Analysis of oxygen saturation levels recorded during dental intravenous sedations – a retrospective quality assurance of 3,500 cases.

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A thesis submitted in partial requirement for the degree Master of Philosophy.

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2011.
AUTHOR’S STATEMENT

I hereby certify that this work has been carried out through the Department of Oral Surgery, Faculty of Dentistry, University of Sydney and has not been submitted for a higher degree at any other university or institution.

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March 2011.
ARTICLES RELATED TO THIS THESIS

The data and statistical analysis presented in this thesis forms the foundation for a paper that was submitted in December 2009 for publication in Anesthesia Progress: A Journal for Pain and Anxiety Control in Dentistry. Anesthesia Progress is the official journal of the American Dental Society of Anesthesiology. This retrospective quality assurance analysis was presented at the Faculty Research Day, 24th September 2009, and won the R G Schamschula Prize for the best Research Presentation by a postgraduate student.
ABSTRACT

**Background:** The death of a patient under dental intravenous sedation in New South Wales, Australia, in 2002 while being treated by a dentist with appropriate training in intravenous conscious sedation (ICS), (Graduate Diploma in Clinical Dentistry; Conscious Sedation and Pain Control, University of Sydney) has once again brought into question the safety of ICS. The cause of death was irreversible cerebral hypoxia following a cardiac arrest, which was precipitated by numerous periods of ever-deepening hypoxaemia.

**Aim:** This retrospective, quality-assurance audit investigated whether safe oxygen saturation levels could be maintained during single operator/sedationist dental sedations, when operating within the joint Royal Australasian College of Dental Surgeons (RACDS) and Australian and New Zealand College of Anaesthetists (ANZCA) PS21 guidelines for conscious sedation.

**Methodology:** Safe oxygen saturation levels were defined as pulse oximeter readings of 94% and above. The recording of two or more readings of less than 94% during a sedation procedure was defined as the outcome of interest. The association of the variables of age (eighteen and over), gender, weight, the American Society of Anesthesiologists (ASA) Classification I or II and the use of propofol in addition to midazolam and fentanyl, to low saturations, was examined. Two sub-cohorts were randomly generated: 1,750 patients were sedated with
midazolam and fentanyl and 1,750 patients received propofol, in sub-anaesthetic increments, in addition to midazolam and fentanyl. All patients received supplemental oxygen. Initial sedation was established using midazolam and fentanyl in both sub-cohorts. The second sub-cohort received sub-anaesthetic increments of propofol during times of noxious stimulation. Statistical analysis of the data used cross-tabulation of the variables by outcome, an associated chi-squared test and corresponding logistic regression analysis, together with odds ratio (OR) and a 95% confidence interval (95%CI).

Results: Patient exposure to two or more oxygen de-saturations below 94% was uncommon. The null hypothesis could not be rejected because there was no significant difference between the saturation levels recorded for each sub-cohort ($\mu_1 - \mu_2 = 0$), where $\mu_1$ was the cohort that received propofol in addition to midazolam and fentanyl, and $\mu_2$ was the cohort that received midazolam and fentanyl only. Analysis of the two population groups found them to be quite different in make-up. Had the two population groups been similar in make-up, then $\mu_1 - \mu_2$ may not have equaled 0, and the outcome of the hypothesis test may have been to reject $H_0$. The variables that were significantly associated with low saturations were age, gender and weight. The data showed that males were three times more likely than females to experience low saturations. Patients 45 years and older were nearly eight times more likely to experience low saturations than patients 25 years or younger. Patients classified as being in the gender-specific high weight group were twice as likely to experience low saturations than
those in the low and medium weight groups. Neither the dose of midazolam, nor the additional use of propofol were significant risk factors, even after adjusting for the variables of age, gender and weight. ASA Classification (I or II) was not a determinant of risk.

**Conclusion**: Within the limitations of this study, the data support that a single operator/sedationist, working within the RACDS/ANZCA document PS21 guidelines, and supported by a team of experienced dental nurses, can consistently maintain safe oxygen saturation levels when working on ASA I or II patients, regardless of age, gender, gender-specific weight, dose of midazolam, or the additional use of propofol.
ACKNOWLEDGEMENTS

May I record my sincere appreciation to Dr Malcolm Coombs, Head of the Department of Oral Surgery and Diagnostic Imaging, Sydney Dental Hospital, Faculty of Dentistry, University of Sydney, for the opportunity to undertake a higher degree and for his assistance and guidance during the preparation of this work.

My sincere thanks also to Dr Karen Byth, Westmead Hospital bio-statistician, for her statistical analysis of the data and her encouragement throughout this project. Never did I have to wait for data to be processed and her guidance during the initial pilot project, as well as the processing of the final data, is most appreciated.

I am deeply indebted to Dr Gregory Mahoney, my external supervisor, for his constant motivation and enthusiasm. At times this project seemed to overwhelm me and Greg was always ready to give me a nudge. Dr Mahoney has given up many hours of his personal time to guide and help me. Thank you for the insight that you have given me into the analysis and interpretation of the data and for your constructive critique.

I would like to thank my daughter, Claudine, with whom I spent many hours uploading what seemed to be a never-ending stream of patient data (I would do
this project again, Claudine, just to spend the time with you!). I could not have completed this mind-numbing task without her data management skills.

To Marilyn, my wife and best friend, I acknowledge the deep debt of gratitude that I owe you for your support and tolerance throughout this project. Thank you for acting as a sounding board for many of my ideas.

Finally, I would like to thank Professor Douglas Stewart, my intravenous sedation mentor, and my friend, whose suggestion it was that I gather up my data and make a contribution to sedation in dentistry.
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SECTION 1: REVIEW OF THE LITERATURE

INTRODUCTION

Intravenous conscious sedation (ICS) is a term used to describe the administration of intravenous sedative drug(s) in order to alter a patient's state of consciousness so that a medical or dental procedure can be carried out that would not normally be tolerated in the fully conscious state. The alteration in consciousness should be such that spontaneous, effective ventilation is maintained, as well as the gag and cough reflexes and a level of communication appropriate to the patient. In the dental setting, local anaesthetic would also be used to provide analgesia.

The ideal intravenous sedative should provide relaxation, anxiolysis, amnesia and analgesia. It should have a rapid on-set and rapid recovery and be reversible, should there be a need for this requirement. In addition, it should not cause any significant haemodynamic change, or suppression of respiratory drive. The ideal drug remains elusive and often a combination of drugs is used in an attempt to provide ideal sedation.

Historically, many drugs have been used to provide ICS. These include the benzodiazepine valium (diazepam), the barbiturate methohexital, the narcotic agents pethidine and pentazocine and the dissociative anaesthetic ketamine.
None of these drugs meet the requirements of the ideal sedative and this has lead to the development of newer agents. The most commonly used modern day drugs are the benzodiazepine midazolam, the narcotic fentanyl, and the hypnotic agent, propofol. Midazolam may be used as the sole agent (Runes & Ström 1996) or together with a narcotic (Milgrom, Beirne, Fiset, Weinstein, Tay & Martin 1993). Propofol may be used as sole agent (Leitch, Sutcliffe & Kennt 2003) or in combination with midazolam and fentanyl (Perrott, Yuen & Dodson 2003). Whilst these drugs are an improvement on the older agents, they may still cause profound respiratory depression and delayed recovery and therefore, the potential for morbidity or mortality remains. ICS may expose the patient to anaesthetic risk should oversedation occur. It is therefore important to be able to measure the safety of modern day ICS and define risk factors.

A review of the literature was undertaken to examine the use of midazolam, fentanyl and propofol to provide modern-day ICS, both separately and in combination. A review of articles and papers relating to the safety and the associated risk factors of intravenous conscious sedation was also undertaken.

Much has been published about the medical use of intravenous sedation (Lytle & Stamper 1989; D'Eramo 1999; Rozario, Sloper & Sheridan 2008). Gastroenterologists, cardiologists, intensivists and radiologists all routinely use ICS. Medical sedations may differ in many ways from dental sedations. For example, medical sedations often do not utilize local anaesthesia to cover painful
aspects of the procedure. This lack of pain control may require much higher doses of sedative drug(s) to mask the pain, which in the dental setting, would be provided by local anaesthetic.

The range in the health status (ASA classification) of patients undergoing medical procedures is much broader than dental patients treated in the private practice setting. Dental sedations in the private setting are only performed on ASA I or II patients, whilst medical sedations additionally may include ASA III and IV patients, with associated increased risk.

Medical sedations include a wider age-range (from very young paediatric to very old geriatric patients) than would normally be treated in the private practice dental setting. Jastak & Peskin (1991) noted a higher incidence of adverse outcomes in the dental setting with extremes of age.

For the reasons listed above, data obtained from medical sedations may be quite different from ICS data generated in the dental setting. Therefore, dentists need to harvest and generate their own data, specific to dental sedation, to which we can refer.

In the dental setting, hypoxaemia is the most likely risk factor associated with an adverse outcome (Hovagin, Vitkin, Manecke & Reiner 1989; Jastak & Peskin 1991). A review of the literature indicates that most dental references use lack of
morbidity (for example, nausea, vomiting, syncope, delayed recovery) or mortality, rather than recorded saturation levels as a measure of safety. Only one dental reference (Walton, Boyle & Thompson 1991) was found where oxygen saturation levels recorded during ICS were used as a measurement of safety.

Pain and anxiety management has always been an integral part of dentistry. Two recent UK surveys reported that over half of the UK’s adult population is anxious about dental treatment. This in turn leads to avoidance of treatment, with irregular attendance. Dentists too, reported that treating nervous patients was a major source of their personal stress. Most dentists surveyed were keen to deal with this problem and nearly three quarters of the dentists surveyed felt there was a need for sedation and for formal training in this area of dentistry (Adult Dental Health Surveys UK, 1988 & 1998). Leitch and Macpherson (2007) reviewed the current state of sedation care in dentistry. The authors report on the use of oral sedation with benzodiazepines, inhalation sedation, and intravenous sedation with both midazolam and propofol. A positive outcome using propofol was noted as well as the fact that further research in this area of intravenous sedation is needed.

Dentists generally use local anaesthetic to cover painful procedures. Some procedures, however, require greater levels of pain and anxiety control than can be provided by local anaesthetic alone. Coulthard and Craig (1997) suggest that
intravenous sedation is not a replacement for a caring and sympathetic attitude towards the patient, but rather a useful adjunct along with effective local anaesthetic techniques. They emphasise the importance of monitoring and postgraduate training.

Many authors (Kingon 1990; Milgrom, Beirne, Fiset, Weinstein, Tay & Martin 1993; Perrott, Yuen & Dodson 2003; Rogers 2005) report on the very positive patient response to treatment carried out under intravenous sedation, as well as an improved working environment for the proceduralist.
GUIDELINES FOR DENTAL SEDATION

The early nineteen nineties saw the introduction of guidelines for dental intravenous sedation procedures in Australia. These guidelines evolved as a result of discussions between the Australian and New Zealand College of Anaesthetists (ANZCA) and the Royal Australasian College of Dental Surgeons (RACDS), along with members of the newly formed Sedation Clinic at Westmead hospital and representatives of the Australian Society of Dental Anaesthesiology (ASDA). This original joint policy document was called P21 (1996) and after review in 2003, became PS21 (Appendix1). PS21 defined accepted Australian standards for in-surgery conscious dental sedation. The guidelines cover general principles that include the appropriate qualifications of the dentist sedationist, staffing requirements and training, facilities, monitoring, oxygenation, commonly used drugs, required specialised equipment and post-operative discharge. Emergency equipment and emergency drugs are also defined.

In April 2010, ANZCA unilaterally disestablished PS21 and a revised version of PS9 was published which recommends guidelines for both medical and dental sedation procedures. The RACDS later became signatory to PS9, despite strong opposition from ASDA and many Australian and New Zealand dentists. In November 2010, the Australian Dental Association, with input from ASDA introduced its own guidelines for ICS in Australia.
PHARMACOLOGY OF AGENTS CURRENTLY USED TO PROVIDE INTRAVENOUS CONSCIOUS SEDATION IN AUSTRALIA

Three intravenous sedative agents are predominantly used to provide ICS in Australia. These include midazolam, fentanyl and propofol. The composition, actions, pharmacodynamics, pharmacokinetics, indications, contraindications and dosage of each drug (MIMS Annual 2010) are briefly reviewed below:

(i) Midazolam:

(a) Composition: The benzodiazepine midazolam is marketed by Roche as Hypnovel in Australia. Its chemical name is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4] benzodiazepine.

(b) Actions: Midazolam is a short acting central nervous system depressant that induces sedation, hypnosis, amnesia and anaesthesia.

(c) Pharmacodynamics: Benzodiazepines appear to intensify the inhibitory mechanisms mediated by gamma aminobutyric acid (GABA), the most common inhibitory neurotransmitter in the brain. When used as an IV sedative, sedation is reached within 3 to 5 minutes, depending on whether a narcotic has been administered.
Approximately two hours are required for full recovery and this period may be affected if other drugs are used in combination. Intravenous midazolam decreases the sensitivity of the ventilatory response to elevated carbon dioxide levels. Midazolam has no other negative pulmonary effects. At levels used for sedation, midazolam has no deleterious effects on cardiac haemodynamics.

(d) Pharmacokinetics: The pharmacokinetic profile of midazolam in humans is linear in the drug range used during intravenous sedation procedures. In normal subjects, the drug exhibits a short elimination half-life of 1 to 2.8 hours, a large volume of distribution and a rapid plasma clearance. The mean absolute bioavailability of midazolam is greater than 90%. The drug is rapidly metabolised in the liver with subsequent excretion in the urine. Ninety seven percent (97%) of midazolam becomes bound to plasma proteins.

(e) Indications: Midazolam is used widely as an agent for conscious intravenous sedation in both dentistry and medicine. It can also be used for intravenous induction of anaesthesia, or as a pre-medication prior to general anaesthetic induction.

(f) Contraindications: Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma and they should not be used on
patients who have a hypersensitivity to benzodiazepines.

(g) Precautions when used in the dental setting: Care should be taken to slowly titrate the drug to the desired end point, as there can be a wide variation in individual response. Care should also be taken in the older patient group, as they tend to be more sensitive to this drug. Midazolam has a respiratory depressant effect and therefore, should be used with care on patients who suffer any form of pulmonary disease. Concomitant use of other central nervous system depressants increases the risk of under ventilation or apnoea and this factor should be taken into account when multiple agents are used. Patients should also be advised not to drive a vehicle or operate a machine until the effects of the drug have subsided or until the day after the sedative procedure.

(h) Dosage: Intravenous midazolam should not be administered as a single bolus, but slowly, in 1 milligram increments and titrated to the desired sedative end point, such as slurring of speech. The initial dose should be given over a period of at least two minutes. In healthy adults the initial dose is approximately 2.5 milligrams, however, some patients may respond to as little as 1 milligram. Further doses of 1 milligram may be given as necessary to reach the desired end point, such as the Verrill sign or ptosis (Donaldson, Harrop & Kliennecht
A total dose greater than 5 milligrams is not usually necessary. If a narcotic is used in conjunction with the midazolam, the dose of midazolam should be lowered by 25 to 30%.

(i) Overdosage: In the case of overdose, respiration, pulse rate and blood pressure should be monitored and general supportive measures should be employed. Flumazenil can be used to reverse the effects of the midazolam. Caution should be observed when using flumazenil in cases of mixed drug overdose such as when midazolam is used in combination with fentanyl. Patients who are being treated with benzodiazepines for epilepsy should be reversed with caution.

(ii) Fentanyl:

(a) Composition: Fentanyl is an opioid analgesic and is marketed in Australia by AstraZeneca Pty Ltd. Its chemical name is N-(1-phenethyl - 4 - piperidyl) propionanilide citrate.

(b) Actions: Fentanyl is a short acting synthetic narcotic and may be used during conscious intravenous sedation procedures in conjunction with the benzodiazepine midazolam.
(c) Pharmacodynamics: A dose of 100 micrograms of fentanyl is approximately equivalent in analgesic activity to 10 milligrams of morphine or 75 milligrams of pethidine. The principle therapeutic values of fentanyl are analgesia and sedation. Fentanyl interacts with opiate receptors, decreasing pain impulse transmission at the spinal cord level and higher in the central nervous system. Fentanyl is a potent µ-opiate receptor agonist. Fentanyl also causes peripheral vasodilation, increasing venous capacitance and decreases venous return by depressing the responsiveness of alpha-adrenergic receptors. Since it decreases both preload and afterload, it may decrease myocardial oxygen demand. Of note is that the respiratory depressive effect associated with opioid analgesics may last longer than the analgesic effect. Fentanyl appears to have less emetic activity than other opioids and less significant histamine release occurs with the use of fentanyl. Doses of fentanyl 50 micrograms and above may produce apnoea. The duration and degree of respiratory depression is dose related. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following the injection.

(d) Pharmacokinetics: The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, re-distribution of 13 minutes and a terminal elimination
half-life of 219 minutes. The onset of action is almost immediate when the drug is given via the intravenous route, however, the maximum analgesic and respiratory depressant effects may not be noted for several minutes. Duration of action is normally 30 to 60 minutes following a single intravenous dose of fentanyl. Fentanyl is primarily metabolised in the liver and excreted in the urine. A small amount is excreted in the faeces.

(e) Indications: Being a short acting opioid, fentanyl is often useful in combination with midazolam during intravenous conscious sedation procedures. It may also be useful for pain management in the immediate post-operative period.

(f) Contraindications: A known intolerance to fentanyl contraindicates its use, as does the common use of monoamine oxidase inhibitors (MAOI). Lastly, myasthenia gravis contraindicates the use of fentanyl, as this drug may cause muscle rigidity upon intravenous administration.

(g) Precautions when used in the dental setting: Fentanyl should be used with caution in patients with severe impairment of pulmonary function and other forms of chronic obstructive pulmonary disease because of the possibility of respiratory depression. Fentanyl should
also be used with caution in combination with other central nervous system depressant drugs and when used in combination, the dosage of fentanyl required will be less than usual.

(h) Dosage: Dosage should be individualised according to age, body weight, physical status and the use of other drugs. During intravenous conscious sedation, an initial dose of 50 to 100 micrograms is usual.

(i) Overdosage: Respiration may need to be assisted or controlled and an adequate airway maintained. Naloxone, an opioid antagonist, will reverse the effects of fentanyl. It should be remembered, however, that the duration of respiratory depression may be longer than the duration of action of the opioid antagonist and the patient should be closely monitored if there is a need to utilise the reversal agent. Bradycardia may be treated by administering atropine. Hypertension may be treated by administering the appropriate parental fluids and repositioning the patient may improve venous-return to the heart.

(iii) Propofol

(a) Composition: The active ingredient is propofol which is present in a solution of soy oil, glycerol, egg lecithin, sodium hydroxide and water for injection. The chemical name is 2, 6 – diisopropylphenol.
(b) Actions: Propofol is a short acting general anaesthetic agent with a rapid onset of action of approximately 30 seconds. Propofol also has a rapid rate of recovery.

(c) Pharmacodynamics: The mechanism of action of propofol is still under investigation, however Trapani, Altomore, Liso, Sanna & Biggio (2000) suggest that propofol may have several mechanisms of action, both through potentiation of GABA-A receptor activity, thereby slowing the channel-closing time, and also by acting as a sodium channel blocker. Recent research has also suggested that the endocannabinoid system may contribute significantly to propofol's anaesthetic action and to its unique properties (Fowler, 2004). The clinical effects are proportional to the dose or concentration in the blood. These doses are also rate dependent and therefore, low doses of propofol given slowly can cause conscious intravenous sedation rather than induction of anaesthesia. Low doses (10 - 15mg) of propofol, such as would be used during conscious intravenous sedation cause minimal reduction in blood pressure, however, the higher doses (120 - 200mg) used for general anaesthetic induction can cause arterial hypotension and decreased heart rate. Similarly, low doses of propofol cause little ventilatory depression, however, at higher doses profound respiratory depression can occur.
(d) Pharmacokinetics: The pharmacokinetics of propofol follows a three compartment open model (Cherruault & Sarin, 1986), with the compartments being the plasma; superficial, rapidly equilibrating tissues; and deeper, more slowly equilibrating tissues. Following an intravenous bolus dose, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, thus accounting for the rapid onset of anaesthesia. Plasma levels initially decline rapidly as a result of both distribution and metabolic clearance. The initial redistribution half-life is between two and four minutes, followed by a rapid elimination phase with a half-life of 30 to 60 minutes and followed by a slower final phase, representative of redistribution and metabolism of propofol from poorly perfused tissue. Accumulation may occur if higher than necessary infusion rates are used. Propofol is primarily metabolised by the liver and excreted via the urine.

(e) Indications: Propofol may be used as a general anaesthetic induction agent. It may also be used as a short acting intravenous anaesthetic agent in adults and children. Propofol may be used for monitored conscious sedation, as sole agent or in combination with a benzodiazepine and opioid.
(f) Contraindications: Known allergy to propofol or any of the other ingredients contained in the solution. In the dental setting, when propofol is used for ICS, the patient should be continuously monitored by a person not involved in the conduct of the surgical or diagnostic procedure. Facilities for maintenance of the patient’s airway should be readily available including oxygen and the ability to provide positive pressure ventilation. As is the case with midazolam, elderly patients may be more sensitive to propofol and monitoring during the procedure and during the recovery period should be in accordance with the needs of the patient.

(g) Dosage: Most patients will require 0.5 to 1 milligram per kilogram over one to five minutes for the onset of sedation. Maintenance of sedation may be accomplished by titrating the infusion to the desired level of sedation, Most patients will require 1.5 to 3 milligram per kilogram per hour. In the older patient, the dose requirement for induction of sedation is reduced.

(h) Overdosage: There is no reversal agent for propofol and overdose is likely to cause cardio-respiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require fluids, as well as repositioning of the patient (head down, legs raised).
INTRAVENOUS CONSCIOUS SEDATION: REGULATION, TRAINING AND TECHNIQUES USED IN AUSTRALIA

Dentists are required to be registered and approved by the Dental Board of Australia (DBA) to provide ICS. Registration as a dentist in itself is no longer a sufficient requirement to practise intravenous sedation and it is now an additional endorsement. The majority of dental practitioners carrying out ICS procedures are graduates of the post-graduate Diploma in Clinical Dentistry (Conscious Sedation and Pain Control), University of Sydney. Dentists who have not completed the Sydney Diploma require assessment by the DBA, and they may be endorsed, based on equivalent overseas training or their experience-base, or both. Continuation of registration also requires annual refresher training in Advanced Life Support and Emergency Management by a Board approved body (Appendix 5).

The graduate Diploma in Clinical Dentistry (Conscious Sedation and Pain Control) is a two year part time program that provides in-depth education and training in all facets of modern day ICS, including advanced CPR management, defibrillation and advanced airway management, such as intubation and the use of laryngeal masks (LMAs). Candidates are seconded to the Department of Anaesthesia, Westmead Hospital for anaesthetic and sedation training. The most common drugs used include midazolam, fentanyl and the use of sub-anaesthetic doses of propofol.
Depending on the type of procedure being carried out, the sedationist may choose to employ one of three drug techniques: single agent, double agent or multiple agent.

(i) Single agent:

(a) Midazolam sedation

Intravenous midazolam by itself provides sedation, anxiolysis and amnesia and when used in conjunction with profound local anaesthesia, may provide a safe and effective operating environment. Runes and Ström (1996) reported on 372 oral surgery cases that were not suitable for treatment under local anaesthetic. All cases were treated with midazolam and local anaesthetic only. Oxygen saturation levels were recorded and in only 10% of cases was there a transient fall below 95%. In all but three cases, conscious intravenous sedation allowed the procedures to be carried out without resorting to the general anaesthetic environment. ICS was found to be a valuable complement to established methods for managing anxious patients requiring oral surgery with a very low incidence of hypoxaemia.

(b) Propofol sedation

The benzodiazepine midazolam is the most commonly used intravenous sedative. Quine, Bell, McCloy, Charlton, Devlin and Hopkins (1995)
reported in the medical literature that up to 13% of patients undergoing endoscopy, desaturate to below 80% in the recovery room, following the procedure. Desaturation in the recovery room may be due to the longer clinical half-life of midazolam as compared to propofol. Medical mortality has been reported in 0.05% of patients with 60% due to hypoxaemia.

An alternative technique to using the longer acting midazolam, is to use propofol as the sole sedative agent. Leitch et al (2003) reported on dental patient maintained sedation (PMS) using propofol as the sole sedative agent. A cohort of 20 patients underwent oral surgical procedures (one apicectomy, the rest extractions). A safe and favourable outcome was reported for both the patient and the surgeon. Oxygen saturation levels were recorded and the mean lowest saturation was 94%. Interestingly, supplemental oxygen was not used and was required in only one case (ASA III) to correct a single desaturation to 87%. In-surgery sedation negates the need to expose the patient to a general anaesthetic, which requires a hospital environment that may be hard to access and expensive for the uninsured. Both patient and surgeon satisfaction was high and this has encouraged the authors to carry out a prospective, randomized controlled trial against the more established incremental midazolam technique.
(ii) Double agent:

(a) Benzodiazepine and narcotic sedation

The addition of a narcotic to the benzodiazepine is a well-recognized technique. However, it does carry with it the risk of increased apnoea, resulting in hypoxaemia. Walton et al (1991) examined whether there were any differences in oxygen saturations recorded in patients exposed to single drug midazolam sedation, as opposed to those who received a synthetic narcotic (nalbuphine), in addition to the benzodiazepine.

A cohort of 40 patients was divided into two groups – one group received midazolam only and the second received nalbuphine, in addition. All patients were ASA 1 and all required third molar removal. The study was of open design due to the potential dangers of administering the sedation agents in a blind fashion. The authors do not mention whether supplemental oxygen was used. The cohort that received the narcotic was given nalbuphine (0.2mg/kg) first and then two minutes later, the midazolam was titrated to the desired patient response. It was noted that less midazolam (a mean of 5.3 milligram as compared with a mean of 8.1 milligram) was required in the combination group.

Sixty percent (60%) of the narcotic and midazolam cohort experienced severe episodes of hypoxia (saturations of less than 84%). In addition, the combination cohort experienced more frequent and more severe
episodes of hypoxaemia.

Fifteen percent (15%) of the midazolam group also experienced moderate to severe desaturation and this important implication should not be overlooked, because it reinforces the fact that single drug techniques may also result in significant desaturations. Of importance too is the use of adequate electronic patient monitoring and the ready availability of adequate resuscitation equipment. The authors do not recommend the combination technique for the inexperienced clinician.

Milgrom et al (1993) reported on 207 intravenous sedations that tested the hypothesis that combined drug therapy results in significantly poorer safety (as determined by apnoeic events) but no difference in efficacy, compared to the single drug approach. All patients were ASA I or II and were to undergo wisdom tooth removal. Unlike the study of Walton et al (1991), the drugs were prepared by the research pharmacy and administered blindly by the anaesthetist. In this study, fentanyl (.0014mg/kg) was used rather than nalbuphine, along with midazolam (maximum 15 milligram, based on patient response). The authors found that the addition of the narcotic resulted in apnoea in 63% of cases, as compared to 3% in the midazolam-only group. Interestingly, the authors found no difference in patient recall of the oral surgery ninety minutes after the procedure, although patients in the combination drug group
were four times more likely to report an 'excellent sedation' as compared with 'good, fair or poor' in the single drug group. Also of note was the fact that the combination group was less restless during the surgical procedure.

(b) Propofol and a narcotic

Modern day programmable infusion pumps that can be individualised to the patient (age, gender, weight, length of procedure) allow the infusion of propofol together with, but via a separate infusion pump, of an ultra-short acting narcotic (remifentanyl) that establishes ICS. As the clinical effect of both drugs is ultra short, this technique allows very rapid post-operative recovery once the infusion is turned off. Recovery is significantly faster than from a midazolam-induced sedation. The future may see this technique gaining acceptance over the use of the longer acting benzodiazepines.

(iii) Multiple agents

Although effective sedation can mostly be established using either a single agent or double agent technique, there may be a need for brief deepening of the sedation to cover times of noxious stimulation (tooth elevation, for example). A very short acting agent like propofol can be useful to provide brief deepening of base-line sedation to cover these noxious periods.
RISK FACTORS AND SAFETY OF INTRAVENOUS SEDATION

Adverse outcomes (morbidity and mortality) under dental sedation is rare. There have been only two deaths related to dental sedation in Australia over the past 30 years. In America, with its large population, there have been a greater number of deaths and a review of published mortality under dental sedation provides information on potential high-risk situations that should be avoided in the private practice dental setting.

Jastak and Peskin (1991) reported on 13 deaths under dental sedation in the dental office between 1974 and 1989 in the United States. Whilst many of the drugs used today differ from those used on this cohort, the data are still relevant to adverse events today. The authors examined

(i) the age, sex and health of the patient
(ii) dental procedure initiated and reported duration
(iii) anaesthetic/sedative technique used
(iv) monitoring and personnel used
(v) drugs and doses administered
(vi) type of complication and time of occurrence
(vii) management and outcome

in an attempt to uncover risk factors. They found that most patients were classified as ASA II or III, with significant pre-existing conditions such as obesity, cardiac disease and heavy smoking. Only two patients were classified as ASA I.
They identified significant underlying medical conditions (risk factors), in order of frequency, as:

(i) obesity (3)
(ii) cardiac disorder (3)
(iii) heavy smoking (3)
(iv) hypertension (2)
(v) epilepsy (2)
(vi) barbiturate allergy (1)
(vii) local anesthetic allergy (1)
(viii) anaemia (1)
(ix) asthma (1)
(x) chronic obstructive pulmonary disease (1)
(xi) diabetes (1)
(xii) upper respiratory tract infection (1)
(xiii) hyperthyroidism (1)
(xiv) bull neck (1)

Several patients had multiple medical diagnoses. Polypharmacy (defined here as the use of three or more drugs causing CNS depression) was frequent, with eight patients receiving 4.4 drugs. Most cases were carried out using a team approach with multiple personnel, but in all cases the dentist was the operator/sedationist and in none of the cases was an anaesthetist present. All cases revealed a lack of intraoperative monitoring. Four patients had no monitoring at all and a further two had occasional palpation of pulse only. The
main cause of morbid events appeared to be hypoxaemia, secondary to airway obstruction. Hypoxaemia, and not the drug or combination of drugs used, was the principal cause of unanticipated adverse outcomes in the peri-operative period. The authors felt that since hypoxaemia may occur during ICS, monitoring for its incipient onset is of critical importance. Patient selection, based on pre-existing systemic medical conditions, is also very important. The authors felt that sedation risks increased significantly in patients with an ASA score of greater than one. Extremes of age (paediatric, and over the fifth decade) was also associated with higher risk. Ten out of 13 cases were considered avoidable by use of appropriate patient selection, monitoring and timely response to the adverse event.

Modern-day ICS uses different drugs to those used in the aforementioned study. In addition, non-invasive monitoring has become relatively inexpensive and readily available and is employed routinely. Perrott et al (2003) recently published a landmark report regarding the safety of office-based oral surgical sedation procedures. This prospective cohort study reported on 34,391 patients who underwent oral surgical procedures using various anaesthetic techniques, including local anaesthetic, intravenous conscious sedation and deep sedation/general anaesthesia (DS/GA) between January 2001 and December 2001. There were no exclusion criteria for patients. The study is the largest of its kind and drew data from the six defined American Association of Oral and Maxillofacial Surgeons (AAOMS) districts in the USA. Participant surgeons had to be an AAOMS member involved in sedation and general anaesthesia, have
internet access and treat patients in an office based setting. Of 34,391 patients, 5,321 were treated using intravenous conscious sedation. Twenty four thousand seven hundred and thirty seven (24,734) patients received deep sedation or general anaesthesia. Almost all patients fell into the ASA I or II classification. Most surgical procedures were third molar removal, dentoalveolar procedures or implant surgery. The most commonly used drugs were midazolam, fentanyl, methohexital and propofol. Most patients were monitored with pulse oximetry, blood pressure, ECG and about 17% used capnography in addition. In almost all of the ICS and DS/GA cohort, the surgeon was also the primary manager of the anaesthesia. Ninety eight point seven percent (98.7%) of patients reported no complications or problems. Complications that were reported were minor and self-limiting (1.3%) and no patients required hospitalization due to anaesthetic problems. The most common complication was vomiting, followed by prolonged recovery and syncope. These are the same common problems reported by Rogers (2005). Of note is the fact that although 96% of the time the surgeon also provided the sedation, at least two or three support personnel were utilised during ICS. The use of supplemental oxygen during ICS was recommended, as was measurement of at least three parameters (pulse oximetry, blood pressure and ECG). The authors concluded that intravenous conscious sedation was safe, and associated with a high level of patient satisfaction. This study is relevant to the Australian situation because most practising Australian dental sedationists have received formal post-graduate training in sedation, similar to that received by the American oral surgeons during their training. A similar safe outcome can
therefore be expected in Australia.

Rogers (2005) published a follow up paper to the Perrot et al (2003) study. Rogers looked at 2,889 in-surgery intravenous sedations performed for oral surgical procedures between 1994 and 2001. This study is also relevant to the Australian model because:

(i) the surgeon was the operator/sedationist
(ii) he had received formal post-graduate training in ICS
(iii) he and his staff completed annual CPR training
(iv) he undertook Advanced Cardiovascular Life Support training biennially
(v) the drugs used were midazolam, fentanyl and methohexital (propofol would be used in Australia).

This level of staff and operator education and operating environment closely reflects the Australian model. All patients were monitored by a dedicated monitoring nurse using non-invasive blood pressure, pulse oximetry and ECG. There were no known deaths the week following surgery. Of the 2,889 procedures, 77 adverse events were recorded. The most common adverse events were syncope (26), restlessness (20) and nausea and vomiting (10). Rogers concludes that there is a “growing volume of literature supporting the continued administration of intravenous sedation by the operating surgeon”.
SECTION 2: RESEARCH PROJECT

INTRODUCTION

Midazolam, fentanyl and propofol all depress respiratory drive and increase risk of apnoea and as a consequence, hypoxaemia. Since in-surgery dental sedations should only be carried out on healthy, ambulatory patients (ASA I and II), one measure of safety is to examine the oxygen saturation levels recorded during ICS to ensure that patients are consistently being kept at normoxaemic levels, because it is hypoxaemia that poses the greatest risk of morbidity or mortality to this otherwise healthy population (Jastak & Peskin 1991).

For the purposes of this audit, safe oxygen saturation levels were defined as 94% and above. There is no single safe saturation value that can be referenced to define normoxaemia. The safe value may vary from person to person, in accordance with the health status of that individual. For example, a person with chronic emphysema may have a saturation level of 87%, which is normal for them, but which would represent an acute hypoxaemic crisis in a healthy ASA I person. In the private practice dental setting, patients fall into the healthy, ambulatory ASA I or II category. Normal saturation levels in this group of patients are defined by Fearnley (1995) as:

- 95% and above is normoxaemic,
- 93 - 94% is mildly hypoxaemic,
90 - 92% is hypoxaemic and 
below 90% is seriously hypoxaemic.

The oxyhaemoglobin de-saturation curve is sigmoidal, not linear and therefore, de-saturation occurs very rapidly once levels of 92% and below are reached. Rapid de-saturation is an adverse event and in-surgery dental sedations should operate with a margin of safety. Modern-day pulse oximeters are accurate to within 2% (Nickerson, Sarkisian & Tremper 1998). A value of 94% was therefore chosen, as it provides a 2% safety factor to cover the possible margin of error and hysteresis (lag in the reading displayed on the monitor) associated with the pulse oximeter reading.

The University of Sydney, Faculty of Dentistry, Graduate Diploma in Clinical Dentistry (Sedation) teaches candidates to set their pulse oximeter alarms at 94%.

The pulse oximeter used in this study was calibrated annually by a certified bio-technician.
AIMS OF THE INVESTIGATION

The review of the literature established that hypoxaemia was the key risk factor during ICS. There is a paucity of published research on oxygen saturation levels maintained during ICS. The two most significant current studies on the outcome and safety of modern day ICS (Perrot et al 2003 & Rogers 2005) do not examine the safety of ICS based on oxygen saturation levels that were maintained. They summarise intra-operative and post-operative morbidity (nausea, syncope, delayed recovery, etc).

The aim of this retrospective quality assurance audit was to determine whether safe saturation levels were consistently maintained during a pre-determined number of dental sedation procedures. Should the data confirm that safe oxygen levels can be consistently maintained, this would provide evidence to support the safety of ICS, since safety and avoidance of hypoxaemia go hand-in-hand. Should the data show that hypoxaemic events occurred commonly, this would bring the safety of ICS into question.

Propofol can be a profound respiratory depressant, especially in doses used to induce general anaesthesia (120 - 200 milligram). The respiratory depressant effect is less in sub-anaesthetic doses (10 to 15 milligram). This audit examined a second patient cohort that received sub-anaesthetic doses of propofol, following the establishment of base-line sedation using midazolam and fentanyl.
Should the data confirm that the additional use of sub-anaesthetic doses of propofol was associated with an increase in exposure to hypoxaemic events, its use would have to be questioned because of its impact on safety. Should the use of propofol in sub-anaesthetic doses prove not to be associated with an increase in hypoxaemic events, this would add to our evidence base with regards to the safety and efficacy of this drug.

The null hypothesis can be a useful tool in testing the significance of differences between treatment and control cohorts, such as the two cohorts described above. Depending on the data, the null hypothesis either will, or will not, be rejected as a viable possibility. The null hypothesis \((H_0)\) is that \(\mu_1 - \mu_2 = 0\) where \(\mu_1\) is the population that gets the drug being tested and \(\mu_2\) is the control group.

In the case of this retrospective audit, the null hypothesis would be:

\(H_0\): there is no difference in oxygen saturation levels recorded between the midazolan/fentanyl cohort, and the midazolan/fentanyl/propofol cohort.

\(\mu_1\) is the cohort that received propofol in addition to midazolam and fentanyl.
\(\mu_2\) is the cohort that received midazolam and fentanyl only.

The alternate hypothesis would be:

\(H_1\): there is a difference in oxygen saturations recorded when propofol is used in addition to midazolam and fentanyl.
If \( \mu_1 - \mu_2 = 0 \), then we do not reject \( H_0 \), the null hypothesis. Importantly, this does not necessarily mean that the null hypothesis is true, it only suggests that there is not sufficient evidence against \( H_0 \) in favour of \( H_1 \).

As is evident in the RESULTS section of this thesis, the null hypothesis cannot be rejected because there was no significant difference between the saturation levels recorded for each sub-cohort (\( \mu_1 - \mu_2 = 0 \)). It should be noted however, that the two population groups are quite different in make-up because of selection bias on the part of the sedationist. Indeed, younger, thinner, female patients in ASA classification I, were more likely to receive propofol (see Table 3). Had the two population groups been similar in make-up, then \( \mu_1 - \mu_2 \) may not have equaled 0, and the outcome of the hypothesis test may have been to reject \( H_0 \) in favour of \( H_1 \).
METHODOLOGY

Approval to undertake the study:

This analysis of human data required Human Resources Ethics Committee (HREC) approval prior to accessing and analyzing the data. Approval requires justification that the study adds value to the evidence base. HREC approval was sought and received for the analysis of the de-identified patient data. All patients were 18 years and older.

Preliminary analysis:

A preliminary statistical analysis of the data collected from 100 sedations was carried out to determine the number of sedation cases required to give adequate power to the study. A cohort of 100 was divided up into 50 patients who received midazolam and fentanyl only, and 50 patients who received propofol in addition to the midazolam and fentanyl. The preliminary analysis determined that a total cohort of 3,500 sedation cases, divided into two sub-cohorts of 1,750 would provide the required power to the study.

Patient data base:

Archived dental sedation records, which were generated by a single dentist in private practice between 1996 and 2006, were accessed from secure storage. The data was retrieved and uploaded onto an Excel spreadsheet, and only after data analysis was completed, were the data de-identified. This allowed for review
of any patient record that required further scrutiny. For example, the few records that recorded oxygen saturation levels of below 90% were further assessed to see if any of these low readings were sequential.

**Recording the data:**

Although one dentist provided all sedations, several different nurses over the ten years of data collection recorded the data on a standardised personal and anaesthetic chart (Appendix 2). An initial, pre-sedation and pre-operative measurement of vital signs was recorded, and following the commencement of the ICS, additional recordings were made during the sedation procedure at five-minute intervals. Weight was assessed preoperatively by self-reporting or it was estimated to the nearest 5 kilograms.

Record was made of:

**Patient information:**

(i) Age

(ii) Gender

(iii) Weight

**Sedation data:**

(i) Dose midazolam

(ii) Dose fentanyl

(iii) Propofol (yes/no)

(iv) ASA Classification (I or II)

(v) Oxygen saturation levels
The required number of cases for each sub-cohort (1,750) was randomly selected from the data pool until the required number of cases was recorded. The recordings of oxygen saturations were divided into three categories:

(i) less than 90% (acute hypoxemic crisis)
(ii) between 90 and 93% (hypoxemic)
(iii) 94% and above (normoxemic)

Measuring equipment:
A CritiCare 8100\(^1\) monitor was attached to each patient to record oxygen saturation levels, capnography, blood pressure and ECG. The monitor was serviced and calibrated annually by a certified bio-technician.

Methods:
All sedations were used during oral surgical procedures. Patients were placed in a supine position and supplemental oxygen was provided via a nasal hood at a rate of 4 litres per minute (Hardeman, Sabol & Goldwasser 1990, Rozario et al 2008). Supplemental oxygen was provided throughout the sedation and for at least the first 45 minutes from commencement of the sedation. If difficulty was experienced in maintaining post-procedural normoxaemic readings, a Hudson mask was placed on the patient until recovered and stable. A non-invasive monitor was used to provide pulse-oximetry, capnography, ECG and blood pressure monitoring (Tinker, Dull, Caplan, Ward & Cheney 1989).

\(^1\) CritiCare Systems, Inc, 20925 Crossroads Circle, Suite 100 Waukesha, WI 53186, USA
Intravenous access was established via a 23G cannula and a continuous saline drip was administered via intravenous infusion. Both sub-cohorts received midazolam first, which was administered slowly over a period of a few minutes to a dose of 2 to 5 milligrams and titrated until conscious sedation was established. Fentanyl was then administered slowly to a dose of 50 to 100 micrograms, based on patient response (Weaver 2002). Local anaesthetic was then administered.

The first sub-cohort received additional titrated increments of midazolam during the procedure if required to deepen the sedation, but propofol was not used. The second sub-cohort received propofol in addition to midazolam and fentanyl. Propofol was never given simultaneously with either midazolam or fentanyl and was only given after base-line sedation had been established. Propofol was given to this sub-cohort because of an operator-perceived need to briefly deepen the sedation to cover short periods of intense noxious stimulation, e.g. elevation of a tooth (Hendrickx, Eger, Sonner & Shafer, 2008). This was used, rather than using the slower acting and longer lasting midazolam, to deepen the sedation. Propofol was given in 10 to 15 milligram sub-anaesthetic increments.

Nitrous oxide, in addition to oxygen, was provided to the patients via a Porter scavenging nasal hood during most sedations in the patient group 18 to 60 years of age. Maximum concentration of nitrous oxide was 33% (2/4 litres per minute). The significance of the additional use of nitrous oxide with regards to oxygen
saturation levels, lies in the fact that these patients were not receiving 100% supplemental oxygen, but rather 67% or greater. The lungs of older patients are not as efficient as the younger cohort, and for this reason, most patients over 60 years received 100% oxygen. If difficulty was experienced in maintaining oxygen saturation levels at or above 94% with any patient, the nitrous oxide was turned off and the patient received 100% oxygen.

The dental team comprised the dental sedationist, two nurses assisting with the surgical procedure and a dedicated monitoring nurse, experienced in sedation, outside the surgical circle. Vital signs and saturations were recorded at five-minute intervals for a minimum of 45 minutes, or for at least 30 minutes after cessation of the procedure. The pulse oximeter alarm was set at 94%.

Capnography was used during all sedations (Koniaris, Wilson, Drugas & Simmons 2003; Nager & Krauss 2008). The capnograph probe was inserted into the nasal mask. Used in this manner the sensor is in an open circuit (as opposed to a closed circuit with an intubated patient) and therefore the carbon dioxide concentrations that were recorded were inaccurate. Nonetheless, a waveform is generated on the monitor with each exhalation, which provides a visual reference of effective ventilation (Srinivasa & Kodall 2004). Because the circuit is open, a flat line on the capnograph trace is not necessarily an indication of apnoea (it could be an indication of mouth breathing) but it was used as a prompt for the monitoring nurse to ask the patient to take a breath, even if saturation levels were
94% or greater. The use of a capnograph during intravenous sedation gave the sedation team warning that effective ventilation may not be occurring well before the pulse oximeter began to show signs of desaturation (Sandlin 2002). Readings of less than 94% required the team to cease operations until effective ventilation and safe oxygen saturation levels were re-established.

Gender-specific tertiles were used as categories that made it possible to create low, medium and high weight groups, where the categories are determined separately by gender. The analysis of the effect of low, medium and high weight on outcome permits all the subjects to be used, giving greater power to the statistical results. The gender-specific weight tertiles in kilograms are defined in Table 1 below.

Table 1: Gender-specific weight tertiles

<table>
<thead>
<tr>
<th>Gender</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>less than or equal 60kg</td>
<td>less than or equal 74kg</td>
</tr>
<tr>
<td>Medium</td>
<td>61 to 68kg</td>
<td>75 to 85kg</td>
</tr>
<tr>
<td>High</td>
<td>greater than 69kg</td>
<td>greater than 86kg</td>
</tr>
</tbody>
</table>
RESULTS

The total cohort of 3,500 cases generated 35,035 individual oxygen saturation readings. These readings are presented in the three defined categories of oxygen saturation levels and are also expressed as a percentage for each category in Table 2.

Table 2: Summary of the number and percentage of oxygen saturation readings recorded in each of the three defined saturation categories.

<table>
<thead>
<tr>
<th></th>
<th>No propofol</th>
<th>Propofol</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of $\text{SaO}_2 \geq 94%$</td>
<td>17,288 97.3%</td>
<td>16,892 97.9%</td>
<td>34,180 97.6%</td>
</tr>
<tr>
<td>Number of $\text{SaO}_2 90-93%$</td>
<td>480 2.7%</td>
<td>350 2.03%</td>
<td>830 2.37%</td>
</tr>
<tr>
<td>Number of $\text{SaO}_2 &lt;90%$</td>
<td>17 0.095%</td>
<td>8 0.046%</td>
<td>25 0.07%</td>
</tr>
<tr>
<td>Total for each category</td>
<td>17,785 100%</td>
<td>17,250 100%</td>
<td>35,035 100%</td>
</tr>
</tbody>
</table>

An adverse outcome (low saturations) was defined as two or more recordings of saturation levels less than 94% during the same ICS procedure. The records in the less than 90% category were examined to see if any patients had two or more sequential readings of less than 90% and none were sequential. Of the 25 desaturation levels recorded at less than 90%, four cases occurred at the start of the procedure, eight during the intra-operative phase and thirteen at the end of
the procedure, when the patient was not receiving supplemental oxygen and was conscious and communicative. Statistical analysis for each variable of interest was undertaken using:

(i) Cross-tabulation of the variable by outcome - two or more saturation readings of less than 94% (low saturations)

(ii) Associated chi-squared test

(iii) Corresponding logistic regression analysis together with odds ratio (OR), and 95% confidence interval (95%CI).

A difference in patient profile was noted between the two sub-cohorts (propofol = no; propofol = yes).

Table 3: Summary of the difference between the propofol and non-propofol sub-cohorts

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CATEGORY</th>
<th>Propofol Absent (n=1750)</th>
<th>Propofol Present (n=1750)</th>
<th>P VALUE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
<td>60.1</td>
<td>59.5</td>
<td>0.705</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>39.9</td>
<td>40.5</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>&lt;=25</td>
<td>21.1</td>
<td>38.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>26-35</td>
<td>15.8</td>
<td>25.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>36-45</td>
<td>26.9</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 45</td>
<td>36.1</td>
<td>16.7</td>
<td></td>
</tr>
<tr>
<td>Weight tertiles *</td>
<td>(gender specific)</td>
<td></td>
<td></td>
<td>0.325</td>
</tr>
<tr>
<td>Low (&lt;= 60 female, &lt;=74 male)</td>
<td></td>
<td>38.2</td>
<td>39.5</td>
<td></td>
</tr>
<tr>
<td>Medium (61 - 68 female, 75-85 male)</td>
<td></td>
<td>32.2</td>
<td>33.2</td>
<td></td>
</tr>
<tr>
<td>High (&gt;=69 female, &gt;=86 male)</td>
<td></td>
<td>29.6</td>
<td>27.3</td>
<td></td>
</tr>
<tr>
<td>Midazolam Dose</td>
<td>&lt;=5</td>
<td>56.2</td>
<td>47.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 and &lt;=6</td>
<td>19.3</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 6</td>
<td>24.5</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>ASA class</td>
<td>I</td>
<td>92.1</td>
<td>96.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>7.9</td>
<td>4.0</td>
<td></td>
</tr>
</tbody>
</table>

* p-value for chi-squared test of association
Table 3 shows that younger, thinner, female patients in ASA class I were more likely to receive propofol. ASA II patients rarely received propofol. The exodontia patients predominantly underwent wisdom tooth removal and were mostly younger and propofol was used to mask the noxious stimulation experienced during tooth elevation. The second group underwent implant placement and propofol was rarely required. Implants were required mostly in the older patient group, who were heavier.
A summary of the analysis using cross-tabulation of the variable by outcome (two or more saturation readings <94%) is seen in Table 4 below.

Table 4: Table of the crude associations between the variables and the outcome.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>CATEGORY</th>
<th>n</th>
<th>% WITH LOW SATS</th>
<th>OR(95%CI)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female*</td>
<td>2,093</td>
<td>3.5</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>1,407</td>
<td>9.0</td>
<td>2.71 (2.02 to 3.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;=25*</td>
<td>1,051</td>
<td>1.7</td>
<td>Referent</td>
<td>&lt;0.001#</td>
</tr>
<tr>
<td></td>
<td>26-35</td>
<td>715</td>
<td>3.6</td>
<td>2.17 (1.18 to 3.98)</td>
<td>0.013</td>
</tr>
<tr>
<td></td>
<td>36-45</td>
<td>809</td>
<td>5.6</td>
<td>3.38 (1.94 to 5.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt; 45</td>
<td>925</td>
<td>12.1</td>
<td>7.91 (4.77 to 13.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight tertiles**</td>
<td>Low*</td>
<td>1,360</td>
<td>4.3</td>
<td>Referent</td>
<td>&lt;0.001#</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>1,144</td>
<td>5.1</td>
<td>1.20 (0.83 to 1.74)</td>
<td>0.340</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>996</td>
<td>8.5</td>
<td>2.10 (1.48 to 2.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midazolam dose (mg)</td>
<td>&lt;=5*</td>
<td>1,814</td>
<td>6.7</td>
<td>Referent</td>
<td>0.031#</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 and &lt;=6</td>
<td>798</td>
<td>4.1</td>
<td>0.60 (0.41 to 0.90)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>&gt; 6</td>
<td>888</td>
<td>5.3</td>
<td>0.78 (0.55 to 1.11)</td>
<td>0.165</td>
</tr>
<tr>
<td>ASA class</td>
<td>I*</td>
<td>3,292</td>
<td>5.6</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>208</td>
<td>8.7</td>
<td>1.61 (0.97 to 2.67)</td>
<td>0.065</td>
</tr>
<tr>
<td>Propofol</td>
<td>No*</td>
<td>1,750</td>
<td>6.9</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1,750</td>
<td>4.6</td>
<td>0.66 (0.49 to 0.88)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

* reference category
** the unequal numbers in the weight tertiles is due to the ‘lumpy’ nature of the self-reported or estimated weights.
# p-values for test of overall homogeneity of risk if more than two levels for a factor

The association of the variables gender, age, gender-specific weight, dose of midazolam, ASA class, and use of propofol, to the exposure of two or more low saturation events, is as follows:

(i) Gender: Males were almost three times more likely to experience low saturations than females.

(ii) Age: The chance of experiencing low saturation levels increased with
age. Using 25 years of age or less as the reference category, the 26 to 35 year-olds were twice as likely to experience low saturations, the 36 to 45-year-olds more than three times as likely, and the over 45 year-olds nearly eight times more likely to experience low saturation levels.

(iii) Weight: There was no significant difference in the risk of low saturation levels between the low and medium gender-specific weight groups. The high weight group was nearly twice as likely as the low weight group to experience low saturation levels.

(iv) Midazolam dose: An increase in the dose of midazolam was not associated with an increase in the chance of experiencing two or more low saturation events. Fifty percent (50%) of patients required 5 milligrams or less for their sedation procedure.

(v) ASA class: There was little difference in the risk of an ASA I or an ASA II patient experiencing low saturation levels.

(vi) Propofol: The use of propofol in addition to midazolam and fentanyl was not a factor in the chance of a patient experiencing low saturation levels. The propofol group had 2% less exposure to low saturation levels. Based on this data, there is no evidence to suggest that the additional use of sub-anaesthetic doses of propofol increases the risk of exposing a patient to multiple low saturation events.
Multiple logistic regression analysis of the data was also carried out. Table 5 shows a multiple logistic regression model, adjusting for all variables. This did not show any indication of a significant propofol effect (OR=0.921, 95%CI 0.678 to 1.253, p=0.601).

Table 5: Multiple logistic regression analysis of low saturations and putative variables.

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>OR</th>
<th>95.0% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Gender (* female)</td>
<td>&lt;0.001</td>
<td>2.777</td>
<td>2.048</td>
</tr>
<tr>
<td>Age groups</td>
<td>&lt;0.001#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 and less (*)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-35yrs</td>
<td>0.035</td>
<td>1.937</td>
<td>1.048</td>
</tr>
<tr>
<td>36-50yrs</td>
<td>&lt;0.001</td>
<td>2.938</td>
<td>1.662</td>
</tr>
<tr>
<td>&gt; 50yrs</td>
<td>&lt;0.001</td>
<td>6.613</td>
<td>3.875</td>
</tr>
<tr>
<td>Weight tertiles</td>
<td>&lt;0.001#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=60 female, &lt;=74 male (*)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61 – 68 female, 75 – 85 male</td>
<td>0.796</td>
<td>0.950</td>
<td>0.646</td>
</tr>
<tr>
<td>&gt; 68 female, &gt; 85 male</td>
<td>0.004</td>
<td>1.711</td>
<td>1.190</td>
</tr>
<tr>
<td>Midazolam group</td>
<td>0.338#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=5mg (*)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5, &lt;=6mg</td>
<td>0.178</td>
<td>0.752</td>
<td>0.497</td>
</tr>
<tr>
<td>&gt; 6mg</td>
<td>0.333</td>
<td>0.833</td>
<td>0.575</td>
</tr>
<tr>
<td>ASA class (* 1)</td>
<td>0.424</td>
<td>0.805</td>
<td>0.474</td>
</tr>
<tr>
<td>Propofol (* no)</td>
<td>0.601</td>
<td>0.921</td>
<td>0.678</td>
</tr>
</tbody>
</table>

* reference category
# p value for test of overall homogeneity of risk if more than two levels for a factor
Backward stepwise variable selection using likelihood ratio testing was used to identify the independent predictors of low saturation levels. The independent predictors were gender, age group and gender-specific weight tertile. The model including propofol and these independent predictors is shown in Table 6.

Table 6: Multiple logistic regression model of low saturation levels including the independent predictors identified by backward stepwise elimination together with propofol.

<table>
<thead>
<tr>
<th>Variables</th>
<th>p-value</th>
<th>OR</th>
<th>95.0% CI for OR Lower</th>
<th>95.0% CI for OR Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (* female)</td>
<td>&lt;0.001</td>
<td>2.705</td>
<td>2.000</td>
<td>3.658</td>
</tr>
<tr>
<td>Age groups</td>
<td>&lt;0.001#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25yrs and less (*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26-35yrs</td>
<td>0.031</td>
<td>1.967</td>
<td>1.065</td>
<td>3.633</td>
</tr>
<tr>
<td>36-50yrs</td>
<td>&lt;0.001</td>
<td>3.080</td>
<td>1.748</td>
<td>5.426</td>
</tr>
<tr>
<td>&gt; 50yrs</td>
<td>&lt;0.001</td>
<td>6.977</td>
<td>4.143</td>
<td>11.750</td>
</tr>
<tr>
<td>Weight tertiles</td>
<td>0.002#</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=60 female, &lt;=74 male (*)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61 – 68 female, 75 – 85 male</td>
<td>0.675</td>
<td>0.921</td>
<td>0.628</td>
<td>1.352</td>
</tr>
<tr>
<td>&gt; 68 female, &gt; 85 male</td>
<td>0.007</td>
<td>1.633</td>
<td>1.144</td>
<td>2.333</td>
</tr>
<tr>
<td>Propofol (* no)</td>
<td>0.671</td>
<td>0.936</td>
<td>0.688</td>
<td>1.272</td>
</tr>
</tbody>
</table>

* reference category
# p value for test of overall homogeneity of risk if more than two levels for a factor

Gender, age and weight are potential confounding variables but the OR associated with propofol use, after adjusting for the effects of these variables, remained not statistically significant and less than 1 (adjusted OR=0.936, 95%CI 0.688 to 1.272, p=0.671).
DISCUSSION

There are two fundamental requirements that must be fulfilled in order to avoid an adverse outcome during conscious intravenous sedation. Firstly, the haemodynamics must be stable, and secondly, there must be continuous, effective ventilation.

Neither midazolam, fentanyl nor propofol cause significant change in patient haemodynamics at the low doses that are used for ICS. Dental surgery results in only relatively minor blood loss and little change in haemodynamics.

The key to avoidance of adverse outcomes during conscious intravenous sedation lies in continuous, effective ventilation that avoids exposure of the patient to periods of hypoxaemia.

Therefore, a retrospective analysis of oxygen saturation readings recorded during dental sedations is a valid measure of the safety of dental sedation. The properly monitored patient cohort ASA I and II should not experience an adverse hypoxaemic event, when sedated within RACDS/ANZCA PS21 guidelines. This is especially true when capnography is employed because it gives a visual trace on the monitor that effective ventilation is taking place.

The sedation technique used in this study provided spontaneous, effective
ventilation, with communication possible throughout the procedures. Should the results of such a review reveal that hypoxaemic events were common-place, then a reappraisal of current techniques and drug regimes would be required.

All sedative and anaesthetic agents suppress respiratory drive. Therefore, if not carefully monitored and controlled, hypoxaemia remains the one factor that has the potential to cause serious complications or even mortality. Midazolam by itself has the least depressive effect on respiratory drive. However, the addition of a narcotic (such as fentanyl) significantly suppresses respiratory drive (Milgrom et al 1993). Propofol was developed as a general anaesthetic induction agent and is a powerful respiratory depressant when used in the doses to induce general anaesthesia. In low dose, propofol may be used safely, however some still regard it as a drug suitable for use only by anaesthetists (Appendix 3, PS9).

The literature supports the fact that propofol can be used to provide conscious intravenous sedation (Horiuchi, Nakayama, Hidaka, Ichise, Kajiyama & Tanaka 2009). Propofol has other useful and beneficial effects when used in sub-anaesthetic doses of 10 to 15 milligrams. Borgeat, Oliver, Wilder-Smith and Suter (1994) examined the non-hypnotic applications of propofol. Several useful effects were reported on and these include:

(i) ten to fifteen milligrams (10 - 15mg) of intravenous propofol was effective in preventing and treating postoperative nausea. Onset of effect was rapid and there were no serious side effects. Duration of
effect was over 30 minutes in 70% of patients.

(ii) narcotic induced pruritus may cause the patient to scratch their nose, interfering with an optimal working environment. Eighty four percent (84%) of patients who received 10 milligrams of propofol, as compared to the placebo group (16%), reported reduction in itch and the clinical effect was for 40 minutes to an hour. Ninety percent (90%) of the placebo group who did not respond to the placebo had a positive response to a dose of propofol.

(iii) propofol possesses anticonvulsant properties, although the dosage needed remains unclear.

(iv) propofol is an anxiolytic. A 10 milligram, sub-hypnotic dose of propofol provided effective anxiolysis as compared to placebo.

(v) propofol is euphoric in sub-anaesthetic doses and may cause amorous behaviour or intense dreaming. It therefore has abuse potential.

(vi) propofol may have analgesic properties, with some authors reporting a reduction in need for post-operative analgesia.

The authors conclude that because of the favourable pharmacokinetic properties of propofol, use of low doses for its antiemetic, antipruritic and anxiolytic is safe in clinical practice and devoid of serious side effects.

A more recent paper by Vasileiou, Xanthos, Koudouna, Perrea, Klonaris, Katsargyris and Papadimitriou (2009) also examined the non-anaesthetic effects of propofol. Propofol’s quick onset and rapid emergence is acknowledged. Some
of the secondary effects discussed in this paper are not relevant to the dental sedation setting. The authors did note propofol’s direct antiemetic effect. Propofol was also shown to produce a significant reduction in pain in sub-anaesthetic doses. The anxiolysis-like profile was noted, as was its amnesic properties. The non-anaesthetic properties require further investigation that may expand its pharmacological and clinical use.

Analysis of the data presented in this thesis demonstrated that the addition of propofol did not result in an increased risk of recording two or more saturation levels of less than 94% (low saturations) during the sedation procedure. Of the 35,035 oxygen saturation readings recorded, only 25 were below 90%. Specific examination of these 25 case records showed that no desaturations were sequential (there were normal readings on either side of the single low reading) and none were associated with an adverse outcome.

It is the author’s opinion that strict adherence to the guidelines of PS21 for conscious sedation as well as the use of a capnographic trace to detect apnoea, is the reason for the very low number of saturation readings recorded below 90%.

Risk factors associated with low saturations were examined. These included: gender, age and weight.

(i) Gender: Males were almost three times more likely than females to
experience low saturations at any given dose of midazolam, with or without propofol. This is possibly due to the fact that males smoke more than females (Australian Institute of Health and Welfare 2005). Unfortunately, no record was made of this variable when the data was recorded and this is unfortunate, as the information was noted on the patient medical history. Any future studies should record this information for analysis.

(ii) Age: The younger patient cohort has a very low risk (1.7%) of experiencing two or more desaturation events. This finding is in keeping with the cardiopulmonary health of this cohort. Risk increased with increasing age. By 45 years of age, the odds ratio of experiencing two or more desaturation events increased to nearly 8.00 (95% CI). This means that the older group of patients should routinely receive 100% oxygen to reduce risk, preferably without the additional use of nitrous oxide, which reduces the concentration of oxygen in the inhalation mix (Yano, Lishi, Tatsuta, Sakai, Narahara & Omori 1998; Yilmaz, Aydin, Karasu, Gunsar & Ozutemiz 2003; Muller, Prolla, Maguilnik & Breyer 2004).

(iii) Weight: The author did not record patient height, therefore body mass index (BMI) could not be calculated and examined as a variable. Gender specific weight posed a risk factor for the high weight groups only, which doubled the risk. Hovagim et al (1989) found that a BMI greater than 30 posed a similar risk factor. Patient record (Appendix 2)
should include height so that the BMI can be calculated for future studies.

Non-risk factors were found to be: the dose of midazolam, ASA classification (I or II) and use of propofol.

(i) Dose of midazolam: Approximately half the total cohort received 5 milligrams of midazolam or less, whilst 23% received 6 milligrams and 26% received greater than 6 milligrams. The highest dose used on any patient was 15 milligrams. No correlation was found between the dose of midazolam that the patients received and the risk of experiencing two or more low saturation readings. The author believes that this is because all sedations were conscious and the drug(s) were carefully titrated. Bolus doses of any drug were never given; rather the drug was titrated slowly to the desired endpoint. Midazolam was also the drug that was given first, and if initially there were signs of over-sedation or respiratory depression, the administration of the narcotic was delayed or reduced (167 patients received 50 milligrams of fentanyl or less).

(ii) ASA Classification: The ASA classification was developed as a means of determining the risk that a general anaesthetic posed to a patient. The classification was not developed to determine the risk of experiencing low oxygen saturations during conscious sedation. The
results of this study show that the use of the ASA classification to determine the risk of experiencing low saturations during ICS was not predictive. Rather, age, weight and gender are factors that should be used to determine the risk of developing hypoxaemia. Accepting that in Australia dentists should only be sedating ASA I and II patients, the author suggests that the most meaningful determination of patient risk should include the use of the acronym ‘WAG’ (weight, age and gender) as a guide to determining risk during ICS (chance of exposure to hypoxaemia).

(iii) Propofol: This drug can have a profound short-term depressive effect on respiratory drive. It is therefore interesting to note that the propofol sub-cohort did not have a higher incidence of experiencing low saturations. The use of propofol allows a lower initial dose of midazolam to be given – in other words, the ‘base-line sedation depth’ can be kept quite light, and brief periods of noxious stimulation can be covered by small, sub-anaesthetic doses of propofol. This is especially effective as painful stimuli are covered by the use of local anaesthesia. In these small doses, the deepening of the sedation that propofol provides is of short duration only (not more than one or two minutes) and a fully saturated patient will not de-saturate within this short period, even if the propofol causes brief respiratory depression or apnoea. All patients were monitored using capnography, and the use of capnography has been
shown to improve our ability to monitor apnoea and reduce patient exposure to hypoxaemia (Heuss, Schnieper, Drewe, Pfimlin & Beglinger 2003).

The primary limitation of this study lies in the fact that one operator/sedationist generated all the data. It would be useful for other dental sedationists to undertake similar audits of oxygen saturation levels recorded, which would add to the evidence base. In addition, retrospective and case-control studies are also relatively low in the hierarchy of evidence.

Accepting these limitations, the data support that a single operator/sedationist, working within the RACDS/ANZCA document PS21 guidelines, and supported by a team of experienced dental nurses, can consistently maintain safe oxygen saturation levels regardless of age, gender, gender-specific weight, dose of midazolam, ASA class (I or II) or the additional use of propofol.
CONCLUSION

The following conclusions may be made from the literature review and from analysis of the data collected for this study:

(i) Intravenous sedation can provide efficient and effective pain and anxiety management for procedures that would otherwise require a general anaesthetic environment.

(ii) A review of the current literature shows that intravenous conscious sedation is safe with a high-level of patient and operator satisfaction.

(iii) Exposure to hypoxaemia remains the single most potentially life-threatening risk-factor.

(iv) This study found that:

- Males were almost three times more likely to experience low saturations than females.
- The chance of experiencing low saturations increased with age.
- High weight groups are nearly twice as likely as low weight groups to experience low saturations.
- An increase in the dose of midazolam was not associated with an increase in the chance of experiencing two or more low saturation
events.

• There is little difference within the ASA I and II classes, in the risk of a patient experiencing low saturations.

• The use of propofol in addition to midazolam and fentanyl did not increase the risk of experiencing two or more events of low saturations.

This retrospective audit of oxygen saturation levels recorded during dental intravenous sedations adds to our evidence base with regards to the safety of ICS when performed by an appropriately trained operator/sedationist. The risk of experiencing two or more hypoxaemic events that the additional use of propofol may or may not pose, and the possible effect of age, gender, weight, ASA classification and midazolam dose were analysed. These results should assist both dentists and anaesthetists to form an evidence-based opinion.