CONSIDERATIONS IN THE MANAGEMENT OF LYMPHOEDEMA FOR A PAEDIATRIC POPULATION

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ABSTRACT

Lymphoedema is the presence of swelling in regions of the human body, caused by excessive retention of lymphatic fluid. In children, lymphoedema can be either due to primary or secondary causes. Primary lymphoedema is caused by genetic mutations, while secondary lymphoedema is caused by structural and functional damage to the lymphatic vasculature. Primary lymphoedema is the more common type of lymphoedema in children. Lymphoedema is a chronic condition, and therefore requires lifelong treatment. However, there appears to be little in the literature to guide how to treat paediatric lymphoedema most effectively. More problematically, the safety of the most common treatment, compression, for use with growing skeleton has not been investigated. The aim of this thesis, therefore, was: 1) to determine the efficacy of all kinds of treatments for paediatric lymphoedema, mainly including conservative, and surgical treatments; 2) to examine the growth pattern and describe the prescription of the compression in children with lymphoedema who have been treated with compression.

There's little evidence available currently to support the best way to treat paediatric lymphoedema. While, two previous systematic reviews have been undertaken, one on conservative treatments and one on surgical treatments, they both found only weak evidence underpinning the treatments for paediatric lymphoedema. However, as the earlier one was done six years ago and the more recent one didn't extensively search a range of databases, it was timely to re-examine the literatures on the efficacy of both conservative and surgical treatments in children with lymphoedema.

A comprehensive search strategy was undertaken in five databases: MEDLINE, CINAHL, EMBASE, Scopus and PEDro. Title, abstract and full paper screening and data extraction were done by two reviewers. The outcomes of interest was a change in limb volume assessed either volume or

circumference. Twenty-one studies were eligible for inclusion, including 13 studies focused on primarily conservative treatments and eight focusing on primarily surgical treatments. For the studies looking at conservative treatments, two were cohort studies and the other 11 were case studies or case series. Nine of them suggested generally positive volume reduction in the lymphoedema limbs with their treatments. There were eight studies on surgical treatments, one cohort study and 7 case series or studies. Six of the surgical treatments were combined with conservative treatments. All studies on surgical treatments found positive outcomes for all patients. All studies were found have numerous issues which introduce risks of bias. While it appears that all of the treatments trialled for paediatric lymphoedema may be effective, the small sample sizes, significant risks of bias in each study and an inability to combine data from various studies due to different outcome measures, prevents firm conclusions from being made. Future research into the efficacy of treatments for paediatric lymphoedema is needed; however, first, if they are safe should be considered.

Compression therapy, the mainstay of lymphoedema treatment in adults, is recommended to be used in children as well according to international guidelines. However, there is no evidence or guidelines to support the use of compression in children. Lower limbs are the most commonly area of paediatric lymphoedema affected, while it is unknown whether compression on growing skeleton has negative impact on growing skeleton or may lead to other adverse event. To provide preliminary evidence on the safety of compressing a growing skeleton, a retrospective study was conducted at the Children's Hospital at Westmead and Sydney Children's Hospital in New South Wales. Data including gender, type of lymphoedema, and age of onset location of swelling and medical history of conditions were extracted. Furthermore, all recorded height measurements were extracted across each individual patient's period of care. Further data extracted for each individual patient visit on the type, use and changes to compression, as well as any clinical notes on adverse events or compliance with use of compression garments were extracted.

Ninety-three patients were identified by the clinicians for inclusion, with 42 eligible for analysis of their growth data. All participants had been prescribed compression garments, with 22 also undergoing bandaging at some point. Height measurements were converted to percentiles, and compared to normative growth charts. A change of more than 15 percentiles was considered abnormal. Seventeen participants had under two years of growth and compression measurements, nine had 2-5 years and sixteen had more than 5 years of records. Overall 38 participants demonstrated no growth fluctuation of more than 15 percentiles at any time, indicating no growth pattern changes with the use of compression. A total of four participants demonstrated an increase in height percentile by more than 15 percentiles between the first and last height assessment, while none decreased by that amount. Only minor adverse events (redness) were reported from the use of compression in the clinical notes and adherence to compression treatments appeared to be good. This study, therefore provides preliminary safety evidence for the use of compression in children with lymphoedema.

In conclusion, there's still no strong evidence found to best treat paediatric lymphoedema. Compression, the mainstay of lymphoedema treatment in adults does not appear to impact on the growth of skeletal bones in children with lymphoedema, indicating it may be safe to use compression to treat lymphoedema in children; its efficacy, however, is not known.

This is to certify that the thesis entitled "**Considerations in the management of lymphoedema for a paediatric population"** submitted by **Junyu Chen** in fulfilment of the requirements for the degree of Master of Applied Science is in a form ready for examination.

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I, **Junyu Chen**, hereby declare that the work contained within this thesis is my own and has not been submitted to any other university or institution as a part or a whole requirement for any higher degree.

I, **Junyu Chen**, hereby declare that I was the principal researcher of all work included in this thesis.

In addition, ethical approval from the appropriate ethics committee was granted for the studies presented in this thesis.

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31/03/2020

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Outline of the thesis

The work contained in this thesis, which has not yet been published, presents aspects of management for lymphoedema in children, organised in four chapters.

Chapter 1: Introduces paediatric lymphoedema, presenting an overview of its physiology and pathophysiology, as well as management.

Chapter 2: Presents the results of a systematic review of the efficacy of the conservative and surgical lymphoedema in children. Results of this systematic review showed no strong evidence on how to most effectively treat lymphoedema in children.

Chapter 3: Presents the results of a medical chart review, which looked at growth pattern over a period of compression treatment.

Chapter 4: Discusses the main findings of Chapter 2 and 3, future directions and presents the conclusions of this thesis.

Dissemination of Research

The abstracts of both Chapter 2 and 3 have been accepted for an oral conference presentation on the 13th Australasian Lymphology Association Conference in Hobart, 28 - 30 May 2020, under the following abstract titles, respectively:

Management of lymphoedema in a paediatric population: A systematic review

Does long-term medical compression for lymphoedema impact skeletal growth in children?

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Chapter 1: Introduction

Lymphoedema is a long-term chronic condition, which causes swelling of the limbs or other parts of the body (1). It is an abnormal accumulation of protein-rich fluid due to lymphatic system insufficiency (2). While most research in lymphoedema is on adults whose lymphoedema was caused by treatment for cancer, lymphoedema can also develop in children. This thesis will only focus on lymphoedema in a paediatric population.

In children, lymphoedema development can be either due to a primary or secondary causes, while primary lymphoedema is the more common form (3). Primary lymphoedema is caused by a range of genetic mutations, which may cause different presentations of lymphoedema, and can present as a part of a syndrome or on its own (non-syndromic) (4). Primary lymphoedema can develop at any point in an individual's life (4). Non-syndromic primary oedema was historically commonly referred as Milroy or Milroy's Disease, but many different phenotypes have now been recognised these days.(5) In contrast, secondary lymphoedema is caused by structural and functional damage to the lymphatic vasculature. (6) Potential causes include: infections, trauma such as fracture or amniotic banding (7). Around the world, infections from mosquito, lymphatic filarasis, are the most common cause for the development of secondary lymphoedema. (8)

As lymphoedema in children is primarily due to genetic mutations, leading to absent or malformed lymphatic pathways, it is pertinent to understand the development the physiology of lymphatic system.

Physiology and Pathophysiology

The lymphatic system runs in alongside to the blood venous system and has a principal role in maintaining tissue fluid homeostasis, absorbing lipid (6), and immune surveillance (9).

Lymph fluid moves into increasingly large vessels, starting from the lymphatic capillaries into lymphatic vessels, trunks and then back into central circulation through the thoracic duct (4). Fluid that ends up in the lymphatic system starts in the vascular system (6). At the vascular capillary level, fluid moves out of the vascular system due to arterial pressures. Through the human body, the blood passes through the arteries and then capillaries. The arterial pressures move the plasma and proteins out of the capillary walls into interstitial space, forming a portion of the extracellular fluid (ECF) (1). The initial lymphatics that extend into the interstitial space have thin, non-muscular walls that consist of a monolayer of endothelial cells. Fluid is pushed into the lymphatic capillaries due to pressure differences between capillary pressure (Pc) and interstitial pressure (Pi)(10). The overlapping leaf-shaped endothelial cells of the initial lymphatic capillaries allow interstitial fluid to enter, but not leave, the lymphatic system. (11-13) Once the fluid enters the lymphatic system it becomes known as lymphatic fluid (1). Although the exact mechanisms of movement of the fluid is still unclear (14), it likely occurs due to a combination of lymphatic vascular smooth muscle contracture, combined with skeletal muscle contraction, arterial pulsation and changes in thoracic pressure promote (15). The presence of lymphatic valves throughout the lymphatic vasculature prevent the backwards movement of fluid in the lymphatic vessels (6).

When the lymphatic system cannot provide adequate drainage, due to excessive fluid levels or failure or absence of lymphatic vasculature, the result is lymphoedema. Interstitial fluid accumulating due to this failure contributes to swelling is the main cause of lymphoedema.

Lymphoedema manifests as a collection of a protein rich fluid tissues as extracellular fluid cannot be removed from the interstitial space (1). The pathophysiology of primary and secondary are very different and so must be considered separately.

Primary lymphoedema is an umbrella term that covers a variety of presentations and conditions. It is a rare disease, estimated affecting 1 of 10000 children (6). However, the prevalence is still unknown and difficult to establish due to challenges in diagnosing primary lymphoedema (5). In recent years, many new genes have been identified that cause various forms of primary lymphoedema (16). Mutations to genes such as FOXC2, SOX18, CCBE1, GJC2, GATA2, KIF11 have been identified as causative for various forms of primary lymphedema, with work ongoing to identify others (4, 16). Mutations to each of these genes results in different conditions, each with different patterns of swelling and other associated issues. In a paediatric population, the most common form of lymphoedema is Milroy disease, which is caused by mutations in the vascular endothelial growth factor receptor-3 gene (VEGFR-3) (16). The main sign of Milroy's disease is pedal oedema, which appears at birth or in the first year of life (17, 18). The vascular endothelial growth factor (VEGF) family genes play a critical roles in the process of angiogenesis and lymphangiogenesis, including endothelial cell migration, proliferation and survival (19, 20). Endothelial cell works as functional components of initial lymphatics, and as a result, the absence of endothelial cells results in an absence of initial lymphatic capillaries (19). Interstitial fluid is, therefore, not able to move into the lymphatic system and accumulates in the tissues, particularly in the legs bilaterally (21). Another form of primary lymphoedema is lymphedema-distichiasis syndrome. This syndrome is caused by FOXC2 gene mutation (22). Lymphoedema-distichiasis syndrome is a syndromic condition in which distichiasis (aberrant eyelashes originating from the Meibomian glands) occurs at birth, while lymphoedema occurs later

after one year old (4). Mutations in the FOXC2 gene, therefore, cause aberrant smooth muscle surrounding initial capillaries. In animal models, aberrant smooth muscle indicates the failure of interstitial fluid absorption rather than an absence of initial lymphatics that is mechanism for this type of lymphedema (23). Each of the currently identified genetic causes of primary lymphoedema will result in different effects to lymphatic system (4). All results in the inability to sufficiently move fluid back into central circulation.

In contrast to primary lymphoedema, secondary lymphoedema develops after the disruption to a previously functional lymphatic system. While it occurs in most adult patients as a consequence of cancer related treatment like lymph node dissection and radiation therapy (2), it rare in children. Trauma such as fracture or amniotic banding, where occurs to the growing foetus, are the more common causes in children (7).

Regardless of the cause of lymphoedema, due to adipogenetic factors in the fluid, swelling can transform from fluid based to fatty and fibrotic tissue (24); however it's unclear when and how it occurs. What is clear, in an adult population anyway, is that lymphoedema in a fluid form is easier to manage than once it transform into the fatty or fibrotic tissue (8, 25). Management of lymphoedema should be commenced as early as possible.

Management of lymphoedema

The only other guidance on management of paediatric lymphoedema is from the International Lymphoedema Framework (ILF). However, neither provide specific guidance on which treatment options should be used, or how effective they are in the management of paediatric lymphoedema.

Lymphoedema, as a life-long condition for children, requires life-long management. Lymphoedema is currently managed through conservative and surgical treatments as it is currently not curable, no matter the cause. There are a large number of treatments available, which are used clinically for both adults and children with lymphoedema, including conservative treatment and surgical treatment. Most evidence, however, is only available on the treatment of lymphoedema for adults (26). The International Lymphoedema Framework (ILF) have produced two expert-opinion documents, which particularly look at paediatric lymphoedema: 'Best Practice for the Management of Lymphoedema'(27), and 'Care of children with lymphoedema' (28). The 'Best practice' document, which is accepted by lots of clinicians as the guideline in treating lymphoedema in adults, does not discuss anything on management of lymphoedema in children. The 'Care of children with lymphoedema' document only suggested that the techniques pertaining to adult lymphoedema should be adapted for lymphoedema presenting in children (28). This document specifies the details of assessment of paediatric lymphoedema and family care; however, in it there is a striking lack of specific details on how to treat or manage paediatric lymphoedema.

Conservative and surgical treatments are both utilised in treating lymphoedema. Complex decongestive therapy (CDT) is the standard method of treatment for lymphedema in adults (29). The first stage of CDT is intensive treatment includes manual lymphatic drainage (MLD), medical compression bandage, exercise, and skin care (30). The second stage of CDT is a maintenance phrase, consisting of the similar procedure as in the first phrase, with compression garments replacing bandaging as the main means of compression therapy (30). A range of surgical options are becoming available as well (31). Surgical options may be categorized into 1) physiological procedures, such as lymphovenous anastomosis (LVA) and

vascularized lymph node transfer (VLNT); 2) Excisional Procedures including Suction-Assisted Lipectomy, Charles' and Modified Charles' Procedure (31) Details on common conservative and surgical treatments are listed in Table 1.

Table 1: different means of treatment for lymphoedema and their decription

Name of treatment	Brief description and possible mechanism of action
Conservative treatments	
Compression	Applied to a region with lymphoedema through garments, bandages or pumps; varying the pressure difference in the tissues to help promote flow of fluid into lymphatic system and up to central circulation through (25).
Manual lymph drainage	Light pressure massage, performed in an upward direction to encourage the lymphatic flow; directed by pressures and flow moves toward the nearest groups of lymph nodes, proximal to the drainage area (32).
Skin care	Undertaken to maintain skin in a good hygiene and well-moisturized, avoiding other infection or injury (25)
Exercise	Can be lymph specific exercises or more general exercises such as swimming and walking and resistance training (25). Exercise

	causes changes interstitial tissue pressure and influences both lymph propulsion and clearance, promote fluid flow and transport inflammatory tissues (33).
Pneumatic compression pump	Inflated sleeve that is applied around the limb with lymphoedema with multiple chambers that provide massage like compression that moves fluid distal to proximally (34).
Lower level laser therapy (LLLT)	Uses light at high frequency. Promotes lymphangiogenesis and stimulates lymphatic motility and improves overall lymphatic flow and reduce interstitial fibrosis (35).
Surgical treatments	
Lymphovenous anastomosis (LVA)	Artificial connections are built between the venous and lymphatic system to direct excess lymph into the venous circulation (36)
Vascularized lymph node transfer	Transfer of functional lymph nodes. Improves lymph drainage and flow. (31)
Suction-Assisted Lipectomy	Also named liposuction; surgical removal of fat component (37)
Charles' and Modified Charles' Procedure	Excisional surgery that removes lymphedematous tissue (31)

How effective any of these treatments are in children is not clear. Two previous systematic reviews have investigated the efficacy of conservative (3) and surgical (38) management of children respectively. The review on conservative treatment, conducted in 2014, included studies on pneumatic compression, manual cervical stimulation and low level laser therapy. They found no strong evidence that supported the efficacy of any conservative treatments as all studied were with low level of evidence and small sample sizes (3). In contrast, the systematic review on the surgical treatment options for paediatric lymphoedema was published more recently (2019) and found evidence to support the improvements in lymphoedema presentation after excisional procedures only (38). However, this review only searched three publicly available databases, which could prevent them from finding all the relevant articles, therefore reducing the generalisability of their findings. It is therefore timely to review the literature to determine if there is now stronger evidence to support the use of more than major excisional procedures in children with lymphoedema.

In the previous systematic reviews, most treatment options studied were adapted from what is done in adults. There is lack of evidence to support the idea the techniques usd to adult lymphoedema should be adapted for lymphoedema presenting in children. Children are fundamentally different from adults as they are still growing. Children continually grow as well as have multiple periods of accelerated growth from the time of birth through to when their growth plates closes at late puberty (39). As treatment for lymphoedema is life-long, much of this treatment will be undertaken while the child is growing. If the efficacy of treatments are unclear, it may be prudent to consider their safety first. One treatment of which the safety of use in children is not known is compression.

Compression therapy is regarded as the foundation in treating lymphoedema in adults (40). Compression may be applied to a body region with lymphoedema through bandaging,

compression garments or pneumatic pump. Whether compression is frequently used in children is unclear. Furthermore, whether it is safe to continually compress a growing skeleton has also not been investigated. Evidence from facial compression in children with burns provides some evidence of an effect on the growth of bones (41). Whether this would apply to long-bone growth as well is not known. Access to an opportunistic set of data, through a medical chart audit, could provide preliminary evidence of the effect of compression on skeletal growth in kids with lymphoedema.

The aims of this thesis, therefore, it to:

1) Determine the evidence for efficacy for the conservative and surgical treatment of lymphoedema in children; and
2) Determine preliminary evidence on the safety of long-term compression on the growing skeleton of children with lymphoedema

Together these studies will provide some evidence to support clinicians in treating lymphoedema in children.

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Chapter 2: Management of lymphoedema in a paediatric population: A systematic review

Abstract

Background Lymphoedema is a debilitating disease that causes a permanent swelling of a body region. Children with lymphoedema will require lifelong treatment. Management on lymphoedema currently focuses in adult populations, resulting in limited evidence in paediatric population. The aim of the review is to determine the efficacy of conservative, surgical and medical treatments for paediatric lymphoedema.

Methods Searches were done in five databases: MEDLINE, CINAHL, EMBASE, Scopus and PEDro. Inclusion criteria included: Studies looking at all means of management of lymphoedema were identified. Result could only be descriptively summarised as there was little consistency in the outcome measures used.

Result Overall, 21 studies met the inclusion criteria, of which 13 studies focused primarily on conservative treatments and eight focused primarily on surgical treatments. Most studies (19 of 21) showed volume reduction in the lymphoedema limbs, however the studies were all with small size and low level of evidence.

Conclusion: From the studies identified in this review, the evidence currently suggests that all the treatment were effective for paediatric lymphoedema; however, this needs to be interpreted cautiously due to the poor quality of evidence. Further research is required to include more research with higher level of evidence and use more consistent outcome measures to identify the efficacy of the management for paediatric lymphoedema.

Introduction

In a paediatric population, lymphoedema, a permanent swelling of a body region due to deficiencies of the lymphatic system, can arise due to primary or secondary causes (1, 2). Primary lymphoedema results from rare genetic mutations (3), while secondary lymphoedema results from disease, trauma, or surgery that affects the lymphatic system (4). Primary lymphoedema is the more common form of lymphoedema in a paediatric population (5). However, no matter the cause, lymphoedema manifests as a swelling due to the accumulation of protein rich fluid in the tissues (6, 7). As lymphoedema is a permanent condition, once it is developed, it will require lifelong treatment.

The optimal treatment for children with lymphoedema has been unclear. In adults, a wide variety of both conservative and surgical treatment options may be used. The conservative interventions include compression therapy in the form of bandages and garments, manual lymph drainage massage, exercise Pneumatic Massage and low level laser therapy (LLLT). The main surgical interventions include lymphovenous-anastomosis (LVA), lymph node transfer, Lipectomy and Charles' Procedure (6). However, the use and efficacy of many of these treatments in children is not clear. A previous systematic review on the conservative treatment of paediatric lymphoedema which was done six years ago, found no strong evidence that supported the efficacy of any conservative treatments. More problematically, all studies were of low quality (5). A systematic review on the surgical treatment options for paediatric lymphoedema was published in 2019 (8). The major weakness of the review was that they only searched three publicly available databases which could prevent them from finding all the relevant articles (8), thereby reducing the generalisability of their findings. The only other guidance on management of paediatric lymphoedema is from the International Lymphoedema Framework (ILF), which have produced two expert-opinion documents, 'Best Practice for the Management of Lymphoedema'(6) and 'Care of children with lymphoedema'

(9). However, neither document provide specific guidance on which treatment options should be used, or how effective they are in the management of paediatric lymphoedema. There appears to be few firm recommendations on how to treat lymphedema in paediatric populations.

Recently, there has been significant advances in understanding the genetic underpinnings of primary lymphoedema. Furthermore, there has been a dramatic increase in the number of articles looking at the treatment for lymphoedema in adult populations (10). Whether this developing understanding of the causes of primary lymphoedema and the treatments for adult lymphoedema have resulted in new evidence to support the treatment of children with lymphoedema is unknown. The aim of this systematic review, therefore, is to determine the efficacy of conservative, and surgical treatments for paediatric lymphoedema.

Method

The review protocol was registered prospectively with PROSPERO (ID: CRD42020142830)

Search strategy

The search strategy was developed in consultation with a research librarian at the Sydney School of Health Science at The University of Sydney. Studies were identified by both medical subject headings (MeSH) and keywords. Five database searches were undertaken on 29 March 2019: MEDLINE, CINAHL, EMBASE, Scopus and PEDro. An example of the search strategy is available (Medline; Appendix 1). A total of 4835 were identified from the search. After 1970 duplicates were removed, 2865 articles proceeded to title and abstract review (Fig 1- PRISMA). Two authors (JC and ED) completed the title and abstract review, with a third reviewer available to adjudicate if there was disagreement (SK). Overall 226

papers were retrievable for full text review, which was also undertaken by two reviewers (JC and ED). A total of 21 studies met the inclusion criteria.

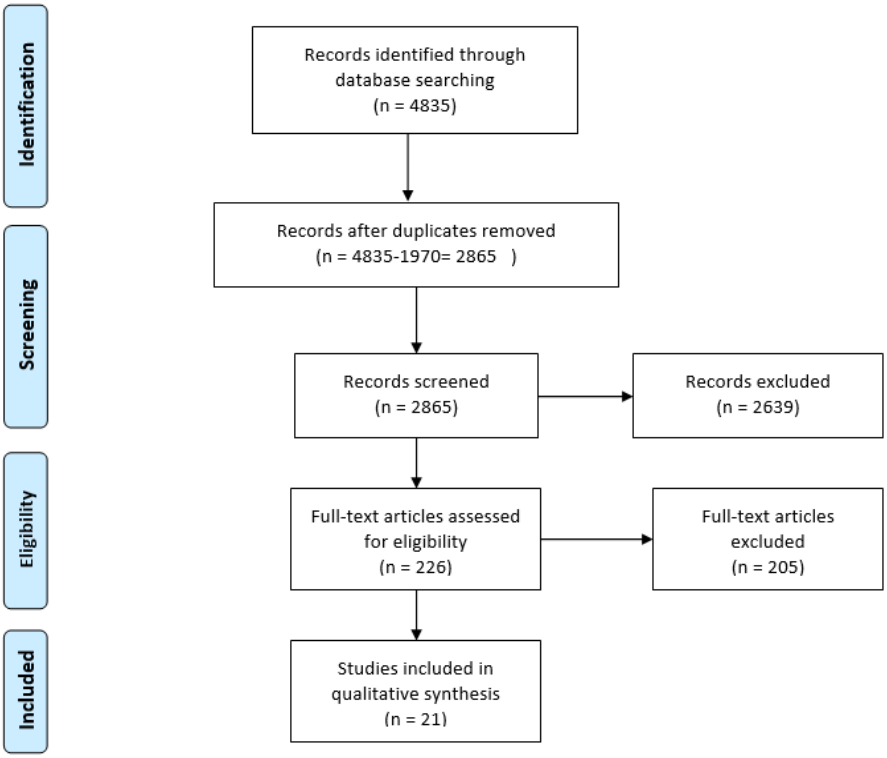

Fig 1. PRISMA flow chart of search results.

Inclusion and exclusion criteria

Any study on the surgical or conservative management of a child (under 18 years old) with lymphoedema was included. Randomised control trials, prospective or retrospective cohort studies, case series and case report designs were included. If a study included both children and adults and the children's data was individually extractable, it was included; however, if the children's data could not be extracted or outcomes were not presented in an objective manner, the study was excluded. Further exclusion criteria were studies on lymphedema caused by filariasis and parasitic infection; if the data was presented in a letter to the editor or an editorial; and studies didn't have objective outcomes were excluded.

Outcome

The primary outomce of interest was a change in limb volume assessed either using volume or circumference measurements.

Data extraction

For each study, the following details were extracted by two reviewers (JC and ED): population and setting (country, study type, setting, participants' age, gender and number, and lymphoedema details including type and location, etc.); lymphoedema treatment details (treatment, duration of treatment, follow-up period and comparison, duration of comparator treatment, follow-up period); results and findings. A third person was available if there was disagreement (SK).

Assessment of methodological quality

Each included study was assessed for quality using an assessment tool designed for case series and case report (11). The scale consists of eight items categorised into four domains: selection, ascertainment, causality and reporting. Two reviewers completed the risk of bias assessment (JC and ED), with a third reviewer (SK) available if there were disagreements.

Data analysis

Due to the nature of the included studies, meta-analysis of the data was not possible. The studies were, therefore, organised by primary treatment types based on whether the treatment was conservative or surgical and the results were summarised descriptively. The focus of the analysis was the effectiveness of treatments, assessed primarily by change in limb volume or size. A tool developed by Murad was used to evaluate the methodological quality of the

included case reports and case series (11). The overall summary scores were not reported; the tool was used as a simple checklist to investigate possible sources of bias in included studies, in agreement with Kennedy et al (12) who noted these items may not be equally weighted.

Result

Across the 21 studies, a total of 114 participants were included. The participant's ages ranged from 2 months to 17 years old. Sixty-two males, forty-one females and twelve participants whose gender was not specified were included. Ninety-one participants were undergoing treatment for primary lymphoedema. One hundred and seven participants were undergoing treatment on their legs.

Thirteen of the 21 studies focused primarily on conservative treatment and eight focused primarily on surgical treatments. The study characteristics of all 21 studies are summarized in Table 1.

Conservative treatments

The 13 studies that focused on conservative treatment included: one prospective cohort study, one retrospective cohort study, two case series reports and nine case reports.

The prospective study investigated "cervical stimulation", a type of massage or manual therapy developed by the authors for treating lymphoedema (13). In this study, participants either received cervical stimulation (n=10) or cervical stimulation plus a compression garment (n=4), although there were no criteria given for which participant received which treatment. Both groups demonstrated a significant reduction in the circumference of the foot, measured at 3 and 6 cm from the base of the big toe along the dorsum of feet after two years

of treatment. However, the treatment was primarily performed by mother at home with no reporting of adherence, nor whether other treatments had been sought during that time.
A retrospective study investigated the efficacy of the 'lymphapress" pneumatic pump in combination with compression, exercise and skin care in 16 participants (14). Twenty percent presented improvement of more than 10% in volumetric measurements, after 19 to 96 months of treatment, while 73% maintained their limb volume. However, the amount of pressure needed to maintain or improve limb size reduced through the course of treatment.

The remaining studies were case series (n=3; (15-17)) or case studies (n=8; (18-25)). Four studies investigated complete decongestive treatment (CDT), which consisted of manual lymph drainage, compression therapy in forms of bandages and garments, exercise and skin care. A further two looked at the use of pneumatic pump devices. In addition, one study on each of the following treatments: low level laser (LLLT); CDT combined LLLT; compression bandaging combined with heat treatment; a compressive wrap system; and an intra-arterial infusion of autologous lymphocytes combined with CDT. Nine of the case series and case studies (16-21, 23, 25) reported an improvement in lymphoedema presentation with their treatments. Improvements were determined using varying measurement methods, such as percentage change in volume or circumferential measurement or bioimpedance spectroscopy. For example, six studies used circumferential measurement at differing locations on the lower limbs and found a decrease in circumference ranging from 2 to 8 cm at mid-calf with their treatment (16, 17). In contrast, two studies did not find uniformly improving outcomes with their treatment (23, 24). The case study reported by Avery et al (24), in which a pneumatic pump device was evaluated, found that the participant had a decrease in leg circumference at the ankle and mid-calf, but an increase in leg circumference at the arch of the foot and below the knee after 2 months treatment. This pattern of changes

was seen on both the affected and unaffected limbs despite only undergoing treatment to the affected limb. The case study by Akbayrak et al (23), which used a two phase CDT treatment combined with the medication sirolimus, found an initial volume decrease in the affected leg from 1750 to 1250 ml after 8 weeks of daily intensive treatment. However, the leg volume had increased back to 1350ml at a one year follow up with only a maintenance treatment program.

Surgical treatments

The eight studies that focused on surgical treatment included one prospective cohort study and seven case series studies. Six studies combined surgery and post-surgical conservative management (26-31) (Table 1)

One prospective cohort study (n=59) was undertaken using subcutaneous excision procedures, which required either two or four large operations (32). Participants were aged between 2 and 15 years at the time of surgery and followed for one year following surgery. At the six month post-operative follow-up assessment, there was an average pre- to post-circumference reduction of 19%, 29% and 23% circumference reduction at the supra-malleolar, midcalf and midthigh level respectively. At the one year follow up assessment, 52 (87.83%) patients subjectively reported symptom and complaint free with minimal limb swelling and without disability, while the average circumference reduction remained stable at 17%, 33% and 25% at the supra-malleolar, midcalf and midthigh level respectively.

The other seven surgical studies involved case series or studies investigating: supra-microsurgical lymphaticovenular anastomosis (LVA) (31, 33), lymph node transfer (29, 30), enteromesenteric bridge surgery (26), LVA combined lymphaticovenous implantation (27),

and a Charles procedure (28). All participants who underwent surgery for their lymphoedema demonstrated improvement in the limb size or volume at varying periods of follow-up determined using variable measurement methods. For example, two studies investigated the efficacy of outcome by using circumference reduction (28) (29). Postoperative outcomes for two participants aged 16 and 17 years from the Charles procedure in which the lymphedematous tissue is radically excised (28) revealed a circumference reduction of 37% and 32% reduction respectively measured at four levels. In contrast, the outcomes from a lymph node transfer only resulted in 9% circumference reduction at 6 months follow up, measured at several different levels (29).

Risk of Bias

All included studies failed to fulfil most criteria, suggesting that they had high risk of bias. (Table 2) None of the studies presented any details or explanations of dose–response effect and only one study reported challenge/ rechallenge phenomenon. Fourteen of 21 studies did not present whether their participants were representative of the population seen in their facility and 13 did not present whether other alternative causes might explain their findings.

Discussion:

Paediatric lymphoedema will affect patients for their entire life. While research into treatment for lymphoedema in adults is progressing, little has been known about how to treat it in children. Twenty-one studies were found in the literature on the treatment of paediatric lymphoedema, including 13 focusing on conservative and eight on surgical treatments. Across all the studies, 19 of 21 demonstrated general maintenance or decrease in limb volume, regardless whether surgical or conservative treatment were undertaken. Similar to a previous systematic review on conservative treatments (5), all of the study designs of the

articles included in this systematic review only provide low level of evidence. The highest evidence levels of evidence came from two prospective (13, 32) and one retrospective (14) cohort study, representing level III evidence at best (34). The vast majority of studies were case series or single case studies, whose level of evidence were at best Level IV. In addition, most of the studies had potentially high risk of bias. This was primarily due to a lack of reporting on critical issues such as whether the subject of the case study was an example representative of a larger population, lack of sufficient details provided so that the treatment could be replicated, and whether other alternative causes that may explain the observation ruled out. A further challenge to interpreting the efficacy of treatments was that all studies used multiple treatments in combination.

Both conservative and surgical treatment studies typically combined multiple treatments together (14-19, 22, 23, 25-31), making it difficult to ascertain the efficacy of any a specific treatment. Furthermore, most of the treatment protocols were extremely onerous, requiring multiple surgeries or hours of daily treatments. For example, in the single prospective surgical study, patients underwent two to four large surgeries to achieve the final one year result of an average of a 20% circumference reduction (32). The volume of treatments provided with conservative options were also high. Three studies involved nearly daily treatments over multiple weeks to months (16, 22, 23). Whether any of the treatment studied found sufficient improvement to clinically justify the volume of treatment is difficult to determine. Furthermore, it unclear whether the conservative treatment protocols would be replicable in most clinical settings, who may be unable to provide such extensive treatments or whether similar outcomes can be obtained with less treatment. It was also hard to compare efficacy between studies and treatment protocols due to the wide range of assessment methods used.

Across the studies, a wide range of assessment tools and measurement protocols were used to determine the degree of limb volume reduction. As a consequence, the data from the trials which investigated similar treatments could not be synthesized. Research into lymphoedema, whether in children or adult populations is affected by this challenge (35). In research into children, measurement of limb size or volume is further complicated as they are changing due to growth. This challenge of interpreting volume change data was only mentioned in one of the included studies (14). This is not surprising as there is little to guide researchers and clinicians on how to assess limb changes in growing children. One study, using bioimpedance spectroscopy (36), looked at normative changes in extra-cellular fluid volume in growing children. They found younger patients had a greater extracellular fluid content. Future studies need to put 'growing' into consideration for assessment.

One of the issues we encountered in this review was the need to exclude 205 studies at the full paper review stage. The major reasons for excluding the papers were: i) not reporting the outcomes from an intervention using objective assessments or ii) not being able to extract data specific to children from a sample that included children and adults. If this data were available, we may have been able to provide more evidence for efficacy of one or more treatments. However, by including all studies designs, we have considered as many studies as possible. Future research of the treatment of paediatric lymphoedema need to provide objective findings in children under 18 or separate from an adult population in looking at their results. It would be also interesting that whether different type of treatment would be more effective for different ages. Future studies could separate the age to look at a particular age group, such as infancy or adolescence. Consistency in measurement protocol and degree

of the limb size changes, and the impact of growth should also be considered in interpreting the findings.

Conclusion

There is little evidence to support the efficacy of any one treatment for paediatric lymphoedema. While, most treatments appeared to lead to improvements, the data supporting the treatments is limited. As a consequence, how to best treat paediatric lymphoedema is still unclear, particularly due only a small number of studies being conducted, involving few patients and all having high risk of bias. This is an area needs significant attention in the future.

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Table 1: Characteristics of included studies

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Conservative						
Akbayrak, T., et al. (2002). Complex decongestive physical therapy	Case study	N=1 6.5-month old female Congenital LL affected from 2 months of age	Manual lymphatic massage, multi-layered inelastic compression bandaging, remedial exercises and meticulous skin care; lasted for 2.5 month, 5 days per week; Mother educated on technique and asked to repeat at home	6 months	Volumetric measurement (ml) Circumferential measurement (cm)	First visit --> after 2.5-month treatment-->6 months after R: 250-->200-->125 L: 250-->175-->125
Akbayrak, T., et al. (2016) Complex decongestive physical therapy	Case report	N=1 11-year-old male Congential lymphovascular malformation Left UL	First phase of CDT- skin-care, manual lymphatic drainage, low-pressure bandage application, and exercises; 3 times a week for 8 weeks, a total of 24 sessions, each session took about an hour. Maintenance phase of CDT- skin care, self-drainage, and exercises. Thoracic compression garment, compression sleeve for the hand and arm regions separately were prescribed	1 year	1. Water displacement 2. 10-cm visual analog scale- for disease-related complaints, a was used to assess the pain, iscomfort-heaviness and tension experienced by the patient 3. Joint movement ranges using a goniometer	Pretreatment-posttreatment-1 year follow up: 1. left hand: 1,750-->1,250-->1,350 ml 2. 8.1--> 4.2--> 5.3 3. Elbow Flexion: 100-110-110 Extension: 105-112-114 Wrist Flexion: 75-82-85 Extension: 50-60-65 Ulnar deviation: 30-32-35 Radial deviation: 20-20-20

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Boris, M., et al. (1994). Noninvasive complex lymphedema therapy	Cohort study with three paediatric patients extracted	N=3 3 Y F, secondary, UL affected for 2 years 16 Y M, primary, LL affected for 16 years 2 YM, primary, LL affected for 2 years	Non-invasive complex lymphedema therapy (CLT), 4 hours/day, 30 days; skin care, gentle manual pressure, banding, lymph exercises Bandaging on rest of time	none	Percentage change in edema = (Vf-Vi)/ (Vi-Vn)x100 Vi=initial volume Vf=final volume Vn=normal limb volume Circumference measurements taken every 10cm; converted into volume for each segment using the formula for a truncated cone;	Percent reduction Pt1 (3YF): 127% decrease in volume Pt2(16YM): 295% decrease in volume; Pt3 (2YM): 61% decrease in volume
Avery, K. B., et al. (2000) Sequential intermittent pneumatic compression therapy	Case report	N=1 5-month-old M Congenital right LL	A pneumatic compression device was instituted with a custom-sized inflation boot ordered to fit the patient's small size	2 month	Circumferential measurement at arch, ankle, mid-calf, below knee	Leg circumference change Arch: L+1.5cm; R+1.5cm Ankle: L-3cm, R-1cm mid-calf: L-1cm, R-0.5cm below knee: L +3.5cm; R+4cm

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
de Godoy, J. M. P., et al. (2012). The Godoy & Godoy cervical stimulation technique	Prospective cohort study	9 boys and 5 girls, aged from 2m to 8.5y Primary congenital LL	10 only with cervical stimulation; 4 with cervical stimulation combined low stretch cotton polyester compression stockings Recommended 15 to 20 min per day Mothers were trained in the manual cervical stimulation technique and continued treatment in their own homes. Mothers were requested to perform stimulation for 15 to 20 min per day at 20 to 30 stimuli per minute using light movements.	2 years	Perimetric measurements of the feet at two points, 3 and 6 cm from the base of the big toe along the dorsum of the feet.	A significant reduction in the perimeter of feet was identified in both groups
Eyigör, S., et al. (2015). Complete decongestive therapy (CDT)	Case report	N=1, 14 year old female Secondary (sirolimus therapy postoperative month 3; discontinued after 34 weeks) Bilaterally UL and LL for 6 months	Left UL- lymphedema compression garment LL- The patient was treated with CDT: patient education, manual lymphatic drainage (self-massage, compression therapy with a short stretch bandage for 23 h per day/5 days/week), exercise, and skin care in the intensive phase. Maintenance phase- low stretch elastic garments.		Volume calculations in agreement with the International Society of Lymphology guidelines	Decreases in 22.3% and 14.1% of volumes of the R and L leg respectively Left upper limb swelling disappeared (no detail provided)

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	1. Result
Hassall, A., et al. (2001). Lymphapress pump	Retrospective study	16 children; 7 boys 9 girls Age: 6 to 26 3 Unilateral UL; 7 unilateral LL; 6 bilateral LL	Lymphatic pump, graded compression garments, advice on exercise and skin care		1. Percentage difference between measurement of volume= affected limb volume decreased/ unaffected one Water displacement at either the groin or axillary level of the affected and unaffected (clinically significant: 10% difference, improvement>10% difference)	2. 20% improved, 73% maintained, 7% deteriorated (one participant unable to comply to volumetric measurement)
Hwang, W. T., et al. (2015). Complex decongestive physical therapy and low-level laser therapy	Case report	N=1, 2 Y F Congenital Left UL	(two operation before 2 years old) CDPT, remedial exercise, modified low-tension bandages (?only 2 days), LLLT (LLLT was applied perpendicular to the left armpit for 10 min.) 7 sessions over 10 days		Circumferences BIS-Inbody	Underneath the armpit, 18 cm-->18cm; middle of the upper arm 21.5 cm-->21cm; elbow, 24 cm--> 21; middle of the forearm, 21 cm-->21cm; wrist, 15.5 cm-->15cm; hand, 19 cm--> 17cm Amount of water: 1,050 mL -->980ml Moisture ratio=(i.e. extracellular fluid/total water amount): 0.412% --> 0.405

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Lawrance, S. (2008). Short-stretch compression wrap system	Case report	N=1, 16 Y F Primary lymphoedema distichiasis syndrome, with mutation of FoxC2 Bilateral LL	Farrow Wrap-for night use Patient initially received routine advice about skin care, calf-pump exercises, and the importance of leg elevation at rest. She was then booked for 10 sessions of MLD and full-leg MLLB over two weeks	2 weeks	The method of limb volume measurement for the following case reports uses 4cm measurements along the length of the limb and the formula:	Right distal volume was 4,850ml, indicating a reduction of 368ml, and the left was 5,965ml, indicating a reduction of 560ml
Mahram, M. and M. Rajabi (2011). low level laser therapy (LLLT)	Case report	N=1, 15 Y F Primary lymphoedema Right LL	Treatment sessions were totally 24, each cycle containing 12 every other day 15-minute sessions, and one month free between the cycles. Two probes, KLO3 and LO7, were used for 22 points on inferior, posterior and lateral sides of the leg (30 seconds/point). Same probes used for two points on the involved thigh (1 min/point) and on two points at lateral sides of umbilicus (1 min/point). MLO1K probe on 14 points on posterior side of affected leg, knee and groin (2 min/point),.	3 months?	Changes of diameter at 3 locations- just below the knee; 5cm above the knee; above the ankle	 34.5cm-->32.5cm; 36.5cm -->32.5cm; 23.5cm-->21.5cm

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Ti-sheng, Z., et al. (1984). Heat and bandage treatment	2 Case studies in a larger cohort study	N=2 15 Y M, 13 Y F M-primary left LL at 5, left thigh and dorsum also affected at 14 F-left LL	Heat and bandage treatment followed by bandaging; 3 course of treatment , (one course 20 treatments, one treatment daily for an hour, interval between course was 7-10 days	Not specified	Circumference at 5 locations- I, middle part of the foot; II, ankle joint; III, midcalf, IV, fibula head; V, mid thigh Volumetric water displacement measurement	15YM//13YF (cm) 24-->22//20-->20 30-->21//21-->19 45-->31//28-->26 39-->28//28-->26 45-->38//40-->33 4414ml decreased//1074ml decreased
Zelikovski, A., et al. (1980). Lympha-press. (A new pneumatic device)	Cohort study with four paediatric patients extracted	N=4 14 Y F-Congential; 8 Y M-Congential; 17 Y F-Irradiation 16 Y F-Traumatic	Lymph press range used 120-140mmHg, duration 3h, 3h, 8h, 2h Bandages applied after lympha pressure and discharge with elastic bandages	Not specified	Circumference in the middle of calf	Decrease of 3,2,8,2cm in the 4 subjects respectively
Nagata, Y., et al. (1994). Intraarterial infusion of autologous lymphocytes	Cohort study with one paediatric patients extracted	N=1, 14 year old female Primary aplasia right leg	intraarterial infusion of autologous lymphocytes from patient's own venous	3 months	Percentage change in limb circumference=difference between affected and normal limb after treatment/ difference before treatment. Measured location not specified	50 --> 100, outcome good

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Surgical treatments						
Abalmasov, K. G., et al. (1993). Enteromesenteric bridge surgery	Case report	N=1, 16 year Male Primary R leg, genitals and abdominal wall below the umbilicus	Enteromesenteric bridge surgery- lymph nodes from stomach area moved towards pelvis in large surgery Pre operation: diuretics and pneumocopressive massage; Post: 3 weeks course of massage therapy pressure from 10th day onwards being gradually increased from 20 to 40mHg	3weeks	Circumferential measurements at 20cm above knee; 10cm below tibial tuberosity; medial malleolus; midfoot (right)	(before operation -->3 weeks after) 54.5cm-->47.5cm; 36cm --> 29.5cm; 28cm --> 24cm; 24.8cm--> 22.8cm
Demirtas, Y., et al. (2009). Supermicrosurgical lymphaticovenular anastomosis and lymphaticovenous implantation	Case study in a larger cohort study	N=1, 15 Y M stage III lymphedema (Campisi staging) right LL for a duration of 4 years	Three lymphaticovenular anastomoses and one lymphaticovenous implantation were performed through two incisions. Pre operation: rarely used elastic stocking Post: bandaged 1-month followed by a custom-made pressure garment for 5 months. free of any conservative treatments at 2 years of follow-up	2 years	Volumetric evaluation Standardized measurements of the circumference beginning from the ankle throughout the inguinal region with 4-cm intervals. The unaffected extremity was used as a control, and the oedema volume in lymphedematous extremity calculated as the difference between its volume and that of the normal limb on each occasion.	a 53.0% reduction of 2089 ml edema

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Gennaro, P., et al. (2016). Supramicrosurgical lymphaticovenular anastomosis (LVA)	Case study in a larger cohort study	N=1, 16 Y F primary, grade III (Campisi grading) LL	7 lymphatico-venular anastomosis (LVA) Post: oral antibiotic therapy 6 days	1 year	Sum of diameters (Not specified in study) Satisfaction index to evaluate feeling after LVA (1=not satisfied; 4=extremely satisfied)	Before LVA 149cm, after LVA 146.5 reported reduction of 56% (unaffected side 144.5cm) Satisfaction: 4
Karonidis, A. and H. C. Chen (2010). Charles procedure	Case study in a larger cohort study	N=2, 16 YM, 17 YM primary, right LL for 3 years	Charles procedure with toe preservation- the lymphedematous tissue is radically excised Post: Coban compression dressings are applied to the toes after wound healing. Compressive garment for the foot, leg, and thigh, is used after 1 month, when the skin graft is stabilized.	Follow up period ranged from 2 to 4 years (not specified in this case)	Circumferential reduction-by measuring limb circumference at each of the 4 levels of standard measurement comparing the preoperative and postoperative results	above knee: 19%, blew knee: 46%, ankle: 49%, foot: 34%; average reduction: 37%
Koshima, I., et al. (2003). lymphaticovenular anastomosis	Cohort study (one paediatric patient)	N=1, 12 Y F Primary, right LL of 2 years duration	History of conservative treatment ineffective 5 Lymphaticovenular anastomosis (two thigh, two lower leg, and one foot). Post : leg elevation at night and low tension bandaging, later with constant compressive therapy	8y	Circumference measurement at knee	7cm to -7cm, 100% effectiveness (7 cm: 100 percent of the excess circumference) has been achieved)

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Venkatramani, H., et al. (2017). lymph node transfer	Case report	N=1, 16 Y M primary, grade III lymphedema (ISL) right LL	Vascularized Lymph Node Transfer From Thoracodorsal Axis Patient started on regular massage and complete decongestive therapy from age of 2. Post: Patients were kept with lower limb elevation post operatively for 10 days. After 2 weeks gentle compression with crepe bandage was given and non-weight bearing mobilization started at 3 weeks. custom made compression garments were given	6 months	Volume reduction-by measuring limb circumference at standard levels of standard measurement comparing the preoperative and postoperative results EQ5D health state feedback	9% reduction From 70% pre-operatively to 95%
Sachanandani, N. S., et al. (2018). Vascularized lymph node flaps	Cohort study with one paediatric patient extracted	N=1, 13 Y child Congential lymphoedema grading 1 and vascular malformation from birth	Lymphoedema surgery: right submental Flap to LLE; LVA (side to end; inner thigh, just above knee) to RLL. 6 nodes transferred	30 months	Circumferential reduction rate - preoperative difference between the circumferences of the lesions and healthy limbs minus the postoperative difference, divided by the preoperative difference	12month: above knee: 90%; below knee: 66.7 % Final: above knee: 52%; below knee: 55 %

Author/ Date/ Main intervention	Study design	Patients	Experimental Intervention	Follow up period	Outcomes measured	Result
Mousavi, S. R. and Z. Mehdikhah (2008) Subcutaneous excision beneath flaps	prospect ive cohort study	N=59 35 M+14F, 10 unknown Unspecified 10 bilateral LL; 49 unilateral LL	Surgery- subcutaneous excision beneath flaps- in 2 or 4 stages Later stages done on higher up leg 3 months after initial operation	1 year	Circumferential reduction at 6 months and 12 month Subjective report of symptoms	Supramalleolar 6Mon: 19% 12Mon: 17% Midcalf 6Mon: 29%; 12Mon:33% Midthigh 6Mon: 23%; 12Mon: 25% After one year follow up, 52 (87.83%) patients were symptom and complaint free with minimal limb swelling and without disability. 7 (11/8%) patients had acceptable results and became socially active but a disfiguring edema remained.

Y, years old; M, male; F, female; LL, lower limb; UL, upper limb, CDT, Complex decongestive physical therapy; LLLT, lower level laser therapy

Table 2: Risk of bias evaluation for all studies

First author	Does the patient(s) represent(s) the whole experience of the centre or is the selection method unclear, with other patients with similar presentation may not be reported?	Was the exposure adequately ascertained?	Was the outcome adequately ascertained?	Were other alternative causes that may explain the observation ruled out?	Was there a challenge/ rechallenge phenomenon ?	Was there a dose–response effect?	Was follow-up long enough for outcomes to occur?	Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?
Conservative								
Boris	N	Y	Y	Y	N	N	Y	Y
de Godoy	N	N	N	N	N	N	Y	N
Eyigör	Y	Y	N	Y	N	N	Y	Y
Hassall	N	Y	Y	Y	N	N	Y	Y
Hwang	N	Y	Y	Y	N	N	Y	Y
Lawrance	N	N	N	Y	N	N	Y	Y
Mahram	N	Y	Y	N	N	N	Y	Y
Ti-sheng	N	Y	Y	N	N	N	Y	N
Zelikovski	N	Y	Y	Y	N	Y	Y	Y
Akbayrak (2002)	N	Y	Y	N	N	N	Y	Y
Avery	N	N	Y	N	N	N	Y	N
Akbayrak (2016)	N	Y	Y	N	N	N	Y	Y
Nagata	N	N	N	N	N	N	Y	N
Surgical								
Abalmasov	N`	Y	Y	N	N	N	Y	N
Demirtas	Y	Y	Y	N	N	N	Y	Y
Gennaro	Y	Y	Y	Y	N	N	Y	Y

Karonidis	Y	Y	Y	N	N	N	Y	N
Venkatramani	N	N	N	N	N	N	Y	N
Sachanandani	N	Y	Y	N	N	N	Y	Y
Koshima	Y	Y	Y	N	N	N	Y	N
Mousavi	Y	Y	Y	N	N	N	Y	N

Appendix 1. Example of search strategy: Medline

Search Strategy:	
1	(lymphedema or lymphoedema).mp. or lymphedema/ (10678)
2	((swollen or swell* or oedema or edema) adj3 chronic).mp. (1453)
3	(Milroy* disease or Milroy* syndrome).mp. (131)
4	Lymphatic Abnormalities/ (424)
5	infant*.mp. or Infant/ (1173164)
6	(child or children).mp. or Child/ (2094713)
7	(kid or kids).mp. (5986)
8	(baby or babies).mp. (59618)
9	adolesce*.mp. or adolescent/ (1948898)
10	(youth* or juvenile* or teen*).mp. (156579)
11	p?ediatric*.mp. or pediatrics/ (317946)
12	therap*.mp. or Therapeutics/ (5380594)
13	(manage or management).mp. (1038462)
14	surgery.mp. or General Surgery/ (2347380)
15	intervention.mp. (461077)
16	(treat or treatment*).mp. (4211324)
17	1 or 2 or 3 or 4 (12342)
18	5 or 6 or 7 or 8 or 9 or 10 or 11 (3691665)
19	12 or 13 or 14 or 15 or 16 (8903709)
20	17 and 18 and 19 (1230)

Chapter 3: Does long-term medical compression for lymphoedema impact skeletal growth in children?

Abstract

Background Lymphoedema is an accumulation of fluid due to the impaired lymphatic drainage, resulting in permanent swelling of a body region. Children with lymphoedema will require lifelong treatment. The mainstay of lymphoedema treatment in adults is compression therapy. However, if it is safe for use in children, with their growing skeletons, is unclear. The aim of this study is to: a) describe the compression prescription in paediatric lymphoedema patients at two major children's hospitals in New South Wales and b) examine the growth pattern of children with lymphoedema who have been treated with compression.

Method A retrospective medical chart review was undertaken. Clinicians at two major children's hospitals in Sydney Australia compiled a list of all lymphoedema patients on their records. The medical charts and physiotherapy files of all potential participants at the two centers were reviewed. Data from each visit were extracted, including: height, age, use and changes to compression. Abnormal growth pattern was determined by comparing each individual patient's height and its percentile against normative growth charts.

Result Ninety-three patients were identified by the clinicians, with 42 having sufficient height measurements for further analysis of their growth data. All 42 patients were prescribed garments or garments combined with bandaging. In the short-term compression group (< 2 years compression treatment), all of the 17 participants demonstrated no growth fluctuation of more than 15 percentiles at any time. In the medium-term compression group (2-5 years), one participant's height percentile increased by more than 15 percentiles between the first and last height assessment. In the long-term compression group (>5 years), five participants had no fluctuations in the height percentile over time. Eight participants' height percentile fluctuated by more than 15 percentiles at some point during their period of

compression use, but returned to be within 15 percentile of the initial height measured by the time of the last assessment recorded. Three participant's height percentile increased by more than 15 percentiles between the first and last height assessment. No participant in any group demonstrated a decrease in their height percentile.

Conclusion

No participants were found to decrease their height percentile by more than 15%, even with extended periods of compression. This suggests that compression does not appear to impact on the growth of skeletal bones in children with lymphoedema.

Introduction

Lymphoedema is a chronic, debilitating condition that causes permanent swelling of the limbs or other parts of the body (1, 2). In a paediatric population, lymphoedema can either be due to primary or secondary causes, with primary lymphoedema the more common form (3). Primary lymphedema is a genetic mutation that leads to faulty lymphatic vascular development, which gives rise to either a structural and/or functional abnormality that impairs lymph drainage (4). Mutations to genes such as FOXC2, SOX18, CCBE1, GJC2, GATA2, KIF11 have been identified as causative for various forms of primary lymphedema, with work ongoing to identify others (5). Secondary lymphoedema is defined as deficiency of the lymphatic system as a result of disease, trauma, or surgery (6). Regardless of the cause, once lymphoedema develops, it requires lifelong treatment.

The mainstay of lymphoedema treatment in adults is compression therapy, often in the form of bandages or compression garments (7). Best practice documents suggest that similar treatments used in adults should be used in children (8). However, there is no evidence or guidelines to support the use of compression in children, nor whether it is commonly used in paediatric patients. Furthermore, whether the long-term use of compression on a growing paediatric skeletal could be problematic is unknown. A study of paediatric patients with facial burns using compression for a one year period (n=6) found that use of facial compression has appeared to lead to small changes in bone growth (9). Maxillary growth was found being affected with compression, especially horizontal growth. When compression was discontinued, some, but not all, changes in bone growth patterns reversed. An increase in the vertical length of the lower facial bones remained once compression garments were no longer required. As children with primary lymphoedema will continue to wear compression

garments for much longer than one year, it should be determined if similar impacts on bone growth could occur in kids with lymphoedema

Increases in height during periods of growth occur, partially, due to increases in the long bones of the legs. The most common area of paediatric lymphoedema is affected is the lower limbs (10). If compression causes disruption of bone growth, this may be visible as decreasing height. Typical growth patterns in children's growth has been well documented and devised into normative percentiles on a growth chart (11). Normative growth chart were first constructed by the World Health Organisation (WHO) in 1977, and revised in 2006, using longitudinal length and weight data measured at frequent intervals. Another growth chart recommended for 2-18 years old in most countries was developed by The Centers for Disease Control and Prevention (CDC) in 2000 (12). For an individual child, serial length or height measurements can be taken over time and plotted on the growth chart. A major deviation in growth percentiles would be suspected as abnormality, while some shifts in growth percentile is regarded as normal (11).

If a group of children could be followed through periods of childhood, this could give a preliminary insight into the risk of growth disruption due to compression garment use. Although the long bones of the legs are very different from the irregular facial bones in terms of both the shape and the growth patterns, the findings from prolonged use of compression in children suggest it is worthy to investigate the impact of compression in children with lymphoedema.

The aim of the study is, therefore, to: a) describe the compression prescription in paediatric lymphoedema patients at two major children's hospitals in New South Wales and b) examine the growth pattern of children with lymphoedema who have been treated with compression.

The findings of this study will provide preliminary evidence on the use of compression in growing children.

Method

A retrospective medical chart review was conducted. The medical charts and physiotherapy files at the Children's Hospital at Westmead and Sydney Children's Hospital were reviewed for patients with lymphoedema between 2000 and 2019. Clinicians at the two centers provided a list of all lymphoedema patients on their records. Patients with either primary or secondary lymphoedema were eligible for inclusion.

This study was approved by The Sydney Children's Hospitals Network Human Research Ethics Committee (SCHN HREC; Protocol number: 2018/ETH00550). Site-specific assessment (SSA) for both sites where the research was conducted was approved.

Medical records for all lymphoedema patients were reviewed, with data initially extracted regarding: gender, type of lymphoedema, height, age of onset location of swelling and medical history of conditions that may cause changes in growth patterns. Next, data was extracted for each individual patient visit on the type, use and changes to compression, as well as any clinical notes on adverse events or compliance with use of compression garments.

Only participants for whom more than two height measurements were available after compression was prescribed were included for analysis. Participants with no height recorded or only one height recorded after compression applied were excluded for growth pattern analysis. Two different groupings of patients were considered: 1) those with a recorded

height measurement from recently before commencing compression treatments (Pre-compression Group) and 2) those without a recorded height measurement prior to commencing compression treatments (Post-Compression Group).

Normative growth charts were used as a comparison to determine whether changes in each patient's growth pattern were seen. Following the recommendations of the Australian National Health and Medical Research Council (NHMRC) (13), for children aged 0-2 years old the WHO chart was used for comparison, and the CDC chart was used for once children were over 2 years old. Poor growth is characterised by weight or length dropping percentiles. Height percentile changes of more than 15% was chosen as the criteria for abnormal change. This was a conservative definition of abnormal change as clinicians look for an increase or decrease across two major percentile lines. Between the two growth charts, they report different major percentile lines. The CDC Height growth charts shows the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentile, while the WHO length for kids under two years old shows the CDC growth charts include predefined major percentile lines to highlight the 3rd, 15th, 50th, 85th and 97th percentile.(11, 14)

Data analysis

Participant characteristics were described using frequency tabulations. The prescription compression details was obtained from the data spreadsheet.

To determine if compression appeared to impact on a child's growth pattern, we analysed our data into groups dependent on the length of time with both compression garments and height assessments. Data is therefore presented as short (<2 years), medium (2-5 years) and long-term (>5 years) compression/monitoring time. All height measurements were converted into percentiles using an online calculator (https://www.infantchart.com/child/childrenstatureage.php). Trends in changes of height

percentiles available were viewed for every participant to see whether change occurred in height percentile of more than 15% at any time.

Results

Ninety-three patients were identified by the clinicians for inclusion. Eighty participants had primary lymphoedema and eleven participants had secondary lymphoedema, with further two patients having unclear history, preventing determination of type of lymphoedema. Almost all (n=90) had their lower limb(s) affected (Table 1).

Table 1: Participants' characteristics (whole group n= 93, growth group n=42)

	Whole group Number	Growth group Number
Sex		
Male	35	18
Female	56	24
Type of lymphoedema		
Primary	80	34
Secondary	11	7
Unspecified	2	1
Site of lymphoedema		
Lower limb		
Unilateral *	48	21
Bilateral	41	21
Upper Limb	4	5
Other areas	7	6
Age of first time of prescription[#]	5 month – 16 years	5 month – 16 years

* number may be higher than 93 because some participants had multiple body regions with lymphoedema; # range

Height monitoring

Forty-two participants were eligible for analysis of their growth data. Reasons for exclusion of other potential participants included: presence of syndrome or other musculoskeletal conditions that cause growth disorders, for example, Noonan Syndrome and spinal bifida (n=8); only a single height assessment recorded during their period of compression (n=3); or compression treatment was only applied to the upper limbs (n=3). The follow-up period after first application of a compression treatment ranged from 4 months to 15 years.

Compression usage

All included participants were prescribed compression garments. Twenty-two (52%) of included participants had undergone treatment with a combination of garment and bandage, while 20 (n=48%) had only been prescribed a compression garment. Compression bandages use was seen in young babies who were not suitable for garment (n=9) as well as older children in whom it was found that a compression garment was insufficient to maintain limb volume or size (n=13). Where mentioned, adherence to bandaging programs appears to be good (n=20). Few adverse events were noted due to the use of either compression bandages or garments, beyond redness (n=16). Day time compression garment were used by all participants. In addition, night compression garments were prescribed to 7.1% (n=3). There was a range of time for replacement of compression garments between 4 months to 1 year. Seventeen participants were included in the short-term compression group, where there was up to two years of compression and height assessments completed (range 4 months to 2 years). For those in whom a baseline measure was available (Pre-Compression group, n=11),

no growth fluctuations of more than 15 percentiles were seen at any time (Table 2). The same pattern of stable growth percentiles was seen in the Post-Compression group (n=6).

Nine participants were included in the medium-term compression group, with compression and height measurements over a period of 2-5 years. Two in Pre-Compression Group and six in Post-Compression Group demonstrated no change in height percentile of more than 15% at any time. One participant in the Pre-compression height increased by more than 15 percentiles between the first and last height assessment. At the time of being prescribed their first compression garment, they were aged 12 years old, and in the 5th percentile for height. Over the next 3 years, their height percentile slowly increased to the 23rd percentile at last measurement; therefore, changing by 18 percentiles. Nothing was noted in their file about their growth. No participants were found to decrease their height percentile with medium-term use of compression.

Table 2: Details of height percentile changes by more than 15%

	Number	Δ15% Y:N	Δ15% ever Y↑ : Y↓ : N	Δ by 15% from first to last height measurement Y↑ : Y↓ : N
Pre-compression group <2 y	11	0 : 11	0 : 0 : 11	0 : 0 : 11
Post-compression group <2 y	6	0 : 6	0 : 0 : 6	0 : 0 : 6
Pre-compression group 2-5 y	3	1 : 2	1 : 0 : 2	1 : 0 : 2
Post-compression group 2-5 y	6	0 : 6	0 : 0 : 6	0 : 0 : 6
Pre-compression group >5 y	4	3 : 1	3 : 1 : 1	2 : 0 : 2
Post-compression group >5 y	12	8 : 4	6 : 6 : 4	1 : 0 : 11

Y= yes; N=no; Δ= change; y= year

Sixteen participants were included in the long-term compression group, for whom compression and height measurements were available for more than 5 years (range 5 to 15 years). For the participants with long term compression, the height percentile was seen to be stable in five. One in Pre-Compression Group and seven in Post-Compression Group demonstrated fluctuations of 15 percentiles at some point over the period for which data was available, although they returned to be within 15 percentiles of the initial height measured. The rest of two in Pre-Compression Group and one in Post-Compression Group demonstrated a fluctuation in over the time and ended up increasing by more than 15 percentiles than the initial height measured.

Discussion

Compression suggested to be the main form of treatment for paediatric lymphoedema; however, there is little evidence to support its frequency of use or its safety. This retrospective study provides initial evidence of common use of compression treatments in paediatric patients. Furthermore, growth patterns appeared to occur along normal growth charts, despite the use of compression garments for between 4 months and 17 years. This suggests the notion that compression garment use on growing long bones does not impact on their development.

The growth patterns of the long bones of the legs and arms differ from irregular shape bones of the face

Compression treatment for paediatric lymphoedema will likely be a life-long treatment. Though the changes has ever been found in the facial bone with garment treatment (9), the bones of the legs are long bones and the facial bones are irregular bones. The different type of bones may result in differing impacts in their growth with the use of compression. Many things

can affect growth patterns in children, including family history, and over or undernutrition (11, 14). Despite all of these potential confounders to growth, our sample followed a basically normal growth pattern. Periods during the first two years of life, as well are puberty critical times for following growth as growth sprout normally occurs during these two period (15). Twenty-five of our 41 participants were followed during one these prime periods of growth and none of our participants demonstrated any change in their trajectory of growth. However, future research over a longer period of time and with a larger sample is required to confirm this.

Measurement of height

In this study, all the height related measurements were extracted from the paper folders and e-medical charts which were recorded manually by different departments in the hospital, which may cause the deviation of measuring and recording. Although generally found to be reliable (16) , there are a number of factors that have been identified that may cause errors in measuring heights in children, including that children being in slightly different positions has the most impact (17). Unfortunately, we had to exclude a large percentage of our original sample due to a lack of recording of height information.

Use of compression in paediatric patients

Compression treatment is commonly used in treatment of adult lymphoedema (7). Many participants in this study received multiple forms of compression across the period that they had been seen in clinic, including bandaging, pneumatic pumps as well as daytime and nighttime garments. A number of small prospective cohort and case studies have looked at the efficacy of compression treatments, in combination with other treatment modalities (18). However, none of these studies have examined the safety or efficacy of bandaging or

compression garments alone. In addition to no evidence of effects on growth, we found little evidence of adverse events associated with compression treatments. The most common reported adverse events was skin redness. There were two cases of cellulitis in the group with compression; however, there is no evidence that this is attributable to compression. This study provides useful preliminary evidence to support the safety of compression treatment in the paediatric patient. However, what is not known is the optimal forms and treatment regimens for using compression in children.

Limitations and future direction

The limitations of this study should be acknowledged. As a retrospective study, we had no control over the recording of height data; this resulted in having to exclude a significant number of participants from the original sample of 93. Furthermore, changes in hospital records across time made the data lost due to shifting from mixed paper to e-medical records. Another limitation for this study is only 12 participants were followed for more than 5 years. Future studies need to specially look at the growth pattern over long period of time. A larger sample size is anticipated.

Conclusion

All participants were found to follow a basically normal growth pattern, even with extended periods of compression. This would provide preliminary evidence on that compression does not appear to impact on the growth of skeletal bones in children with lymphoedema as well as the safety use of compression on a growing skeleton in clinic.

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Chapter 4: Discussion

The treatment for lymphoedema in children is burdensome and can cause significant challenges. For example, the use of compression garments could lead to bullying for being different (1) as they may be viewed as abnormal. In addition, lymphoedema service centres are not accessible to some families with lymphoedema paediatric patients locally, making lymphoedema visits time-consuming and expensive (1). Children who develop lymphoedema will require treatment for their condition for their entire lives. It is known that treating lymphoedema as early as possible before tissues changes makes it easier to manage in the long-term. However, how best to treat lymphoedema or whether those treatments are safe for a growing lymphoedema patient is unclear. To address these issues, two studies were undertaken. Our first study is to look at the efficacy of any treatment in children, then to examine whether one of the treatments,compression, affects paediatric height.

Chapter 2 presented a systematic review undertaken to determine the efficacy of any form of treatments for paediatric lymphoedema. A comprehensive search strategy was undertaken in five databases. After screening by two reviewers, 21 studies meeting the inclusion criteria were included in this review. These studies covered both conservative treatments (n=13) and surgical treatments (n=8). Almost all studies (n=18) were case studies and interestingly, most of the studies (n=16) studies combined multiple treatments together. Overall, the vast majority of studies (19 of 21) found improvements in the limb volume or size in the lymphoedematous limb, regardless the type of treatment studied. Due to the variety of outcome measures used to assess the lymphoedema and the variety of treatments, we could not pool the data to determine if any forms of treatment were more effective than others. A further challenge to the interpretation of the findings was that all the articles had many potential sources of introduced bias and were with low level of evidence, which was similar to finding in a previous systematic review (1). Most studies poorly reported dose-response

effect, challenge/ re-challenge phenomenon, whether population chosen were representative; and whether other alternative causes that may explain the observation ruled out, resulting in potential high risk of bias. In both conservative and surgical studies, a combination of extreme long-term or underwent treatment in high intensity, making the treatment hard to replicable in clinic and also hard to find which individual treatments made contribution to the reduction of limb volume. Seven different measurement protocols were used to assess the limb volume change. In addition, there was no agreement on a clinically important improvement in limb volume. The objective outcomes were sort of "subjective" with so many variables in measures, positive outcome criteria and outcome interpreting.

The last systematic review on the conservative treatment of paediatric lymphoedema was completed in 2014 (2). Unfortunately, our findings were the same as their conclusions: there is little evidence to support the efficacy of any form of treatment for paediatric lymphoedema. It is therefore critical that more research is needed to be done in the future to guide clinicians on how to most effectively treatment lymphoedema in children. Most of the treatment options that were considered in Chapter 2 were similar or the same as treatments used in adult patients with lymphoedema. However, there are significant differences between children and adults, including most importantly, that children are still growing. The safety of treatments for use in children must therefore be considered before studying their efficacy. The most common form of treatment used in adults is compression (3). Whether using compression long-term on a growing skeleton is safe is not known. If it was detriment for a growing skeleton to be compressed, it may be seen in falling growth percentiles curves. To begin to investigate the safety of compression treatment, we therefore, undertook a retrospective medical chart review of a large group of paediatric patients with lymphoedema.

Chapter 3 presented the results of the medical chart review. Ninety-three potential participants were considered from two major children's hospitals in Sydney, Australia. To allow the determination of whether long-term compression appeared to affect growth, included participants needed to be prescribed compression and have had their height measured at least twice after their compression had been prescribed. Forty-two participants were included for further analysis of their growth data. All these 42 patients had been prescribed compression garments, with 22 having been prescribed bandaging as well at some point. While three periods of growth tracking, short (less than 2 years), medium (2-5 years) and long (more than 5 years) were considered separately, the results were remarkably similar regardless of how long the participant had used compression for. Most participants (n=30) demonstrated a stable growing pattern, with a lower than 15% percentile change in height, at any time over the period. Though the remaining 12 demonstrated a fluctuation over the period they were on compression, eight of them returned to be within 15 percentiles of the initial height measured, and four ended up increasing more than 15 percentiles than the initial height measured. There were no participants found ended up with decrease their height percentile by more than 15 percentiles. This retrospective study provides preliminary evidence suggesting the notion that compression garment use on growing long bones does not impact on their development. Furthermore, few adverse events were noted due to the use of either compression bandages or garments, beyond redness. However, due to the retrospective nature of this study, more research in the future is needed to confirm the findings from this study.

Future directions

To improve our understanding of the treatment of lymphoedema, more consideration needs to be given to how lymphoedema is assessed in children. As the treatment for paediatric

lymphoedema often lasts through childhood and into adulthood, more research into how best to assess changes in limb size in a growing child is needed. However, only one study has been completed looking at changes in a lymphoedema assessment outcome in growing children (4). The study using bioimpedance spectroscopy (2) found younger patients had a greater extracellular fluid content. Future studies need to: 1) undertaken on how best to assess for lymphoedema in children and 2) better consider growth in assessing the limb volume in studies on the treatment for lymphoedema. Future studies that included a larger sample size would allow for better analysis of the impact of gender and age on bone related changes due to the long-term use of compression. Furthermore, looking at the whether slight changes to bone shape or density are occurring with compression using assessment methods such as DEXA or X-ray. Likely for both the assessment and treatment for paediatric lymphoedema populations, novel methods will have to be found for this population, rather than simply copying from adult strategy.

This thesis demonstrates that we are still unclear what the best treatment for paediatric lymphoedema is. However, preliminary evidence suggests that compression appears to be a safe option for paediatric lymphoedema patients. Future research is needed to better support clinicians in determining how to assess growing lymphoedema patients as well as how to safely and effectively treatment them. This is critical to start our paediatric patients on a lifetime of good management for their chronic condition. Overall, the field of paediatric lymphoedema is neglected, and under researched, more evidence is needed to support treating children.

Reference

1. Quéré I & Moffat C. Care of children with lymphoedema. International Lymphoedema Framework. 2010

2. Phillips JJ, Gordon SJ. Conservative management of lymphoedema in children: a systematic review. JPRM. 2014;7(4):361-72.

3. Mosti G, Cavezzi A. Compression therapy in lymphedema: Between past and recent scientific data. Phlebology. 2019;34(8):515-22.

4. Avila ML, Ward LC, Feldman BM, Montoya MI, Stinson J, Kiss A, et al. Normal values for segmental bioimpedance spectroscopy in pediatric patients. PLoS One. 2015;10(4):e0126268.

Appendix

Appendix 1: SCHN HREC ethics approval

The Sydney children's Hospitals Network
care, advocacy, research, education

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7 February 2019

Dr Elizabeth Dylke
Faculty of Health Science
University of Sydney

Dear Dr Dylke,

HREC Reference:	**2018/ETH00550**
Project title:	**Does long-term medical compression for chronic oedema impact skeletal growth in children?**
Sites:	**The Children's Hospital at Westmead** **Sydney Children's Hospital, Randwick**

Thank you for submitting the above project for single ethical and scientific review. This project was considered by the Sydney Children's Hospitals Network Human Research Ethics Committee's Executive at its meeting 29 January 2019 and subsequently on 4 February 2019.

This HREC has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review, and by the National Health and Medical Research Council as a certified committee in the review of multi-centre clinical research projects.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and *CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise that the Committee has granted ethical approval of this research project. Your approval is valid for five (5) years, effective the date of this letter.

This application has been assessed in accordance with, and meets the requirements of the National Statement on Ethical Conduct in Human Research (2007).

The documents reviewed and approved by the Committee are:

Document Reviewed	*Version*	*Date*
Data extraction sheet	V1	7 Nov 2018
Project Registration		11 Jan 2019
HREA	V2	21 Jan 2019
Paeds LO Medical Review- Ethics Response		29 Jan 2019
Study Protocol	V3	29 Jan 2019
Waiver of Consent	V2	28 Nov 2018

Please note the following conditions of approval:

1. This approval is restricted to research being conducted in accordance with the approved documents, and the review of the medical records you have nominated. There is to be no contact with patients, parents/guardians or other family members.

2. The Coordinating Investigator will immediately report anything which may warrant review of ethical approval of the project in accordance with the SCHN adverse event reporting policy.

3. All proposed changes to the research protocol, including the conduct of the research, changes to site or personnel, or an extension to HREC approval, are to be provided to the HREC or its delegate for review before those changes can take effect.

4. The HREC will be notified, giving reasons, if the project is discontinued at a site before the expected date of completion.

5. The co-ordinating investigator will provide an annual report to the HREC on the anniversary of this approval letter, and a final report on completion of the study.

6. Your approval is valid for five (5) years from the date of the final approval letter. If your project extends beyond that five year period and you are still actively recruiting you will be required to resubmit your application incorporating any amendments within six (6) months of that approval expiry date. If your project is in follow up on, or analysis, please submit an application for amendment to extend the approval period. Ethics approval can be extended for a period of twelve (12) months at a time.

7. In the event of a project **not having commenced** within 12 months of its approval, the approval will lapse and reapplication to the HREC will be required.

Should you have any queries about the HREC's consideration of your project please contact the Research Ethics Administration Assistant on (02) 9845 1253.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained. A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The HREC wishes you every success in your research.

Yours faithfully

[REDACTION]

Associate Professor Sarah Garnett
Chair, Sydney Children's Hospitals Network Human Research Ethics Committee Sydney Children's Hospitals Network Human Research Ethics Committee