of procedures, laser treatments in general were significantly shorter (57min, IQR 40-91.5) compared to non-laser procedures (87min, IQR 60-115; $p<0.001$), especially if the procedures consisted of only AFL-CO_2 (51min, IQR 39-75; $p<0.001$). However, if the laser was combined with other surgical treatments, the anaesthetic time significantly increased by almost half an hour (121min, IQR 105-141, $p<0.001$, Figure 11). Of the laser cases, 125 (49.8%) of the procedures could be performed under topical or local anaesthetic only, and 126 of the cases (50.2%) required a full general anaesthetic.

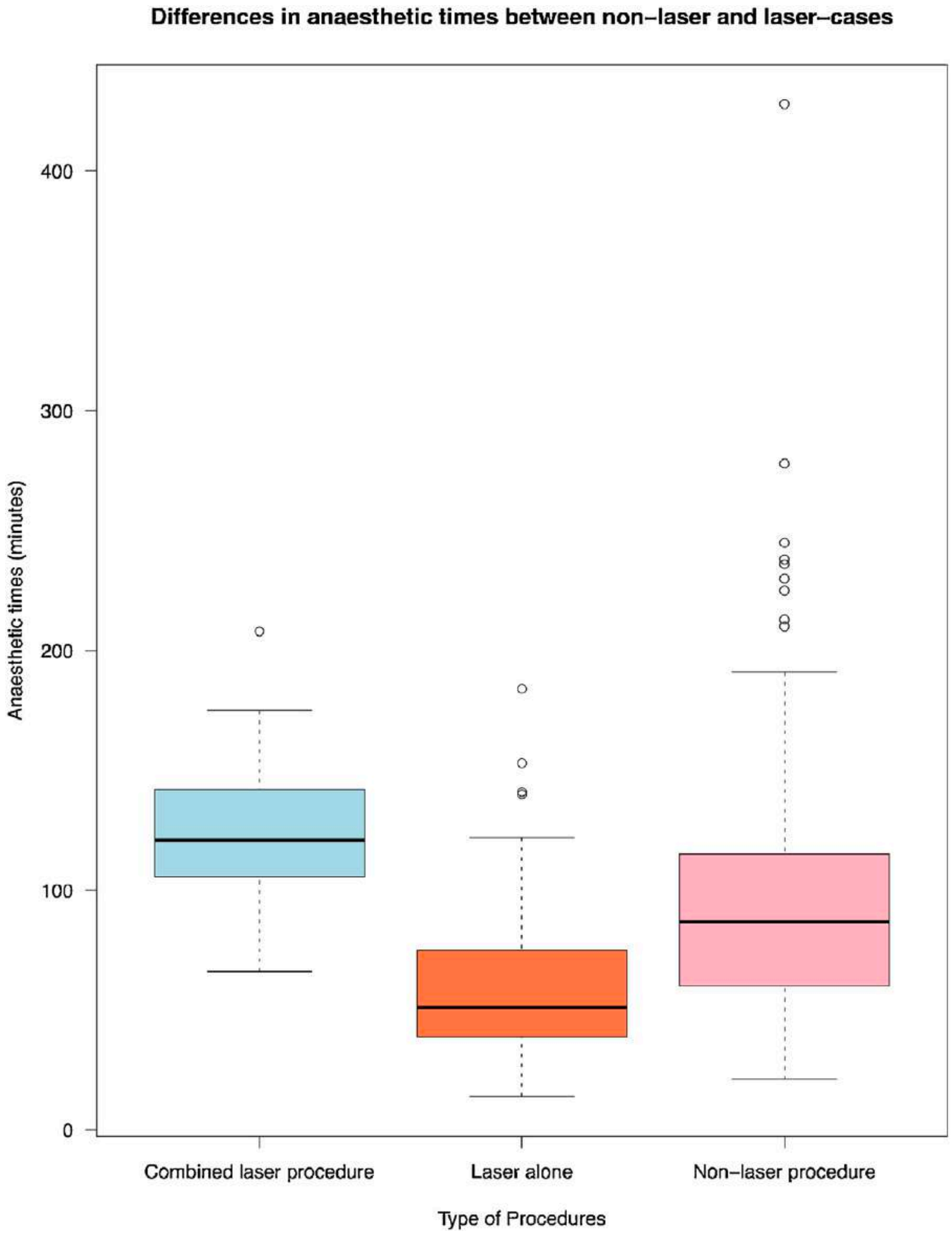

Figure 11. Differences in anaesthetic times depending on what type of reconstructive procedure was performed

4.4.6. Effect of the AFL-CO_2 introduction on patient hospital length of stay

Prior to laser introduction, 32.9% of the patients undergoing an elective reconstructive procedure were required to be admitted as an inpatient to the hospital for one or more nights. This figure dropped substantially following laser introduction, where only 7.5% of patients required an inpatient admission ($p<0.001$, Table 14). When specifically looking at non-laser versus laser procedures, it was observed that only 1.6% (4 cases) of all laser cases required admission overnight, whereas following laser introduction 29.7% of the non-laser patients were admitted overnight ($p<0.001$). Not surprisingly, the actual LOS in hospital was significantly shorter for the laser cases at 0.36days (range 0.1-7.33) compared to 1.96days (range 0.12-46.2; $p<0.001$). However, when analysing the LOS of inpatients alone, no statistically significant difference in LOS could be identified although the mean LOS was 2days shorter for laser patients compared to non-laser patients (3.21days vs. 5.71days, $p=0.77$; Table 17). It is also worth mentioning that of the four patients requiring overnight admission following AFL-CO_2 treatment, one patient was admitted due to the extent of the combined surgical procedure (large excision of abdominal scar, mini abdominoplasty), two patients stayed at the day-surgery unit overnight as they had nobody to pick them up following a general anaesthetic and one patient was admitted for treatment of an incidental finding of asymptomatic episodes of complete heart blocks.

Table 17. Effect of different types of reconstructive procedures performed at CRGH from September 2013 to June 2017 on length of stay at the hospital.

Admission type		**Pre-Laser (n=82)**	**Post-Laser (n=322)**	**p-value**
Day only procedure	-	55 (67.1%)	298 (92.5%)	<0.001
Overnight/inpatient	-	27 (32.9%)	24 (7.5%)	
Admission type		**Non-Laser** (n=158)	**Laser** (n=246)	**p-value**
Day only procedure	-	111 (70.3%)	242 (98.4%)	<0.001
Overnight/inpatient	-	47 (29.7%)	4 (1.6%)	
Length of stay	**All procedures**	**Non-Laser**	**Laser**	**p-value**
Mean length of stay (days, range)	0.33 (0.28 – 0.41)	1.96 days (0.12-46.2)	0.36 days (0.10-7.33)	<0.001
Only inpatient (n=51)	2.27 (1.1 – 46.2)	5.81 days (1.0-46.2)	3.21 days (1.0-7.33)	0.77

4.4.7. Outcome analysis of patients treated with the AFL-CO_2

Forty-one patients with 93 scars have completed their full treatment with the AFL-CO_2. All analysed objective parameters dropped significantly including normalized scar thickness as measured with ultrasound which decreased from a median of 2.5mm-1.7mm ($p<0.001$) and a concomitant VSS-drop from a median of 8 to 5 ($p<0.001$). The overall POSAS observer and patient scales decreased from a median 5 to 3 ($p<0.001$) and 9 to 4 (<0.001) respectively. Intriguingly, neuropathic pain and pruritus also decreased significantly (median 5 to 2 and 16 to 11; both $p<0.001$). The post-burn quality of life, as assessed by the BSHS-B, increased by 14 points (median 126 – 140; $p<0.001$). All of the identified changes following AFL-CO_2 were irrespective of scar maturation status (> vs. <2years).

4.5. The prophylactic potential of ablative fractional resurfacing in acute management of facial burn injuries

Severe burn injury to the pan-facial region is recognised as one of the most challenging areas of the body to treat [184-187]. Early rigorous nonsurgical scar management has been shown to be effective in minimising oro-facial contractures [188, 189], however in some patients the development of microstomia and ectropion are unavoidable despite all non-surgical scar contracture management efforts. In these cases, the indication for early reconstruction to maintain function is often necessary. Further, whilst function may be restored, aesthetic results are frequently suboptimal particularly as surgical reconstructions may need to be repeated numerous times.

As described in the previous Chapter 4.4. there is evidence that AFL-CO_2 may potentially reduce the indication or extent of major reconstructive surgery in the burn patient, while favouring more optimal patient functional, aesthetic and quality of life outcomes. This concept subsequently holds considerable potential to reduce the financial burden on the health care system as less surgical resources are required and length of hospital stay is reduced.

The literature supporting AFR has been predominantly reported in patients with stable or mature burn scars at least 18 months post injury [129] and there is no cases described where AFL-CO_2 is utilised in the acute care environment in a severely burnt patient along with nonsurgical scar contracture management techniques to manage aggressive scar contracture formation over the pan-facial region. Appendix E.

4.5.1. Case report

4.5.1.1. Setting & background information

A 39-year-old male of Asian background (Fitzpatrick skin type 3) was admitted to the CRGH Burns Intensive Care Unit (ICU) with 68% TBSA flame burn injury including deep dermal pan-facial burn wounds and airway involvement. The facial burn wounds were initially bluntly debrided and Biobrane® xenograft was applied: standard procedure for all facial burn injuries with an epidermal detachment in CRGH Burns Unit. Due to a protracted period of mechanical ventilation tracheostomy ensued at day 18. Nonsurgical orofacial scar contracture management was instigated within 48h of admission as per the regime published by Clayton et al. [188].

While still in ICU, bilateral upper and lower eyelid ectropion and early lower lip eversion were observed (Figure 12).

Figure 12. Day 43—bilateral upper and lower eyelid ectropia and early lower lip eversion.

At day 43, surgical release with full-thickness skin grafts for the eyelid ectropion was discussed to avoid corneal damage. Nonsurgical scar contracture measures such as taping had not been initiated at this stage, as the newly healed tissue remained unstable with several areas not epithelialized. For corneal protection, regular assessment by an appropriately qualified ophthalmologist was conducted and topical lubricant applied frequently as prescribed. Due to the positive effect of AFL-CO_2 on immature scars, the decision was made to trial full face resurfacing with the ablative fractional CO_2 Ultrapulse® laser.

4.5.1.2. Treatment

Protracted healing of skin grafts and areas with wound infection necessitated repeat debridement and re-grafting to 20% TBSA of limb wounds. During the re-grafting procedure, ablative fractional resurfacing of the entire pan-facial region, from the superior hairline to the upper neck crease was simultaneously performed (Figure 13). AFL-CO_2 was repeated on four occasions under general anaesthetic, at regular subsequent intervals (6–8 weeks), throughout the patient's acute and rehabilitative hospital admission. Corneal eye shields were inserted, laser safety measurements implemented, and the patient received a 5-day course of prophylactic Valacyclovir (500mg daily). The ablative fractional CO2 Ultrapulse® laser (Lumenis® UltraPulse®, Yokneam, Israel) machine was used with the following settings. First treatment: DeepFX™: energy = 12.5 to 17.5 mJ, density = 5 to 10%, rate = 300Hz. Second treatment: DeepFX™: energy = 15 to 22.5 mJ, density = 10%, rate = 300 Hz. Third treatment: SCAAR FX™: energy = 60 mJ, density = 5%, rate = 250 Hz and DeepFX™: energy = 17.5 to 40 mJ, density = 5–10%, rate = 300 Hz, and laser facilitated infiltration of corticosteroids (Kenacort A40). Fourth treatment: SCAAR FX™: energy = 60 to 110 mJ, density = 1 to 5%, rate = 250 Hz and DeepFX™: energy = 40 to 50mJ, density = 5%, rate = 300 Hz, and laser facilitated infiltration of corticosteroids (Kenacort A40). Lower energy, higher density settings were applied in the periorbital area. During the last treatment, areas of considerable erythema were additionally treated with the M22™ laser system: Nd:YAG: double pulse, pulse duration 8.5 ms and 11.5 ms with 20 ms delay and fluence of 120 J/cm2.

Nonsurgical scar contracture management continued to be provided concurrently as per site specific standard protocols. Lower eyelid taping was introduced (day 133) to promote complete eye closure once the surrounding cutaneous tissue was considered stable and robust enough to withstand the application of a silicon-based adhesive tape Opsite Gentle Flexifix® and continued daily (Figure 14). Nonsurgical scar contracture management was ceased for the day of AFL-CO_2 treatment and resumed to the full program the following day. Taping was ceased for 5 days following AFL-CO_2 and re-commenced once cutaneous tissue was suitably stable to endure the tape. Nonsurgical scar contracture management was weaned once stabilisation of pan-facial scar tissue and functional goals attained with nil change over 3 months following scar stabilisation. Treatment weaning started with reducing the frequency and duration of both the mouth splint and eye taping, and subsequently the active range of movement (ROM) exercises. Once treatment was ceased, monitoring for a further 3 months to ensure no regression in eye and mouth closure and maximal range occurred.

Figure 13. Intraoperative image.
Note the pixelated pattern of the ablated columns, the thin epithelium and rich vascular perfusion reflecting the early stage of wound healing.

Figure 14. Method of taping to reduce lower eyelid ectropion (inset - without taping)

4.5.1.3. Outcome Measures

Measurements and photographic data specific to deficits in eye and mouth competence were obtained at rest and on active closure, along with maximal opening at baseline and routinely until completion of scar stabilisation. Each participant underwent measures of maximal mouth opening (vertical and horizontal), deficit in mouth closure, maximal eye opening, and deficit in eye closure before and throughout the course of treatment. As defined previously in Clayton et al. [188], vertical mouth opening range was recorded as the measurement in millimetres while in the stretched position from the inner border of the medial lower lip to the inner border of the medial upper lip. Horizontal mouth opening range was recorded as the measurement in millimetres while in the stretched position from one lateral oral commissure to the other lateral oral commissure. Mouth closure deficit was recorded as the measurement in millimetres of the gap while in the closed position from the inner border of the medial lower lip to the inner border of the medial upper lip. Eye opening range was defined as the measurement in millimetres while in the maximal opening position between the lower and upper eyelid. Eye closure deficit was defined as the measurement in millimetres of the gap while in the closed position between the lower and upper eyelid.

Treatment duration, maximal ROM values (taken in person at the time of treatment), and photographic images were subsequently compared with groups of historical burn patients and historical healthy controls. The historical burn patient group all experienced deep partial or full-thickness facial burn injuries [189], received the same nonsurgical orofacial scar management and traditional surgical reconstructive procedures as clinically indicated. The group of the historical healthy controls [188] had never previously experienced a facial burn injury or any head and neck surgery that would compromise their orofacial ROM.

4.5.2. Results

4.5.2.1. Clinical outcome

The patient underwent four sessions of AFL-CO_2 over an 8-month period at 6- to 8-week intervals. Nonsurgical scar contracture management was continued concurrently during this period. The patient demonstrated considerable gains in response to the combined nonsurgical scar contracture management and AFL-CO_2 throughout the duration of treatment. Deficits in eye and mouth closure reduced to 0 mm and maximal mouth ROM increased to 40mm vertically and 61mm horizontally.

Figure 15 reveals photographic evidence of patient progress and ROM of the eye and mouth structures.

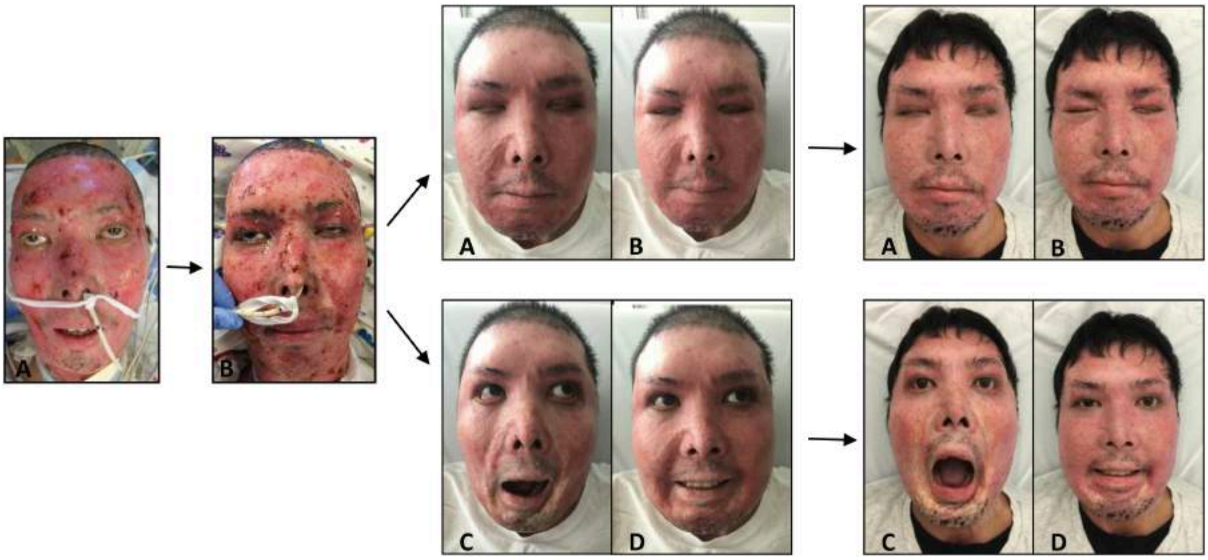

Figure 15. Progress in range of movement of the eye and mouth structures at days 43, 49, 176, and 251.
A. Eye closure at rest. B. Maximal active eye closure. C. Vertical mouth opening. D. Horizontal mouth opening.

At the conclusion of treatment, 8 months after initial burn injury, the patient exhibits full eye closure with negligible ectropion, complete oral competence, and functional mouth ROM. He has proficient oral access with functional ability to: consume a full oral diet without any restrictions, attend to dental cares and has sufficient mouth opening to enable blind intubation. He also demonstrates excellent facial ROM necessary to convey the emotive aspects of language via facial expression.

4.5.2.2. Comparison to the historical group

Compared with the historical group of burn patients (n = 14, eight debrided and grafted, five debrided and treated with Biobrane® xenograft with subsequent small grafts on remaining unhealed areas, one debrided and treated with Biobrane® xenograft only) who received the same nonsurgical orofacial scar contracture management (n = 14) and traditional surgical reconstructive procedures (n = 9), vertical and horizontal mouth ROM measures for the patient at the conclusion of treatment in the current study were found to be comparable. (As per Clayton et al[189]; end-treatment range for vertical mouth opening = 32 to 43mm; end-treatment range for horizontal mouth opening = 58 to 80mm).

Compared with the historical non-burn healthy controls (n = 120), the patient's vertical and horizontal mouth ROM was also found to be comparable and within the normal range. (As per Clayton et al [188]: normal range for vertical mouth opening = 40–75mm; normal range for horizontal mouth opening = 55–83mm). See Table 18 for a summary of these results.

Further to this, treatment duration in the current case (251 days), when compared with the historical burn cohort of Clayton et al [189] (range = 82–1235 days; mean = 513 days) was found to be significantly shorter. Although the observation in AFL-CO_2 treated case is anecdotal, the striking difference (251 days vs 513 days) is worth further investigation in more patients to verify the potential of AFL-CO_2.

Table 18. Comparison between outcomes for AFL-CO_2, burn, and healthy controls

	Case AFL-CO_2 (n = 1)	Burn control group (n = 14)	Healthy control group (n = 120)
Vertical mouth opening (mm); mean (SD)	40	40(SD = 7.071)	53.642 (SD = 7.446)
Horizontal mouth opening (mm); mean (SD)	61	63.214 (SD = 14.142)	69.133 (SD = 5.787)

Chapter 5. Discussion

Chapter 5: Discussion

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5.1. Light based therapies for burn scar management & the CRGH data collection – general comments and limitations

As described earlier, there is a plethora of nonsurgical and surgical approaches to improve burn scarring including compression, silicone products, physical therapy, intralesional injections of medications, surgical excision, shaving or release of the scars and a whole range of surgical reconstructive options. The evidence for most of these procedures has been more historical than scientific, but most approaches are widely accepted as standard care [91, 92]. To ultimately release tension and increase the range of motion of contracted scars, surgical reconstruction remains the main and most effective approach [5, 91, 93]. However, aside from the associated morbidity, resulting donor-site and limitation of the treatment effect to one surgical site, there are several factors which cannot be addressed with surgery, such as neuropathic pain, heat intolerance and burn scar pruritus. Due to the complexity and diversity of burn scar presentations, light based therapies can close the void between the traditional occupational therapy and surgery [5]. As illustrated in Chapter 4, it allows the surgeon to address the scar holistically, releasing the scar, improving vascularization, relieving symptoms and simultaneously resurface a large body surface area.

Many lasers have been applied for hypertrophic burn scars over the past decade, however pulsed dye laser therapy (PDL) and AFL-CO_2 appear to be most effective for burn patients [5, 91, 103].

PDL has often been advocated to reduce erythema, pain, and pruritus due to the selective photolysis which leads to a targeted vascular destruction resulting in collagen realignment and remodelling through tissue hypoxia, collagen fibre heating, and catabolism which prevents excessive collagen deposition. [44, 115, 125, 190]. However, the limitation lies within the limited penetration of thicker scar tissue, which decreases the effectiveness of the selected photolysis if the scar is thicker than 1.0 cm and also when tension is present [5].

Based on the experience gathered throughout this thesis, it appears that the introduction of AFL-CO_2 has been a milestone in reconstructive burn surgery as it completes the current scar management approaches and has the capacity to improve various aspects of the burn scar, including debulking tissue, resurfacing, releasing tension, improving vascularization and pigmentation, and thus ultimately reducing scar-related symptoms. The exact molecular mechanisms are still very poorly researched and underlying mechanisms by which these results are achieved not yet understood. When the preliminary analysis on the effect of one treatment with the AFL-CO_2 was performed at our institution, the reports on this treatment modality were sparse and mostly small in case numbers. Further, there was little focus of reports on patient reported outcome measures including pain and pruritus and no reports on the impact on burn specific quality of life [40]. Since then, there is a growing consensus between experts on this treatment that the effects are practice changing and have a substantial positive impact on the overall quality of life of burn survivors.

Due to the various existing burn scar characteristics as well as the numerous effects of AFR, our prospective data collection aimed to capture a large amount of information on all of these treatment related facets by utilizing various scores to facilitate more conclusive analyses. However, even though scar assessment scores are widely accepted, there are certain limitations associated with most of these scores. Most scar assessment scores are thought to still have quite a substantial subjective component involved [40, 191]. For example, one study reported that the accuracy of the estimated thickness in the VSS is only around 67% [40, 192]. In an attempt to reduce this subjectivity, the CRGH protocol also involved the objective measurement of the scar thickness by ultrasound as well as additional scores evaluated by both the observer and the patient.

The interesting phenomenon that patients may feel a more drastic improvement compared to the observer, was not only noted in our initial analysis [40], but also in some previously published small case series [127, 128, 130]. It suggests that patient's perception and subjective evaluation of their scars may be influenced by depressive symptoms [40, 193], which was also supported by our initial analysis by the poor “affect” domain in the BSHS-B questionnaire. Nevertheless, whilst this may reflect a potential bias of the patient assessed scores, there seems to be a lack of true objective outcomes when aiming to capture effects of scar treatment and emphasizes the necessity to include various scores and assessments to capture a more accurate overall picture rather than relying on one single outcome measurement [40]. Various objective scores allow for a more global assessment of the scar, including the measurement of aspects that cannot be measured by subjective assessment tools alone.

One of the shortcomings of this data collection is that considering scar thickness measured by ultrasound as the only "truly” objective outcome is probably not sufficient to reflect overall treatment effect achieved with AFR. It would be very beneficial for future research projects to include even more objective metrics. For example, a 3D wound measurement camera system (for assessment of surface area, texture, volume and colour), a DSM II colorimeter (for colour measurements), a cutometer system (for viscoelastic measurements), or a tewameter (for the measurement of trans-epidermal water loss), as advocated in a recent review[40]. Unfortunately, there is a lack of the ideal gold standard to validate objective scar assessment instruments [191] and thus this remains an area of ongoing research.

5.2. Effectiveness & safety of ablative fractional CO_2 laser for the treatment of burn scars: a case-control study

The results of the case control study (Chapter 4.2.) suggest that patients undergoing one treatment with AFL-CO_2 achieve substantial improvement in a variety of objective and subjective burn scar related outcome domains including QoL, when compared to patients who do not undergo AFL-CO_2 but receive standard burn scar care. These findings are supported by existing reports on the effects of AFL-CO_2 for burn scar management [103, 177, 194]. Furthermore, data in Chapter 4.2. demonstrates significant improvements particularly in burn scar related QoL, irrespective of scar maturation status. Thus, even patients with old scars that may have exhausted conventional treatments may still benefit from AFL-CO_2.

Looking at the demographics and information on burn mechanism no statistically significant differences between the case and control groups were found. Added to that, retrospective patient allocation to either treatment or control groups, was largely random. Patients who served as a control group did so due to external factors and irrespective of their actual scars. Thus, it was deemed the groups are comparable and there was no further formal matching performed. Although not statistically significant, the only parameter differing between the two groups was prolonged wound healing (>3 weeks following burn injury/procedure) with 60% of patients who experienced prolonged healing in the control group vs 37% in the treatment group ($p = 0.08$). However, this did not result in differences in the “scar severity” as assessed by the various outcomes such as ultrasound scar thickness, scar assessment scores and questionnaires about symptoms and QoL. We believe that any noted differences may be explained by our unit’s approach to often choose a more conservative approach in smaller burns of mixed or unclear depth, which in certain cases may result in grafting after more than 3 weeks post injury.

In Chapter 4.2., the median time since injury of our two evaluated patient cohorts was 16 months and the timeframe between initial assessment and the median follow up was ~5 months for the treatment and the control group. Scarring tends to develop 6 to 8 weeks after re-epithelialization and natural scar maturation requires at least 6 to 18 months [195, 196]. Symptoms improve during the scar maturation process, however in approximately 40% of long-term burn survivors, pain and pruritus can continue for years after the initial injury [197]. This is also our experience, and together with stigma, tightness, heat intolerance and inability to sweat contribute heavily to ongoing poor QoL of burns survivors.

As previously mentioned, 3 to 6 treatment cycles are generally recommended for an optimal outcome [5, 91], and it is very likely that the demonstrated positive effects accumulate with more treatment cycles as illustrated in Figures 7 and 8. It has been our observation that patients frequently describe an improvement of the scars which often appears not to be entirely captured with the available outcome measurement tools. This is also reflected by Chapter 4.2., in particular in the immature scar group. In the immature case and control cohorts all the variables assessed by an observer (health practitioner), namely the VSS, POSAS-O and POSAS-O overall, were deemed to have significantly improved in the treated and untreated groups. Interestingly, the scar thickness decreased in the immature control group (even though not significantly) but remained unchanged in the mature control group. Accordingly, this is in line with the argument that scars will improve during their natural maturation status regardless of any intervention. All the other patient reported outcome measures did not improve significantly in the control group regardless of scar maturation status. This supports the notion that the patients' and clinicians' perceptions may diverge and thus we may value different aspects of the scar. Thus, it is entirely possible that not all the variables relevant to patients are captured with the current available assessment tools and reinforces the requirement to capture patient-reported outcomes. Thus, our burns specific QoL assessment revealed interesting findings.

The treated cohort consistently reported an increase in the overall score for QoL of 10 points for the immature group ($p<0.001$) and by 17 points in the mature group ($p<0.001$). In contrast, the overall score decreased in the untreated control cohort. Patients with immature scars showed a decrease of 14 points in the evaluated timeframe ($p<0.05$) and a decrease of 10 points in the mature group ($p=0.9$). This raises the question if there is an additional subconscious component to the improvements noted in the treatment cohort such as hope associated with the new treatment, which may influence patients' perception of their QoL. To make a conclusive statement on this matter it may be valuable to conduct a long term follow up study and assess if the QoL further changes years after the reconstructive intervention.

In relation to QoL measures, the most significant changes were seen in the domain of heat sensitivity. Patients with immature scars rated an improvement of heat sensitivity of 6 points ($p<0.001$) following just one treatment with the AFL-CO_2, whereas the control group with immature scars only experienced a non-significant increase of 0.5 points. The mature treated cohort also described an increase of 3 points ($p=0.03$), whereas the untreated mature group reported a decrease of 3.5 points ($p<0.05$). This phenomenon may be explained by the change in vascularity in scars induced by AFL-CO_2. Treatment with AFL-CO_2 results in a decrease of vascularization in immature scars and an increase of vascularization for mature scars [198]. Thus, a normalization/improvement of the vascular anatomy within the scar may contribute to improve heat exchange, resulting in better heat tolerance. Added to that, the change in sensation such as sensitivity, pain and itch may also be related to the effect of laser treatment on peripheral nerve system or currently unknown molecular factors.

Although data in Chapter 4.2. demonstrated substantial improvement in various outcome parameters, there are limitations which should be considered. The presented objective outcome measures only include ultrasound measurements for scar thickness as a true objective device. All other assessments were based on an observer and thus may still be subject to observation bias. Thus, it would have been valuable to include an objective measurement tool for elasticity and pliability such as a torque meter, as a recently published analyses reported a substantial improvement in mechanical properties, such as elastic stretch, elastic recovery and total extensibility of burn scars following treatment with the AFL-CO_2 [194]. Optical coherence tomography would also be a great objective tool to assess vasculature and the connective tissue in scars [42, 199]. However, to ensure that the same portion of the scar is measured each time during the ultrasound measurement, topical maps on transparency paper marking the location of the thickest area, may be of greater value than mapped out photographs alone [194]. Lastly, there is a lack of objective measurement tools for burn scar related pain and pruritus and even other variables not yet entirely understood contributing to the improvements experienced by patients, as such the patient-reported outcome measures are inherently subject to reporting bias, but this aspect cannot be corrected for. Equally, psychological effects of having undergone treatment (particular after a long period of scar maturation) may equally have positively influenced some of the patient-specific reported outcomes compared to those having undergone treatment delays, and thus the exact independent effect of AFL-CO_2 on patient outcomes remains difficult to assess. Another limitation is that the majority of assessed patients received laser facilitated infiltration of corticosteroids (KenacortA40). Thus, it remains unclear if the effects are from the laser itself, due to evenly distributed intralesional corticosteroids or a combination of both. Generally, corticosteroids are injected intralesionally with a fine needle, however, as the drug is injected into the dense structure of the scar, it often results in an accumulation of the medication. As such, intralesionally injected corticosteroids can result in atrophy, white flecks, telangiectasia, and hypopigmentation. However, as more detailed outlined in Chapter 2.2.3., several animal models as well as clinical studies have been published about the enhanced bioavailability of drugs administered via laser assisted drug delivery [137, 141-146]. It is generally considered that due to the laser facilitated delivery the drug is much more evenly distributed via the fractional ablated wells compared to when it is topically applied or injected. The application of corticosteroids after AFL-CO_2 is thus very different to regular injection as the solution is evenly spread throughout the tissue. The choice of either injecting or topically applying the corticosteroids is generally based on scar thickness, which was not significantly different between the two groups as reported with the ultrasound measured scar thickness of the initial assessment. Unfortunately, we did not prospectively capture the data on how the corticosteroids were applied (injection or topical application) which would have been valuable to differentiate.

Lastly, in 10% of cases a simultaneous surgical procedure was performed such as Z-plasties, scar releases or excisions and/or simultaneous fat-grafting. Thus, in these instances it is not clear to what extent these surgical procedures have contributed to the improved patient outcomes. In cases with a clear contracture band, ectropion or similar, surgical reconstructive procedures are routinely performed in conjunction with AFL-CO_2. Generally, the simultaneously performed procedures are only very small and serve as a symbiotic adjunct to the treatment with the AFL-CO_2. Resurfacing a scar prior to any surgical intervention reduces tension and improves vascularization of the scar, preparing the scar for an optimal outcome if small local tissue rearrangements are performed. As such, the fact that 10% of cases had simultaneous surgical reconstructions needs to be considered when interpreting our findings. A separate analysis of patients undergoing multimodality treatment is in preparation.

The data presented in Chapter 4.2. illustrates that AFL-CO_2 is a well-tolerated and effective treatment modality which leads to a substantial benefit for burn survivors as has been reported by other units [91, 194]. As a sole treatment modality or in combination with local tissue rearrangements, AFL-CO_2 has greatly reduced the need for scar excisions and larger reconstructive procedures [93, 176], and thus provides a valuable tool in the armamentarium of Burn surgeons aiming to improve the outcomes of patients suffering from the long-term sequelae of burn injuries. Whilst not a randomized trial, Chapter 4.2. reports a case-control study, focusing on patient related outcome measures, namely QoL. Thus, it provides robust data supporting the positive results experienced by many other Burns centres around the globe.

Data in Chapter 4.2. demonstrates that burn scars can be effectively and safely treated with the AFL-CO_2. Objective and subjective outcomes improve significantly following just one treatment with the AFL-CO_2 compared to conservative and traditional treatments. In particular, burn specific quality of life showed a significant improvement following treatment AFL-CO_2 compared to an untreated control group. Long-term data are required to determine how sustained these changes are and if any further improvements can be achieved with multiple AFL-CO_2 treatments.

5.3. Ablative fractional resurfacing with laser-facilitated steroid delivery for burn scar management: does the depth of laser penetration matter?

To our knowledge, there are no guidelines regarding what laser settings, in particular how much energy should be used for a successful clinical outcome for burn scars treated with AFL-CO_2. Thus, Chapter 4.3. represents a first attempt to analyse how the depth of penetration with AFL-CO_2 influences patient outcomes. Whilst hypothesis generating due its retrospective design, our findings may assist clinicians in the choice of settings for the treatment of hypertrophic burn scars.

The results of Chapter 4.3. show that if scars were penetrated up to 75% of their thickness, a significant reduction of scar thickness could be achieved after one treatment, irrespective of scar maturation status. Highest improvements (1100μm) could be achieved if the scar was penetrated 51-75%. Penetration of 75% - 100% revealed a non-significant improvement, and if penetrated >100%, scar thickness even increased, although one should consider that the evaluated number of patients in this group was low (n=3). The median scar thickness was 3400μm and the median laser scar penetration depth was 900μm, which correlates to a median energy of 30mJ for which we generally use a density of 5-10%. This means in the majority of cases only 25-50% of the entire scar thickness was penetrated with good results. This may seem low, but "scar thickness" was always measured at the thickest area of the scar and it may well be, that the penetration depth around this area may have been deeper given the heterogeneity of burn scars. Furthermore, if tension is released in one part of the scar by remodelling, it can affect the entire scar. Thus, it can be argued that the actual penetration depth of the rest of the scar was actually deeper than at the point of highest thickness with a beneficial effect on the measured outcomes.

Nevertheless, our median scar thickness is in line with other reports, such as the study of Bloeme-Eberwein et al, who presented a mean burn scar thickness of a similar treatment cohort of 3.15mm (SD+/- 0.37) [200]. Various units have different protocols of preferred settings for the management of hypertrophic burn scars: authors mention using energies of 30-60mJ with densities of 5% (Response to Discussion [103]), energies of 20-40mJ with densities ranging from 5-15% [180], and 20mJ and 10-15% density [201].

As described by Paasch and Haedersdal (2011), in human explants, ex vivo pig skin and in vivo human skin, the penetration depth as well as the epidermal ablation width increases with raising energies [179]. It was shown that with high energies, the zone of coagulation increases and the zone of necrosis remains persistent, if a short pulse duration is used [179]. However, large-area heating and with it, most likely, the zone of necrosis is diminished by the fractionated technology and the incorporation of scanned laser beam [179]. This means, that according to the pulse duration of a laser device, the recommendation of the choice of energy (penetration depth) has to be taken into account as well. But even more importantly, whilst dealing with a burn population various other factors need to be considered. Burn scars are multifactorial, have multiple characteristics (altered vascularisation, dyschromia, structural changes, tension, contour abnormalities) and respond differently to any sort of external influence depending on various patients and burn mechanism factors [5]. In our unit, Fitzpatrick skin types, ethnicity, and scar maturation status greatly influence our clinical choice of settings for any sort of laser treatment. This may suggest the results of the present analysis should be interpreted with caution. Settings were chosen based on clinical experience factoring in the mentioned multiple facets of a burn survivor, which may have influenced the outcomes through all treatment and penetration depth groups. Thus, whilst we believe that this study supports the principle that a 51-75% penetration of the scar is probably a good guideline for ablative fractional resurfacing, other factors must be considered when settings are chosen.

Moreover, laser facilitated infiltrations (n=152) may be another substantial contributor to the documented outcomes. We routinely topically apply or intralesionally inject Kenacort A40 immediately following treatment with the AFL-CO2. Laser assisted delivery of drugs is an evolving technique [202, 203], enhancing the bioavailability of topically applied drugs, and the positive effects of corticosteroids on burn scars are well known [94, 95, 136, 137]. Thus, to what extent this treatment influenced our results remains to be clarified.

Despite our findings in Chapter 4.3. as a retrospective study, the analysis is subject to important limitations. First, scar thickness was determined by the measuring the thickest area of the treated burn scar. Given the heterogeneity of burn scars, it is thus possible that the penetration depth varied across a given treatment area. Accordingly, some uncertainty exists as to how areas of deeper penetration may have affected documented outcomes. However, we chose to adapt our settings during the treatment of a scar to decrease penetration depths whilst passing over thinner areas etc. Thus, it is assumed, that the current penetration depth calculations – whilst subject to some uncertainty – may still reflect the “maximum treatment effects” achieved during a single treatment session. We acknowledge that this lack of standardization introduces an unmeasurable variable in the present analysis, which cannot be adequately adjusted for. Equally, we suggest that future studies should aim at confirming actual treatment depth in human tissue, by measuring it with ultrasound or optical coherence tomography immediately after laser application. This would allow for an improved comparison of the response in areas of similar scar depth. This is of particular importance for any future project, as De Bruler et al. and Bauman et al. suggested in their porcine model studies that there is little difference in outcomes as a function of laser pulse energy, and their results indicate that there is a non-linear correlation of laser energy and penetration depth and laser stacking [204, 205]. Thus, first and foremost for any future project it would be essential to determine if the suggested penetration depth of 4mm is actually achieved in human tissue by using the maximal laser energy of 150mJ, or if the penetration depth varies depending on scar and patient characteristics (i.e. ethnicity, Fitzpatrick skin type, collagen density, scar maturation, etc.)

Another limitation of our study is the concomitant use of AFL-CO_2 and laser-facilitated drug infiltration. One-hundred and fifty-two scars (96%) were subject to this combined treatment, and as such the evaluated intervention is not only AFL-CO_2 but the combination of scar ablation and laser-facilitated steroid delivery. It is unclear, to which proportion the laser and/or drug treatment contribute to the observed effects and further research is required to clarify these individual interventions. Finally, whilst the data analysed in the present study stems from a prospectively maintained database, it is a retrospective study which is subject to issues such as selection bias. Equally, the creation of treatment groups based on assumed penetration depths was performed retrospectively, hence resulting in small patient numbers in certain groups. As such, the results of the present analysis should be regarded as "hypothesis generating" and further, prospective trials need to be performed to help elucidate the exact effect of penetration depth on burn scar outcomes.

To conclude, Chapter 4.3. suggests that AFL-CO_2 scar penetration depth significantly influences subjective and objective pathologic burn scar modulation if the scar is penetrated up to 75% of the scar thickness, irrespective of scar maturation status. Our results suggest that a scar penetration of 51-75% achieves the greatest reduction in scar thickness. Nevertheless, various other factors, such as Fitzpatrick skin type, ethnicity, scar maturation as well as type of scar should be considered when choosing the appropriate settings of AFL-CO_2 for burn scar management and future research will be required to help clarify how these and other factors influence the outcomes of burn scars being treated with AFL-CO_2.

5.4. Ablative fractional resurfacing for burn scar management affects the number & type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay

To our knowledge, the research in Chapter 4.4. is the first study analysing the effect the introduction of AFL-CO_2 has on the burns reconstructive surgical case-mix, anaesthetic times and hospital length of stay in a high-volume Western burn unit. The analysis presented in Chapter 4.4. shows that AFL-CO_2 can be used either alone or in combination with conventional burns scar reconstructive procedures, resulting in a replacement of more extensive procedures, whereby shortening operative times and patient hospital length of stay. Whilst the exact cost-saving of such changes to elective burn patient management remain to be elucidated, we believe our data supports the notion that AFL-CO_2 has become a valuable and potentially cost-effective tool in the management of these complex patients. It could be argued that the decrease in conventional reconstructive procedures and increase in laser procedures following the laser introduction reflects the use of a novel technology following a big financial investment. However, as can be seen in the presented data, the replacement of conventional reconstructive procedures with AFL-CO_2 was gradual and occurred with increasing device experience as well as learning what results could be achieved. The rise of use of AFL-CO_2 was encouraged by good clinical outcomes and patient satisfaction, leading to an increase in new referrals for scar management with the AFL-CO_2 [5]. Furthermore, it is important to note that the overall numbers of admissions to the CRGH Burns Unit and visits to the CRGH Burns Outpatient Clinic increased substantially over the study period, thus leading to more patients being seen who may have benefited from this new treatment. Hence, the change in elective procedural case-mix also represents a learning-curve of our burn unit regarding patient selection. We acknowledge that the cohorts pre- and post-laser introduction may be heterogeneous in nature and may not necessarily contain patients with comparable burn scars. This could be attributed either to the type of burn injuries sustained during the time period or due to surgical and non-surgical advances in acute burn care management that prevented patients from ending up with contractures that needed surgical intervention. Nevertheless, as shown in Table 4, we demonstrate that (where data was available) the population, type and age of burn scars were comparable in both cohorts, before and after introduction of AFL-CO_2. As also indicated by our data, we believe that this treatment approach allows us to address problematic scars in a way which was previously not possible which may also contribute to the increase of patient referrals during the analysed timeframe. This is reflected by the fact, that amongst other more complex reconstructive procedures, eyelid and lip ectropion releases were less frequently performed following laser introduction. We found that the complexity of reconstructive procedures decreased following laser introduction, which may be related with a change in the time-point of intervention. Current paradigms suggest to await complete burn scar maturation before reconstructive procedures are planned, unless intervention is needed to prevent secondary damage [93]. The projects presented in this thesis as well as other reports have outlined that early intervention with the AFL-CO_2 for the treatment of immature scars can positively influence scar rehabilitation, accelerating scar maturation, improving early mobility, and enhancing as well as accelerating the entire rehabilitative process [5, 40, 135]. Further, Chapter 4.5. illustrates that AFL-CO_2 can successfully avoid the surgical release of ectropia with skin grafts if used in an early-stage post injury. Thus, early intervention with the AFL-CO2 and the positive effect on scar rehabilitation may well contribute to the phenomenon that certain more complex procedures are not needed once the scars are fully mature. Whilst comparative outcome data before and after AFL-CO_2 introduction (laser vs non-laser) is missing in the presented analysis, our data demonstrated clear benefits of AFL-CO_2 treatment. Significantly improved objective and subjective outcome parameters could be shown with clear benefits for the patients as they were able to receive a fast, effective, alternative treatment compared to the traditional surgical approaches. The above data are encouraging, but they are limited by the fact that it usually takes 3-6 treatments with the AFL-CO_2 to achieve an optimal result [5] compared to one procedure for a conventional reconstructive surgical intervention. As such, it is entirely possible that AFL-CO_2 may increases the burden on operating theatres due to increased number of overall procedures, which may lead to increased waiting lists for elective procedures as well as total costs to a Burns Unit. However, conversely all scars are usually treated during the same AFL-CO_2 treatment session, whereas in the majority of other reconstructive procedures only one area is addressed at a time to reduce periprocedural morbidity. Furthermore, it has been estimated that the mean number of reconstructive procedures required per burn patient during their lifetime following the burn injury is 3.6 [206]. Our analysis of the total number of procedures per patient in the pre- vs. post-laser era only looked at a timeframe of 1.5 years in the pre-laser ear and not a “lifetime”. This means that it could well be that the actual number of laser procedures is in fact comparable to traditional reconstructive procedures if the number of elective reconstructive procedures per patient per lifetime were to be accounted for. Further, due to the shorter anaesthetic times, more cases can be completed during one operating list, potentially offsetting any previous financial investment and associated costs [183]. However, we acknowledge that the actual financial implications may vary from country to country due to associated billing codes and reimbursement practices for this novel procedure [183]. Chapter 4.4. showed that anaesthetic times dropped significantly by over 30min following the introduction of the AFL-CO_2. A recently published study analysing the impact of treatment of burn scars with an erbium-YAG laser on a burn operating rooms flow and productivity, reported similar findings [183]. Their mean anaesthetic time for reconstructive procedures pre-laser was 157.5 – 65.0 min and laser procedures only in the post-laser era dropped to 79.2 – 33.4 min ($p<0.001$) which is similar to our experience. As a result, like Madni et al. (2018) we have also experienced that more reconstructive cases can now be completed with up to 8 – 10 cases performed per day during a dedicated laser reconstruction operating list [207]. A great number of the AFL-CO_2 cases can be treated under topical or local anaesthetic only (almost 50% in our data set), which means that a significant financial saving could be made as these cases can all be performed without the presence of an anaesthetist, anaesthetic nurse and recovery personnel. However, one of the most profound impacts our unit has experienced since the introduction of the AFL-CO_2 is the change in admission patterns. Of the 246 laser procedures performed, only 4 (1.6%) required overnight admission, with an average length of stay 2 days shorter than conventional, non-laser reconstructive procedures. Two of these four cases were admitted for one night due to social reasons, one patient was admitted due to a medical indication, and one patient was admitted due to the extent of the combined procedure. Thus, only one admission was actually related to scar treatment.

This is largely due to the fact that the AFL-CO_2 procedures can easily be performed as a day-only procedure, sometimes only requiring local anaesthetic. Most patients also only remain off work for a few days following the AFL-CO_2 procedure and can reintegrate seamlessly into previous activities. Further, for patients suffering from severe pruritus, neuropathic pain and paraesthesia requiring medications such as narcotics, antihistamines, anxiolytics and antidepressants, treatment with AFL-CO_2 can decrease these pharmacological requirements [208]. Thus, this may also result in an ultimate cost reduction by reducing the need of expensive drug regimens and a more rapid re-integration into the workplace [208]. Consequently, whilst the cost-savings associated with laser introduction remain entirely hypothetical, we believe our data supports their plausibility. To conclusively define the economic impact of laser introduction on burn scar management a rigorous cost analysis should be performed taking considerations of other factors such as occupational and physiotherapy requirements, medication, time-off work, and rehabilitation/re-integration into the workforce in addition to procedural operating times and hospital length of stay. Equally, to potentially correct for a "hype" effect of the laser studying an extended period to include a longer "post laser introduction era" would be sensible. Additionally, an analysis across multiple units would potentially also allow for a somewhat more unbiased assessment of the impact of the introduction of AFL-CO_2 to any scar program.

Following introduction of the laser at CRGH Burns Unit, 76.1% of all elective burns reconstructive surgeries performed were laser-based procedures. In our facility, AFR with or without Z-plasties, excision of scars and local flaps appear to have replaced more complex reconstructive procedures. Anaesthetic times have also significantly reduced following laser introduction. Furthermore, the requirement to admit a patient for a reconstructive procedure has decreased significantly since the introduction of AFL-CO_2, as 98% of procedures can be performed as a day-only procedure. As such, the minimally invasive nature and minimal side effect profile of AFL-CO_2 (no donor-sites, no foreign material, and no complex procedures) make it a valuable tool for burn scar management. It potentially allows for more timely and efficacious rehabilitation, and reintegration into workplace compared with conventional reconstructive procedures. Whilst future, prospective and randomized studies are required to further validate the efficacy of this novel treatment, the effect it has in altering patient burn care and hospital admission patterns is clearly illustrated and supports further research into this evolving area of burn care.

5.5. The prophylactic potential of ablative fractional resurfacing in acute management of facial burn injuries

To our knowledge, Chapter 4.5. is the first report documenting the positive effects of AFL-CO_2 in managing scar contracture formation in the early acute care setting. Traditional early reconstructive procedures such as ectropion releases with full-thickness skin grafts and oral commissuroplasty were able to be avoided in this case, with excellent functional and potentially more acceptable aesthetic results.

As presented in Chapter 4 and other early reports, ablative fractional resurfacing is described to positively influence and accelerate scar maturation, expediting the rehabilitative phase and workplace-reintegration [134]. Nevertheless, it may seem somewhat paradoxical that micro-injuries within a wound/scar should promote wound healing and positively influence scarring. The size of the wound appears to be a precipitating factor in scar formation, with the transition between nonscarring and scarring dermal thickness wounds occurring at a diameter of approximately 0.3 to 0.5 mm [209]. The healing response to the unique pattern of fractional laser injury initiates the tissue remodelling. Several histologic analyses propose that the particular fractional wound stimulates a molecular cascade, including heat shock proteins, matrix metalloproteinases and other inflammatory actions, initiating a rapid healing response and protracted neocollagenesis with consequent collagen remodelling, reduction in type I collagen and growth in type III collagen [127-130]. Additionally, in 2015, a group from Western Australia described an increase in vascularisation in mature scars and a decrease in vascularisation in immature scars [198]. Particularly, this latter aspect might explain the accelerated scar maturation and in the presented case may have even prevented further scar formation.

Some areas of the presented patient’s face were not fully epithelialized or still very fragile during the first laser procedure 6 weeks following the burn injury. To promote a wound healing response with healthier tissue, debridement of poorly healing areas from wounds is a widely established approach [134]. It is postulated that the same applies for the photo-micro-debridement of the vaporized portions of dysfunctional scar tissue and wound debris following fractional resurfacing, thus accelerating a rapid healing chronic wounds [134]. It may be counterintuitive to apply additional injury to a recently healed, still fragile wound. However, the presented patient would have undergone surgical releases of his upper and lower eyelid ectropion and the resulting defect from the lack of tissue and tension would have been filled with full-thickness skin grafts. Surgical ectropion releases like this are by nature a much more invasive approach with, in our opinion, functionally equal, but cosmetically inferior outcomes.

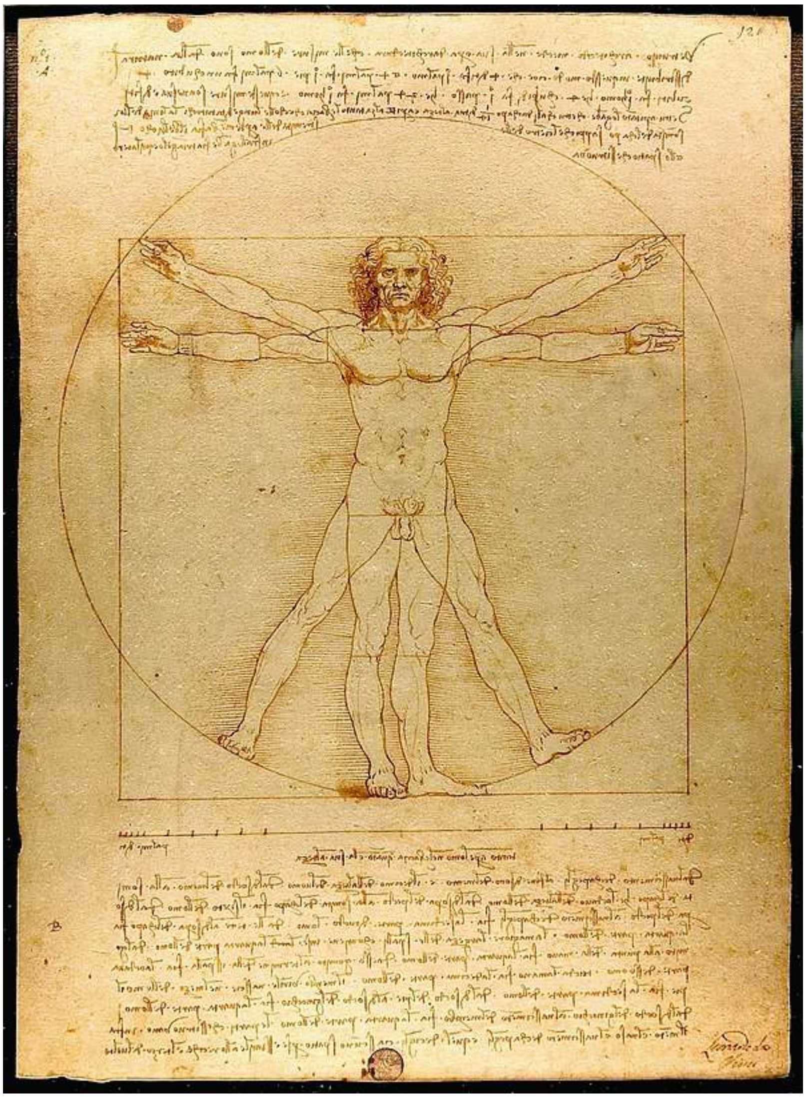
The case report presented in Chapter 4.5. illustrates that the wound contraction during the regular wound healing process leads to tension very early after epithelialization, which is a known pre-requisite of pathological scarring [93]. We believe that stimulation of tissue regeneration and collagen rearrangement immediately following epithelialization may positively influence the formation of pathological scarring and may help to reduce tension in the healing scar.

Although Chapter 4.5. presents encouraging functional and aesthetic outcomes in response to combined AFL-CO_2 and nonsurgical scar contracture management, there are certain limitations. This multifaceted treatment program was trialled on one patient only and as such the results should be interpreted with caution. Despite this, the treatment program described in the current study is practical, is minimally invasive with minimal adverse effects, and holds high potential feasibility for implementation in the severe burn population.

Consequently, larger cohort studies are required to confirm these positive functional and aesthetic results across a broader patient demographic group and also to inform the most appropriate frequency of AFL-CO_2 treatment and combination of nonsurgical rehabilitation strategies.

To conclude, combined AFL-CO_2 and nonsurgical scar contracture management can be utilised with great success in the early acute care period to assist in managing pan-facial scarring and contractures that can lead to considerable functional deficits. The case presented in Chapter 4.5. additionally, demonstrates that this combination of treatment may also eliminate the need for other traditional surgical reconstructive procedures that often are required to be performed early to maintain functional ability.

Chapter 6. Rethinking conventional burn scar management



Source: https://en.wikipedia.org/wiki/Vitruvian_Man

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6.1. Lessons learnt

Based on the experience gained by the preceding studies, it can be concluded that AFR and laser facilitated steroid infiltration is an excellent tool to compliment a burn surgeons' armamentarium. However, for burn scars involving a large %TBSA, it is important that a well-thought-through approach of which areas should be lasered has to be chosen to achieve a successful outcome. Further, conventional reconstructive procedures are still needed and should be performed as an adjunctive treatment together with the AFL-CO_2 to address the entire complexity of burn scar symptomatology. As such, Chapter 6 discusses the lessons learnt from the studies documented in Chapter 4, reflects on underlying problems of burn scar development, and how these need to be addressed in order to optimize the clinical integration of AFL-CO_2 into routine burn scar management whilst constantly adapting to individual patients' needs. As such the following chapters take a wider look at burn scar development and illustrate how the AFL-CO2 has helped not only identify but also address some of these fundamental problems facing burn victims.

6.2. The nature of burn scars

Understanding scars and defining the origin of the disease is of utmost importance in order to be able to effectively establish a successful treatment plan tailored to each individual patient. Thus, some of the most important factors described in Chapter 1 are summarized and further elaborated on in this chapter.

As described earlier, burn scars have multiple characteristics, such as altered vascularization, dyschromia, structural changes, tension, and contour abnormalities. To achieve an optimal outcome, all aspects of a burn scar should ideally be addressed by a holistic treatment approach.

For the prevention and treatment of scars, differentiating pathologic from non-pathologic scarring appears to be important to understand the different cellular and biochemical mechanisms which result in scarring [13]. But what actually defines a scar as pathologic/abnormal in a deep dermal or full thickness burn wound? If only a flat, almost invisible scar following a skin grafting procedure is considered to be a "normal/non-pathological" scar, it can be concluded that a very large percentage of burn victims have pathological scars, in particular in specific ethnic groups. Overall, it is exceedingly rare to see a completely “normal”, thin, pliable, almost invisible scar in a burn survivor. In certain ethnic groups (e.g. Chinese, Nepalese, central African, etc.) this is a true exception. As such, when considering the nature of the burn injury, it would make sense that most burn scars can be considered pathological scars. The “burn-burden” for abnormal/pathological scarring can probably be explained by two main pathophysiological mechanisms which are interconnected:

1. Hyperinflammatory wound and prolonged wound healing: Burn wounds are highly inflammatory in nature. Inflammation is virtually always present in a burn injury and a larger burn injury even leads to a systemic inflammatory response. Due to various reasons (conservative management approach, catabolic state of the patient, etc.), burn wounds often undergo a prolonged phase of wound healing. These are all known factors contributing to hypertrophic scarring and also the reason why early debridement and grafting is advocated in the literature [21].

   Alteration in skin colour is another major component to hypertrophic burn scars and likely due to the inflammatory component of the burn scar as well as the natural maturation/remodelling process. Pigment alterations in burns scars derive from two main components: melanin (brown hues) and oxyhemoglobin (red hues, erythema) [41]. The melanin (brown pigmentation) produced by the melanocytes in the epidermis results in hypopigmentation and/or hyperpigmentation and often occurs as a function of the inflammatory process in the tissues. Generally, it slowly subsides with maturation of the scar. Equally, the red component of hypertrophic scars (oxyhemoglobin), resulting from proliferating and dilated micro-vessels, is a consequence of inflammation due to the burn injury itself, and/or due to resulting skin tension during healing. Once the remodelling phase is completed, the erythema resolves reflecting a mature scar, unless there is persistent tension present in which case the erythema often persists.

2. Contraction in wound healing and tension: In a normal acute wound, myofibroblasts are responsible for wound closure, however if they persist, fibrosis and tissue contracture are the consequence [27]. Contracture is part of any wound healing process, regardless of if a burn wound is grafted or healed by secondary intention. In burn wounds there are two effects at play: First there is an obvious shortage of skin due to the injury itself, and secondly because of the contractile forces of the myofibroblasts, wounds, grafts, as well

as scar tissue contract, resulting in contour abnormalities, tension and contractures [93]. Tension as a hallmark is clinically present and associated in essentially every hypertrophic scar, except if the tension is released by scar relaxation or surgical correction [40, 210].

Commonly it is not only one component leading to a pathology. Inflammation, prolonged wound healing, contraction and tension are all interconnected. However, through the structured and systematic assessment as well as treatment of burn scars as outlined throughout the present thesis, it seems apparent that a further factor influences burn scarring.

It is acknowledged that hypertrophic scarring is more prevalent on flexor surfaces, over joints as well as over the shoulders and chest. However, little attention has been paid in the medical literature to the importance of the dynamics of movements or the so-called kinetic chains or functional kinematics in scar development. Together with the embryological development of skin, the importance of these chains of movements appears to be intimately involved in scar development and addressing this aspect serves as a key for a successful outcome of any scar intervention.

6.3. The importance of biomechanics & the kinetic chains of human movement in the development of burn scars

Originating from engineering, the concept of “kinetic chain” or “kinematic chain” is a well-reviewed principle in the teaching of physiotherapy and rehabilitation to describe human movement [211, 212]. The concept originated in the 19th century, by Franz Reuleaux, a mechanical engineer, who proposed in 1876 in his book *“The Kinematics of Machinery”*, that in a rigid-link system, pin joints connected rigid, overlapping segments. This created a system whereby movement at one joint produced or affected movement at another joint in the kinetic link [212]. Over the next century, this idea evolved and was adapted to synergistic muscle actions. In the human body Steindler defined that the kinetic chain as “a combination of several successively arranged joints constituting a complex motor unit” [213].

The definition of terms surrounding these movements are the following: Biomechanics is defined as the study of effects of forces on the motion of bodies as an application of the mechanics of motion produced by biologic systems. Kinetics refers to the study of the effect of forces and torques on the motion of bodies having a mass. Dynamics is often synonymously used to describe kinetics. Kinematics on the other hand, is the study of the geometrically possible motion of a body or system of bodies without considering the causative forces [213] (www.britannica.com).

Even in burn survivors with what is deemed an excellent outcome, there are almost always thicker areas or contracture lines within the scar. These are often in areas exposed to movements of greatest range of motion within the lines of kinetic chain of movements, and across joints with 3-dimentional movements (e.g. neck, shoulders, elbows, axillae, and finger web-spaces). What remains unclear is if there is accentuated tension present in these areas from the beginning of wound healing compared to other body locations, or if the tension is a result of the mechanical strain that occurs in these areas, which in turn results in the production of thicker collagen, again resulting in further tension. This is clinically well-known, where we empirically observe increased rates of contractures during regular healing in areas exposed to larger ranges of motion. The propensity of these areas to contract more compared to other body locations, could also be explained by the additional mechanical strain of maximal movement.

However, there must be an additional explanation as there is a contradicting element behind this observation. Considering that there is a higher amount of mechanical strain in areas exposed to a large range of motion seems somewhat paradox, as stretching and splinting of scars (physio- & occupational therapy) is a widely accepted treatment modality to help prevent extensive contracture/scarring in the rehabilitative phase. If stretching of an area under tension would imply that there is an additional mechanical strain which could lead to worse scarring, this would indicate that the widely and successfully applied stretching exercises and splinting techniques would make the scars worse rather than better. Thus, it seems that there are additional components responsible for this phenomenon, which raises the question regarding the influence of functional kinetic chains as well as the impact of early embryological development. This latter thought arises, because during the very early phase of life, the entire body starts to develop from of a 2-dimensional state into a 3-dimensional embryo evolving around a central midline, which appear to be very similar to these contracting forces along the lines of functional kinetics towards the midline. This hypothesis of the influence of embryological is discussed in more detail in Chapter 6.3.2.

However, regardless of the origin of increased contractures/tension, the result is a shortage of tissue and overall, the quality of the scar is quite poor with either a very thin and fragile or thickened/hyperkeratotic epidermis on top of a dense and thickened dermis. This latter observation may be explained by the underlying function of the dermis which is supposed to provide the skin with durability, strength, elasticity, regulates temperature and sensation and provides sebum and sweat [214]. Thus, it appears to be a very natural response of the scarred dermis to thicken during the maturation process in order to maintain its' function to provide durability despite the shortness/lack of tissue which is under constant movement with subsequent additional tension.

6.3.1. The role of myofibroblasts

In normal acute wounds, myofibroblasts (which differentiate from fibroblasts) are the cell type responsible for wound closure. However, if they persist, fibrosis and tissue contractures occur. This persistence of myofibroblasts is regulated by a complex feed-back loop that incorporates the mechanical sheer stresses of the environment, extrinsic growth factor activation signals, intrinsic cellular tension signalling and gene expression pathways [27].

Fibroblasts are a highly mechanoresponsive cell type and wounds on areas under high tension and stretching are more prone to develop hypertrophic scars and contractures [45]. Mechanical forces play an integral role in myofibroblast formation, function and fate, such as extracellular growth factor activation and intracellular transcription factor regulation [27, 29, 215]. During tissue repair, (myo-)fibroblasts and their microenvironment form an evolving network with reciprocal actions, thus if the dialogue between (myo-)fibroblasts and their microenvironment is altered, repair defects can occur [216]. There are in vitro studies suggesting that mechanical strain upregulates matrix remodelling genes and downregulates normal cellular apoptosis, resulting in more cells, each of which produces more matrix.

Mechanical tension plays an important role in promoting and maintaining controlled signalling pathways that keep the myofibroblasts active [27]. This “double burden” may underlie the pathophysiology of hypertrophic scars [45]. As such, the reduction of tension in the surrounding tissues of the wound may have a significant therapeutic effect on the myofibroblasts in scars themselves.

6.3.2. Scar bands/cords following the kinematic chains

The typical downward slant of the lateral canthus with or without a lower eyelid ectropion, the lateral and downward pull of the lip commissure with or without lower lip ectropion and contracted neck are commonly present features of burn survivors. To the best of my knowledge there is no explanation in the literature as to why these contractures consistently form in these directions. (Figures 16-20).

As mentioned before, through the systematic assessment of burn scars we have observed that scar bands always form lines which follow the laws of functional kinetics. The bands are almost always found across the lines of greatest range of movement and appear to be under greatest tension when the whole functional chain is fully extended, even though the scar may appear relaxed when assessed in a neutral position. For example, a contracture band reaching from the tip of the thumb, across the flexor aspect of the elbow, to the anterior axillary fold, and across the lateral neck reaching the lip and eyelid commissures through a common "plate-like" scar over the cheek leading is a classic appearance of a burn survivor. Again, it is possible that the only visible feature in the neutral position is a slight pull on the lower eyelid, which can turn into a full lower eyelid ectropion with a visible band across all these interconnected structures only becoming apparent when the patient fully extends the whole chain of associated body parts. Equally, to achieve a successful outcome with the lowest chance of recurrence, it is of utmost importance to assess the entire kinematic chain of a patient presenting with a contracture and plan the surgical release accordingly. With this in mind, it thus becomes clear, that prior to performing an extensive contracture release of the neck a surgical scar release of a contracted anterior axillary fold is required not only to decrease the extent of the required surgery, but also to reduce the risk of recurrence due to persisting traction of the adjacent joints of the kinematic chain. Equally, the neck contracture will change and most likely improve following release of the adjacent contractures, especially if simultaneously performed with AFL-CO_2 to the entire kinematic chain.

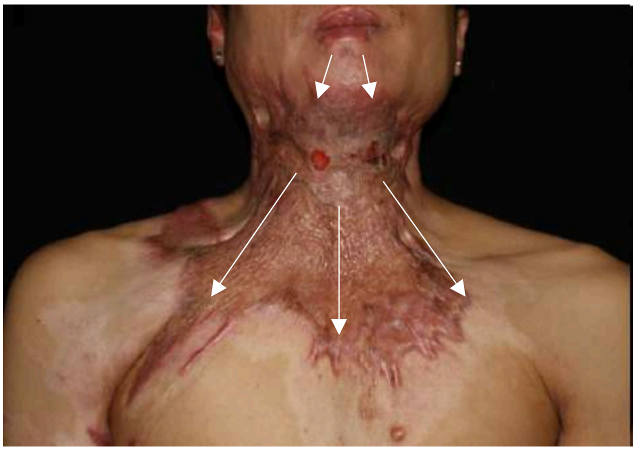
Figure 16

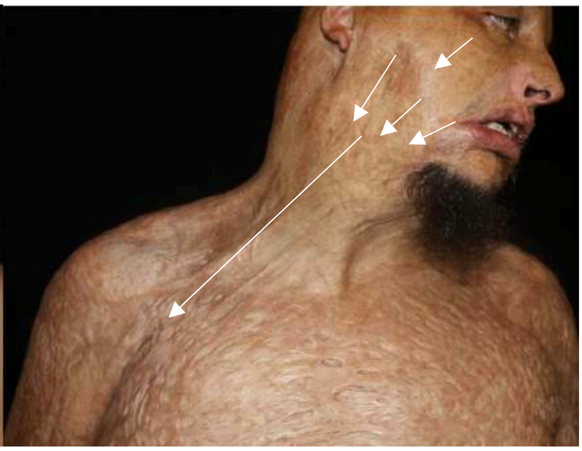
Figure 17

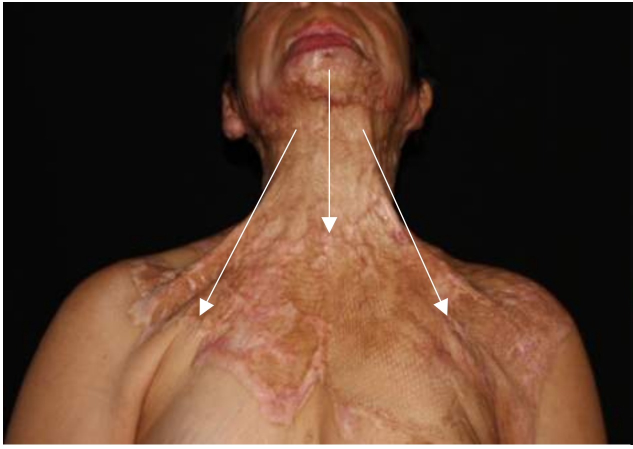
Figure 18


Figure 19


Figure 20

Figures 16-20. Lines of tension with resulting scar bands.
Figure 16 illustrates the classic neck contracture of a burn survivor with main tension across the midline towards the sternum as well as the lateral bands reaching across the anterior axillary fold. Figure 17 illustrates the same lateral bands across the anterior axillary fold, including the plate-like scar across cheek, slant of lip commissure as well as mild ectropion of the lower eyelids. These typical features are prominent if the entire area is burnt (intrinsic contracture), but a slight ectropion or commissural slant can be even be present if the face is unburnt (extrinsic contracture). Figure 18 & 20 illustrate again the classic lateral scar bands with maximal tension across the anterior axillary fold towards the thumb or little finger. In this case, the axilla and upper limb was unburnt, with the exception of that small scar on the thumb. However, the patient complains of tightness in her axilla, across the elbow and limited flexion of the MCPJ of the thumb. Figure 20 illustrates again the classic contracture band across anterior axillary fold, radial side of cubital fossa towards the thumb according the lines of functional kinetics. Also evident on this image is the tension related breakdown of the scar resulting in a small wound reflecting the unstable scar under constant tension.

As discussed earlier, an imbalance in biosynthesis and tissue degradation during wound-healing initiates an excess of collagen production and fibroblast proliferation in hypertrophic and keloid scars, so that they become firm and raised with an irregular surface and tension [44]. When the body moves, there is constant pulling across these lines of functional kinetics, according to the biomechanical laws described earlier. Interestingly, I have observed that aside from increased collagen bundles in dermal layers of the dermis, there are also always cord-like structures above the fascia underneath the "healthy" appearing subcutaneous layer Figures 21-23). The nature of these bands is unclear to me, but they seem to be involved in the development of scars requiring treatment and further investigations are currently underway to better understand the aetiology and composition of these bands.

Figures 21-23. Epi-fascial connective tissue cords along the lines of tension according to functional kinetics.
The cord-like structures of connective tissue underneath healthy subcutaneous tissue are aligned with the lines of greatest tension according to the laws of functional kinetics. As illustrated in Figure 20 these cords also seem to be apparent underneath unburnt skin which could explain why patients feel tightness or even restricted range of motion in areas distant to the obvious cutaneous scar.

Figure 21

Figure 22

Figure 23

The skin is continuously in development and plays an integral role in the homeostasis of the human body. Embryologically, the epidermis (as part of the structures which are in contact to the outside world) originates from the ectoderm [217]. The dermis, the underlying adipose layer, but also the fascia derives from the mesoderm. Thus, embryologically, the fascia is the continuation of the connective tissue [218]. A three-dimensional continuum of soft, collagen-based, loose and dense fibrous connective tissue forms the fascial system, which infiltrates the entire body and allows it's musculoskeletal and adherent systems to operate in a synchronized manner [219, 220]. As previously described, regular wound healing consists of four stages, whereby the last stage, the remodelling phase, can last for years. Type 3 collagen is replaced by the stronger type 1 collagen in a disorganized manner resulting in more strength but less pliability [17, 221]. It has been hypothesized that neuroinflammatory stimuli and a release of neuropeptides can prolong the production of growth factors and cytokines leading to an excess of extracellular matrix [222, 223]. An increase of nerve fibres with accumulated neuropeptides has been reported in hypertrophic scars and is believed to be stimulated by abnormal tension originating from the injured site [15, 56, 224]. It is known that deep injuries can affect the fascia which is rich with neurologic corpuscles and contractile fibres [223]. Thus, is possible that through the functional limitation of the scarred skin with resulting tension, fibroblasts throughout the connective tissues, fascial fibroblasts, as well as the recently described fasciocytes, may respond through neurogenic inflammatory arcs with an increased production of collagen which can then be clinically identified underneath the subcutaneous layers of a contracture band.

The reason this is mentioned here is that the described tension lines and deeper epi-fascial cords are in line with the proposal that the scar formation occurs across the lines of functional kinetics. Accordingly, addressing these pathological aspects is of utmost importance when planning local tissue-rearrangements and choosing the laser settings, as a successful result can only be achieved, if the entire surface across these scar bands is treated (Figure 24). Of equal importance is the treatment of scar plates acting as a contracting "tension" plate (Figure 26). Furthermore, the power of prophylactic use of the AFL-CO_2 could be explained by the laser prohibiting the development of these deeper cords and thus, the resulting collagen bundles are not as dense as in more mature scars, and consequently more susceptible to further burn scar modulation with the AFL-CO_2.

[redacted]

Figures 24. The importance of releasing entire surface of the scarbands.
36yo following a 33% TBSA burn 19years ago with a significant contracture band reaching from her thumbs, across the radial side of the cubital fossa to the anterior axillary fold. Her neck was released with a free flap a decade earlier, which has shifted the tension from her neck more caudal and connected the contractures from both upper limbs.
A illustrates the contracture pre-operatively and **B** immediately postoperatively following a release of the bands with several Z-plasties as well as simultaneously performed resurfacing with AFL-CO_2 and laser facilitated steroid infiltration. To avoid a recurrence or shif of tension/shift of contracutre bands it is very important to resurface the enitre chest with the laser as well as the entire width of the scars on the upper limbs in order to achieve a more global release with an overall superior outcome. As outlined in this Chapter, patients with neck contractures often present with a contracture in the anterior axillary fold, thus, the release of the axilla prior to the neck, may result in a less accentuated neck contracture.

Figure 25. Scar plates leading to a restricted range of motion. 71yo female 13 months post 18% TBSA flame burn illustrating a limited range of motion of her left shoulder due to a hypertrophic scar plate as well as a contracture band along her posterior axillary fold towards the flank. When surgically releasing this posterior axillary fold with a local flap of normal skin transposed into the line of greatest tension, it is important to resurface the entire back scar with the AFL-CO_2 to achieve an overall release of the constricting forces and avoid recurrence of the contracture on a more posterior level (shift of tension).

6.4. Local tissue re-arrangements combined with AFL-CO_2

As described in Chapter 4 resurfacing of burn scars with the AFL-CO_2 seems to be effective to improve cosmesis, symptoms and functional outcomes. Nevertheless, in more severe cases treatment with the AFL-CO_2 alone does not replace surgical contracture releases but has the potential to limit the extent of surgery, as it prepares the tissues by optimising its vascularisation and pliability and serves as a valuable adjunct so that simple surgical techniques can be successfully used with good outcomes. Additionally, with a less invasive approach, postoperative morbidity can be reduced, and workplace-reintegration accelerated.

Together with the development of plastic surgery as a specialty, the reconstructive approach for scar management has evolved and changed dramatically over the past century. Techniques have advanced and microvascular tissue transfer has been introduced facilitating complex reconstructive therapeutical options for tissue coverage [86]. However, a burn scar often involves large surfaces across various anatomical areas and composes of several different scar characteristics in an often psychologically traumatised patient cohort [5, 40]. Complex surgical approaches are associated with significant morbidity, donor-sites, and time off work [5, 40]. Further, due to the limitation to the actual surgical site, as well as the formation of iatrogenic new scars due to the nature of surgery, pain, pruritus, dyspigmentation and hypertrophy often remain [5].

6.4.1. Establishing a reconstructive treatment plan

Ablative fractional resurfacing allows the surgeon to treat large scars of patients with very large %TBSA burn injuries. However, a burn patient who survived a very large injury may display so many scars, that it appears sometimes difficult to decide which areas should be addressed and prioritized.

If a patient is consulting a scar clinic for the first time, it is essential to clearly define the patient's main concerns, needs, and expectations. Very often the obvious deformity may not be the main concern for a patient but rather a smaller itchy, less visible scar or a tight scar leading to chronic pain in an adjacent joint. It is the duty of the surgeon to set realistic goals, explain the variety of surgical treatment options and elaborate the risks and benefits of each treatment discussed. Together with the patient, a plan according to medical urgency should be established. Obviously, an ectropion leading to an organ at risk or a contracted joint limiting the daily function of a patient should be prioritized.

Once the goals and priorities are set, a treatment plan should be established, utilizing the considerations from Chapters 6.1. – 6.3. to help decide when and how to use the AFL-CO_2. As such, a profound understanding of the pathophysiology of burn scar development and factors contributing to hypertrophic scarring is crucial to be able to establish the correct and appropriate treatments as well as what individual laser settings are required. However, there are also further considerations that are required to achieve an optimal result, which are discussed in the subsequent chapters.

6.4.2. Choosing the time-point of intervention

As outlined in Chapter 4, AFL-CO_2 is effective even in immature scars and most likely positively influences the entire rehabilitative process. Thus, if a surgical approach is required in addition to the AFL-CO_2, the most important contributing factor is the maturation status of the scar. In contrast to laser resurfacing, surgical intervention very often leads to recurrence or even worse scarring if applied too early, which is why it is the general recommendation not to start any reconstructive surgical intervention until a scar is mature, unless an organ or joint is at risk [93]. However, as AFL-CO_2 appears to accelerate the natural scar maturation process and if combined with local tissue rearrangements modulates the surgical peri-wound, relaxing Z-plasties for example may be performed even in the immature scar if combined with AFR. Further individual, ethnic, environmental and genetic factors contributing to hypertrophic scarring, as well as co-morbidities and social support systems are other important factors to consider in order to achieve a successful reconstructive treatment approach. Thus, it appears logical that in particular in patients with predisposing factors for hypertrophic scarring, a "preparation" of the scar with the AFL-CO_2 in order to optimize the vascularization/scar maturation and pliability of the scar is key to a successful surgical outcome by utilizing local tissue re-arrangement. Further, it should be considered which contracture should be surgically released *first* in order to potentially avoid or limit the extent of a necessary contracture release of another area especially if surgery is combined with AFL-CO_2 (for example releasing of the anterior axillary fold before attempting a more extensive surgical release of a contracted neck, as outlined above).

As burn patients are all different and each treatment approach requires the consideration of burn mechanism, scar location, scar maturity, ethnicity, co-morbidities etc. it is difficult to determine how many resurfacing laser interventions are ideally performed before the surgical release. Equally, in some cases like the patient in Figure 21, the surgical release was performed at the same time as the first laser treatment. Aside from the previously mentioned demographics, burn and scar related aspects, patients' individual professional and personal circumstances will require an individually tailored treatment approach. Thus, there is and should not be one standard treatment and nor guideline of how many treatments are necessary at what time, but rather the recommendation that AFL-CO_2 and small surgical reconstructive procedures act symbiotically and complement each other. Such a combined approach allows for all aspects of burn scars to be addressed holistically with minimal morbidity, quick rehabilitation and minimal time off work.

6.4.3. Preparation of the scar-tissue

Whilst surgery is very effective in restoring range of motion, it has previously been shown that AFR can address other aspects of a hypertrophic burn scar such as symptoms, thickness, function, and quality of life [40, 103, 135].

Tension is the prerequisite for the evolution of pathological scarring and post burn deformities. Normal body contours are distorted due to this tension which draws the attention to the injured site [93]. The extent of the existing tension within a scar often only becomes evident, once a surgical release is performed and one single incision leads to the unfurling of a significant skin defect.

In the early phases of wound healing of immature scars, this tension is believed to contribute significantly to the hyper-vascular, inflamed, painful and itchy nature of young burn scars [93]. Thus by releasing tension, a scar has the opportunity to respond naturally by softening and flattening and mature as well as possible [93].

In mature scars, if chronic tension has persisted over some time, the resulting ischemia and fragile epidermal layer leads to chronic wound breakdown and the so-called unstable scars. The elimination of tension as well as an improvement of vascularisation leads to a healing of these chronic wounds and transforming mature unstable scars into healed more pliable and better perfused scars.

Conclusively, the elimination of tension as well as an improvement in vascularisation appears to be the key to optimally prepare a burn scar for subsequent surgery. AFL-CO_2 achieves this release of tension with subsequent scar flattening most-likely through two mechanisms: Firstly, by vaporising hundreds of small little tissue columns in the scar, an immediate, but temporary mechanical release takes place which is often noted by the patients immediately postoperatively. In a second step, the induced remodelling process and change of collagen type results in an overall decrease in tension [127]. Gong et al. showed that CO2-AFR can lead to a decrease in vascularisation in immature scars and an increase in vascularisation in mature scars [42]. By improving the vascularisation, pliability and thickness of the scar, the overall skin/scar quality is enhanced, so that optimal conditions can be created for good flap take, wound healing, and reducing tension around the surgical field (Figure 26).

The limitation of Z-plasties or other local tissue rearrangements alone, is often a shift of tension resulting in a recurrence of the contracture and was thus often not a first-line therapy in burn scar contracture prior to the introduction of AFL-CO_2. However, the described benefits of AFR allow the surgeon to fall back on these simple local tissue rearrangements by optimising the overall scar quality and achieving a good condition for flap take.

Figure 26. Reduction of tension turns unstable scar into stable scar.
19yo male chef, 18month post 4% TBSA hot oil burn to anterior ankle before and 6 weeks after one treatment with AFL-CO_2. Before the treatment this patient suffered from chronic wound breakdown of the scar on the dorsum of his foot and was not able to wear his work-boots. One treatment with the AFL-CO_2 has led to a reduction in tension and improved vascularization with subsequent healing of the chronic wound.

6.4.4. The power of Z-plasties

In a Z-plasty, the central limb along the line of greatest tension gains length, by medial transposition of the lateral flaps. This transposition results in a reduction of the longitudinal tension and a decrease in scar width [22]. Transposing a local flap of healthy skin into the area of greatest tension is obviously ideal for an optimal outcome. However, if the contracture band lies within scarred tissue, and if a Z-plasty is used as a single modality, wound breakdown/dehiscence, wound infection and a shift of tension occurs quite frequently due to the poor quality and vascularization of the scar. In these cases, fractional resurfacing can dramatically improve flap survival and avoid a shift of tension due to a more global release of the tissues.

When designing the Z-plasties or any other surgical reconstructive procedure, it is of utmost importance to differentiate if the contracture is intrinsic or extrinsic. Intrinsic contractures occur if there is a shortage of tissue in the affected location leading to a distortion of that respective area. Extrinsic contractures, however, result if there is a shortage of tissue distant from the affected contracture site [93]. Thus, a precise diagnosis is essential and contractures must be assessed with care to ensure treatment of the underlying cause of contractures so that healthy skin remains intact and additional scars can be prevented [93].

If the common adverse effects of Z-plasties and other local tissue rearrangements (wound healing issues, recurrence, etc.) are optimized, these procedures are of great value. The flaps are raised from the same or adjacent anatomical area with close matching of color and quality, there is no donor-site morbidity, there is minimal morbidity associated with it and more extensive reconstructive procedures are still possible.

6.5. Illustrative cases supporting the proposed hypotheses

Figures 27. Before and after combined approach (AFL-CO$_2$ with Z-plasties)
A./C. 37yo male of Middle Eastern background and Fitzpatrick skin type 3, 9.5 years following a 48% TBSA flame burn injury with hypertrophic, pruritic, contracted scars. **B./D**. Same patient after 2 treatment cycles with the AFL-CO$_2$ and laser facilitated steroid infiltration.

E. Same patient during his procedure undergoing a contracture release with 2 Z-plasties simultaneously with his 3rd treatment cycle of AFL-CO_2. This procedure is performed as a day-only surgery. The patient who has an office job went back to work after 3days.

F/H. Before treatment. **G/I**. 3 years later and almost 6month after 4x AFL-CO_2 with laser facilitated steroid infiltration & simultaneously performed Z-plasties during his 3rd laser treatment. The lateral views of his face illustrate a good jawline with no webbing.

Figures 28. Before and after combined approach (AFL-CO_2 with Z-plasties)
A.76yo female, 1year post 14.5% TBSA flame burn injury. **B.** Same patient, 18months later and 2months post 3 treatment cycles of AFL-CO_2 and laser facilitated steroid infiltration, of which the 2nd and 3rd laser procedure was combined with small simultaneously performed Z-plasties. All of these procedures were performed as a day-only surgery. Due to multiple co-morbidities and unwillingness to spend more time in the hospital, she would not have been a candidate for any larger reconstructive procedure and was able to have her contracture released with minimal morbidity and without interrupting her daily routine.

By improving vascularisation, pliability and thickness of the scar, the overall skin/scar quality is enhanced, so that optimal conditions can be created for good flap take, wound healing, and reducing tension around the surgical field. In the illustrated case (Figure 27), if simple Z-plasties were to be used as a single modality, a shift of tension would have most likely occurred. Thus, without the option of AFL-CO_2, Z-plasties may not have been our primary reconstructive approach. AFR allows the surgeon to fall back on these simple local tissue rearrangements by optimising the overall scar quality and achieving a good condition for flap take.

Donelan et al. previously described that pulsed dye laser therapy and Z-plasties are an effective alternative to burn scar excision [44]. Our experience confirms that small surgical tissue rearrangements such as Z-plasties combined with AFL-CO_2 and laser facilitated infiltration with corticosteroids act synergistically, providing a holistic and modern approach for burn scar reconstruction. Rearranging tissue locally requires no donor-sites, is autologous, contains tissue of natural origin and is hence the best material to work with. Modern technologies, such as AFR should be combined with surgical techniques to treat a scar holistically and with minimal morbidity. Further, treatment with the AFL-CO_2 can effectively be utilized to “pre-treat” a surgical area and create an optimal ground for more complex reconstructive surgery, hence minimizing the extent of a reconstructive procedure. Considering these positive results, we may need to focus on refining these simple techniques of surgical local tissue rearrangements in an attempt to empower the body's capabilities of restoring itself by reducing tension locally.

A combined approach of local tissue rearrangement together with ablative fractional CO2 laser represents an elegant reconstructive approach and alternative to burn scar excision. It enables the surgeon to address the scars more holistically, avoids donor-sites, and allows for earlier scar treatment. The extent of reconstructive surgical procedures and the length of stay at the hospital for elective reconstructive procedures might be reduced. Hence, good results can be achieved by empowering a local restoration process with minimal morbidity and great patient satisfaction.

6.6. Multimodal therapy for burn scars

Over the past 15 years, AFR-CO_2 has become more and more appreciated by clinicians as well as patients as one of the most revolutionary treatment modalities for hypertrophic burn scars because it's potential to holistically address various aspects within the burn scar. In particular if used in a multimodal setting, AFR has the potential to avoid or decrease the extent of the required reconstructive procedure, with reduced morbidity, accelerated rehabilitation, social as well as workplace-reintegration and enhanced overall outcomes (see Chapter 4).

Due to the capacity to improve various aspects of the burn scar and the ability to treat a relatively large body surface area, AFR-CO_2 with or without surgical reconstructive procedures is becoming the main component of a multimodal therapeutical approach.

As discussed in Chapter 2.2.3., LADD of corticosteroids and 5-fluorouracil is an integral component and goes hand-in-hand with AFR to further improve pliability and decrease thickness of hypertrophic scars [137, 144].

Another essential component of a multimodal therapeutic approach is occupational therapy (compression, silicone, physiotherapy, and massaging). In immature scars, pressure garments, silicone products and physiotherapy should always be continued throughout the course of AFR-CO_2 treatment. AFR induces an improvement in vascularization, namely a decrease of vascularization in immature scar, and an increase of vasculature in mature scars [198]. Thus, together with the induced tissue remodelling and rearrangement within the scar, even a mature scar will benefit from concomitant conventional occupational therapy (pressure garments, silicone products, etc.).

Erythema and dyschromia can be addressed with other lasers in addition to AFL-CO_2. Whilst AFL-CO_2 can improve the vasculature within the scar, vascular lasers are an effective addition to reduce erythema and associated symptoms (pruritus and neuropathic pain). PDL lasers have probably been the most extensively described vascular laser in the literature for burn scars. PDL decreases hypervascularity by selective photo-thermolysis of blood vessels [225]. Excessive collagen deposition is prevented by targeted vascular destruction which leads to tissue hypoxia, collagen fibre heating and catabolism, which ultimately results in collagen realignment and remodelling [5, 115, 226]. To work synergistically, both AFL-CO_2 and the vascular laser can safely be combined during the same procedure [5, 91].

The same applies for scars with hyperpigmentation, which can be simultaneously treated by laser targeting melanin (e.g., nanosecond-domain Q-switched Nd:YAG or Alexandrite lasers). In some cases, AFL-CO_2, if used in a superficial mode, can also effectively treat superficial hyperpigmentation. In addition, compound creams including Hydroquinone, Corticosteroids and Retinoids (Vit A) can be used prior or after the laser treatments. Hypopigmentation can be addressed by AFL- CO_2 with or without the addition of LADD of bimathoprost 0.03% (not TGA approved).

Vascular lasers, lasers targeting melanin, AFL-CO_2 including LADD of corticosteroids can all be used during the same treatment session or with intervals [5]. However, to avoid too much heat, it is probably safer and more efficient to either use a vascular laser or a laser targeting melanin together with the AFR instead of all three laser modalities at once.

In conclusion, a multimodal therapy tailored to each patient and scar provides the most effective overall outcome. The choices are wide with vascular lasers and AFL-CO_2 for erythema, pruritus and neuropathic pain; lasers targeting melanin, AFL-CO_2 and compound creams for hyperpigmentation; AFL-CO_2 and LADD of medication for hypopigmented scars; AFL-CO_2 with or without surgical procedures for hypertrophic scars to release tension; occupational therapy (pressure, silicone, massaging, and physiotherapy) for all scars. All these therapies can be combined and used simultaneously or with intervals to achieve an optimal result with high patient satisfaction.

6.7. Conclusion

Scarring and fibrosis are an enormously large disease burden, which has been estimated to account for up to 45% of all chronic diseases in the western world [227].

Wound contraction and scarring is part of the regular healing process [14]. Contraction leads to tension, a prerequisite for the development of hypertrophic, erythematous, painful and pruritic scars [93]. However, even if the scar does not become hypertrophic, nor erythematous or painful, the contracting element or embryological factors yet unknown, may lead to the development of pathological scars, causing an extrinsic contracture depending on the anatomical location following the principles of functional kinetics. These type of scar contractures may lead to ectropia or limit the patient's range of motion. With this, patients suffer not only from the burden of the stigma, but moreover from pruritus, neuropathic pain, and compromised skin functions such as sweating and thermal regulation, resulting in heat intolerance. Psychological consequences, post-traumatic stress and depression are further sequelae of the burn injury [228]. These emotional scars from the initial injury and the subsequent challenging recovery time, demand for simple solutions with minimal morbidity when aiming to help burn survivors achieve improved quality of life. The complexity of these treatment requirements has become even more relevant with the advances in burn care and associated increased survival rates [40].

As outlined in this thesis, it is the nature, clinical efficacy, and minimal invasiveness of AFL-CO_2 which makes this treatment approach very attractive for patients and surgeons alike. From a clinical point of view the morbidity associated with this procedure is minimal compared to other reconstructive procedures. Most conventional reconstructive procedures are associated with admissions to hospital, general anaesthetics, time off work and a sometimes, prolonged rehabilitative phase, whereas as documented in the present thesis, treatments with AFL-CO_2 can often occur as outpatients or with a substantially reduced length of stay. Whilst much remains to be learned about the optimal AFL-CO_2 settings, treatment intervals, the timing of treatment and how best utilise the laser and combine it with reconstructive procedures, the present thesis provides a framework to better understand its position in the reconstructive ladder of burns surgery.

The implementation of AFL-CO_2 into the routine burn scar management at the CRGH Burns Unit has altered the approach of managing burn scars. The utilization of advances in modern technology and a profound understanding of burn wound healing and scarring allows the surgeon to stimulate the body’s own ability to heal and remodel itself and address the scar burden at its origin, rather than excising or releasing the affected area according to old treatment paradigms. An increase in patient satisfaction can be observed, an increasing demand for this type of treatment witnessed, and as a result, a reduction in the need of traditional more complex surgical reconstructive procedures has been documented.

Despite these advances and encouraging results, laser resurfacing does not replace conventional reconstructive surgery, occupational therapy and physiotherapy, but these approaches may work synergistically and holistically in the rehabilitative phase of a burn survivor to achieve better outcomes not previously achievable.

However, what the application of AFL-CO_2 has uncovered is more profound. Through the utilization of AFR it has become apparent, that a single approach is not enough to address a burn scar. Instead, a multimodal approach should be chosen with treatments being tailored to each individual patient, resulting in varying settings, approaches, combinations with other modalities according to patient needs, scarring potential, ethnicity, skin type, scar location and maturity. As simple as this sounds, tailoring the approaches to each individual, rather than addressing one type of scar with one type of treatment, remains the key to a successful outcome and yields optimal patient satisfaction.

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Appendix A: Ablative fractional CO2 laser for burn scar reconstruction: An extensive subjective and objective short-term outcome analysis of a prospective treatment cohort

Issler-Fisher AC, Fisher OM, Smialkowski AO, Li F, van Schalkwyk CP, Haertsch P, Maitz PK. Burns. 2017 May;43(3):573-582.doi:10.1016/j.burns.2016.09.01 4. Epub 2016 Oct 1

BURNS 43 (2017) 573–582

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns

Ablative fractional CO_2 laser for burn scar reconstruction: An extensive subjective and objective short-term outcome analysis of a prospective treatment cohort

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ARTICLE INFO

Article history:
Accepted 13 September 2016

Keywords:
Ablative fractional CO_2 laser
Ablative fractional laser resurfacing
Burn scar reconstruction
Scar resurfacing
Subjective and objective outcome
Quality of life

ABSTRACT

Background: The introduction of ablative fractional CO_2 lasers (CO_2-AFL) for burn scar management shows promising results. Whilst recent studies have focused on objective scar outcomes following CO_2-AFL treatment, to date no data on patient subjective factors such as quality of life are available.

Methods: A prospective study was initiated to analyze the safety and efficacy of the CO_2-AFL. Various objective and subjective outcome parameters were prospectively collected from the date of first consultation and follow-up following treatment. Objective factors include the Vancouver Scar Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS), and ultrasound measurements of the thickness of the scar. Subjective parameters included the assessment of neuropathic pain and pruritus, as well as the evaluation of improvement of quality of life following CO_2-AFL with the Burns Specific Health Scale (BSHS-B). For treatment effect analysis, patients were stratified according to scar maturation status ($>$ or $<$2 years after injury).

Results: 47 patients with 118 burn scars completed at least one treatment cycle. At a median of 55 days (IQR 32–74) after CO_2-AFL treatment all analyzed objective parameters decreased significantly: intra-patient normalized scar thickness decreased from a median of 2.4 mm to 1.9 mm ($p < 0.001$) with a concomitant VSS-drop from a median of 7 to 6 ($p < 0.001$). The overall POSAS patient scale decreased from a median of 9 to 5 ($p < 0.001$) with similar effects documented in POSAS observer scales. Both pain and pruritus showed significant reduction. Quality of life increased significantly by 15 points (median 120 to 135; $p < 0.001$). All of the identified changes following CO_2-AFL were equally significant irrespective of scar maturation status.

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http://dx.doi.org/10.1016/j.burns.2016.09.014

Conclusion: Our preliminary results confirm significant improvement in thickness, texture, colour, and symptoms following treatment with CO_2-AFL. Foremost, quality of life of patients with both immature and mature scars (up to 23 years after injury) improved significantly after just one treatment session. To our knowledge, this is the first study to document such holistic treatment effects in burn patients treated by CO_2-AFL.

1. Introduction

Scarring remains a major clinical outcome of severe burn wound healing. Despite assiduous efforts in traditional scar management, severe scars often persist to significantly diminish quality of life by disfigurement, pain, itchiness, and by contractures restraining the motion of body and joints [1]. Various non-surgical therapeutic options for improving scars have been assessed and implemented into the daily practice to improve burn scar management, ranging from physical therapy, compression, local medical therapy to different types of laser treatments [2]. Surgery remains the main therapeutic approach for contracted scars and aims to relieve tension ultimately improving the range of motion of affected areas [3]. Although highly effective, surgical treatment is associated with considerable morbidity, high recurrence rates and the efficacy limited to the surgical site [2]. In the last decade, laser therapy has become a more and more popular treatment modality for severe burn scars, particularly the use of ablative fractional CO_2 lasers (CO_2-AFL) [2,4]. Several case series, and before and after studies revealed substantial improvement of cosmetic and functional outcome of this novel treatment modality [4–7]. However, besides the scarcity of a well-designed randomized controlled trial, there is also a lack of evidence about the ultimate outcome of a burn survivor, namely their quality of life following this novel treatment. It is important to recall what burn patients are confronted with, once their wounds are closed, and what then dictates their quality of life: Scars remain as a permanent reminder of the damage that occurred and with improvements in the management of burn patients and the herewith associated improved survival rates, these scars can create significant morbidity. Besides the obvious stigma, patients often suffer from severe pruritus, neuropathic pain, and contractures [4,8], which may have detrimental physical, aesthetic, and social consequences associated with substantial financial costs for modern health-care systems.

The so far largest study on laser therapy for hypertrophic burn scars was published in 2014 in Annals of Surgery by Hultman et al. [4] revealing substantial improvement of signs and symptoms of hypertrophic scars. However, this before and after cohort included treatment with multiple different lasers and did not focus on the CO_2-AFL. Further, there was a lack in objective metric measures, such as scar thickness documented by ultrasound as well as an assessment of the effect on patients' quality of life (QOL).

For this reason, a large prospective before and after study was initiated at the Burns Unit of Concord Repatriation General Hospital (CRGH) in Sydney, Australia, assessing various subjective and objective parameters, including standardized measurement of the scar thickness by ultrasound and QOL, in an attempt to provide a holistic picture of burn patient outcomes following treatment with CO_2-AFL.

2. Materials and methods

2.1. Study setting and patient population

Following approval from the Sydney Local Health District Human Research Ethics Committee, a prospective study was initiated at the Burns Unit of Concord Repatriation General Hospital (CRHG) in Sydney, Australia, a 450-bed tertiary referral facility for burn patients and a teaching hospital of the University of Sydney. The Burns Unit (BU) of CRGH is a statewide referral unit for burns patients and comprises a high-volume Burns Outpatient Clinic. From December 2014 until February 2016 data was prospectively collected from all burn patients with severe scars treated with the CO_2-AFL. Inclusion criteria involved patients aged 16–80 years, being able to provide informed consent, and with burn scars comprising structural changes (atrophic, hypertrophic, keloid scars). Exclusion criteria involved impairing psychiatric or medical co-morbidity prohibiting the provision of informed consent, adherence to the treatment regimen, tolerance of general anaesthesia or data collection. To be included in the quantitative analysis, patients had to have completed one first treatment with the CO_2-AFL and at least one first follow-up. To evaluate the impact of natural scar maturation on outcome parameters, the patient cohort was further split into two groups. One group consisted of patients with young, immature scars, who presented for their first treatment less than 2 years following the burn/last operation. The second group comprised of patients with mature scars having their initial treatment more than 2 years after the burn/last operation.

2.2. Treatment protocol

All procedures were performed in the dedicated burns theatre within the Burns Unit of CRGH, approved by the local laser safety committee. Patients underwent treatment with the fractional ablative, 10,600-nm wavelength CO_2 Ultrapulse® laser (by Lumenis) including ActiveFX and DeepFx hand pieces with or without other surgical reconstructive procedures (e.g. scar release with Z-plasties). All procedures were conducted with an anaesthetist present under local anaesthetic with or without sedation, or under general anaesthesia where appropriate. For hypertrophic scars, laser treatment was immediately followed by laser facilitated drug delivery of corticosteroids (Kenacort A10 or A40) topically or intralesionally injected. Wound care after laser therapy included application of topical Vaseline for 7–10 days. Patients were allowed to wear their pressure garments again after 3 days or once their wounds were fully epithelialized if these were still being used.

2.3. *Data collection, treatment and follow-up protocol*

At the date of enrolment patient's demographics, including skin type according the Fitzpatrick Scale [9,10], and ethical background, as well as information about the burn itself were documented. As a prospective study, various subjective and objective outcome parameters are collected at the date of enrolment to assess patients' baseline status, at follow-up 4–6 weeks after each treatment cycle, and at 12 months after final laser therapy. Importantly however, to assess the immediate impact of CO_2-AFL, the data presented here only includes results after one single treatment session.

2.4. *Objective outcome measures*

All scars were assessed with the Vancouver Scar Scale (VSS) [11] and the Patient and Observer Scar Assessment Score (POSAS) [12]. The VSS comprises 4 domains: vascularity (0-3 points), pliability (0-5 points), pigmentation (0-2 points), and height (0-3 points) with a maximal score of 13 [11]. The POSAS consists of two parts: a Patient Scale and an Observer Scale. Both scores contain six items, scored numerically on a ten-step scale. The total score of the Patient and Observer Scale results from tallying the scores of each of the six items, and thus ranges from 6 to 60, respectively. Added to that, patients and observers rate their general overall opinion of the scar quality ranging from 1 (normal skin) to 10 (worst imaginable scar) (www.posas.org & [12]).

For ultrasound measurements, each scar was mapped out with a drawing and was always measured at the same position of the thickest area of the scar. The adjacent thickness of the uninjured skin was also measured, so that the thickness of each scar could be normalized to each patient.

2.5. *Subjective outcome measures*

All scars were assessed by the patients with the Patient Scar Assessment Score of the Patient and Observer Scar Assessment Score (POSAS) [12]. Further subjective outcome parameters included questionnaires about pain using the Douleur Neuropathique 4 Questions (DN4) [13], pruritus using a modified 5-D itch scale (4-D Pruritus Scale) [14], and QOL using the Burns Specific Health Scale – Brief (BSHS-B) [15]. The DN4 questionnaire was developed to explore both sensory descriptors as well as signs related to a bedside examination. The total score is the tally of 10 items, with a cut-off value of 4/10 required for the diagnosis of neuropathic pain [13]. The 5-D Pruritus Scale is a multidimensional questionnaire that was designed to capture outcomes in clinical trials. The original description of the score includes duration, degree, direction, disability and distribution. The latter aspect was excluded in our study as the location of pruritus is given by the site of the scar. Thus, our modified 4D Pruritus Score (containing duration, degree, direction and disability) ranges from a minimum score of 7 (no itch) to 35 (worst itch). The BSHS-B is an outcome scale designed for burn patients, containing important aspects of distress. It includes 40 questions within 9 well defined fields (simple abilities, hand function, affect, body image, interpersonal relationship, sexuality, heat sensitivity, treatment regimens, and work). The maximal amount of points is 160, which is equal a normal QOL. This means the higher the number, the better the QOL [15]. Finally, as a summary subjective assessment, at each follow-up patients rated their overall improvement since the last treatment as "worse", "unchanged", "improved a little bit", "improved quite a bit," and "improved extremely".

2.6. *Statistical analysis*

Only patients with complete follow-up data were analyzed, meaning that in certain instances the number of patients and scars analyzed may be different from the total cohort. Therefore, the total number of patients and scars contributing to the results of subjective/objective outcomes is clearly denoted. Quantitative quality of life data analysis was also performed on those with complete data in each domain, with a subgroup analysis accomplished on only those patients showing abnormal baseline scores or those displaying changes in scores following laser treatment. Continuous variables were compared using Student's t-test, Wilcoxon rank sum test, one-way analysis of variance (ANOVA) and the Kruskal–Wallis test where appropriate. Where necessary, log2 transformation of continuous data was performed to achieve normal distribution for these analyses. Differences between proportions derived from categorical data were analyzed using Pearson's chi-squared test or Fisher's exact test where appropriate. Data are presented as median with interquartile range (IQR) unless denoted otherwise. For quality of life data visualization, a heat map was constructed following the development of a matrix, which annotated whether or not there had been a change in the analyzed quality of life domain. Improvements were coded as +1, no changes as 0 and score reductions as -1 for each individual patient and domain to allow for uniform visualization across domains, regardless if baseline scores were abnormal or not and also irrespective of the magnitude of postoperative changes. To explore possible interrelationships of domains, hierarchical clustering was performed using complete agglomeration and Euclidean distance metrics. All *p*-values ≤ 0.05 were regarded as statistically significant and all statistical analyses were performed using R Statistical Packages [16].

3. Results

3.1. *Patient demographics & burn mechanism*

During the study period all patients presenting in the CRGH scar clinic were evaluated for laser treatment. Of these, one patient was excluded of a psychiatric co-morbidity which would have impaired adherence to the treatment protocol and data collection. All other patients were included in this study. So far 78 patients with 174 scars (median of 2 scars/patient [IQR 1–6]) have been prospectively recruited to this study and so far no patient is lost to follow-up. Of these 78 patients, 47 patients with 118 scars have completed at least one treatment and one follow-up with the CO_2-AFL. A summary of these patients' demographic features is provided in Table 1.

All the scars included, presented with structural changes (hypertrophic, atrophic, cobble-stone appearance, contractures, etc.). Thirteen percent ($n = 6$) underwent a combined surgical reconstructive procedure, such as contracture release with Z-plasties, which was simultaneously performed during the same procedure together with the laser treatment.

3.2. *Treatment with the CO_2-AFL & Follow-Up*

47 patients with 118 scars completed a first treatment and a first follow-up. Treatment with the CO_2-AFL was initiated after a median of 17.9 months (IQR 10.9–43.1 months) after burn and a median of 14.8 months (IQR 8.8–19.0 months) after the last operation (debridement and skin graft or xenograft). 18 of the patients who completed one treatment cycle (38%) were treated under local anaesthetic with or without sedation, and 29 patients (62%) underwent a full general anaesthesia. Forty-two (89%) of the cases were simultaneously treated with laser facilitated steroid infiltration. Median time to first follow-up was 55 days (IQR 32–74) following first treatment with the CO_2-AFL. No patient suffered a wound infection following laser treatment.

3.3. *Objective outcomes–scar thickness, VSS and POSAS-O*

At first follow-up, the normalized scar thickness, as assessed by standardized ultrasound, decreased from a median of 2.4 mm (IQR 1.8–3.1) to 1.9 mm (IQR 1.4–2.8; $p < 0.001$, 32 patients, 82 scars; Fig. 1A). Equally, the VSS (maximal score: 13) dropped significantly from a median of 7.0 (IQR 6.3–8.8) to 6.0 (IQR 4.3–7.0; $p < 0.001$, 47 patients, 118 scars, Fig. 1B). The same applied to the Observer Scar Assessment Score of the POSAS (POSAS-O; maximal score 60), which decreased from a median of 29.0 (IQR 24.0–33.0) to 21.0 (IQR 18.0–25.0; $p < 0.001$, 47 patients, 118 scars), and the overall POSAS-O (maximal score 10) which decreased from 5.0 (IQR 4.0–6.3) to 4.0 (IQR 3.0–4.3; $p < 0.001$, 46 patients, 116 scars; Table 2).

3.4. *Subjective outcomes – POSAS-P, neuropathic pain, pruritus*

Subjectively, the Patient Score of the POSAS (POSAS-P, maximal score 60) dropped significantly from a median of 36.0 (IQR 27.0–42.0) at initial assessment to a median of 23.0 (IQR 17.0–32.0; $p < 0.001$) following one treatment with CO_2-AFL. Equally, the overall POSAS-P score (maximal score 10) improved by 4 points from 9.0 (IRQ 8.0–10.0) to 5.0 (IRQ 4.0–8.0; $p < 0.001$, Table 2).

Neuropathic pain as assessed by the DN4 Pain Questionnaire (maximum 10 points) decreased from a median of 3.0 (IQR 1.0–6.0) to 2.0 (IQR 0.0–5.0; $p < 0.001$, Fig. 1C).

Table 1 – Patient's demographics and burn mechanisms (patients $n = 47$; scars = 118).

Variable	Number (n)	Percentage (%)
Gender		
Male	13	28
Female	34	72
Age	34 years (IQR 24.5–48.0)	
Smoker	5	10.6
Co-morbidities		
Cardiac	1	2.1
Vascular	0	0
Pulmonal	2	4.2
Diabetes mellitus	2	4.2
Neurological	4	8.5
Psychiatric	3	6.4
Substance abuse	0	0
Other	7	14.9
Ethnical background		
Anglo-Saxon/Celtic	27	57.4
South East Asian	6	12.8
South Central Asian	1	2.1
North East Asian	3	6.4
South East European	2	4.3
North African/Middle Eastern	3	6.4
South American	1	2.1
Maori Pacific Islander	3	6.4
Australian Aboriginal	1	2.1
Fitzpatrick skin type		
Type 1	2	4.2
Type 2	11	23.4
Type 3	23	48.9
Type 4	6	12.8
Type 5	5	10.6
Type 6	0	9
Burn mechanism		
Flame	24	51.1
Scald	8	17.0
Contact	3	6.4
Hot oil	5	10.6
Explosion	3	6.4
Other	4	8.5
TBSA	15% (IQR 5–36.3%)	
Scar location		
Face	9	7.6
Neck	8	6.8
Chest	3	2.5
Abdomen/Flank	1	0.8
Shoulder	2	1.7
Upper limb	14	11.9
Lower limb	7	5.9
Burn wound treatment		
Skin graft	19	40.4
Re-graft	4	8.5
Xenograft	11	23.4
Conservative	7	14.9
Other	6	12.8
Prolonged wound healing (>3 wk)	17	14.4
Burn wound infection receiving antimicrobial treatment	5	4.2

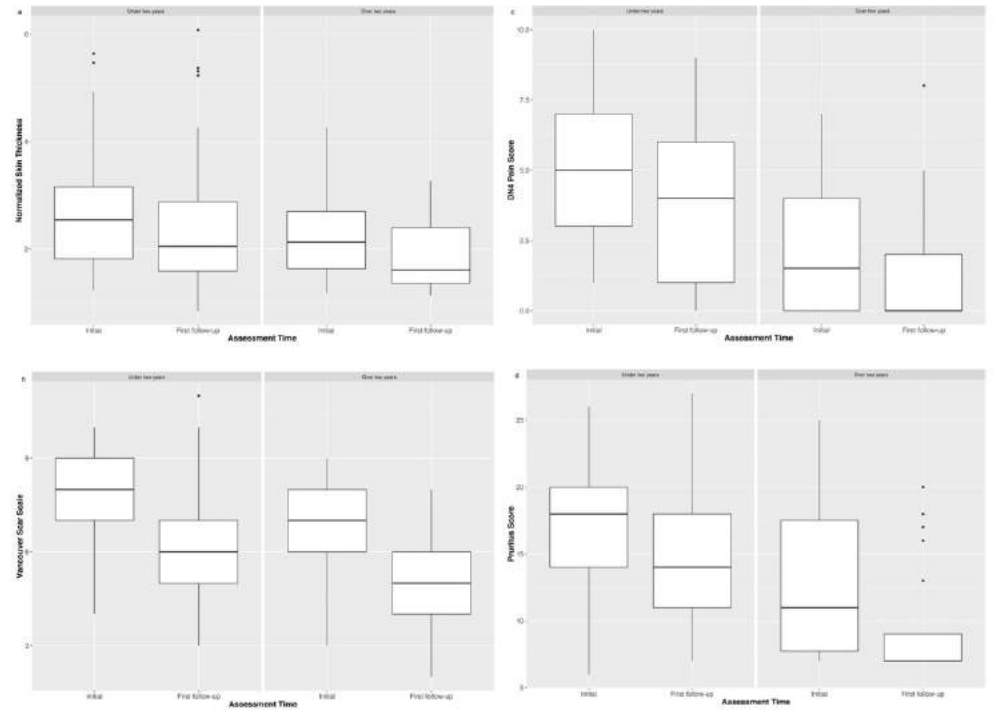

Fig. 1 – The effect of CO_2-AFL on subjective and objective aspects of burn scars before and 6 weeks after the first treatment session. For each outcome parameter: the left panel of box-plots illustrates results of patients with immature scars (under two years since injury) and the right of patients with mature scars (over two years since injury). (A) Effects on the normalized scar thickness assessed by ultrasound. (B) Effects on the Vancouver Scar Scale (VSS). (C) Effects on pain assessed by the Douleur Neuropathique 4 Questions (DN4). (D) Effects on pruritus assessed by the modified 5-D itch scale (4-D Pruritus Scale). Improvements are statistically significant following just one treatment session in both cohorts (immature and mature scars) for all evaluated outcome parameters.

Concurrently, the modified 4D Pruritus Score (maximal score 35) also dropped by 2.5 points from 16.0 (IQR 9.8–20.0) to 13.5 (IQR 7.0–18.0; $p < 0.001$) following one single treatment with the CO_2-AFL (Fig. 1D).

3.5. *Quality of life*

A summary of changes in quality of life are presented in Table 3 and Fig. 2. Thirty-three patients (81%) showed an improvement, 7 (17%) a reduction and 1 (2%) no change in overall quality of life scores following one treatment with the CO_2-AFL. For the total cohort, overall QOL increased by 16 points from a median of 120 (IQR 110–139) at baseline to a median of 136 (IQR 104–149; $p < 0.001$) at first follow-up. The domains showing the most consistent improvements following AFL-CO_2 were treatment regimens (63% improved, 12% decreased, 24% unchanged) and body image (49% improved, 17% decreased, 34% unchanged). Intriguingly, heat sensitivity also showed consistent improvement following laser treatment (54% improved, 20% decreased, 27% unchanged).

For patients displaying abnormal baseline scores or changes in scores following treatment with the CO_2-AFL the following quality of life domains improved significantly: simple abilities, hand function, body image, heat sensitivity, treatment regimen, work. Sexuality, interpersonal relationships and affect did not show any statistically significant changes following laser treatment.

3.6. *Overall improvement*

When the patients were asked at their first follow up if they feel that their scar improved, 5 (11%) said "extremely", 16 (34%) "quite a bit", 20 (43%) "a little bit" and 6 (13%) said that they thought the treated area was "unchanged". Despite some of the quality of life domains showing reduction in scores,

Table 2 – Comparison of objective and subjective outcome parameters when stratifying patient cohort according to scar maturation status.

Outcome measure (score units and range)	Total cohort Pre-treatment score → Post-treatment score[a]	Immature scars (<2 year after injury/surgery) Pre-treatment score → Post-treatment score[a]	Mature scars (>2 year after injury/surgery) Pre-treatment score → Post-treatment score[a]
Ultrasound measured thickness *(mm)*			
Total $n = 32$ patients	2.4 (1.8–3.1) → 1.9 (1.4–2.8)	2.5 (1.8–3.2) → 2.0 (1.6–2.9)	2.1 (1.6–2.7) → 1.6 (1.4–2.4)
26 immature, 56 mature scars	$p < 0.001$	$p = 0.002$	$p = 0.001$
VSS *(0–13)*			
Total $n = 47$ patients	7.0 (6.3–8.8) → 6.0 (4.3–7.0)	8.0 (7.0–9.0) → 6.0 (5.0–7.0)	7.0 (6.0–8.0) → 5.0 (4.0–6.0)
76 immature, 42 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
POSAS-O *(0–60)*			
Total $n = 47$ patients	29.0 (24.0–33.0) → 21.0 (18.0–25.0)	29.0 (24.0–34.3) → 21.0 (18.0–25.0)	29.0 (24.0–31.8) → 21.0 (16.5–25.8)
76 immature, 42 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
POSAS-O overall *(0–10)*			
Total $n = 46$ patients	5.0 (4.0–6.3) → 4.0 (3.0–4.3)	5.0 (4.0–7.0) → 4.0 (3.0–5.0)	5.0 (4.0–6.0) → 3.5 (3.0–4.0)
76 immature, 40 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
POSAS-P *(0–60)*			
Total $n = 45$ patients	36.0 (27.0–42.0) → 23.0 (17.0–32.0)	37.0 (30.0–49.0) → 26.0 (21.0–35.0)	30.0 (19.8–38.0) → 20.5 (15.0–26.3)
69 immature, 40 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
POSAS-P overall *(0–10)*			
Total $n = 46$ patients	9.0 (8.0–10.0) → 5.0 (4.0–8.0)	9.0 (9.0–10.0) → 7.0 (4.0–8.0)	8.0 (4.8–10.0) → 5.0 (3.8–7.0)
71 immature, 40 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
DN4-Pain Questionnaire *(0–10)*			
Total $n = 42$ patients	3.0 (1.0–6.0) → 2.0 (0.0–5.0)	5.0 (3.0–7.0) → 4.0 (1.0–6.0)	1.5 (0.0–4.0) → 0.0 (0.0–2.0)
69 immature, 36 mature scars	$p < 0.001$	$p < 0.001$	$p = 0.02$
Modified D4 Pruritus Questionnaire *(7–35)*			
Total $n = 45$ patients	16.0 (11.0–21.0) → 14.0 (8.0–18.0)	18.0 (14.0–20.0) → 14.0 (11.0–19.5)	11.0 (8.0–19.0) → 7.0 (7.0–9.0)
75 immature, 37 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$
BSHS-B Total Score *(0–160)*			
Total $n = 41$ patients	120.0 (109.0–139.0) → 135.0 (104.8–149.0)	122.0 (111.0–139.0) → 128 (103.2–139.0)	117 (98.0–146.0) → 145.0 (105.0–155.0)
74 immature, 31 mature scars	$p < 0.001$	$p < 0.001$	$p < 0.001$

[a] Scores reported as median with interquartile range (IQR) unless denoted otherwise.

none of the patients reported were unsatisfied or unhappy with having undergone laser treatment.

3.7. *Comparison of immature versus mature scars*

To evaluate the impact of natural scar maturation over time, we compared mature scars (>2 years old) vs. immature scars (<2 years) of patients that received CO_2-AFL. As shown in Table 3, all of the identified changes following CO_2-AFL remained significant irrespective of scar maturation status.

4. Discussion

The efficacy of burn scar treatment with AFL has been documented in previous reports [2,4,17,18] and is supported by the present analysis. However, aside from the study by Hultman et al. [4] the available literature on this topic is limited to smaller case series and thus sparse. Furthermore, to our knowledge no previous report exists, that has extensively assessed subjective burn patient outcomes including quality of life.

The exact mechanisms, by which the CO_2-AFL induces these beneficial scar changes remains poorly understood. Histologic analyses have been reported in previous studies, indicating that the unique pattern of fractional laser injury induces a molecular cascade including heat shock proteins and matrix metalloproteinases as well as inflammatory processes that lead to a rapid healing response and prolonged neocollagenesis with subsequent collagen remodelling [18–20]. Ozog et al. reported a significant decrease in type I collagen, and significant increase in type III collagen, together with an improved architectural dermal layer with finer and more fibrillar collagen following treatment with AFL [21]. This might be an explanation for the increased pliability of the treated scars and may explain improvement of the associated clinical scores. In line with previous reports [4,18,21,22], our treatment cohort also revealed a significant decrease in the VSS even after just one treatment session. But, despite the objective nature of these scar assessment measures, there is still quite a substantial subjective component involved in these scores [23]. It has been shown that the accuracy of the estimated thickness in the VSS is only around 67% [24]. Therefore, in contrast to any of the previously published

Table 3 – Quality of life (QOL) rated by the Burns Specific Health Scale – Brief (BSHS-B) of patients who reported a baseline abnormal scores and/or changes in the assessed quality of life score domains.

BSHS-B (score units and range)	Initial assessment[a]	1st Follow-up	*p*-value
Simple abilities *(min 0–max 12)* n = 13 patients, 37 scars	8.0 (8.0–11.0)	11.0 (9.0–12.0)	<0.001
Hand function *(min 0–max 20)* n = 17 patients, 48 scars	16.0 (11.0–19.0)	17.5 (14.0–19.0)	<0.001
Affect *(min 0–28)* n = 32 patients, 78 scars	24.0 (20.00–26.0)	25.5 (18.0–28.0)	0.12
Body image *(min 0–max 16)* n = 41, 105 scars	8.0 (5.0–12.0)	11.0 (4.0–14.0)	<0.001
Interpersonal relationship *(min 0–max 16)* n = 14 patients, 31 scars	15.0 (14.5–15.0)	15.0 (13.0–16.0)	0.26
Sexuality *(min 0–max 12)* n = 18 patients, 42 scars	9.5 (6.0–11.8)	10.0 (6.3–11.0)	0.43
Heat sensitivity *(min 0–max 20)* n = 39 patients, 99 scars	6.0 (2.0–12.0)	10.0 (5.0– 16.0)	<0.001
Treatment regimen *(min 0–max 20)* n = 36 patients, 93 scars	14.0 (11.0–16.0)	17.0 (12.0–19.0)	<0.001
Work *(min 0–max 16)* n = 33 patients, 84 scars	10.0 (7.5–12.0)	12.0 (8.8–16.0)	<0.001
Total score *(min 0–max 160)* n = 41 patients, 105 scars	120.0 (110.0–139.0)	136.0 (104.0–149.0)	<0.001

[a] Scores reported as median with interquartile range (IQR) unless denoted otherwise.

reports, our study includes ultrasound measurements as a standardized and quantifiable assessment tool to provide a more objective evaluation of the scar [23]. Thus, to our knowledge this is the first study documenting a significant decrease in scar thickness as assessed by ultrasound following just one treatment session with CO_2-AFL.

In the present analysis, we also demonstrate a significant improvement for both the patient and the observer portion of the POSAS score after only one treatment with the CO_2-AFL. Very similar improvements have been described by other authors but these have been after 3 to 4 treatment sessions and in smaller series of 7, 8 and 10 patients, respectively [18,20,21]. Nevertheless, these studies also revealed a steeper drop of the score in the patient portion compared to the observer portion of the POSAS [18,20,21]. This may indicate, that patients may feel a more drastic improvement compared to the observer and it has been described that patient's perception and subjective evaluation of their scars is influenced by depressive symptoms [25]. This latter aspect was not formally assessed in the present study, but it is suggested by the poor "affect" domain of the BSHS-S questionnaire in our treatment cohort. Whilst this presents a potential bias of our current analysis, it also indicates the lack of true objective parameters when aiming to capture improvements following scar treatment and the necessity to laboriously include various aspects of burn patient scars and not simply rely on a single questionnaire or measurement.

Patients often reported that an increase in pliability and a decrease in pruritus and neuropathic pain was the most valuable improvement following CO_2-AFL. Especially for patients who live with chronic pruritus and pain for years, a decrease in these symptoms can contribute substantially to improvements in their overall quality of life. According our evaluation with the DN4 Pain Questionnaire, the score reduced to 2.0 across the cohort, which is below the cut-off value for the definition of neuropathic pain [13]. To further objectify this improvement, we are now investigating if CO_2-AFL treatment also has an influence on the prescribed amount and dosage of long term medications, such as pregabalin. Regardless, in support of our findings, Hultman et al. [4] also reported a significant decrease in their UNC4P Scar Scale (which includes the assessment of pruritus, pain, paraesthesia, and pliability) after one single laser treatment, however this burn patient cohort was treated using 4 different types of lasers, thus making it difficult to interpret which laser contributed to improvements to each of the domains.

Finally, the ultimate outcome for patients suffering from injuries that affect such a wide variety of systems, functions and daily activities, is quality of life (QOL). But, more generally health related QOL is recognized as an increasing crucial outcome to capture in medicine and health care [26]. Whilst various QOL scores exist, we chose to record QOL data using a burns-specific health questionnaire, owing to the unique nature of this patient population. Using this, we documented a significant improvement of 15 points after only one treatment session. The domains attributing the most to an improvement in QOL included treatment regimen (63%), heat sensitivity (54%) and body image (49%). Interestingly, the domain "heat sensitivity" showed the lowest single baseline score and starkest improvement of the all of the assessed domains. This finding, that poor heat sensitivity has a substantial negative impact on burn patient's health is well documented [15,27]. Thus, our data indicates that the overall improvement in QOL may be substantially attributed to an improvement in heat

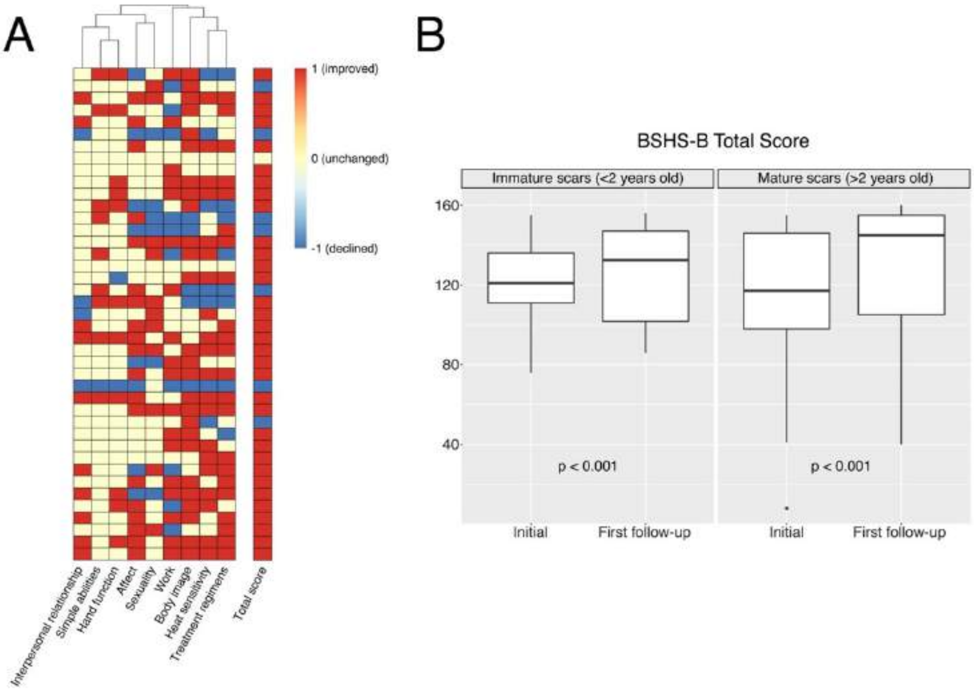

Fig. 2 – Quality of life assessed (QOL) with the Burns Specific Health Scale – Brief (BSHS-B) before and 6 weeks after a first treatment with CO_2-AFL. (A) This figure is a heatmap. Rows represent individual patients and columns each domain that was assessed. Red indicates improvement, yellow no change, blue reduction in scores of the assessed domains. Based on profiles, unsupervised hierarchical clustering was performed to determine, which domains show the most similar changes follow CO_2-AFL and groups are illustrated through the dendrogram on the top. (B) The boxplots demonstrate how the overall QOL score increases significantly after just one treatment with the AFL-CO_2 irrespective of scar maturation status.

sensitivity, an aspect of burn scars that was only very difficult to address. A potential explanation for this could be that AFL induces a beneficial change in vascularization [28], thus improving the scars capacity for heat exchange. Further, an anecdotal series of three patients, which was published in 2011 [29], indicate that patients who presented with hairless scars, had a regrowth or regeneration of hair growth, and regained the ability to sweat following fractionated CO_2 laser therapy. Ito et al. [30] presented the idea that non-hair follicle stem cells in the epidermis could acquire competence to form hair follicles in response to wounding through manipulation of the Wnt signalling pathway. It is possible that a similar mechanism occurred in the patients treated with a fractionated CO_2 laser and thus de novo hair or accessory gland synthesis. Future studies are planned.

Although this study demonstrates substantial improvements in a great variety of subjective and objective outcome measurements, there are legitimate limitations which we and others aim to address in future clinical trials. First of all, more objective metrics should be included such as a 3D wound measurement camera system (for assessment of surface area, texture, volume and colour), a DSM II colorimeter (for colour measurements), a cutometer system (for viscoelastic measurements), or a tewameter (for the measurement of transepidermal water loss), as recommended by a recently published review of objective burn scar measurements [23]. However, there is a lack of an ideal gold standard to validate objective scar measurement devices, and subjective scores can provide a more global assessment of the scar, and allow the measurement of aspects that are currently not captured by objective measurement tools alone [23]. Secondly, it can be argued that the documented positive outcomes might be product of natural scar maturation. But, our first treatment session with the CO_2-AFL was initiated after a median of 19 months after burn and over one year after the last operation. This temporal data suggests that the majority of the treated burn scars were already mature, and hence, there might be little natural progress after more than 1.5 years following burn [31,32]. Furthermore, comparing the immature (<2 years) versus our mature ($\geq$2 years) scars, we could document the same statistically significant changes of the evaluated outcome parameters in both cohorts, thus indicating that the CO_2-AFL induced improvements are scar age independent. Thirdly, contrary to other cohorts, most of our scars were also treated with laser facilitated steroid infiltration immediately following CO_2-AFL. As fractional laser therapy creates precise, uniform columns of tissue vaporization which helps facilitate drug delivery past the epidermal barrier and evenly distribute drugs in the dermal layer. This concept has been shown in several animal models to enhance the bioavailability of topically applied drugs [33–35] and the use of laser assisted infiltration of corticosteroid in scars reported in some case series [36–38]. Nevertheless, it raises the question if our results are a consequence of properly delivered and evenly distributed corticosteroids, or of the laser treatment itself. Whilst our data are overwhelmingly in line with previous reports, we are currently exploring this aspect in a trial at our unit. A further potential limitation and bias of this study is that whilst some patients who had scars in more complex locations such as eyelids, ears, lips and genitals were treated with the CO_2-AFL, our quantitative analysis is not based on the data of the scars in these locations, but on those more amenable to subjective and objective assessment within the same patient. Lastly, by way of design, this study did not include a control group. Whilst ethical considerations may prohibit the fair and effective design of such a study, we acknowledge the need of a randomized controlled trial, using a control group receiving medical and/or occupational therapy only, to ultimately prove the efficacy of this treatment modality compared to conventional burn scar treatment.

5. Conclusion

In summary, this study strongly supports previous reports that burn scars can be dramatically improved in various domains by using the CO_2-AFL for scar management including texture, colour, function and wide variety of symptoms. However, to our knowledge this is the first report that shows that CO_2-AFL treatment induces strong improvements in patient quality of life. Whilst CO_2-AFL does not replace reconstructive surgery, it may well decrease the extent of subsequent surgical procedures, and prepares the scar for an optimal outcome. Furthermore, treatment with the CO_2-AFL provides a novel treatment modality for a holistic scar improvement, which until now has not been available. Finally, the entire rehabilitative process may be enhanced and accelerated by this treatment, which may in turn lead to a faster re-integration in workplace and social life of burn victims and thus presents a milestone in burn patient management.

Financial disclosure

The authors declare that there is no source of financial or other support, or any financial or professional relationships, which may pose a competing interest.

Author contributions

Andrea C. Issler-Fisher	Patient acquisition and treatment, study design, institutional ethics board approval, data acquisition and compilation, data analysis and interpretation, drafting and editing of manuscript following critical review
Oliver M. Fisher	Data & statistical analysis, interpretation and critical manuscript review
Ania O. Smialkowski	Patient treatment, critical manuscript review
Frank Li	Data acquisition, critical manuscript review
Constant P. van Schalkwyk	Patient treatment, critical manuscript review
Peter Haertsch	Patient acquisition and treatment, data interpretation, critical manuscript review
Peter K. M. Maitz	Patient acquisition and treatment, study design, data interpretation, critical manuscript review

Acknowledgements

We wish to thank Sara Seidl and Michelle McSweeney for their assistance with data acquisition. Further, we would like to thank Ana Rodriguez and the Burns Theatre staff for their efforts and assistance.

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Appendix B: Effectiveness and safety of ablative fractional CO_2 laser for the treatment of burn scars: A case-control study.

Issler-Fisher AC, Fisher OM, Haertsch PA, Li Z, Maitz PKM. Burns. 2020 Oct 17:S0305-4179(20)30549-0. doi: 10.1016/j.burns.2020.10.002. Online ahead of print.

JBUR 6254 No. of Pages 11
ARTICLE IN PRESS
burns xxx (2020) xxx –xxx

Available online at www.sciencedirect.com
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journal homepage: www.elsevier.com/locate/burns

Effectiveness and safety of ablative fractional CO_2 laser for the treatment of burn scars: A case-control study

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Burn scars
Ablative fractional CO_2 laser
Ablative fractional resurfacing
Reconstructive burn surgery
Case control study

ABSTRACT

Background: Burn scars are a major clinical challenge. The aim of this study was to determine the effectiveness and safety of one treatment with the ablative fractional CO_2 laser (AFL-CO_2) compared to standard burn scar treatment.

Method: From December 2014 to October 2018 patients were prospectively recruited and treatment effects analyzed by assessing various outcome parameters from the date of first consultation and after treatment. A case control study was conducted looking at the impact of one AFL-CO_2 treatment compared to a cohort subjected to conventional conservative treatment. Adverse effects were noted at follow up.

Results: 187 patients were included, with 167 in the AFL-CO_2, and 20 in the control cohort. Baseline demographics and scar characteristics showed no significant differences. Ultrasound measured scar thickness as well as the Vancouver Scar Scale (VSS) revealed a significant reduction in the treatment cohort, but no significant improvement in the control group. The POSAS-O was significantly improved in both cohorts. Subjective parameters (POSAS-P, DN4-Pain, and modified D4Pruritus scores) decreased significantly in the AFL-CO_2 cohort but remained unchanged in the control group. The BSHS-B quality of life score increased significantly in the AFL-CO_2 group, but worsened at the follow up of the untreated patients. Sub-domain analyses found the biggest differences in Affect, Body Image, Heat Sensitivity, Treatment and Work. Complications occurred in 5 patients (2.9%).

Conclusions: This study demonstrates that AFL-CO_2 is an effective and safe treatment modality for burn scars improving thickness, symptoms and quality of life of burn survivors when compared to conventional scar treatment.

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https://doi.org/10.1016/j.burns.2020.10.002
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Please cite this article in press as: A.C. Issler-Fisher, et al., Effectiveness and safety of ablative fractional CO_2 laser for the treatment of burn scars: A case-control study, Burns (2020), https://doi.org/10.1016/j.burns.2020.10.002

1. Introduction

Burn scars are a major challenge, particularly due to improved survival rates and social expectations [1,2]. Hypertrophic scarring results from various compounding factors including genetics, type of injury, wound healing/complications and the systemic patient condition [2–4]. Symptoms resulting from hypertrophic burn scars include heat intolerance, neuropathic pain, and pruritus even years after the initial injury [5]. Contractures, tightness, and thickness lead to functional impairment with physical limitations and reduced range of motion [2,6]. Together with the stigma associated with burn injuries, these factors may have lifelong detrimental psycho-social consequences for burn survivors [2].

Fractional resurfacing has been described as a promising adjunct to traditional burn scar management over the last decade [7–9]. The introduction of ablative fractional CO_2 laser (AFL-CO_2) has led to a change in choices of surgical burn scar reconstruction with a shift toward simpler local tissue rearrangements combined with the laser treatment, with reduced length of stays, quicker rehabilitation times, which positively influence the psychosocial rehabilitation of burn survivors [10]. There is a paucity of higher-level data on the use of AFL-CO_2 for burn scars and control groups usually involve the same scar of the treated patients in a so-called “split scar” approach [3,11]. However, there is an increased understanding that the effects induced by AFL-CO2 may have a positive effect on adjacent zones. Equally, if one side of the scar is treated and tension is released, it will subsequently influence the neighboring area of the untreated scar [3]. Some experts believe that it is possible, that the treatment of a larger body surface area with AFL-CO_2, may have systematic effects and potentially positively influences scars located at other sites. Further, the impact of natural scar maturation on many of the aspects impairing burn patients has not been studied nor compared to AFL-CO_2.

Accordingly, we performed a nested case-control study to evaluate the effect of AFL-CO_2 on various objective and subjective outcomes, including conventional ultrasound for scar thickness, scar assessment scores (VSS and POSAS), questionnaires on neuropathic pain and pruritus (Douleur Neuropathique 4 Questionnaire and a modified 5-D Itch Scale), as well as burn specific quality of life (QoL) assessed with the Burns Specific Health Scale–Brief (BSHS-B). To account for the impact of normal scar maturation, patients were stratified into immature and mature scar groups and the differences in case and control cohorts were further analyzed according to their scar maturation status.

2. Materials and methods

2.1. Study setting and patient population

The Burns Unit of Concord Repatriation General Hospital (CRGH) in Sydney, Australia, is a statewide referral center for burn patients. Following ethics approval (CH62/6/2014-187, CH62/6/2017-008), data on all burn patients undergoing treatment with the AFL-CO_2 has been collected since December 2014 for quality outcome analysis. Inclusion criteria were the ability to provide informed consent and patients with burn scars comprising structural changes (hypertrophic and keloid scars). Exclusion criteria were impairing psychiatric or medical co-morbidity prohibiting the provision of informed consent.

For the present analysis, a nested case control study was performed by retrospectively analyzing our prospectively maintained database of all patients who present for assessment and treatment in our Burns Scar Clinic. Twenty patients were assessed in the scar clinic, but their actual treatment was deferred due to lacking theater time (elective patients are often canceled if the number of patients scheduled for acute burn procedures exceed operating theater capacity) or patient related factors (for example: unfit for an anesthetic due to respiratory illness, etc.). These 20 patients were then subsequently re-assessed immediately before their treatment with AFL-CO_2 and served as a control group, which had undergone simple conservative treatment measures (silicone, pressure garments, etc.) until they received AFL-CO2 treatment. To be included in the quantitative analysis for the case-control study, patients in the treatment group had to have completed one first treatment with the AFL-CO_2 and at least one first follow-up (patients generally receive 3–6 treatment cycles with the AFL-CO_2 for an optimal outcome [1]). The outcome measures were further stratified according to the maturation status of the scar (immature <2 years after injury, mature >2 years after injury) [3,5,9,12].

2.2. Treatment protocol

Procedures were performed with the 10,600-nm AFL-CO_2 Ultrapulse® (by Lumenis®), including ActiveFx™ (80–125 mJ Energy, 3–45% Density, 250–300 Hz Rate), DeepFx™ (15–50 mJ Energy, 5–15% Density, 300 Hz Rate) hand pieces and the SCAAR Fx™ mode (60–150 mJ Energy, 1–5% Density, 250 Hz Rate). The settings were adapted for each patient factoring in ethnicity, Fitzpatrick skin type, scar quality, thickness, maturation status and pigmentation. Treatment of hypertrophic burn scars was always immediately followed by laser facilitated topical and/or injected intralesional delivery of corticosteroids (Kenacort® A40).

Depending on the extent of the procedure (usually kept under 30%TBSA), patients were treated under local or general anesthesia. Post-operative wound care included double layer Bactigras for 48 h, followed by topical Paraffin twice daily for 7 days. Pressure garments were generally worn again after 3 days. Patients routinely received Valacyclovir orally for 5 days if a scar adjacent to the perioral area was treated with the AFL-CO_2. Patients with hypertrophic scars in areas of facial hair with recurrent acute on chronic folliculitis episodes received one single dose of pre-operative intravenous Cefazoline 2 g. No other routine prophylactic antibiotics or antiviral medication was used.

The control group was subjected to conventional scar management including pressure garments, silicone treatments, and physiotherapy if applicable until the time of treatment with AFL-CO_2.

Please cite this article in press as: A.C. Issler-Fisher, et al., Effectiveness and safety of ablative fractional CO_2 laser for the treatment of burn scars: A case-control study, Burns (2020), https://doi.org/10.1016/j.burns.2020.10.002

Table 1 – Comparison case versus control demographics and burn mechanism.

Demographics	Total (*n* pt=187)	Case (*n* pt=167)	Control (*n* pt=20)	*p*-value
Age (years)	39 (IQR 27–49)	37 (IQR 27–50.5)	43 (IQR 25.5–47.3)	0.98
median				
Gender:	112 (59.9%)	101 (60.5%)	11 (55%)	0.64
Female	75 (40.1%)	66 (39.5%)	9 (45%)	
Male				
Ethnicity:	87 (46.5%)	79 (47.3%)	8 (40%)	0.89
Anglo-Saxon	16 (8.6%)	14 (8.4%)	2 (10%)	
East European	15 (8%)	13 (7.8%)	2 (10%)	
Middle Eastern	1 (0.5%)	1 (0.6%)	0	
African	59 (31.6%)	51 (30.5%)	8 (40%)	
Asian	7 (3.7%)	7 (4.2%)	0	
Indigenous Australian, Maori, Pacific Islanders	2 (1.1%)	2 (1.2%)	0	
South American				
Fitzpatrick skin type:	5 (2.7%)	5 (3%)	0	0.68
1	39 (20.9%)	35 (21%)	4 (20%)	
2	86 (46%)	76 (45.5%)	10 (50%)	
3	38 (20.3%)	32 (19.2%)	6 (30%)	
4	16 (8.6%)	16 (9.6%)	0	
5	3 (1.6%)	3 (1.8%)	0	
6				
Smoker	19 (10.2%)	19 (11.4%)	0	0.23
Co-morbidities:	21 (11.2%)	18 (10.8%)	3 (15%)	0.45
Cardiac	4 (2.1%)	3 (1.8%)	1 (5%)	0.37
Vascular	4 (2.1%)	4 (2.4%)	0	1
Pulmonal	11 (5.9%)	9 (5.4%)	2 (10%)	0.33
Diabetes mellitus	6 (3.2%)	5 (3%)	1 (5%)	0.50
Neurological	21 (11.2%)	19 (11.4%)	2 (10%)	1
Psychiatric	39 (20.9%)	37 (22.2%)	2 (10%)	0.26
Other				
Prolonged wound healing (>21 days to epithelialization)	74 (39.6%)	62 (37.1%)	12 (60%)	0.08
Burn information				
% TBSA, *median*	10 (IQR 3–30)	10 (IQR 3–35)	4 (IQR 1.5–19)	0.43
Burn mechanism:	78 (41.7%)	74 (44.3%)	4 (20%)	0.16
Flame	40 (21.4%)	34 (20.4%)	6 (30%)	
Scald	18 (9.6%)	14 (8.4%)	4 (20%)	
Contact	20 (10.7%)	17 (10.2%)	3 (15%)	
Hot oil	11 (5.9%)	10 (6%)	1 (5%)	
Explosion	5 (2.7%)	4 (2.4%)	1 (5%)	
Chemical	2 (1.1%)	2 (1.2%)	0	
Electrical	13 (6.9%)	12 (7.2%)	1 (5%)	
Other (friction, etc.)				
Time since injury (months), *median*	16 (IQR 9–47)	17 (9–51.5)	11.5 (8–25.8)	0.34
Duration 1st treatment to follow-up (months), *median*	5.1 (IQR	5.1 (IQR 2.8–7.5)	4.9 (IQR 4.1–8.6)	0.11
Scar information	**Total**	**Case**	**Control**	
	(*n* scar=337)	(*n* scar=305)	(*n* scar=32)	
Scar per patient	2 (Range 1–8)	2 (IQR 1–2)	2 (IQR 1–2)	0.69
median				
Maturity	209 (62%)	186 (61%)	23 (71.9%)	0.23
Immature (<2 years)	128 (38%)	119 (39%)	9 (28.1%)	
Mature (>2 years)				
Scar thickness (µm)	3.2 (IQR 2.2–4.5)	3.2 (IQR 2.2–4.5)	3.1 (2.35–3.95)	0.89
Median	3.48 (1.61)	3.48 (1.64)	3.48 (1.32)	
Mean (sd)				
Type of scar:	54 (16%)	48 (15.7%)	6 (20%)	0.95
Conservative	180 (53.4%)	165 (54.1%)	15 (50%)	
Grafted	36 (10.7%)	32 (10.5%)	4 (13.3%)	
Re-grafted	47 (13.9%)	42 (13.8%)	5 (16.7%)	
Xenograft	5 (1.5%)	5 (1.6%)	0	
Donor-site	13 (3.9%)	13 (4.3%)	0	
Other[a]				
Concomitant scar management:	69 (20.5%)	60 (35.9%)	9 (47.4%)	0.33
Silicone	121 (35.9%)	107 (64.1%)	14 (73.7%)	0.46
Massage				

(continued on next page)

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Table 1 *(continued)*

Demographics	Total (*n* pt=187)	Case (*n* pt=167)	Control (*n* pt=20)	*p*-value
Garments	81 (24%)	69 (41.3%)	12 (63.2%)	0.09
Physiotherapy	23 (6.8%)	19 (11.4%)	4 (21.1%)	0.26
Localization:	42 (12.5%)	39 (12.8%)	3 (9.4%)	0.99
Face	19 (5.6%)	18 (5.9%)	1 (3.1%)	
Neck	32 (9.5%)	29 (9.5%)	3 (9.4%)	
Chest	15 (4.5%)	14 (4.6%)	1 (3.1%)	
Abdomen/Flank	13 (3.6%)	12 (3.9%)	1 (3.1%)	
Back/Buttock	144 (42.7%)	129 (42.3%)	15 (46.9%)	
Upper limb	72 (21.4%)	64 (21%)	8 (25%)	
Lower limb				
Laser combined with surgical procedure	32 (9.5%)	30 (10.1%)	2 (7.1%)	0.69

[a] Other=excision of scar, full-thickness skin graft, cultured epithelial autograft, flap, etc.

2.3. *Data collection, treatment and follow-up protocol*

Patient's demographics, including Fitzpatrick skin type [13,14], ethnicity, and information about the burn injury were documented at the date of study enrolment together with several subjective and objective outcome parameters to assess patients' baseline status. These outcome parameters were measured again after one treatment with AFL-CO_2 (treatment group) and before the first AFL-CO_2, if treatment was deferred (control group). With regards to scar site-specific documentation of factors, a photograph was taken at the initial consultation and the thickest point/scar landmark assessed marked to ensure that the same area was assessed each time.

2.4. *Assessment of outcomes*

Scar assessment was performed using the Vancouver Scar Scale (VSS) [15] and the Observer Scar Assessment Score (POSAS-O) [16] by the same two experienced burn clinicians. Due to often persisting erythema after treatment, the observers were not blinded to the assignment group, but did not have access to previous assessment scores. Scar thickness was measured with ultrasound as described previously [5].

Patients assessed their own scars with the Patient Scar Assessment Score of the POSAS (POSAS-P) [16]. Pain and pruritus were assessed using the Douleur Neuropathique 4 Questionnaire (DN4) [17] and the modified 5-D Itch Scale (4-D Pruritus Scale) [18] as described previously [5]. QoL was measured using the Burns Specific Health Scale–Brief (BSHS-B) [19] with a maximum 160 points, which is equal to normal QoL. Accordingly, the higher the number, the better the QoL [19].

Lastly, patients rated their progress since their last assessment with a global assessment according to a Likert-scale consisting of: “worse”, “unchanged”, “improved a little bit”, “improved quite a bit,” and “improved extremely”.

2.5. *Statistical analysis*

Only patients with complete baseline and follow-up data were analyzed. Continuous variables were compared using Student's *t*-test, Wilcoxon rank sum test, one-way analysis of variance (ANOVA) and the Kruskal–Wallis test where appropriate. Where necessary, log2 transformation of continuous data was performed to achieve normal distribution for these analyses. Differences between proportions derived from categorical data were analyzed using Pearson's chi-squared test or Fisher's exact test where appropriate. Statistical analyses were performed within patient groups (treatment group pre vs. post AFL-CO_2 and after initial and subsequent assessment for the control group) as well as between treatment groups (treatment vs. control groups). Where within group analyses were performed, these were performed as paired tests. Data are presented as median with interquartile range (IQR) as well as mean (± standard deviation [SD]) unless denoted otherwise. All *p*-values ≤ 0.05 were regarded as statistically significant and all statistical analyses were performed using R Statistical Packages [20].

3. Results

3.1. *Demographics*

187 patients were included in the analysis with 167 in the AFL-CO_2 treatment and 20 patients in the control group.

Age, gender, ethnicity, Fitzpatrick skin type, smoking status, co-morbidities, and prolonged wound healing showed no significant differences between the two groups (Table 1). The same applied to data relating to the burn mechanism and %TBSA. The time since injury was 17 months (IQR 9–51.5) in the AFL-CO_2 group and 11.5 months (IQR 8–25.8) in the control group (p=0.34). Equally, the duration between the initial assessment and the follow-up was comparable with 154 days (IQR 84–224) in the AFL-CO_2 cohort and 148 days (IQR 123–259) in the control group (p=0.28, Table 1).

Data on scar characteristics and associated previous management was also similar between groups. Accordingly, it was deemed that the case and the control cohorts were comparable for further comparative outcome analyses (Table 1).

3.2. *Comparison of scar-related outcomes – ultrasound measured scar thickness*

Scar thickness showed a significant reduction in the AFL-CO_2 treatment group (3.2 μm (IQR 2.3–4.5)→ 2.6 μm (IQR 1.9–3.4),

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Table 2 – Comparison case versus control outcome parameters.

Variables	Case (n pt=167)	p-value	Control (n pt=20)	p-value	p-value for case vs control
Scar thickness (US), μm	3.2 (2.3–4.5) → 2.6 (1.9–3.4)	<**0.001**	3.1 (2.4–4.0) → 2.3 (1.9–3.8)	0.47	0.59
Median (IQR)	3.6 (1.6) → 2.9 (1.4)		3.4 (1.4) → 3.1 (1.8)		
Mean (SD)					
VSS (0–13)	8 (7–9) → 6 (5–7)	<**0.001**	9 (8–9.8) → 8 (7–9)	0.03	<**0.001**
Median (IQR)	7.7 (1.8) → 6.0 (1.9)		8.6 (1.8) → 8.1 (1.6)		
Mean (SD)					
POSAS-O (6–60)	26 (22–32.5) → 20 (16–24)	<**0.001**	27 (24–31) → 22 (20.5–27)	<**0.001**	<**0.001**
Median (IQR)	27.5 (7.5) → 20.4 (5.9)	<**0.001**	27.3 (6.3) → 23.7 (6.2)	<**0.001**	0.01
Mean (SD)	5 (4–6)→ 3 (3–4)	<**0.001**	5 (4–6) → 4 (3–5)	0.99	<**0.001**
POSAS-O overall (1–10)	5.0 (1.72) → 3.7 (1.38)	<**0.001**	5.1 (1.4) → 4.4 (1.5)	1	**0.009**
Median (IQR)	35 (28–40) →24 (19–32)		32 (27–39) → 33 (27.5–38)		
Mean (SD)	34.6 (10.2) → 25.1 (9.8)		32.7 (9.3) → 33 (8.1)		
POSAS-P (6–60)	8 (7–10) → 5 (4–8)		7 (5–9) → 7 (5–8)		
Median (IQR)	8.0 (2.1) → 5.8 (2.4)		7.1 (2.3) → 6.4 (2.0)		
Mean (SD)					
POSAS-P overall (1–10)					
Median (IQR)					
Mean (SD)					
DN4-Pain Score (0–10)	4 (1–6) → 3 (0–3)	<**0.001**	4 (3–5.3)→4 (2–5)	0.11	0.03
Median (IQR)	3.9 (2.8) → 2.9 (2.5)		4.2 (2.5) → 3.7 (2.0)		
Mean (SD)					
Modified D4 Pruritus	16 (10–20) → 12 (7–17)	<**0.001**	17 (10.5–19.5) → 17 (12–19)	0.23	0.04
Questionnaire (7–35)	15.6 (6.1) → 13.3 (5.7)		16.8 (6.5) →15.7 (5.8)		
Median (IQR)					
Mean (SD)					
BSHS-B	119 (101–143) → 133 (106.5–147.5)	<**0.001**	130.5 (124–141)→120 (101–143.8)	0.1	0.01
(total score: 0–160)	116.8 (29.2) →126.1 (27.4)		126.3 (24.5) → 113 (38.0)		
Median (IQR)					
Mean (SD)					
Outcomes global impression	21 (9.8%)		15 (53.6%)		<**0.001**
Unchanged	99 (46.4%)		13 (46.4%)		
A little bit	61 (28.5%)		0		
Quite a bit	33 (15.4%)		0		
Extremely					

$p < 0.001$), and a non-significant decrease in the control group (3.1 μm (IQR 2.4–4.0)→2.3 μm (IQR 1.9–3.8), $p=0.47$). However, there was no difference in scar thickness between the AFL-CO_2 case vs control group (Table 2, Fig. 1).

3.3. *Comparison of scar-related outcomes – Vancouver Scar Scale (VSS)*

The VSS reduced by two points (8 (IQR 7–9)→6 (IQR 5–7), $p < 0.001$) in the treatment group and by one point (9 (IQR 8–0.9)→8 (IQR 7–9), $p=0.03$)) in the control group. This improvement was significantly higher when compared between the treatment and control group (Fig. 2).

3.4. *Comparison of scar-related outcomes – Observer Scores of the Patient and Observer Scar Assessment Score (POSAS-O)*

The POSAS-O showed a difference in both cohorts which appeared to be significant when both groups were compared, but not significant for the POSAS-O overall score (Table 2, Fig. 3).

3.5. *Comparison of subjectively assessed outcomes – Patient Reported Scores of the Patient and Observer Scar Assessment Score (POSAS-P)*

The POSAS-P as well as the POSAS-P overall scores showed statistically significant differences between the case and the control cohorts respectively, with the treatment group reporting a reduction of 11 points ($p < 0.001$), whereas in the control group there was an increase of the score by 1 point ($p=0.99$). Similarly, the POSAS-P overall score in the treatment group decreased by 3 points ($p < 0.001$), whereas in the control group it remained the same ($p=0.23$, Table 2).

3.6. *Comparison of subjectively assessed outcomes – neuropathic pain scores*

Looking at pain scores, there was a significant improvement in the treatment group whereas the control group described the same scores in their initial assessments and follow-ups (Table 2). If only patients with previous neuropathic pain scores were included in the analysis (scores ≥4), results remained the same regardless of maturation status of the scars (Supplementary Table 1).

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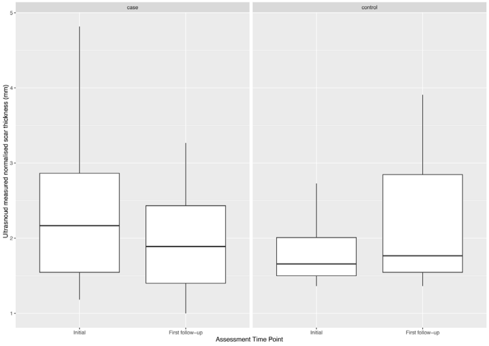

Fig. 1 – Boxplot demonstrating the effect of one treatment with the ablative fractional CO_2 laser vs the control group on normalized scar thickness.

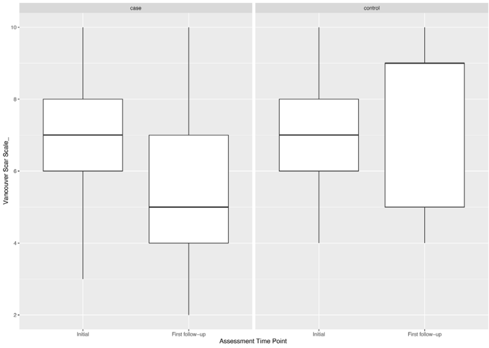

Fig. 2 – Boxplot demonstrating the effect of one treatment with the ablative fractional CO_2 laser vs the control group on the Vancouver Scar Scale.

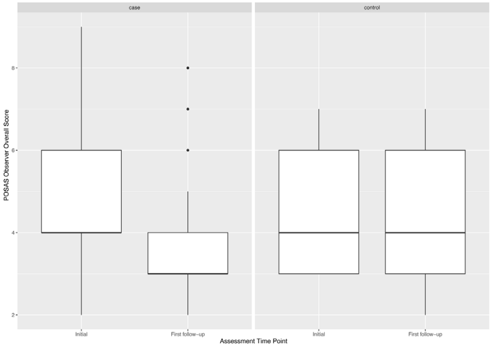

Fig. 3 – Boxplot demonstrating the effect of one treatment with the ablative fractional CO_2 laser vs the control group on the overall Observer Score of the POSAS.

Pruritus scores dropped by 4 points in the treatment cohort ($p < 0.001$), whereas the control group remained unchanged (Table 2).

3.7. *Comparison of subjectively assessed outcomes – burn specific quality of life*

Patients rated their burn specific QoL being improved by 14 points after just one AFL-CO_2 treatment (119 (IQR 101–143) before treatment to 133 (IQR 106.5–147.5) post-treatment, $p < 0.001$). In the control group scores got worse from 131 (IQR 124–141) to 120 (IQR 101–143.8, $p = 0.1$). When QoL subdomain-analyses were performed, the biggest differences in Affect, Body image, Heat Sensitivity, Treatment and Work were observed. Body image significantly improved in the treated group, whereas it was rated worse in the control group. Heat sensitivity overall also significantly improved in the treatment group by 4 points ($p < 0.001$). The subdomain "Treatment" (i.e. QoL associated with treatment regiments undertaken for burn scars) generally improved in the treated cohort but worsened or remained unchanged in the control group. An overview of the QoL outcome analysis is provided in Table 3. Fig. 4 illustrates improvement of facial scarring following AFL-CO_2, simultaneously enhancing the patients QoL by relieving symptoms of painful chronic folliculitis.

3.8. *Comparison of treatment and control cohorts stratified by scar maturation status*

All of the assessed domains showed a statistically significant improvement in the AFL-CO_2 treatment cohort in the immature as well as the mature scar groups. The control cohort only showed significant improvement in the immature scar group in the domains VSS, POSAS-O, POSAS-O overall and BSHS-B, but revealed no significant changes in the other assessed domains. In the mature control group, there were no significant changes reported in any of the evaluated outcomes (Supplementary Tables 2 and 3). Fig. 5 illustrates a relatively mature hypertrophic scar following treatment with AFL-CO_2 and laser facilitated steroid infiltration.

3.9. *Complications and side effects of AFL-CO_2 treatment*

Five of 167 patients (2.99%) had complications following the laser treatment. One patient (0.60%) developed a wound infection at the treated site, one patient who had simultaneous fat-grafting developed an in infection of the fat graft (0.60%), and two patients (1.20%) had a wound-break down (of which one was due to a blunt trauma to the site during a sporting injury). One patient (0.60%) reported persistent itchiness. Equally, three patients (1.80%) reported persistent erythema in the treated areas. No outbreak of Herpes simplex was recorded.

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4. Discussion

The results of the present study suggest that patients undergoing one treatment with AFL-CO_2 achieve substantial improvement in a variety of objective and subjective burn scar related outcome domains including QoL, when compared to patients who do not undergo AFL-CO_2 but receive standard burn scar care. These findings are supported by existing reports on the effects of AFL-CO_2 for burn scar management [2,3,7]. Furthermore, the present case-control study demonstrates significant improvements particularly in burn scar related QoL, irrespective of scar maturation status. Thus, even patients with old scars that may have exhausted conventional treatments may still benefit from AFL-CO_2.

Looking at the demographics and information on burn mechanism we found no statistically significant differences between the case and control groups. Added to that, retrospective patient allocation to either treatment or control groups, was largely random. Patients who served as a control group did so due to external factors and irrespective of their actual scars. Thus, we deemed the groups as comparable and did not perform any further formal matching. Although not statistically significant, the only parameter differing between the two groups was prolonged wound healing (>3 weeks following burn injury/procedure) with 60% of patients who experienced prolonged healing in the control group vs 37% in the treatment group (p=0.08). However, this did not result in differences in the "scar severity" as assessed by the various outcomes such as ultrasound scar thickness, scar assessment scores and questionnaires about symptoms and quality of life. We believe that any noted differences may be explained by our unit's approach to often choose a more conservative approach in smaller burns of mixed or unclear depth, which in certain cases may result in grafting after more than 3 weeks after injury.

In the present study, the median time since injury of our two evaluated patient cohorts was 16 months and the timeframe between initial assessment and the median follow up was ~5 months for the treatment and the control group.

Table 3 – Comparison case versus control: domains of BSHS-B.

BSHS-B *median (IQR)*	Case (*n* pt=167)	*p*-value	Control (*n* pt=20)	*p*-value	*p*-value for case vs control
Simple abilities	12 (10–12) → 12 (11–12)	<**0.001**	12 (12–12) → 12 (11.5–12)	1	0.02
Immature	12 (10–12) → 12 (11–12)	<**0.001**	12 (12–12) → 12 (10–12)	1	<**0.001**
Mature	12 (12–12) → 12 (12–12)	0.01	12 (12–12) → 12 (12–12)	NA	0.35
Hand function	20 (16–20) → 18 (18–20)	<**0.001**	20 (18.3–20) → 20 (17.8–20)	0.71	0.3
Immature	20 (16–20) → 20 (18–20)	**0.001**	20 (18.8–20) → 20 (18–20)	0.4	0.04
Mature	20 (14–20) → 20 (18–20)	**0.003**	20 (17.8–20) → 20 (17.8–20)	NA	0.44
Affect	25 (20.8–28) → 26 (21–28)	0.01	26 (19–27.8) → 21 (16.8–27)	0.08	<**0.001**
Immature	25 (21–28) → 26 (21–28)	0.7	26.5 (25.3–28) → 22.5 (17–26.3)	0.02	**0.003**
Mature	26 (15–27)→ 27 (19.5–28)	<**0.001**	17 (11–24.5) → 21 (12–26.3)	0.1	0.20
Body image	8 (4–12) → 9.5 (4–13)	<**0.001**	7.5 (3.5–10) → 6 (3.8–13)	0.09	0.05
Immature	8 (4–13) → 10 (4–14)	<**0.001**	8.5 (6.5–10) → 7 (4–12)	0.5	0.08
Mature	8 (4–11) → 9 (4.5–12.5)	<**0.001**	3 (0.8–5.3) → 4 (1–12.3)	0.2	0.31
Interpersonal	16 (16–16) → 16 (16–16)	0.16	16 (14–16) → 15.5 (13.8–16)	0.8	<**0.001**
relationships	16 (16–16) → 16 (16–16)	0.8	16 (14–16) → 14 (14–16)	0.3	<**0.001**
Immature	16 (15–16) → 15 (16–16)	0.10	13 (10.8–15.3) → 14.5 (11–15)	0.61	0.12
Mature					
Sexuality	12 (10–12) → 12 (10–12)	0.05	12 (12–12) → 11.5 (7.8–12)	0.02	0.09
Immature	12 (10–12) → 12 (10–12)	0.3	12 (12–12) → 12 (8.5–12)	0.03	0.05
Mature	12 (8.5–12) →12 (9.8–12)	0.03	12 (8.3–12) → 11 (8–11.8)	0.2	0.89
Heat sensitivity	8 (3–16) → 12 (5–17)	<**0.001**	13.5 (11–14.8) to 10 (3–16.5)	0.5	0.6
Immature	6 (3–14) → 12 (5–16)	<**0.001**	13 (11–14) to 13.5 (5–15.8)	0.7	0.9
Mature	9 (4–16)→ 12 (4–19.5)	0.03	16.5 (3.8–19.5) to 13 (0.8–14.3)	0.5	0.27
Treatment	15 (11–18) → 17 (13–20)	<**0.001**	18 (12–19.8) to 16 (9.8–18.3)	0.05	0.2
Immature	14 (11–17) → 16 (13–19)	<**0.001**	17.5 (12–19.3) to 13 (10–18.8)	0.07	0.1
Mature	16 (10.5–18) → 18 (13–20)	0.10	18 (11.3–19.5) to 18 (11.3–18)	0.36	0.94
Work	11 (8–15) to 14 (10–16)	<**0.001**	12.5 (4.5–16) → 10 (4–16)	0.9	**0.07**
Immature	12 (8–15) to 14 (11–16)	<**0.001**	13.5 (5.5–16) → 9.5 (4–16)	0.7	**0.07**
Mature	11 (4–16) to 14 (9–16)	<**0.001**	10.5 (2–13) → 16 (4–16)	0.13	0.62
Total score (0–160)	119 (101–143) → 133 (106.5–147.5)	<**0.001**	130.5 (124–141) → 120 (101 –143.8)	**0.09**	0.01
Median (IQR)	116.8 (29.2)→ 126.1 (27.4)	<**0.001**	126.3 (24.5) → 113 (38.0)	0.04	**0.006**
Mean (SD)	120 (105–139.5) → 130 (109–147)	<**0.001**	133.5 (124–140.8) → 119.5 (102 –140.5)	0.9	0.5
immature	116.8 (29.2) → 133.0 (27.4)				
Median (IQR)	117 (87–144) → 134 (105–149.5)		126.3 (24.5) → 113.0 (38.0)		
Mean (SD)	112.7 (36.5) → 123.3 (34.0)		130 (80.5–139) → 120 (78–145.5)		
mature			112.8 (38.4) → 113.3 (41.4)		
Median (IQR)					
Mean (SD)					

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Fig. 4 – Before and after figures. (A) 19 year old Caucasian male patient with Fitzpatrick skin type 2, 10.5 months following a 67% TBSA burn injury by an explosion with hypertrophic scarring and chronic folliculitis. (B) Same patient 6 months later (9 weeks following his first treatment cycle with ablative fractional CO_2 laser (Lumenis UltraPulse, Yokneam, Israel). DeepFX handpiece with settings DeepFx 50 mJ Energy, 3% Density, 300-Hz) plus laser facilitated delivery of Kenacort A40. (C) 1.5 years following 3 treatment cycles with ablative fractional CO_2 laser and laser facilitated infiltration of corticosteroids.

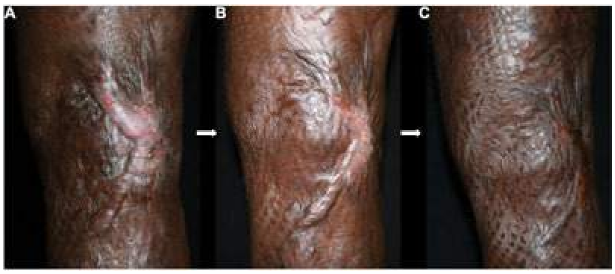

Fig. 5 – Before and after figures. (A) 32 year old Sri-Lankan male patient with Fitzpatrick skin type 6, 22 months following a 41% TBSA flame burn injury with hypertrophic scarring. (B) Same patient 6 months (11 weeks following his first treatment cycle with ablative fractional CO_2 laser (Lumenis UltraPulse, Yokneam, Israel). DeepFX handpiece with settings ScarFX 80 mJ Energy, 3%, 250-Hz and DeepFx 30 mJ Energy, 10% Density, 300-Hz) plus laser facilitated delivery of Kenacort A40. (C) 2.5 years following 3 treatment cycles with ablative fractional CO_2 laser and laser facilitated infiltration of corticosteroids.

Scarring tends to develop 6–8 weeks after re-epithelialization and natural scar maturation takes at least 6–18 months [21,22]. Symptoms improve during the scar maturation process, however in approximately 40% of long-term burn survivors pain and pruritus can continue for years after the initial injury [23]. This is also our experience, and together with stigma, tightness, heat intolerance and inability to sweat contribute heavily to ongoing poor quality of life of burns survivors.

For the past 5 years treatment with AFL-CO_2 has been implemented in the routine scar management at our unit as an adjunct or sole treatment for problematic burn scars. Three to 6 treatment cycles are generally recommended for an optimal outcome [1,8], and it is very likely the demonstrated positive effects accumulate with more treatment cycles as illustrated in Figs. 1 and 2. It has been our observation that patients frequently describe an improvement of the scars which often appears not to be entirely captured with the available outcome measurement tools. This is also reflected by the present study, in particular in the immature scar group. In the immature case and control cohorts all the variables assessed by an observer (health practitioner), namely the VSS, POSAS-O and POSAS-O overall, were deemed to have significantly improved in the treated and untreated groups. Interestingly, the scar thickness decreased in the immature control group (even though not

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significantly) but remained unchanged in the mature control group. Accordingly, this is in line with the argument that scars will improve during their maturation status regardless of any intervention. All the other patient reported outcome measures did not improve significantly in the control group regardless of scar maturation. This supports the notion that the patients' and clinicians' perceptions may diverge and thus we may value different aspects of the scar. Accordingly, it is entirely possible that not all the variables relevant to patients are captured with the current available assessment tools and reinforces the benefit of capturing patient-reported outcomes. Thus, our burns specific QoL assessment revealed interesting findings.

The treated cohort consistently reported an increase in the overall score for QoL of 10 points for the immature group ($p < 0.001$) and by 17 points in the mature group ($p < 0.001$). In contrast, the overall score decreased in the untreated control cohort. Patients with immature scars showed a decrease of 14 points in the evaluated timeframe ($p < 0.05$) and a decrease of 10 points in the mature group ($p = 0.9$). This raises the question if there is an additional subconscious component to the improvements noted in the treatment cohort such as hope associated with the new treatment, which may influence patients' perception of their quality of life. To make a conclusive statement on this matter it may be valuable to conduct a long term follow up study and assess if the quality of life further changes years after the reconstructive intervention.

In relation to quality of life measures, the most dramatic changes were seen in the domain of heat sensitivity. Patients with immature scars rated an improvement of heat sensitivity of 6 points ($p < 0.001$) following just one treatment with the AFL-CO_2, whereas the control group with immature scars only experienced a non-significant increase of 0.5 points. The mature treated cohort also described an increase of 3 points ($p = 0.03$), whereas the untreated mature group reported a decrease of 3.5 points ($p < 0.05$). This phenomenon may be explained by the change in vascularity in scars induced by AFL-CO_2. Treatment with AFL-CO_2 results in a decrease of vascularization in immature scars and an increase of vascularization for mature scars [24]. Thus, a normalization/improvement of the vascular anatomy within the scar may improve heat exchange, resulting in better heat tolerance. Added to that, the change in sensation such as sensitivity, pain and itch may also be related to the effect of laser treatment on peripheral nerve system or currently unknown molecular factors.

Although this study demonstrated substantial improvement in various outcome parameters, there are limitations which should be considered. The presented objective outcome measures only include ultrasound measurements for scar thickness as a true objective device. All other assessments were based on an observer and thus may still be subject to observation bias. Thus, it would have been valuable to include an objective measurement tool for elasticity and pliability such as a torque meter, as a recently published analyses reported a substantial improvement in mechanical properties, such as elastic stretch, elastic recovery and total extensibility of burn scars following treatment with the AFL-CO_2 [2]. Optical coherence tomography would also be a great objective tool to assess vasculature and the connective tissue in scars [25,26]. However, to ensure that the same portion of the scar is measured each time during the ultrasound measurement, topical maps on transparency paper marking the location of the thickest area, may be of greater value than mapped out photographs alone [2]. Lastly, there is a lack of objective measurement tools for burn scar related pain and pruritus and even other variables not yet entirely understood contributing to the improvements experienced by patients, as such the patient-reported outcome measures are inherently subject to reporting bias, but this aspect cannot be corrected for. Equally, psychological effects of having undergone treatment (particular after a long period of scar maturation) may equally have positively influenced some of the patient-specific reported outcomes compared to those having undergone treatment delays, and thus the exact independent effect of CO2-AFL on patient outcomes remains difficult to assess. Another limitation is that the majority of assessed patients received laser facilitated infiltration of corticosteroids (KenacortA40). Thus, it remains unclear if the effects are from the laser itself, due to evenly distributed intralesional corticosteroids or a combination of both. Generally, corticosteroids are injected intralesionally with a fine needle, however, as the drug is injected into the dense structure of the scar, it often results in an accumulation of the medication. As such, intralesionally injected corticosteroids can result in atrophy, white flecks, teleangiectasia, and hypopigmentation. However, several animal models as well as clinical studies have been published about the enhanced bioavailability of drugs administered via laser assisted drug delivery [27–33]. It is generally considered that due to the laser facilitated delivery the drug is much more evenly distributed via the fractional ablated wells compared to when it is topically applied or injected. The application of corticosteroids after AFL-CO_2 is thus very different to regular injection as the solution is evenly spread throughout the tissue. The choice of either injecting or topically applying the corticosteroids is generally based on scar thickness, which was not significantly different between the two groups as reported with the ultrasound measured scar thickness of the initial assessment. Unfortunately, we did not prospectively capture the data on how the corticosteroids were applied (injection or topical application) which would have been valuable to differentiate.

Lastly, in 10% of cases a simultaneous surgical procedure was performed such as Z-plasties, scar releases or excisions and/or simultaneous fat-grafting. Thus, in these instances it is not clear to what extent these surgical procedures have contributed to the improved patient outcomes. In cases with a clear contracture band, ectropion or similar, surgical reconstructive procedures are routinely performed in conjunction with AFL-CO_2. Generally, the simultaneously performed procedures are only very small and serve as a symbiotic adjunct to the treatment with the AFL-CO_2. Resurfacing a scar prior to any surgical intervention reduces tension and improves vascularization of the scar, preparing the scar for an optimal outcome if small local tissue rearrangements are performed. As such, the fact that 10% of cases had simultaneous surgical reconstructions needs to be considered when

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interpreting our findings. A separate analysis of patients undergoing multimodality treatment is in preparation.

Nevertheless, we believe that the present study provides data illustrating that AFL-CO_2 is a well-tolerated and effective treatment modality which leads to a substantial benefit for burn survivors as has been reported by other units [2,8]. As a sole treatment modality or in combination with local tissue rearrangements, AFL-CO_2 has eradicated the need for scar excisions and larger reconstructive procedures [6,10], and thus provides a valuable tool in the armamentarium of Burn surgeons aiming to improve the outcomes of patients suffering from the long-term sequalae of burn injuries. Whilst not a randomized trial, the present study is a case-control study, in particular focusing on patient related outcome measures, namely quality of life. Thus, it provides robust data supporting the positive results experienced by many other Burns centers around the globe.

5. Conclusion

The present study demonstrates that burn scars can be effectively and safely treated with the AFL-CO_2. Objective and subjective outcomes improve significantly following just one treatment with the AFL-CO_2 compared to conservative and traditional treatments. In particular, burn specific quality of life showed a significant improvement following treatment AFL-CO_2 compared to an untreated control group. Long-term data are required to determine how sustained these changes are and if any further improvements can be achieved with multiple AFL-CO_2 treatments.

Conflict of interest

ACIF has received personal fees from Lumenis Australia for services rendered including honoraria for proctoring as well as lectures and conference attendances. Lumenis Australia however had no role in the conception, study design, data collection and analysis of the present study, nor in the drafting and editing of the final manuscript. All other authors declare that there is no source of financial or other support, or any financial or professional relationships, which may pose a competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.burns.2020.10.002.

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Appendix C: Ablative fractional resurfacing with laser-facilitated steroid delivery for burn scar management: Does the depth of laser penetration matter?

Issler-Fisher AC, Fisher OM, Haertsch P, Li Z, Maitz PKM.Lasers Surg Med. 2020 Feb;52(2):149-158. doi: 10.1002/lsm.23166. Epub 2019 Sep 30.

Lasers in Surgery and Medicine

Ablative Fractional Resurfacing With Laser-Facilitated Steroid Delivery for Burn Scar Management: Does the Depth of Laser Penetration Matter?

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Background and Objective: To investigate whether the depth of ablative fractional CO_2 laser (CO_2-AFL) penetration of pathological burn scars influences clinical outcomes.

Study Design/Materials and Methods: All patients presenting to the Concord Repatriation General Hospital (CRGH) Scar Clinic received ultrasound measurement at the thickest point of their burn scars. Subsequently, the effect of various CO_2-AFL settings (energy which correlates to penetration depths) on different outcome parameters was analysed. Patients were divided into five groups depending on minimal scar penetration depth.

Results: Seventy-eight patients (158 scars) had complete data allowing for analysis. Median scar thickness was 3,400 μm and median laser scar penetration depth was 900 μm. Scar penetration categories were as follows: 0–25% ($n = 40$), 25–50% ($n = 67$), 50–75% ($n = 31$), 75–100% ($n = 8$), >100% ($n = 3$) of scar thickness. The median reduction in maximum scar thickness was 800 μm following one treatment ($P < 0.001$). However, this effect depended on scar penetration depth, whereby scars that were penetrated ≥75% showed no significant improvement in scar thickness and those penetrated >100% indicated a tendency to become worse. Other assessed outcome parameters included: the Vancouver Scar Scale, the Patient and Observer Scar Assessment Scale, a neuropathic pain score (DN4 Pain Questionnaire), and a pruritus score (modified D4 Pruritus Score). All these factors showed significant improvement in the categories up to 75% scar penetration depth.

Conclusions: CO_2-AFL scar penetration depth significantly influences subjective and objective pathologic burn scar modulation. The penetration depth of 51–75% achieves the greatest reduction in scar thickness. Lasers Surg. Med. © 2019 Wiley Periodicals, Inc.

Key words: burn scars; ablative fractional CO_2 laser; depth of laser penetration; scar thickness; scar assessment scores

INTRODUCTION

With increased survival rates of burn victims, severe burn scarring remains a modern clinical challenge [1]. The addition of ablative fractional laser resurfacing to routine burn scar management seems promising and provides an excellent treatment modality complementing, if not replacing, the traditional reconstructive surgical approaches [1–3].

Ablative fractional laser devices, such as the ablative fractional CO_2 laser (CO_2-AFL), apply the laser beam to fractions of the skin surface. On the basis of water absorption and bulk heating, epidermal and dermal structures are removed, resulting in microscopic ablative zones (MAZ) [4]. High energy and a short pulse duration in CO_2-AFL facilitate precise effects with minimal side effects so that islands of undamaged skin can serve as reservoirs to trigger small wound healing reactions and subsequent scar remodeling [5]. CO_2-AFL devices ablate micro-columns vertically through epidermis and dermis [4]. The effective depth of these MAZs depends on the amount of energy applied and skin conditions, such as hydration and surface temperature [4]. The SCAAR™ mode of the ablative fractional 10,600-nm wavelength CO2 Ultrapulse® laser (by Lumenis®), for example, can penetrate to reach a depth of up to 4.0 mm with a narrow

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and have disclosed the following: The authors declare that there is no source of financial or other support, or any financial or professional relationships, which may pose a competing interest. Lumenis Australia has paid for one of the corresponding authors conference attendances (ANZBA Australian & New Zealand Burn Association) 2018 in Brisbane Australia.

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Accepted 11 September 2019

DOI 10.1002/lsm.23166

zone of coagulation and minimal collateral damage. However, laser density plays a crucial role as well, because if too high densities are used, it may result in bulk heating and total scar ablation [4,16].

Various reports have shown positive clinical efficacy of CO_2-AFL for burn scar management [1,6–8], however, to date, the importance of the individual laser settings for laser-tissue interactions and patient outcomes is not entirely understood. Thus, we performed a retrospective audit of our practice to investigate whether the maximum depth of CO_2-AFL penetration in pathological burn scars influences burn scars and patient outcomes.

MATERIALS AND METHODS

Study Setting and Patient Population

Concord Repatriation General Hospital (CRGH) in Sydney, Australia, is a 470-bed tertiary referral facility and a teaching hospital of the University of Sydney with a statewide referral unit for burn patients. The high-volume Burns Outpatient Clinic reviews up to 1,000 patients per month and since 2015 a dedicated Burn Scar Clinic has been established.

Burn victims suffering from the sequelae of their injury are referred to the Burn Scar Clinic, where their scars are evaluated, and a treatment plan established including non-invasive therapies, laser treatments, and reconstructive surgical procedures.

Scars suitable for fractional resurfacing are treated with the ablative fractional 10,600-nm wavelength CO_2 Ultrapulse® laser (by Lumenis® Melbourne, Australia) including ActiveFX™ and DeepFX™ handpieces and the SCAAR FX™ mode. Treatment settings are chosen according to clinical judgement which incorporates a variety of factors to help guide laser setting selections. These include patient factors such as specific scar locations, thickness (as measured by ultrasound at the thickest area), scar maturity, type of scar, Fitzpatrick skin type, ethnicity, etc. Typically, the laser treatment is started at the thickest point of the scar with the maximum energy levels and subsequently these are adapted while passing across the thinner areas of the scar. However, for energies up to 35 mJ, densities of 5–10% are chosen. Energies between 40 and 60 mJ are usually combined with a density of 5%, 70–80 mJ with a density of 3%, and 90–150 mJ with a density of 1% (with the DeepFX™ handpiece). Laser facilitated drug delivery of corticosteroids (Kenacort A40) topically and/or by intralesional injection (of hypertrophic/nodular areas) following treatment of hypertrophic burn scars with the CO_2-AFL Ultrapulse® represents part of our standard treatment protocol [9]. Depending on the extent of the required intervention, all procedures (laser and surgical reconstructive treatments) are performed under local or general anesthesia in our dedicated burns theatre within the Burns Unit of CRGH.

Data Collection and Analysis

From December 2014 to June 2018 data were prospectively collected from all burn patients treated with the CO_2-AFL (IRB approved: CH62/6/2017-008). Data collection included: patient demographics, information on the burn mechanism, treatment settings and subjective and objective outcome parameters at the date of enrolment and ~6 weeks following each treatment. Objective outcome measurements included: ultrasound measurement of the scar thickness, the Vancouver Scar Scale (VSS) [10], and the Patient and Observer Scar Assessment Score (POSAS) [11]. For the ultrasound measurements, each scar was marked on a photograph and was always measured at the same location of the thickest scar area. Subjective outcome parameters involved the Patient Scar Assessment Score of the POSAS [11], questionnaires about pain using the Douleur Neuropathique 4 Questions (DN4) [12] and pruritus using a modified 5-D itch scale (4-D Pruritus Scale) [1,13].

The primary outcome of this retrospective study was to determine the influence of the depth of laser penetration on the scar thickness measured by ultrasound. To evaluate the impact of natural scar maturation, the patient cohort was split into two groups according their scar maturation: the first group consisted of patients with young, immature scars, who presented for their first treatment less than 2 years following the burn injury/last operation, and the second group included patients with mature scars, who had their initial treatment more than 2 years after the burn injury/last operation. Secondary outcomes included the effect of penetration depth on the above-mentioned objective and subjective outcome parameters.

Statistical Analysis

Laser handpiece energy settings directly correlate with penetration depth. As such to assess the depth of scar penetration the maximum penetration depth was divided by the scar thickness at the thickest point of each scar to calculate the percentage of tissue penetration. Patients were subsequently divided into five groups depending on minimal scar penetration depth: 0–25%, 26–50%, 51–75%, 76–100%, and >100% penetration of scars.

Subsequent data are reported as median with interquartile range (IQR) unless denoted otherwise. Continuous variables were compared using Student's t test, Wilcoxon rank-sum, one-way analysis of variance (ANOVA) and/or Kruskal–Wallis tests as appropriate. Differences between proportions of categorical data were compared using Pearson's χ^2 or Fisher's exact test where appropriate. All analyses were stratified according to patient groups as defined above. A $P < 0.05$ was accepted as statistically significant. All statistical analyses were performed using R Statistical Packages [14].

RESULTS

Demographics and Burn Mechanism

A summary of patient demographics is provided in Table 1. Briefly, 78 patients with 158 scars had complete data allowing for analysis of which 59.0% ($n = 46$) were female and 41.0% ($n = 32$) were male with a median age of 40 years (IQR, 29.0–51.8). Most patients were

TABLE 1. Patient Demographics and Information on Burn Mechanism

Demographics	$n = 78$ patients
Gender: female/male (%)	46 (59%), 32 (41%)
Age (years) (median)	40 (IQR, 29–51.8)
Ethnical background: (%)	
Anglo-Saxon/Celtic	45 (57.7%)
Southeast Asian	13 (16.7%)
North-East Asian	5 (6.4%)
South & Central Asian	6 (7.7%)
Southeast European	2 (2.6%)
North African/Middle Eastern	4 (5.1%)
Maori/Pacific Islander	2 (2.6%)
South American	1 (1.3%)
Fitzpatrick skin type: (%)	
Type 1	3 (3.9%)
Type 2	18 (23.1%)
Type 3	42 (53.9%)
Type 4	8 (10.3%)
Type 5	6 (7.7%)
Type 6	1 (1.3%)
Smokers (%)	4 (5.1%)
% TBSA burnt (median)	7.5 (IQR, 3–80)
Burn mechanism: (%)	
Flame	39 (50%)
Scald	15 (19.2%)
Hot oil	7 (9.0%)
Contact	6 (7.7%)
Other (chemical, electrical, friction, etc.)	11 (14.1%)
Scar information:	**$n = 158$ scars**
Scar maturation: (%)	
Immature scars (<2 y post-injury)	108 (63.4%)
Mature scars (>2 y post-injury)	50 (31.6%)
Type of scar: (%)	
Conservative treatment	24 (15.2%)
Grafted	75 (47.5%)
Re-grafted	25 (15.8%)
Biobrane xenograft	25 (15.8%)
Other (e/o graft, full-thickness skin graft (FTSG), donor-site, etc.)	9 (5.7%)
Scar location	
Abdomen	3 (1.9%)
Back	5 (3.2%)
Buttock	3 (1.9%)
Chest	14 (8.9%)
Face	17 (10.8%)
Flank	4 (2.5%)
Lower limb	34 (21.5%)
Neck	8 (5.1%)
Shoulder	6 (3.8%)
Upper limb	64 (40.5%)
Scar per patient (median)	2 (range, 1–5)
Scar thickness (µm) (median)	3,400 (IQR, 2,500–4,500)
Scar penetration with CO_2-AFL (µm) (median)	900 (IQR, 900–1,800)
Concomitant scar management: (%)	
Silicone	41 (25.9%)
Massage	58 (36.7%)
Garments	44 (27.8%)
Physiotherapy	14 (8.9%)

IQR, inter-quartile range.

Anglo-Saxon/Celtic with a Fitzpatrick skin type 3 ($n = 42$, 54%). The median total burn surface area (TBSA) resulting in scarring was 7.5% and most scars were caused by flame injuries. 66.7% of scars were regarded as immature (<2years post-injury) and most hypertrophic scars resulted from grafted wounds ($n = 75$, 47.5%).

Effects of laser penetration depth on burn scar thickness

Of the 158 analysed scars, the median scar thickness measured at the thickest point was 3,400 µm (IQR, 2,500–4,500) and the median laser scar penetration depth was 900 µm (IQR, 900–1,800). Scar penetration categories were as follows: 0–25% ($n = 40$), 25–50% ($n = 76$), 50–75% ($n = 31$), 75–100% ($n = 8$), >100% ($n = 3$). The median reduction in maximum scar thickness was 800 µm following one treatment ($P < 0.001$; Table 2). However, this effect depended on the depth of scar penetration, whereby scars penetrated ≥75% showed no significant improvement in scar thickness and those penetrated >100% showed a tendency to become worse (Fig. 1). Similar results we found when the analysis was stratified according to scar maturation status. Immature (<2 years post-injury) and mature (>2 years post-injury) scars decreased significantly by a median of 800 and 600 µm, respectively (Table 3). In the immature scar group, the biggest effect was achieved when the maximum penetration reached 51–75% of the scar thickness, resulting in a drop of 1,400 µm following one treatment ($P = 0.011$). If 76–100% was penetrated, the difference was not statistically significant anymore and if >100% was penetrated the scar became thicker, although these groups only included five and one patients, respectively. Similar results could be observed in the mature scar group, with the only difference being that the largest improvement in ultrasound measured scar thickness was achieved in the 26–50% penetration depth group (Table 3) (Fig. 2).

Objective and Subjective Outcome Parameters Stratified According to Penetration Depth

All evaluated objective and subjective outcome parameters improved significantly in all penetration depth

TABLE 2. Outcomes Stratified According to Scar Penetration Depth

Outcome parameter median (IQR)	Penetration depth	Before first treatment	After first treatment	P value
Scar thickness (μm)	All ($n = 158$)	3,400 (2,500–4,500)	2,600 (2,025–3,575)	<0.001
	0–25% ($n = 40$)	3,850 (3,400–6,000)	3,100 (2,275–4,050)	<0.001
	26–50% ($n = 76$)	3,200 (2,175–4,400)	2,600 (1,900–3,400)	<0.001
	51–75% ($n = 31$)	3,400 (2,250–4,550)	2,300 (1,900–3,300)	0.002
	76–100% ($n = 8$)	2,650 (1,650–3,100)	2,400 (2,000–2,850)	0.800
	>100% ($n = 3$)	2,800 (2,650–3,400)	3,700 (3,350–4,750)	0.250
VSS (0–13)	All ($n = 158$)	8.0 (7.0–9.0)	6.0 (5.0–8.0)	<0.001
	0–25% ($n = 40$)	8.0 (7.0–9.0)	6.0 (5.0–7.0)	<0.001
	26–50% ($n = 76$)	8.0 (6.8–9.0)	6.0 (4.0–8.0)	<0.001
	51–75% ($n = 31$)	9.0 (7.0–10.0)	7.0 (6.0–8.0)	<0.001
	76–100% ($n = 8$)	8.5 (8.0–9.0)	7.0 (6.0–7.0)	0.002
	>100% ($n = 3$)	10.0 (9.0–10.5)	8.0 (7.5–8.0)	0.1
POSAS O (0–60) (0–60)	All ($n = 158$)	27.0 (23.0–33.8)	20.0 (17.0–25.0)	<0.001
POSAS O overall (0–10)		5.0 (4.0–7.0)	4.0 (3.0–4.75)	<0.001
	0–25% ($n = 40$)	30.0 (24.0–36.5)	21.5 (17.75–27.25)	<0.001
		6.0 (4.0–7.0)	4.0 (3.0–5.0)	<0.001
	26–50% ($n = 76$)	26.5 (21.75–32.25)	19.5 (16.0–24.0)	<0.001
		5.0 (4.0–6.25)	3.0 (3.0–4.0)	<0.001
	51–75% ($n = 31$)	28.0 (23.0–33.5)	21.0 (17.0–25.0)	<0.001
		5.0 (4.0–6.0)	4.0 (3.0–5.0)	<0.001
	76–100% ($n = 8$)	27.0 (22.25–29.25)	19.0 (17.0–19.25)	0.014
		5.0 (4.0–5.0)	3.0 (3.0–3.25)	0.018
	>100% ($n = 3$)	27.0 (23.0–30.00)	25.0 (22.0–25.0)	0.371
		5.0 (4.0–6.0)	5.0 (4.0–5.0)	1
POSAS P (0–60)	All ($n = 153$)	33.0 (27.0–40.0)	24.0 (20.0–32.0)	<0.001
POSAS P overall (0–10)		8.0 (7.0–10.0)	5.0 (4.0–8.0)	<0.001
	0–25% ($n = 35$)	38.0 (33.0–44.0)	28.0 (21.0–37.0)	<0.001
		9.0 (8.0–10.0)	6.0 (5.0–8.0)	<0.001
	26–50% ($n = 76$)	30.0 (22.75–39.25)	22.5 (16.0–29.0)	<0.001
		8.0 (6.0–9.25)	5.0 (4.0–7.0)	<0.001
	51–75% ($n = 31$)	33.0 (31.0–38.0)	26.0 (23.0–34.0)	<0.001
		8.0 (7.0–9.0)	7.0 (5.0–7.0)	<0.001
	76–100% ($n = 8$)	31.0 (27.75–38.0)	22.5 (21.0–24.25)	0.008
		7.5 (5.0–8.5)	5.0 (4.0–6.25)	0.198
	>100% ($n = 3$)	34.0 (33.0–35.0)	30.0 (30.0–33.0)	0.371
		7.0 (7.0–7.5)	8.0 (7.5–8.0)	0.773
DN4-Pain (0–10)	All ($n = 151$)	5.0 (2.0–6.0)	4.0 (1.0–5.0)	<0.001
	0–25% ($n = 35$)	5.0 (4.0–7.0)	4.0 (2.0–6.0)	<0.001
	26–50% ($n = 76$)	3.0 (1.0–6.0)	2.5 (0.0–4.0)	<0.001
	51–75% ($n = 31$)	5.0 (3.5–6.0)	4.0 (2.5–5.0)	<0.001
	76–100% ($n = 8$)	3.0 (1.5–4.25)	3.5 (0.75–4.25)	1
	>100% ($n = 1$)	–	–	–
Modified D4 Pruritus (7–35)	All ($n = 144$)	17.0 (11.0–21.0)	14.0 (9.0–18.25)	<0.001
	0–25% ($n = 33$)	20.0 (19.0–24.0)	17.0 (14.0–22.0)	0.005
	26–50% ($n = 71$)	15.0 (8.0–18.0)	10.0 (7.0–17.0)	<0.001
	51–75% ($n = 31$)	15.0 (13.0–21.0)	13.0 (11.0–18.5)	0.003
	76–100% ($n = 8$)	17.5 (8.3–19.0)	14.5 (8.3–20.0)	0.784
	>100% ($n = 1$)	–	–	
Global impression	All ($n = 158$)			
Unchanged			16 (10.1%)	
A little bit			67 (42.4%)	
Quite a bit			44 (27.8%)	
Extremely			21 (13.3%)	

IQR, inter-quartile range; POSAS, Patient and Observer Scar Assessment Score; VSS, Vancouver Scar Scale.

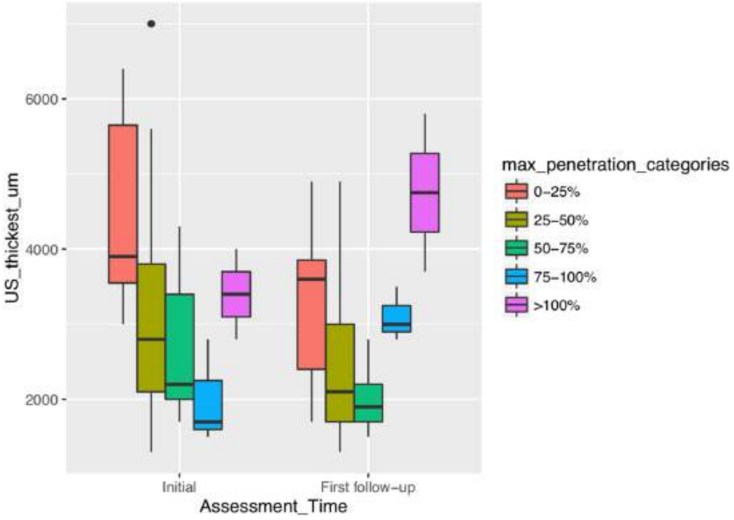

Fig. 1. Boxplot demonstrating the effect of different penetration categories on scar thickness before and after one treatment with the CO$_2$-AFL.

groups up to 75% scar penetration depth (Table 2). If penetrated 76–100% and >100%, the VSS, the POSAS-O and POSAS-O overall, as well as the POSAS-P still improved, however, without statistical significance. The POSAS-P overall even deteriorated if scars were penetrated >100%, albeit only three patients were in this group. The VSS and the POSAS-O and *P* showed significant improvement after one treatment throughout all penetration depths in immature scars. In mature scars, however, the improvements were only significant up to 75% penetration depth (Table 3).

Neuropathic pain assessed with the DN4 Pain questionnaire showed significant improvement across all penetration categories, except for those penetrated >75%, where a trend to worsening symptoms was observed (Table 2). If only patients with neuropathic pain before treatment were assessed—defined by a DN4 pain score of ≥4 ($n = 31$)—the scores dropped significantly from 6.0 (IQR, 5.0–8.0) to 4.0 (IQR, 4.0–6.0; $P < 0.001$) following one treatment. This effect was consistent across all penetration categories (0–100%) and in immature (<2 years) scars, whereas in patients with mature scars (>2 years) there was a slight worsening of pain scores by 0.5 points in those penetrated 0–25%, but improvements in those with higher penetration categories (Table 3).

Itch, measured with the modified D4 Pruritus Scale, showed significant improvement across all penetration categories up to 75% and overall if stratified according to scar maturation (Tables 2 and 3).

DISCUSSION

To our knowledge, there are no guidelines regarding what laser settings, in particular, how much energy should be used for a successful clinical outcome for burn scars treated with CO$_2$-AFL. Thus, to our knowledge, this represents first attempt to analyze how the depth of penetration with CO$_2$-AFL influences patient outcomes. While hypothesis-generating due its retrospective design, our findings may assist clinicians in the choice of settings for the treatment of hypertrophic burn scars.

Our results show that if scars were penetrated up to 75% of their thickness, a significant reduction of scar thickness could be achieved after one treatment, irrespective of scar maturation status. Highest improvements (1,100 μm) could be achieved if the scar was penetrated 51–75%. Penetration of 75–100% revealed a non-significant improvement, and if penetrated >100%, scar thickness even increased, although one should consider that the evaluated number of patients in this group was low ($n = 3$). The median scar thickness was 3,400 μm and the median laser scar penetration depth was 900 μm, which correlates to median energy of 30 mJ for which we generally use a density of 5–10%. This means in the majority of cases only 25–50% of the entire scar thickness was penetrated with good results. This may seem low, but "scar thickness" was always measured at the thickest area of the scar and it may well be, that the penetration depth around this area may have been deeper given the heterogeneity of burn scars. Furthermore, if tension is released in one part of the scar by remodeling, it can affect

TABLE 3. Change of Outcomes Stratified According Scar Penetration Depth and Maturation Status

Scar thickness (μm)	Penetration depth	Before first treatment	After first treatment	*P* value
Immature scars	All ($n = 108$)	3,600 (2,575–4,700)	2,800 (2,100–3,850)	<0.001
	0–25% ($n = 29$)	3,800 (3,200–6,000)	3,000 (2,100–4,200)	<0.001
	26–50% ($n = 51$)	3,200 (2,400–4,450)	3,000 (2,100–3,900)	0.019
	51–75% ($n = 22$)	4,100 (2,850–4,700)	2,700 (2,100–3,750)	0.011
	76–100% ($n = 5$)	3,000 (2,500–3,400)	2,100 (1,700–2,200)	0.100
	>100% ($n = 1$)	2,500 (2,500–2,500)	3,000 (3,000–3,000)	–
Mature scars	All ($n = 50$)	3,000 (2,100–3,875)	2,400 (1,900–3,200)	<0.001
	0–25% ($n = 11$)	3,900 (3,550–5,650)	3,600 (2,400–3,850)	0.002
	26–50% ($n = 25$)	2,800 (2,100–3,800)	2,100 (1,700–3,000)	0.002
	51–75% ($n = 9$)	2,200 (2,000–3,400)	1,900 (1,700–2,200)	0.022
	76–100% ($n = 3$)	1,700 (1,600–2,250)	3,000 (2,900–3,250)	0.25
	>100% ($n = 2$)	3,400 (3,100–3,700)	4,750 (4,225–5,275)	0.5

VSS (0–13)	No. of patient	Before first treatment	After first treatment	*P* value
Immature scars	All ($n = 108$)	8 (7.0–9.0)	6 (5.0–7.0)	<0.001
	0–25% ($n = 29$)	8 (7.0–9.0)	6 (5.0–7.0)	<0.001
	26–50% ($n = 51$)	8 (6.5–9.0)	6 (4.0–8.0)	<0.001
	51–75% ($n = 22$)	9 (8.0–10.0)	7 (6.0–8.8)	0.007
	76–100% ($n = 5$)	9 (9.0–9.0)	7 (6.0–7.0)	0.001
	>100% ($n = 1$)	–	–	–
Mature scars	All ($n = 50$)	8 (7.0–9.0)	6 (4.25–7.0)	<0.001
	0–25% ($n = 11$)	8 (7.0–8.5)	6 (4. 5–6.0)	0.002
	26–50% ($n = 25$)	7 (7.0–9.0)	5 (4.0–7.0)	<0.001
	51–75% ($n = 9$)	7 (7.0–9.0)	6 (5.0–7.0)	0.05
	76–100% ($n = 3$)	8 (7.5–8.0)	7 (6.5–7.5)	0.38
	>100% (n = 2)	10.5 (10.3–10.8)	8 (8.0–8.0)	0.04

POSAS-O	No. of patient	Before first treatment	After first treatment	*P* value
Immature Scars	All ($n = 108$)	27.0 (22.0–35.0)	20.0 (17.0–25.0)	<0.001
score (0–60)		5.0 (4.0–7.0)	3.5 (3.0–5.0)	
overall (0–10)	0–25% ($n = 29$)	30.0 (23.0–38.0)	20.0 (17.0–27.0)	<0.001
		6.0 (4.0–7.0)	4.0 (3.0–5.0)	
	26–50% ($n = 51$)	25.0 (21.0–31.0)	19.0 (16.5–23.5)	<0.001
		5.0 (3.5–6.0)	3.0 (3.0–4.0)	
	51–75% ($n = 22$)	29.0 (23.3–35.0)	22.0 (19.3–25.8)	<0.001
		5.0 (4.0–7.0)	3.0 (3.0–5.0)	
	76–100% ($n = 5$)	29.0 (25.0–29.0)	19.0 (19.0–20.0)	<0.001
		5.0 (5.0–5.0)	3.0 (3.0–4.0)	0.006
	>100% ($n = 1$)	–	–	–
Mature Scars	All ($n = 50$)	28.5 (23.0–32.0)	21.0 (17.0–25.0)	<0.001
score (0–60)		5.0 (4.0–7.0)	4.0 (3.0–4.0)	<0.001
overall (0–10)	0–25% ($n = 11$)	31.0 (24.5–34.0)	22.0 (21.0–28.0)	0.006
		5.0 (4.0–7.0)	4.0 (4.0–4.5)	0.06
	26–50% ($n = 25$)	29.0 (26.0–33.0)	21.0 (15.0–25.0)	<0.001
		5.0 (4.0–7.0)	4.0 (3.0–4.0)	<0.001
	51–75% ($n = 9$)	23.0 (23.0–26.0)	17.0 (17.0–18.0)	0.01
		4.0 (4.0–5.0)	3.0 (3.0–3.0)	0.02
	76–100% ($n = 3$)	20.0 (20.0–25.0)	17.0 (17.0–18.0)	0.17
		4.0 (3.5–4.5)	3.0 (3.0–3.0)	0.16
	>100% ($n = 2$)	30.0 (28.5–31.5)	25.0 (25.0–25.0)	0.5
		6.0 (5.5–6.5)	5.0 (5.0–5.0)	1

PSOSAS-P	No. of patient	Before first treatment	After first treatment	*P* value
Immature Scars	All ($n = 103$)	35 (30.0–44.0)	26 (21.0–35.0)	<0.001
score (0–60)		8.0 (7.0–10.0)	6.0 (4.0–8.0)	0.001
overall (0–10)	0–25% ($n = 24$)	38 (33–51)	30 (23–36.3)	<0.001

(*Continued*)

Table 3. (*Continued*)

PSOSAS-P	No. of patient	Before first treatment	After first treatment	*P* value
		9.5 (8–10)	7 (4–8)	
	26–50% ($n = 51$)	34 (24.5–43.5)	25 (17.0–32.0)	<0.001
		8.0 (6.5–10.0)	5.0 (4.0–7.5)	
	51–75% ($n = 22$)	32.5 (31.0–38.8)	26 (23.3–35.0)	<0.001
		8.0 (7.0–9.0)	7.0 (5.0–7.0)	0.001
	76–100% ($n = 5$)	32 (30.0–38.0)	24 (23.0–25.0)	0.04
		7.0 (5.0–8.0)	4.0 (4.0–5.0)	0.1
	>100% ($n = 1$)	–	–	–
Mature Scars	All ($n = 50$)	32.0 (22.0–35.0)	22.0 (20.0–28.0)	<0.001
score (0–60)		8.0 (6.0–9.75)	5.0 (5.0–7.0)	0.003
overall (0–10)	0–25% ($n = 11$)	38.0 (33.0–40.0)	23.0 (20.0–41.0)	0.45
		8.0 (6.0–9.0)	5.0 (5.0–7.5)	0.40
	26–50% ($n = 25$)	27.0 (21.0–32.0)	21 (16.0–23.0)	0.006
		7.0 (3.0–8.0)	5.0 (4.0–7.0)	0.03
	51–75% ($n = 9$)	34 (32.0–36.0)	28 (23.0–30.0)	0.02
		9.0 (8.0–10.0)	7.0 (6.0–8.0)	0.06
	76–100% ($n = 3$)	29.0 (25.5–33.5)	21.0 (21.0–21.5)	0.14
		10.0 (7.5–10.0)	10.0 (7.5–10.0)	1
	>100% ($n = 2$)	33.0 (32.5–33.5)	30.0 (30.0–30.0)	0.5
		7.0 (7.0–7.0)	8.0 (8.0–8.0)	0.35

DN4 Pain Score	Penetration depth	Before 1^{st} treatment	After 1^{st} treatment	*P* value
Immature scars	All ($n = 98$)	5.0 (3.0–8.0)	4.0 (2.0–5.0)	<0.001
	0–25% ($n = 29$)	6.0 (2.0–8.0)	4.0 (1.0–6.0)	<0.001
	26–50% ($n = 41$)	6.0 (3.0–8.0)	4.0 (2.0–6.0)	<0.001
	51–75% ($n = 22$)	5.0 (3.0–6.0)	3.5 (3.0–4.0)	<0.001
	76–100% ($n = 5$)	4.0 (3.0–5.0)	4.0 (4.0–5.0)	0.58
	>100% ($n = 1$)	–	–	–
Mature scars	All ($n = 45$)	2.0 (0.0–4.5)	0.0 (0.0–4.0)	0.005
	0–25% ($n = 6$)	4.5 (4.0–5.0)	5.0 (5.0–7.3)	0.4
	26–50% ($n = 25$)	1.0 (0.0–2.0)	0.0 (0.0–0.0)	0.02
	51–75% ($n = 9$)	2.0 (0.0–4.5)	0.0 (0.0–4.0)	0.2
	76–100% ($n = 3$)	0.0 (0.0–1.0)	0.0 (0.0 – 1.5)	0.8
	>100% ($n = 2$)	–	–	–

4D Pruritus Score	Penetration depth	Before first treatment	After first treatment	*P* value
Immature scars	All ($n = 103$)	18.5 (14.0–21.0)	15.5 (12.0–21.0)	<0.001
	0–25% ($n = 27$)	20.0 (19.0–25.0)	21.0 (14.0–22.0)	0.06
	26–50% ($n = 49$)	17.0 (14.0–19.0)	14.0 (9.0–17.0)	<0.001
	51–75% ($n = 22$)	15.0 (14.0–21.0)	17 (13.0–19.0)	0.13
	76–100% ($n = 5$)	19.0 (19.0–19.0))	20.0 (17.0–20.0)	0.85
	>100% ($n = 1$)	–	–	–
Mature scars	All ($n = 40$)	8.0 (7.0–16.25)	7.0 (7.0–12.0)	<0.001
	0–25% ($n = 6$)	19.5 (17.0–22.0)	17.0 (16.3–17.8)	0.10
	26–50% ($n = 22$)	7.0 (7.0–8.0)	7.0 (7.0–7.0)	0.01
	51–75% ($n = 9$)	13.0 (11.0–19.0)	7.0 (7.0–12.0)	0.01
	76–100% ($n = 3$)	0.0 (0.0–8.0)	0.0 (0.0–6.0)	0.85
	>100% ($n = 0$)	–	–	–

Median is reported unless denoted otherwise. Immature Scars: <2 years following initial burn injury; Mature Scars: >2 years following initial burn injury.

IQR, inter-quartile range; POSAS, Patient and Observer Scar Assessment Score; VSS, Vancouver Scar Scale.

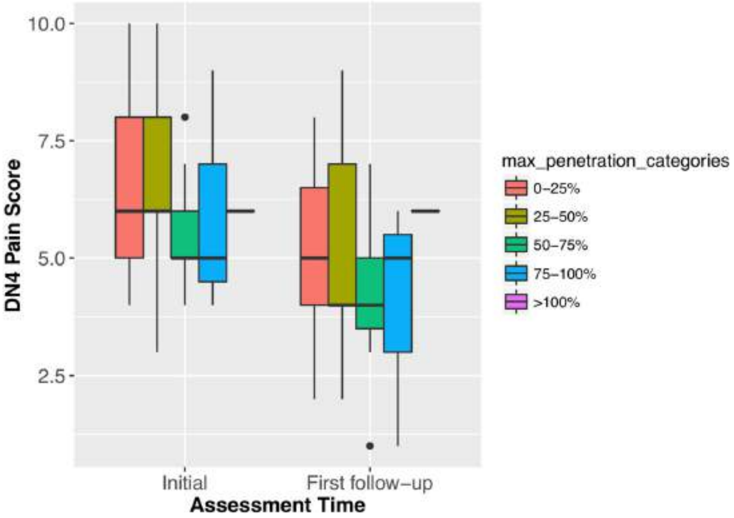

Fig. 2. Significant reduction in D4 pain scores both overall and in patients with immature and mature scars.

the entire scar. Thus, it can be argued that the actual penetration depth of the rest of the scar was actually deeper than at the point of highest thickness with a beneficial effect on the measured outcomes.

Nevertheless, our median scar thickness is in line with other reports, such as the study of Bloeme-Eberwein et al. [15] who presented a mean burn scar thickness of a similar treatment cohort of 3.15 mm (SD ± 0.37). Various units have different protocols of preferred settings for the management of hypertrophic burn scars: authors mention using energies of 30–60 mJ with densities of 5% (Response to Discussion [6]), energies of 20–40 mJ with densities ranging from 5% to 15% [16], and 20 mJ and 10–15% density [17].

As described by Paasch and Haedersdal [4], in human explants, *ex vivo* pig skin and *in vivo* human skin, the penetration depth as well as the epidermal ablation width increases with raising energies. It was shown that with high energies, the zone of coagulation increases and the zone of necrosis remains persistent if a short pulse duration is used [4]. However, large-area heating and with it, most likely, the zone of necrosis is diminished by the fractionated technology and the incorporation of scanned laser beam [4]. This means, that according to the pulse duration of a laser device, the recommendation of the choice of energy (penetration depth) has to be taken into account as well. But even more importantly, whilst dealing with a burn population various other factors need to be considered. Burn scars are multifactorial, have multiple characteristics (altered vascularization, dyschromia, structural changes, tension, contour abnormalities) and respond differently to any sort of external influence depending on various patients and burn mechanism factors [5]. In our unit, Fitzpatrick skin types, ethnicity, and scar maturation status greatly influence our clinical choice of settings for any sort of laser treatment. This is why we believe the results of the present analysis should be interpreted with caution. Settings were chosen based on clinical experience factoring in the mentioned multiple facets of a burn survivor, which may have influenced the outcomes through all treatment and penetration depth groups. Thus, whilst we believe that this study supports the principle that a 51–75% penetration of the scar is probably a good guideline for ablative fractional resurfacing, other factors must be considered when settings are chosen.

Moreover, laser facilitated infiltrations ($n = 152$) may be another substantial contributor to the documented outcomes. We routinely topically apply or intralesionally inject Kenacort A40 immediately following treatment with the CO_2-AFL. Laser-assisted delivery of drugs is an evolving technique [18,19], enhancing the bioavailability of topically applied drugs, and the positive effects of corticosteroids on burn scars are well known [20–23]. Thus, to what extent this treatment influenced our results remains to be clarified.

Despite our findings as a retrospective study, the present analysis is subject to important limitations. First, scar thickness was determined by measuring the thickest area of the treated burn scar. Given the heterogeneity of burn scars, it is thus possible that the penetration depth varied across a given treatment area. Accordingly, some insecurity exists as to how areas of deeper penetration may have affected documented outcomes. However, we chose to adapt our settings during the treatment of a scar to decrease penetration depths whilst passing over thinner areas, etc. Thus we believe, that the current penetration depth calculations—while subject to some uncertainty—may still reflect the "maximum treatment effects" achieved during a single treatment session. We acknowledge that this lack of standardization introduces an unmeasurable variable in the present analysis, which cannot be adequately adjusted for. Equally, we feel that future studies should aim at confirming actual treatment depth, by measuring it with ultrasound immediately after laser application. This would allow for improved comparison of the response in areas of similar scar depth.

Another limitation of our study is the concomittant use of CO_2-AFL and laser-facilitated drug infiltration. One-hundred and fifty-two scars (96%) were subject to this combined treatment, and as such the evaluated intervention is not only CO_2-AFL but the combination of scar ablation and laser-facilitated steroid delivery. It is unclear, to which proportion the laser and/or drug treatment contribute to the observed effects and further research is required to clarify these individual interventions. Finally, whilst the data analysed in the present study stems from a prospectively maintained database, it is a retrospective study which is subject to issues such as selection bias. Equally, the creation of treatment groups based on assumed penetration depths was performed retrospectively, hence resulting in small patient numbers in certain groups. As such, the results of the present analysis should be regarded as "hypothesis-generating" and further, prospective trials need to be performed to help elucidate the exact effect of penetration depth on burn scar outcomes.

CONCLUSION

To conclude, this study suggests that CO_2-AFL scar penetration depth significantly influences subjective and objective pathologic burn scar modulation if the scar is penetrated up to 75% of the scar thickness, irrespective of scar maturation status. Our results suggest that a scar penetration of 51–75% achieves the greatest reduction in scar thickness. Nevertheless, various other factors, such as Fitzpatrick skin type, ethnicity, scar maturation as well as type of scar should be considered when choosing the appropriate settings of CO_2-AFL for burn scar management and future research will be required to help clarify how these and other factors influence the outcomes of burn scars being treated with CO_2-AFL.

ACKNOWLEDGMENTS

We wish to thank Frank Li, Ana Rodriguez, and Monica Ditu for their efforts and assistance.

AUTHORS' CONTRIBUTION

A.C.I.-F.: Patient acquisition and treatment, study design, data acquisition and compilation, data analysis and interpretation, drafting and editing of manuscript following critical review; O.M.F.: Data and statistical analysis, interpretation and critical manuscript review; P.H.: Critical manuscript review; Z.L.: Data interpretation, critical manuscript review; P.K.M.M.: Patient acquisition and treatment, study design, data interpretation, critical manuscript review.

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Appendix D: Ablative fractional resurfacing for burn scar management affects the number and type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay.

Issler-Fisher AC, Fisher OM, Aggarwala S, Haertsch P, Maitz PK. Burns 2020 Feb;46(1):65-74. doi: 10.1016/j.burns.2019.01.004. Epub 2019 Dec 14.

BURNS 46 (2020) 65 –74

Available online at www.sciencedirect.com

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Ablative fractional resurfacing for burn scar management affects the number and type of elective surgical reconstructive procedures, hospital admission patterns as well as length of stay

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ARTICLE INFO

Article history:
Accepted 1 January 2019

Keywords:
Severe burn scars
Ablative fractional CO_2 laser
Ablative fractional resurfacing
Reconstructive burn surgery
Hospital length of stay
Complex reconstructive procedures

ABSTRACT

Background: Reconstructive surgery remains the main approach to address burn scar contractures. Ablative fractional resurfacing is an increasingly popular tool for severe burn scar management, but its effect on overall burns reconstructive case-mix, operating time and patterns of hospital admission have not been reported.

Methods: Retrospective analysis of hospital administrative data from September 2013 to June 2017 was performed evaluating these effects of ablative fractional CO_2 laser (CO_2-AFL).

Results: The total number of acute burn patients treated at CRGH increased substantially over this timeframe, resulting in 412 elective procedures including 82 before and 330 after introducing CO_2-AFL. The proportion of traditional non-laser reconstructive procedures dropped considerably to 23.9% in about 2.5 years following CO_2-AFL introduction. This change in approach had a profound effect on LOS with average LOS being 1.96days for non-laser and 0.36days for CO_2-AFL-procedures ($p < 0.001$). Anaesthetic times also decreased significantly, with median durations at 90min pre-laser and 64min post-laser introduction ($p < 0.001$), and median anaesthetic times at 87min (non-AFL) and 57min (AFL procedures) ($p < 0.001$).

Conclusion: AFL profoundly affects elective reconstructive burn case mix with a replacement of conventional reconstructive operations in favour of AFL-procedures. This results in reductions of average LOS and anaesthetic times. Consequently, increased use of AFL in burn scar management could potentially reduce overall costs associated with burn scar reconstruction.

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https://doi.org/10.1016/j.burns.2019.01.004
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1. Introduction

Wound contraction and scarring is part of the regular healing process [1]. Contraction leads to tension, a prerequisite for the development of hypertrophic, erythematous, painful and pruritic scars [2]. These type of scar contractures may limit the patient's range of motion and compromise other skin functions such as sweating and thermal regulation, and lead to heat intolerance [3–5]. Psychological consequences, such as post-traumatic stress and depression are further sequelae of a severe burn injury [6]. With the advances in burn care and associated increased survival rates, all these issues have become increasingly evident in patients surviving extensive burn injuries [5].

Approaches for burn scar treatment range from non-surgical options (such as silicone products and pressure garments), laser treatments, to injecting small hypertrophic scars with corticosteroids as well as radiotherapy for keloid scars, and surgical reconstruction. The surgical reconstructive options for burn scar management comprise of dermabrasion and cultured epithelial autografting, contracture release and grafting, excisional grafting, the use of tissue expanders and different tissue flaps [2,7]. However, most of these surgical reconstructive options are associated with considerable morbidity, involving a lengthy, painful process, donor-sites, time off work and admissions to the hospital [2,8].

Several groups have reported significantly improved scar assessment scores, increased pliability, decreased thickness, and improvement in function, symptoms, and quality of life following the use of laser to treat burn scars [4,5,9–11]. As such, ablative fractional resurfacing was implemented in 2014 into the routine scar management at the Concord Repatriation General Hospital (CRGH) burns unit and the positive outcomes of previous reports were confirmed [5]. This retrospective study analyzed all elective burns reconstructive procedures performed at the CRGH Burns from September 2013 to June 2017 stratified by pre- versus post laser introduction. By analyzing the number and pattern of laser cases performed in that time frame, we intended to determine if CO_2-AFL has led to a replacement of conventional reconstructive procedures, impacted the elective reconstructive case mix, and how it has affected patient operating times, admission patterns as well as hospital length of stay.

2. Materials and methods

2.1. *Study setting & patient population*

Concord Repatriation General Hospital in Sydney, Australia, is a 470-bed tertiary referral facility for burn patients and a teaching hospital of the University of Sydney. The unit is a statewide referral center for burns patients and includes a high-volume Burns Outpatient Clinic reviewing up to 1000 patients per month. In 2015 a Burn Scar Clinic was developed dedicated to the clinical assessment and treatment of burn scarring sequalae. Anecdotally, the number of admissions as well as outpatient visits of burn patients have increased substantially over the last few years at the CRGH Burns Unit. In total, 1507 procedures were performed between September 2013 and June 2017, of which 1095 were acute cases. For this study, only elective reconstructive procedures were analysed.

2.2. *Treatment protocol & scar algorithm*

Burn patients requiring burn scar management are referred to our outpatient Burn Scar Clinic. Patients and their pathologies are evaluated, and a treatment plan established, including non-invasive therapies, laser treatments, and reconstructive surgical procedures (Fig. 1).

Patients suitable for ablative fractional resurfacing are treated with the ablative fractional CO_2 Ultrapulse® laser with

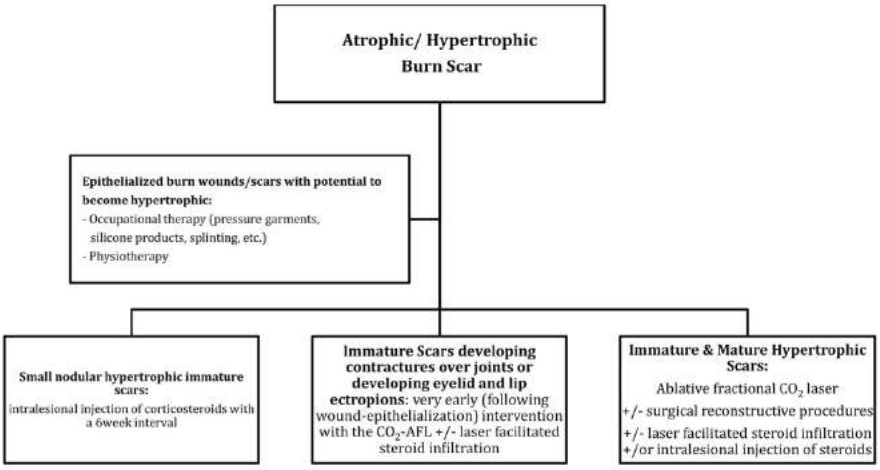

Fig. 1 – Treatment Algorithm for Burn Scars, Burns Unit, Concord Repatriation General Hospital (CRGH).

wavelength of 10,600-nm (by Lumenis®) including ActiveFx™ (80–125mJ Energy, 3–45% Density, 250–300Hz Rate) and DeepFx™ (15–50mJ Energy, 5–15% Density, 300Hz Rate) hand pieces and the SCAAR Fx™ mode (60–150mJ Energy, 1–5% Density, 250Hz Rate). CO_2-AFL treatment of hypertrophic burn scars with CO_2-AFL is almost always immediately followed by laser facilitated topical and/or injected intralesional delivery of corticosteroids (Kenacort® A10 or A40). Settings are chosen and tailored individually for each patient, taking considerations of scar quality, thickness, ethnicity, Fitzpatrick skin type, vascularization, pigmentation, and scar maturation status.

Any elective surgical procedures are generally performed following scar maturation, unless the risk for secondary damage is mandated due to presence of contracture (severe contracture of joints, eyelids or lips). However, laser intervention may be initiated as early as full epithelialization has been achieved to prevent further contracture. For example, in eyelid ectropions as highlighted in Fig. 1, or if immature scars are cause for disabling symptoms such as tightness, pruritus or neuropathic pain to favorably impact scar maturation. All procedures (laser and surgical reconstructive treatments) are performed in our dedicated burns theatre within the CRGH Burns Unit under local or general anaesthesia depending on the extent of the required procedure. We aim to treat all problematic areas/scars of a burn victim in one treatment session, however the areas treated with the CO_2-AFL are usually kept under 30% TBSA (total body surface area) based on our clinical experience on what is well tolerated by the patients and due to time restriction in theatres.

2.3. *Data collection*

Burn scar treatment with the CO_2-AFL was introduced in our facility during the fourth quarter of 2014. Hospital's data was collected through CRGH administrative and electronic medical records from September 2013 until June 2017. Information on patient demographics and details on the initial burn injury (where available) was collected through the database of the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service as well as from our prospective database of all patients who are treated with the CO_2-AFL.

Firstly, the number and types of elective reconstructive procedures performed pre- and post-laser introduction as well as changes in the number of cases over time (stratified by

Table 1 – Demographic data of patients undergoing elective reconstructive procedures performed at CRGH from September 2013 to June 2017.

	All procedures	Pre-laser era	Post-laser era	p-Value	Non-laser cases	Laser cases	p-Value
Number of cases	412 (100%)	82 (100%)	330 (100%)	–	161 (39.0%)	251 (60.9%)	–
Gender							
Female	242 (58.7%)	47 (57.3%)	195 (59.1%)	0.77	74 (46.0%)	168 (66.9%)	<0.001
Male	170 (41.3%)	35 (42.7%)	135 (40.9%)		87 (54.0%)	83 (33.1%)	
Age (years) median	37 (27.0–49.0)	36 (27.0–47.3)	38 (27.3–49.0)	0.43	36 (28.0–38.8)	38 (27.0–39.7)	0.58
% TBSA[a] burnt median	15 (5.6–38.0)	18.25 (3.0–30.8)	15 (6.0–38.0)	0.43	23 (4.9–38.0)	15 (6.6–36.8)	0.85
% TBSA[a] grafted median	5 (2.0–25.8)	15 (2.0–30.0)	5 (2.0–25.0)	0.48	6 (2.0–30.0)	5 (3.0–25.0)	0.53
Type of burn injury	238	56	182	0.02	104	134	0.01
-Flame	153 (64.3%)	29 (51.8%)	124 (68.1%)		59 (56.7%)	94 (70.1%)	
-Scald	35 (14.7%)	7 (12.5%)	28 (15.4%)		13 (12.5%)	22 (16.4%)	
-Contact	17 (7.1%)	6 (10.7%)	11 (6.0%)		11 (10.6%)	6 (4.5%)	
-Other	33 (13.9%)	14 (25.0%)	19 (10.4%)		21 (20.2%)	12 (9.0%)	
Time since burn injury (months): median	19 (10.3–34.0)	15.5 (9.0–31.3)	19.5 (11.0–34.0)	0.22	15 (6.8–29.5)	21.5 (14–36.5)	<0.001
-Immature scars (<2 years)	143 (60.1%)	34 (60.7%)	109 (59.9%)	0.91	67 (64.4%)	76 (56.7%)	0.22
-Mature scars (>2years)	95 (39.9%)	22 (39.3%)	73 (40.1%)		37 (35.6%)	58 (43.3%)	
Type of scar	474[b]	118[b]	356[b]		210	264	
-Conservative	30 (6.3%)	7 (5.9%)	23 (6.5%)	0.83	10 (4.8%)	20 (7.7%)	0.15
-Skin graft	208 (43.9%)	49 (41.5%)	159 (44.7%)	0.98	94 (44.8%)	114 (54.3%)	0.22
-Re-graft	82 (17.3%)	24 (20.3%)	58 (16.3%)	0.13	41 (19.5%)	41 (19.5%)	0.16
-Biobrane®	154 (32.5%)	38 (32.2%)	116 (32.6%)	0.57	65 (31%)	89 (42.4%)	0.53

The information in Table 2 could only be collected from patients who sustained their burn injury after 2013, who were initially treated at Concord Hospital for their acute burn injury, or received treatment with the CO_2-AFL.

[a] TBSA=total body surface area.

[b] Total sums of previous scar treatments are greater than the number of cases as some patients received multiple treatments to their injuries before being referred for scar reconstruction.

annual quarter) was analyzed and compared. Subsequently, the effect of the change in practice on operating/anaesthetic times as well as the overall hospital length of stay was evaluated and compared before and after the introduction of the CO_2-AFL. Anaesthetic time was chosen as a more accurate indicator for total procedural (operating theatre) time, as for example the treatment of multiple areas during one anaesthetic may require repositioning and re-draping of patients.

Lastly, to evaluate the efficacy of treatment with the CO_2-AFL treatment we have carried out an interims and prospective analysis of 41 patients with 93 scars who have completed their full treatment with the CO_2-AFL, analyzing various subjective and objective outcome measures. The prospective data collection of all CO_2-AFL patients includes patient demographics and information about the burn mechanism. A set of objective and subjective outcome parameters are collected prior to and at 6 weeks after each laser treatment, including the Vancouver Scar Scale (VSS) [11], Patient and Observer Scar Assessment Score (POSAS) [12], scar thickness measured by ultrasound, questionnaires regarding pain using the Douleur Neuropathique 4 Questions (DN4) [5], pruritus using a modified 5-D itch scale (4-D Pruritus Scale) [13], and QOL using the Burns Specific Health Scale — Brief (BSHS-B) [14]. These outcome measures were further stratified according to the maturation status of the scar (immature=<2years post injury, mature=>2years post injury).

2.4. *Statistical analysis*

Data are reported as median with inter-quartile range (IQR) unless denoted otherwise. The continuous variables were compared using Student's t-Test, Wilcoxon rank-sum, one-way analysis of variance ANOVA and/or Kruskal–Wallis tests as appropriate. Differences between proportions of categorical data were compared using Pearson's χ^2- or Fisher's exact test where appropriate. Analyses were stratified both according to the treatment "era" (i.e. pre- vs. post-laser introduction) as well as according to whether CO_2-AFL was included in the patient's reconstructive surgical procedure or not. A p-value of <0.05 was accepted as statistically significant. All statistical analyses were performed using R Statistical Packages [12].

3. Results

3.1. *Number of elective reconstructive procedures before and after CO_2-AFL introduction*

In total 412 elective burns scar cases (including 82 prior CO_2-AFL and 330 post CO_2-AFL) were treated during September 2013 to June 2017. While all 100% (82/82) patients received conventional reconstructive procedures prior to CO_2-AFL

Table 2 – Numbers and types of elective reconstructive procedures performed at CRGH from September 2013 to June 2017.

	All procedures	Pre-laser era Sept 2013–Dec 2015	Post-laser era Dec 2015–June 2017
Number of cases	412 (100%)	82 (100%)	330 (100%)
Laser (alone or combined)	251 (60.9%)	–	251 (76.1%)
Laser to multiple scars	184 (44.7%)	–	184 (55.7%)
1xlaser	–	–	95 (37.8%)
2xlaser			73 (29.1%)
3 × laser	–	–	42 (16.7%)
4 × laser	–	–	24 (9.6%)
5 × laser	–	–	9 (3.6%)
6 × laser	–	–	3 (1.2%)
7 × laser	–	–	3 (1.2%)
8 × laser	–	–	2 (0.8%)
Non-laser	161 (39.0%)	82 (100%)	79 (23.9%)
Combined procedures	126 (30.6%)		
Non-laser combined	86 (20.9%)	43 (52.4%)	43 (13.0%)
Laser combined	40 (9.7%)	–	40 (12.1%)
E/O[a] scar	73 (17.7%)	40 (48.8%)	33 (10%)
Serial E/O[a] scar	6 (1.5%)	4 (4.9%)	2 (0.6%)
Z-Plasties	91 (22.1%)	26 (31.7%)	65 (19.7%)
Release & STSG[b]	29 (7.0%)	29 (36.4%)	0
Release & dermal template	2 (0.5%)	2 (0.5%)	0
Dermabrasion & CEA[c] or STSG[b]	8 (1.9%)	5 (6.1%)	3 (0.9%)
Eyelid ectropion release/canthoplasty	7 (1.7%)	5 (6.1%)	2 (0.6%)
Lip ectropion/mouth angle release	12 (2.9%)	7 (8.5%)	5 (1.5%)
Local (except Z-plasties)	13 (3.2%)	6 (7.3%)	8 (2.4%)
Regional/free llaps	3 (0.7%)	3 (0.7%)	0
Expander	4 (1%)	4 (1%)	0
Other[d]	34 (8.3%)	8 (9.8%)	26 (7.9%)

[a] E/O=excision of.

[b] STSG=split thickness skin graft.

[c] CEA=cultured epithelial autograft.

[d] Other=resection-arthrodesis, stump revision, fat grafting, removal of heterotopic ossification, etc.

introduction, only 23.9% (79 out of 330) had conventional reconstructive procedures post CO_2-AFL introduction. CO_2-AFL treatment accounted for 60.9% (251/412) of total procedures (pre- and post-laser introduction) and 76.1% (251/330) procedures post CO_2-AFL introduction. Significantly more female patients received laser procedures compared to male patients (67% vs. 46%, $p<0.001$) and patient median age was 37 years (36 non-laser, 38 laser-based procedures, $p=0.58$).

Information regarding the burn mechanism, including % TBSA burnt, type of burn injury, type of scar, and scar maturation, were not statistically significant between the pre- and post-laser era Table 1. However, the time interval from initial burn injury to first scar intervention appeared a bit longer in the laser cases compared to the non-laser cases Table 1.

3.2. *Type of elective reconstructive procedures and the change in procedural case-mix following CO_2-AFL introduction*

A detailed summary of the types of procedures performed during the analyzed timeframe is provided in Table 2. Interestingly, more than half of the elective cases prior to laser introduction were combined surgeries, which means that more than one type of reconstructive procedure was performed. However, following CO_2-AFL introduction only 13% of the non-laser cases included more than one surgical procedure. Equally, the treatment of multiple scars during one anaesthetic was more evident, with 55.7% of all laser cases received the treatment to multiple scars (median of 2 scars/per procedure in the range 1–6).

Comparing the non-laser cases, pre- vs. post-laser introduction, a clear change of reconstructive surgical procedures was seen. For example, prior to laser introduction, the procedures performed were predominantly scar excisions (48.8%), release and split thickness skin grafts (36.4%), and Z-plasties (31.7%), whereas after laser introduction, scar excisions decreased substantially to only 10%, Z-plasties accounted for only 19.7% of all surgical procedures and no releases with STSG or dermal templates were performed. Additionally, dermabrasion as well as eyelid and ectropion releases were much less frequently performed after laser introduction. There were no regional flaps, free flaps or tissue expanders performed anymore following CO_2-AFL introduction. Finally, when analyzing the cases performed after laser introduction, 12.1% of all laser cases were combined with other reconstructive surgical techniques, 82.5% of which were Z-plasties (Supplement Table 1).

The indications for post burn reconstruction were summarized into three broad categories: Resurface (removal and resurfacing of unsightly or symptomatic burn scar by excision and closure either directly, serially, with a graft, substitute or flap), release (release of contracture and graft, skin substitute or flap) and/or replace (Reconstruction of missing parts — nose, ears, digits, etc.). As demonstrated in Table 3, one could observe a significant shift in the resurface group with the laser being used to improve the appearance and symptoms of the scar. We also found a significant reduction in releasing procedures alone comparing pre- vs post laser introduction. As such, a substantial reduction in the numbers of conventional reconstructive procedures as well as the associated procedural complexity following laser introduction could be observed (Fig. 2).

3.3. *Increase in number of treatments per patients following CO_2-AFL introduction*

Ablative fractional resurfacing may result in multiple treatments being required to achieve the final results [14]. However, some data indicate that the number of reconstructive procedures per burn patient life-time may be as a high as 3.6 [17]. Thus, we looked at how many treatments patients underwent on average pre- vs. post-laser introduction. We found that the median number of treatments pre laser were 1 (range 1–4), whereas post laser introduction it increased to 2 (range 1–6, $p<0.001$). Equally, when stratified by laser vs. non-laser cases, the median number of treatments in the laser group was higher (2 [range 1–8] vs. 1 [range1–6], $p<0.001$).

3.4. *Effect of CO_2-AFL introduction on operating/ anaesthetic times*

The median anaesthetic time for all reconstructive procedures performed for the entire study duration was 70min (IQR 45–103). The median anaesthetic time prior to laser introduction was 90min (IQR 61.5–109.8) and dropped significantly to 64min (IQR 44–100.50) following CO_2-AFL introduction ($p<0.001$). Examining the type of procedures, laser treatments in general were significantly shorter (57min, IQR 40–91.5) compared to non-laser procedures (87min, IQR 60–115; $p<0.001$), especially if the procedures consisted of only CO_2-AFL (51min, IQR 39–75; $p<0.001$). However, if the laser was combined with other surgical

Table 3 – Changes in post burn reconstruction procedure group types, when grouped by scar resurfacing, releasing and replacement.

Indication	Pre-laser (n=82)[a]	Post-laser (n=329)	p-Value	Non-laser (n=160)	Laser (n=251)	p-Value
Resurface	41 (50%)	204 (62%)	<0.001	68 (42.5%)	177 (70.5%)	<0.001
Release	35 (42.6%)	62 (18.8%)		68 (42.5%)	29 (11.6%)	
Resurface & release	3 (3.7%)	43 (13.1%)		7 (4.4%)	39 (15.5%)	
Replace	3 (3.7%)	16 (4.9%)		13 (8.1%)	6 (2.4%)	

[a] For the total number of procedures pre & non-laser, there were 4 other reconstructive procedures which did not allow for clear classification as per the groups above and thus were excluded for the statistical analysis.

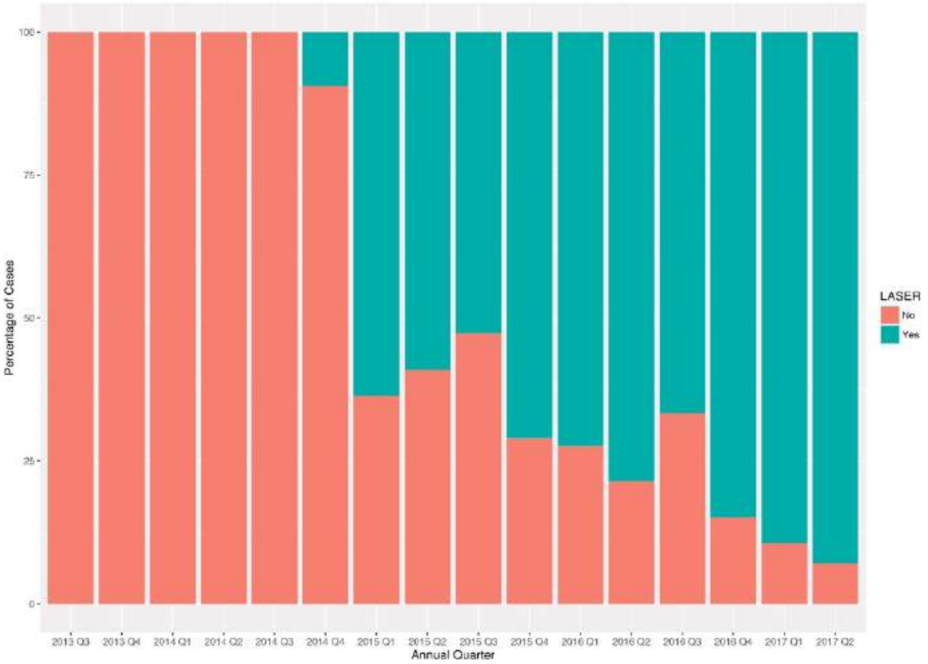

Fig. 2 – Change in proportion of laser cases for elective burn scar reconstruction since introduction of the AFL-CO_2 at CRGH.

treatments, the anaesthetic time significantly increased by almost half an hour (121 min, IQR 105–141, $p<0.001$, Fig. 3).

Of the laser cases, 125 (49.8%) of the procedures could be performed under topical or local anaesthetic only, and 126 of the cases (50.2%) required a full general anaesthetic.

3.5. *Effect of the CO_2-AFL introduction on patient hospital length of stay*

Prior to laser introduction, 32.9% of the patients undergoing an elective reconstructive procedure were required to be admitted as an inpatient to the hospital for one or more nights. This figure dropped substantially following laser introduction, where only 7.5% of patients required an inpatient admission ($p<0.001$, Table 2). When specifically looking at non-laser versus laser procedures, we observed that only 1.6% (4 cases) of all laser cases required admission overnight, whereas following laser introduction 29.7% of the non-laser patients were admitted overnight ($p<0.001$). Not surprisingly, the actual length of stay in hospital was significantly shorter for the laser cases at 0.36 days (range 0.1–7.33) compared to 1.96 days (range 0.12–46.2; $p<0.001$). However, when analyzing the length of stay of inpatients alone, no statistically significant difference in LOS could be identified although the mean LOS was 2 days shorter for laser patients compared to non-laser patients (3.21 days vs. 5.71 days, $p=0.77$; Table 4).

It is also worth mentioning that of the four patients requiring overnight admission following CO_2-AFL treatment, one patient was admitted due to the extent of the combined surgical procedure (large excision of abdominal scar, mini abdominoplasty), two patients stayed at the day-surgery unit overnight as they had nobody to pick them up following a general anaesthetic and one patient was admitted for treatment of an incidental finding of asymptomatic episodes of complete heart blocks.

3.6. *Outcome analysis of patients treated with the CO_2-AFL*

Forty-one patients with 93 scars have completed their full treatment with the CO_2-AFL. All analysed objective parameters dropped significantly including normalized scar thickness as measured with ultrasound which decreased from a median of 2.5mm–1.7mm ($p<0.001$) and a concomitant VSS-drop from a median of 8 to 5 ($p<0.001$). The overall POSAS observer and patient scales decreased from a median 5 to 3 ($p<0.001$) and 9 to 4 (<0.001) respectively. Intriguingly, neuropathic pain and pruritus also decreased significantly (median 5 to 2 and 16 to 11; both $p<0.001$). The post-burn quality of life, as assessed by the BSHS-B, increased by 14 points (median 126–140; $p<0.001$). All of the identified changes following CO_2-AFL were irrespective of scar maturation status (> vs. <2 years).

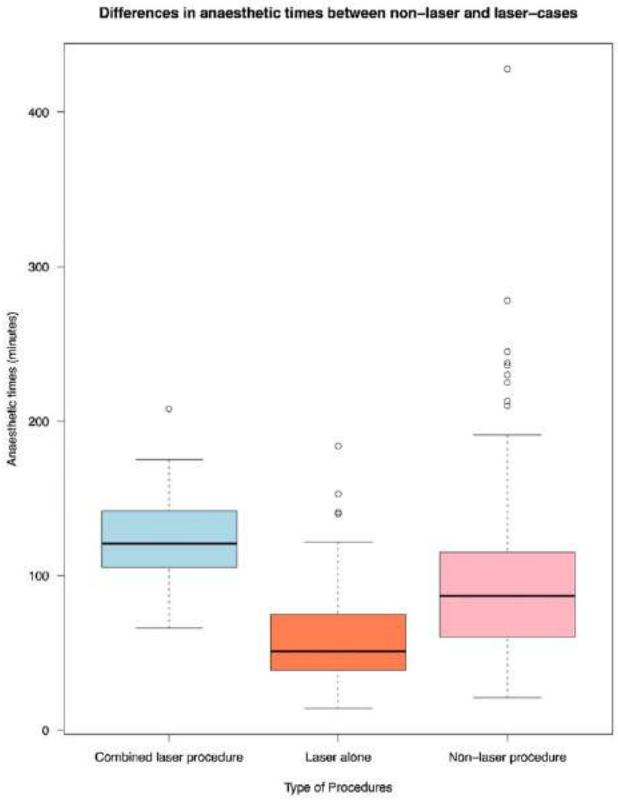

Fig. 3 – Differences in anaesthetic times depending on what type of reconstructive procedure was performed.

Table 4 – Effect of different types of reconstructive procedures performed at CRGH from September 2013 to June 2017 on length of stay at the hospital.

Admission type		Pre-laser (n=82)	Post-laser (n=322)	p-Value
Day only procedure	–	55 (67.1%)	298 (92.5%)	<0.001
Overnight/inpatient	–	27 (32.9%)	24 (7.5%)	
Admission type		Non-laser (n=158)	Laser (n=246)	p-Value
Day only procedure	–	111 (70.3%)	242 (98.4%)	<0.001
Overnight/inpatient	–	47 (29.7%)	4 (1.6%)	
Length of stay	All procedures	Non-laser	Laser	p-Value
Mean length of stay (days, range)	0.33 (0.28–0.41)	1.96 days (0.12–46.2)	0.36 days (0.10–7.33)	<0.001
Only inpatient (n=51)	2.27 (1.1–46.2)	5.81 days (1.0–46.2)	3.21 days (1.0–7.33)	0.77

4. Discussion

To our knowledge, this is the first study analysing the effect the introduction of CO_2-AFL has on the burns recontructive surgical case-mix, anaesthetic times and hospital length of stay in a high-volume Western burns unit. Our study shows that CO_2-AFL can be used either alone or in combination with conventional burns scar reconstructive procedures, resulting in a replacement of more extensive procedures, whereby shortening operative times and patient hospital length of stay. Whilst the exact cost-saving of such changes to elective burn patient management remain to be elucidated, we believe our data supports the notion that CO_2-AFL has become a valuable and potentially cost-effective tool in the management of these complex patients.

It could be argued that the decrease in conventional reconstructive procedures and increase in laser procedures following the laser introduction reflects the use of a novel technology following a big financial investment. However, as can be seen in the presented data, the replacement of conventional reconstructive procedures with CO_2-AFL was gradual and occurred with increasing device experience as well as learning what results could be achieved. The rise of use of CO_2-AFL was encouraged by good clinical outcomes and patient satisfaction, leading to an increase in new referrals for scar management with the CO_2-AFL [5].

Furthermore, it is important to note that the overall numbers of admissions to the CRGH Burns Unit and visits to the CRGH Burns Outpatient Clinic increased substantially over the study period, thus leading to more patients being seen who may have benefited from this new treatment. Hence, the change in elective procedural case-mix also represents a learning-curve of our burns unit regarding patient selection. We acknowledge that the cohorts pre and post laser introduction may be heterogenous in nature and may not necessarily contain patients with comparable burn scars. This could be attributed either to the type of burn injuries sustained during the time period or due to surgical and non-surgical advances in acute burn care management that prevented patients from ending up with contractures that needed surgical intervention. Nevertheless, as shown in Table 1, we demonstrate that (where data was available) the population, type and age of burn scars were comparable in both cohorts, before and after introduction of CO_2-AFL.

As also indicated by our data, we believe that this treatment approach allows us to address problematic scars in a way which was previously not possible which may also contribute to the increase of patient referrals during the analyzed time-frame. This is reflected by the fact, that amongst other more complex reconstructive procedures, eyelid and lip ectropion releases were less frequently performed following laser introduction.

We found that the complexity of reconstructive procedures decreased following laser introduction, which may be related with a change in the time-point of intervention. Current paradigms suggest to await complete burn scar maturation before reconstructive procedures are planned, unless intervention is needed to prevent secondary damage [2]. Several reports have outlined that early intervention with the CO_2-AFL for the treatment of immature scars can positively influence scar rehabilitation, accelerating scar maturation, improving early mobility, and enhancing as well as accelerating the entire rehabilitative process [10,13,14]. Further, recent reports showed that CO_2-AFL can successfully avoid the surgical release of ectropions with skin grafts if used in an early stage post injury [15,16]. Thus, early intervention with the CO_2-AFL and the positive effect on scar rehabilitation may well contribute to the phenomenon that certain more complex procedures are not needed once the scars are fully mature.

Whilst comparative outcome data before and after CO_2-AFL introduction (laser vs non-laser) is missing in the presented analysis, our data demonstrated clear benefits of CO_2-AFL treatment. Significantly improved objective and subjective outcome parameters could be shown with clear benefits for the patients as they were able to receive a fast, effective, alternative treatment compared to the traditional surgical approaches.

The above data are encouraging, but they are limited by the fact that it usually takes 3–6 treatments with the CO_2-AFL to achieve an optimal result [14] compared to one procedure for a conventional reconstructive surgical intervention. As such, it is entirely possible that CO_2-AFL may increases the burden on operating theatres due to increased number of overall procedures, which may lead to increased waiting lists for elective procedures as well as total costs to a Burns Unit. However, conversely all scars are usually treated during the same CO_2-AFL treatment session, whereas in the majority of other reconstructive procedures only one area is addressed at a time to reduce periprocedural morbidity. Furthermore, it has been estimated that the mean number of reconstructive procedures required per burn patient during their life-time following the burn injury is 3.6 [17]. Our analysis of the total number of procedures per patient in the pre- vs. post-laser era only looked at a timeframe of 1.5years in the pre-laser ear and not a "life time". This means that it could well be that the actual number of laser procedures is in fact comparable to traditional reconstructive procedures if the number of elective reconstructive procedures per patient per lifetime were to be accounted for. Further, due to the shorter anaesthetic times, more cases can be completed during one operating list, potentially offsetting any previous financial investment and associated costs [18]. However, we acknowledge that the actual financial implications may vary from country to country due to associated billing codes and reimbursement practices for this novel procedure [18].

Our study found that anaesthetic times dropped significantly by over 30min following the introduction of the CO_2-AFL. A recently published study analysing the impact of treatment of burn scars with an erbium-YAG laser on a burn operating rooms flow and productivity, reported similar findings [18]. Their mean anaesthetic time for reconstructive procedures pre-laser was 157.5 ± 65.0 and laser procedures only in the post-laser era dropped to 79.2 ± 33.4 ($p < 0.001$) which is similar to our experience. As a result, like Madni et al. we have also experienced that more reconstructive cases can now be completed with up to 8–10 cases performed per day during a dedicated laser reconstruction operating list [18]. A great number of the CO_2-AFL cases can be treated under topical or local anaesthetic only (almost 50% in our data set), which means that a significant financial saving could be made as these cases can all be performed without the presence of an anaesthesist, anaesthetic nurse and recovery personnel.

However, one of the most profound impacts our unit has experienced since the introduction of the CO_2-AFL is the change in admission patterns. Of the 246 laser procedures performed, only 4 (1.6%) required overnight admission, with an average length of stay 2days shorter than conventional, non-laser reconstructive procedures. Two of these four cases were admitted for one night due to social reasons, one patient was admitted due to a medical indication, and one patient was admitted due to the extent of the combined procedure. Thus, only one admission was actually related to scar treatment.

This is largely due to the fact that the CO_2-AFL procedures can easily be performed as a day-only procedure, sometimes only requiring local anaesthetic. Most patients also only remain off work for a few days following the CO_2-AFL procedure and can reintegrate seamlessly into previous activities. Further, for patients suffering from severe pruritus, neuropathic pain and paraesthesias requiring medications such as narcotics, antihistamines, anxiolytics and antidepressants, treatment with CO_2-AFL can decrease these pharmacological requirements [19]. Thus, this may also result in an ultimate cost reduction by reducing the need of expensive drug regimens and a more rapid re-integration into the workplace [19]. Consequently, whilst the cost-savings associated with laser introduction remain entirely hypothetical, we believe our data supports their plausibility. To conclusively define the economic impact of laser introduction on burn scar management a rigorous cost analysis should be performed taking considerations of other factors such as occupational and physiotherapy requirements, medication, time-off work, and rehabilitation/re-integration into the workforce in addition to procedural operating times and hospital length of stay.

5. Conclusion

Following introduction of the laser at CRGH Burns Unit, 76.1% of all elective burns reconstructive surgeries performed were laser-based procedures. In our facility, ablative fractional resurfacing with or without Z-plasties, excision of scars and local flaps appear to have replaced more complex reconstructive procedures. Anaesthetic times have also significantly reduced following laser introduction. Furthermore, the requirement to admit a patient for a reconstructive procedure has decreased significantly since the introduction of AFL-CO_2, as 98% of procedures can be performed as a day-only procedure. As such, the minimally invasive nature and minimal side effect profile of CO_2-AFL (no donor-sites, no foreign material, no complex procedures) make it a valuable tool for burn scar management. It potentially allows for more timely and efficacious rehabilitation, and reintegration into work place compared with conventional reconstructive procedures. Whilst future, prospective and randomized studies are required to further validate the efficacy of this novel treatment, the effect it has in altering patient burn care and hospital admission patterns is clearly illustrated and supports further research into this evolving area of burn care.

Conflict of interest

The authors declare that there is no source of financial or other support, or any financial or professional relationships, which may pose a competing interest.

Financial disclosure

The authors declare that there is no source of financial or other support, or any financial or professional relationships, which may pose a competing interest.

CRediT authorship contribution statement

Andrea C. Issler-Fisher: Conceptualization, Investigation, Methodology, Validation, Visualization, Project administration, Writing - original draft. **Oliver M. Fisher:** Formal analysis, Methodology, Validation, Visualization, Writing - review & editing. **Nicola A. Clayton:** Writing - review & editing. **Shivani Aggarwala:** Data curation. **Peter A. Haertsch:** Validation, Writing - review & editing. **Zhe Li:** Validation, Visualization, Writing - review & editing. **Peter K.M. Maitz:** Conceptualization, Supervision, Writing - review & editing.

Acknowledgements

We wish to thank Ana Rodriguez and the Burns Theatre staff for their efforts and assistance. Further, we wish to thank Anne Darton and the New South Wales Agency for Clinical Innovation Statewide Burn Injury Service Data Registry for their assistance with data acquisition.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.burns.2019.01.004.

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Appendix E: Ablative fractional resurfacing in acute care management of facial burns: a new approach to minimise the need for acute surgical reconstruction.

Clayton NA, Haertsch PA, Maitz PK, Issler-Fisher AC. J Burn Care & Research. 2019. Apr 26;40(3):368-372. doi: 10.1093/jbcr/irz030

CASE REPORT

Ablative Fractional Resurfacing in Acute Care Management of Facial Burns: A New Approach to Minimize the Need for Acute Surgical Reconstruction

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Current evidence suggests awaiting for scars to fully mature before engaging surgical reconstruction unless acute indications to prevent secondary damage, such as microstomia and eyelid ectropion are apparent. To evaluate the efficacy of ablative fractional CO_2 laser intervention early in the acute treatment of panfacial burn injury. A 39-year-old Asian male with 60% TBSA flame burns including panfacial involvement was developing microstomia and upper and lower eyelid ectropion early proceeding epithelialization. At 6-weeks postinjury, ablative fractional CO_2 laser treatment was commenced while still in the intensive care unit, and subsequently delivered at regular intervals. Nonsurgical scar contracture management was provided concurrently as per site specific standard protocols. Measurements and photographic data relative to deficits in eye and mouth competence were obtained at rest, as well as maximal opening at baseline and routinely until scar stabilization was reached. The outcomes were subsequently compared with facial burn patient historical data within our facility. No significant difference was identified in the functional ROM for mouth and eye regions; treatment duration was, however, shorter and aesthetic outcomes were considered superior to their surgical reconstruction counterparts in the historical cohort. This case report reveals that early ablative fractional CO_2 resurfacing treatment, coalesced with nonsurgical scar management is an efficacious interventional approach to abate contractures to the face, accelerates and enhances scar maturation processes and may alleviate the need for surgical scar reconstructions. Moreover, optimal aesthetic outcomes may be achieved compared with traditional reconstructive methods.

Severe panfacial burn injury is recognized as one of the most challenging areas of the body to treat.[1–4] Early rigorous nonsurgical scar management has been shown to be effective in minimizing orofacial contractures,[5,6] however in some patients, development of microstomia and ectropion are unavoidable despite all nonsurgical scar contracture management efforts. In these cases, early reconstruction to maintain function is often necessary. Further, while function may be restored, aesthetic results are frequently suboptimal particularly as surgical reconstructions may need to be repeated.

The introduction of ablative fractional CO_2 lasers (CO_2-AFL) in scar management following severe burn injury has been reported as an alternative or adjunct to traditional reconstructive surgery with the evidence indicating promising results.[7–10] CO_2-AFL is often used combined with other laser therapies targeting hemoglobin or melanin.[10] Further, the microcolumns in the dermal layer of the scar are ideal to combine with laser facilitated infiltration of corticosteroids or other medications.[9,10] Positive impacts on color, texture, pliability, and height of the burn scar with subsequent beneficial aesthetic and functional results have been demonstrated.[8,11–13] Further to this, a recent study conducted by Issler-Fisher *et al*[9] reports that the use of laser treatment may not only improve cosmetic and functional outcome, but also improve quality of life in patients with either mature or immature scar tissue.[9]

Evidence suggests that with the technological advances of CO_2-AFL, this treatment may potentially reduce the indication or extent of major reconstructive surgery in the burn patient, while favoring more optimal patient functional, aesthetic and quality of life outcomes. This concept subsequently holds considerable potential to reduce the financial burden on the health care system as less surgical resources and length of hospital stay are required.

To date, the literature supporting ablative fractional resurfacing has been predominantly reported in patients with stable or mature burn scars at least 18 months postinjury.[14] To our knowledge, this report presents the first case where CO_2-AFL is utilized in the acute care environment along with nonsurgical scar contracture management techniques to manage aggressive scar contracture formation over the panfacial region.

CASE REPORT

Setting and Background Information

A 39-year-old male of Asian background (Fitzpatrick skin type 3[15,16]) was admitted to the Concord Repatriation General

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Conflict of interest statement. The authors declare that there is no source of financial or other support, or any financial or professional relationships which may pose a competing interest.

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doi:10.1093/jbcr/irz030

Hospital (CRGH) Burns Intensive Care Unit (ICU) with 68% total body surface area (TBSA) flame burn injury including deep dermal panfacial burn wounds and airway involvement. The facial burn wounds were initially bluntly debrided and Biobrane™ xenograft was applied: standard procedure for all facial burn injuries with an epidermal detachment in CRGH Burns Unit. Due to a protracted period of mechanical ventilation, tracheostomy ensued at day 18. Nonsurgical orofacial scar contracture management was instigated within 48 h of admission as per the regime published by Clayton *et al*.[6]

While still in ICU, bilateral upper and lower eyelid ectropion and early lower lip eversion were observed (Figure 1). At day 43, surgical release with full-thickness skin grafts for the eyelid ectropion was discussed to avoid corneal damage. Nonsurgical scar contracture measures such as taping had not been initiated at this stage, as the newly healed tissue remained unstable with several areas not epithelialized. For corneal protection, regular assessment by an appropriately qualified ophthalmologist was conducted and topical lubricant applied frequently as prescribed. Due to the positive effect of CO_2-AFL on immature scars, the decision was made to trial full face resurfacing with the ablative fractional CO_2 Ultrapulse® laser.

Treatment

Protracted healing of skin grafts and areas with wound infection necessitated repeat debridement and re-grafting to 20% TBSA of limb wounds. During the re-grafting procedure, ablative fractional resurfacing of the entire panfacial region, from the superior hairline to the upper neck crease was simultaneously performed. CO_2-AFL was repeated on four occasions under general anesthetic, at regular subsequent intervals (6–8 weeks), throughout the patient's acute and rehabilitative hospital admission. Corneal eye shields were inserted, laser safety measurements implemented, and the patient received a 3-day course of prophylactic Valacyclovir (500 mg twice daily). The ablative fractional CO_2 Ultrapulse® laser (Lumenis® UltraPulse®, Yokneam, Israel) machine was used with the following settings. First treatment: DeepFX™: energy = 12.5 to 17.5 mJ, density = 5 to 10%, rate = 300 Hz. Second treatment: DeepFX™: energy = 15 to 22.5 mJ, density = 10%, rate = 300 Hz. Third treatment: SCAAR FX™: energy = 60 mJ, density = 5%, rate = 250 Hz and DeepFX™: energy = 17.5 to 40 mJ, density = 5–10%, rate = 300 Hz, and laser facilitated infiltration of corticosteroids (Kenacort A40). Fourth treatment: SCAAR FX™: energy = 60 to 110 mJ, density = 1 to 5%, rate = 250 Hz and DeepFX™: energy = 40 to 50 mJ, density = 5%, rate = 300 Hz, and laser facilitated infiltration of corticosteroids (Kenacort A40). Lower energy, higher density settings were applied in the periorbital area. During the last treatment, areas of considerable erythema were additionally treated with the M22™ laser system: Nd:YAG: double pulse, pulse duration 8.5 ms and 11.5 ms with 20 ms delay and fluence of 120 J/cm^2.


Figure 1. Day 43—bilateral upper and lower eyelid ectropions and early lower lip eversion.

Nonsurgical scar contracture management continued to be provided concurrently as per site specific standard protocols. Lower eyelid taping was introduced (day 133) to promote complete eye closure once the surrounding cutaneous tissue was considered stable and robust enough to withstand the application of a silicon-based adhesive tape Opsite Gentle Flexifix® and continued daily. Nonsurgical scar contracture management was ceased for the day of CO_2-AFL treatment and resumed to the full program the following day. Taping was ceased for 5 days following CO_2-AFL and re-commenced once cutaneous tissue was suitably stable to endure the tape.

Nonsurgical scar contracture management was weaned once stabilization of panfacial scar tissue and functional goals attained with nil change over 3 months following scar stabilization. Treatment weaning started with reducing the frequency and duration of both the mouth splint and eye taping, and subsequently the active range of movement (ROM) exercises. Once treatment was ceased, monitoring for a further 3 months to ensure no regression in eye and mouth closure and maximal range occurred.

Outcome Measures

Measurements and photographic data specific to deficits in eye and mouth competence were obtained at rest and on active closure, along with maximal opening at baseline and routinely until completion of scar stabilization. Each participant underwent measures of maximal mouth opening (vertical and horizontal), deficit in mouth closure, maximal eye opening, and deficit in eye closure before and throughout the course of treatment. As defined previously in Clayton *et al*,[6] vertical mouth opening range was recorded as the measurement in millimeters while in the stretched position from the inner border of the medial lower lip to the inner border of the medial upper lip. Horizontal mouth opening range was recorded as the measurement in millimeters while in the stretched position from one lateral oral commissure to the other lateral oral commissure. Mouth closure deficit was recorded as the measurement in millimeters of the gap while in the closed position from the inner border of the medial lower lip to the inner border of the medial upper lip. Eye opening range was defined as the measurement in millimeters while in the maximal opening position between the lower and upper eyelid. Eye closure deficit was defined as the measurement in millimeters of the gap while in the closed position between the lower and upper eyelid.

Treatment duration, maximal ROM values (taken in person at the time of treatment), and photographic images were subsequently compared with groups of historical burn patients and historical healthy controls. The historical burn patient group all experienced deep partial or full-thickness facial burn injuries, received the same nonsurgical orofacial scar management and traditional surgical reconstructive procedures as clinically indicated.[6] The group of the historical healthy controls[5] had never previously experienced a facial burn injury or any head and neck surgery that would compromise their orofacial ROM.

Statistical Analysis

Descriptive statistics were used to draw comparisons for the difference between the patient's outcome and those of the historical cohorts.

RESULTS

Clinical Outcome

The patient underwent four sessions of CO_2-AFL over an 8-month period at 6- to 8-week intervals. Nonsurgical scar contracture management was continued concurrently during this period.

The patient demonstrated considerable gains in response to the combined nonsurgical scar contracture management and CO_2-AFL throughout the duration of treatment. Deficits in eye and mouth closure reduced to 0 mm and maximal mouth ROM increased to 40 mm vertically and 61 mm horizontally. Figure 2 reveals photographic evidence of patient progress and ROM of the eye and mouth structures.

At the conclusion of treatment, 8 months after initial burn injury, the patient exhibits full eye closure with negligible ectropion, complete oral competence, and functional mouth ROM. He has proficient oral access with functional ability to: consume a full oral diet without any restrictions, attend to dental cares and has sufficient mouth opening to enable blind intubation. He also demonstrates excellent facial ROM necessary to convey the emotive aspects of language via facial expression.

Comparison to the Historical Group

Compared with the historical group of *burn patients* (n = 14, eight debrided and grafted, five debrided and treated with Biobrane™ xenograft with subsequent small grafts on remaining unhealed areas, one debrided and treated with Biobrane™ xenograft only) who received the same nonsurgical orofacial scar contracture management (n = 14) and traditional surgical reconstructive procedures (n = 9), vertical and horizontal mouth ROM measures for the patient at the conclusion of treatment in the current study were found to be comparable (As per Clayton *et al*[6]; *end-treatment range* for vertical mouth opening = 32 to 43 mm; end-treatment range for horizontal mouth opening = 58 to 80 mm).

Compared with the historical *non-burn healthy controls* (n = 120), the patient's vertical and horizontal mouth ROM was also found to be comparable and within the normal range (As per Clayton *et al*[5]: *normal range* for vertical mouth opening = 40–75 mm; normal range for horizontal mouth opening = 55–83 mm). See Table 1 for summary of these results.

Further to this, treatment duration in the current case (251 days), when compared with the historical burn cohort of Clayton *et al*[6] (range = 82–1235 days; mean = 513 days) was found to be shorter although not statistically significant (P = .247).

Figure 2. Progress in range of movement of the eye and mouth structures at days 43, 49, 176, and 251. A. Eye closure at rest. B. Maximal active eye closure. C. Vertical mouth opening. D. Horizontal mouth opening.

Table 1. Comparison between outcomes for AFL, burn, and healthy controls

	Case CO_2-AFL (n = 1)	Burn control group (n = 14)	Healthy control group (n = 120)
Vertical mouth opening (mm); mean (SD)	40	40(SD = 7.071)	53.642 (SD = 7.446)
Horizontal mouth opening (mm); mean (SD)	61	63.214 (SD = 14.142)	69.133 (SD = 5.787)

CO_2-AFL, ablative fractional CO_2 laser.

DISCUSSION

To our knowledge, this is the first report documenting the positive effects of CO_2-AFL in managing scar contracture formation in the early acute care setting. Traditional early reconstructive procedures such as ectropion releases with full-thickness skin grafts and oral commissuroplasty were able to be avoided in this case, with excellent functional and potentially more acceptable aesthetic results.

Ablative fractional resurfacing is described to positively influence and accelerate scar maturation, expediting the rehabilitative phase and workplace-reintegration.[17] Nevertheless, it may seem somewhat paradoxical that micro-injuries within a wound/scar should promote wound healing and positively influence scarring. The size of the wound appears to be a precipitating factor in scar formation, with the transition between nonscarring and scarring dermal thickness wounds occurring at a diameter of approximately 0.3 to 0.5 mm.[18] The healing response to the unique pattern of fractional laser injury initiates the tissue remodeling. Several histologic analyses propose that the particular fractional wound stimulates a molecular cascade, including heat shock proteins, matrix metalloproteinases and other inflammatory actions, initiating a rapid healing response and protracted neocollagenesis with consequent collagen remodeling, reduction in type I collagen and growth in type III collagen.[14,19–21] Additionally, in 2015, a group from Western Australia described an increase in vascularization in mature scars and a decrease in vascularization in immature scars.[22] Particularly, this latter aspect might explain the accelerated scar maturation and in the presented case may have even prevented further scar formation.

Some areas of the presented patient's face were not fully epithelialized or still very fragile during the first laser procedure 6 weeks following the burn injury. To promote a wound healing response with healthier tissue, debridement of poorly healing areas from wounds is a widely established approach.[17] It is postulated that the same applies for the photomicrodebridement of the vaporized portions of dysfunctional scar tissue and wound debris following fractional resurfacing, thus accelerating a rapid healing chronic wounds.[17]

It may be counterintuitive to apply additional injury to a recently healed, still fragile wound. However, the presented patient would have undergone surgical releases of his upper and lower eyelid ectropion and the resulting defect from the lack of tissue and tension would have been filled with full-thickness skin grafts. Surgical ectropion releases like this are by nature a much more invasive approach with, in our opinion, functionally equal, but cosmetically inferior outcomes. This case report illustrates that the wound contraction during the regular wound healing process leads to tension very early after epithelialization, which is a known pre-requisite of pathological scarring.[23]We believe that stimulation of tissue regeneration and collagen rearrangement immediately following epithelialization may positively influence the formation of pathological scarring and may help to reduce tension in the healing scar.

Limitations

Although this article presents encouraging functional and aesthetic outcomes in response to combined CO_2-AFL and nonsurgical scar contracture management, there are certain limitations. This multifaceted treatment program was trialed on one patient only and as such the results should be interpreted with caution. Despite this, the treatment program described in the current study is practical, is minimally invasive with minimal adverse effects, and holds high potential feasibility for implementation in the severe burn population. Consequently, larger cohort studies are required to confirm these positive functional and aesthetic results across a broader patient demographic group and also to inform the most appropriate frequency of CO_2-AFL treatment and combination of nonsurgical rehabilitation strategies.

CONCLUSION

Combined CO_2-AFL and nonsurgical scar contracture management can be utilized with great success in the early acute care period to assist in managing panfacial scarring and contractures that can lead to considerable functional deficits. The case presented in this article additionally demonstrates that this combination of treatment may also eliminate the need for other traditional surgical reconstructive procedures that often are required to be performed early to maintain functional ability.

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Appendix F: Patient Information Form

CONCORD
REPATRIATION GENERAL
HOSPITAL

Ablative fractional CO2 laser for the treatment of severe burn scars:

Prospective data collection for qualitative outcome analyses

PARTICIPANT INFORMATION FORM

You are being invited to participate in this research project, which will collect information about your scar, your medical history, and the treatment you are about to have.

Why are we doing this project?

A new laser technique for the management of burn scars has been introduced as routine treatment in many burn units all over the world, including Australia. Specialists in scar management have reported their findings of this laser technique, revealing substantial improvement of functional and cosmetic outcomes including enhancement in scar pliability, texture, colour, overall appearance, and, most importantly, increased range of motion. However, there are no well-established and researched guidelines for the use of the fractional ablative CO_2 laser.

The aim of this project is to collect data about your scar, the symptoms you have, the impact of your scar and injury on your overall quality of life, and details about the treatment you are receiving.

We will look at the effects of the laser at different time-points during your treatment with the aim of optimizing treatment processes. We intend to compile all this data in an anonymous, de-identified database, which would allow us to conduct further studies on treatment with the fractional ablative CO_2 laser.

What is involved in this study?

If you agree to participate in this study, we will record the following information at different time-points of your treatment:

- De-identified personal data (age, sex etc.)
- Information about the injury which caused the scar
- Symptoms & quality of life
- The nature of your scar (using scar assessment scores, photo-documentation of the scar, and ultrasound)

- If skin biopsies are provided, the nature of your scar will also be assessed microscopically and by other molecular analysis. Biopsies will be taken for research purposes only and are not standard of care. If you agree to also provide tissue biopsies for microscopic and molecular scar analysis, then we will perform:
    1. Two small biopsies of healthy skin in the vicinity of the scar under local anaesthesia and two small biopsies of the scar tissue itself immediately before your first treatment (when the area is already numb for your laser treatment).
    2. Further we will take two small biopsies of the scarred skin immediately before your second treatment and at the last follow-up appointment under local anaesthesia.
- Information about your previous & current treatment

Are there any risks associated with this research-project?
There are no associated risks if you agree to participate the prospective data collection. With regards to the tissue collection with biopsies, possible adverse effects include pain (during and after the biopsy), potential for wound healing problems, infection, and scarring.

What are financial consequences of participating in this project?
Participating in this research-project is purely voluntary. There won't be any remuneration or costs involved for you.

Confidentiality?
If you agree to take part in this project, your hospital medical records will be inspected by the researchers, by regulatory authorities, or by the Concord Hospital Human Research Ethics Committee. By signing the attached consent form, you are giving permission for this to be done.
All information will be de-identified. The data will be stored by subject number in electronic files under a password-protected system at Concord Hospital. All paper files will be kept in a locked office in Concord Hospital. Electronic data will be stored 5-7 years. Reports of this study may be submitted for medical publication, but individual participants will not be identifiable in such a report.

Do I have to take part?
Participation in this research-project is entirely voluntary. You are in no way obliged to participate and – if you do participate – you can withdraw at any time, and the data collected for this research-project destroyed. Withdrawal from the study will not affect your treatment, nor your relationship with the hospital or treating doctor.

This research-project has been approved by the Sydney Local Health District Human Research Ethics Committee, Concord Repatriation General Hospital (CRGH). If you have any concerns or complains about the conduct of the research study, you may contact the Executive Officer of the Ethics Committee, on (02) 9767 5622.

Principal Investigator:

Dr. Andrea C Issler-Fisher	Burns & Reconstructive Surgery Fellow, Burns Unit, CRGH, (02) 9767 7775

Co-Investigators:

Dr. Zhe Li	Senior Scientist, Skin Lab, Burns Unit, CRGH (02) 9767 5832
Frank Li	Senior Physiotherapist, Burns Unit, CRGH (02) 9767 7775
Prof. Peter Maitz	Medical Director, Burns Unit, CRGH (02) 9767 7775

Appendix G: Patient Consent Form

CONCORD
REPATRIATION GENERAL
HOSPITAL

Ablative fractional CO2 laser for the treatment of severe burn scars: Prospective data collection for qualitative outcome analyses

PARTICIPATION CONSENT FORM

I have read and understood the Information for Participants for the above named research project and have discussed the aim and purpose of the project with the Burn Unit Staff.

All my questions about the research project were clarified.

- I understand that during the course of the study my medical records may be accessed by the researchers, by regulatory authorities, or by the Ethics Committee approving the research in order to verify results and determine that the study is being carried out correctly.
- I freely choose to participate in this study and understand that I can withdraw at any time.
- I also understand that the research study is strictly confidential.
- I hereby agree to participate in this research study.

I also agree to the provision of skin biopsies for microscopic and molecular scar characterization: ☐Yes ☐No

Name *(Please Print)*:

____

Signature: ___________________________ Date:

Appendix H: Data Collection: Initial assessment

PROSPECTIVE DATA COLLECTION FOR SCAR-TREATMENT WITH THE ABLATIVE FRACTIONAL CO2 ULTRAPULSE® LASER:
Appendix 1

Demographics:

Patient Code _______________

Attendance Date __ / __ / ______ (dd/mm/yy)

Age __ years

Gender ☐M ☐F

Smoking ☐Yes ☐No

Co-Morbidities
☐Pulmonary Disease
☐Cardiac disease
☐Diabetes mellitus
☐Psychiatric
☐Vascular Disease
☐Renal disease
☐Neurological Disease
☐Other: ___________________________

Ethnical type
☐Australian Aboriginal
☐Torres Strait Islander
☐North West European
☐North East Asian
☐South & Central Asian
☐South American
☐Anglo-Saxon/Celtic
☐Maori Pacific Islander
☐Southern Eastern European
☐South East Asian
☐North African/Middle East
☐Sub-Saharan African
☐Not stated/inadequately described
Country: ____

Fitzpatrick-Scale	☐Type I	Pale white skin; blond/red hair; blue eyes; freckles → Always burns, never tans
	☐Type II	White skin; fair; blond/red hair; blue/green/hazel eyes → Usually burns, tans minimally
	☐Type III	Cream white/light brown skin; fair with any hair/eye color; (common) → Sometimes mild burn, tans uniformly
	☐Type IV	Moderate brown skin; typical Mediterranean skin tone → Rarely burns, always tans well
	☐Type V	Dark brown skin; Middle Eastern skin types → Very rarely burns, tans very easily
	☐Type VI	Deeply pigmented dark brown to black skin → Never burns, tans very easily

Burn Injury

Date of Injury __ / __ / ______ (dd/mm/yy) **Time since burn** __ / __ (y/m)
TBSA: _____%

Mechanism: ☐Flame ☐Contact ☐Scald ☐Chemical
☐Electrical ☐Friction ☐Other: ___________________________

Localisation (scar) ☐Face ☐Neck ☐Chest
☐Abdomen ☐Upper Limb ☐Lower Limb
☐Back ☐Buttocks ☐
Detailed Location(s):____

Wound healing / treatment:
☐ Time since epithelialisation of ≥95% of wound: __ / __ (y/m)
☐ Prolonged wound healing __ / __ (y/m)
☐ Wound infection
☐Conservative
☐Xenograft __/__/____ ☐Grafted __/__/____
☐Re-grafted __/__/____ ☐Other: __________________ __/__/____

Current scar management:
☐Silicone ☐Massage ☐Garments ☐Physiotherapy
Other: ____

Regular pain/pruritus medication/dosage:
____
____

Limited ROM ☐No ☐Yes
Joint: ______________, Direction: ____________, _______ (degree)
Direction: ____________, _______ (degree)

Necessity of surgical intervention ☐Yes ☐No
Planned Procedure:___________________________________

Ultrasound-Assessment
→ Normal skin: __________ : ___mm → Area: ___________ : ___mm
→ Normal skin: __________ : ___mm → Area: ___________ : ___mm

Completed by: ____
Signature: ____

Appendix I: Data Collection: Follow-ups

PROSPECTIVE DATACOLLECTION FOR SCAR-TREATMENT WITH THE ABLATIVE FRACTIONAL CO2 ULTRAPULSE® LASER: Appendix 2 (F/U)

Attendance Date __ / __ / ______ (dd/mm/yy)

Impression: ☐worse ☐unchanged ☐improved a little bit
☐improved quite a bit ☐improved extremely

Adverse Effects post laser ☐Erythema: _____ (time) ☐Pinpoint bleeding
☐Pain: _____(time) ☐Infection (Abx: yes/no)
☐Hyperpigmentation ☐Other: ____________________

Limited ROM ☐No ☐Yes
Joint: ______________, Direction: ____________, _______ (degree)
Direction: ____________, _______ (degree)

Necessity of surgical intervention ☐Yes ☐No
Planned Procedure:__________________________________
Date of Procedure: __________________________________

Current scar management
☐Silicone ☐Massage ☐Garments ☐Physiotherapy
Intralesional Steroid Injections: ☐Yes ☐No No: _____
Other: ____

Regular pain/pruritus medication: ____

Ultrasound-Assessment completed
→ Normal skin: ________mm → Area: __________ : ___mm
→ Area: __________ : ___mm → Area: __________ : ___mm

Completed by: ____

Signature: ____

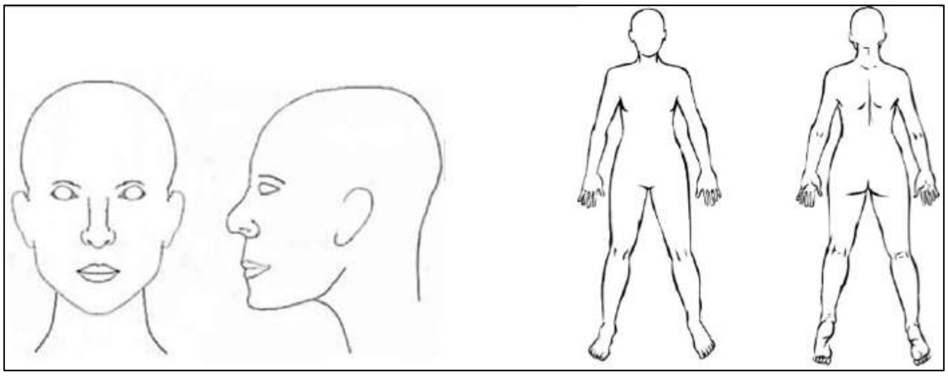
Appendix J: Treatment settings

PROSPECTIVE DATA-COLLECTION FOR SCAR-TREATMENT WITH THE ABLATIVE FRACTIONAL CO2 ULTRAPULSE® LASER:
Laser-Session

Attendance Date __ / __ / ______ (dd/mm/yy) **Number of Laser-Session** _______

Anaesthetics ☐GA ☐LA: _________________ ☐Other: ____________________

Location: Areas to be numbered



Deep Fx/ Active Fx	Location (Nr)	Shape (Nr)	Density (%)	Energy (mJ)	Rate (Hz)	Nr of passes	Steroids (y/n)

Direct effects post laser ☐Erythema ☐Pinpoint bleeding
☐Pain ☐Other: ____________________

Completed by: _____________________ **Signature:** ________________________________

Appendix K: Vancouver Scar Scale (VSS)

VANCOUVER SCAR SCALE (VSS)

Vascularity:	☐ Normal	0
	☐ Pink	1
	☐ Red	2
	☐ Purple	3
Pliability:	☐ Normal	0
	☐ Supple	1
	☐ Yielding	2
	☐ Firm	3
	☐ Ropes	4
	☐ Contracture	5
Pigmentation:	☐ Normal	0
	☐ Hypo	1
	☐ Hyper	2
Height:	☐ Flat	0
	☐ < 2mm	1
	☐ 2-5mm	2
	☐ > 5mm	3

TOTAL Score: __

Appendix L: Patient and Observer Scar Assessment Score (POSAS)

POSAS Observer scale

The Patient and Observer Scar Assessment Scale v 2.0 / EN

Date of examination:

Observer:

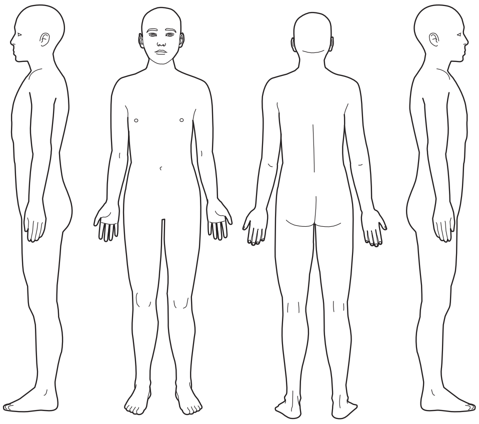
Location:

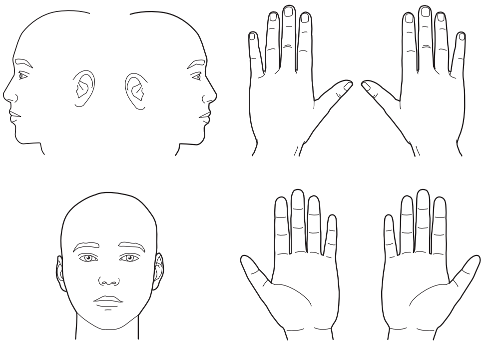
Research / study:

Name of patient:

Date of birth:

Identification number:





1 = normal skin — worst scar imaginable = 10

PARAMETER	1	2	3	4	5	6	7	8	9	10	CATEGORY
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ('like normal skin') to 10 ('worst scar imaginable').
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

Explanatory notes on the items:

- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

POSAS Patient scale

The Patient and Observer Scar Assessment Scale v2.0 / EN

Date of examination:

Observer:

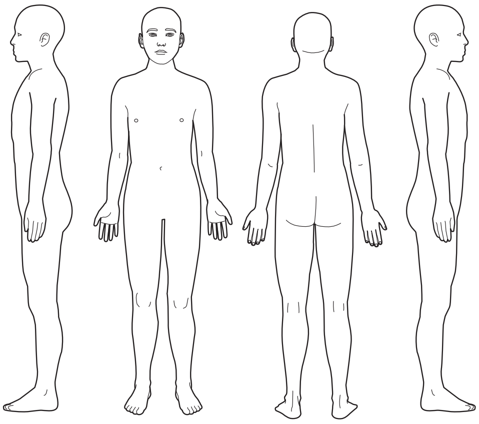
Location:

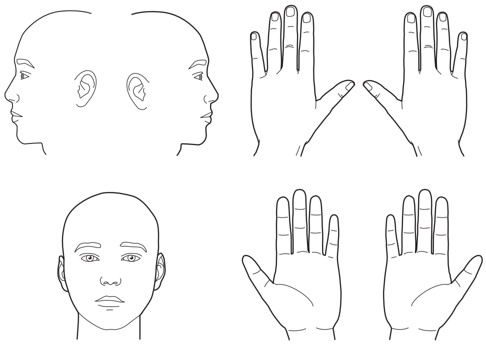
Research / study:

Name of patient:

Date of birth:

Identification number:





	1 = no, not at all									yes, very much = 10
	1	2	3	4	5	6	7	8	9	10
HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○
HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○

	1 = no, as normal skin									yes, very different = 10
IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○

	1 = as normal skin									very different = 10
	1	2	3	4	5	6	7	8	9	10
WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?	○	○	○	○	○	○	○	○	○	○

Appendix M: Neuropathique 4 Questions (DN4)

DN4 QUESTIONNAIRE

Please complete this questionnaire by ticking one answer for each item in the 4 questions below:

INTERVIEW OF THE PATIENT:

1. **Does the pain have one or more of the following characteristics?**

	YES	NO
1 – Burning	☐☐	☐
2 – Painful cold	☐☐	☐
3 – Electric shocks	☐☐	☐

2. **Is the pain associated with one of more of the following symptoms in the same area?**

	YES	NO
4 – Tingling	☐☐	☐
5 – Pins & needles	☐☐	☐
6 – Numbness	☐☐	☐☐
7 – Itching	☐☐	☐☐

EXAMINATION OF THE PATIENT:

3. **Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?**

	YES	NO
8 – Hypoesthesia to touch	☐☐	☐
9 – Hypoesthesia to prick	☐☐	☐

4. **In the painful area, can the pain be caused or increased by:**

	YES	NO
10 – Brushing	☐☐	☐☐

Current Medication(s): ____

Appendix N: 4-D Pruritus Scale

Modified 5-D Pruritus Scale (4-D Pruritus Scale)

1. Duration: **During the last 2 weeks, how many hours a day have you been itching?**

☐ 1 Less than 6h/d
☐ 2 6-12h/d
☐ 3 12-18h/d
☐ 4 18-23h/d
☐ 5 All day

2. Degree: **Please rate the intensity of your itch over the past 2 weeks**

☐ 1 Not present
☐ 2 Mild
☐ 3 Moderate
☐ 4 Severe
☐ 5 Unbearable

3. Direction: **Over the past 2 weeks has your itching gotten better or worse compared to the previous month?**

☐ 1 Completely resolved
☐ 2 Much better, but still present
☐ 3 Little bit better, but still present
☐ 4 Unchanged
☐ 5 Getting worse

4. Disability: **Rate the impact of your itching on the following activities over the last 2 weeks**

Sleep
☐ 1 Never affects sleep
☐ 2 Occasionally delays falling asleep
☐ 3 Frequently delays falling asleep
☐ 4 Delays falling asleep and occasionally wakes me up at night
☐ 5 Delays falling asleep and frequently wakes me up at night

1Never… 2Rarely… 3Occasionally… 4Frequently… 5Always…

Leisure/Social ☐☐☐ ☐☐☐☐ ☐ ☐ ☐ ☐☐☐☐ ☐☐ ☐ ☐ ☐ ☐ ☐

Housework/ Errands ☐☐☐ ☐☐☐☐ ☐ ☐ ☐ ☐☐☐☐ ☐☐ ☐ ☐ ☐ ☐ ☐

Work/School ☐☐☐ ☐☐☐☐ ☐ ☐ ☐ ☐☐☐☐ ☐☐ ☐ ☐ ☐ ☐ ☐

… affects this activity.

☐

Appendix O: Burns Specific Health Scale – Brief (BSHS-B)

Burns Specific Health Scale (BSHS-B): Quality of Life Questionnaire

	0	1	2	3	4
Items	**Extremely**	**Quite a bit**	**Moderately**	**A little bit**	**Not at al**
1. SIMPLE ABILITIES					
How much difficulty do you have?					
1. Bathing independently					
2. Dressing by yourself					
3. Getting in and out of a chair					
2. HAND FUNCTION					
4. Signing your name					
5. Eating with utensils					
6. Picking up coins from a flat surface					
7. Unlocking a door					
8. Tying shoelaces, bows, etc.					
3. AFFECT					
To what extent does each of the following statements describe you?					
9. I often feel sad or blue					
10. At times, I think I have an emotional problem					
11. I am troubled by feelings of loneliness					
12. I have feelings of being trapped or caught					
13. I don't enjoy visiting people					
14. I have no one to talk to about my problems					
15. I am not interested in doing things with my friends					
4. BODY IMAGE					
16. The appearance of my scars bothers me					
17. My general appearance really bothers me					
18. Sometimes, I would like to forget that my appearance has changed 19. I feel that my burn is unattractive to others					

Items	**Extremely**	**Quite a bit**	**Moderately**	**A little bit**	**Not at al**
5. INTERPERSONAL RELATIONSHIP					
20. I don't like the way my family acts around me					
21. I would rather be alone than with my family					
22. My family would be better off without me					
23. My injury has put me further away from my family					
6. SEXUALITY					
24. I feel frustrated because I cannot be sexually aroused as I used to					
25. I am simply not interested in sex any more					
26. I no longer hug, hold, or kiss					
7. HEAT SENSITIVITY					
27. Being out in the sun bothers me					
28. Hot weather bothers me					
29. I can't get out and do things in hot weather					
30. It bothers me that I can't get out in the sun					
31. My skin is more sensitive than before					
8. TREATMENT REGIMENS					
32. Taking care of my skin is a bother					
33. There are things that I've been told to do for my burn that I dislike doing					
34. I wish that I didn't have to do so many things to take care of my burn					
35. I have a hard time doing all the things I've been told to take care of my burn					
36. Taking care of my burn makes it hard to do other things that are important to me					
9. WORK					
37. My burn interferes with my work					
38. Being burned has affected my ability to work					
39. My burn has caused problems with my working					
40. Working inyour old job performing your old duties					

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