THE EFFICACY AND SAFETY OF INTRAVENOUS SEDATION IN CHILDREN UNDER THE AGE OF 10 YEARS

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Thesis/dissertation in fulfillment of the requirements for the research Masters degree (MSc) in Sedation and Pain Control at the Faculty of Dentistry, University of the Western Cape.

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6. Ketamine
7. Propofol
8. Sufentanil
9. Intravenous sedation in children
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11. Safety
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ABSTRACT:

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This study was done to show that sedation is a safe and a viable option in young children. Dental procedures were done on children aged two to ten years. Two hundred children were included in the study. In all of these children the procedures were completed. Only two children were excluded, because an intravenous line could not be placed on the one child, and the other child was unmanageable under sedation.
The safety of sedation was evaluated looking at the incidence of adverse events and complications.
No serious adverse effects or complications occurred.
The complications that occurred were all corrected with minimal or non-invasive interventions. Only six of the two hundred children required oxygen to correct a drop in oxygen saturation.

DECLARATION:

I declare that this research MSc (Anaesthesiology and Sedation) in sedation and pain control is my own work, that it has not been submitted for any other degree or examination in any other University, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

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CHAPTER ONE

INTRODUCTION

In the British Dental Journal of the 10th of May 2003 an article was published with the topic: "Intravenous conscious sedation in patients under 16 years of age. Fact or fiction?" (Robb, Hosey & Leitch 2003). They found in the study of 18 patients between 11 and 15 years of age, that the patients could be managed successfully with conscious sedation. They suggested that further studies in this population group be carried out. This was indeed a very encouraging statement coming from clinicians who were sceptical that conscious sedation is not possible in children.

The aim of this research study was to prove that intravenous sedation in children, with different drugs, done by an experienced and trained sedation practitioner, can be done safely and effectively in children outside the operating room.

From 1985 – 1992, before The American Academy of Paediatrics (AAP) revised the guidelines for paediatric sedation, the guidelines only referred to sedation as being light, conscious sedation, or deep sedation (Cravero & Blike 2004). In recent years new definitions and guidelines have been developed. Revised guidelines from both the AAP and the American Society of Anesthesiologists (ASA) have eliminated and largely replaced the term conscious sedation with the term moderate sedation and analgesia (Cravero & Blike 2004:1355-1356). This is probably a more descriptive term of what sedation really is.

The term procedural sedation is also used today. This term describes a depressed level of consciousness and is used by some as a substitute for the term conscious sedation. This creates a wrong impression as conscious sedation is only one level of the different levels of procedural sedation and analgesia. Kraus and Green (2000:938) stated that procedural sedation should be viewed as a continuum of sedation levels ranging from light or minimal sedation to deep sedation. The depth of sedation can easily be titrated by selective administration of sedatives and analgesics. The term procedural sedation is used by some physicians to practice deeper levels of sedation – sedation is titrated according to the type of procedure. Supporters of procedural sedation however claim, and rightly so, that nobody should be allowed to practice sedation without adequate training and experience.

In children, especially, it is widely believed that conscious sedation is not always possible – in fact it is called by some physicians a myth. Children can also easily slip unintentionally into a deeper level of sedation. Therefore we have to be very diligent and watchful when we sedate children. The use of monitoring equipment is essential according to sedation guidelines when we sedate children.

It is therefore of critical importance that research studies be done to evaluate sedation techniques, as paediatric sedation is becoming a very important part of patient care. In fact, paediatric sedation is one of the fastest growing areas in anaesthesia care.

CHAPTER TWO

SEDATION IN A NUTSHELL

2.1 THE HISTORY OF SEDATION

Craig and Skelly (2004:1) stated that dentists played a huge role in the development of general anaesthesia and later also in the introduction of local anaesthesia and conscious sedation. As early as 1844 Horace Wells used nitrous oxide for the first time, and in 1846 William Morton used ether for dental extractions (Craig & Skelly 2004:2). Reports that dentists used nitrous oxide for conscious sedation appeared in the early 1900s (Craig & Skelly 2004:2). In 1904 procaine was available for use in dental patients. Lignocaine followed in the late 1940's.

Through the years with the development of various different drugs the techniques used for conscious sedation developed. Today, paediatric sedation is one of the components of anaesthesia that is developing the fastest. The barbiturates were developed as follows: 1912 phenobarbitone, the 1930s hexobarbitone and thiopentone, the 1960s intravenous methohexitone (Craig & Skelly 2004:3). The next very important drug that became available was propofol in 1977 (Craig & Skelly 2004:6). One of the most important benzodiazepines that we use today is midazolam that became available in 1983 (Craig & Skelly 2004:6).

With the development of pulse oximetry and portable monitoring equipment, the practice of sedation outside of the operating room became a safer option to many patients.

2.2 DEFINITIONS OF SEDATION

There are different levels of sedation. It is important for every sedation practitioner to understand this, as levels of sedation in actual fact means the level of consciousness. These levels of sedation are on a continuum which begins with anxiolysis (minimal sedation) and end with general anaesthesia. Patients can easily unintentionally slip from one level of sedation into another, and this is especially true in children. This means that medical personnel performing sedation on children should be trained to evaluate and recognize the different levels of sedation, and also be vigilant in monitoring while doing sedation.

A paediatric sedation programme at the University of Wisconsin Children's Hospital (2008) and lecture notes of Dr. M. Jansen van Rensburg (2007), and Prof. J. Roelofse, explains the following terms:

Mild sedation/anxiolysis: This is a drug induced state where the patient can respond normally to verbal commands. Respiratory and cardiovascular functions remain

unimpaired. There may be mild alteration to gross motor function. Clinical monitoring of the patient is all that is necessary.

Moderate sedation and analgesia: In the past this level was referred to as conscious sedation. This is a drug induced depression of consciousness. The patients can still maintain their airway adequately, and respond to verbal commands or light tactile stimulation. Cardiovascular function is maintained.

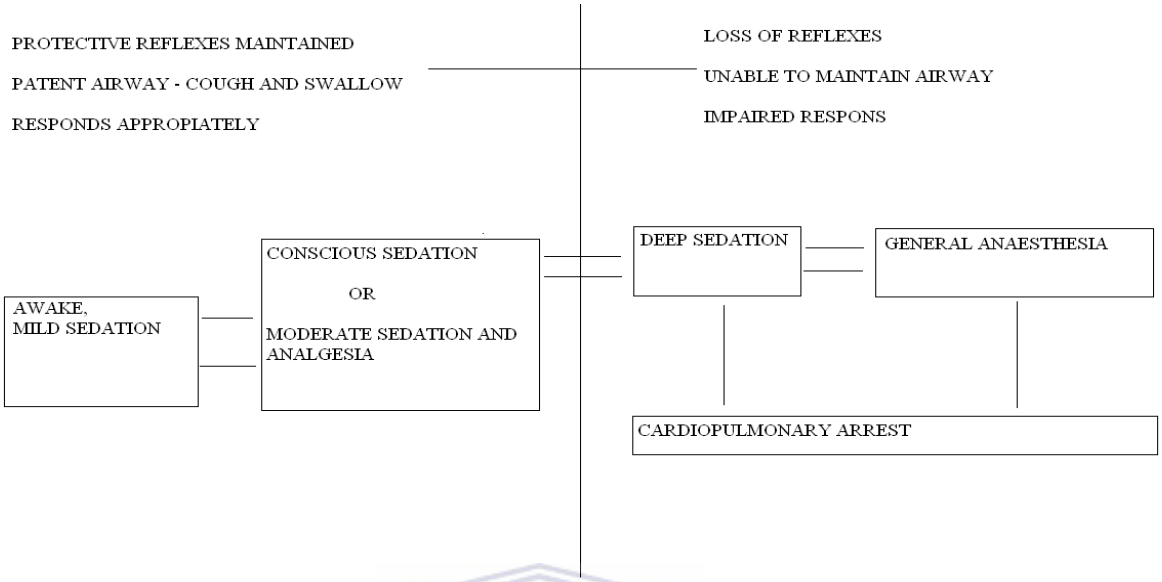
Dissociative sedation: This is another term in sedation which is used specifically when ketamine is used to perform the sedation. The patients are in a trans-like cataleptic state. Protective airway reflexes and breathing are intact. Patients have analgesia, sedation, amnesia, without loss of consciousness. It is believed that this level of sedation is different to any level that we define on the sedation continuum.

Procedural sedation and analgesia: Procedural sedation should be viewed as a continuum of sedation levels ranging from light to deep sedation. Sedative, hypnotic, analgesic and dissociative drugs are used to provide anxiolysis, analgesia, sedation and motor control. The depth of sedation can easily be titrated by selective administration of sedatives and analgesics. The term procedural sedation is used by some physicians to practice deeper levels of sedation – sedation is titrated according to the type of procedure.

Deep sedation and analgesia: This is also a drug induced depression of consciousness, where the patient responds purposefully to repeated or painful stimulation. Spontaneous ventilation may be inadequate and patients may require assistance in maintaining their airway. Cardiovascular function is usually maintained. There is diminished muscle tone.

2.3 THE CONTINUUM OF SEDATION

Graphic explanation of the sedation continuum (in conversation with Prof. J. Roelofse).



It is important to realise that sedation is a continuum that starts with anxiolysis (minimal sedation and analgesia) and ends with general anaesthesia. There are different levels of sedation and children can very easily slip from one level to a deeper level. To ensure the level of the patient, stimulation/verbal commands may be necessary. Unfortunately we do not want to disturb a child in the middle of a procedure because this will influence the surgeon in performing the procedure. For this reason a sedation practitioner needs to be trained to be able to recognize the depth of sedation without disturbing the child. The level of sedation, whether it be moderate sedation or any other level of procedural sedation, must be evaluated by the sedation practitioner according to the procedure done and the co-operation of the child.

Deep sedation might not always be a safe option outside of the operating room, but the sedation practitioner must be able to rescue a child who slips into deep sedation unintentionally.

In an article by Cotè, Notterman, Karl, Weinberg and McCloskey (2000), the authors found that the biggest contributing factor to morbidity and mortality when sedating children is a failure to rescue.

2.4 LITERATURE REVIEW

Over the years the sedation practice outside of the operating theatre has become a very contentious subject. From all over the world articles on this topic have begun to appear in medical and dental journals, and on the internet. The researcher will discuss a few of these articles to emphasize important factors concerning sedation.

Cotè (1994) mentions different organizations in the United States that each have protocols for sedation. He states that some of the protocols have been written for the convenience of the practitioners practising sedation, and not for the safety of the patients. The Committee on Drugs (COD) of the American Academy of Paediatrics (AAP) has spent considerable time addressing the difficult issue of appropriate care for sedated paediatric patients. They emphasized the importance of monitoring, medical evaluation of the patient's condition, clinical skills, pre- and post-sedation evaluation, and the nil per os status of the patient. Cotè (1994) stated that the most important goal of the guidelines by the AAP has been accomplished by stirring the debate of discussion concerning the topic of the safety of paediatric sedation.

The purpose of the study by Roelofse, Joubert and Roelofse (1996) was to evaluate a new sedation technique for children having dental procedures. One hundred patients were included in this study. Fifty received midazolam alone, and fifty received a combination of midazolam and ketamine rectally. The conclusion was that both methods are safe and effective in sedating children, although the incidence of hallucinations in the midazolam group was markedly increased.

The study of Gremse, Kumar and Sacks (1997) retrospectively reviewed the medical records of 116 patients receiving sedation. They were divided in 2 groups. The one group received midazolam less than 0.3mg/kg and the second group received midazolam more than 0.3mg/kg. Meperidine 1mg/kg was used with the midazolam. The authors found both regimes were highly successful. Even with the higher dosage of midazolam there were no complications or adverse events in their study. They stated that for safe and effective intravenous sedation personnel are required who are experienced in paediatric sedation. Monitoring is essential and paediatric resuscitation equipment should be available.

In the study of Egelhoff, Ball, Koch and Parks (1997), 6006 paediatric outpatients in a radiology department were retrospectively reviewed for safety and efficacy of sedation. Sedation guidelines from the AAP were used. They reported no serious complications or adverse events. Minimal interventions were required for complications that occurred. They had a one percent failure rate. They concluded that sedation can be done in a safe and efficacious manner in a radiology department for children.

Morton and Oomen (1998) developed a selection and monitoring protocol for sedation in children. A survey in Scotland found that only 3 out of 38 hospital departments, which sedate children, had a formal protocol for paediatric sedation. The principles underlying the protocol concerned the following: informed consent, fasting guidelines, contra-indications to sedation, monitoring, trained personnel and discharge criteria.

In the study of Pena and Krauss (1999), 1180 patients were sedated with different medication regimes in an emergency department over a period of one year. No serious morbidity or mortality was documented. The conclusion was that emergency physicians practised procedural sedation safely.

In the study of Havel, Strait and Hennes (1999), 91 patients were enrolled. The authors found the drugs comparable in efficacy and adverse events. In the propofol group, the recovery time was shorter.

The article by Krauss and Green (2000) gives general information about sedation and how it should be done. Clinical monitoring is seen as very important. The pharmacology of drugs being used in sedation is discussed. The new ultra short-acting drugs are mentioned and discussed. The authors also state that further research is necessary to evaluate drugs like propofol and remifentanil in the practise of paediatric sedation.

Coté, *et al*. (2000) reviewed 95 cases where serious adverse events occurred in paediatric sedation. Their conclusion was that the morbidity and mortality found in this study was due to the following factors: inadequate monitoring, errors in managing complications, inadequate pre-procedure medical evaluation, medication errors, inadequate recovery procedures, and the lack of an independent observer. They state most of these complications could have been prevented.

In the study of Hoffman, Nowakowski, Troshynski, Berens and Weisman (2002), the authors tested the hypothesis that application of an AAP/ASA-structured model would reduce the risk of sedation-related adverse events. Their conclusions were that the use of these guidelines by non-anaesthesiologists does reduce the risk of adverse events in paediatric sedation.

Two regimens of sedation medications were compared in the study by Godambe, Elliott, Matheny and Pershad (2003). One hundred and thirteen patients between the ages of 3 and 18 were included in this study. The authors conclude that although propofol has a greater potential for respiratory depression and airway obstruction as compared to ketamine, it offers unique advantages including a quicker onset, and smoother recovery profile.

Pitette, Singh and Pierce (2003) studied 1244 sedation procedures in 1215 patients. The incidence of complications related to procedural sedation was 17.9%. All the complications were easily treated and no serious adverse events took place. Sedation was successful in 98.6% of patients. The authors concluded that procedural sedation and analgesia can be safely and effectively provided by non-anaesthesiologists.

The review article by Cravero and Blike (2004) looked at the historical role of anaesthesiologists in the practice of paediatric sedation. The author further writes about the current status and trends of sedation practice. Safety issues are also discussed, as well as the need for further research and developing of guidelines to practice safe and efficacious sedation.

The literature concerning the efficacy and safety of ketamine for sedation during procedures in paediatric emergency departments was reviewed by Mistry and Nahata (2005). The term dissociative sedation is used in this article. The conclusion was that ketamine is a safe drug to use in the sedation of children by those who are trained to use this drug.

The objective of the study by Roback, Wathen, Bajaj and Bothner (2005) was to compare the frequency and severity of adverse events associated with different drug regimes. The incidence of adverse events in this study was 17%. Certain drug regimes were associated with specific adverse events. Ketamine with or without midazolam had a higher incidence of nausea and vomiting. Midazolam and fentanyl were more likely to give respiratory adverse events.

In this study by Sanborn, Michna, Zurakowski, Burrows, Fontaine, Conner and Mason (2005) the incidence of respiratory adverse events was much lower, at 0.4%, if compared to the study of Roback *et al*. (2005). The authors attribute this fact to the training and experience of their personnel. They also mention that a history of respiratory illness could increase the risk of an adverse respiratory event.

Blike, Christoffersen, Cravero, Andeweg and Jensen (2005) developed a single scenario of a possible adverse event with the technology of a human simulator. The scenario was reproducible with realistic physiology that degraded over time if no interventions occurred and improved when treated appropriately. Sedation teams from the radiology and emergency departments were evaluated to identify latent system errors. This study measured rescue capability and revealed vulnerabilities in personnel structure and in care systems.

Sadhasivam, Ganesh, Robison, Kaye and Watcha (2006) in their study concluded that the bispectral index monitor (BIS) is an objective and non-disruptive tool for measuring the depth of sedation in children older than one year, and who did not receive ketamine. Not

everybody agrees with this finding as not many studies have validated the use of the BIS monitor to measure the depth of sedation.

Coté, Wilson and the Work group on sedation (2006) updated the guidelines on paediatric sedation. This was a joint effort between the AAP and the American Academy of Paediatric Dentistry (AAPD). This article includes comprehensive guidelines about paediatric sedation from the pre-operative assessment to discharge of the patient.

The study objective of Anderson, Junkins, Pribble and Guenther (2007) was to evaluate the relationship between continuous capnography and observed airway and respiratory adverse events, and the depth of propofol sedation for paediatric orthopaedic procedures. Their conclusion was that capnography detects most airway and respiratory events leading to intervention before clinical diagnosis or pulse oximetry.

The article on pharmacologic behaviour management by Kerins, McWhorter and Seale (2007) was a mailed survey to dentists in Texas. The conclusion was that they treat an increasing number of patients with ADD (Attention Deficit Disorder) and ADHD (Attention Deficit Hyperactivity Disorder). The dentists reported using a wide variety of pharmacologic management techniques. They supported the creation of guidelines to better manage this group of patients.

In 2001 Yagiela published an article to advocate the use of office- based sedation for a variety of patient groups that need dental treatment. These patients included all patients who are nervous or even terrified of dental appointments, young children, the behaviourally or medically challenged, and individuals who are undergoing extensive procedures or have problems with gagging or local anaesthesia. The article concluded that the different methods that were discussed can provide complementary benefits to both the patient and the treating dentist.

A very important question was raised by Flick and Clayhold (1998), namely who should determine the medical necessity of dental sedation and general anaesthesia? In the financially driven world we live in, this can be very frustrating when treating patients are secondary to financial concerns.

CHAPTER THREE

PHARMACOLOGY OF DRUGS USED

3.1 INTRODUCTION

The administration of drugs plays an important part in the safety of patients during procedural sedation and analgesia. Pharmacologic principles involve the pharmacokinetics and pharmacodynamics of drugs. Any sedation practitioner must have a clear understanding of pharmacologic principles concerning drugs. The pharmacokinetics and pharmacodynamics of drugs will be discussed according to Sommers (2000:353-366) and Morgan and Mikhail (1996:128-132).

3.1.1 PHARMACOKINETICS is the "study of the relationship between a drug's dosage, tissue concentration, and time since administration."(Morgan & Mikhail 1996:128) Simply put, it describes how the body affects a drug. This can be divided in the following parameters:

- Absorption,
- Distribution,
- Metabolism and
- Excretion.

ABSORPTION: Absorption is the physical passing of drugs from the outside to the inside of the body thus reaching the blood stream. Morgan and Mikhail (1996:128) describes absorption as the process by which a drug leaves its site of administration to enter the blood stream.

Different routes of administration are possible to use: oral, nasal, sublingual, transdermal, rectal, and parental.

- With **oral** administration, the majority of all absorption occurs in the intestines, where drugs must pass through the intestinal wall to enter the blood. It is important to distinguish between those interactions in which the rate of absorption is altered and those in which the total amount absorbed are altered. With oral administration there is also the first-pass hepatic metabolism that influences the bio-availability of drugs. It simply means that not all of the drug taken orally will eventually reach the effect site.

- **Nasal** administration of drugs therefore seems a good way of reaching an effective plasma concentration.

- **Sublingual or buccal** administration bypasses the first-pass hepatic metabolism, because the veins in the mouth drain directly into the superior vena cava. This means in effect that a bigger concentration of the administered drug is available.

- **Transdermal** drug administration, rarely used for sedation, has the advantage of prolonged and continuous absorption.

- **Rectal** administration is an alternative route of administration, specifically in uncooperative patients. This way of administration can also be safely used in small children. Absorption from the rectum can be erratic, and can cause irritation of the rectal mucosa. The venous drainage of the rectum also bypasses the liver.

- **Parenteral** injection can be subcutaneous, intramuscular or intravenous. Subcutaneous and intramuscular administration depends on the rate of diffusion, and that is dependent on the blood flow to the specific area. Intravenous administration completely bypasses the process of absorption, because it is delivered directly into the blood stream.

Hogan, Zucchero, Schultz and Curren (1992) explained the absorption of drugs in a practical way as follows:

- With medications administered chronically, such as Coumadin (warfarin), the rate of absorption is usually not important, provided that the total amount absorbed is not altered significantly. For a medication administered as a single dosage and intended to be absorbed rapidly, such as analgesics or hypnotics, a high concentration needs to be achieved rapidly for efficacy, thus, a reduced absorption rate may result in failure to attain adequate serum levels.

- Drug passage through the gastric mucosa is by passive diffusion that depends on the amount of drug that is non-ionized. Absorption can thus be influenced by the pKa and lipid solubility of the medication, and the pH of the stomach contents. Thus, an alteration in gastric pH by anti-acids can alter absorption of drugs.

- Medications that alter the rate of gastric emptying and gastro-intestinal motility e.g. the opiates also affect drug absorption, as many medications are primarily absorbed in the upper part of the small intestines. Slower gastro-intestinal motility means the drug stays in the intestines for a longer period of time and there will be an increase in absorption. Metoclopramide is one drug that decreases the gastro-intestinal motility.

DISTRIBUTION: After absorption, drugs need to be delivered to the target area to exert their effect. Distribution refers to the process in which drugs are carried in the blood stream and released to different parts of the body. A drug's distribution depends primarily upon organ perfusion, protein binding, and lipid solubility. Drug interactions can occur during the distribution phase if the drug has a narrow therapeutic index and is highly protein-bound. Protein binding can be a significant source of drug interactions. Binding to plasma proteins is reversible, and equilibrium is established between those drug molecules bound and unbound, with only those molecules unbound and in solution being pharmacologically active. The molecules that are bound to plasma proteins are inactive and protected from metabolism, and prevented from being excreted. Albumin often binds to acidic drugs like barbiturates, while ð1-acid glycoprotein (AAG) binds to basic drugs, like local anaesthetics. If a drug is 99% plasma protein bound and another drug reduces this binding to 95%, this results in an increase in the unbound drug fraction from 1% to 4%, a four-fold increase. This displacement of drug molecules from protein binding sites to the plasma is only likely to increase the number of free molecules significantly if most of the unbound drug is in the plasma, instead of within the tissues. Only medications with a low apparent volume of distribution will be affected. The apparent volume into which a drug has been distributed is called its volume of distribution, and is determined by dividing the dosage of the drug administered by the resulting plasma concentration. There are other factors that also influence drug distribution, for example the blood-brain barrier and redistribution.

METABOLISM: Most drugs are metabolized by the liver to inactive metabolites. Hepatic microsomal enzymes, concentrated mainly in the endothelium of liver cells, change the parent molecule. This is a very important point for sedation practitioners as liver disease my decrease the metabolism of drugs e.g. midazolam, with a prolonged action.

Metabolic biotransformation can be divided into phase 1 and phase 2 reactions.

- Phase 1 reaction convert a parent drug into more polar metabolites through oxidation, reduction, or hydrolyses.
- Phase 2 reactions couple (conjugate) a parent drug or a phase 1 metabolite with a endogenous substrate to form a highly polar end product that can be eliminated in the urine. Although this usually happens in sequence, a phase 1 metabolite may be excreted without being converted to a phase 2 metabolite, and sometimes phase 2 can occur first. In the last stages of metabolism, water-soluble molecules are added to the parent molecule to form a large molecule that is water-soluble, inactive and readily excreted.

Hepatic clearance is the rate of elimination of a drug as a result of liver bio-transformation. The hepatic clearance depends upon the hepatic blood flow and the fraction of the drug removed from the blood by the liver. This is the hepatic extraction ratio.

If the liver enzymes were induced to slow down its metabolism, drugs would be inactivated at a slower pace and the overall effectiveness of the substance would be higher, and vice versa. In general, drugs that induce liver metabolism do not exert an immediate effect. The rate of liver metabolism changes slowly over several weeks. Therefore, the effect of increased or decreased liver metabolism is not seen until several weeks after the initiation of drug therapy. Some examples of drugs that increase liver metabolism are phenytoin, carbamazepine, phenobarbitals, rifampicin, ethanol, tobacco and glucocorticoids. Patients on these drugs might need higher dosages of medication e.g. midazolam to achieve the desired level of sedation. On the other hand, drugs that inhibit liver metabolism have an immediate onset of action. The rate of liver metabolism may be greatly impaired within a few days. Therefore, there is a greater risk of drugs accumulating in the body as the function of the liver to inactivate them is compromised. Examples of drugs that inhibit liver metabolism include cimetidine, erythromycin, fluconazole, itraconazole, ketoconazole, antivirals, calcium channel blockers and grapefruit juice. If benzodiazepines are used smaller dosages are needed, and drugs should be titrated.

The cytochrome P-450 iso-enzymes are a group of structurally related enzymes that are divided into families, subfamilies and genotypes. CYP1, CYP2 and CYP3 appear to be involved with drug metabolism. These families make up approximately 72% of the total available CYP. When two or more medications that share the same metabolic pathway are administered concurrently, metabolizing enzyme systems may become saturated, leading to a possible decrease in the metabolic rate of one or both medications, with subsequent increase in plasma levels.

EXCRETION:

- The kidneys are the principal organs of excretion. Non-protein bound drugs freely cross from plasma into the glomerular filtrate. The non-ionized fraction of the drug is reabsorbed in the renal tubules, while the ionized portion is excreted. This means that an alteration in the pH of the urine can influence the excretion of drugs. If the kidneys are damaged, the rate of elimination by the kidneys would be slowed down, leading to an accumulation of drugs in the body. This is rarely a problem in daily sedation practice outside the operating theater as only ASA 1 and 11 patients are accepted.

- Very few drugs depend on biliary excretion, since they are reabsorbed in the intestine, and then excreted in the urine. This is called entero-hepatic recirculation, and this can be responsible for the delayed toxic reactions that can occur.

- The lungs are responsible for the excretion of volatile agents.

3.1.2 PHARMACODYNAMICS refers to the study of how drugs affect the human body. The extent of these effects determines a drug's efficacy, potency and therapeutic ratio. Pharmacodynamics describes the mechanism of action, drug interactions, and structure-activity relationships. There can be synergistic or antagonistic interaction between drug molecules. These reactions are generally more difficult to predict and prevent than pharmacokinetic interactions.

With the above as background, each of the drugs that were used in this research study, will be discussed separately.

3.1.3 THE IDEAL SEDATIVE DRUG

One is tempted to ask whether there is an ideal sedative drug.
According to Craig and Skelly (2004:28) the ideal intravenous sedation agent should have the following properties:

1. The drug should provide anxiolysis, analgesia and amnesia.
2. A rapid onset of action.
3. It must be easy to titrate.
4. The drug must have predictable a sedative and anxiolytic action.
5. Induction and recovery must be rapid.
6. No side effects or systemic toxicity.
7. The speed of change in sedation level must be rapid.
8. It must be reversible.
9. Undergo rapid metabolism to inactive metabolites.
10. The drug must have minimal cardiovascular and respiratory side effects.
11. The potential for anaphylactic/allergic reactions must be low.
12. The drug must be water soluble with a long shelf-life at room temperature.

There is no single drug available today that has all these properties. To achieve this, a combination of drugs must be used. The synergistic effect [1+1=3] plus the additive effect [1+1=2] can be used when the sedation practitioner uses a combination drug technique. Using more than one drug means that smaller dosages of each individual drug can and should be used. When using smaller dosages, the potential for side effects is lower. Even when using small dosages, the drugs used must still be titrated to effect in each individual patient.

3.2 MIDAZOLAM [DORMICUM®]

The discussion of midazolam is based on the approved package insert (Annexure K).

3.2.1 CHEMICAL STRUCTURE

Midazolam is a short acting benzodiazepine that became available in 1983 (Craig & Skelly 2004:6). It is a clear, colourless liquid in a glass ampoule. Midazolam is available in 5mg/ml (midacum®), 5mg/5ml, 15mg/3ml and 50mg/10ml concentrations. The ampoules can be administered nasally, orally, rectally and intravenously. There are different dosages for each route of administration. Benzodiazepines have a large therapeutic index and the availability of a specific receptor antagonist, flumazenil, makes it reasonably safe to administer. Midazolam is a drug used commonly for sedation procedures.

3.2.2 PHARMACODYNAMICS

Midazolam is a derivative of the imidazo-benzodiazepine group. The free base is a lipophilic substance with a low solubility in water. The basic nitrogen in position 2 of the imidazo-benzodiazepine ring system enables the active substance to form water-soluble salts with acids. Midazolam has different effects depending on the percentage of receptor occupancy. It acts as an anticonvulsant, an anxiolytic and has sedation properties. Anterograde amnesia may occur after administration. In high dosages, midazolam has muscle relaxation properties (Sommers 2000:151).

Mechanism of action: The binding site is found on the alpha subunit of the beta2 GABA-receptor. These receptors are found in the cerebral cortex, cerebellum, hippocampus, substantia nigra, corpus striatum, brainstem and spinal cord. Midazolam increases the permeability of the chloride channels, thus hyperpolarizing the membrane with increased resistance to neuron excitation (Sommers 2000:151).

3.2.3 PHARMACOKINETICS

Absorption of midazolam

- After oral administration is 10 to 30 minutes.
- After intramuscular injection absorption is rapid and complete. The maximum plasma concentration is reached within 30 minutes, and bio-availability is over 90%.
- After buccal, nasal or sublingual administration time to peak effect is 10 to 15 minutes, and the duration of action is 20 to 60 minutes.
- Administering Midazolam rectally results in a peak effect in 10 to 20 minutes.

- When Midazolam is administered intravenously the time to peak effect is 10 minutes, and the duration of action is 20 to 60 minutes (SASA sedation guideline 2010:11).

Distribution: When midazolam is injected intravenously, plasma concentration shows a short distribution phase of 5 – 15 minutes, followed by an elimination phase. Studies show a protein binding of 96 – 98%.
Metabolism: Midazolam is completely metabolized and the primary metabolite is a α-hydroxy-midazolam. The fraction extracted by the liver is 40 – 50%. This active metabolite conjugates with glucoronic acid and is then eliminated by the kidneys more rapidly than Midazolam.

Elimination: The elimination half life is between 1.5 – 2.5 hours in adults. In children it is shorter, namely 1 – 1.5 hours. About 50 – 70% of midazolam is eliminated by the kidneys in the form of a conjugate of the α-hydroxy-metabolite.

3.2.4 DOSAGE AND DIRECTIONS FOR USE

Midazolam is a potent and popular sedative agent that requires slow administration and individualisation of dosage. The dosage should be individualized and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication of each patient. Remember that time to peak effect after intravenous administration is 10 minutes (SASA sedation guideline 2010:11).

Pre-medication: In children the dosage ranges between 0.25 – 0.5 mg/kg orally with a maximum dosage of 7.5mg.

Moderate sedation and analgesia/Conscious sedation: In this study Midazolam was used as part of a combination drug sedation technique. The dosage for intravenous midazolam ranges between 0.05 – 0.1mg/kg to a maximum bolus dosage of 2mg. The recommended maximum dosage is 3mg.

Midazolam may also be administered by the following routes (SASA sedation guideline 2010:11):

- Orally: 0.25 – 0.5mg/kg with onset of action between 10 – 30 minutes and duration of action is 60 minutes.
- Buccal/sublingual: 0.25 – 0.3mg/kg with time to peak effect 10 – 15 minutes and duration of action between 20 – 60 minutes.
- Per rectum: 0.5 – 0.75mg/kg with time to peak effect 10 – 20 minutes and duration of action is 60 minutes.
- Intranasally: 0.2 – 0.3mg/kg. The time to peak effect is 10 – 15 minutes and the duration of action is 20 – 60 minutes.

- Intramuscularly: 0.1 – 0.2mg/kg with an onset of action between 5 – 10 minutes.

3.2.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

- The side-effects most commonly encountered are drowsiness and over-sedation.
- Less common are depression of mood and affect, disorientation or confusion, lethargy and ataxia.
- Effects like nausea and vomiting, headache, hiccoughs, laryngospasm, dyspnoea and hallucinations have also been reported.
- Double vision can be a problem in smaller children.

Midazolam can be considered a safe agent in the correct sedative dosage, but overdosage can cause paradoxical reactions, confusion or life threatening respiratory depression and coma.

Flumazenil reverses the sedative and respiratory depressant effects of benzodiazepines. It should be readily available whenever benzodiazepines are used for sedation. The dosage is 10µg/kg. The titration interval is 2 minutes with a maximum dosage of 1mg/kg. It is important to realize that the duration of action is only 1 hour (Sommers 2000:154), which means that re-sedation may occur if large dosages of benzodiazepines are administered (Sommers 2000:155). Patients who have taken Midazolam must always be discharged in the care of a responsible person.

3.2.6 DRUG INTERACTIONS

The suppression of the central nervous system is increased if used with the following drugs: antipsychotics, hypnotics, anxiolytics, anaesthetic drugs, narcotic analgesics, antidepressants, antiepileptic drugs, alcohol, and sedative antihistamines.

Drugs that inhibit hepatic enzymes (especially cytochrome P450 III A) can lead to increased effect and sedation. The following drugs are included: cimetidine, ranitidine, erythromycin, diltiazem, verapamil, ketoconazsole and itraconozole.

Midazolam potentiates the effect of the opiates.

3.2.7 PERSONAL EXPERIENCE

In my experience the use of Midazolam as pre-medication is essential to facilitate the placement of the intravenous cannula. Many parents find the idea of placing a “needle” on the hand of their child very frightening. With the help of midazolam and an EMLA patch, this procedure is relatively easy.

In this study population, most of the children had a surgical procedure before, which is helpful if the parents can give a history of paradoxical reactions to midazolam. In these cases you have to avoid using midazolam. Hydroxyzine (Aterax®) at a dosage of 0.6mg/kg could be an alternative in these cases.

The children received 3.75mg (½ a 7.5mg tablet) per os if they were younger than 6 years. Children older than 6 years received a full 7.5mg tablet. Most of the children do not have problems swallowing a tablet. These days most children take vitamins and are used to taking tablets. If they have problems taking the tablet, they should be encouraged to chew and swallow with water. In the few cases who could not take the tablet, the liquid ampoule solution was used at a dosage of 0.5mg/kg. The midazolam liquid was then combined with panado or ponstan syrup made up to a volume of 5ml.

With the induction of sedation, a dosage of 0.5mg midazolam was used intravenously. Usually this dosage was sufficient with the combination drug technique. In a few cases where it was clear that the child is still anxious, further dosages of 0.5mg were titrated to effect. A further benefit of using midazolam is that it counteracts the possibility of hallucinations that can be caused by the use of ketamine.

Midazolam tends to make children disinhibited. Patients who are of a happy disposition tend to be happy, but patients who are of a sad temperament tend to become more morose. These patients can be tearful during the procedure, and increasing the dosage of midazolam tends to worsen this occurrence (Whitwam & McCloy 1998:134). I have seen this reaction in a few patients, mostly adult females

3.3 PROPOFOL [DIPRIVAN®]

The discussion of propofol is based on the approved package insert (Annexure L).

3.3.1 CHEMICAL STRUCTURE

Propofol is a 2,6 diisopropylphenol which is classified as a sedative-hypnotic with a quick onset of action, and recovery. It is a milk white substance marketed in 20ml glass ampoules for single use, and also 50ml vials for infusions as a 1% solution at 10mg/ml.

The formulation at present consists of 1% propofol, soyabean oil, glycerol and egg phosphatite. This means that 1.0 ml of propofol contains 0.1 gram of fat. This substance is an oil emulsion at room temperature. It is highly fat-soluble. Propofol is stable at room temperature and not sensitive to light. The pH is 7. The drug is compatible with 5% dextrose water.

3.3.2 PHARMACODYNAMICS

Propofol has a rapid onset of action of approximately 30 seconds, which makes it an ideal drug for sedation practice.

Falls in mean arterial blood pressure and slight changes in heart rate are observed when propofol is administered for induction and maintenance of anaesthesia. Bradycardia and hypotension have been reported. This is rarely a problem with sedation as smaller dosages are used.

Respiratory effects are a drop in tidal volume, but increase in respiratory rate. When using propofol as an anaesthetic induction agent at a dosage of 1.5 – 2.5mg/kg, respiratory depression can occur. This is not the dosages used for induction of sedation.

Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism.
Recovery from anaesthesia and sedation is usually rapid and the patients are clearheaded within 2 – 8 minutes. This is an ideal characteristic for sedation as patients can return home soon after the operation.
Propofol has anti-emetic properties, and can also act as an anti-pruritic. It must be noted that propofol has no analgesic properties, therefore analgesics have to be added to any sedation regime if the procedure is painful.

Mechanism of action: The mechanism of action is poorly understood, but it may involve facilitation of inhibitory neurotransmission mediated by γ-aminobutyric acid.

3.3.3 PHARMACOKINETICS

Absorption: Propofol can only be administered intravenously and is highly fat soluble. The sedation induction dosage of propofol is 0.5mg/kg. The onset of action is 45 - 90 seconds if the titration interval is 1 minute (SASA sedation guideline 2010:12-13). Propofol metabolism can be described by a three compartment model (Whitwam & McCloy 1998:27).

Distribution: The distribution half -life of propofol is 2 – 4 minutes, which is the first part of the three compartment model. In order to maintain sedation at a constant level, it is therefore desirable to administer propofol by a continuous infusion technique (Craig & Skelly 2004:39).

Metabolism: The second phase is a rapid metabolism [half-life of 30 – 60 minutes], with a slower final phase [184 – 502 minutes] of redistribution from poorly perfused tissue (Whitwam & McCloy 1998:27). Propofol is metabolized in the liver, but the high

clearance rate of 2 liters/minute implicates the existence of extra hepatic metabolism. Inactive conjugates are formed (Morgan & Mikhail 1996:145).

Elimination: An inactive metabolite of propofol is excreted in the urine. The pharmacokinetics is linear over the recommended range of infusion rates of propofol.
With the usual maintenance regimes no significant accumulation of propofol occurs.

3.3.4 DOSAGE AND DIRECTIONS FOR USE

Propofol has a narrow margin of safety, therefore only an experienced sedation practitioner skilled in airway management should administer propofol. It must not be used if the operator is also the sedation practitioner (SASA sedation guideline 2010:12). However, there are single operator sedation practitioners e.g. endoscopists who use propofol for sedation.

Propofol is not recommended for sedation for children under 3 years of age. The dosage required decreases with the increase in age.

- The general dosage for induction of **anaesthesia** is 1.5 – 2.5mg/kg by slow bolus injection, titrated against the response of the patient until clinical signs show onset of anaesthesia.
- The dosing schedule according to the SASA sedation guidelines (2010:12) when using propofol for **sedation** is as follows: the induction bolus dosage is 0.5mg/kg. The onset of action is 45 – 90 seconds with duration of action of 5 – 8 minutes.
- When using intravenous infusions for sedation the rate of administration is 2 – 4mg/kg/h, titrated to clinical effect. With target controlled infusions the effect site concentration should be between 1 - 2µg/ml.
- In elderly and debilitated patients the dosage of propofol should be reduced.

3.3.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

- Cardiovascular side effects that occur commonly with propofol use are tachycardia, hypotension, flushing and hypertension. This is rare during sedation.
- Nervous system side effects include involuntary movements and excitation. Epileptiform movements including convulsions and opisthotonos have rarely been reported.
- Common respiratory side effects are apnoea, hiccup, and coughing when propofol is used in anaesthetic dosages.
- Local pain at the injection site is a very common side effect. The manufacturers recommend the co-administration of lignocaine, or the use of a bigger vein on the forearm or the cubital fossa. Tramadol is also used to prevent pain.
- Anaphylaxis has been reported but is very rare.

- Propofol is contra-indicated in patients with egg and soy allergies. The egg yolk is used in manufacturing propofol, but most egg allergies is to egg white (Morgan & Mikhail 1996:145).
- Propofol is preservative free and it is a lipid emulsion, which make it an ideal bacterial growth medium. For this reason all unused propofol must be discarded after six hours.
- Respiration must be monitored to ensure adequate gas exchange. Special care should be taken if propofol is used together with other respiratory depressants like the opiates and benzodiazepines.

3.3.6 PROPOFOL INFUSION SYNDROME (PRIS)

This condition is an adverse drug event associated with high dosages and long-term use of propofol. This was reported in critically ill children at first, but recently several cases have been reported in adult patients as well. The priming factor is critical illness. The triggering factors are high dosage propofol (>4mg/kg/h and >48 hours duration), glucocorticoids and catecholamines. The presenting symptoms are severe metabolic acidosis, rhabdomyolysis, hyperkalemia, lipemia, renal failure, hepatomegaly and cardiovascular collapse. To improve the outcome of this potentially fatal disease, early recognition and discontinuation of the propofol infusion is essential (Zaccheo & Bucher 2008).

3.3.7 DRUG INTERACTIONS

Fentanyl and alfentanil concentrations may be increased by concomitant administration of propofol. Special care should be used when propofol is used together with other respiratory depressants like the benzodiazepines and the opiates.

3.3.8 PERSONAL EXPERIENCE

In this study, propofol was used successfully as a continuous infusion as part of a multidrug regime with no adverse events or an escalation in care.

3.4 GLYCOPYRROLATE [ROBINUL®]

The discussion of glycopyrrolate is based on the approved package insert (Annexure M).

3.4.1 CHEMICAL STRUCTURE

Glycopyrrolate is classified as an anticholinergic (antisialogue) agent. It is a synthetic quaternary ammonium containing mandelic acid in the place of tropic acid (Morgan and Mikhail 1996:174). Glycopyrrolate is presented in 1ml and 2ml clear glass ampoules. The clear liquid contains 0.2mg/ml of glycopyrrolate. Chlorbutanol 0.5% is added as a preservative.

3.4.2 PHARMACODYNAMICS

Glycopyrrolate, like other anticholinergic agents, inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic nerves and on smooth muscle that respond to acetylcholine, but lacks cholinergic innervations.

The peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrio-ventricular node, exocrine glands and to a limited degree in the autonomic ganglia. Therefore, glycopyrrolate diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions. Glycopyrrolate antagonizes muscarinic symptoms such as bronchospasm, bradycardia and intestinal hypermotility induced by cholinergic drugs.
Glycopyrrolate has a highly polar quaternary ammonium group in its structure, which limits its passage over lipid membranes, such as the blood brain barrier. In contrast, atropine has a non-polar tertiary amine which penetrates lipid barriers e.g. the blood brain barrier easily.

3.4.3 PHARMACOKINETICS

Absorption: With intravenous injection, the onset of action is generally evident within one minute. After intramuscular or subcutaneous injection, peak effects occur after 30 to 45 minutes.

Elimination: Glycopyrrolate is excreted in the bile and urine.

3.4.4 DOSAGE AND DIRECTIONS FOR USE

- Glycopyrrolate can be administered intramuscularly, intravenously or subcutaneously.
- The recommended dosage in children up to twelve years when used as a pre-anaesthetic medication is 0.004 – 0.008mg/kg (0.02 to 0.04ml/kg) intramuscularly.

- For use intra-operatively to block vagal responses, a single dosage of 0.1mg (0.5ml) should be given intravenously. This dosage can be repeated at intervals of 2 – 3 minutes when necessary.
- Peak effects occur approximately 30 to 45 minutes after subcutaneous or intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialogogue effects persist for up to 7 hours.

3.4.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

- Side effects in general may include a dry mouth, urinary hesitancy, blurred vision, tachycardia and palpitations.
- Glycopyrrolate should be used with caution in patients with myasthenia gravis, coronary artery disease, congestive heart failure and hypertension.

3.4.6 PERSONAL EXPERIENCE

Glycopyrrolate is useful in paediatric sedation to block the vagal effect of alfentanil and reduce the secretions caused by ketamine. There is not agreement whether all patients should receive an antisialogue for sedation. It has been reported that there is a higher incidence of respiratory complications when this drug is used with ketamine. The author has not noted this in this research study.

3.5 KETAMINE

The discussion of ketamine is based on the approved package insert (Annexure N).

3.5.1 CHEMICAL STRUCTURE

Ketamine is a phencyclidine derivative and was introduced for clinical use in 1970. It is a noncompetitive *N*-methyl-D-aspartate glutamate (NMDA) receptor antagonist (Roelofse 2010). The NMDA receptor is important for memory.

Ketamine is presented as a hydrochloride salt made isotonic with sodium chloride. Ketamine is presented in three different strengths. In South-Africa the rasemic mixture is available in vials containing 10mg/ml [20ml vial], 50mg/ml [10ml vial], and 100mg/ml [10ml vial].

The commercial preparation of ketamine is a racemic mixture of two enantiomers, S (+) and R (-). The enantiomers exhibit pharmacologic and clinical differences. The S (+) enantiomers, marketed as ketanest® but not available in South Africa, has four times the potency of the R (-) enantiomers (ketamine®) and twice the analgesic potency of the

racemate. The S (+) isomer appears to be cleared more rapidly, resulting in a shorter duration of action and a faster offset, which allow for easier titration when using an infusion (Roelofse 2010).

3.5.2 PHARMACODYNAMICS

Ketamine is best described as a "**Dissociative Sedatio**n" drug. Ketamine dissociation occurs with maintenance of respiration and a patent airway probably because its primary site of action is the cerebral cortex and limbic systems and not the brainstem. No dosage-response continuum is observed with ketamine when used for procedural sedation and patients are either dissociated or they are not (Howes 2004).

Krauss and Green (2000:941) defined dissociative sedation thus: "A trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability."

Ketamine has cardiovascular effects, which are due to the central stimulation of the sympathetic nervous system. These effects are increases in arterial blood pressure, heart rate and cardiac output (Morgan & Mikhail 1996:143). Myocardial oxygen demand increases as well as myocardial sensitivity to adrenaline. This is of clinical significance especially in dental sedation cases where local anaesthetic agents containing adrenaline are used.

Rapid administration of ketamine may cause respiratory depression (SASA sedation guideline 2010:13). When sedative dosages are used and ketamine boluses are given slowly, airway patency and respiration will be intact (Howes 2004:275). Ketamine stimulates the production of saliva and trachea-bronchial secretions. This side-effect can be diminished by administering an antisialogogue like glycopyrrolate (Morgan & Mikhail 1006:143).

Emergence delirium may be associated with the use of ketamine. Midazolam can be co-administered (≤0.05mg/kg) to reduce the incidence further, but will deepen and prolong sedation and increase the probability of apnoea. Ketamine increases cerebral oxygen consumption, cerebral blood flow and intracranial pressure. It also increases ocular pressure.

3.5.3 PHARMACOKINETICS

The pharmacokinetic findings were consistent with a two-compartment model for intravenous administration of the rasemic ketamine (Roelofse 2010).

Absorption: Ketamine has high lipid solubility. Only 12 – 27% is bound to albumin, which allows a rapid transfer across the blood-brain barrier and placenta (Whitwam & McCloy 1998:31).

Ketamine can be administered through almost any route (SASA sedation guideline 20102:13).

- Oral administration results in peak effect within 30 minutes.
- Intravenous ketamine has an onset of action of < 1 minute and time to peak effect of 3 – 5 minutes.
- Intramuscular and nasal administration takes 20 minutes to reach peak effect.
- Rectal administration takes 30 minutes to peak effect which is dosage related.

Distribution: The distribution half-life is 10 – 15 minutes. Awakening is due to redistribution to peripheral compartments (Morgan & Mikhail 1996:143).

Metabolism: Ketamine is metabolized in the liver to several metabolites. One of the metabolites, norketamine, has weak hypnotic properties but prolongs analgesia for another 4 hours. Hepatic dysfunction may elevate plasma levels and delay elimination. (Whitwam & McCloy 1998:31)

Elimination: The elimination half-life is 2 hours. Ketamine is excreted through the kidneys.

3.5.4 DOSAGE AND DIRECTIONS FOR USE

Pre-medication: In this study, ketamine was used as an oral pre-medication in children that was not co-operative after the midazolam pre-medication. The dosage was 2mg/kg. This is the dose used when combined with other sedatives and analgesics.

Conscious (moderate) sedation: Ketamine may also be administered by the following routes: (SASA sedation guidelines 2010:13)

- Orally: When ketamine is administered as a single agent orally, the dosage is 4 – 6mg/kg. The onset of action is more than 5 minutes, time to peak effect is 30 minutes and duration of action is 4 – 6 hours. The drug has a bad taste and must be disguised with panado or ponstan syrup.
- Intravenous: 0.5 – 1mg/kg with onset of action <1minute. The time to peak effect is 3 – 5 minutes and the duration of action is 5 – 10 minutes.

- Intramuscular: 2 – 4mg/kg with the onset of action between 2 – 5 minutes. Time to peak effect is 20 minutes and the duration of action is 30 minutes. There is however a higher incidence of nausea and vomiting after intramuscular ketamine administration.
- Per rectum: 4 – 6mg/kg with onset of action >5minutes. Time to peak effect is 30 minutes and duration of action is 30 – 120 minutes.
- Intranasally: 5mg/kg with onset of action of 10 minutes. Time to peak effect is 20 minutes and duration of action is 1 hour. This route is not recommended because it can be distressing for the patient.

3.5.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

- Emergence reactions in recovery are common, including vivid and often unpleasant dreams, confusion, hallucinations and irrational behavior. Children appear to be less sensitive. The incidence of emergence reactions is controversial; it is probably related to the dosage of ketamine administered.
- Patients may also experience increased muscle tone which is not really a problem during sedation.
- Blood pressure and heart rate may be temporarily increased by ketamine.
- Respiration may be depressed, especially during too rapid intravenous injection. Apnoea and laryngospasm have occurred.
- Diplopia and nystagmus may occur. It is good practice to especially warn the parents of children about this; they can be very upset if the child complains that he/she cannot see.
- Nausea and vomiting, lachrymation and hypersalivation have been reported but seem to be dosage-related.
- Raised intra-ocular and cerebrospinal fluid pressure has also been reported. It is however highly unlikely that ketamine will raise the intracranial pressure in the dosages used.
- Transient skin rashes and pain at the injection site can occur.

The following special precautions should be adhered to when ketamine is administered for sedation:

- The necessary equipment for airway support, intubation and resuscitation should always be readily available.
- Patients with a history of epilepsy, psychiatric illnesses or porphyria. There are however reports of using ketamine for status epilepticus.
- Cardiac function should be monitored in patients with mild hypertension or cardiac decompensation.
- Verbal, tactile and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.

- Don’t inject ketamine rapidly with intravenous administration.
- Make certain patients are not using ketamine for recreational purposes.

3.5.6 DRUG INTERACTIONS

The combination of theophylline and ketamine may predispose patients to seizures. Ketamine produces myocardial depression when given to patients anaesthetized with halothane, or to a lesser extent, other volatile anesthetics (Morgan & Mikhail 1006:143). This is however not seen when ketamine is used as a sedative agent.

3.5.7 PERSONAL EXPERIENCE

Ketamine is a remarkable and versatile drug that has in recent years made a comeback in clinical practice. The fact that it can be given orally as part of a pre-medication regime, means that even the most anxious of children can be sedated without traumatizing them with the IV procedure. The author uses ketamine as a second pre-medication agent specifically in children where the placement of the intravenous line is difficult. The state of dissociative sedation that is achieved with ketamine use is beneficial in children. The dissociative state means that you have a relaxed and co-operative child without losing the protective reflexes. In this state there is analgesia, sedation, amnesia and minimal effects on the cardiovascular and respiratory systems. The unique qualities of ketamine as previously discussed, make ketamine an ideal sedation drug if all the guidelines as to administration are followed.

3.6 SUFENTANIL [SUFENTA®]

The discussion of sufentanil is based on the approved package insert (Annexure O)

3.6.1 CHEMICAL STRUCTURE

Sufentanil is an extremely potent short acting opioid analgesic related to fentanyl. It is a clear, colourless liquid in a glass ampoule. Each milliliter contains 0.005mg of sufentanil and 9.0mg sodium chloride in water for injection. Sufentanil is available in 2ml and 10ml see-through glass ampoules. Opioids can be classified by either their chemical structure or action on receptors. Sufentanil falls in the group of phenylpiperidines.

3.6.2 PHARMACODYNAMICS

Sufentanil is a mu (μ) opioid agonist with hypnotic properties. Intravenous sufentanil produces a dosage-related attenuation of catecholamine release, particularly noradrenaline. When used in balanced general anaesthesia, it is 5 – 10 times as potent as fentanyl. Sufentanil is twice as lipophilic as fentanyl and is rapidly absorbed from the nasal mucosa (SASA sedation guideline 2010:14).

Mechanism of action: Opioids bind to specific receptors located throughout the central nervous system and other tissues. Four major types of opioid receptors have been identified, namely mu (μ, with subtypes μ-1 and μ-2), kappa (κ), delta (δ) and sigma (σ). Opioids provide some degree of sedation which is in effect a side -effect, but they are most effective at producing analgesia. The agonists are capable of receptor activation. Opioid-receptor activation inhibits the presynaptic release and postsynaptic response to excitatory neurotransmitters (Morgan & Mikhail 1996:137).

3.6.3 PHARMACOKINETICS

Absorption: Sufentanil is usually given intravenously as adjunct to general anaesthesia in a dosage of 0.25 – 30μg/kg (Morgan & Mikhail 1996:141). It has a rapid onset of action and short duration of action which is an advantage when being used in procedural sedation and analgesia.

- After bolus intravenous administration the time to peak effect is 5.6 minutes and the duration of action is 30 minutes.
- Sufentanil can also be used as a continuous infusion. The time to peak effect with an infusion is 6.5 minutes and the duration of action is 240 minutes after a 2 hour infusion (SASA sedation guidelines 2010:14).
- Sufentanil can also be administered intranasally at a dosage of 1.5 – 3.0μg/kg (SASA sedation guidelines 2010:14).

Distribution: The pharmacokinetics of intravenous sufentanil can be described as a three-compartment model with an average distribution time of 0.72 minutes, and a redistribution time of 13.7 minutes. Plasma protein binding is approximately 92.5%. Redistribution terminates the action of small dosages, while larger dosages must depend on biotransformation to adequately lower plasma levels.

Metabolism: Sufentanil is metabolized in the liver and the intestines; 80% of the administered dosage is excreted in 24 hours. The end products of sufentanil are inactive.

Elimination: The elimination half-life of sufentanil is 148 minutes. Sufentanil is excreted in the urine and bile.

3.6.4 DOSAGE AND DIRECTIONS FOR USE

The following dosages and directions are discussed according to the SASA sedation guidelines (2010:14).

- The intranasal dosage of sufentanil for procedural sedation is 1μg/kg. With this dosage the time to peak effect is 20 minutes and the duration of action is >60 minutes.
- When using sufentanil as an intravenous bolus the dosage is 0.02μg/kg.

- Sufentanil can also be used as a continues intravenous infusion. The dosage ranges between 0.2 – 0.4µg/kg/hr.
- The dosage of sufentanil should be individualized. Factors to be considered in determining the dosage are age, body mass, physical status, underlying pathological condition, and the use of other medicines.

3.6.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

- Nausea and vomiting are side effects that are encountered regularly with opioid use often depending on the dosage given.
- Pruritus and urinary retention have also been reported.
- Bronchospasm, cough and hiccups are respiratory side effects that can occur.
- Opioids can also cause chest wall rigidity, severe enough to prevent adequate ventilation . This is centrally mediated, and mostly seen after a large drug bolus. It can be treated with muscle relaxants.

Special precautions: Respiratory depression is dosage related and can be reversed by the specific narcotic antagonist, naloxone. A repeated dosage of the antagonist may be necessary because the duration of respiratory depression may last longer than the duration of action of the opioid antagonist. Marked respiratory depression accompanies profound analgesia. It can persist into the post-operative period, and if sufentanil has been given intravenously it can recur. Therefore patients should remain under appropriate observation. Resuscitation equipment and narcotic antagonists should be readily available. Vital signs should be monitored routinely.

3.6.6 DRUG INTERACTIONS

Barbiturates, benzodiazepines, and other central nervous system depressants (e. g. alcohol) can have synergistic cardiovascular, respiratory and sedative effects with opioids. When patients have received central nervous system depressants, the dosage of sufentanil required will be less than usual.

The combination of opioids and monoamine oxidase inhibitors may result in respiratory arrest, hypertension or hypotension, coma and hyperpyrexia. To prevent this, monoamine oxidase inhibitors should be discontinued two weeks prior to the administering of sufentanil.

3.6.7 PERSONAL EXPERIENCE

Sufentanil does not produce reliable sedation without significant respiratory depression. Therefore the author uses sufentanil in combination with propofol, midazolam and ketamine. This combination of drugs also allows one to use small dosages of the opioid.

3.7 MEPYRAMINE MALEATE [ANTIHIST®]

The discussion of mepyramine maleate is based on the approved package insert (Annexure P).

3.7.1 CHEMICAL STRUCTURE

Mepyramine acts as an H1 receptor-antagonist with anti-allergy properties. It is presented in 2ml brown glass ampoules. Each millilitre contains 25mg mepyramine maleate. The chemical group of mepyramine is an ethylenediamine (Reynolds 1993:926).

The antihistamines have become useful agents for sedation and analgesia. They produce drowsiness, potentiate the sedative effects of the BZD, have anti-allergic properties, and prevent nausea and vomiting. Care must be taken in the elderly as the drugs may cause extra pyramidal symptoms.

3.7.2 PHARMACODYNAMICS

Mepyramine maleate can have the following effects:

- It can cause ventricular arrhythmias, and in high dosages bradycardia followed by tachycardia.
- In the respiratory system antihistamines show some anticholinergic activity, and this decreases secretions in the lung and sinuses, and thereby inhibit drainage and promote stasis.
- In the central nervous system sedation is a side-effect of some antihistamines. Some patients may show central nervous system stimulation, specifically in children.
- Secondary to antimuscarinic effects, patients can have a dry mouth.
- Urinary retention can occur, also secondary to antimuscarinic effects.
- The above side-effects are rarely seen with the low dosages we use for sedative purposes.

Mechanism of action: Mepyramine acts as a competitive antagonist to histamine at the H1 receptors. The antigen-antibody reaction or other histamine-liberating stimulus is unaltered, but the histamine is prevented from acting on the effector organ (Meyers, Jawetz & Goldfien 1972:177).

3.7.3 PHARMACOKINETICS

Absorption: The antihistamines are well absorbed after oral administration. After oral administration onset of action is between 10 to 30 minutes. In this study the mepyramine was used parentally, which bypasses first pass metabolism.

Metabolism: Antihistamines are metabolized in the liver and kidney.

Elimination: Antihistamines are excreted by the kidneys.

3.7.4 DOSAGE AND DIRECTIONS FOR USE

The different antihistamines have different dosages. The newer antihistamines have longer dosage intervals. In this study mepyramine was used intravenously in very small total dosages of less than 5mg. Mepyramine maleate 1mg was added to the sedation mixture that was used in the infusion pump. In adult patients the dosage for use as an antihistamine in case of treatment or prevention of an allergic reaction is 25 to 50mg intramuscularly or intravenously.

3.7.5 SIDE EFFECTS AND SPECIAL PRECAUTIONS

According to Reynolds (1993:926-927) the following side-effects can occur:

- Mepyramine exhibits central nervous system activity. The most common side-effect is sedation, ranging from mild drowsiness to deep sleep. When practising sedation, it is this side-effect that we use to our advantage.
- Other side-effects can include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea or constipation and epigastric pain when used orally.
- Headache, tinnitus, nightmares, dryness of the mouth and tightness in the chest may occur.
- Paradoxically, you can get central nervous system stimulation, especially in children.
- Hypersensitivity reactions may also occur.
- Very rarely blood disorders have been reported.
- Because of antimuscarinic properties, it should be used with caution in patients with closed-angle glaucoma, urinary retention, prostatic hypertrophy, and pyloro-duodenal obstruction.
- Elderly patients and those on antidepressants may get extra pyramidal symptoms and signs when antihistamines are used.

3.7.6 DRUG INTERACTIONS

Antihistamines may enhance the sedative effects of central nervous system depressants like alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and neuroleptics. MAOIs may enhance the antimuscarinic effects of antihistamines. Antihistamines have an additive antimuscarinic action if used with other antimuscarinic drugs, such as atropine and tricyclic antidepressants.

CHAPTER FOUR

RESEARCH DESIGN AND METHODOLOGY

The previous discussion shows the obvious need for research on combinations of drugs for intravenous sedation in children to be done.

4.1 PATIENT SELECTION

Two hundred and two children who were healthy and under 10 years of age, and who needed dental treatment under sedation, were selected for this study. Two children were excluded because the intravenous cannula could not be placed in one child, and in the other child the sedation was stopped because the child was unmanageable. These two patients accounts for the 1% failure rate in this study. The remaining 200 patients were included in the data of this study.

Sedation and dental treatment took place in a fully equipped dental surgery, meeting all the criteria for sedation outside the operating theatre, with all back-up systems in place in case rescue was needed.

The dentists selected the patients who needed sedation for the procedure. Two hundred children, male and female, were recruited for the study that lasted 2 years. Only ASA I and ASA II patients (healthy patients) qualified for selection for sedation outside the operating room. Patients with short term illnesses, especially upper respiratory tract infections were postponed for at least 4 weeks.

4.2 INSTRUCTIONS TO PATIENTS

- All patients received verbal as well as written instructions, and information on the dental and sedation procedure.
- They were also informed about the research project.
- The ethical statement (Annexure B) as well as a consent form (Annexure A) was signed by the parent or legal guardian.
- A medical history questionnaire was given to the parent to complete before any pre-medication was given.
- All children were nil per mouth for at least 4 hours before the procedure. If they had anything to eat or drink within 4 hours of the procedure, the operation was cancelled.
- Transport was available to take the children home when they were ready to go after the procedure.

- A responsible adult, preferably the parent or legal guardian, accompanied the child home.
- Full post-operative instructions, were given verbally as well as written information (Annexure C).
- The parents were informed about the recovery process, the time it would take for the drugs to wear off, and the supervision needed once they were home.
- Possible side effects of the drugs used, like nausea and vomiting, disorientation, sleepiness, double vision, amnesia, as well the numbness around the mouth because of the local anaesthetic were discussed.
- Contact telephone numbers of both the dentist and sedation practitioner were given to the parents in case they wanted to discuss or report anything.

4.3 PRE-SEDATION MEDICATION

- All children were given an Emla local anaesthetic patch to put over a suitable vein on the hand or in the cubital fossa 2 hours before the procedure. The Emla patch contains a mixture of lignocaine and prilocaine, which numb the skin for painless cannulation of a vein. This we use to minimize the trauma that can result from cannulation. Instructions were given to the parents on how to use the patch correctly as this was quite important to make the intravenous cannulation a painless procedure.
- All children had to be at the surgery 30 minutes before the procedure. Here they received oral midazolam, a sedative, for pre-sedation medication.
- It was ensured that the children fasted according to the guidelines.
- Children younger than 6 years received 3.75mg (half a tablet) of midazolam orally. Children older than 6 years received 7.5mg of midazolam orally. The children were given the tablet to swallow with 10 – 15ml of clear water. If they were unable to swallow the tablet, they were then instructed to chew the tablet and then swallow it with water. In the few children who refused to take the tablet, the parenteral solution was used. The parenteral solution was given at a dosage of 0.5mg/kg to a maximum of 5mg. It was mixed with paracetamol or ponstan syrup to mask the taste of the midazolam. Children under 2 years of age did not receive any premedication. If the child was not co-operative after the midazolam pre-medication, ketamine 2mg/kg was added orally. The parenteral solution was used. This was mixed with paracetamol or ponstan to mask the taste of the ketamine.
- The drug was administered in the dentist's room and not at home. Patients react very differently to midazolam, and their level of sedation varies individually. Therefore the pre-medication must be administered under supervision of the sedation practitioner.

- An important aspect of a successful sedation technique always is behaviour management. This can be challenging in a child. You have to make contact with your patient on their level, and not be intimidating. Explaining to the children and parents what you were going to do, goes a long way in ensuring them that they are not going to be hurt. It's all about gaining their trust.

- All patients were covered with a blanket to comfort them, as well as to keep them warm.

4.4 BOLUS SEDATION PROCESS

Boluses of drugs were used for shorter procedures such as extractions for orthodontic indications and small fillings. These procedures were 15 – 30 minutes in duration.
The drugs used were midazolam and ketofol. Ketofol is made up of a mixture of ketamine and propofol.

In this bolus sedation technique, the children received 0.5 mg of midazolam intravenously and 1ml of ketofol. An additional dosage of 0.5mg midazolam and 1ml of ketofol was titrated to effect if necessary. If the procedures lasted longer than 10 to 15 minutes, the ketofol dosage of 1ml was repeated when necessary. Bolus sedation techniques for children for short procedures are often used in the sedation world and have become very popular.

4.5 USING AN INFUSION PUMP

Procedures lasting longer than 30 minutes were done with this technique using an infusion pump. It is well known that we have better control over drug administration as well as more predictable sedation levels when using infusion pumps. The children also received a bolus of midazolam 0.5 – 1mg, glycopyrrolate 0.5ml (0.1mg) and before local infiltration of the local anaesthetic agent, ketamine 0.25mg/kg intravenously. The infusion rate of drugs with the infusion pump was set according to their weight in mg/kg. The following drugs were drawn up in a 20ml syringe which was administered through the infusion pump:

- propofol 100mg (10ml),
- mepyramine maleate 12.5mg (0.25ml),
- ketamine 25mg (0.5ml), and
- sufentanil 2.5µg (0.5ml).

This mixture was made up to 12ml with sterile water. Each ml of solution contained propofol 8.3mg, mepyramine maleate 1mg, ketamine 2mg and sufentanil 0.2µg.
Of this mixture children received a bolus of 0.5mg/kg and then the pump was set between 1-4 mg/kg/hr, where the propofol was used to calculate dosages. In this study a multidrug infusion technique was used. To be able to administer the multidrug mixture in one

infusion pump, all the different drugs were mixed together as described in the previous paragraph. To be able to calculate dosages, only one drug in the syringe is used as a reference. In this mixture the propofol was used as reference for calculating the dosages.

4.6 MONITORING

The children were monitored throughout the procedure with a Welch Allyn Propac LT® haemodynamic monitor, measuring pulse rate, oxygen saturation, blood pressure, respiratory rate, and a 3 lead ECG tracing. The level of sedation (LOC) according to the Wilson scale (Annexure G), was also continuously monitored by the sedation practitioner who was present during the whole procedure.

The ideal would be to use a Bispectral Index (BIS) monitor, which measures LOC in patients. Unfortunately these monitors are very expensive and not readily available outside the hospital setting. These monitors have not been validated for sedation. It is also difficult to place electrodes on the heads of children as this may make them very anxious.

All patients were left to sleep undisturbed for 30 minutes after the procedure. If their observations were back to normal after 30 minutes they were sent home with written and verbal instructions. The Steward scale (Annexure F), was used as an indication for discharge criteria. BP, pulse rate, respiratory rate and saturation levels were monitored before induction and every 10 minutes during the procedure. The last reading was done before the child was left in their parents care. The ECG was monitored continuously.

4.7 FACILITIES FOR RESUSCITATION

Resuscitation equipment was unpacked and ready to use with every procedure. This included: oxygen, ambubag, airways, endotraceal tubes, laryngeal masks, laryngoscope, suction catheter, defibrillator and emergency drugs as stated in all international guidelines . Drugs used as reversal agents for the opiates and midazolam, namely naloxone and flumazenil were readily available. Facilities need to be available if an escalation in care occur.

4.8 EVALUATION CRITERIA

All patients were evaluated during sedation and surgery using the following criteria:

1. Age.
2. Gender.
3. Medical History.
4. Weight.
5. Reasons for Surgery.

6. Pre-sedation Medication Received.
7. Ease of Cannulation.
8. Comparison of Sedation and Surgery Time.
9. Sedation Level according to the Wilson Sedation Scale.
10. Observations.
11. Steward Recovery Score.
12. Surgeon Evaluation.
13. Sedation Practitioner Evaluation.
14. Parent Evaluation.

All these different parameters were analyzed to evaluate the safety and efficacy of techniques used. Results are discussed in the following chapter.

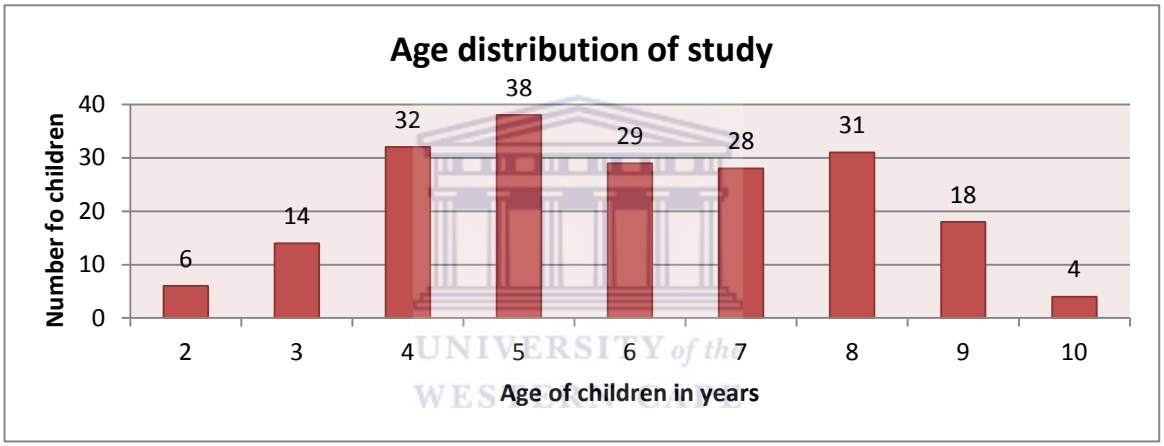
CHAPTER FIVE

RESEARCH FINDINGS AND ANALYSIS

The research findings and analysis will be discussed and mainly presented in graphic format.

5.1 AGE

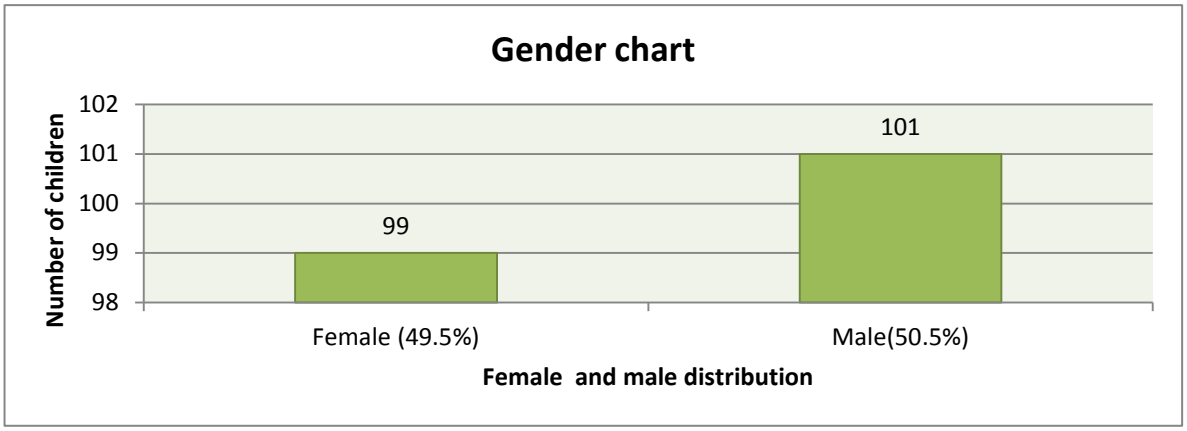
This study was done on children between the age groups of two to ten years of age. The graph shows that the largest group of children were between four to eight years of age. There were six children included in the study who were two years old. These children were evaluated before the procedure to ensure that their airways were suitable for a sedation procedure. The average age in this study was 5.9 years and the median age was 6 years.



Graph 5:1

5.2 GENDER

The gender ratio was almost 50:50 with 101 male patients and 99 female patients as shown in the graph below.

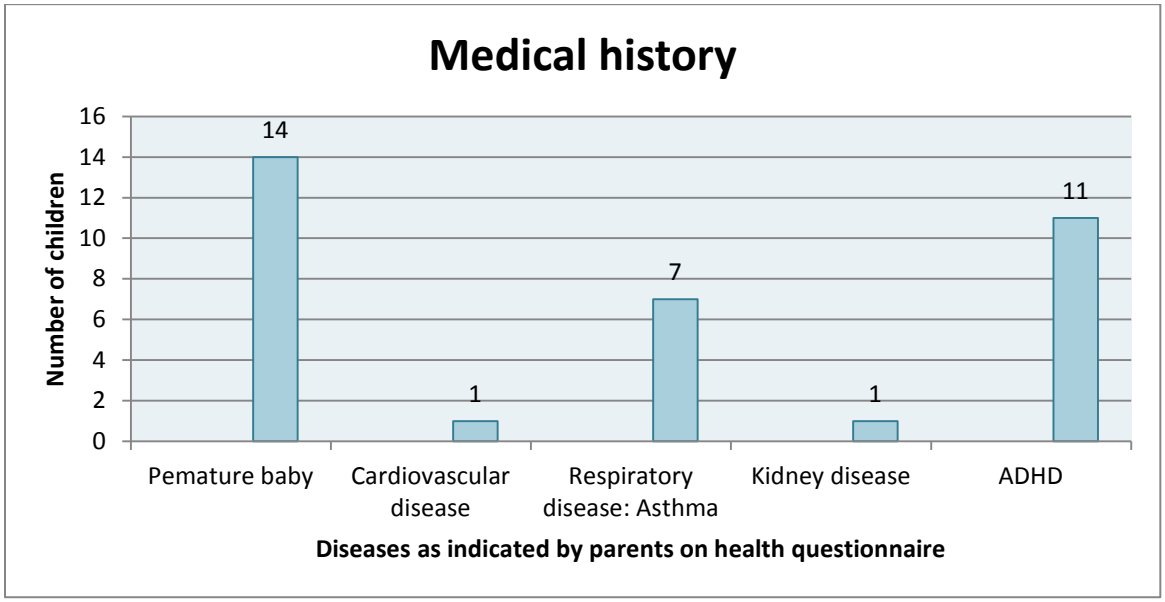


Graph 5.2

5.3 MEDICAL HISTORY

For sedation outside an operating room, only ASA 1 and 11 patients should qualify according to all international guidelines on sedation. This is a very important rule to adhere to, specifically when working with children. This is supported by our local sedation guidelines for children. The following graph shows interesting reading as to medical disease reported by parents or guardians on the medical history questionnaire:

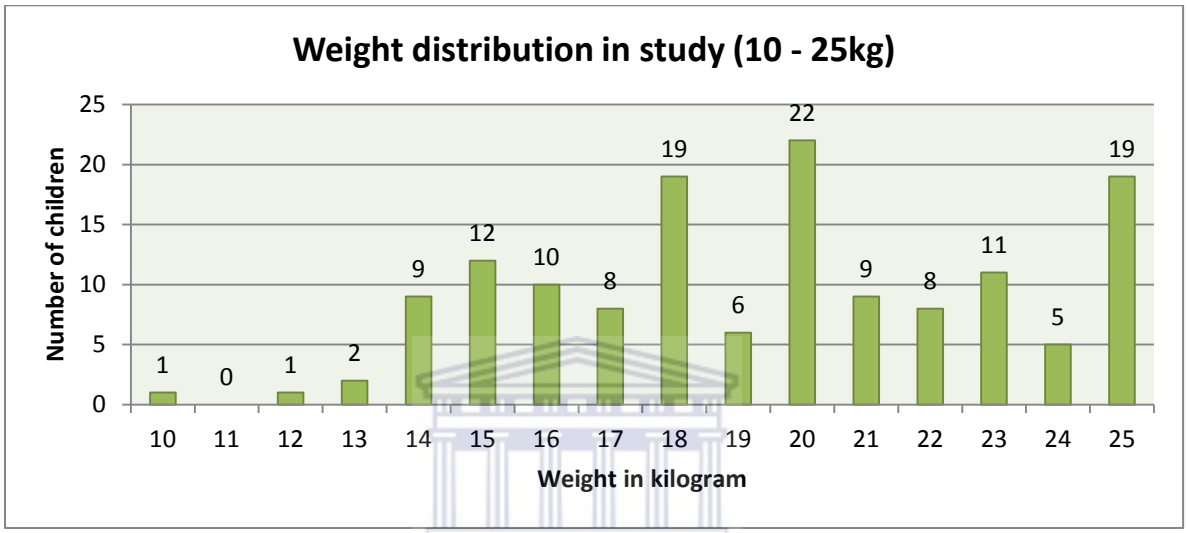
- Fourteen of the children were born as premature babies. All international guidelines caution about the wisdom of doing those cases outside the operating room.
- The one child who had cardiovascular disease had a one out of six heart murmur. She was six years old and was seen by a paediatric cardiologist. She never had any invasive cardiac procedures and was not on any medication. She could perform any physical activity according to her age, and was therefore classified as an ASA 2 patient.
- Seven of the children included in the study had asthma. All of these children were on medication that controlled their symptoms. On the day of the sedation, these children were well with no coughing or wheezing. The sedation procedures in these children were all done without any respiratory adverse events, and no oxygen was used.
- One of the children had kidney disease. This child was born with one kidney. Kidney function was normal.
- Eleven of the children included in the study were on medication for Attention Deficit Disorders (ADHD). Only two of these children were difficult to sedate. These patients are sometimes difficult to work with, but being on methylphenidate hydrochloride or atomoxetine hydrochloride does not necessarily mean that they are difficult to sedate.



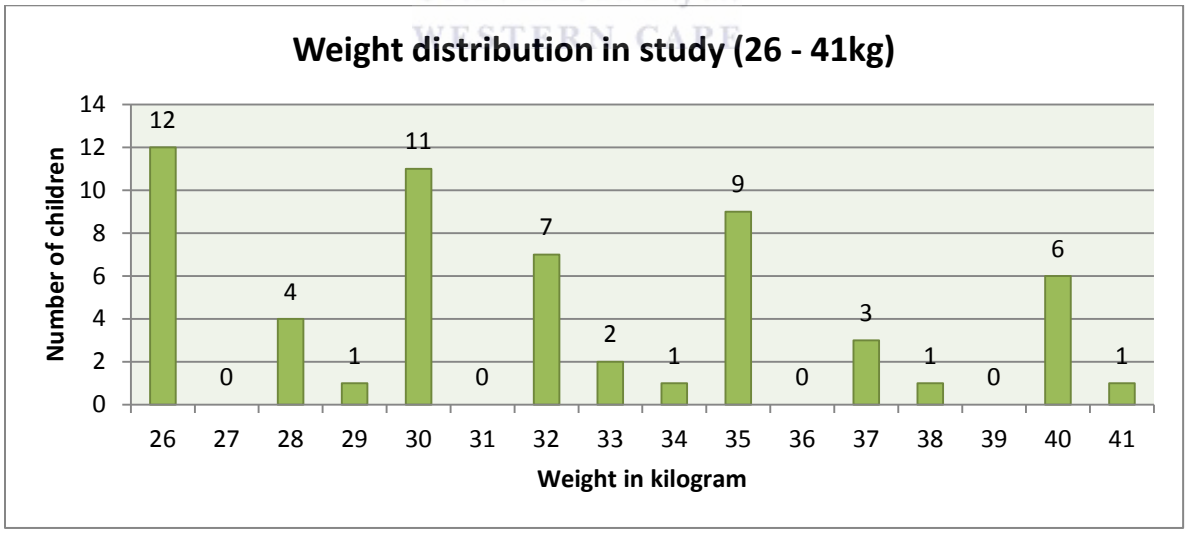
Graph 5.3

5.4 WEIGHT

The weight chart is shown below. None of the children were cancelled because of obesity, but children weighing less than 10kg were not included in this study. The bottom horizontal line of the graph shows the weight in kilogram and the legend above each line shows how many children with the same weight were studied. The first graph shows the weight distribution from 10 to 25kg and the second graph from 26 to 41kg. The average weight was 23.055kg. The median weight was 22kg.



Graph 5.4.1



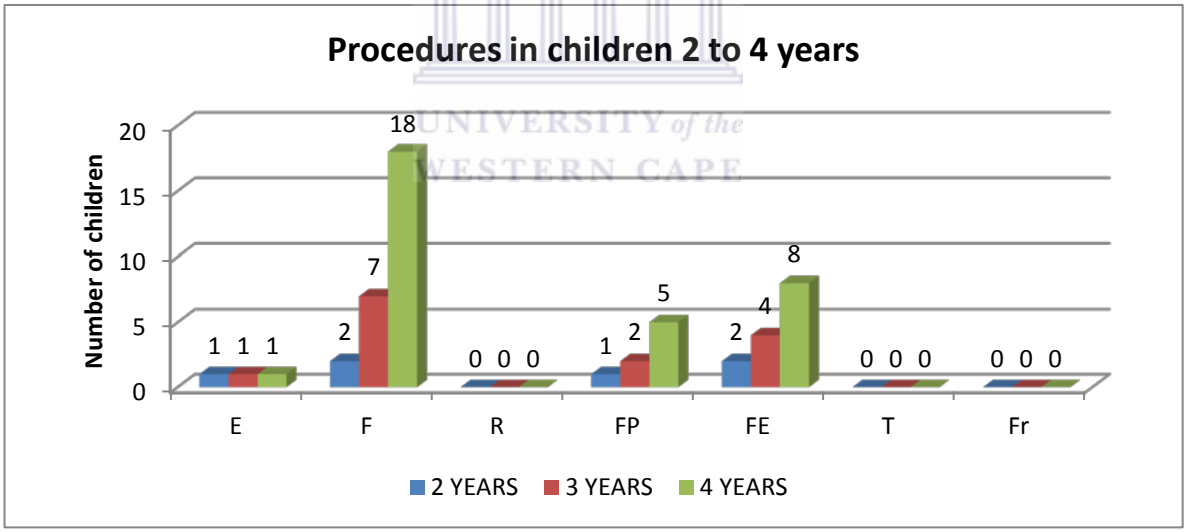
Graphs 5.4.2

5.5 REASONS FOR SURGERY

The indications for surgery and sedation are shown in the following graphs. The children were evaluated according to their age; 2 – 4 years, 4 – 6 years, 7 – 8 years, and 9 – 10 years, with the different procedures done shown.

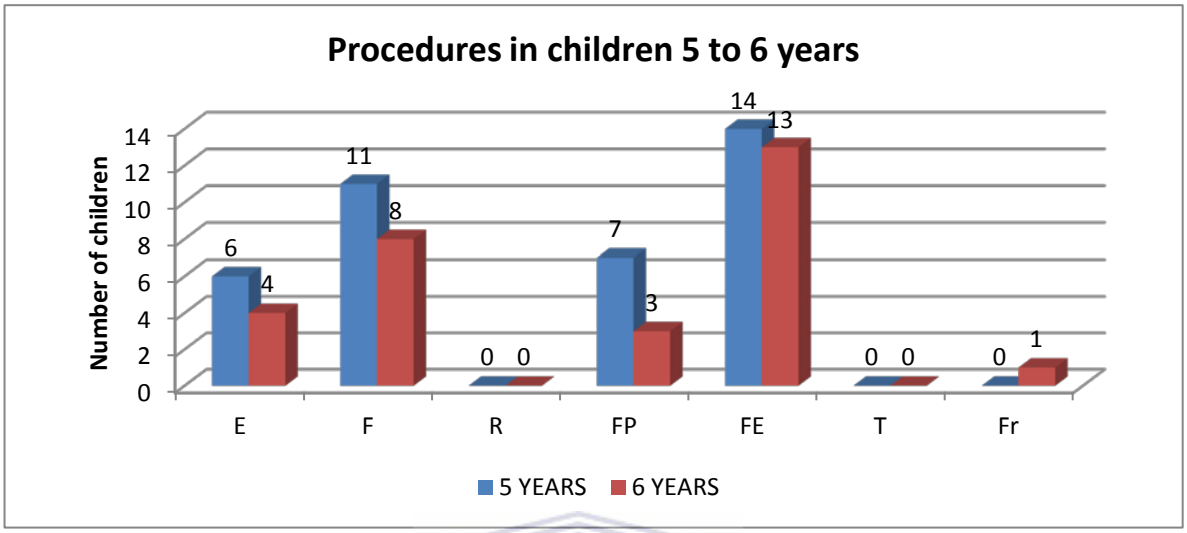
The following legends were used as abbreviations for the type of procedures on the graphs:
E- Extractions,
F – Fillings,
R- Rootcanal,
FP – Fillings and pulpotomy's,
FE – Fillings and extractions,
T – Tooth exposure and
Fr – Frenectomy.

In the age group 2 to 4 years which included 49 children, all the procedures were fillings, or fillings with extractions or pulpotomy's. Only 3 children had only extractions done. Most of the children booked for sedation needed work on multiple teeth. This is quite an interesting observation as it may indicate that more fillings are done in this age group to prevent children losing teeth.



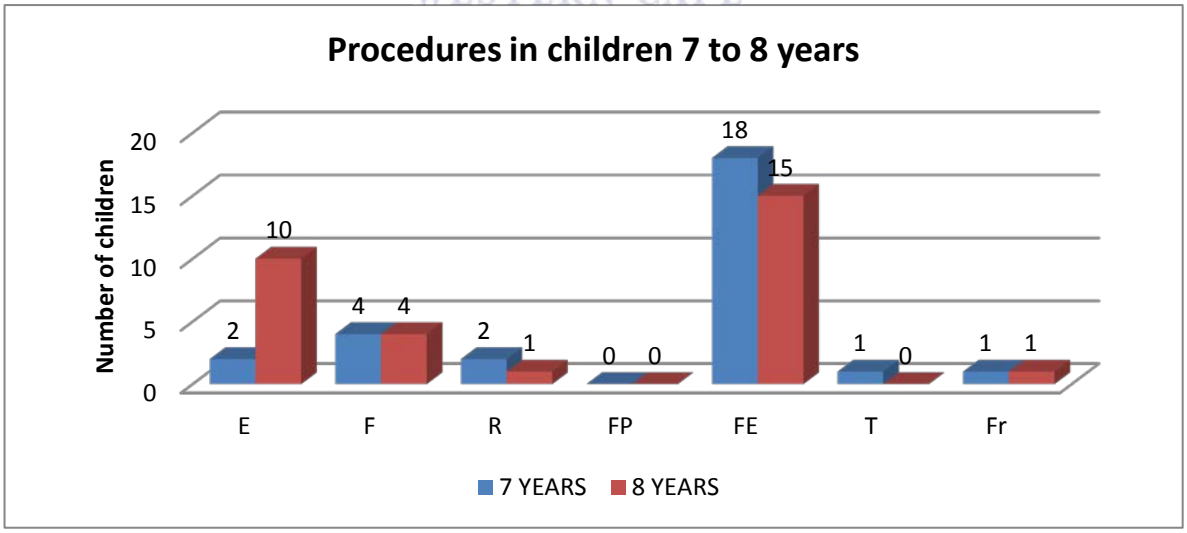
Graph 5.5.1

In the age group 5 to 6 six years there were 67 children. Again in this group the procedures included extractions, fillings, and fillings with pulpotomy's or extractions. One child had a frenectomy done. This procedure is ideally suited for sedation since the administering of the local anaesthetic agent can be quite painful.



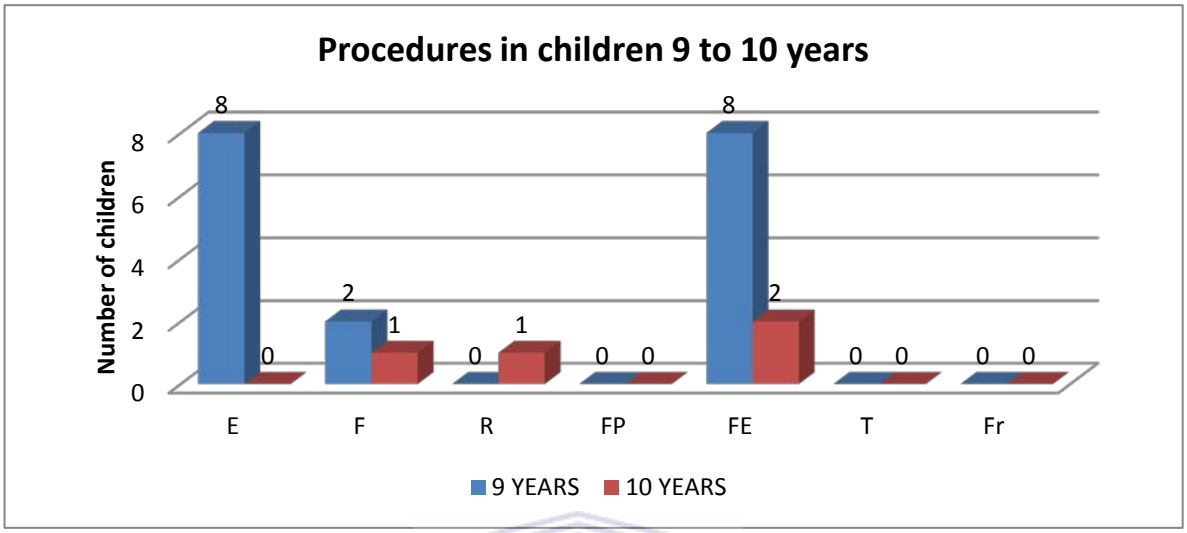
Graph 5.5.2

In the age group 7 to 8 years there were 59 children. In this group the procedures were varied. Extractions, fillings, fillings and extractions and frenectomy's were done. Also included in this group were 3 root canal treatments on the number 6 teeth (first permanent tooth to erupt). One child had a tooth exposure.



Graph 5.5.3

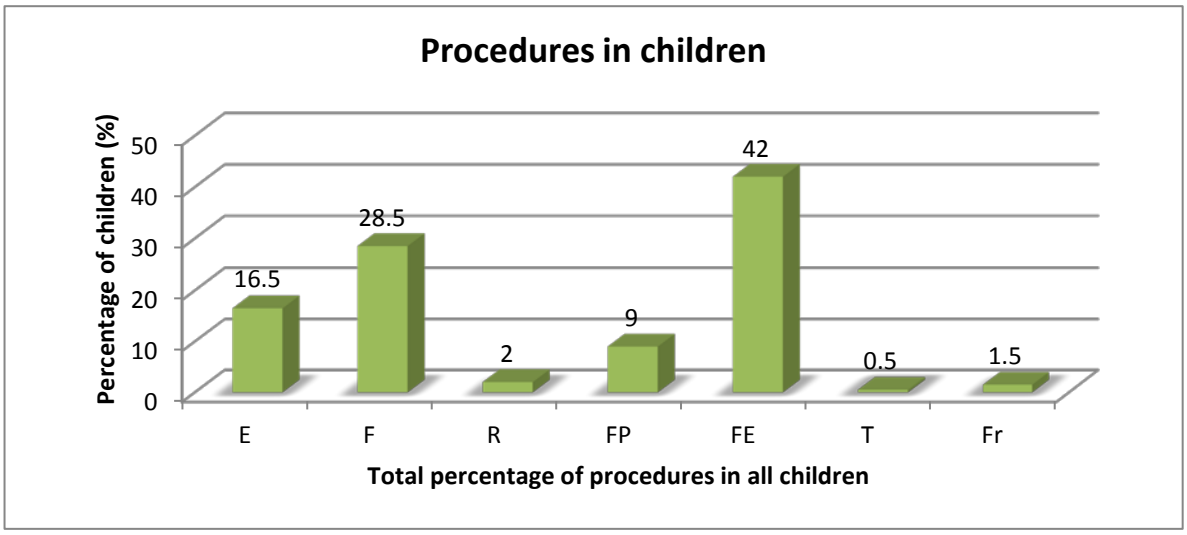
The group 9 to 10 years only included 22 children. The smaller number of children is an indication that the older the children are, the better they co-operate for dental treatment. The indications for extractions included orthodontic extractions in this group. Only one child had a root canal treatment.



Graph 5.5.4

When we look at the overall picture in graph 5.5.5 we see that:

- 37.5% of the sedations were done for fillings or fillings with pulpotomy's
- 58.5% of the procedures were done for extractions or extractions and fillings
- 1.5% frenectomy's
- 2% root canal treatments
- 0.5% tooth exposure



Graph 5.5.5

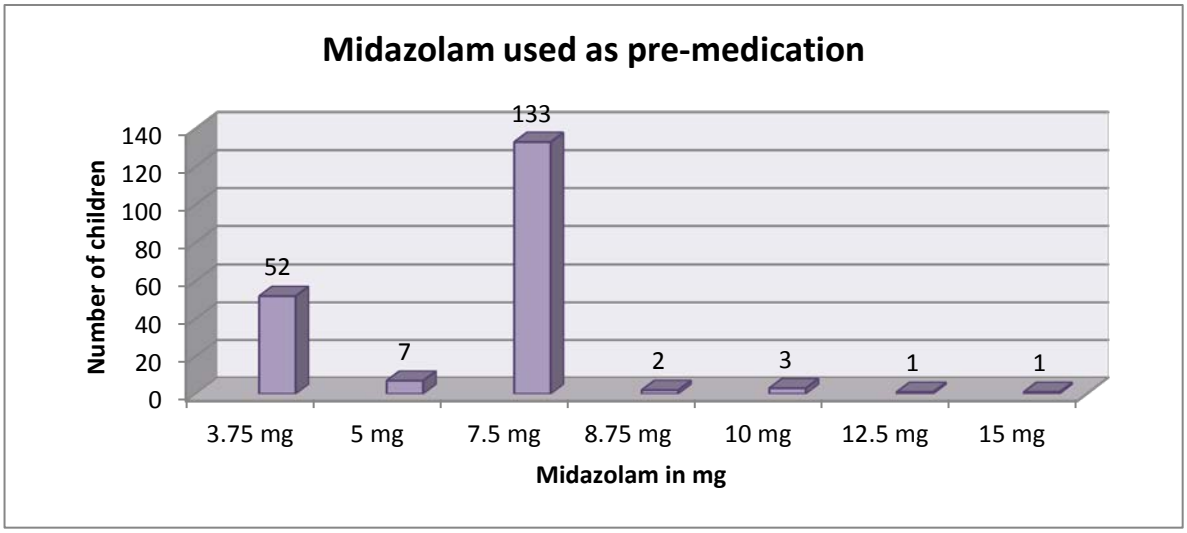
5.6 PRE-SEDATION MEDICATION RECEIVED

Pre-sedation medication was given to all the children. Although this is a controversial topic we felt it best that children be calm and relaxed when they enter the dental surgery. Many children had traumatic experiences in the past therefore sedative drugs can be very helpful in these cases; amnesia is useful. We understand that there is no ideal sedative drug yet available but overall midazolam does offer benefits.

The following dosing schedule was used:

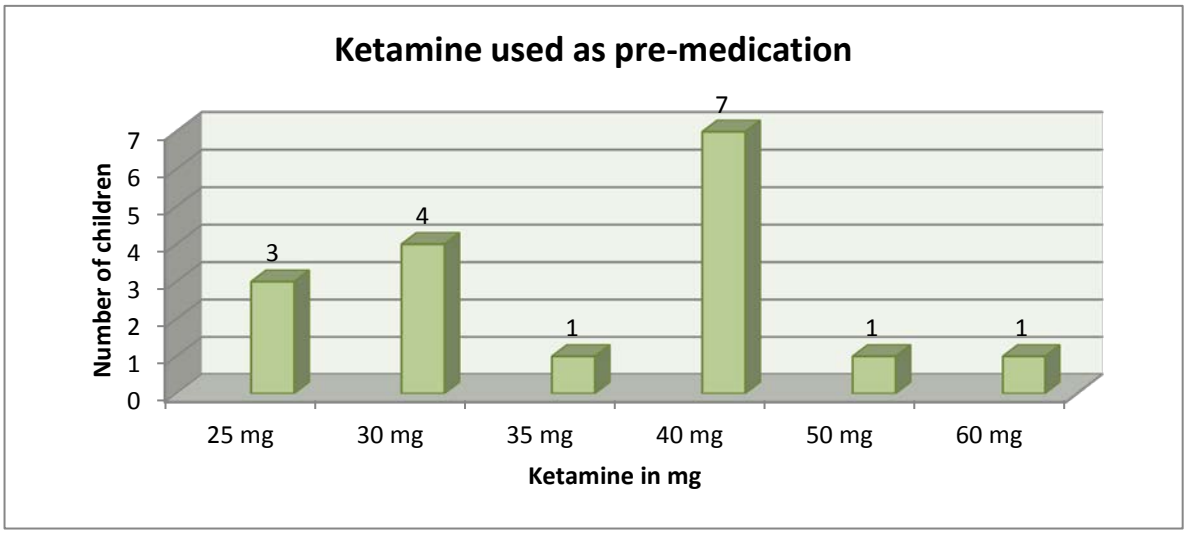
- Children under the age of six years received midazolam 3.75mg. This was given as half a 7.5mg tablet (the normal size) that could either be swallowed or chewed. A small amount of water was given to the children to swallow the tablets.
- Children older than six years of age received a 7.5mg tablet of midazolam.
- If the children were unable to swallow the tablet, they were given the same dosage of the aqueous solution mixed with 3ml (30mg) of mefenamic acid to hide the bitter taste.
- In one case midazolam was not used, because the child had a previous exposure to midazolam with a paradoxical reaction, where he became severely hyperactive. This child only received ketamine per os as pre-sedation medication.
- Sixteen children received a second dosage of pre-sedation medication, because they were un-cooperative with the midazolam pre-medication alone. These children received midazolam liquid solution and ketamine mixed together with mefenamic acid or paracetamol syrup. The ketamine was administered at a dosage of 2mg/kg. With this regime only two children were cancelled, because the intravenous line could not be introduced.

The pre-sedation medications administered, are shown in the following graphs. The first graph (5.6.1) shows the total amounts of midazolam that was used. Sixteen of the children required a second dosage of pre-medication, and the total dosages of midazolam are displayed.



Graph 5.6.1

The second graph (5.6.2) shows the oral ketamine that was given together with midazolam as a second dosage of pre-sedation medication for the unco-operative children. One of these children received only ketamine because of a reciprocal reaction to midazolam.



Graph 5.6.2

5.7 EASE OF CANNULATION

Cannulation can be a traumatic experience in children. We therefore advise mothers to place an EMLA patch over a vein to anaesthetise the skin.
The quality of cannulation was evaluated in every patient.
The following scale was used to evaluate the comfort of placement of the intravenous cannula.

Easy	0	
Difficult	1	
More than one puncture	2	
Impossible, sedation cancelled	3	

Table 1

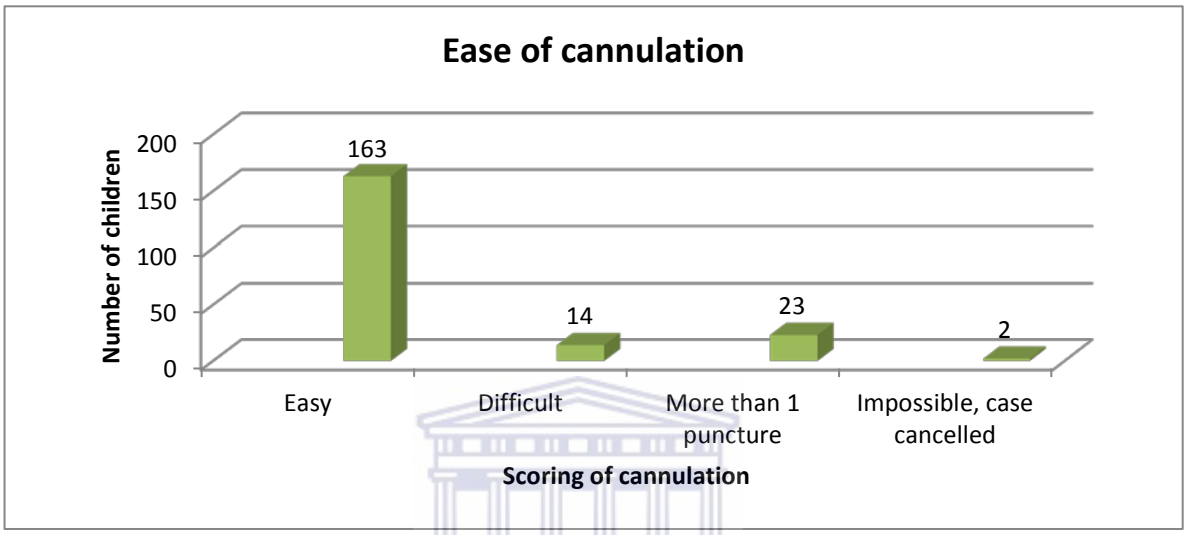
The cannulation was evaluated as easy when the child was calm and co-operative, and the cannula was placed within 2 minutes. Difficult cannulation was noted when the child was anxious and apprehensive, and even crying, and the cannulation took more than 5 minutes.

With the use of proper pre-medication and the use of Emla patches, most of the children allowed a second attempt to place the cannula, if the first attempt was unsuccessful. Only two cases were cancelled because intravenous cannulas could not be placed successfully. Both these children had histories of hospital admissions with difficulty in placing intravenous lines.

Looking at graph 5.7, the cannulation process was rated as follows:

- 80.7% were easy,
- 6.9% were difficult,
- 11.4% of children needed more than one puncture, and
- 1% was cancelled because the intravenous line could not be placed.

Egelhoff et al. in 1997 [8] concluded that they had a sedation failure rate of one percent, which is the same as the researcher found in this study.



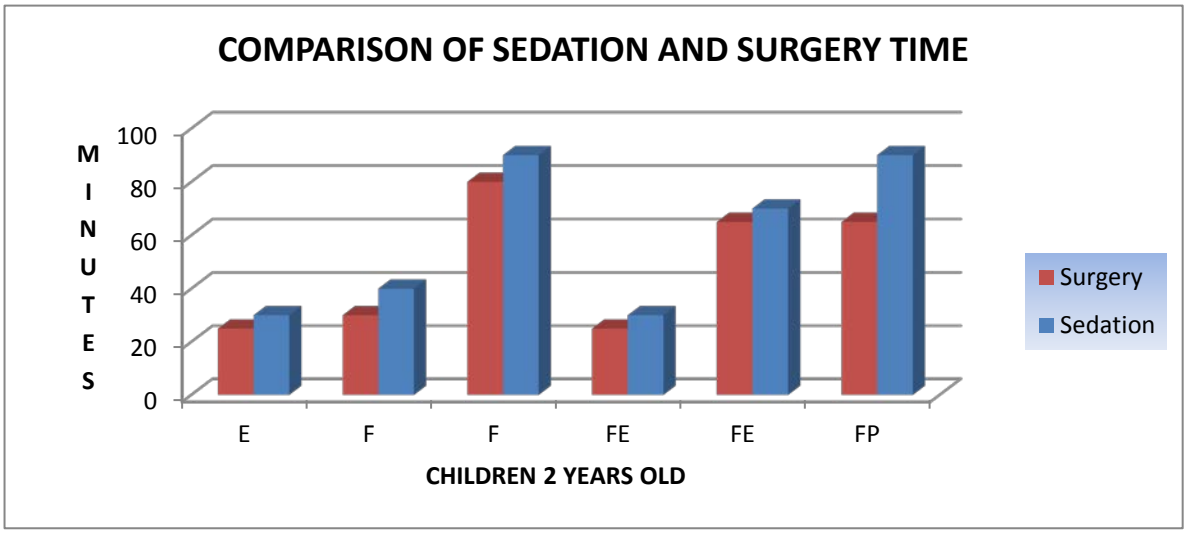
Graph 5.7

5.8 COMPARISON OF SEDATION AND SURGERY TIME

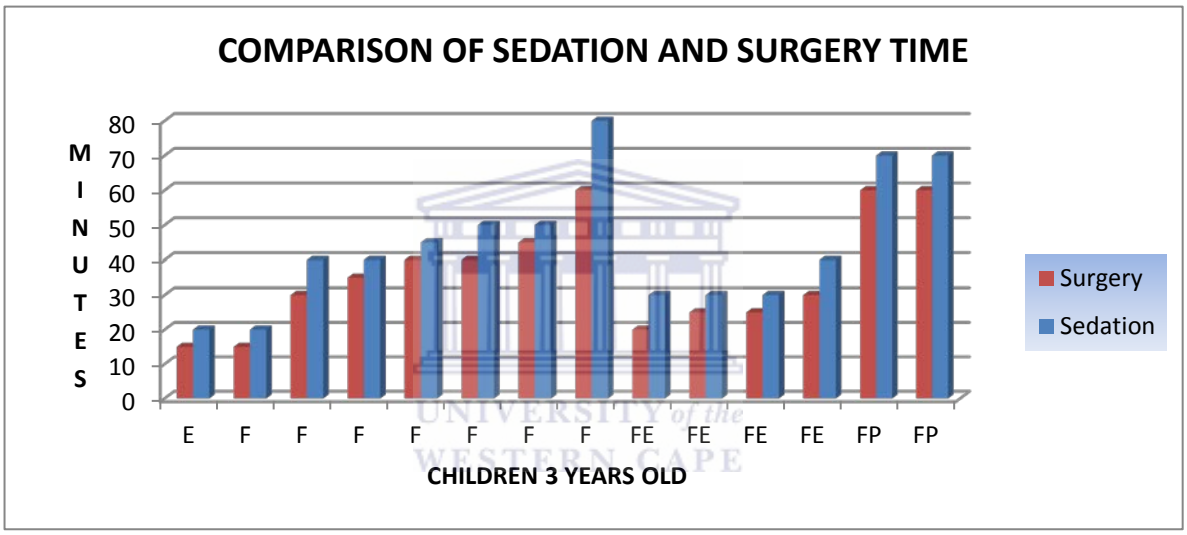
5.8.1 DIFFERENT AGE GROUPS

The following graphs display the sedation and surgery times in the different age groups. The abbreviations that are used on these charts are printed below:

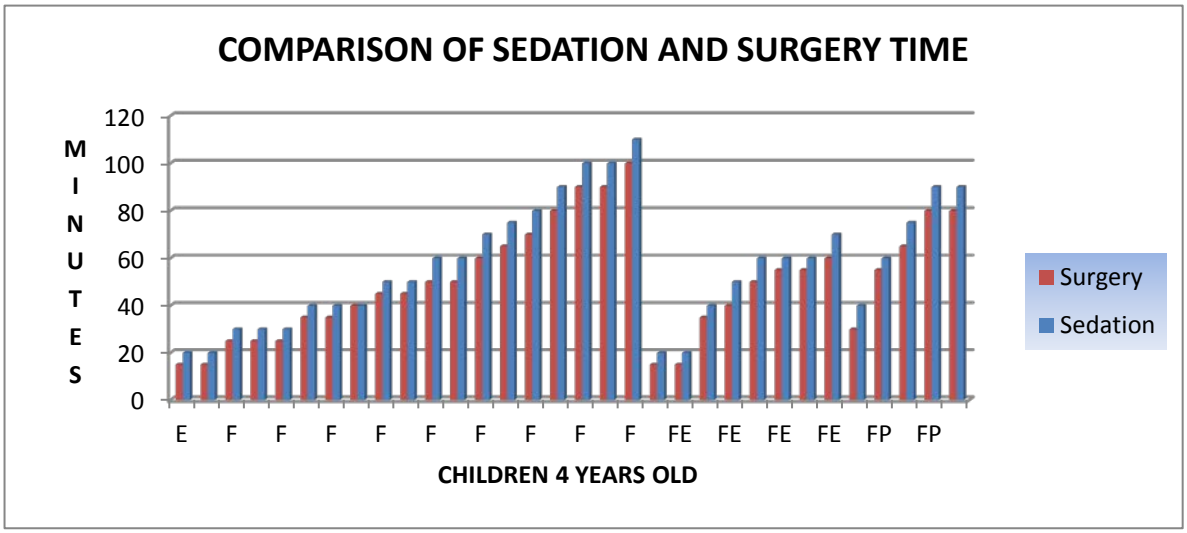
E - Extractions
F - Fillings
R – Root canal
FP - Fillings, and Pulpotomies
FE – Fillings and Extractions
T - Tooth exposures
Fr - Frenectomies



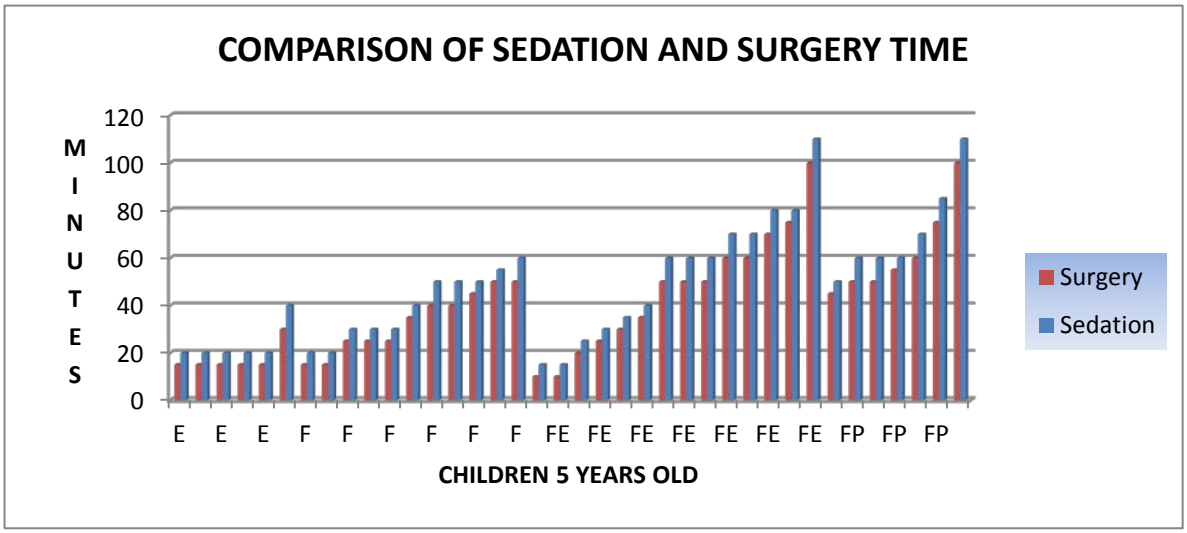
Graph 5.8.1



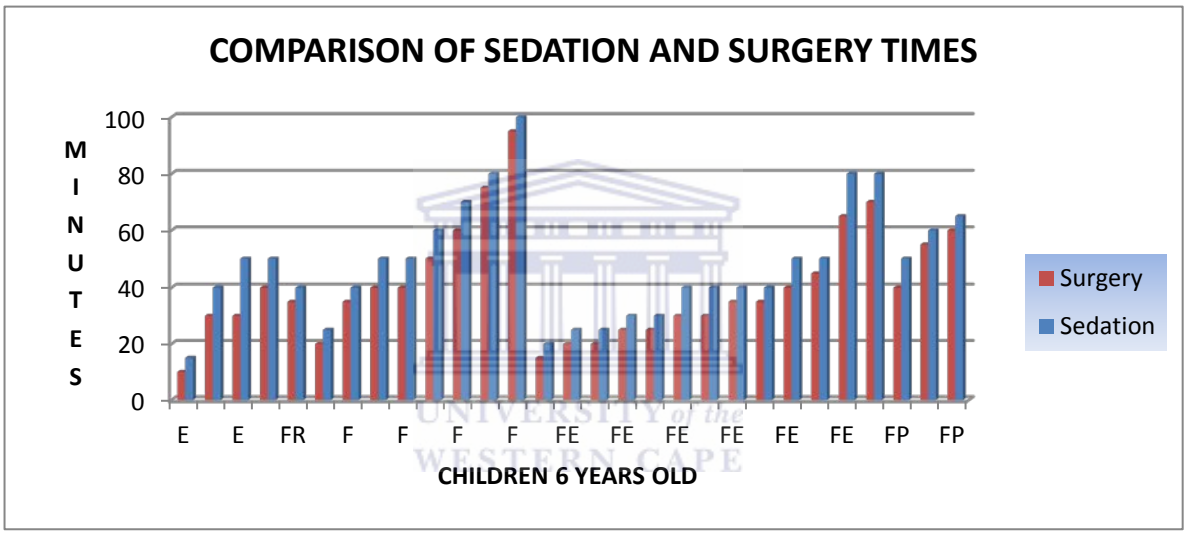
Graph 5.8.2



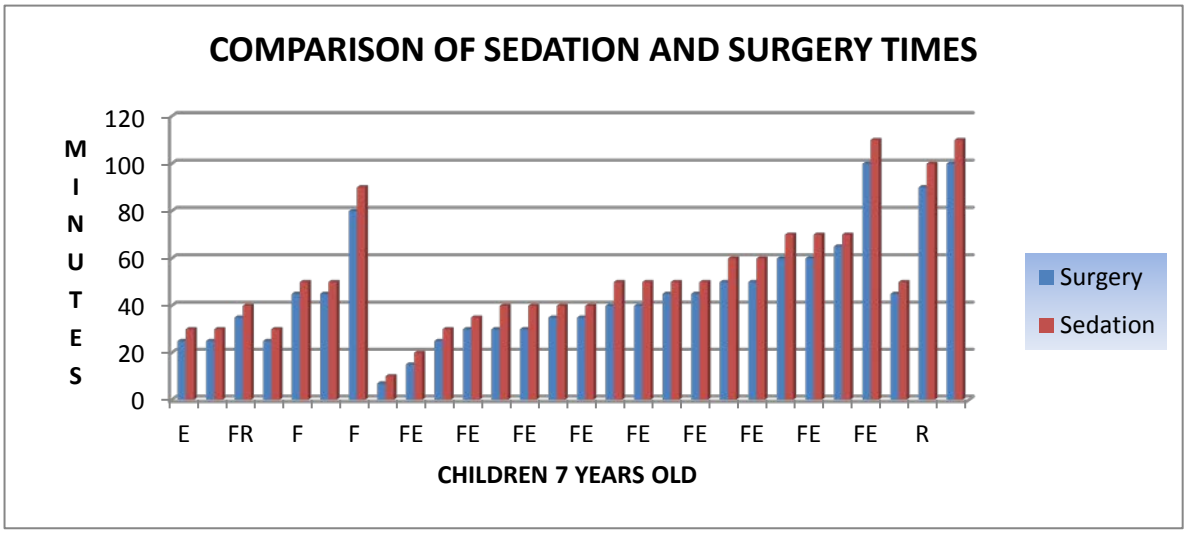
Graph 5.8.3



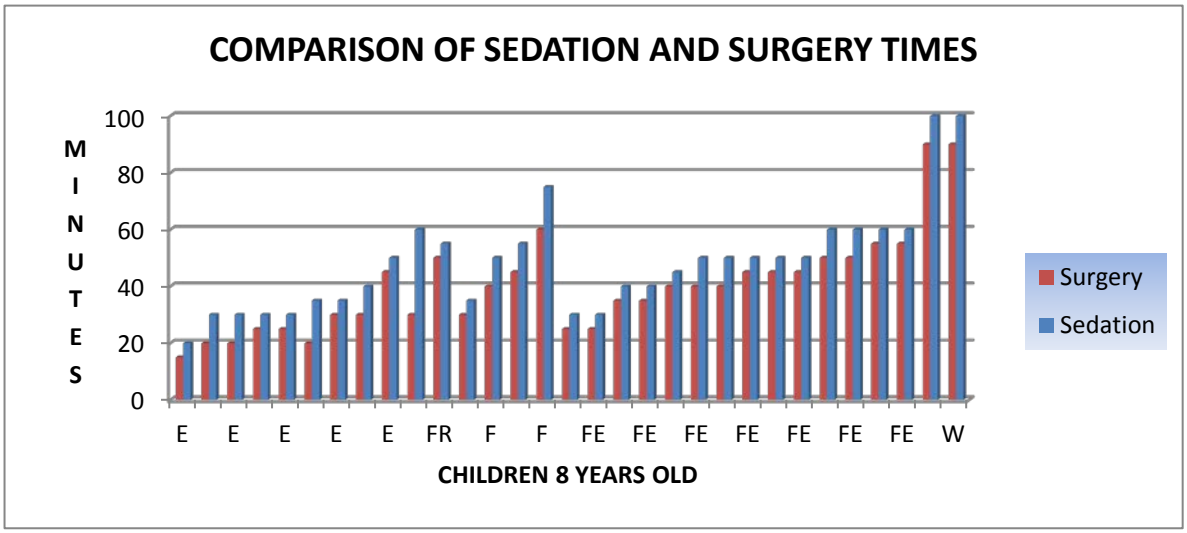
Graph 5.8.4



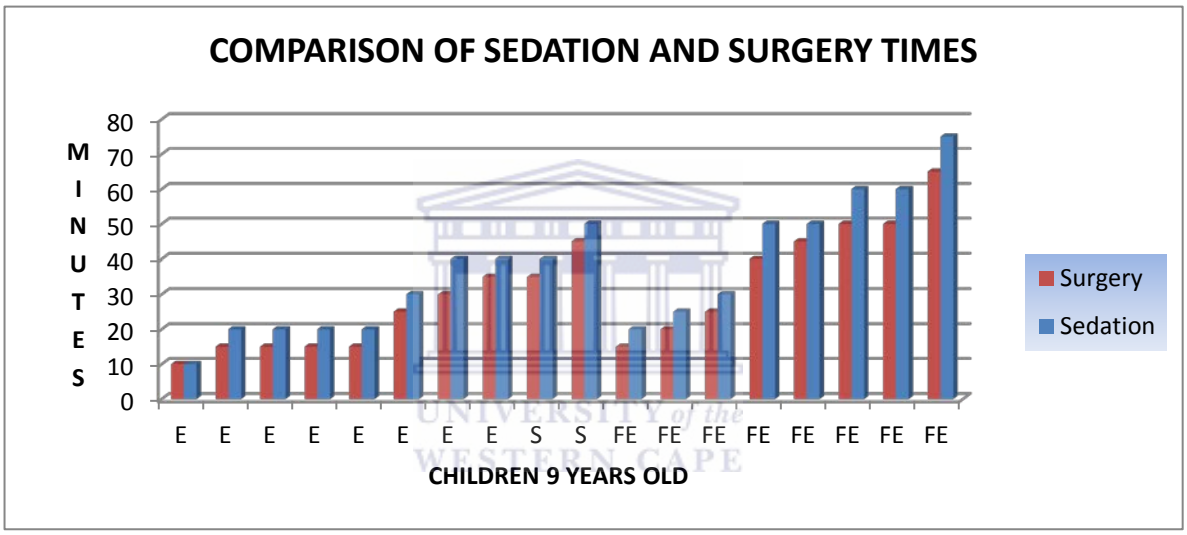
Graph 5.8.5



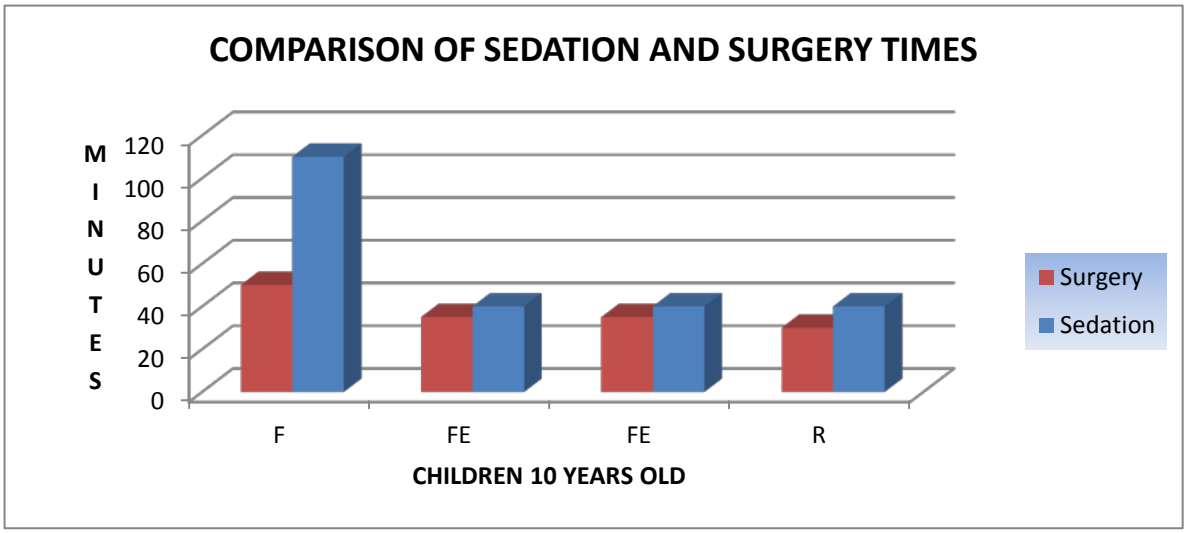
Graph 5.8.6



Graph 5.8.7



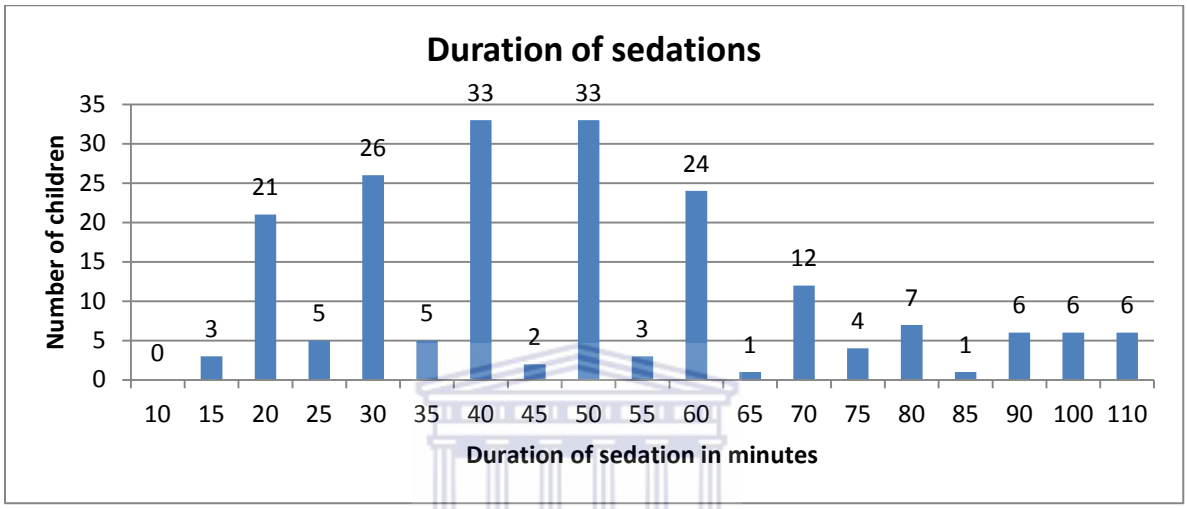
Graph 5.8.8



Graph 5.8.9

5.8.2 DURATION OF SEDATION

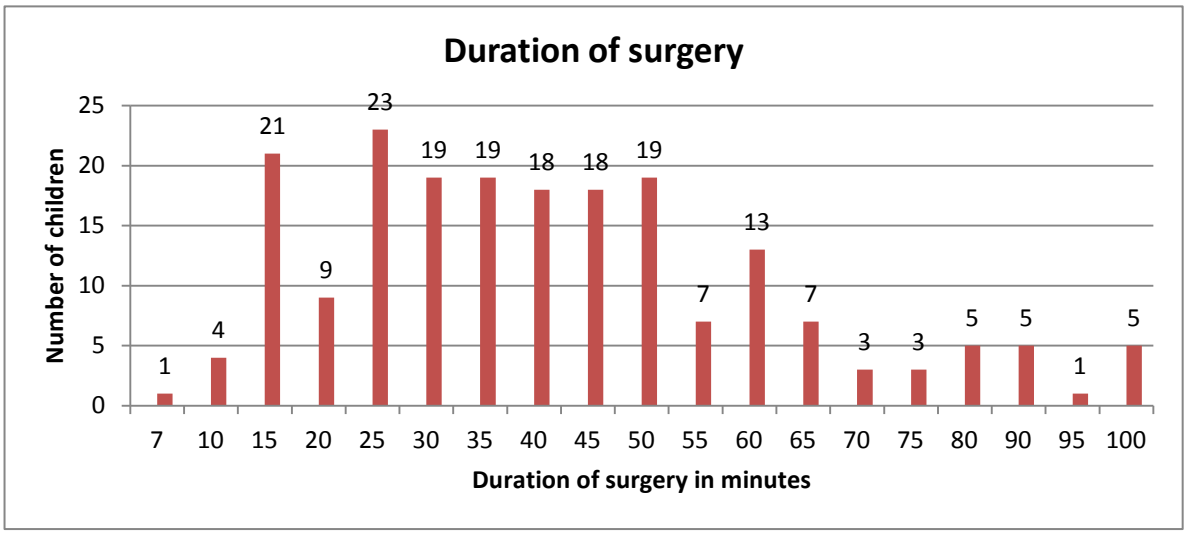
Graph 5.8.10 shows that the sedation times in minutes lasted from as short as 10 minutes to as long as almost two hours. Some of the children tended to get restless if the sedation was very long, and this sometimes made the sedation and the procedure more difficult. Because of this, dentists are advised not to work for more than an hour per case. If there is a lot of work that needs to be done, the parents are also informed before sedation that we might need to finish the work in a second sedation session. If you discuss this possibility before surgery with the parents, they will accept this possibility without hesitation.



Graph 5.8.10

5.8.3 DURATION OF SURGERY

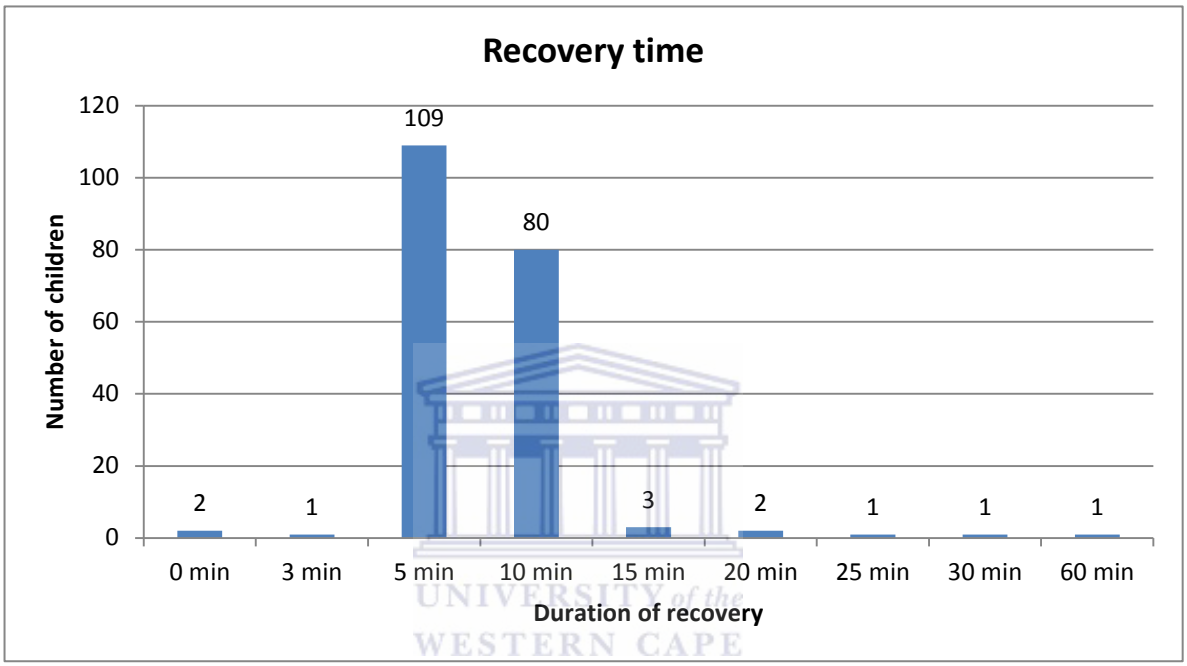
Graph 5.8.11 shows the length of the procedures. It can be seen that most operations lasted less than 60 minutes which is indicative of the excellent planning of dental sedation procedures. In the researcher's practice 30 minutes is added for time booked for each patient. This covers the time from the start of the sedation until discharge criteria is met.



Graphic 5.8.11

5.8.4 RECOVERY TIME

Graph 5.8.12 shows the recovery times of all the patients. Most of the children were opening their eyes or moving their limbs after 5 to 10 minutes. The children were then left in the care of their parents and the recovery staff until they were discharged to go home. One child only recovered after 60 minutes. This child was very difficult to sedate and had excessive movement during the sedation, which required higher dosages of the infusion mixture, which could explain the long recovery time. This is typical of deeper sedation levels; deeper levels will result in longer recovery times.



Graph 5.8.12

5.8.5 CLARIFYING PIVOT TABLE

A clarifying table (p.51), is included that shows the analyzed data concerning the recovery time and types of procedure. The type of procedure has no statistical influence on the time of recovery.

Lepere and Slack-Smith (2002) also did a retrospective study to evaluate the recovery times doing dental sedation. He tried to find a correlation between recovery times, age, weight, procedure type and procedure time. None of the parameters had any influence on the recovery time. No statistical significance was shown.

		REASON							
MF	Values	E	F	S	SE	SP	T	W	Total
F	Count of Diff 'Sedtn - Dur Srgry'	**21**	**1**	**28**	**36**	**9**		**4**	**99**
	Average of Diff 'Sedtn - Dur Srgry'	6.90	5.00	7.50	7.31	8.89		10.00	7.51
	StdDev of Diff 'Sedtn - Dur Srgry'	4.323	#DIV/0!	2.887	2.867	2.205		0.000	3.167
	Min of Diff 'Sedtn - Dur Srgry'	0	5	5	3	5		10	0
	Max of Diff 'Sedtn - Dur Srgry'	20	5	15	15	10		10	20
M	Count of Diff 'Sedtn - Dur Srgry'	**12**	**2**	**29**	**48**	**9**	**1**		**101**
	Average of Diff 'Sedtn - Dur Srgry'	8.33	5.00	9.14	6.98	10.00	5.00		7.97
	StdDev of Diff 'Sedtn - Dur Srgry'	7.177	0.000	10.443	2.471	6.124	#DIV/0!		6.602
	Min of Diff 'Sedtn - Dur Srgry'	5	5	0	5	5	5		0
	Max of Diff 'Sedtn - Dur Srgry'	30	5	60	10	25	5		60
	Total Count of Diff 'Sedtn - Dur Srgry'	**33**	**3**	**57**	**84**	**18**	**1**	**4**	**200**
	Total Average of Diff 'Sedtn - Dur Srgry'	7.42	5.00	8.33	7.12	9.44	5.00	10.00	7.74
	Total StdDev of Diff 'Sedtn - Dur Srgry'	5.466	0.000	7.696	2.636	4.501	#DIV/0!	0.000	5.186
	Total Min of Diff 'Sedtn - Dur Srgry'	0	5	0	3	5	5	10	0
	Total Max of Diff 'Sedtn - Dur Srgry'	30	5	60	15	25	5	10	60

Table 2

If one looks at the recovery times then it is clear that the majority of children recovered within 5 – 10 minutes. This shows that the sedation techniques were well planned and that deep sedation was not done. Most important is that children can be safely done outside the operating room by experienced sedation practitioners.

5.9 SEDATION LEVEL

The sedation levels of the children were evaluated according to the Wilson Sedation Scale which is universally accepted for the evaluation of the level of consciousness (LOC) (Annexure G, p. 103):

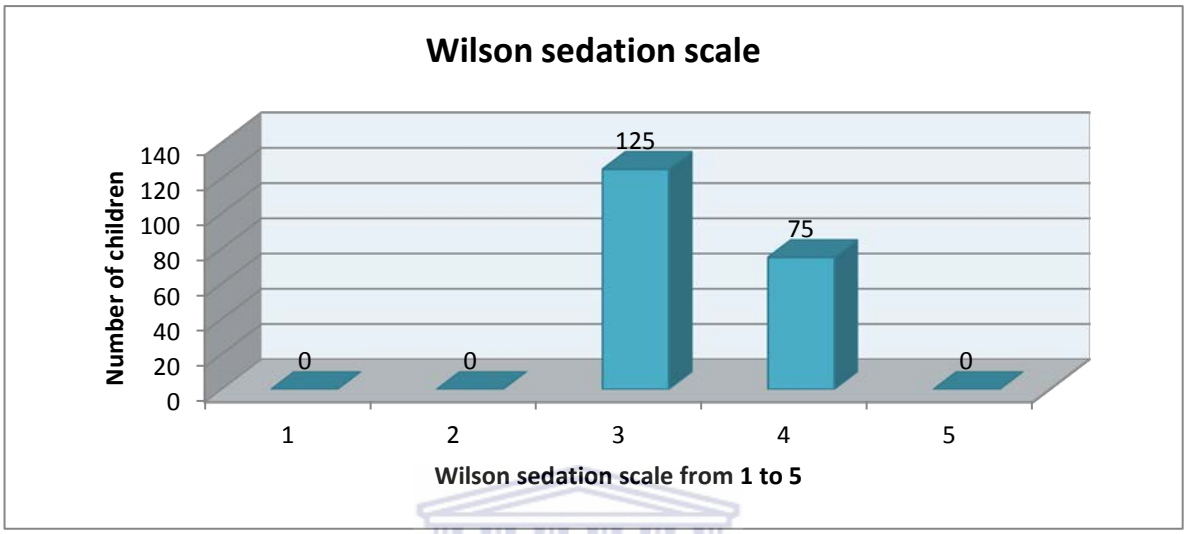
1 Fully awake and oriented
2 Drowsy
3 Eyes closed but rousable to verbal command
4 Eyes closed but rousable to mild physical stimulation (earlobe tug)
5 Eyes closed, not rousable to mild physical stimulation

A level 5 on the Wilson scale equals deep sedation, which is not safe and not allowed outside the operating room. The level of sedation used for this study, varied between a level 3 and 4 on the Wilson scale (which is moderate sedation and analgesia), depending on the co-operation of the children.

Graph 5.9 shows the following:

- 62.5% of the children were done according to a Wilson sedation scale level of 3,
- 32.5% were on a sedation level of 4.

These levels are considered as safe by all international guidelines when children are sedated.



Graph 5.9

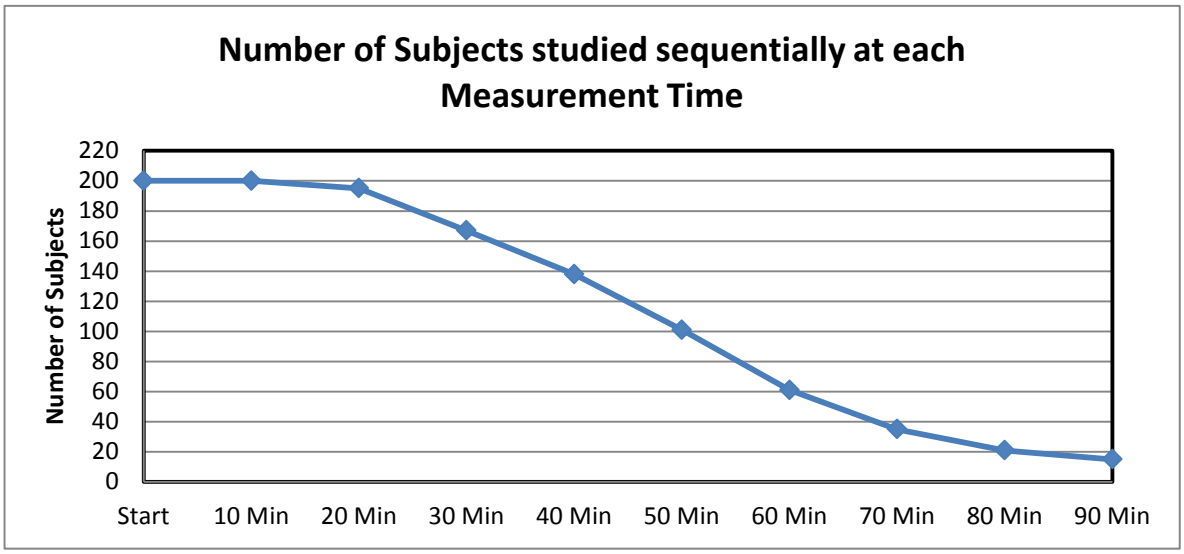
5.10 OBSERVATIONS

In the following discussion the patients' observations will be discussed under the following headings:

- Pulse rate,
- Respiratory rate,
- Oxygen saturation levels and
- Blood pressure.

The observations were recorded every 10 minutes.

The following graph shows the number of subjects that were studied sequentially at each measurement time. The procedures ranged from 10 minutes to 110 minutes. On this graph the time up to 90 minutes is shown.



Graph 5.10.1

Graph 5.10.1 shows something very interesting in terms of procedure and sedation times, and numbers of children done under sedation e.g. 160 children (80%) were done in 30 minutes; 20 children (10%) were done in 80 minutes.

This study shows the trend of current sedation practice as the majority of sedation procedures are short in duration. This obviously will add to the safety of paediatric sedation practice.

5.10.1 PULSE RATE:

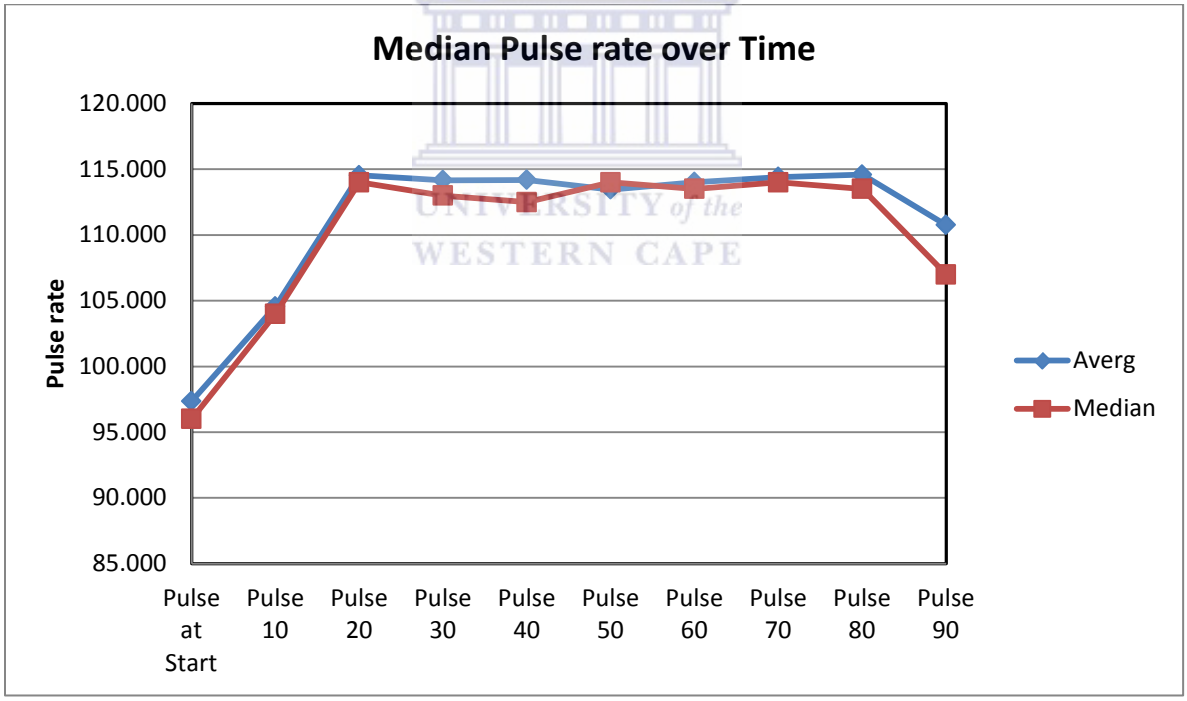
This study included patients from 2 to 10 years of age. The normal values for pulse rates in children not receiving sedation differ in each age group and are as follows (Heese 1992:99)

- 2 – 3 years: 100 – 180 (130) beats per minute
- 4 – 5 years: 60 – 150 (100) beats per minute
- 6 – 8 years: 60 – 130 (100) beats per minute
- 9 – 10 years: 50 – 110 (80) beats per minute

According to the Spearman Correlation report (Annexure J, p. 106) this research study confirms the following:

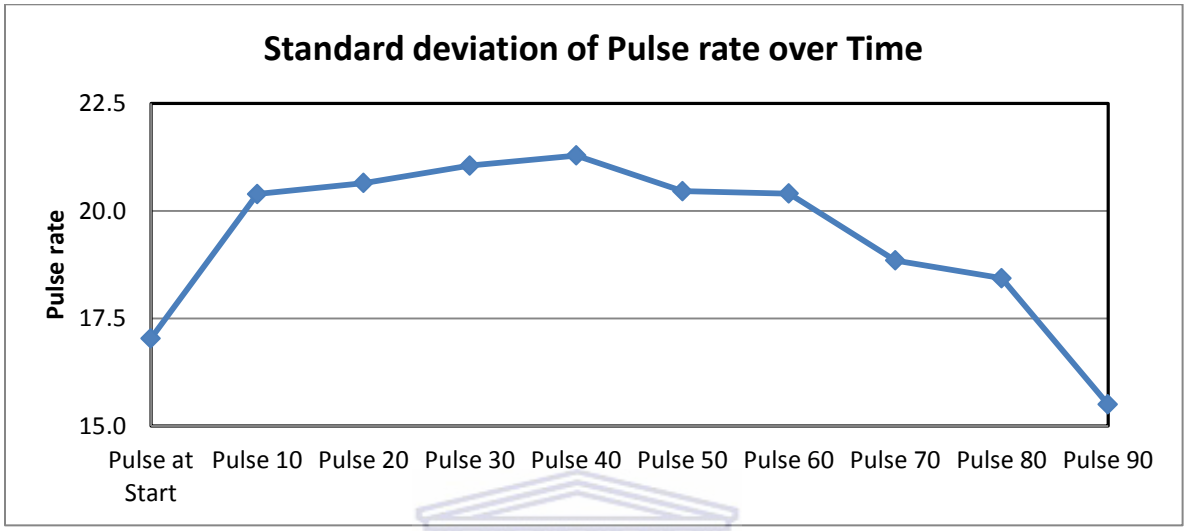
- There is an inverse correlation between the age, weight and pulse rate of the children. The older the children (also the heavier they are), the slower their pulse rates. This is a confounding measurement with a P value of 0.0000. This is to be expected in older children.
- There is an inverse relationship between the pulse rate at the start of the procedure and the pulse rate that was measured at the 10 minute interval (P= 0.0023).
- The maximum pulse rate and the pulse difference at 10 minutes were positively related (P=0.0009). There was an increase in pulse rates.
- The maximum – minimum pulse rate correlates closely to the maximum – minimum respiratory rate (P=0.0000). This is to be expected when the paediatric sedation technique used meets all the requirements of safe paediatric sedation.

Graph 5.10.1.1 shows the median and average pulse rate over time. The values lie between 96 and 114 beats per minute. This is well within the ranges of the pulse rates in any age group as shown above. This is consistent with what we see in paediatric sedation practice.



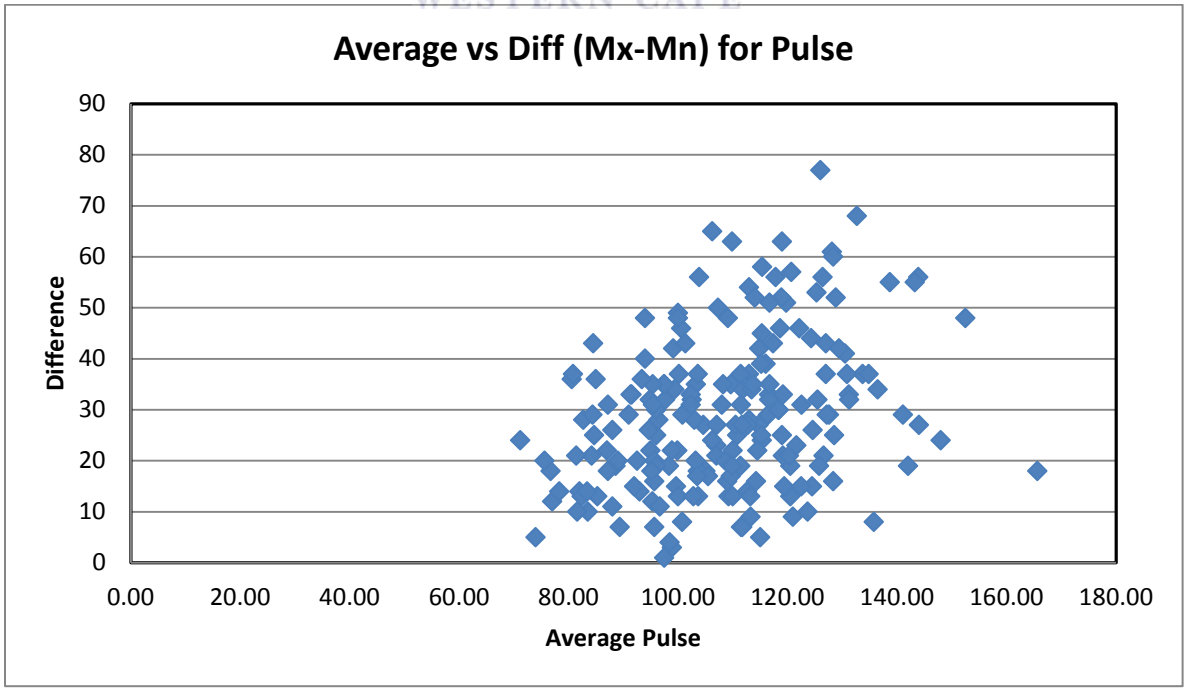
Graph 5.10.1.1

Graph 5.10.1.2 shows the standard deviation of pulse rate over time. The longer the procedure lasted the smaller the deviation in pulse rate. The pulse rate deviation was the highest in the first 40 minutes. The use of glycopyrrolate as part of the induction can explain this increase in pulse rates. Anxiousness in the patients also contributes to the increase in pulse rates.



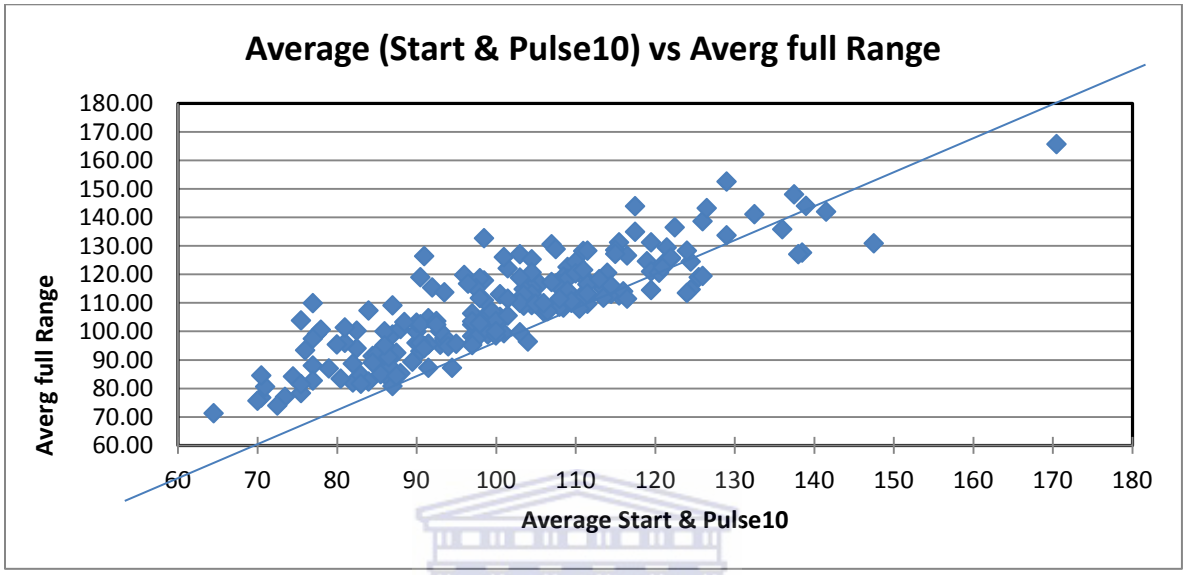
Graph 5.10.1.2

Graph 5.10.1.3 shows the average pulse rate on the horizontal axes and the difference (maximum minus minimum) in pulse rate on the vertical axes. The values are fairly concentrated in the area between 71 to 165 on the horizontal axes and 0 to 77 on the vertical axes. This is to be expected with safe paediatric sedation.



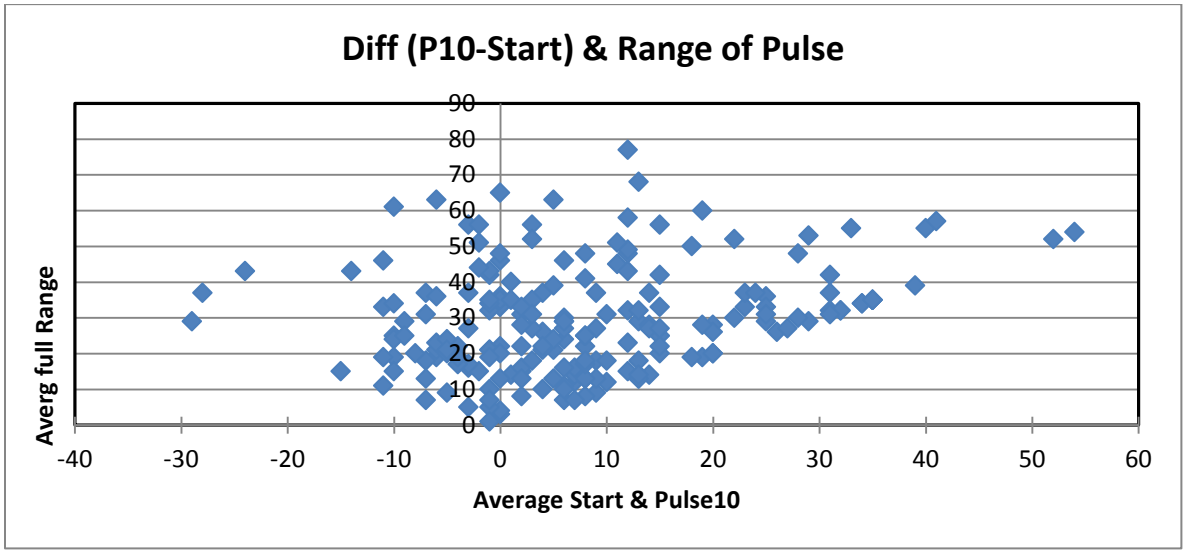
Graph 5.10.1.3

Graph 5.10.1.4 shows the average pulse readings from the start and 10 minute reading compared to the average pulse rate over the full range of time. Most of the values are above the diagonal line on the graph, meaning the average pulse rate was higher than the pulse rate at the beginning of the procedure. This is to be expected as stimulation will add to an increase in pulse rate. This also shows that procedures are done under sedation and not general anaesthesia.



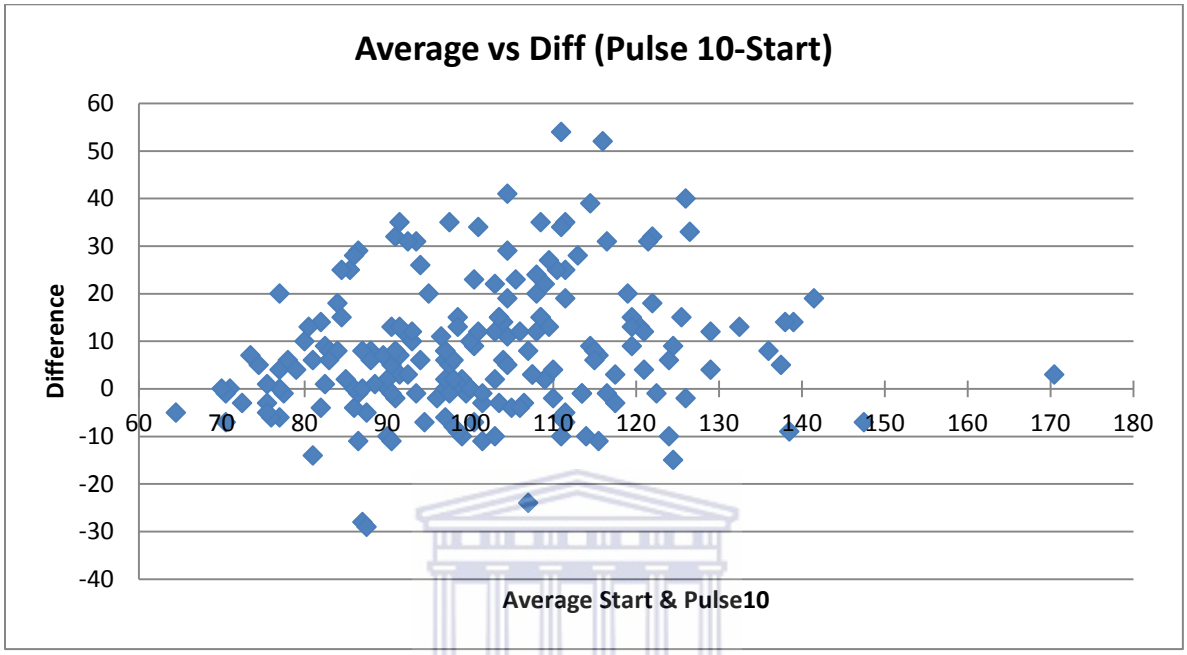
Graph 5.10.1.4

Graph 5.10.1.5 shows the difference in pulse rate (pulse rate at 10 minute reading – the pulse rate in the beginning) compared to the range of the pulse rate. The diagonal trend of the pulse rate on the right hand side of the vertical line is an indication that the pulse rate increased at the beginning of the procedure. This increase in pulse rate is due to the use of glycopyrrolate at the beginning of the procedure. Anxiousness in the patients can also contribute to this finding. Trying to find an adequate level of sedation e.g. not too light sedation versus not too deep sedation may contribute to this finding.



Graph 5. 10.1.5

Graph 5.10.1.6 shows the average pulse rate on the horizontal axes and the difference in pulse rate (pulse rate at 10 minute reading – pulse rate at the start) on the vertical axes. This graph shows that as the pulse rate increase during sedation on the horizontal axes, the difference in the pulse rate on the vertical axes also increases. This is to be expected because drugs are administered to children.



Graph 5.10.1.6

A total of 5% of all the children had a tachycardia of between 160 and 180 beats per minute, and 0.5% (one patient) had a pulse rate of more than 180 beats per minute. The high pulse rates could be caused by the antisialogue administered before induction of sedation. Anxiety could also contribute to this finding.

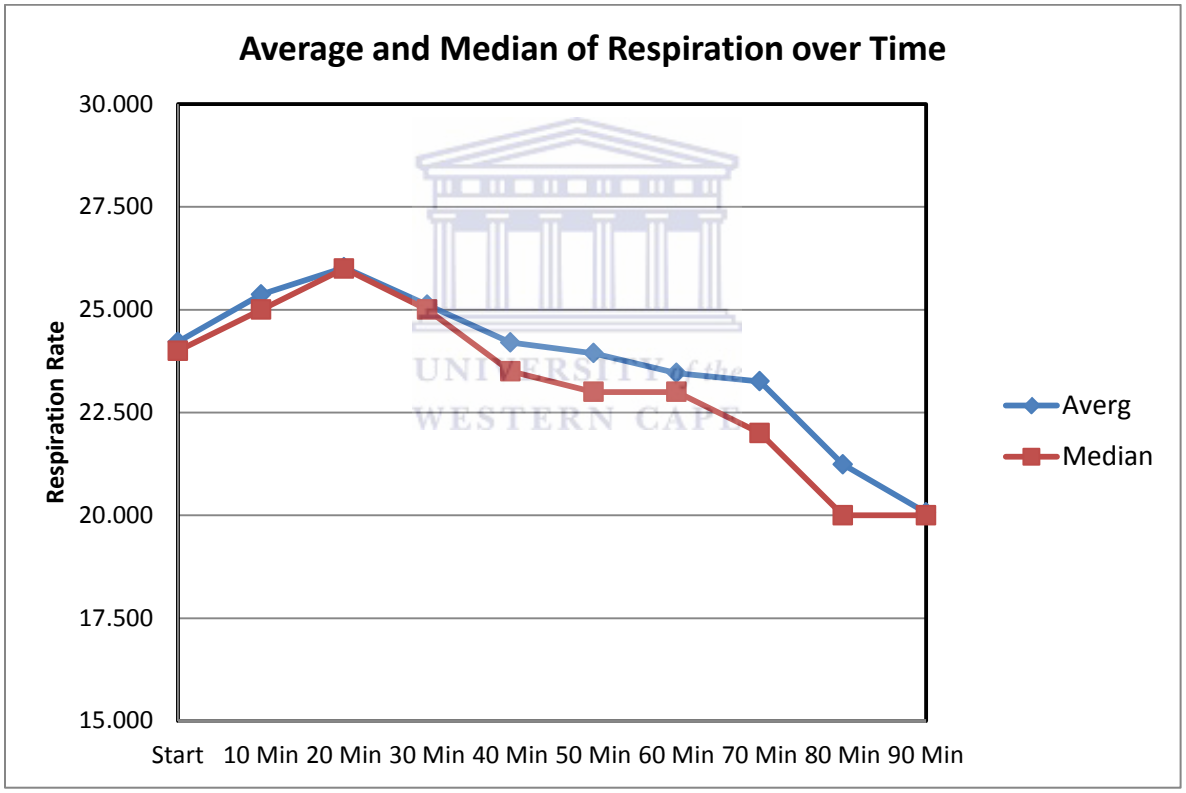
There was an overall increase in the pulse rates after induction at the beginning of the procedures as explained above.

The one patient with the pulse rate of more than 180 per minute had a history of a cleft palate that was surgically repaired. The mother gave a history that she does not tolerate any foreign objects in her mouth, which was very obvious when we inserted the bite block. “Oral defensive” is a well known entity in children with a cleft palate, although it is not well documented. Her pulse rate was between 158 and 182 throughout the procedure. This can be explained because the child was done under sedation and not general anaesthesia.

5.10.2 RESPIRATORY RATE:

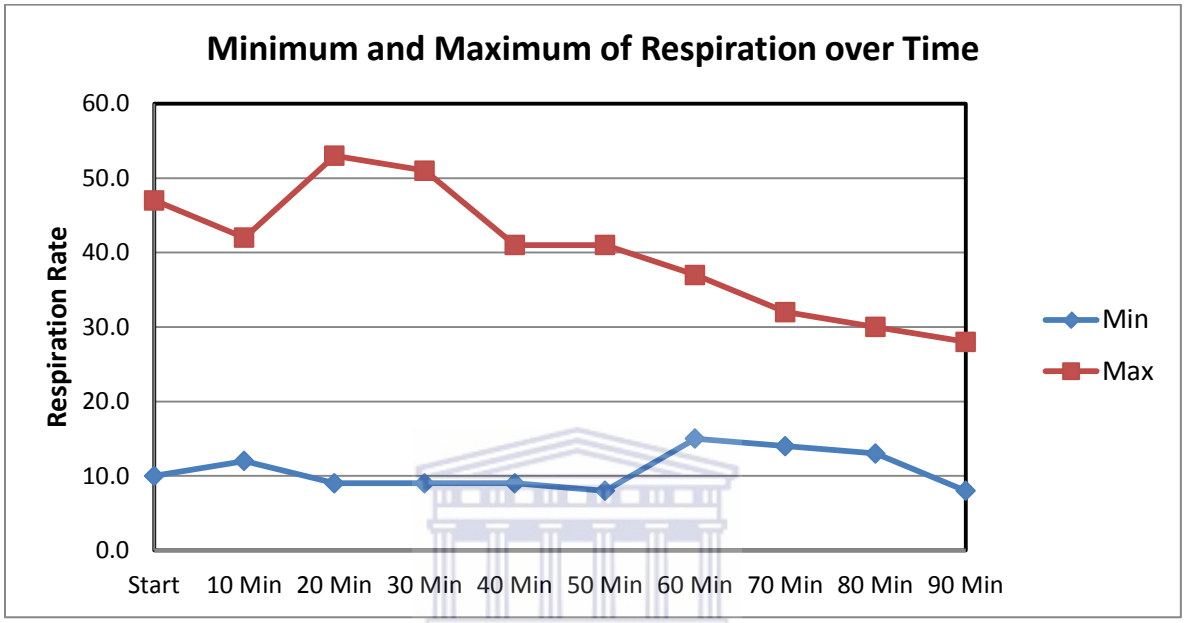
- The Spearman Correlations Report (Annexure J, p 106), show an inverse correlation between the respiratory rate and the age of the patients (P=0.0081).
- Both the pulse rate at the start of the procedure and the average pulse rate show a positive relationship with the respiratory rate (P=0.0000).
- This indicates that the faster the respiratory rate of the patient, the faster the pulse rate was. This is a normal expected physiological finding.

Graph 5.10.2.1 shows a decrease in the respiratory rate over time. The longer the procedure lasted the slower the respiratory rate became. One could argue that there is not much significance in reporting this; however when using opiates in children a decrease in respiratory rate could be an indication of respiratory depression.



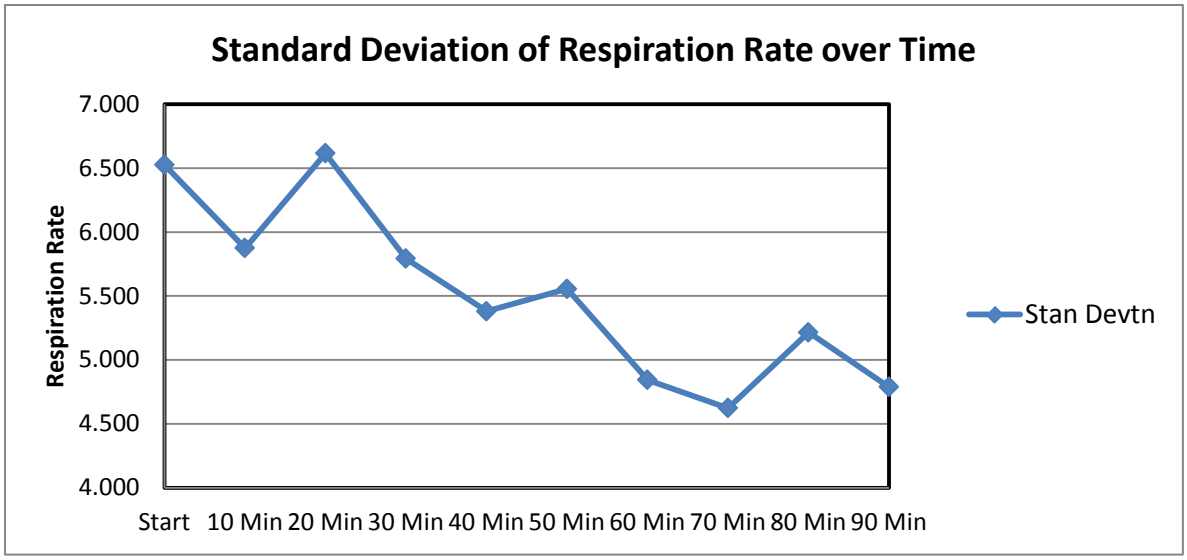
Graph 5.10.2.1

Graph 5.10.2.2 shows the maximum and minimum respiration rates. The maximum respiratory rate and this graph are indicative of tachypnea. This correlates with the tachycardia seen with the one patient who had a cleft palate repair. This increase in respiratory rates may be due to anxiousness, and yet not finding the desired sedation level. However it shows the sensitiveness of the sedation practitioner in not giving over dosages of drugs.



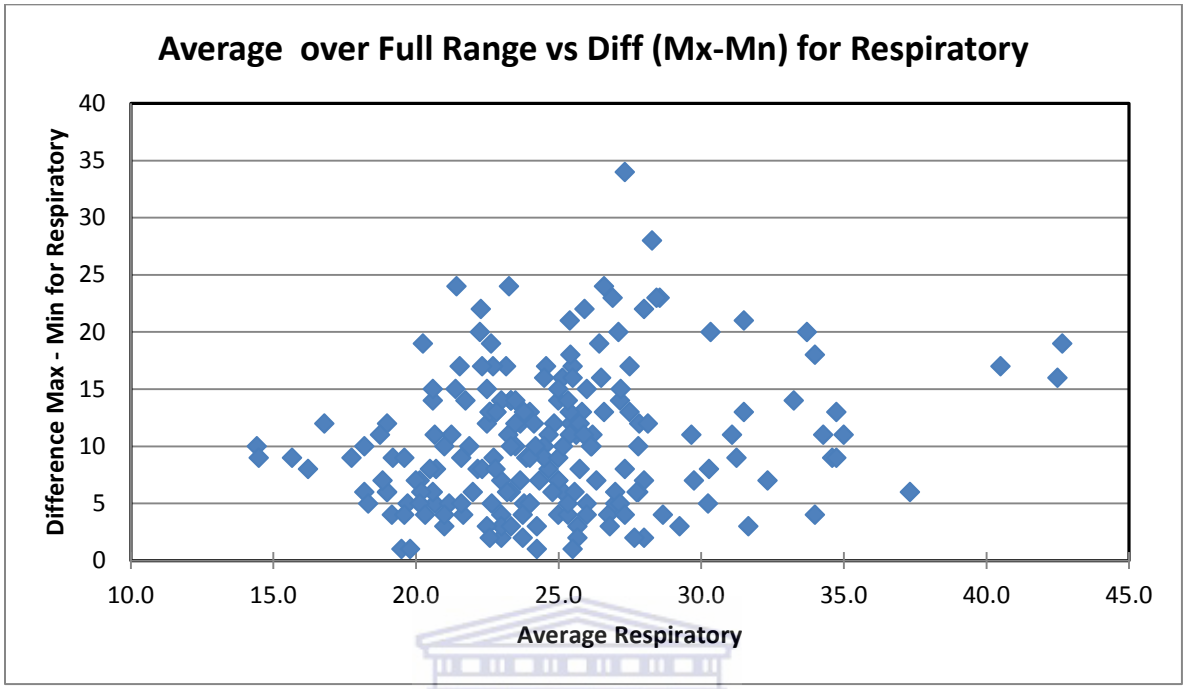
Graph 5.10.2.2

Graph 5.10.2.3 shows the respiration rate slowing down the longer the procedure lasted. Most of the painful stimuli are in the beginning of the procedure with the administration of the local anaesthetic and drilling. Once the patients were sedated their respiratory rate and pulse rate decreased. This is to be expected when we reach a desired level of sedation and indicative of a safe sedation technique.



Graph 5.10.2.3

Graph 5.10.2.4 shows the average respiratory rate on the horizontal axes and the difference between the maximum and minimum respiratory rate on the vertical axes.



Graph 5.10.2.4

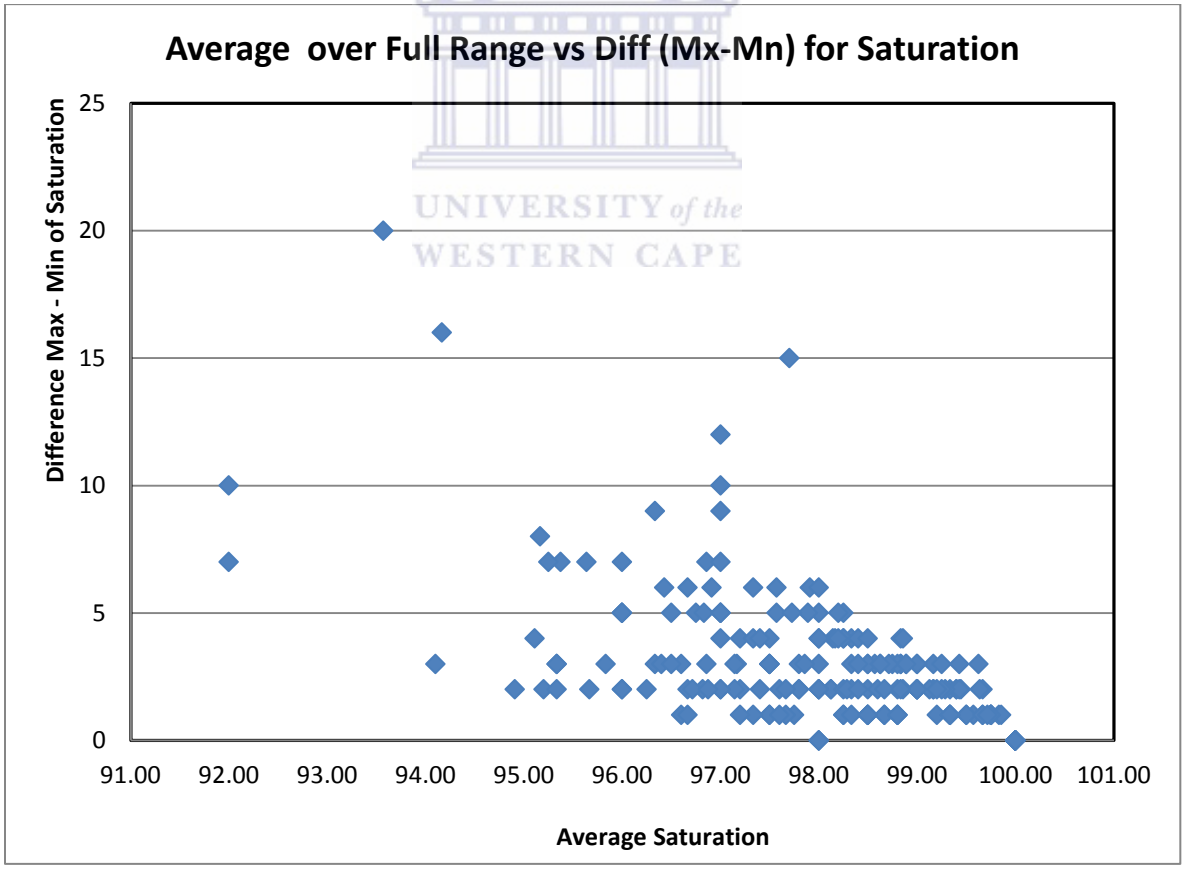
- The respiration rate varied from patient to patient. Most of the patients showed a slight increase in respiration rate after induction, which settled quickly with sedative drugs taking an effect.
- Two of the children started off with tachypnoea. Both of these children were extremely anxious. Their respiratory rates settled soon after induction, once the children were sedated.
- Tachypnoea in children before sedation is a very important observation and care should be taken that the children do not suffer from a respiratory tract infection.
- There was no respiratory depression noted, which can be caused by midazolam, propofol or sufentanil. This is a very important observation when doing sedation in children as it points to safe sedation practice. The absence of respiratory depression is probably due to the extremely low dosages that were used.

5.10.3 OXYGEN SATURATION:

Graph 5.10.3 shows the average oxygen saturation over the full range against the difference (maximum – minimum) in oxygen saturation. The greatest number of patients on the graph lies above 95% oxygen saturation with a difference of less than 5%. Monitoring the oxygen saturation in children is very important because respiratory complications are the most common and life threatening.

One child started with an oxygen saturation reading of 85%. This child was very anxious and moving about which made an accurate reading impossible. As soon as the child was sedated and he settled down, the oxygen saturation improved.

The respiratory complication rate in this study was 7%. Of these only 3% or six patients needed oxygen administration. In all the cases of desaturation it was caused by obstruction of the airway by the dentist while working or too much water on the drill. In all the cases the problem was treated and the oxygen saturation restored within seconds with no serious consequences.



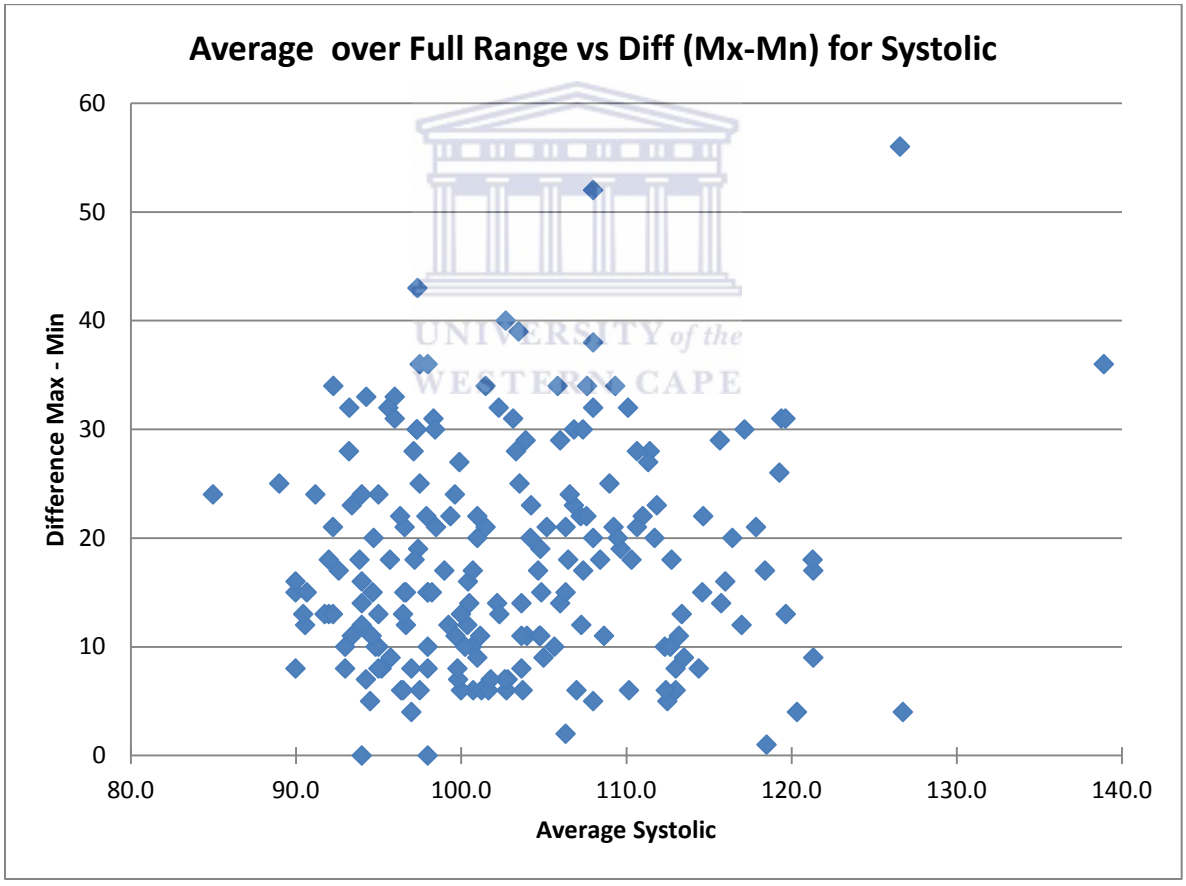
Graph 5.10.3

5.10.4 BLOOD PRESSURE

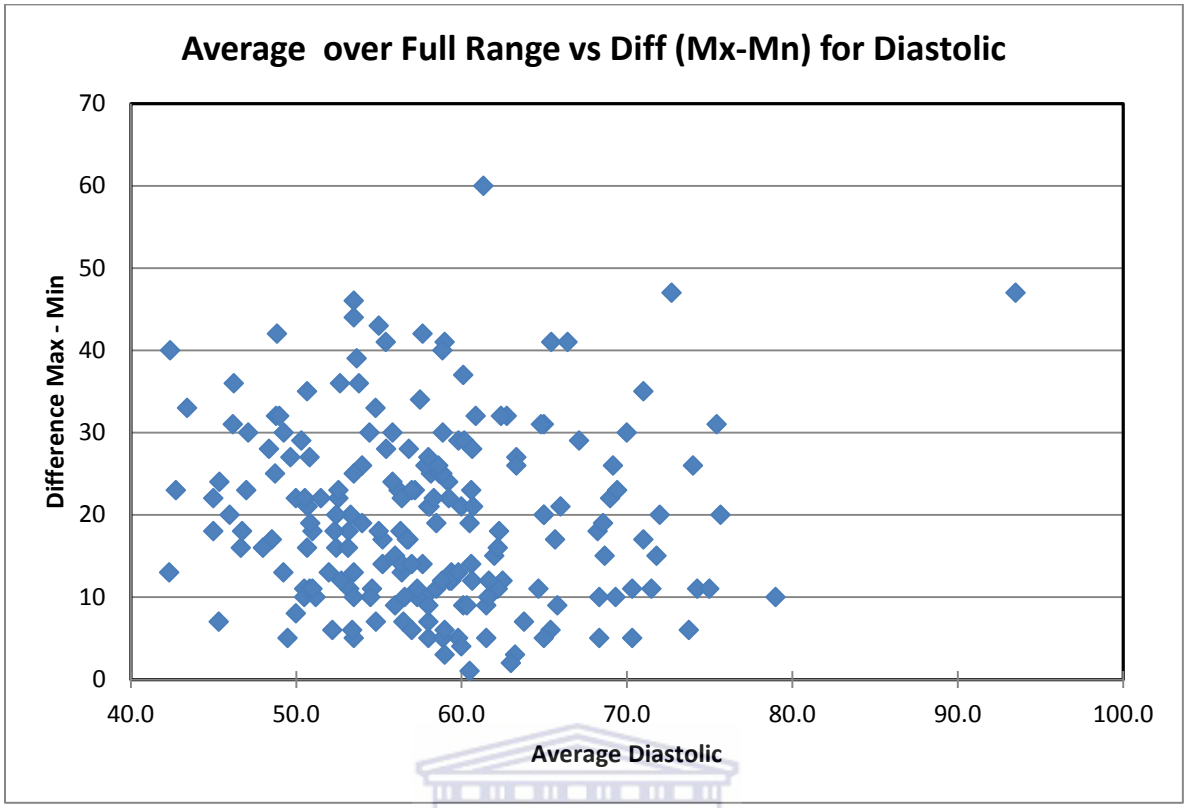
In children the blood pressure is dependent on the pulse rate. Changes and abnormal blood pressure readings will be discussed in the section of adverse events (p74).

There is no clarity on the evaluation of blood pressures in small children. There are arguments that when you inflate the cuff this may change your level of sedation. One expects normal blood pressures in ASA 1 and 2 children.

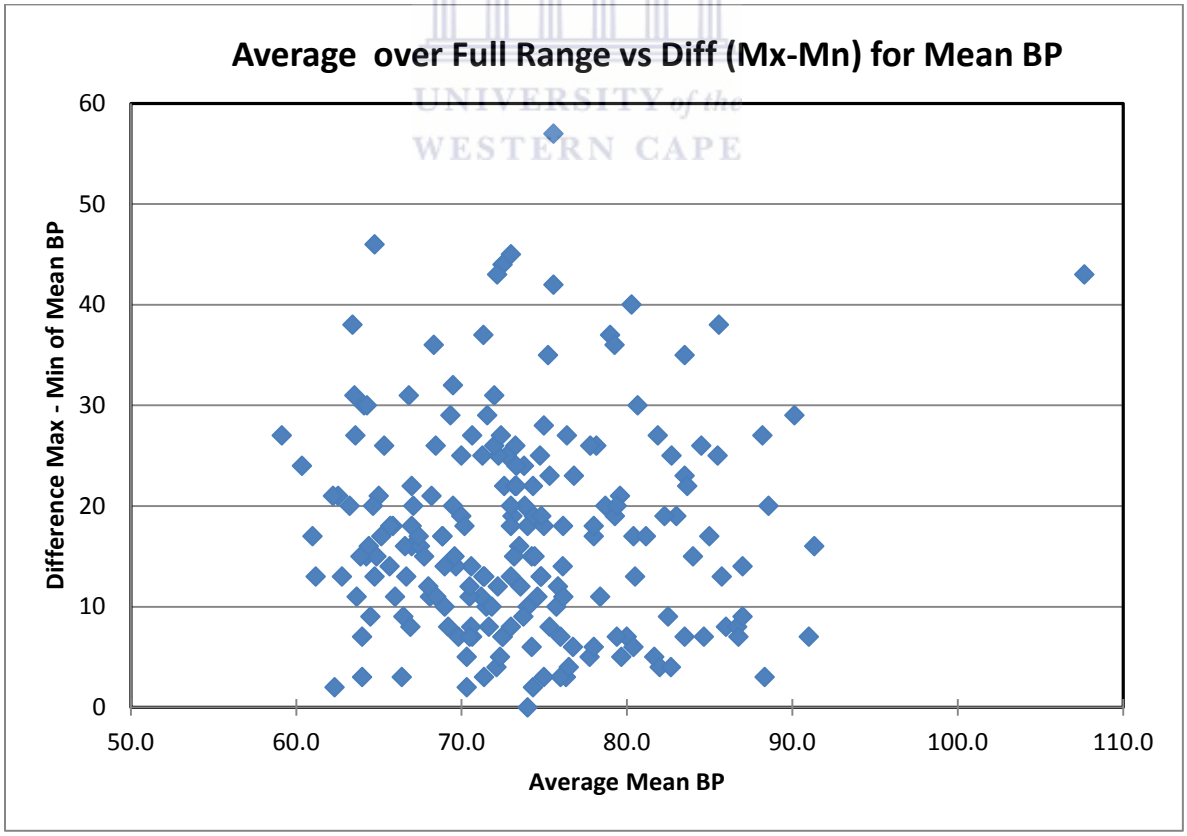
The following three scatter graphs show the average blood pressure readings for systolic, diastolic and mean blood pressure readings. The blood pressure was monitored every 10 minutes during the sedation. These graphs do not show any significant trends in the blood pressure measurements. A drop in blood pressure is rarely seen and not really significant in the ASA 1 and 11 patients.



Graph 5.10.4.1



Graph 5.10.4.2



Graph 5.10.4.3

5.11 STEWARD RECOVERY SCALE

There are quite a variety of recovery scales available to assess recovery which is all subjective. The Steward Recovery scale (Steward 1975) is widely used to evaluate patients before being discharged to go home. The decision on when to discharge a child is very important as adverse events can happen even at home. All children should be fully recovered before they can be sent home. That implies that they must have a Steward score of six. The Steward score is calculated as follows:

PARAMETER	FINDING	POINTS
Consciousness	Awake	2
	Rousable and responding to stimuli	1
	Not responding to stimuli	0
Airway	Coughing on command or crying	2
	Maintaining good airway and breathing easily	1
	Airway requires maintenance	0
Movement	Moving limbs purposefully	2
	Non-purposeful movements	1
	Not moving	0

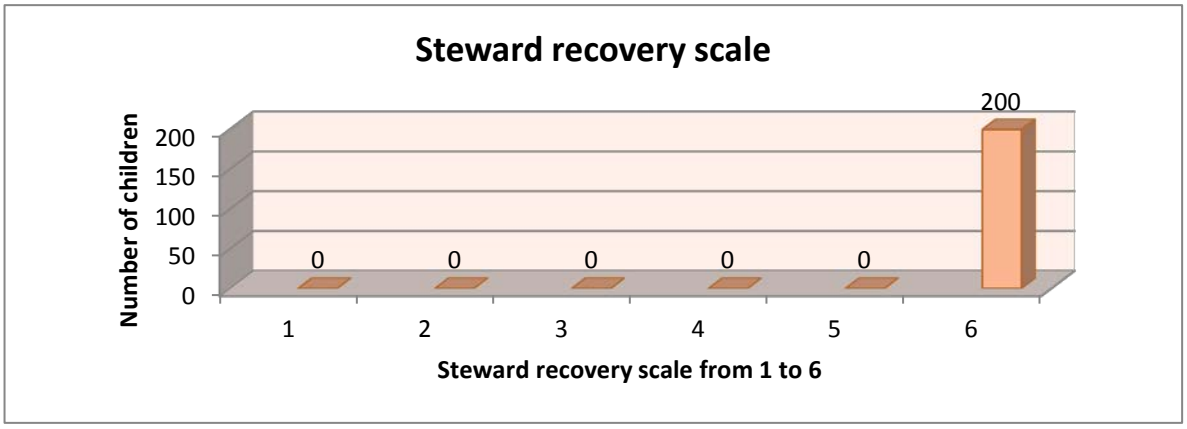
Table 3:

Interpretation:

~ Minimum score 0: fully anaesthetized, not ready to be discharged

~ Maximum score 6: fully recovered

Graph 5.11 below shows that all the children in the study scored a 6 on the Wilson recovery scale meaning they were fit to be discharged. Despite this fact, one parent reported in the second questionnaire that the child was sleeping and difficult to rouse on their journey home. This just accentuated the importance of discharge criteria but also the value of clinical monitoring after sedation. This also adds to our concerns about drug administration to children. Non stimulation may have contributed to slow recovery in the child mentioned.



Graph 5.11

5.12 SURGEON EVALUATION OF EFFICACY OF SEDATION IN CHILDREN

The operator or surgeon is a valuable component of sedation practice. In this study the operator was asked to evaluate the quality of sedation. A table with a scoring system was used (see below) to ensure that the different operators use the same evaluation technique. The children were evaluated according to two parameters, namely movement and vocalising.

Vocalising was evaluated as a

- score of 1 when the patient was talking.
- 2 if the patient was complaining (moaning) with administration of the local anaesthetic.
- 3 if the patient was screaming with local anaesthetic administration or other stimuli.
- 4 in case of uncontrollable screaming and procedure were cancelled.

The following table was used during sedation: (researcher and supervisor)

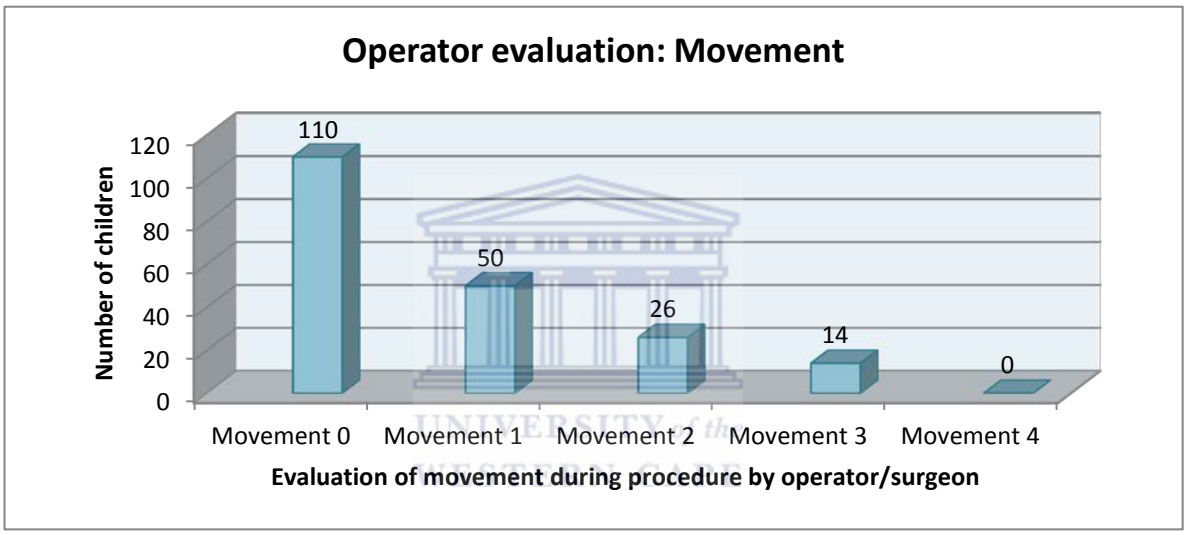
Movement	0 No movement	1 Slight movement, not interfering with procedure	2 Moderate movement, not interfering with procedure	3 Major movement, procedure done with difficulty	4 Uncontrollable movement, procedure not possible
Vocalising	0 No vocalising	1 Slight vocalising, talking	2 Moderate vocalising, with local administration, not disturbing	3 Major vocalising, screaming	4 Uncontrollable vocalising, screaming throughout procedure. (not because of pain)

Table 4

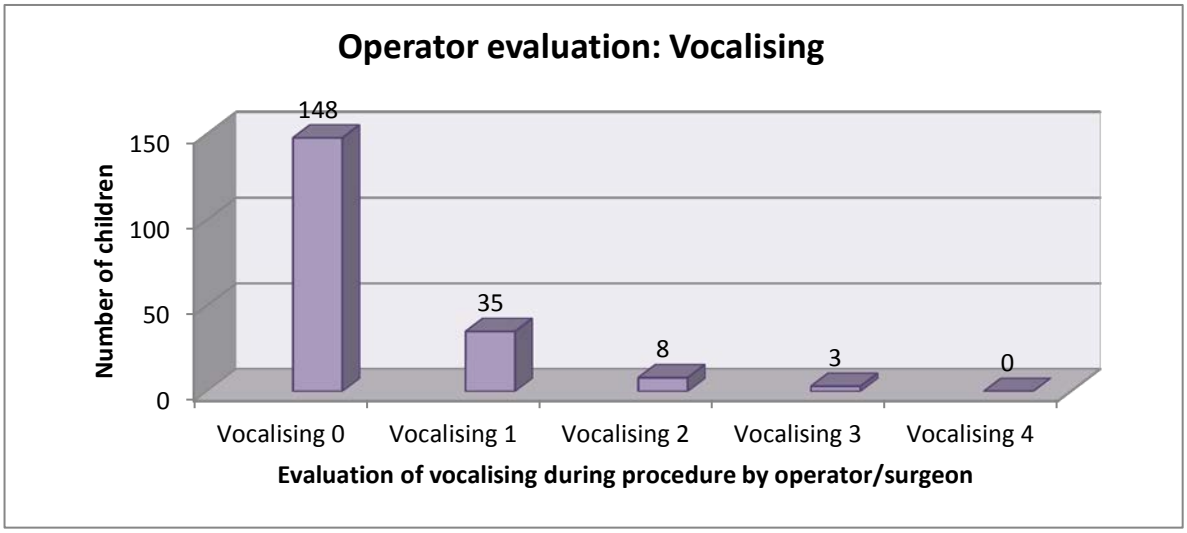
The results of the evaluations of the two above parameters are listed below in graph 5.12.1. Note that none of the patients had a score of 4 which means that it is impossible to complete the procedure. It is debatable whether a child scoring 4 in either category will be suited for a procedure under sedation. It may only be possible with deep sedation. The quality of work performed when the child is moving that much is questionable. Part of the consent form for sedation states that sedation is not a guarantee that the work will be done. In the opinion of the sedation practitioner it is acceptable to cancel sedation in case of excessive movement or vocalising. It is in fact advisable to inform parents before the operation of this possibility. It is no shame in abandoning a procedure and proceed to general anaesthesia.

Eighty percent (80%) of the children scored a 0 or 1 on the movement scale. This implies that the children were co-operative and easy to work on; 91.5% of the children scored a 0 or 1 on the vocalising scale which means that they were quiet, and not talking excessively. The procedure was thus not difficult to complete.

Seven percent (7%) of the children had a score of three when movement was evaluated, and 1.5% scored a three on vocalising. These sedations were marked as difficult. Despite the fact that these sedations were difficult to do, all the work was still completed. The decision whether these children will be scheduled for a future sedation lies with the operator and sedation practitioner together. It must also be remembered that a difficult sedation may not exclude the possibility of sedation in future; this must also be discussed with the parents. This shows the safety and efficacy of the technique used.



Graph 5.12.1



Graph 5.12.2

5.13 SEDATION PRACTITIONER EVALUATION OF SAFETY AND EFFICACY

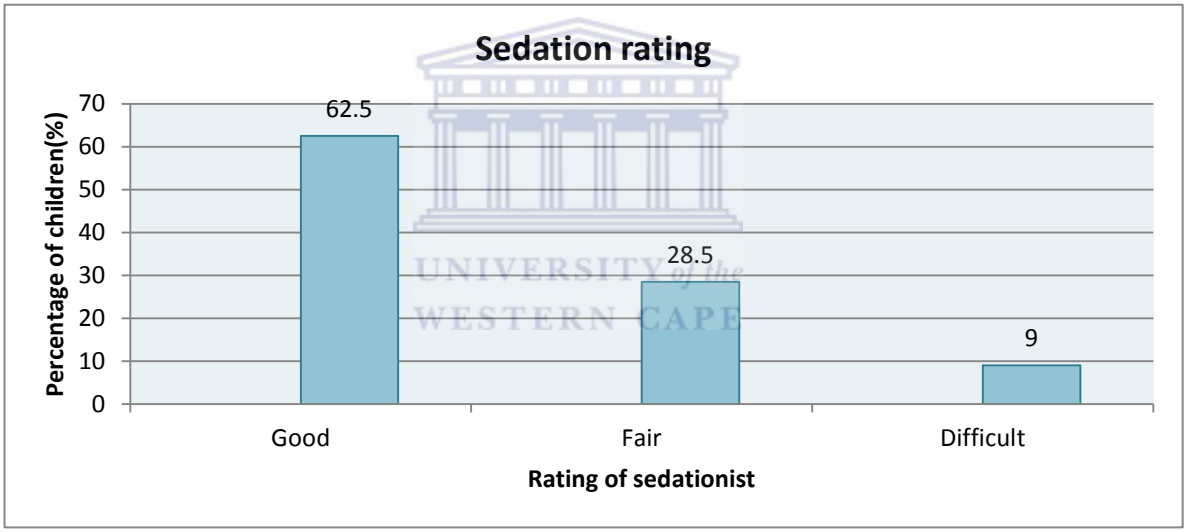
The evaluations from the sedation practitioner's point of view will be discussed in the following section under the following headings: general, post-operative recovery, safety and efficacy. This should give a valuable contribution as to how difficult or easy sedation was. It will also give an indication as to safety and efficacy of the sedation technique.

5.13.1. General

From the sedation practitioner's view, the sedations were evaluated on a three- point scale as:

- good,
- fair, and
- difficult.

The results can be seen in the following graph 5.13.1



Graph 5.13.1

- Good

The largest group was the group that was rated as good. These sedations totaled 62% of the cases that were done. The sedation was rated as good when the child was co-operative, with little or no movement, and they were able to maintain their airway with little or no interference. The surgeon was never requested to stop the operation in this group.

- Fair

The sedation was rated as fair when there was more movement or airway management needed e.g. extending the head or lifting the chin. It was not necessary to administer oxygen to the children. In this group it was necessary to temporarily stop the procedure. This group constituted 29% of the study group. This is a fair indication that sedation in

children is not always easy and that expertise is necessary to manage children, especially protection of the airway.

- Difficult

Sedation was classified as difficult when the children were moving excessively, or airway management was needed throughout the procedure. In these cases the work was completed with difficulty. This group made out 9% of the study group. This group that were found to be difficult to sedate correlates with the findings of the operator/dentist where the results of the vocalizing and movement scores were 8.5% scored as a value of 3, which indicated severe movement or vocalizing. This again shows that even with experienced sedation practitioners involved in paediatric sedation outcome cannot be easily predicted. Maybe one can say not all children qualify for paediatric sedation. Children must be evaluated before sedation as to suitability of sedation.

This study also included a questionnaire that the parents completed. One of the questions asked was about behavior characteristics of the child. This was asked to try to find a common trait that might predict a difficult sedation. With the results that were received, no common denominator could be found to predict a difficult sedation. Craig and Skelly [6] state the following: "Despite a number of recent studies it has not been possible to identify any factor or group of factors which may be used to predict the likelihood of success."

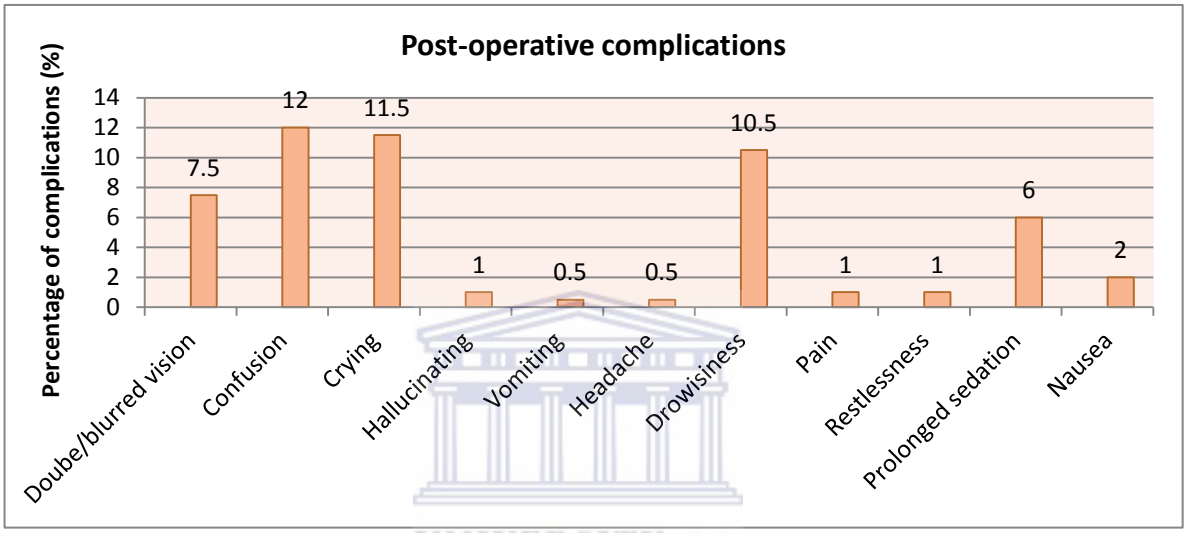
This confirms the researcher's findings that there is no factor that could be found to predict a difficult sedation in ASA 1 and 2 children.

5.13.2. Post Operative Recovery and Side-effects

The success of the sedations procedures also depends on the post-operative recovery characteristics of the children. We do not want to see children are not controllable after sedation or with a high incidence of side effects. The most common side effects and complications are listed in order of prevalence, and were evaluated in every child. Although two patients complained of pain, only one was objectively in pain. Some children confuse the tingling feeling of the local anaesthetic with pain. The following are the post-operative side effects that were seen and are displayed in graph 5.13.2:

Confusion	12%	Restlessness	1%
Crying	10.5%	Pain	1%
Drowsy	10.5%	Hallucinations	1%
Double vision	7.5%	Headache	0.5%
Prolonged sedation	6%	Vomiting	0.5%
Nausea	2%		

- Confusion, crying, drowsiness and double vision were the most common side-effects that were noted.
- The incidence of nausea and vomiting is very low if compared to general anaesthesia. The side effects mentioned are commonly seen after paediatric sedation using intravenous drugs.
- The incidence of hallucinations is only 1%, even with the use of ketamine. None of the children had bad or scary hallucinations. This low incidence of hallucinations is probably due to the low dosages of ketamine used.
- Restlessness, pain and headache were seen very seldom.



Graph 5.13.2

This research study shows that postoperative side effects are inevitable. Children are usually anxious, find themselves in a threatening environment, and receive drugs. All contribute to the incidence of side effects. Despite these side effects mentioned the majority of children recover without any side effects.

5.13.3. Safety

From the sedation practitioner's point of view, the sedations (drug administration) were also evaluated for safety and efficacy.
The **safety** was evaluated according to the following criteria:

- Level of consciousness,
- Maintenance of the airway,
- Respiratory (breathing) pattern and
- Haemodynamic adverse events.

The following table was used to score the patients:

Scoring table to evaluate safety:

Consciousness	**0** Eyes open or closed, responds to verbal stimulation	**-1** Ptosis, responds to physical stimulation	**-2** Eyes closed, only response reflex to stimulation	**-3** Eyes closed, no response to physical stimulation
Airway	**0** Controlled adequately by patient….breathing spontaneously, no accessory muscles involved	**-1** Minimal interference needed to maintain the airway e.g. extend neck	**-2** Airway management e.g. chin lift needed from time to time	**-3** Airway management needed throughout procedure
Respiratory adverse events	**-1** SpO2< 90%	**-1** Signs of respiratory obstruction, wheezing, snoring	**-1** Respiratory pauses > 10s, rib retraction	-2 Apnoea or episodes of apnoea
Haemodynamic adverse events	**-1** BP decrease of >33% from baseline	**-1** Pulse rate > 160/min.		

Table 5

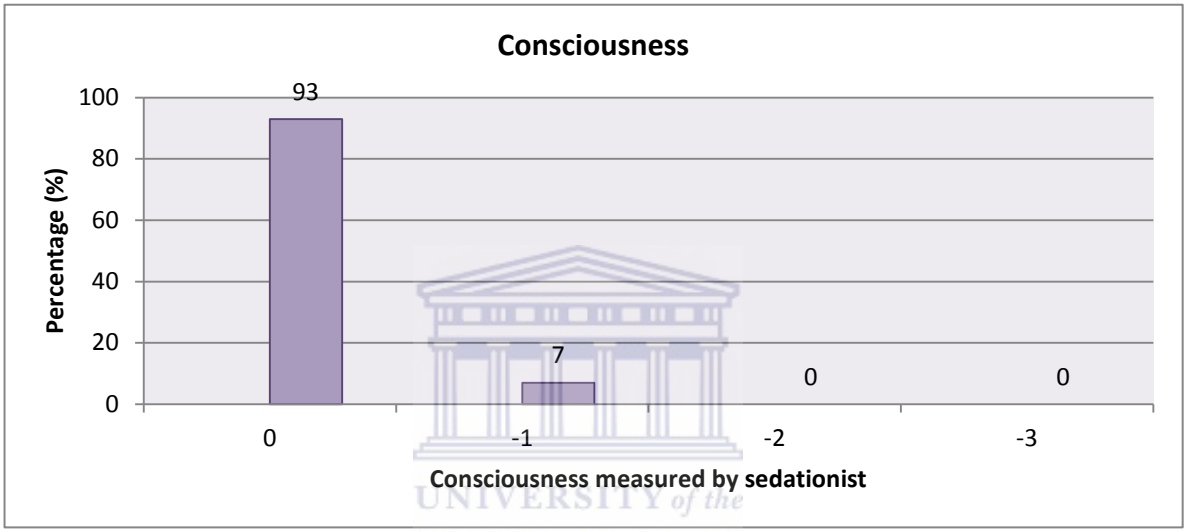
5.13.3.1. Level of Consciousness.

The results are shown in graph 5.13.3.1 below and were as follows:

- 186 children were scored as 0, and
- 14 as -1.

None of the children were rated as either -2 or -3, as this is not conscious sedation, and these levels are closer to anaesthesia, and is not safe outside of a theatre.

This research study clearly shows that paediatric sedation was done according to the sedation guidelines if we look at the level of consciousness, which in effect means sedation.



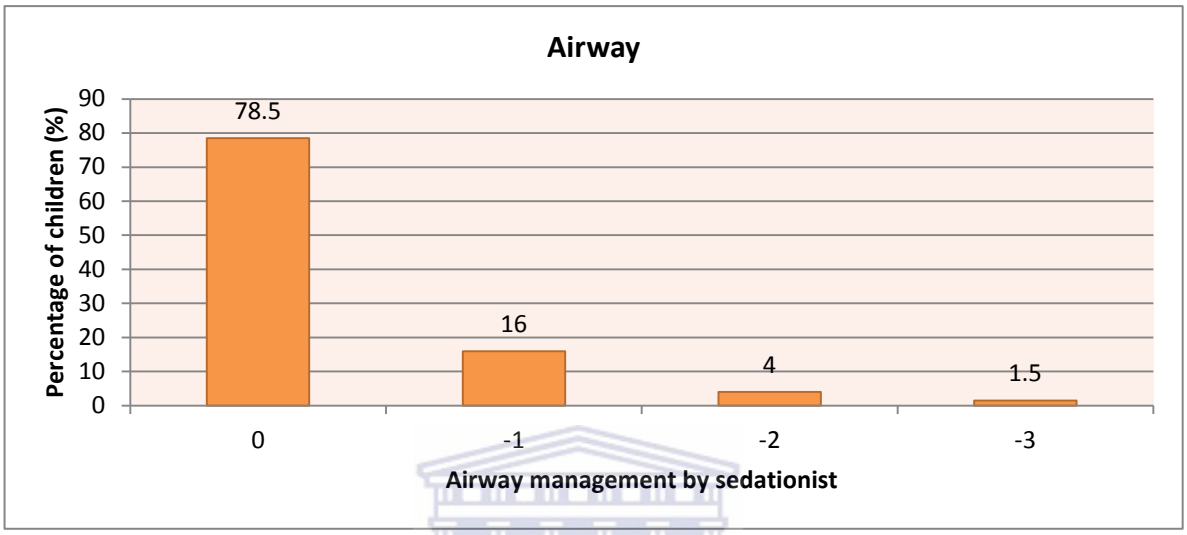
Graph 5.13.3.1

5.13.3.2. Maintenance of the Airway.

The patient's airways were evaluated according to the level of interference that was needed from the sedation practitioner to keep it patent and without obstruction. The scoring chart is shown in table 5 (p. 71) .

- The total number of children who were able to control their own airway (self preservation) without any interference was 78.5%, and this shows that conscious sedation is possible in children if we also take into account the scores discussed under the level of consciousness.
- A total of 16% of children needed minimal interference to keep their airways open. This usually was necessary when the operators depressed the chins when working on the bottom teeth. None of these children desaturated.
- The next group of children under this category was scored as -2. These children needed airway management e.g. chin lift from time to time. They constituted 4% of the study group.

- The last group which were evaluated as 1.5% of the children under this category needed constant airway management e.g. chin lift. This could be due to the fact that some of these children were done at deeper levels of sedation, because the children were not co-operative when doing conscious sedation. Another possibility may be a difficult airway e.g. tonsillar hypertrophy. None of the children in this group received oxygen continuously.



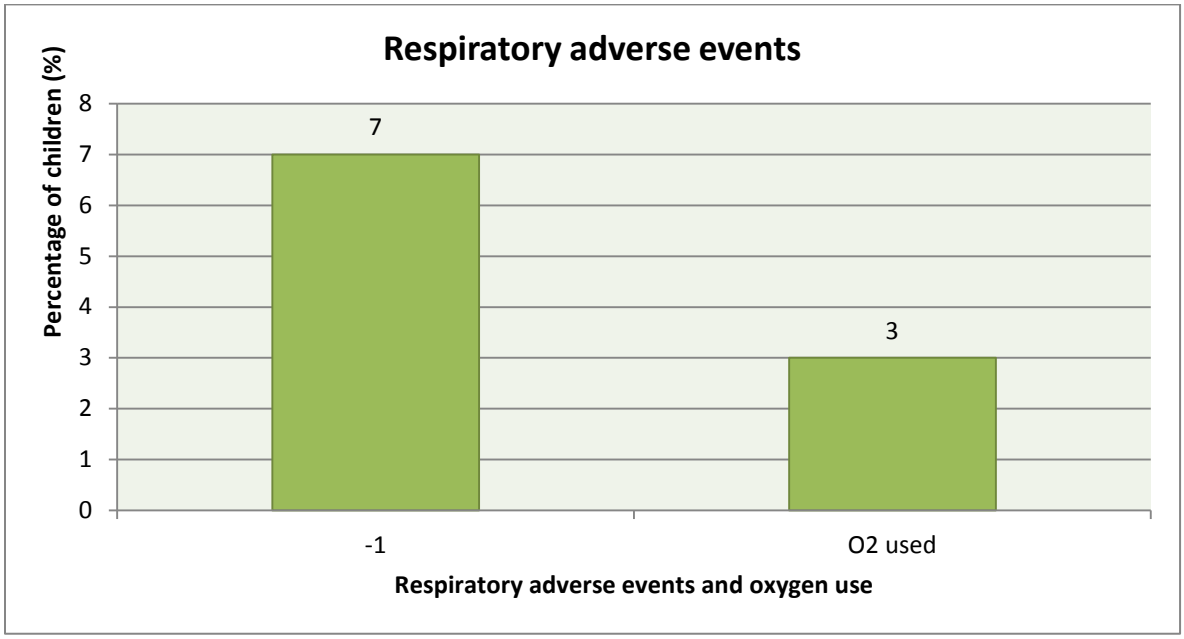
Graph 5.13.3.2

5.13.3.3. Respiratory (breathing) Adverse Events.

Any respiratory adverse incident as defined in Table 5 (p 71) was scored as -1, apart from apnoea or periods of apnoea scored as -2. This included desaturation below 90%, signs of respiratory obstruction, and respiratory pauses for more than 10 seconds. Only 14 children had a respiratory adverse event. Most of these were handled with only airway management as described above and using suction to get rid of secretions. Of these 14 children, who constitute 7% of the study group, only 6, or 3%, needed oxygen administration to treat the respiratory adverse event. In all the cases that needed oxygen, saturation was back to above 90% within 30 seconds of administering the oxygen. The incidence of coughing and desaturation is very closely linked to the expertise of the operator and their use of water.

The researcher can come to the conclusion that all the respiratory adverse events were minor because correction of the causing event was done immediately and effectively. The morbidity and mortality because of respiratory adverse events were 0%.

See graph 5.13.3.3 (p.74) for the results.



Graph 5.13.3.3

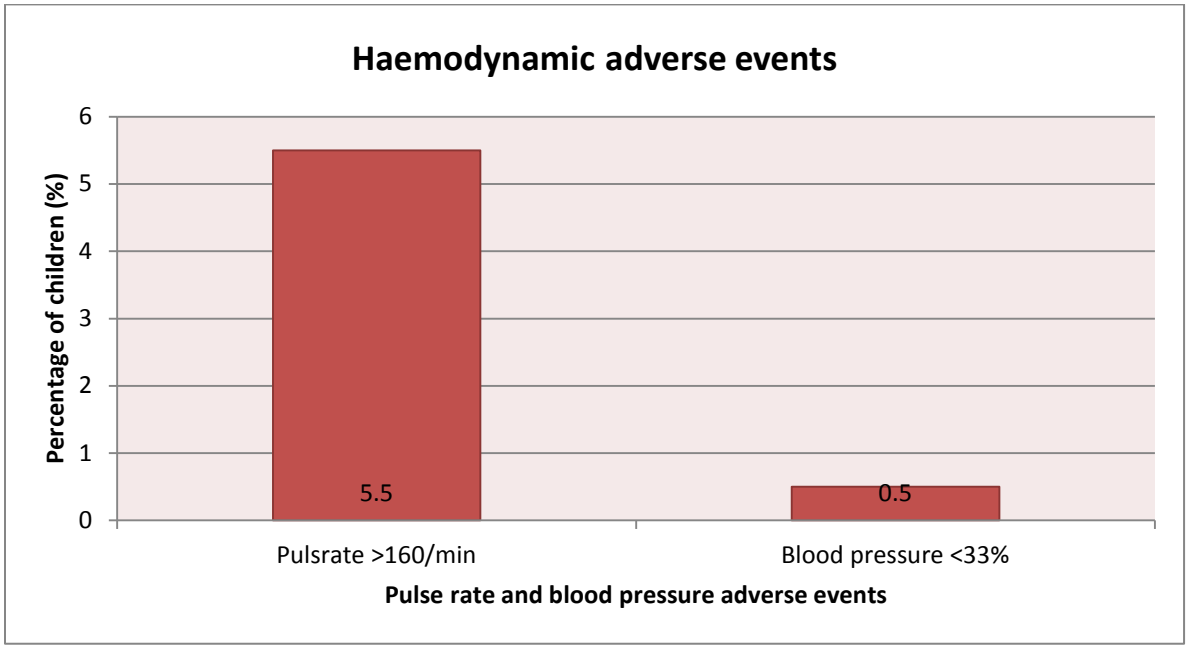
5.13.3.4. Haemodynamic Adverse Events.

These were also scored as -1 for any adverse event as can be seen in Table 5 (p 71). These events are extremely rare in ASA 1 and 2 children during sedation. This can also be seen in the results.

A drop in blood pressure of more than 33% from the baseline, or a pulse rate of more than 160 beats per minute was seen as a haemodynamic adverse event. Haemodynamic adverse events were seen in 6% of children.

- A total of 5% of them had a tachycardia of between 160 and 180 beats per minute.
- 0.5% (one patient) had a pulse rate of more than 180 beats per minute.
- 0.5% (one patient) had a drop in blood pressure of more than 33% from the first blood pressure reading.

The one patient with the pulse rate of more than 180 per minute had a history of a cleft palate that was surgically repaired. The mother gave a history that she does not tolerate any foreign objects in her mouth, which was very obvious when we inserted the bite block. Her pulse rate was between 158 and 182 throughout the procedure. This patient was not a good candidate for sedation, and should be done in theatre with general anaesthesia.
See graph 5.13.3.4 for the graphic results.



Graph 5.13.3.4

5.13.4. Efficacy

The **efficacy** of the sedation technique was evaluated looking at the parameters shown in Table 6: (Patient factors influencing safety)

Pain/Stress/ anxiety	**0** Eyes closed or open, no signs of pain	**1** Signs of complaining, sweating, frowning	**2** Crying, tears, hysterical	
Movement	**0** Quiet, purposeful movement	**1** More movement but not interfering with surgery	**2** Major movement, interfering with surgery	**3** Uncontrolled movement, kicking or biting. Unable to work
Physical signs of discomfort, tachycardia	**0** Baseline pulse rate	**1** Moderate tachycardia 160 -180/min.	**2** Severe tachycardia > 180/min.	

Table 6

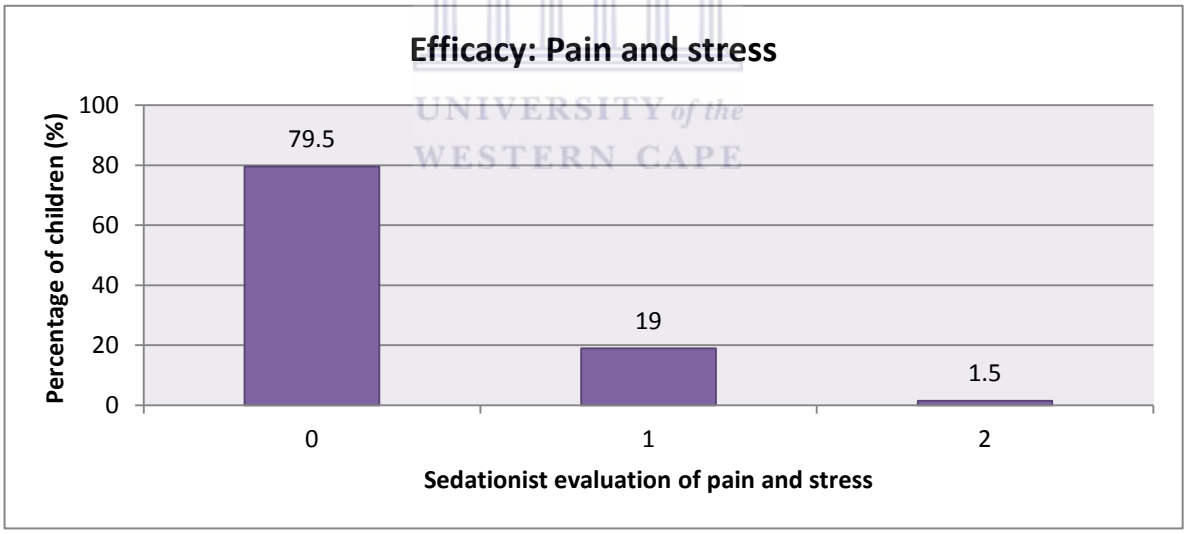
The results will be discussed under the following headings:

- Pain and stress/anxiety,
- Movement and
- Physical signs.

5.13.4.1. Pain and Stress/Anxiety

Pain and stress was mostly an indication of the anxiety level of the patients, how the patients reacted to the administration of the local anaesthetic, and the pressure they feel with extractions. From the total of 200 patients:

- 79.5% showed no signs of pain or stress.
- 19% showed signs of complaining or frowning, mostly with the administration of the local anaesthetic.
- 1.5% or three patients were crying or hysterical. Two of the patients were extremely anxious and agitated from their arrival at the consulting room. One of them settled down after a while into the procedure as he realized that he is not being hurt. The third child was reacting very strongly to the bite block, and every time it was moved, she became hysterical. This is the child who had the cleft palate repair.



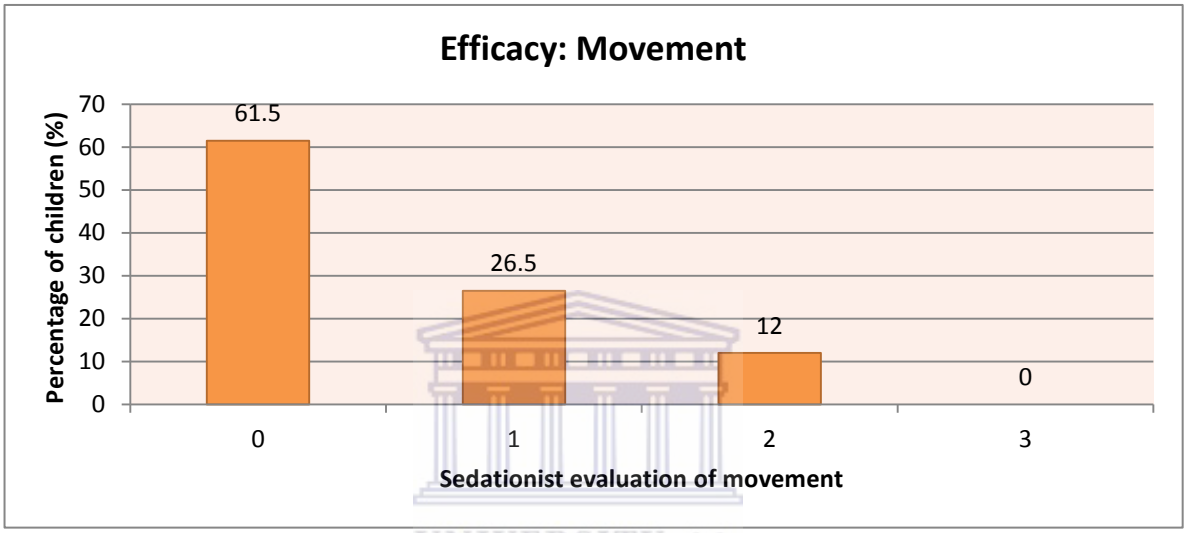
Graph 5.13.4.1

The results above show that sedation is a effective alternative to general anaesthetic to perform painful and traumatic procedures in children.

5.13.4.2 Movement

Movement was the next indicator of the efficacy of the sedation that was evaluated. This was scored as showed in table 6 (p 75).

- 61.5% scored a 0, which means that the patients were quiet with purposeful movements.
- 26.5% were moving a little bit more, but were still not interfering with the procedure. This falls within our definition of conscious or moderate sedation.
- The group that showed major movement was 12% of the study group. Although these sedations were very difficult to do, the procedures were completed. This shows again that paediatric sedation is not always easy.
- None of the patients scored a 3, meaning that procedures would have to be cancelled.



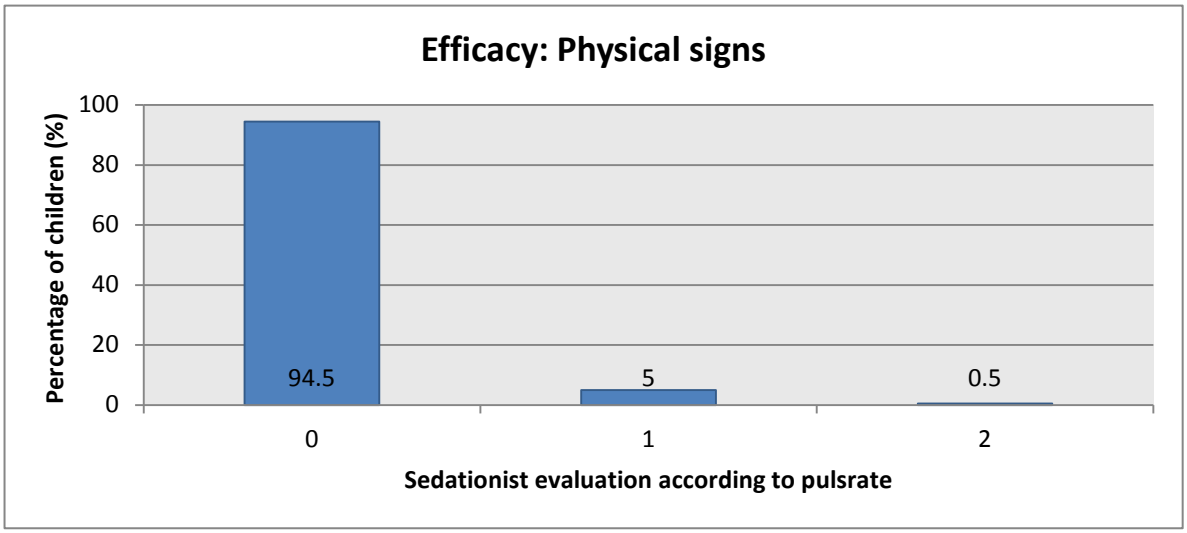
Graph 5.13.4.2

The results above indicate that sedation is an effective treatment option for dental work in children. We must keep in mind that a small percentage of children will always be difficult to manage with sedation.

5.13.4.3 Physical Signs.

Physical signs of discomfort were the last parameter of the evaluation of efficacy in graph 5.13.4.3. This was measured according to the pulse rate of the patients. This correlates very well with the haemodynamic adverse events that were discussed under the topic of safety.

- The largest group, 94.5% in graph 5.13.4.3 had baseline heart rates.
- A total of 5% of the study group showed a moderate tachycardia of 160 – 180 beats per minute.
- Only 0.5% or one patient had a transient tachycardia of more than 180 beats per minute. This is the same child with a cleft palate repair that has been mentioned previously.



Graph 5.13.4.3

The last parameter in the efficacy evaluation also shows that sedation is an acceptable alternative treatment option for dental work in children as 94.5% of the children showed no signs of discomfort.

5.14 PARENT EVALUATION

The parents of the children were asked to complete a questionnaire before the child was discharged (Annexure D, p100). These questions will be discussed and the results shown on graphs in the section first questionnaire.

The parents were also given a second questionnaire to complete the following day. (Annexure E, p 101). Of these second questionnaires 64 were returned, and these results are included in the discussion and the graphs in the section second questionnaire.

FIRST QUESTIONNAIRE

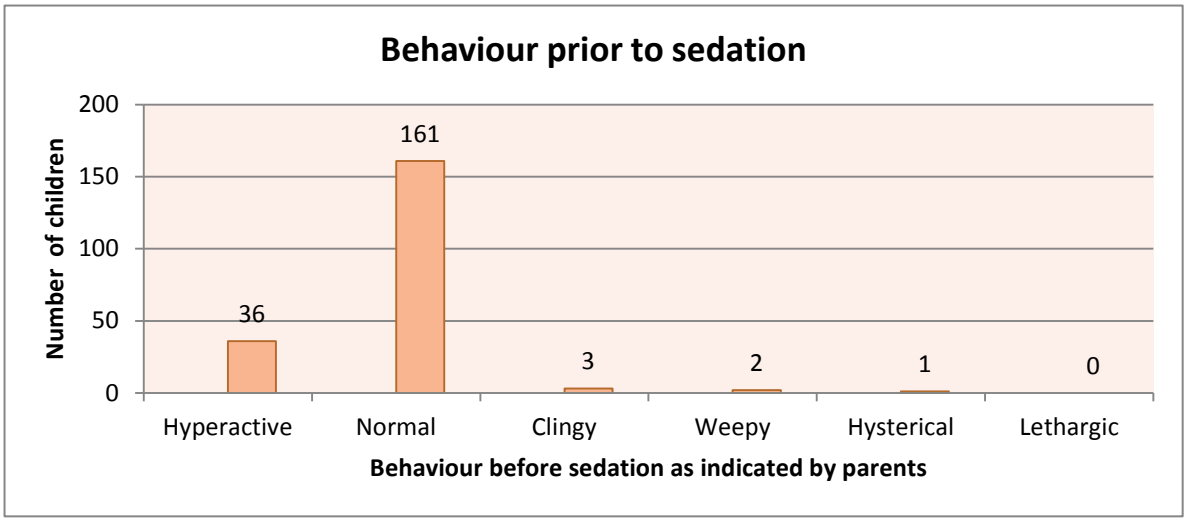
Every parent filled out this questionnaire before their child was discharged.

Question 1 and 2 – Normal Behaviour.

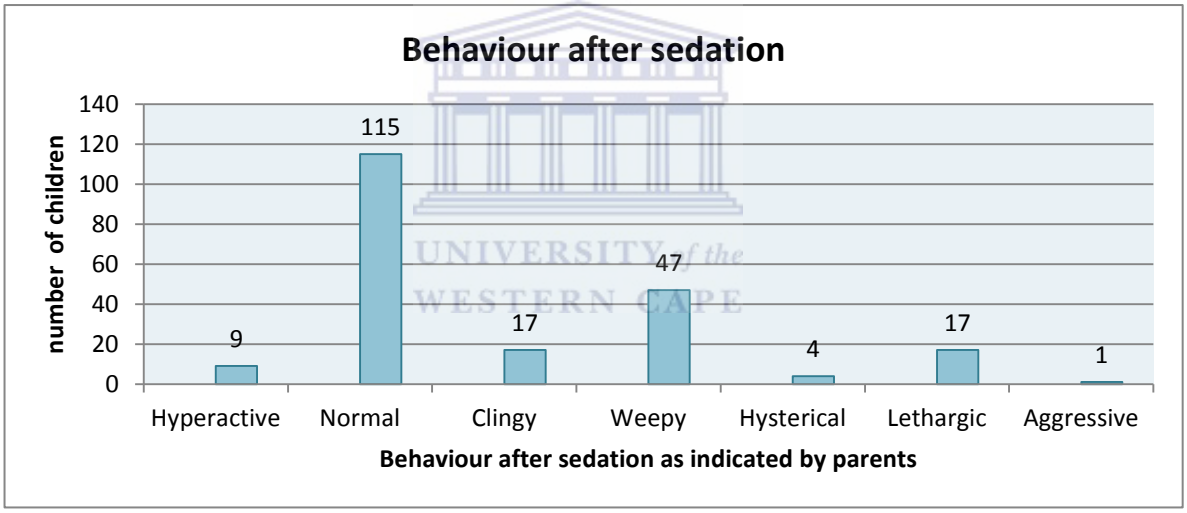
Question one asked the parents about their child's normal, usual behaviour and question 2 asked the parents about their child's behaviour after the sedation. These questions were asked to see if there was any correlation between a child's normal behaviour and how they behave after sedation. The same questions were asked in question 2 after the sedation.

The parents indicated that 36 or 18% of the children were hyperactive. In the medical history questionnaire, only eight of the children were actually on Ritalin® as treatment for hyperactivity. Hyperactive children are sometimes perceived to be difficult to sedate by

sedation practitioners, but in this study, only 4 of the 36 children who were hyperactive, were actually marked as being a difficult sedation.



Graph 5.14.1



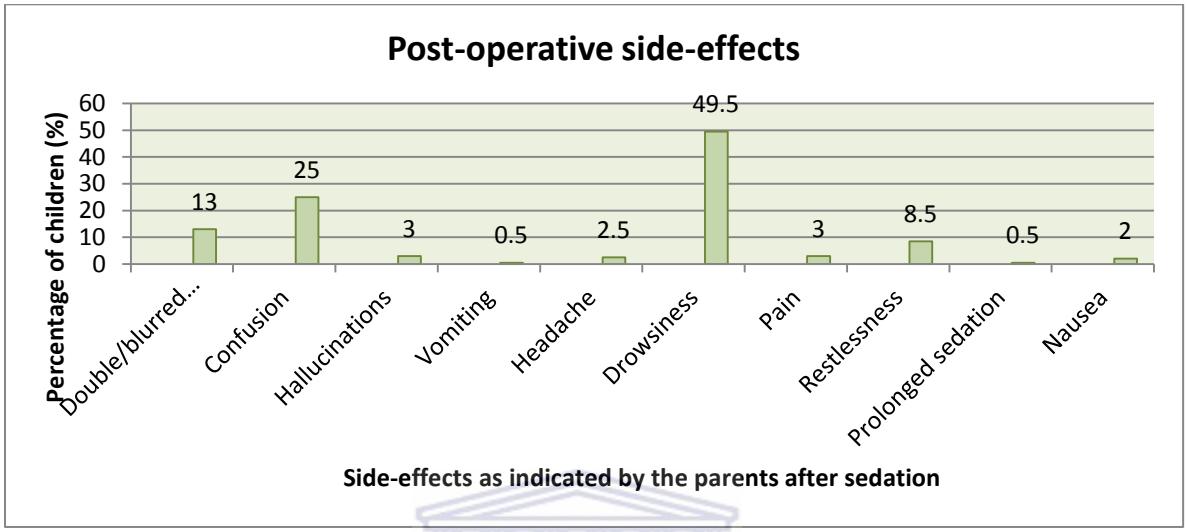
Graphic 5.14.2

In their opinion, 47 of the children were crying after the procedure. This is not an abnormal response after administration of drugs in children. They receive drugs, become awake in a strange environment, and often have visual disturbances, and their mouth is numb from the local anaesthetic. This all may contribute to side effects.

Only one child (0.5%) was aggressive after the sedation. This child has not had a general anaesthetic before, so no comparison could be made. Four of the children who had general anaesthesia before, were very aggressive after the anaesthetic. None of these children showed any aggression after the sedation.

Question 3 – Side-effects of Sedation.

Parents were asked to report possible side-effects after sedation. The most common side-effects were explained to the parents, and they were asked to mark those applicable to their child (possible side effects are shown in the graph). There were no restrictions on how many they could report. The following graph shows the results.

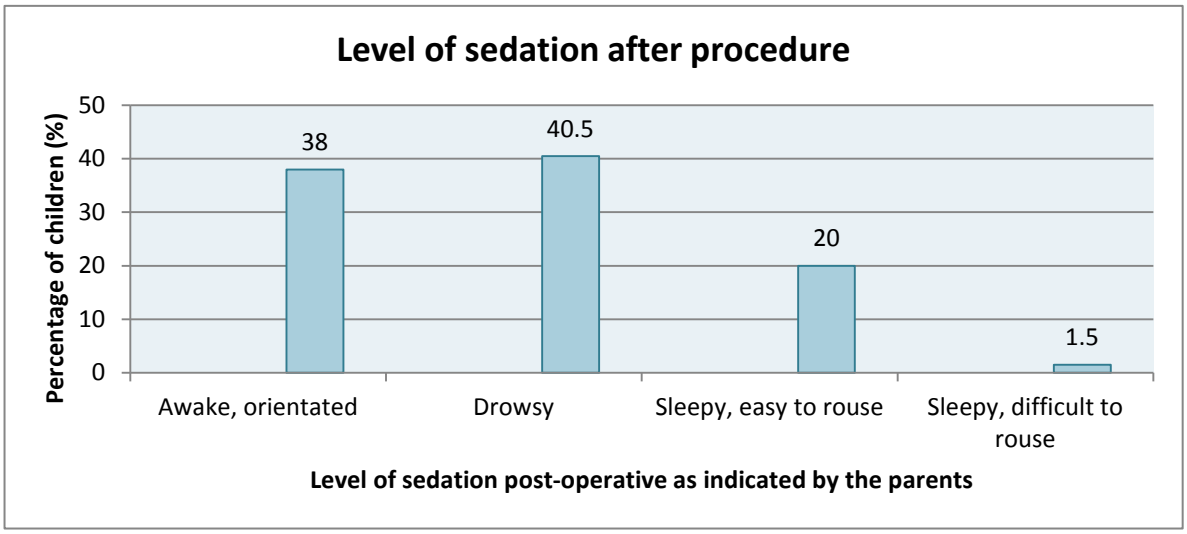


Graphic 5.14.3

- 49.5% of the parents thought that their children were drowsy after the sedation, where the sedation practitioner only evaluated 10.5% as drowsy. This is due to the fact that the sedation practitioner marked the child as drowsy only when the drowsiness was excessive. The parents were also called in to sit with their children as soon as the procedure was completed, and the children were not awake yet.
- The incidence of blurred or double vision was 13%, and this is to be expected. The incidence of side effects was more or less the same as evaluated by the sedation practitioner and the parents.

Question 4 – Level of sedation (consciousness) after procedure.

The parents were asked to evaluate the level of sedation (consciousness), 30 minutes after the sedation. This is an indication of recovery of the children.



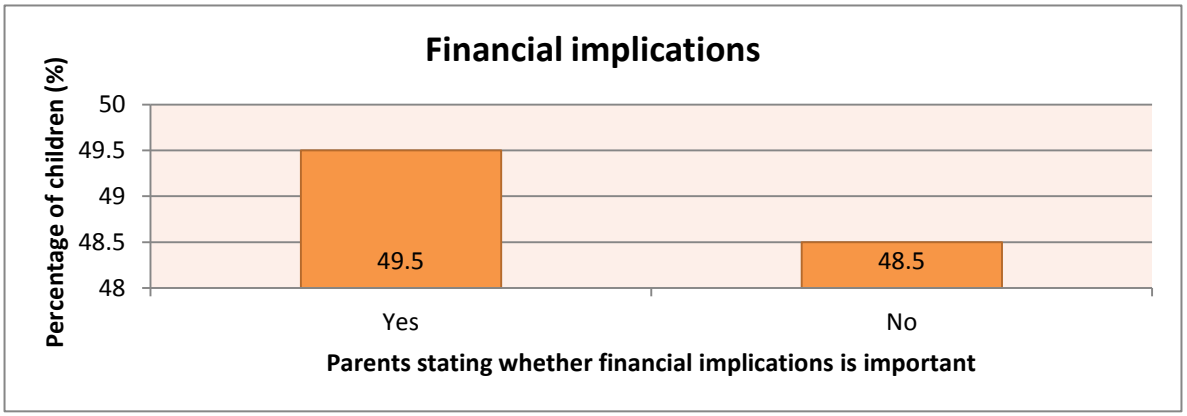
Graphic 5.14.4

- About 38% of parents evaluated their children as awake and orientated after sedation.
- 40.5% of children were still drowsy, but awake.
- 20% of the children were sleeping but easy to rouse.
- Only three children (1.5%) were difficult to rouse, but they still maintained their airway and breathing. The results are shown in the graph 5.14.4.

The above again indicates that post-operative recovery care is extremely important in children.

Question 5 – Financial Implications.

The parents were asked if financial implications will play a role in their decision whether to have sedation or anaesthesia for their children. Four parents did not answer the question.



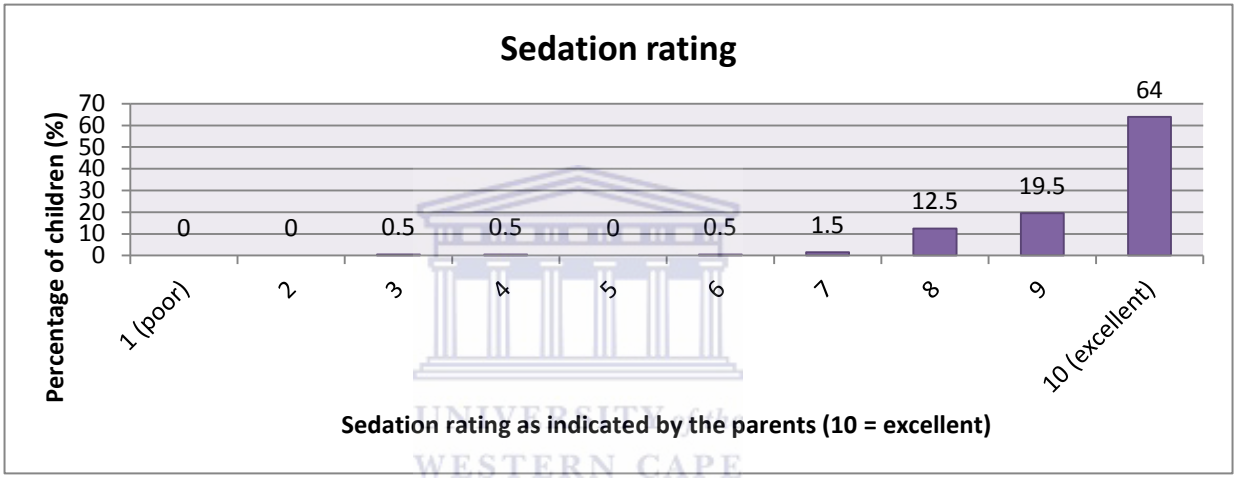
Graph 5.14.5

The parents who answered the question responded as follows:

- 97 said that the financial implications did not play a role in their decision.
- 99 said that finances did make a difference.
- This indicated that 49.5% of the parents considered the financial implications in their decision whether there child will go to theatre for dental work, or have sedation in the consulting room. In the current financial market, this confirms how important cost savings are to parents.

Question 6 – Sedation Experience

The parents were asked to rate the sedation experience on a VAS scale from 1 to 10, where 10 is excellent and 0 poor. The results are displayed on graph 5.14.6



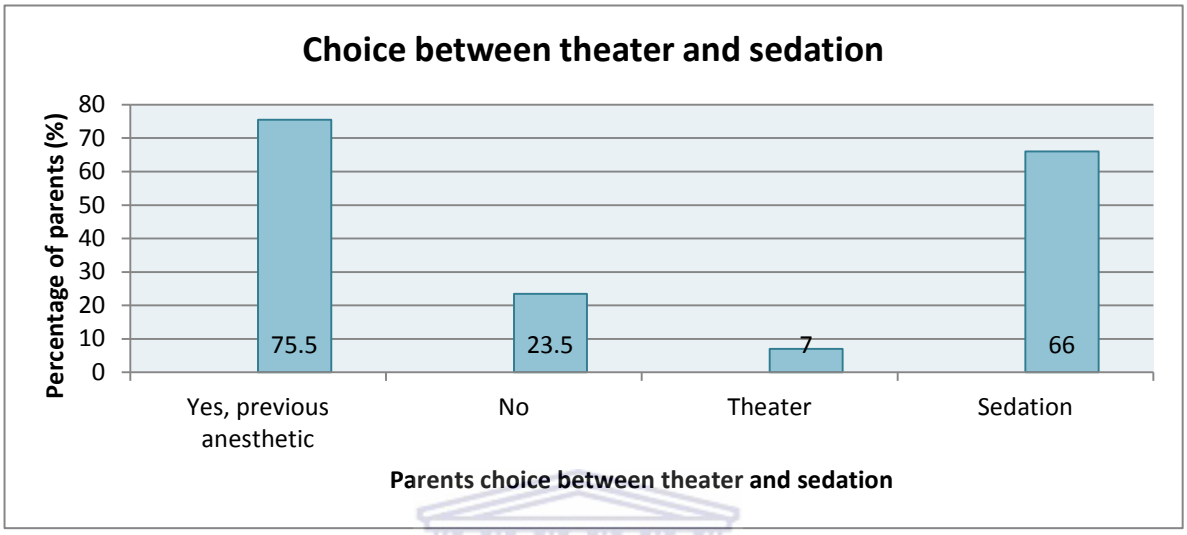
Graph 5.14.6

- The lowest score indicated the sedation experience as three.
- One parent gave a rating as four. Both these parents were expecting something similar to anaesthesia, children will be "knocked out". It is important for a successful sedation for the parents to have realistic expectations. This can only be achieved by communication with the parents and explaining the differences between sedation and general anaesthesia. The operator also needs to explain the procedure to the parents.
- Most of the parents were satisfied with their child's sedation experience, since 96% of the parents rated the sedation between 8 and 10.

Question 7 – Anaesthesia versus Sedation

With this question the parents were asked whether their children had an anaesthetic before, and if they had, would they prefer sedation or anesthesia if it is possible to choose. The study group consisted of patients who are mostly on medical aid. In this group 75.5% of

the patients had previous exposure to general anaesthesia. This gave the parents a good platform to compare sedation and general anaesthesia. Of the 151 parents who answered yes to this question, five said either sedation or general anaesthesia would be acceptable. These five answers were excluded in graph 5.14.7 that shows the choice between sedation and theater.



Graph 5.14.7

146 parents answered this question as follows:

- 14 parents chose general anaesthesia (7%).
- 132 chose sedation (66%). This implies that 2 out of every 3 parents would prefer sedation for dental work.

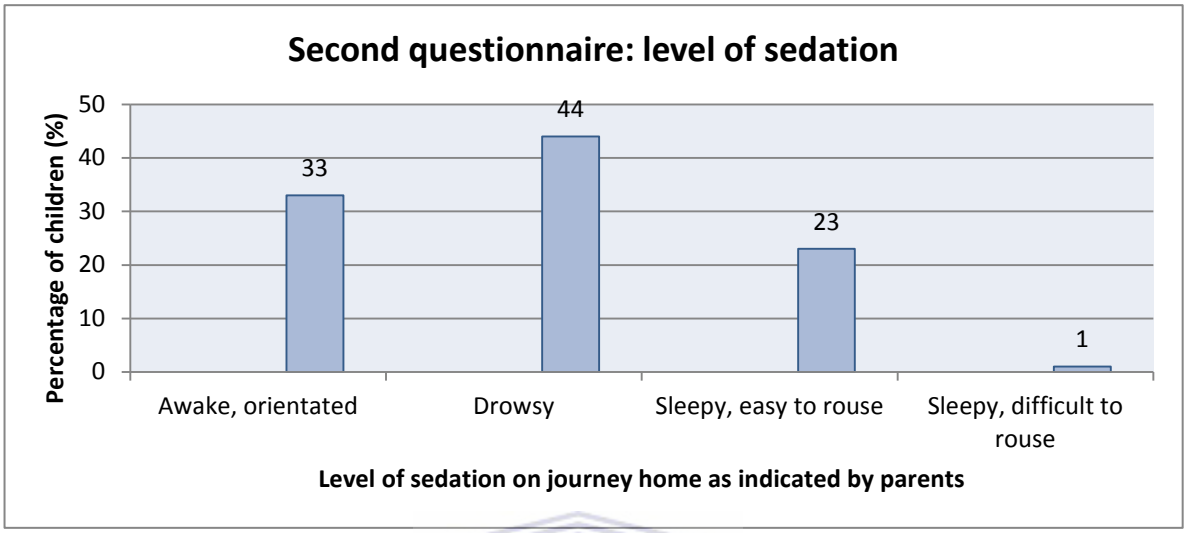
SECOND QUESTIONNAIRE

The second questionnaire (Annexure E, p101) was given to the parents to complete 24 hours after the sedation. Only 65 of these questionnaires were returned and were included in the study. In this section only 3 of the questions will be reported on, as it will contribute to the efficacy and safety aspect of this study, namely:

- Question 3: Level of sedation on the journey home.
- Question 4: Level of sedation 24 hours after sedation.
- Question 6: Child's memory.

Question 3 – Level of Sedation (consciousness).

This question was asked to clarify the level of sedation (consciousness) on their journey home. Results are displayed in graph 5.14.10.



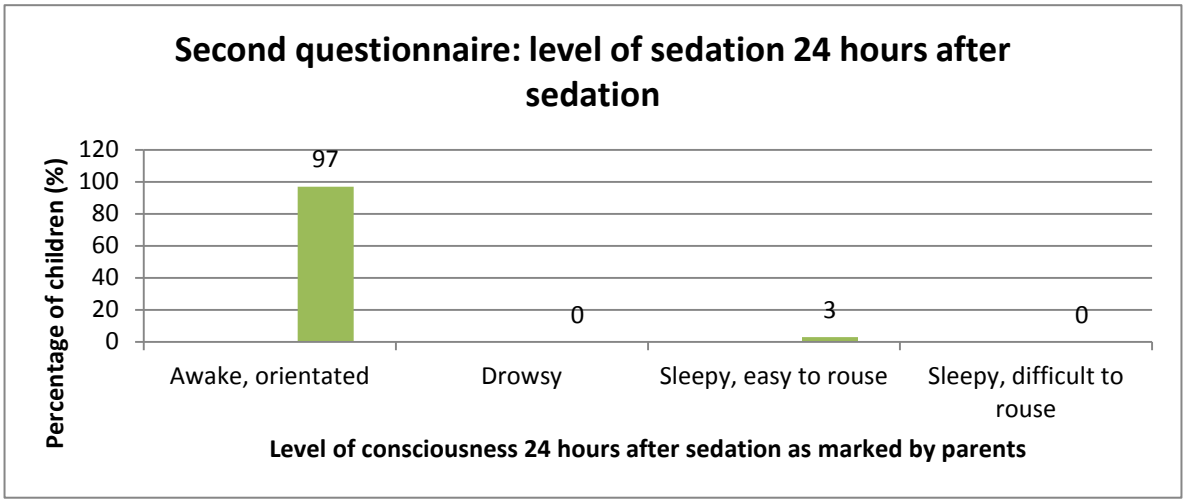
Graph 5.14.8

- Only one parent reported that the child was sleeping and difficult to rouse.
- Most of the children were drowsy, namely 44%. Parents were warned to look after the airway of the children on the journey home.

The response of the one parent that their child was difficult to rouse, again emphasizes the point of the importance of discharge criteria. Children who are not stimulated can slip into a deeper level of sedation, and this can lead to morbidity and mortality in pediatric sedation.

Question 4 – Level of Sedation (consciousness).

This question evaluated the level of sedation 24 hours after the sedation. Results are shown in graph 5.14.9



Graph 5.14.9

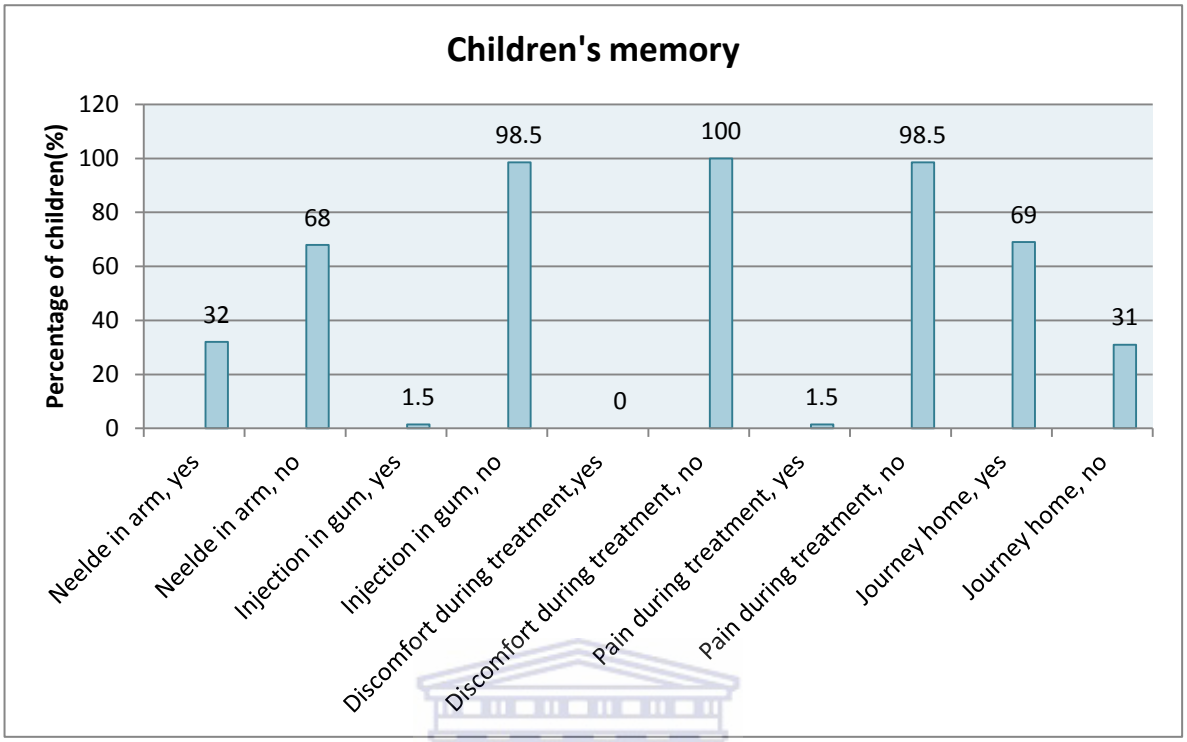
- 97% of the children were awake and oriented.
- 3% were sleepy but easy to rouse.

Question 6 – Child's Memory.

This question was asked to evaluate the child's memory (recollection) of the procedure. The following questions were asked.

- Whether they could remember the start of the intravenous injection.
- Whether they were aware of the injection in the gum.
- Whether they had discomfort during the procedure.
- Whether they had pain during the procedure.
- Whether they could remember the journey home.

The results are shown in graph 5.14.10



Graph 5.14.10

- Although 32% of children said that they could remember the injection, no one said that they had any discomfort during the procedure.
- 1.5% could remember the injection in the gum.
- Only one child stated that he/she had pain during the treatment.
- 31% of the children did not even remember the journey home.

These questions, that were answered by the parents the day after the procedure, again shows the safety and efficacy of sedation for dental procedures in children.

Comments made by the parents are included in Annexure J(p.106).

CHAPTER SIX

CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

In the literature review for this study, the researcher looked at articles that report sedation on a total of more than one thousand eight hundred paediatric patients.

- None of these studies showed any serious morbidity and the mortality rate was zero.
- Minor adverse events were mostly respiratory in nature which was rated as minor with no escalation in care.
- Results were excellent because all of these studies were done in large academic centres where the guidelines for paediatric sedation were followed, from the pre-operative evaluation, dedicated monitoring throughout the procedure and proper recovery and discharge criteria.

The design of this study was planned to evaluate the safety and efficacy of sedation according to certain parameters for children between two and ten years of age, with the focus on sedation done in the dentist's chair/office outside of a theatre environment.

Both the operator and the sedation practitioner used tables with certain parameters and values to score the efficacy and safety of sedations consequently. Conclusions from this study will be discussed under the following headings: General, Safety, Efficacy and Drugs. The discussion of the recommendations will follow with final comments at the end.

6.2 CONCLUSIONS

6.2.1 GENERAL

Patient selection: Children from 3 years of age that fall in an ASA 1 or 2 category is suitable for sedation in the dentist's office. Younger children e.g. between 2 and 3 years should be evaluated by the sedation practitioner beforehand. The operator/dentist should be aware of body mass index guidelines to avoid obese children being booked on the sedation list.

Instructions: All the parents should receive verbal as well as written instructions to prepare for the sedation procedure. The Emla patch used as local anaesthetic for cannulation and the nul per os requirements should be explained.

Pre-medication: Midazolam and ketamine are good choices to use as pre-medication.

Intravenous cannulation: Most children are afraid of needles, and using pre-medication and Emla patches makes the placement of the intravenous cannula easier for the child, the parent and the sedation practitioner.

Techniques used: Different sedation techniques are available to use for paediatric sedation. The decision of whether a bolus or continues infusion technique should be used, must be decided by the sedation practitioner taking into consideration the length and type of the planned procedure.

Monitoring: Pulse rate, saturation, respiratory rate and blood pressure should be monitored throughout the procedure. Vigilant observation from the sedation practitioner is extremely important.

Resuscitation: All necessary resuscitation equipment and an AED suitable for paediatric use should be unpacked and available for every paediatric sedation.

Reasons for surgery: Fillings, pulpotomy's, extractions, tooth exposure, frenectomy's and root canal treatments are suitable procedures that can be done for children with sedation in the dentist's chair.

Time of procedures: The majority of sedation procedures are short in duration. This obviously will add to the safety of paediatric sedation practice.

Failed sedation: The failure rate is extremely low and warrants no further comment than to say that paediatric sedation can be extremely difficult. There is no factor that could be found to predict a difficult sedation in ASA 1 or 2 children. It is no shame to abandon sedation in the interest of safety and to suggest general anaesthesia for certain patients.

Financial implications: In the current economical climate, financial implications of medical care are very important. Sedation is a cost effective alternative to general anaesthesia and theatre costs.

6.2.2 SAFETY

Level of consciousness: The children were reacting to vocal or light physical stimulation. This level of consciousness is required for moderate (conscious) sedation in all guidelines for sedation outside of the operating room.

Evidence of airway compromise: The majority of children should be able to maintain their own airway or need only minimal interference to keep their airway open. This also confirms that moderate or conscious sedation is practised.

Respiratory adverse events: Airway management should be applied timeously to prevent serious complications, morbidity and mortality, as most of the adverse events in children is respiratory in origin. The administration of oxygen should be considered early. When using very low dosages of sedation medication, respiratory depression can be avoided. Tachypnoea pre-operatively is an important observation because it can indicate a respiratory infection.

Haemodynamic adverse events: An increase in pulse rate is the most common haemodynamic adverse event. This is commonly seen in very anxious children. The tachycardia can be treated by adjusting the level of sedation to procedural sedation until the pulse rate stabilizes. Most of the painful stimulation in dental sedation is in the beginning of the procedure with the administration of the local anaesthetic.

Wilson sedation scale: The sedation level of children can be evaluated according to the Wilson sedation scale. Children should respond to verbal or mild physical stimulation. These levels are still moderate sedation, which is acceptable in an office setting outside of a theatre environment.

Steward recovery scale: This recovery scale is widely used and easy to implement. It is essential to have set discharge criteria to prevent complications after discharge of the children. Care should be taken to make note of this score on the monitoring chart in case of medico-legal consequences.

Fasting guidelines: Fasting for 4 hours prior to the procedure is sufficient in children.

Post-operative care: Post-operative care is crucial, because the stimulation from the procedure is absent and children can slip into deeper levels of sedation.

Side-effects: Post-operative side-effects are inevitable when administering medication to children. Children are usually anxious in a strange environment, and receive drugs. This all contribute to side-effects. The low incidence of side-effects in sedation practice is due to the low dosages of medication used.

In this research study no serious adverse events were seen mainly due to:

- Sedation being done by an experienced sedation practitioner
- Pre-operative evaluation and assessment done on all patients
- Careful and discriminate use of drugs
- Behavioural management techniques used
- Monitoring
- Children not being discharged before meeting the required discharge criteria
- Empowerment of the parents.

With all the parameters mentioned above, the sedation practitioner could come to the conclusion that paediatric sedation is safe in an office setting.

6.2.3 EFFICACY

This study evaluated the efficacy of the sedation procedure from the viewpoint of the operator/dentist, sedation practitioner and the parent.

Operator:

- The dentists found the procedures mostly easy to complete.
- They could deliver good quality work with the children keeping still and being quiet.
- This is extremely important and what we want for paediatric sedation.

Sedation practitioner:

- Pain and stress.

Sedation is an effective alternative to general anaesthetic to perform dental procedures in unco-operative and anxious children.

- Movement

Even with slight movement the dental procedures could be completed satisfactory. Minimal movement is expected in moderate (conscious) sedation and actually confirm that the level of sedation is moderate (conscious) sedation.

- Physical signs that included monitoring the pulse rate.

Monitoring the children for signs of distress is important to ensure that they don't experience pain or discomfort. The pulse rate can be used as an indicator of physical distress in the children.

With all the parameters mentioned above the sedation practitioner could come to the conclusion that sedation in children is possible and efficacious.

Parents:

- Most of the parents experienced sedation in a positive way.
- The children's behaviour was normal after 24 hours.
- The side effects in their children are all acceptable in sedation practice. No serious side effects occurred.
- The children were awake or sleeping but easily rousable after the sedation.
- The parents indicated that the financial implications will influence their decision whether to have sedation or general anaesthetic for dental work for their children.
- The parents would prefer sedation in the dentist's room to theatre.

6.2.4 DRUGS

The drugs used included pre-medication that were administered according to the age of the children. Children younger than six years received 3.75mg of midazolam and children older than six years received 7.5mg of midazolam. Some of the children received a second pre-medication that included ketamine 2mg/kg per os if they were not co-operative for placement of the intravenous cannula.

A bolus technique with ketofol was used in 7 patients. These procedures were planned to last 20 minutes or less. The remaining 193 patients received a continuous infusion of the following mixture: each ml of solution contained propofol 8.3mg, mepyramine maleate 1mg, ketamine 2mg and sufentanil 0.2µg. The infusion rate was between 2 to 4mg/kg/h.

- The advantage of using a continuous infusion technique is that the level of sedation can easily be titrated to a deeper level if needed or a more conscious level if the patient slipped into an unintended deeper level of sedation. Some of the children were done at a deeper level of sedation, but still without any serious complications.

- We need to follow international sedation guidelines for the paediatric population.

- The researcher wants to confirm statements in the literature that deep sedation being planned and performed by a trained sedation practitioner does not carry higher risk than conscious sedation, specifically when a pre-operative risk assessment was performed. [13]

- However, whenever excessive movements are encountered, the possibility of deep sedation must always be kept in mind. This is not according to the SASA guidelines on paediatric sedation, but it is sometimes difficult when doing sedation and one is faced with either cancelling the case or going to a deeper level of sedation for a short period of time.

- This shows that one must always consider that sedation is not the only option for children for dental procedures, in certain cases general anaesthesia will have to be considered.

- Throughout the literature studies concerning sedation shows that there are many different regimes of medications that were used and compared to each other. Some combinations of drugs were more efficacious than others.

- The type of procedure also influences the choice of drugs. Patients undergoing painful procedures will need more analgesic medication where less painful procedures will need more sedative drugs.

- It is evident from the above that sedation practitioners must have the knowledge and skills with administration of drugs. The skill of the sedation practitioner and his/her knowledge of the specific drugs they use, are much more important than specific sedation drug regimes.

6.3 RECOMMENDATIONS

The implementation of a mobile sedation service requires careful planning. The following components are of utmost importance:

Sedation practitioner:

- The sedation practitioner has to be experienced in office based sedation outside of the operating theatre.
- Post-graduate training is essential specific in paediatric sedation that can sometimes be extremely difficult.
- Working towards an accreditation system that is overseen by the Medical and Dental Council of South Africa would be a goal to set, specifically because we do have a post-graduate training course available. In South Africa there is no legal regulation currently as to who can perform paediatric sedation in the office based setting. SASA guidelines were published in 2010 that states very clearly who, where and how paediatric sedation can be done, but these are still only guidelines.

Operator:

- The operator/dentist has to be the important link in the sedation service to patients. This usually is the patients' first contact with the sedation procedure. It is important that the operator explains the procedure to the patients so that they do not have expectations that cannot be met e.g. "I want my child to be knocked out". (see comments of parents (Annexure K, p 107).
- The operator/dentist should also be trained in basic life support (BLS) and airway management. The fact that the dentist/operator is skilled in airway management usually makes the sedation easier to do.
- In cases of emergency they have to help to treat the adverse event.
- The operator/dentist also has to accept the limitations of sedation and the fact that they need to adjust their usual method of work to the sedation.
- The experience of the operator/dentist also plays a role in the safety and efficacy of paediatric sedation.

Patient Selection:

- The operator/dentist is responsible for offering sedation as an option to their patients. For this reason they must have a good understanding of selection criteria for sedation patients. The final decision whether to do a patients stays the responsibility of the sedation practitioner. In the office based setting only ASA 1 and 2 patients are suitable, as according to all international guidelines.
- Anxiousness of the patient is extremely important. The patient who is phobic about needles is not a good choice for sedation because we have to start with the placement of an intravenous cannula. Unfortunately we do see patients for sedation who are not really suited because of financial implications.

Facility/Office:

- The facility/office where the sedations will be done must be easily accessible. An office on the second floor of buildings is questionable in their suitability, specifically when emergency and escalation of care occur.
- The size of the office must also be large enough to accommodate the sedation practitioner and all the equipment needed to perform office based sedation.

Communication with parents:

- It is important to give the patients written as well as oral instructions in preparation for sedation.
- Fasting guidelines must be adhered to. In this study the patients were fasting for 4 hours prior to the sedation procedure. Fasting can be difficult in children and the reasons need to be explained to the parents.
- It is also imperative to communicate with parents and explain the concept of sedation to them. They need to understand that there child is not going to be "knocked out", but that they will still be able to breath and even move a little bit, without feeling pain.
- In the cases of long procedures, parents should be informed that their child might need a second appointment to complete the work if they become restless.
- The parents should be warned about commonly occurring side effects, e. g. double vision.

Procedures and time management:

- In dentistry, any procedure that can be done in the dentist's chair with local anaesthetic can be done with sedation. The reasons for the procedures in this study included the following: fillings, extractions, pulpotomy's, tooth exposures, frenectomy's and even root canal treatments.
- For children, sedation is a very good option for procedures that can be unpleasant when the child is awake in the office chair.
- Time management should be applied when sedating children.

Emergency care:

- Awareness of the emergency care availability in the area where the sedation is performed is essential in the case of escalation of care.

Adverse events: To prevent serious adverse events when sedating children the following considerations are very important:

1. The sedation must be done by an experienced sedation practitioner
2. Pre-operative evaluation and assessment must be done on all patients
3. Drugs must be used carefully and discriminately
4. Behaviour management techniques must be used together with pharmacotherapy
5. Monitoring throughout the procedure is crucial
6. Discharge criteria must be implemented and followed strictly
7. The parents must be able to make an informed choice concerning the treatment of their children. This can only be done with good two way communication.

Drug use:

- The use of drugs in children should be done very carefully.
- Titration is extremely important.
- The sedation practitioner should be knowledgeable about the drugs he/she is using.
- Sedative drugs like midazolam, propofol and sufentanil must be titrated to avoid respiratory suppression.
- When using ketamine the following should be kept in mind:
    1. Emergence reactions can be seen in recovery, including vivid and often unpleasant dreams, confusion, hallucinations and irrational behavior. Children appear to be less sensitive. The incidence of emergence reactions is controversial - and is seen relatively seldom with the sedation dosages of ketamine.
    2. Ketamine should be injected slowly to avoid respiratory depression.
    3. Diplopia and nystagmus may occur. It is good practice to warn especially the parents of children about this. They can be very upset if the child complains that he/she cannot see.

Recovery and discharge:

- In all mobile sedation practices it is imperative that children should be recovered and discharged according to international discharge criteria to avoid post-operative morbidity and mortality.

6.4 FINAL COMMENTS

In conclusion, the researcher showed:

- That multidrug intravenous sedation can be administered to children safely and effectively. It is most important to adhere to all guidelines concerning the ability to rescue a patient when an adverse event does occur.
- Furthermore, the selection of patients is critical when working in an office based environment.
- There are a number of different multidrug techniques that have been published. The researcher wants to emphasize the point that the combinations of drugs used are less important than the experience and training of the sedation practitioner.
- The question whether conscious sedation can be done safely and effectively in an office environment for children between 2 and 10 years of age was answered very definitely as yes in this study. Moderate/conscious sedation is possible in children. It is safe to perform outside a theatre environment.

6.5 FURTHER RESEARCH

The following topics can be considered for further research:

- Multicentre studies to compare safety and efficacy data.
- Comparisons of different age groups as to the prevalence of adverse events.
- Multidrug intravenous drug regimes comparisons.

ANNEXURES

ANNEXURE A: Consent form

Doctor performing procedure:_____ Date:_____

I, the undersigned, hereby state that I am legally competent to give consent for this procedure and am aware of the nature and scope of the risks of the procedure and the sedation.
I give permission to the doctors concerned to take any blood tests as may deem necessary in the event of contamination of blood or body fluids to the health worker concerned.
I accept full responsibility for the account in the event that my medical aid should, for whatever reason, fail to settle the account in full.

PATIENT NAME: _____ Signature:_____

ANNEXURE B: Ethical statement

PATIENT INFORMATION

You are invited to take part in a research study by using information gained during the sedation procedure of your child. The efficacy and safety of sedation in children younger than 10 years will be recorded.
I, the undersigned_____
ID_____ the mother/father of_____
Address:_____

A. I confirm that:

1. I was invited by Dr. E. M. Swart to take part in this research study, as part of a thesis for the research MSc in sedation at the University of the Western Cape Dental department.
2. It has been explained to me that:
   - My child will undergo an intravenous sedation for a dental procedure to relief his/her pain and anxiety.
   - The drugs will be given intravenously, either by bolus injection or using an infusion, depending on the length of the planned procedure. The child will receive an Emla patch that should be placed over a suitable vein two hours before the time. This will give local anaesthesia to make the cannulation a painless procedure.
   - The medication used for the sedation is not new. The same medication has been used in anaesthetic practice for many years. Dr. Swart has been practising this technique since 2002.
   - The efficacy and safety of sedation will be evaluated according to set tables and questionnaires. The viewpoint of the dentist, the seditionist, and the parent accompanying the child will be taken into consideration.
   - I have been warned that any drug can cause side effects. The medication used may cause dry mouth, dizziness, double vision, red eyes, rarely nausea and vomiting.
   - My child will be monitored very carefully.
3. 200 Children will partake in this project over the next two years.
4. It has been explained to me that my child will make an important contribution to medical knowledge, so that this technique may be used elsewhere to help other children through unpleasant experiences.
5. All information regarding my child will be kept in strict confidence. The results will be published in a medical journal for the benefit of other researchers.
6. I hereby confirm that I have been told that if I change my mind after first deciding on the sedation, the dentist will offer me the most suitable alternative treatment. The care of my child will not suffer in any way. Dr. Swart may also withdraw my child from the study if it is in his/her best interest.
7. I have not been forced to participate in this study.
8. Participation in this study will not mean any extra costs for me. The cost of the sedation will be charged either to the medical aid or the patient as usually.

B. I hereby declare that I volunteer to participate in this study.

PARENT/LEGAL GAURDIAN

Signed at ___ _____ on_____
Parent_____ _____ witness_____

RESEARCHER

I _____ declare that the information in this document was explained to the parent/guardian in his own language and that he/she understands everything.

Signed at _____ on_____

Researcher _____ Witness_____

IMPORTANT INFORMATION:

If you need any additional information, or in an emergency situation, please contact: DR. E. M. Swart 0828512083.

ANNEXURE C: Instructions

PRE-INTRAVENOUS SEDATION INSTRUCTIONS

1. Please arrive at least 30 minutes before your appointment. This is so that we can give your child a Dormicum tablet. This medication will make them drowsy, so that we can start the intravenous line easily.
2. Please wear comfortable clothes with wide sleeves allowing easy access to the elbow region.
3. If you wear contact lenses, please bring your lens container with you, as you may be asked to remove your contact lenses.
4. Please do NOT eat or drink for 4 hours before your appointment.
5. A responsible adult must accompany the children and look after them for the rest of the day. Adults must arrange for someone to drive them home and stay with them.
6. The children should be kept quiet for the rest of the day, and not partake in any activities that require balancing or concentration.
7. If you take chronic medication on a regular basis, please inform the sedation practitioner, so that he/she can decide whether you should take your medication before the sedation.

POST SEDATION INSTRUCTIONS

1. Please do NOT take any alcohol for the remainder of the day.
2. If you are taking regular medication, please ask the sedation practitioner when you should continue to take them.
3. For PAIN relief you may take Paracetamol, Ponstan or Myprodol, depending on your personal preference and/or tolerance, unless your dentist or sedation practitioner has instructed you otherwise.
4. The sedation may produce AMNESIA. This is temporary, lasting sometimes for a few hours.
5. You may have clear fluids when instructed to do so by the sedation practitioner or dentist. If you feel fine after having clear fluids, and the local anaesthetic has worn of you may then progress onto solids. Keep to soft foods for the rest of the day.
6. You may feel tired and/or low for up to 24 hours after the sedation.
7. In case of bleeding, apply a wet teabag to the bleeding socket and bite on the teabag for at least 20 minutes.
8. We do not anticipate you having any medical problems, but should you become concerned about anything, however trivial it may seem, contact your sedation practitioner, Dr. Swart on 0828512083 or 011-3919015.

ANNEXURE D:

PARENT QUESTIONNAIRE ONE

Date _____ Name _____

Gender: M / F

Please answer the following:

1. Which one of the following would best describe your child's normal behaviour pattern?

Hyperactive	
Normal	
Clingy	
Weepy	
Hysterical	
Lethargic	

2. After the sedation, which one would best describe your child's behaviour pattern?

Hyperactive	
Normal	
Clingy	
Weepy	
Hysterical	
Lethargic	

3. Side-effects that occur with sedation are listed below. Please mark the ones that your child suffered from, if any.

Nausea		Confusion	
Vomiting		Pain	
Headache		Drowsiness	
Blurred/double vision		Hallucinations	
Restlessness		Prolonged sedation	

4. Level of sedation 30 minutes after sedation:

Awake and orientated	
Drowsy	
Sleeping but easy to rouse	
Sleeping but difficult to rouse	

5. Today the financial implications of medical procedures are becoming more important. It is estimated that sedation costs R1 for every R11 of theatre costs. Will the costs involved influence your decision about having sedation?

Yes	
No	

6. Please rate the sedation experience where 10 is the best.

Poor	1	2	3	4	5	6	7	8	9	10	Excellent

7. Has your child had anaesthetics in theatre before? Y/N. If yes, and it is possible to do a procedure with sedation, what would you prefer?

Sedation	
Theatre	

ANNEXURE E

PARENT QUESTIONNAIRE TWO

Date _____ Name _____

Gender: M / F

1. 12 hours after the sedation, which one would best describe your child's behaviour pattern?

Hyperactive	
Normal	
Clingy	
Weepy	
Hysterical	
Lethargic	

2. Side-effects that occur with sedation are listed below. Please mark the ones that your child suffered from, if any.

Nausea		Confusion	
Vomiting		Pain	
Headache		Drowsiness	
Blurred/double vision		Hallucinations	
Restlessness		Prolonged sedation	

3. Level of sedation during your journey home:

Awake and orientated	
Drowsy	
Sleeping but easy to rouse	
Sleeping but difficult to rouse	

4. Level of sedation 12 hours after the sedation:

Awake and orientated	
Drowsy	
Sleeping but easy to rouse	
Sleeping but difficult to rouse	

5. Did your child's behaviour after the sedation correlate with his/her normal behaviour patterns?

Yes	
No	

6. Did your child have any memory of the following?

	Yes	No
Needle in arm or hand		
Injection in the gum		
Discomfort during treatment		
Pain during treatment		
Journey home		

7. Please rate the sedation experience where 10 is the best.

Poor	1	2	3	4	5	6	7	8	9	10	Excellent

8. If you have any comments or suggestions, please write them down.

ANNEXURE F: Steward Recovery Scale

PARAMETER	FINDING	POINTS
Consciousness	Awake	2
	Arousable and responding to stimuli	1
	Not responding to stimuli	0
Airway	Coughing on command or crying	2
	Maintaining good airway and breathing easily	1
	Airway requires maintenance	0
Movement	Moving limbs purposefully	2
	Non-purposeful movements	1
	Not moving	0

Interpretation:

~ minimum score 0: fully anesthetized

~ maximum score 6: fully recovered

(Steward: 1975:111).

STEWARD, D.J. A simplified scoring system for the post-operative recovery room. Canad Anaest Soc J. 1975;22:111-113.

ANNEXURE G: Wilson Sedation Scale

WILSON SCALE

1 Fully awake and oriented
2 Drowsy
3 Eyes closed but rousable to command
4 Eyes closed but rousable to mild physical stimulation (earlobe tug)
5 Eyes closed but unrousable to mild physical stimulation

ANNEXURE H: Health Questionnaire

Please turn to next page

	QUESTIONNAIRE: TO BE COMPLETED BY PATIENT OR PARENT	YES	NO	DETAILS
1	Babies under 6 months: Was the birth premature, if so, how many weeks?			
2	**Illnesses which the patient now has or had**			
	- Heart diseases: Coronary thrombosis, angina, blood pressure, rheumatoid fever, congenital heart disease.			
	- Porphyry			
	- Asthma, bronchitis, emphysema or any other lung diseases.			
	- Cough or cold in the last two weeks.			
	- Jaundice, hepatitis or other liver diseases.			
	- Kidney diseases.			
	- Diabetes (state treatment being taken, as well as time of onset).			
	- Epilepsy (state treatment being taken)			
	- Arthritis			
	- Muscular disease, malignant hyperthermia, any family member with problems with anaesthesia			
3	**Smoking and alcohol**			
	- Alcohol (state average daily consumption)			
	- Smoking (state how much)			
4	**Operations**			
	- Operations undergone by patient (give dates).			
	- Complications or unusual reactions you or a family member had to local or general anaesthesia.			
5	**Medication being taken or taken previously**			
	- Blood pressure drugs			
	- Heart drugs			
	- Cortisone or other steroids (specify for previous two years)			
	- Thyriod drugs			
	- Anti-coagulants (e. g. warfarin, aspirin).			
	- Tranquilizers, sedatives, sleeping tablets or anti-depressant drugs.			
	- Any other drugs (including herbal and natural products, e,g. St. Johns wart, appetite suppressants, Biral)			
6	**General**			
	- False teeth, crowns, capping, loose teeth.			
	- Contact lenses.			
	- Time of last intake of food and liquid.			
	- Allergies and anything else that is relevant.			
	- Please weigh your child at home.			

ANNEXURE I: Spearman Correlation Reports

Please turn to next 2 foldout pages.

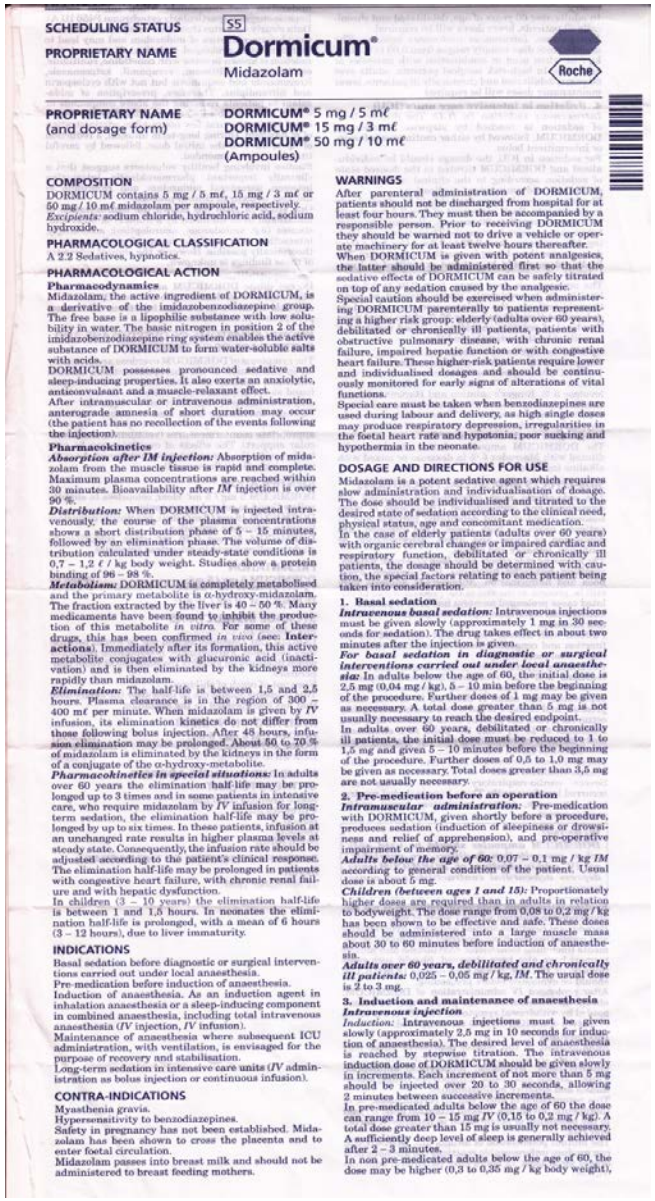
						#nulle	1	0.0000					
							2	0.0000					
							3	0.0000					
							4	**0.0000**					
	Correlation Report												
Spearman Correlations Section (Pair-Wise Deletion)													
	AGE	**WEIGHT**	**Dur_Sedation_Moved**	**Dur_Surgery_moved**	**Puls_start**	**Pul_Diff_10_S**	**Mx_m_Puls**	**Sis_Mx_M**	**Dia_Mx_M**	**Mean_SDia_Mx_M**	**SatU_Mx_M**	**Rp_Diff_10_S**	**ResP_Mx_M**
AGE	1	0.847	-0.100	-0.115	-0.468	0.051	0.003	-0.142	-0.051	-0.033	-0.021	0.113	-0.100
	0	**0.0000**	0.1587	0.1037	0.0000	0.4740	0.9658	0.0450	0.4718	0.6462	0.7640	0.1097	0.1600
	200	200	200	200	200	200	200	200	200	200	200	200	200
WEIGHT	0.847	1	-0.105	-0.121	-0.493	0.081	-0.015	-0.140	-0.051	-0.038	0.032	0.116	-0.097
	0.0000	0	0.1389	0.0876	**0.0000**	0.2531	0.8279	0.0479	0.4764	0.5971	0.6566	0.1028	0.1739
	200	200	200	200	200	200	200	200	200	200	200	200	200
Dur_Sedation_Moved	-0.100	-0.105	1	0.984	-0.023	-0.103	0.383	0.488	0.422	0.429	0.380	-0.097	0.419
	0.1587	0.1389	0	**0.0000**	0.7414	0.1475	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	0.1706	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
Dur_Surgery_moved	-0.115	-0.121	0.984	1	-0.018	-0.116	0.376	0.480	0.396	0.406	0.373	-0.079	0.412
	0.1037	0.0876	0	0	0.7998	0.1027	**0.0000**	**0.0000**	**0.0000**	**0.0000**	**0.0000**	0.2686	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
Puls_start	-0.468	-0.493	-0.023	-0.018	1	-0.215	-0.133	0.119	0.158	0.164	0.088	-0.059	0.092
	0.0000	0.0000	0.7414	0.7998	0	0.0023	0.0599	0.0929	0.0255	0.0206	0.2128	0.4103	0.1949
	200	200	200	200	200	200	200	200	200	200	200	200	200
Pul_Diff_10_S	0.051	0.081	-0.103	-0.116	-0.215	1	0.233	0.044	0.0341	-0.0114	-0.101	0.209	0.134
	0.4740	0.2531	0.1475	0.1027	0.0023	0	0.0009	0.5391	0.6316	0.8723	0.1543	0.0029	0.0595
	200	200	200	200	200	200	200	200	200	200	200	200	200
Mx_m_Puls	0.003	-0.015	0.383	0.376	-0.133	0.233	1	0.279	0.193	0.166	0.105	-0.006	0.315
	0.9658	0.8279	0.0000	0.0000	0.0599	0.0009	0	0.0001	0.0062	0.0185	0.1379	0.9374	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
Sis_Mx_M	-0.142	-0.140	0.488	0.480	0.119	0.044	0.279	1	0.627	0.725	0.248	-0.071	0.352
	0.0450	0.0479	0.0000	0.0000	0.0929	0.5391	0.0001	0	**0.0000**	**0.0000**	0.0004	0.3197	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
Dia_Mx_M	-0.051	-0.051	0.422	0.396	0.158	0.034	0.193	0.627	1	0.889	0.305	-0.048	0.403
	0.4718	0.4764	0.0000	0.0000	0.0255	0.6316	0.0062	0.0000	0	**0.0000**	**0.0000**	0.5000	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
Mean_SDia_Mx_M	-0.033	-0.038	0.429	0.406	0.164	-0.011	0.166	0.725	0.889	1	0.300	-0.088	0.334
	0.6462	0.5971	0.0000	0.0000	0.0206	0.8723	0.0185	0.0000	0.0000	0	**0.0000**	0.2141	**0.0000**
	200	200	200	200	200	200	200	200	200	200	200	200	200
SatU_Mx_M	-0.021	0.032	0.380	0.373	0.088	-0.101	0.105	0.248	0.305	0.300	1	-0.069	0.172
	0.7640	0.6566	0.0000	0.0000	0.2128	0.1543	0.1379	0.0004	0.0000	0.0000	0	0.3296	0.0146
	200	200	200	200	200	200	200	200	200	200	200	200	200
Rp_Diff_10_S	0.113	0.116	-0.097	-0.079	-0.059	0.209	-0.006	-0.071	-0.048	-0.088	-0.069	1	0.130
	0.1097	0.1028	0.1706	0.2686	0.4103	0.0029	0.9374	0.3197	0.5000	0.2141	0.3296	0	0.0666
	200	200	200	200	200	200	200	200	200	200	200	200	200
ResP_Mx_M	-0.100	-0.097	0.419	0.412	0.092	0.134	0.315	0.352	0.403	0.334	0.172	0.130	1
	0.1600	0.1739	0.0000	0.0000	0.1949	0.0595	0.0000	0.0000	0.0000	0.0000	0.0146	0.0666	0
	200	200	200	200	200	200	200	200	200	200	200	200	200

						#nulle	1	0.0000		
							2	0.0000		
							3	0.0000		
							4	**0.0000**		
	Correlation Report									
Spearman Correlations Section (Pair-Wise Deletion)										
	AGE	**WEIGHT**	**Pulse start**	**Duration**	**Averg Pulse**	**Averg SisT**	**Averg DiasT**	**Averg MeaN**	**Averg_SatU**	**Averg ResP**
AGE	1	0.847	-0.468	-0.112	-0.446	0.386	0.217	0.294	0.058	-0.187
	0	**0.0000**	**0.0000**	0.1137	**0.0000**	**0.0000**	0.0020	**0.0000**	0.4165	0.0081
	200	200	200	200	200	200	200	200	200	200
WEIGHT	0.847	1	-0.493	-0.114	-0.495	0.435	0.246	0.335	0.027	-0.170
	0.0000	0	**0.0000**	0.1078	**0.0000**	**0.0000**	0.0004	**0.0000**	0.7074	0.0163
	200	200	200	200	200	200	200	200	200	200
Puls_start	-0.468	-0.493	1	0.004	0.772	-0.113	-0.022	-0.065	-0.226	0.348
	0.0000	0.0000	0	0.9547	**0.0000**	0.1125	0.7582	0.3570	0.0013	**0.0000**
	200	200	200	200	200	200	200	200	200	200
Duration	-0.112	-0.114	0.004	1	0.111	-0.058	-0.180	-0.155	-0.118	-0.096
	0.1137	0.1078	0.9547	0	0.1191	0.4173	0.0107	0.0289	0.0957	0.1768
	200	200	200	200	200	200	200	200	200	200
Averg_Pulse	-0.446	-0.495	0.772	0.111	1	-0.015	0.064	0.033	-0.085	0.423
	0.0000	0.0000	0.0000	0.1191	0	0.8370	0.3679	0.6437	0.2287	**0.0000**
	200	200	200	200	200	200	200	200	200	200
Averg_SisT	0.386	0.435	-0.113	-0.058	-0.015	1	0.654	0.854	0.166	0.077
	0.0000	0.0000	0.1125	0.4173	0.8370	0	**0.0000**	**0.0000**	0.0188	0.2771
	200	200	200	200	200	200	200	200	200	200
Averg_DiasT	0.217	0.246	-0.022	-0.180	0.064	0.654	1	0.928	0.281	0.019
	0.0020	0.0004	0.7582	0.0107	0.3679	0.0000	0	**0.0000**	0.0001	0.7937
	200	200	200	200	200	200	200	200	200	200
Averg_MeaN	0.294	0.335	-0.065	-0.155	0.033	0.854	0.928	1	0.271	0.057
	0.0000	0.0000	0.3570	0.0289	0.6437	0.0000	0.0000	0	0.0001	0.4195
	200	200	200	200	200	200	200	200	200	200
Averg_SatU	0.058	0.027	-0.226	-0.118	-0.085	0.166	0.281	0.271	1	-0.003
	0.4165	0.7074	0.0013	0.0957	0.2287	0.0188	0.0001	0.0001	0	0.9708
	200	200	200	200	200	200	200	200	200	200
Averg_ResP	-0.187	-0.170	0.348	-0.096	0.423	0.077	0.019	0.057	-0.003	1
	0.0081	0.0163	0.0000	0.1768	0.0000	0.2771	0.7937	0.4195	0.9708	0
	200	200	200	200	200	200	200	200	200	200

ANNEXURE J: COMMENTS OF PARENTS

- Patient 5: Thank you for looking after her so well during the sedation. It was appreciated.
- Patient 20: Thank you for your patience and warm affection.
- Patient 43: Sedation is a very comfortable method to treat the kids.
- Patient 44: Best way of taking kids to the dentist for pulling teeth. Will recommend it to everybody with kids.
- Patient 59: Happy with sedation. Less traumatic on the child.
- Patient 95: I would recommend sedation.
- Patient 122: Will recommend at any time.
- Patient 147: Thank you, it was a pleasant experience.
- Patient 153: I am pro sedation. It is also less traumatic.
- Patient 155: Six year old daughter told experience to family with no fear. Simple, short procedure that will be considered for future dental treatment.
- Patient 162: She did very well this time. The previous anaesthetic did not go so well.
- Patient 176: My son is an anxious child, but handled the sedation very well because he was pre-informed. Sedation worked very well for him – thank you.
- Patient 177: His sedation took a lot longer to wear off than his brother's, therefore the possible aggressive behaviour and biting of the tong. I am grateful for the room's suggestion of the black tea to stop the blood. I am however grateful to the sedation practitioner for the pre-informed details, reactions etc. Apart from the cost saving (due to having no medical aid), the sedation choice in rooms instead of hospital was by far the better choice. Thank you. I am sincerely grateful with your professional, friendly service.
- Patient 179: I understood she would be less conscious.
- Patient 182: My child had no side-effects. I am very happy with the sedation. My child handled it very well with no pain. I would refer anybody to you.
- Patient 196: The sedation practitioner's approach to my son was fantastic. The procedure was explained to my son and he was made to feel comfortable. Thank you.

ANNEXURE K: Midazolam



SCHEDULING STATUS
S5

PROPRIETARY NAME
Dormicum®
Midazolam

Roche

PROPRIETARY NAME (and dosage form)
DORMICUM® 5 mg / 5 mℓ
DORMICUM® 15 mg / 3 mℓ
DORMICUM® 50 mg / 10 mℓ
(Ampoules)

COMPOSITION
DORMICUM contains 5 mg / 5 mℓ, 15 mg / 3 mℓ or 50 mg / 10 mℓ midazolam per ampoule, respectively.
Excipients: sodium chloride, hydrochloric acid, sodium hydroxide.

PHARMACOLOGICAL CLASSIFICATION
A 2.2 Sedatives, hypnotics.

PHARMACOLOGICAL ACTION
Pharmacodynamics
Midazolam, the active ingredient of DORMICUM, is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active substance of DORMICUM to form water-soluble salts with acids.
DORMICUM possesses pronounced sedative and sleep-inducing properties. It also exerts an anxiolytic, anticonvulsant and a muscle-relaxant effect.
After intramuscular or intravenous administration, anterograde amnesia of short duration may occur (the patient has no recollection of the events following the injection).

Pharmacokinetics
Absorption after IM injection: Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. Bioavailability after *IM* injection is over 90 %.
Distribution: When DORMICUM is injected intravenously the course of the plasma concentrations shows a short distribution phase of 5 – 15 minutes, followed by an elimination phase. The volume of distribution calculated under steady-state conditions is 0,7 – 1,2 ℓ / kg body weight. Studies show a protein binding of 96 – 98 %.
Metabolism: DORMICUM is completely metabolised and the primary metabolite is α-hydroxy-midazolam. The fraction extracted by the liver is 40 – 50 %. Many medicaments have been found to inhibit the production of this metabolite *in vitro*. For some of these drugs, this has been confirmed *in vivo* (see: **Interactions**). Immediately after its formation, this active metabolite conjugates with glucuronic acid (inactivation) and is then eliminated by the kidneys more rapidly than midazolam.
Elimination: The half-life is between 1,5 and 2,5 hours. Plasma clearance is in the region of 300 – 400 mℓ per minute. When midazolam is given by *IV* infusion, its elimination kinetics do not differ from those following bolus injection. After 48 hours, infusion elimination may be prolonged. About 50 to 70 % of midazolam is eliminated by the kidneys in the form of a conjugate of the α-hydroxy-metabolite.
Pharmacokinetics in special situations: In adults over 60 years the elimination half-life may be prolonged up to 3 times and in some patients in intensive care, who require midazolam by *IV* infusion for long-term sedation, the elimination half-life may be prolonged by up to six times. In these patients, infusion at an unchanged rate results in higher plasma levels at steady state. Consequently, the infusion rate should be adjusted according to the patient's clinical response. The elimination half-life may be prolonged in patients with congestive heart failure, with chronic renal failure and with hepatic dysfunction.
In children (3 – 10 years) the elimination half-life is between 1 and 1,5 hours. In neonates the elimination half-life is prolonged, with a mean of 6 hours (3 – 12 hours), due to liver immaturity.

INDICATIONS
Basal sedation before diagnostic or surgical interventions carried out under local anaesthesia.
Pre-medication before induction of anaesthesia.
Induction of anaesthesia. As an induction agent in inhalation anaesthesia or a sleep-inducing component in combined anaesthesia, including total intravenous anaesthesia (*IV* injection, *IV* infusion).
Maintenance of anaesthesia where subsequent ICU administration, with ventilation, is envisaged for the purpose of recovery and stabilisation.
Long-term sedation in intensive care units (*IV* administration as bolus injection or continuous infusion).

CONTRA-INDICATIONS
Myasthenia gravis.
Hypersensitivity to benzodiazepines.
Safety in pregnancy has not been established. Midazolam has been shown to cross the placenta and to enter foetal circulation.
Midazolam passes into breast milk and should not be administered to breast feeding mothers.

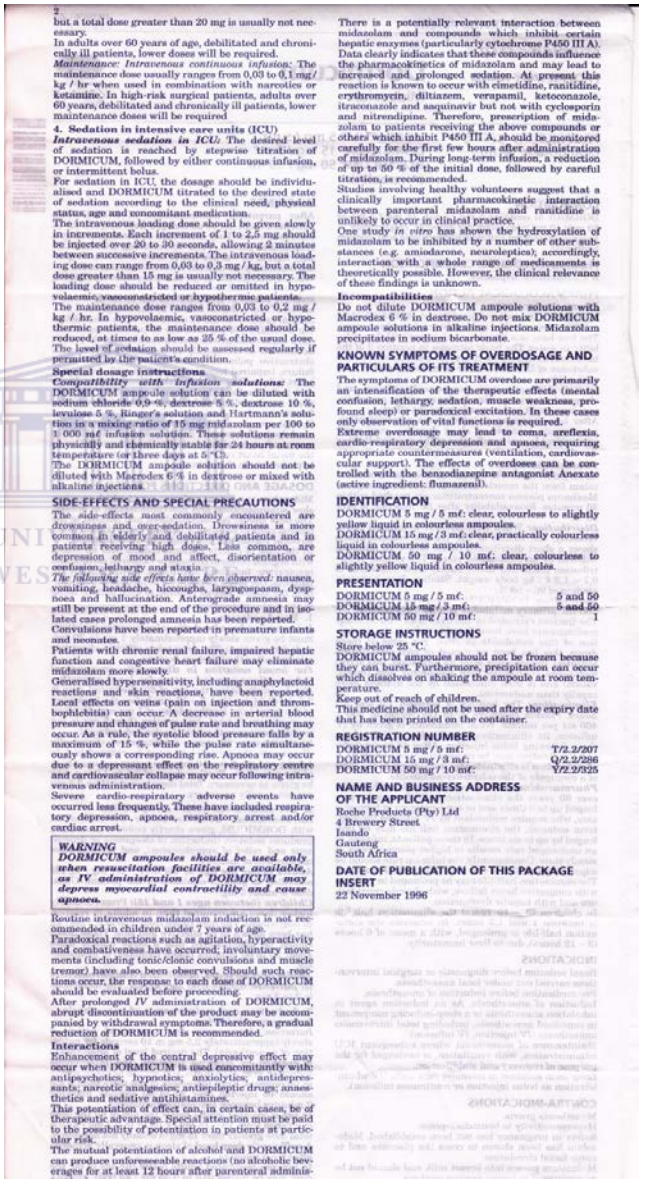
WARNINGS
After parenteral administration of DORMICUM, patients should not be discharged from hospital for at least four hours. They must then be accompanied by a responsible person. Prior to receiving DORMICUM they should be warned not to drive a vehicle or operate machinery for at least twelve hours thereafter.
When DORMICUM is given with potent analgesics, the latter should be administered first so that the sedative effects of DORMICUM can be safely titrated on top of any sedation caused by the analgesic.
Special caution should be exercised when administering DORMICUM parenterally to patients representing a higher risk group: elderly (adults over 60 years), debilitated or chronically ill patients, patients with obstructive pulmonary disease, with chronic renal failure, impaired hepatic function or with congestive heart failure. These higher-risk patients require lower and individualised dosages and should be continuously monitored for early signs of alterations of vital functions.
Special care must be taken when benzodiazepines are used during labour and delivery, as high single doses may produce respiratory depression, irregularities in the foetal heart rate and hypotonia, poor sucking and hypothermia in the neonate.

DOSAGE AND DIRECTIONS FOR USE
Midazolam is a potent sedative agent which requires slow administration and individualisation of dosage. The dose should be individualised and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.
In the case of elderly patients (adults over 60 years) with organic cerebral changes or impaired cardiac and respiratory function, debilitated or chronically ill patients, the dosage should be determined with caution, the special factors relating to each patient being taken into consideration.

1. Basal sedation
Intravenous basal sedation: Intravenous injections must be given slowly (approximately 1 mg in 30 seconds for sedation). The drug takes effect in about two minutes after the injection is given.
For basal sedation in diagnostic or surgical interventions carried out under local anaesthesia: In adults below the age of 60, the initial dose is 2,5 mg (0,04 mg / kg), 5 – 10 min before the beginning of the procedure. Further doses of 1 mg may be given as necessary. A total dose greater than 5 mg is not usually necessary to reach the desired endpoint.
In adults over 60 years, debilitated or chronically ill patients, the initial dose must be reduced to 1 to 1,5 mg and given 5 – 10 minutes before the beginning of the procedure. Further doses of 0,5 to 1,0 mg may be given as necessary. Total doses greater than 3,5 mg are not usually necessary.

2. Pre-medication before an operation
Intramuscular administration: Pre-medication with DORMICUM, given shortly before a procedure, produces sedation (induction of sleepiness or drowsiness and relief of apprehension), and pre-operative impairment of memory.
Adults below the age of 60: 0,07 – 0,1 mg / kg *IM* according to general condition of the patient. Usual dose is about 5 mg.
Children (between ages 1 and 15): Proportionately higher doses are required than in adults in relation to bodyweight. The dose range from 0,08 to 0,2 mg / kg has been shown to be effective and safe. These doses should be administered into a large muscle mass about 30 to 60 minutes before induction of anaesthesia.
Adults over 60 years, debilitated and chronically ill patients: 0,025 – 0,05 mg / kg, *IM*. The usual dose is 2 to 3 mg.

3. Induction and maintenance of anaesthesia
Intravenous injection
Induction: Intravenous injections must be given slowly (approximately 2,5 mg in 10 seconds for induction of anaesthesia). The desired level of anaesthesia is reached by stepwise titration. The intravenous induction dose of DORMICUM should be given slowly in increments. Each increment of not more than 5 mg should be injected over 20 to 30 seconds, allowing 2 minutes between successive increments.
In pre-medicated adults below the age of 60 the dose can range from 10 – 15 mg *IV* (0,15 to 0,2 mg / kg). A total dose greater than 15 mg is usually not necessary. A sufficiently deep level of sleep is generally achieved after 2 – 3 minutes.
In non pre-medicated adults below the age of 60, the dose may be higher (0,3 to 0,35 mg / kg body weight),



2
but a total dose greater than 20 mg is usually not necessary.
In adults over 60 years of age, debilitated and chronically ill patients, lower doses will be required.
Maintenance: Intravenous continuous infusion: The maintenance dose usually ranges from 0,03 to 0,1 mg / kg / hr when used in combination with narcotics or ketamine. In high-risk surgical patients, adults over 60 years, debilitated and chronically ill patients, lower maintenance doses will be required.

4. Sedation in intensive care units (ICU)
Intravenous sedation in ICU: The desired level of sedation is reached by stepwise titration of DORMICUM, followed by either continuous infusion, or intermittent bolus.
For sedation in ICU, the dosage should be individualised and DORMICUM titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.
The intravenous loading dose should be given slowly in increments. Each increment of 1 to 2,5 mg should be injected over 20 to 30 seconds, allowing 2 minutes between successive increments. The intravenous loading dose can range from 0,03 to 0,3 mg / kg, but a total dose greater than 15 mg is usually not necessary. The loading dose should be reduced or omitted in hypovolaemic, vasoconstricted or hypothermic patients.
The maintenance dose ranges from 0,03 to 0,2 mg / kg / hr. In hypovolaemic, vasoconstricted or hypothermic patients, the maintenance dose should be reduced, at times to as low as 25 % of the usual dose. The level of sedation should be assessed regularly if permitted by the patient's condition.

Special dosage instructions
Compatibility with infusion solutions: The DORMICUM ampoule solution can be diluted with sodium chloride 0,9 %, dextrose 5 %, dextrose 10 %, levulose 5 %, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100 to 1 000 mℓ infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature (or three days at 5 °C).
The DORMICUM ampoule solution should not be diluted with Macrodex 6 % in dextrose or mixed with alkaline injections.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS
The side-effects most commonly encountered are drowsiness and over-sedation. Drowsiness is more common in elderly and debilitated patients and in patients receiving high doses. Less common, are depression of mood and affect, disorientation or confusion, lethargy and ataxia.
The following side effects have been observed: nausea, vomiting, headache, hiccoughs, laryngospasm, dyspnoea and hallucination. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.
Convulsions have been reported in premature infants and neonates.
Patients with chronic renal failure, impaired hepatic function and congestive heart failure may eliminate midazolam more slowly.
Generalised hypersensitivity, including anaphylactoid reactions and skin reactions, have been reported. Local effects on veins (pain on injection and thrombophlebitis) can occur. A decrease in arterial blood pressure and changes of pulse rate and breathing may occur. As a rule, the systolic blood pressure falls by a maximum of 15 %, while the pulse rate simultaneously shows a corresponding rise. Apnoea may occur due to a depressant effect on the respiratory centre and cardiovascular collapse may occur following intravenous administration.
Severe cardio-respiratory adverse events have occurred less frequently. These have included respiratory depression, apnoea, respiratory arrest and/or cardiac arrest.

WARNING
DORMICUM ampoules should be used only when resuscitation facilities are available, as IV administration of DORMICUM may depress myocardial contractility and cause apnoea.

Routine intravenous midazolam induction is not recommended in children under 7 years of age.
Paradoxical reactions such as agitation, hyperactivity and combativeness have occurred; involuntary movements (including tonic/clonic convulsions and muscle tremor) have also been observed. Should such reactions occur, the response to each dose of DORMICUM should be evaluated before proceeding.
After prolonged *IV* administration of DORMICUM, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of DORMICUM is recommended.

Interactions
Enhancement of the central depressive effect may occur when DORMICUM is used concomitantly with: antipsychotics; hypnotics; anxiolytics; antidepressants; narcotic analgesics; antiepileptic drugs; anaesthetics and sedative antihistamines.
This potentiation of effect can, in certain cases, be of therapeutic advantage. Special attention must be paid to the possibility of potentiation in patients at particular risk.
The mutual potentiation of alcohol and DORMICUM can produce unforeseeable reactions (no alcoholic beverages for at least 12 hours after parenteral adminis-

There is a potentially relevant interaction between midazolam and compounds which inhibit certain hepatic enzymes (particularly cytochrome P450 III A). Data clearly indicates that these compounds influence the pharmacokinetics of midazolam and may lead to increased and prolonged sedation. At present this reaction is known to occur with cimetidine, ranitidine, erythromycin, diltiazem, verapamil, ketoconazole, itraconazole and saquinavir but not with cyclosporin and nitrendipine. Therefore, prescription of midazolam to patients receiving the above compounds or others which inhibit P450 III A, should be monitored carefully for the first few hours after administration of midazolam. During long-term infusion, a reduction of up to 50 % of the initial dose, followed by careful titration, is recommended.
Studies involving healthy volunteers suggest that a clinically important pharmacokinetic interaction between parenteral midazolam and ranitidine is unlikely to occur in clinical practice.
One study *in vitro* has shown the hydroxylation of midazolam to be inhibited by a number of other substances (e.g. amiodarone, neuroleptics); accordingly, interaction with a whole range of medicaments is theoretically possible. However, the clinical relevance of these findings is unknown.

Incompatibilities
Do not dilute DORMICUM ampoule solutions with Macrodex 6 % in dextrose. Do not mix DORMICUM ampoule solutions in alkaline injections. Midazolam precipitates in sodium bicarbonate.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
The symptoms of DORMICUM overdose are primarily an intensification of the therapeutic effects (mental confusion, lethargy, sedation, muscle weakness, profound sleep) or paradoxical excitation. In these cases only observation of vital functions is required.
Extreme overdosage may lead to coma, areflexia, cardio-respiratory depression and apnoea, requiring appropriate countermeasures (ventilation, cardiovascular support). The effects of overdoses can be controlled with the benzodiazepine antagonist Anexate (active ingredient: flumazenil).

IDENTIFICATION
DORMICUM 5 mg / 5 mℓ: clear, colourless to slightly yellow liquid in colourless ampoules.
DORMICUM 15 mg / 3 mℓ: clear, practically colourless liquid in colourless ampoules.
DORMICUM 50 mg / 10 mℓ: clear, colourless to slightly yellow liquid in colourless ampoules.

PRESENTATION
DORMICUM 5 mg / 5 mℓ: 5 and 50
DORMICUM 15 mg / 3 mℓ: 5 and 50
DORMICUM 50 mg / 10 mℓ: 1

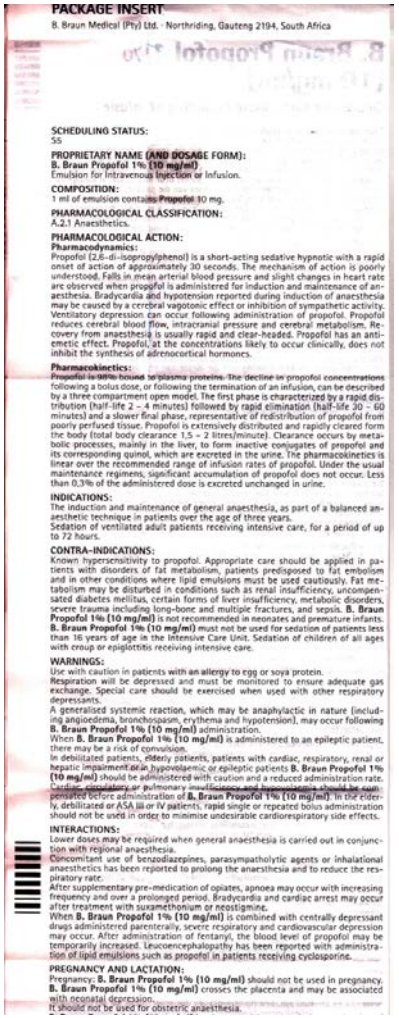
STORAGE INSTRUCTIONS
Store below 25 °C.
DORMICUM ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking the ampoule at room temperature.
Keep out of reach of children.
This medicine should not be used after the expiry date that has been printed on the container.

REGISTRATION NUMBER
DORMICUM 5 mg / 5 mℓ: T/2.2/207
DORMICUM 15 mg / 3 mℓ: Q/2.2/2286
DORMICUM 50 mg / 10 mℓ: Y/2.2/325

NAME AND BUSINESS ADDRESS OF THE APPLICANT
Roche Products (Pty) Ltd
4 Brewery Street
Isando
Gauteng
South Africa

DATE OF PUBLICATION OF THIS PACKAGE INSERT
22 November 1996

ANNEXURE L: Propofol



PACKAGE INSERT

B. Braun Medical (Pty) Ltd. · Northriding, Gauteng 2194, South Africa

SCHEDULING STATUS:
S5

PROPRIETARY NAME (AND DOSAGE FORM):
B. Braun Propofol 1% (10 mg/ml)
Emulsion for Intravenous Injection or Infusion.

COMPOSITION:
1 ml of emulsion contains Propofol 10 mg.

PHARMACOLOGICAL CLASSIFICATION:
A.2.1 Anaesthetics.

PHARMACOLOGICAL ACTION:
Pharmacodynamics:
Propofol (2,6-di-isopropylphenol) is a short-acting sedative hypnotic with a rapid onset of action of approximately 30 seconds. The mechanism of action is poorly understood. Falls in mean arterial blood pressure and slight changes in heart rate are observed when propofol is administered for induction and maintenance of anaesthesia. Bradycardia and hypotension reported during induction of anaesthesia may be caused by a cerebral vagotonic effect or inhibition of sympathetic activity. Ventilatory depression can occur following administration of propofol. Propofol reduces cerebral blood flow, intracranial pressure and cerebral metabolism. Recovery from anaesthesia is usually rapid and clear-headed. Propofol has an anti-emetic effect. Propofol, at the concentrations likely to occur clinically, does not inhibit the synthesis of adrenocortical hormones.

Pharmacokinetics:
Propofol is 98% bound to plasma proteins. The decline in propofol concentrations following a bolus dose, or following the termination of an infusion, can be described by a three compartment open model. The first phase is characterized by a rapid distribution (half-life 2 – 4 minutes) followed by rapid elimination (half-life 30 – 60 minutes) and a slower final phase, representative of redistribution of propofol from poorly perfused tissue. Propofol is extensively distributed and rapidly cleared form the body (total body clearance 1,5 – 2 litres/minute). Clearance occurs by metabolic processes, mainly in the liver, to form inactive conjugates of propofol and its corresponding quinol, which are excreted in the urine. The pharmacokinetics is linear over the recommended range of infusion rates of propofol. Under the usual maintenance regimens, significant accumulation of propofol does not occur. Less than 0,3% of the administered dose is excreted unchanged in urine.

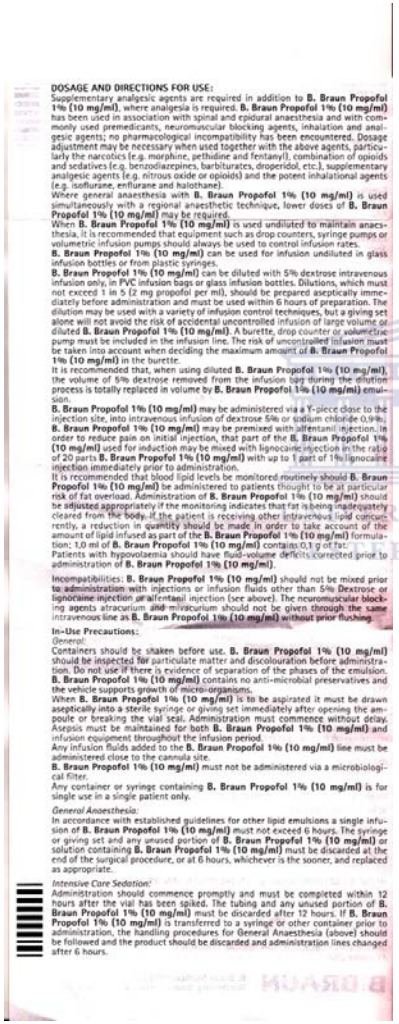
INDICATIONS:
The induction and maintenance of general anaesthesia, as part of a balanced anaesthetic technique in patients over the age of three years.
Sedation of ventilated adult patients receiving intensive care, for a period of up to 72 hours.

CONTRA-INDICATIONS:
Known hypersensitivity to propofol. Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed to fat embolism and in other conditions where lipid emulsions must be used cautiously. Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes mellitus, certain forms of liver insufficiency, metabolic disorders, severe trauma including long-bone and multiple fractures, and sepsis. **B. Braun Propofol 1% (10 mg/ml)** is not recommended in neonates and premature infants. **B. Braun Propofol 1% (10 mg/ml)** must not be used for sedation of patients less than 16 years of age in the Intensive Care Unit. Sedation of children of all ages with croup or epiglottitis receiving intensive care.

WARNINGS:
Use with caution in patients with an allergy to egg or soya protein.
Respiration will be depressed and must be monitored to ensure adequate gas exchange. Special care should be exercised when used with other respiratory depressants.
A generalised systemic reaction, which may be anaphylactic in nature (including angioedema, bronchospasm, erythema and hypotension), may occur following **B. Braun Propofol 1% (10 mg/ml)** administration.
When **B. Braun Propofol 1% (10 mg/ml)** is administered to an epileptic patient, there may be a risk of convulsion.
In debilitated patients, elderly patients, patients with cardiac, respiratory, renal or hepatic impairment or in hypovolaemic or epileptic patients **B. Braun Propofol 1% (10 mg/ml)** should be administered with caution and a reduced administration rate. Cardiac, circulatory or pulmonary insufficiency and hypovolaemia should be compensated before administration of **B. Braun Propofol 1% (10 mg/ml)**. In the elderly, debilitated or ASA III or IV patients, rapid single or repeated bolus administration should not be used in order to minimise undesirable cardiorespiratory side effects.

INTERACTIONS:
Lower doses may be required when general anaesthesia is carried out in conjunction with regional anaesthesia.
Concomitant use of benzodiazepines, parasympatholytic agents or inhalational anaesthetics has been reported to prolong the anaesthesia and to reduce the respiratory rate.
After supplementary pre-medication of opiates, apnoea may occur with increasing frequency and over a prolonged period. Bradycardia and cardiac arrest may occur after treatment with suxamethonium or neostigmine.
When **B. Braun Propofol 1% (10 mg/ml)** is combined with centrally depressant drugs administered parenterally, severe respiratory and cardiovascular depression may occur. After administration of fentanyl, the blood level of propofol may be temporarily increased. Leucoencephalopathy has been reported with administration of lipid emulsions such as propofol in patients receiving cyclosporine.

PREGNANCY AND LACTATION:
Pregnancy: **B. Braun Propofol 1% (10 mg/ml)** should not be used in pregnancy.
B. Braun Propofol 1% (10 mg/ml) crosses the placenta and may be associated with neonatal depression.
It should not be used for obstetric anaesthesia.



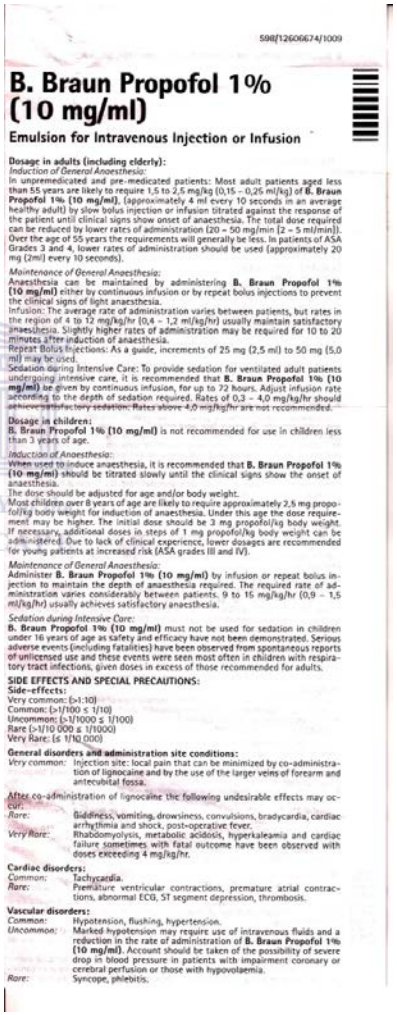
DOSAGE AND DIRECTIONS FOR USE:
Supplementary analgesic agents are required in addition to **B. Braun Propofol 1% (10 mg/ml)**, where analgesia is required. **B. Braun Propofol 1% (10 mg/ml)** has been used in association with spinal and epidural anaesthesia and with commonly used premedicants, neuromuscular blocking agents, inhalation and analgesic agents; no pharmacological incompatibility has been encountered. Dosage adjustment may be necessary when used together with the above agents, particularly the narcotics (e.g. morphine, pethidine and fentanyl), combination of opioids and sedatives (e.g. benzodiazepines, barbiturates, droperidol, etc.), supplementary analgesic agents (e.g. nitrous oxide or opioids) and the potent inhalational agents (e.g. isoflurane, enflurane and halothane).
Where general anaesthesia with **B. Braun Propofol 1% (10 mg/ml)** is used simultaneously with a regional anaesthetic technique, lower doses of **B. Braun Propofol 1% (10 mg/ml)** may be required.
When **B. Braun Propofol 1% (10 mg/ml)** is used undiluted to maintain anaesthesia, it is recommended that equipment such as drop counters, syringe pumps or volumetric infusion pumps should always be used to control infusion rates.
B. Braun Propofol 1% (10 mg/ml) can be used for infusion undiluted in glass infusion bottles or from plastic syringes.
B. Braun Propofol 1% (10 mg/ml) can be diluted with 5% dextrose intravenous infusion only, in PVC infusion bags or glass infusion bottles. Dilutions, which must not exceed 1 in 5 (2 mg propofol per ml), should be prepared aseptically immediately before administration and must be used within 6 hours of preparation. The dilution may be used with a variety of infusion control techniques, but a giving set alone will not avoid the risk of accidental uncontrolled infusion of large volume of diluted **B. Braun Propofol 1% (10 mg/ml)**. A burette, drop counter or volumetric pump must be included in the infusion line. The risk of uncontrolled infusion must be taken into account when deciding the maximum amount of **B. Braun Propofol 1% (10 mg/ml)** in the burette.
It is recommended that, when using diluted **B. Braun Propofol 1% (10 mg/ml)**, the volume of 5% dextrose removed from the infusion bag during the dilution process is totally replaced in volume by **B. Braun Propofol 1% (10 mg/ml)** emulsion.
B. Braun Propofol 1% (10 mg/ml) may be administered via a Y-piece close to the injection site, into intravenous infusion of dextrose 5% or sodium chloride 0,9%.
B. Braun Propofol 1% (10 mg/ml) may be premixed with alfentanil injection. In order to reduce pain on initial injection, that part of the **B. Braun Propofol 1% (10 mg/ml)** used for induction may be mixed with lignocaine injection in the ratio of 20 parts **B. Braun Propofol 1% (10 mg/ml)** with up to 1 part of 1% lignocaine injection immediately prior to administration.
It is recommended that blood lipid levels be monitored routinely should **B. Braun Propofol 1% (10 mg/ml)** be administered to patients thought to be at particular risk of fat overload. Administration of **B. Braun Propofol 1% (10 mg/ml)** should be adjusted appropriately if the monitoring indicates that fat is being inadequately cleared from the body. If the patient is receiving other intravenous lipid concurrently, a reduction in quantity should be made in order to take account of the amount of lipid infused as part of the **B. Braun Propofol 1% (10 mg/ml)** formulation; 1,0 ml of **B. Braun Propofol 1% (10 mg/ml)** contains 0,1 g of fat.
Patients with hypovolaemia should have fluid-volume deficits corrected prior to administration of **B. Braun Propofol 1% (10 mg/ml)**.

Incompatibilities: **B. Braun Propofol 1% (10 mg/ml)** should not be mixed prior to administration with injections or infusion fluids other than 5% Dextrose or lignocaine injection or alfentanil injection (see above). The neuromuscular blocking agents atracurium and mivacurium should not be given through the same intravenous line as **B. Braun Propofol 1% (10 mg/ml)** without prior flushing.

In-Use Precautions:
General:
Containers should be shaken before use. **B. Braun Propofol 1% (10 mg/ml)** should be inspected for particulate matter and discolouration before administration. Do not use if there is evidence of separation of the phases of the emulsion.
B. Braun Propofol 1% (10 mg/ml) contains no anti-microbial preservatives and the vehicle supports growth of micro-organisms.
When **B. Braun Propofol 1% (10 mg/ml)** is to be aspirated it must be drawn aseptically into a sterile syringe or giving set immediately after opening the ampoule or breaking the vial seal. Administration must commence without delay. Asepsis must be maintained for both **B. Braun Propofol 1% (10 mg/ml)** and infusion equipment throughout the infusion period.
Any infusion fluids added to the **B. Braun Propofol 1% (10 mg/ml)** line must be administered close to the cannula site.
B. Braun Propofol 1% (10 mg/ml) must not be administered via a microbiological filter.
Any container or syringe containing **B. Braun Propofol 1% (10 mg/ml)** is for single use in a single patient only.

General Anaesthesia:
In accordance with established guidelines for other lipid emulsions a single infusion of **B. Braun Propofol 1% (10 mg/ml)** must not exceed 6 hours. The syringe or giving set and any unused portion of **B. Braun Propofol 1% (10 mg/ml)** or solution containing **B. Braun Propofol 1% (10 mg/ml)** must be discarded at the end of the surgical procedure, or at 6 hours, whichever is the sooner, and replaced as appropriate.

Intensive Care Sedation:
Administration should commence promptly and must be completed within 12 hours after the vial has been spiked. The tubing and any unused portion of **B. Braun Propofol 1% (10 mg/ml)** must be discarded after 12 hours. If **B. Braun Propofol 1% (10 mg/ml)** is transferred to a syringe or other container prior to administration, the handling procedures for General Anaesthesia (above) should be followed and the product should be discarded and administration lines changed after 6 hours.



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B. Braun Propofol 1% (10 mg/ml)

Emulsion for Intravenous Injection or Infusion

Dosage in adults (including elderly):
Induction of General Anaesthesia:
In unpremedicated and pre-medicated patients: Most adult patients aged less than 55 years are likely to require 1,5 to 2,5 mg/kg (0,15 – 0,25 ml/kg) of **B. Braun Propofol 1% (10 mg/ml)**, (approximately 4 ml every 10 seconds in an average healthy adult) by slow bolus injection or infusion titrated against the response of the patient until clinical signs show onset of anaesthesia. The total dose required can be reduced by lower rates of administration (20 – 50 mg/min [2 – 5 ml/min]). Over the age of 55 years the requirements will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 20 mg (2ml) every 10 seconds).

Maintenance of General Anaesthesia:
Anaesthesia can be maintained by administering **B. Braun Propofol 1% (10 mg/ml)** either by continuous infusion or by repeat bolus injections to prevent the clinical signs of light anaesthesia.
Infusion: The average rate of administration varies between patients, but rates in the region of 4 to 12 mg/kg/hr (0,4 – 1,2 ml/kg/hr) usually maintain satisfactory anaesthesia. Slightly higher rates of administration may be required for 10 to 20 minutes after induction of anaesthesia.
Repeat Bolus Injections: As a guide, increments of 25 mg (2,5 ml) to 50 mg (5,0 ml) may be used.
Sedation during Intensive Care: To provide sedation for ventilated adult patients undergoing intensive care, it is recommended that **B. Braun Propofol 1% (10 mg/ml)** be given by continuous infusion, for up to 72 hours. Adjust infusion rate according to the depth of sedation required. Rates of 0,3 – 4,0 mg/kg/hr should achieve satisfactory sedation. Rates above 4,0 mg/kg/hr are not recommended.

Dosage in children:
B. Braun Propofol 1% (10 mg/ml) is not recommended for use in children less than 3 years of age.

Induction of Anaesthesia:
When used to induce anaesthesia, it is recommended that **B. Braun Propofol 1% (10 mg/ml)** should be titrated slowly until the clinical signs show the onset of anaesthesia.
The dose should be adjusted for age and/or body weight.
Most children over 8 years of age are likely to require approximately 2,5 mg propofol/kg body weight for induction of anaesthesia. Under this age the dose requirement may be higher. The initial dose should be 3 mg propofol/kg body weight. If necessary, additional doses in steps of 1 mg propofol/kg body weight can be administered. Due to lack of clinical experience, lower dosages are recommended for young patients at increased risk (ASA grades III and IV).

Maintenance of General Anaesthesia:
Administer **B. Braun Propofol 1% (10 mg/ml)** by infusion or repeat bolus injection to maintain the depth of anaesthesia required. The required rate of administration varies considerably between patients. 9 to 15 mg/kg/hr (0,9 – 1,5 ml/kg/hr) usually achieves satisfactory anaesthesia.

Sedation during Intensive Care:
B. Braun Propofol 1% (10 mg/ml) must not be used for sedation in children under 16 years of age as safety and efficacy have not been demonstrated. Serious adverse events (including fatalities) have been observed from spontaneous reports of unlicensed use and these events were seen most often in children with respiratory tract infections, given doses in excess of those recommended for adults.

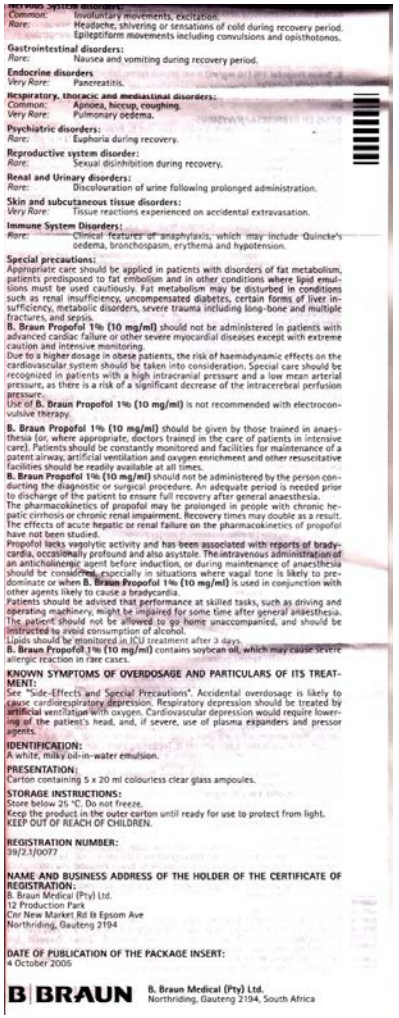
SIDE EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects:
Very common: (>1:10)
Common: (>1/100 ≤ 1/10)
Uncommon: (>1/1000 ≤ 1/100)
Rare (>1/10 000 ≤ 1/1000)
Very Rare: (≤ 1/10 000)

General disorders and administration site conditions:
Very common: Injection site: local pain that can be minimized by co-administration of lignocaine and by the use of the larger veins of forearm and antecubital fossa.

After co-administration of lignocaine the following undesirable effects may occur:
Rare: Giddiness, vomiting, drowsiness, convulsions, bradycardia, cardiac arrhythmia and shock, post-operative fever.
Very Rare: Rhabdomyolysis, metabolic acidosis, hyperkaleamia and cardiac failure sometimes with fatal outcome have been observed with doses exceeding 4 mg/kg/hr.

Cardiac disorders:
Common: Tachycardia.
Rare: Premature ventricular contractions, premature atrial contractions, abnormal ECG, ST segment depression, thrombosis.

Vascular disorders:
Common: Hypotension, flushing, hypertension.
Uncommon: Marked hypotension may require use of intravenous fluids and a reduction in the rate of administration of **B. Braun Propofol 1% (10 mg/ml)**. Account should be taken of the possibility of severe drop in blood pressure in patients with impairment coronary or cerebral perfusion or those with hypovolaemia.
Rare: Syncope, phlebitis.



Nervous System disorders:
Common: Involuntary movements, excitation.
Rare: Headache, shivering or sensations of cold during recovery period.
Epileptiform movements including convulsions and opisthotonos.

Gastrointestinal disorders:
Rare: Nausea and vomiting during recovery period.

Endocrine disorders
Very Rare: Pancreatitis.

Respiratory, thoracic and mediastinal disorders:
Common: Apnoea, hiccup, coughing.
Very Rare: Pulmonary oedema.

Psychiatric disorders:
Rare: Euphoria during recovery.

Reproductive system disorder:
Rare: Sexual disinhibition during recovery.

Renal and Urinary disorders:
Rare: Discolouration of urine following prolonged administration.

Skin and subcutaneous tissue disorders:
Very Rare: Tissue reactions experienced on accidental extravasation.

Immune System Disorders:
Rare: Clinical features of anaphylaxis, which may include Quincke's oedema, bronchospasm, erythema and hypotension.

Special precautions:
Appropriate care should be applied in patients with disorders of fat metabolism, patients predisposed to fat embolism and in other conditions where lipid emulsions must be used cautiously. Fat metabolism may be disturbed in conditions such as renal insufficiency, uncompensated diabetes, certain forms of liver insufficiency, metabolic disorders, severe trauma including long-bone and multiple fractures, and sepsis.
B. Braun Propofol 1% (10 mg/ml) should not be administered in patients with advanced cardiac failure or other severe myocardial diseases except with extreme caution and intensive monitoring.
Due to a higher dosage in obese patients, the risk of haemodynamic effects on the cardiovascular system should be taken into consideration. Special care should be recognized in patients with a high intracranial pressure and a low mean arterial pressure, as there is a risk of a significant decrease of the intracerebral perfusion pressure.
Use of **B. Braun Propofol 1% (10 mg/ml)** is not recommended with electroconvulsive therapy.
B. Braun Propofol 1% (10 mg/ml) should be given by those trained in anaesthesia (or, where appropriate, doctors trained in the care of patients in intensive care). Patients should be constantly monitored and facilities for maintenance of a patent airway, artificial ventilation and oxygen enrichment and other resuscitative facilities should be readily available at all times.
B. Braun Propofol 1% (10 mg/ml) should not be administered by the person conducting the diagnostic or surgical procedure. An adequate period is needed prior to discharge of the patient to ensure full recovery after general anaesthesia.
The pharmacokinetics of propofol may be prolonged in people with chronic hepatic cirrhosis or chronic renal impairment. Recovery times may double as a result. The effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied.
Propofol lacks vagolytic activity and has been associated with reports of bradycardia, occasionally profound and also asystole. The intravenous administration of an anticholinergic agent before induction, or during maintenance of anaesthesia should be considered, especially in situations where vagal tone is likely to predominate or when **B. Braun Propofol 1% (10 mg/ml)** is used in conjunction with other agents likely to cause a bradycardia.
Patients should be advised that performance at skilled tasks, such as driving and operating machinery, might be impaired for some time after general anaesthesia. The patient should not be allowed to go home unaccompanied, and should be instructed to avoid consumption of alcohol.
Lipids should be monitored in ICU treatment after 3 days.
B. Braun Propofol 1% (10 mg/ml) contains soybean oil, which may cause severe allergic reaction in rare cases.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:
See "Side-Effects and Special Precautions". Accidental overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression would require lowering of the patient's head, and, if severe, use of plasma expanders and pressor agents.

IDENTIFICATION:
A white, milky oil-in-water emulsion.

PRESENTATION:
Carton containing 5 x 20 ml colourless clear glass ampoules.

STORAGE INSTRUCTIONS:
Store below 25 °C. Do not freeze.
Keep the product in the outer carton until ready for use to protect from light.
KEEP OUT OF REACH OF CHILDREN.

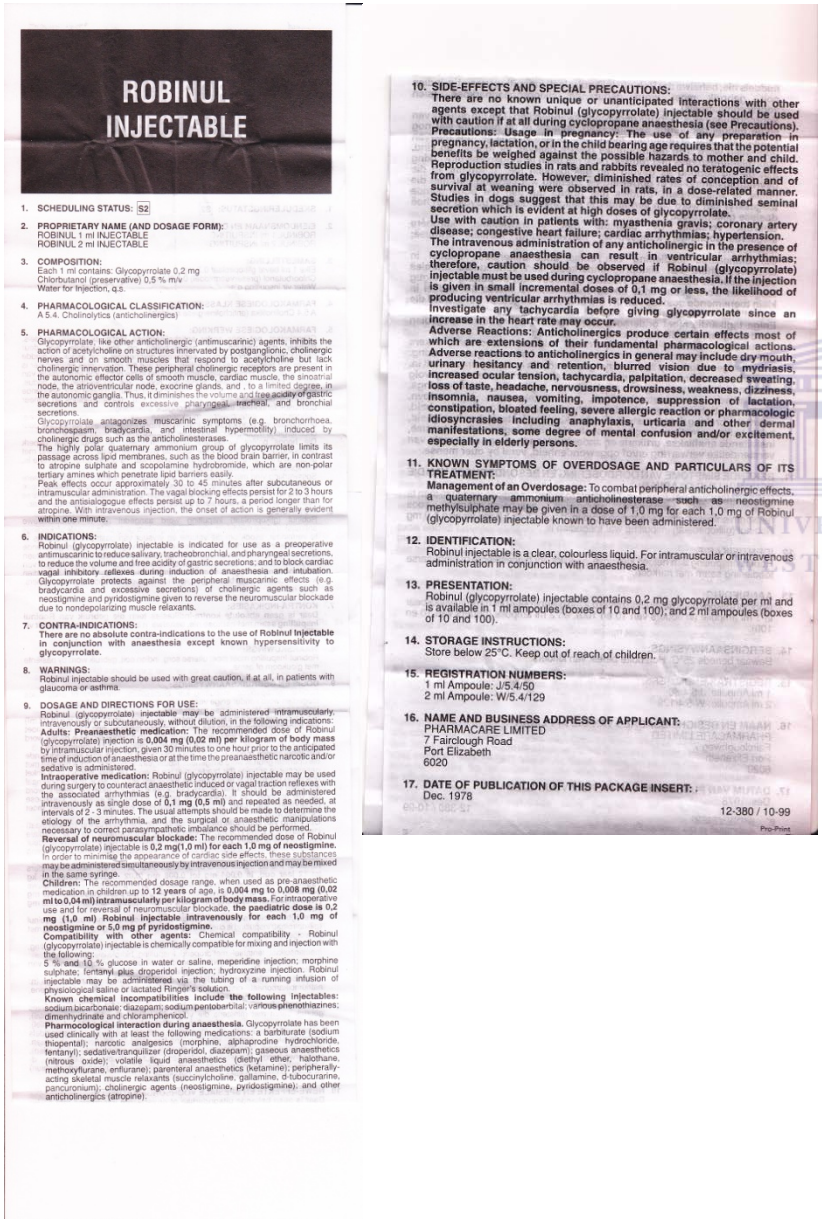
REGISTRATION NUMBER:
39/2.1/0077

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:
B. Braun Medical (Pty) Ltd.
12 Production Park
Cnr New Market Rd & Epsom Ave
Northriding, Gauteng 2194

DATE OF PUBLICATION OF THE PACKAGE INSERT:
4 October 2005

B|BRAUN B. Braun Medical (Pty) Ltd.
Northriding, Gauteng 2194, South Africa

ANNEXURE M: Glycopyrrolate



ROBINUL INJECTABLE

1. **SCHEDULING STATUS:** S2
2. **PROPRIETARY NAME (AND DOSAGE FORM):**
   ROBINUL 1 ml INJECTABLE
   ROBINUL 2 ml INJECTABLE
3. **COMPOSITION:**
   Each 1 ml contains: Glycopyrrolate 0,2 mg
   Chlorbutanol (preservative) 0,5 % m/v
   Water for Injection, q.s.
4. **PHARMACOLOGICAL CLASSIFICATION:**
   A 5.4. Cholinolytics (anticholinergics)
5. **PHARMACOLOGICAL ACTION:**
   Glycopyrrolate like other anticholinergic (antimuscarinic) agents, inhibits the action of acetylcholine on structures innervated by postganglionic, cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands, and , to a limited degree, in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions.
   Glycopyrrolate antagonizes muscarinic symptoms (e.g. bronchorrhoea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.
   The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood brain barrier, in contrast to atropine sulphate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily.
   Peak effects occur approximately 30 to 45 minutes after subcutaneous or intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialogogue effects persist up to 7 hours, a period longer than for atropine. With intravenous injection, the onset of action is generally evident within one minute.
6. **INDICATIONS:**
   Robinul (glycopyrrolate) injectable is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions, to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anaesthesia and intubation. Glycopyrrolate protects against the peripheral muscarinic effects (e.g. bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to nondepolarizing muscle relaxants.
7. **CONTRA-INDICATIONS:**
   There are no absolute contra-indications to the use of Robinul Injectable in conjunction with anaesthesia except known hypersensitivity to glycopyrrolate.
8. **WARNINGS:**
   Robinul injectable should be used with great caution, if at all, in patients with glaucoma or asthma.
9. **DOSAGE AND DIRECTIONS FOR USE:**
   Robinul (glycopyrrolate) injectable may be administered intramuscularly, intravenously or subcutaneously, without dilution, in the following indications:
   Adults: Preanaesthetic medication: The recommended dose of Robinul (glycopyrrolate) injection is **0,004 mg (0,02 ml) per kilogram of body mass** by intramuscular injection, given 30 minutes to one hour prior to the anticipated time of induction of anaesthesia or at the time the preanaesthetic narcotic and/or sedative is administered.
   Intraoperative medication: Robinul (glycopyrrolate) injectable may be used during surgery to counteract anaesthetic induced or vagal traction reflexes with the associated arrhythmias (e.g. bradycardia). It should be administered intravenously as single dose of **0,1 mg (0,5 ml)** and repeated as needed, at intervals of 2 - 3 minutes. The usual attempts should be made to determine the etiology of the arrhythmia, and the surgical or anaesthetic manipulations necessary to correct parasympathetic imbalance should be performed.
   Reversal of neuromuscular blockade: The recommended dose of Robinul (glycopyrrolate) injectable is **0,2 mg(1,0 ml) for each 1,0 mg of neostigmine.** In order to minimise the appearance of cardiac side effects, these substances may be administered simultaneously by intravenous injection and may be mixed in the same syringe.
   Children: The recommended dosage range, when used as pre-anaesthetic medication in children up to **12 years** of age, is **0,004 mg to 0,008 mg (0,02 ml to 0,04 ml) intramuscularly per kilogram of body mass.** For intraoperative use and for reversal of neuromuscular blockade, **the paediatric dose is 0,2 mg (1,0 ml) Robinul injectable intravenously for each 1,0 mg of neostigmine or 5,0 mg of pyridostigmine.**
   Compatibility with other agents: Chemical compatibility - Robinul (glycopyrrolate) injectable is chemically compatible for mixing and injection with the following:
   5 % and 10 % glucose in water or saline, meperidine injection; morphine sulphate; fentanyl plus droperidol injection; hydroxyzine injection. Robinul injectable may be administered via the tubing of a running infusion of physiological saline or lactated Ringer's solution.
   Known chemical incompatibilities include the following injectables: sodium bicarbonate; diazepam; sodium pentobarbital; various phenothiazines; dimenhydrinate and chloramphenicol.
   Pharmacological interaction during anaesthesia. Glycopyrrolate has been used clinically with at least the following medications: a barbiturate (sodium thiopental); narcotic analgesics (morphine, alphaprodine hydrochloride, fentanyl); sedative/tranquilizer (droperidol, diazepam); gaseous anaesthetics (nitrous oxide); volatile liquid anaesthetics (diethyl ether, halothane, methoxyflurane, enflurane); parenteral anaesthetics (ketamine); peripherally-acting skeletal muscle relaxants (succinylcholine, gallamine, d-tubocurarine, pancuronium); cholinergic agents (neostigmine, pyridostigmine); and other anticholinergics (atropine).

10. **SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**
    There are no known unique or unanticipated interactions with other agents except that Robinul (glycopyrrolate) injectable should be used with caution if at all during cyclopropane anaesthesia (see Precautions).
    Precautions: Usage in pregnancy: The use of any preparation in pregnancy, lactation, or in the child bearing age requires that the potential benefits be weighed against the possible hazards to mother and child.
    Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. However, diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner.
    Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate.
    Use with caution in patients with: myasthenia gravis; coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension.
    The intravenous administration of any anticholinergic in the presence of cyclopropane anaesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Robinul (glycopyrrolate) injectable must be used during cyclopropane anaesthesia. If the injection is given in small incremental doses of 0,1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.
    Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur.
    Adverse Reactions: Anticholinergics produce certain effects most of which are extensions of their fundamental pharmacological actions.
    Adverse reactions to anticholinergics in general may include dry mouth, urinary hesitancy and retention, blurred vision due to mydriasis, increased ocular tension, tachycardia, palpitation, decreased sweating, loss of taste, headache, nervousness, drowsiness, weakness, dizziness, insomnia, nausea, vomiting, impotence, suppression of lactation, constipation, bloated feeling, severe allergic reaction or pharmacologic idiosyncrasies including anaphylaxis, urticaria and other dermal manifestations, some degree of mental confusion and/or excitement, especially in elderly persons.
11. **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**
    Management of an Overdosage: To combat peripheral anticholinergic effects, a quaternary ammonium anticholinesterase such as neostigmine methylsulphate may be given in a dose of 1,0 mg for each 1,0 mg of Robinul (glycopyrrolate) injectable known to have been administered.
12. **IDENTIFICATION:**
    Robinul injectable is a clear, colourless liquid. For intramuscular or intravenous administration in conjunction with anaesthesia.
13. **PRESENTATION:**
    Robinul (glycopyrrolate) injectable contains 0,2 mg glycopyrrolate per ml and is available in 1 ml ampoules (boxes of 10 and 100); and 2 ml ampoules (boxes of 10 and 100).
14. **STORAGE INSTRUCTIONS:**
    Store below 25°C. Keep out of reach of children.
15. **REGISTRATION NUMBERS:**
    1 ml Ampoule: J/5.4/50
    2 ml Ampoule: W/5.4/129
16. **NAME AND BUSINESS ADDRESS OF APPLICANT:**
    PHARMACARE LIMITED
    7 Fairclough Road
    Port Elizabeth
    6020
17. **DATE OF PUBLICATION OF THIS PACKAGE INSERT:**
    Dec. 1978

12-380 / 10-99

Pro-Print

ANNEXURE N: Ketamine

1. **SCHEDULING STATUS:** S5

2. **PROPRIETARY NAME (AND DOSAGE FORM):**
Ketamine-Fresenius 10 mg/1 ml (Injection)
Ketamine-Fresenius 50 mg/1 ml (Injection)
Ketamine-Fresenius 100 mg/1 ml (Injection)

3. **COMPOSITION:**
Each 1 ml contains 10, 50 or 100 mg ketamine as the hydrochloride salt.
Preservative: Benzethonium chloride 0,01% m/v
Ketamine-Fresenius 10 mg/1 ml has been made isotonic with Sodium Chloride.

4. **PHARMACOLOGICAL CLASSIFICATION:**
A. 2.1 Anaesthetics

5. **PHARMACOLOGICAL ACTION:**
Ketamine produces dissociative anaesthesia which is characterised by a state of sedation, immobility, amnesia and marked analgesia as well as a strong feeling of dissociation.
It acts on the cortex and the limbic system.
Muscular relaxation is poor and muscle tone may be increased. Respiration is maintained, although transient depression may occur. Pharyngeal and laryngeal reflexes are partially retained, but the cough reflex is depressed. Airway resistance is decreased.
Arterial blood pressure increases by as much as 25% and cardiac output and rate increase. Cerebral metabolism and blood flow increase, leading to a potential increase in intracranial pressure. It has a half life of about 3½ hours. Intense analgesia and amnesia are established rapidly.

6. **INDICATIONS:**
Induction of anaesthesia, or, in combination with oxygenated nitrous oxide, for the maintenance of general anaesthesia.
Ketamine may be used in children for the management of minor surgical and diagnostic procedures or for repeated procedures that require intense analgesia, such as changing burn dressings.

7. **CONTRA-INDICATIONS:**
Hypersensitivity to ketamine hydrochloride. Ketamine is contra-indicated in patients in whom elevation of blood pressure would be a serious hazard including those with hypertension or a history of cerebrovascular accident. It is best avoided in patients with eclampsia or pre-eclampsia and should be used with caution in patients with a history of convulsive disorders or psychiatric disease. It should not be given to patients with increased intra-ocular pressure. Alternative anaesthetics should be considered in patients with penetrating wounds of the eye. Ketamine should be used with caution in patients with elevated CSF pressure. Ketamine does not reliably suppress pharyngeal and laryngeal reflexes and mechanical stimulation of the pharynx should be avoided unless a muscle relaxant is used. Safety in pregnancy and lactation has not been established.

8. **WARNINGS:**
Intracranial pressure may increase.

9. **DOSAGE AND DIRECTIONS FOR USE:**
Doses should be individualized.
Administration should be preceded by atropine or another suitable anti-muscarinic agent.

Route	Dose mg/kg	Onset of anaesthesia	Duration Time
IV	1 - 2	30 seconds	5 to 10 minutes
IM	5 - 10	3 to 4 minutes	12 to 25 minutes

A benzodiazepine, such as diazepam 2,5 to 5 mg intravenously (0,05 to 0,1 mg/kg) decreases the incidence of hallucinations during ketamine anaesthesia and decreases the incidence of emergence reactions.
A. Ketamine may be administered by intravenous or intramuscular injection. Intravenous injection should be over a period of 60 seconds.
B. **Alternative method:**
An Intravenous infusion solution (1 mg/ml) is prepared by mixing 500 mg of ketamine in 500 ml of glucose or saline solution. Induction is accomplished by infusing the solution until induction is complete. In general the induction dose will be approximately 1 mg/kg.
Maintenance intravenous infusion rates need to be individualised to prevent nystagmus and response to surgical stimuli, 1 to 5 mg/kg/hour being the usual dose.
Upon termination of surgery, the ketamine is discontinued.

10. **SIDE EFFECTS AND SPECIAL PRECAUTIONS:**
Emergence reactions in recovery are common including vivid and often unpleasant dreams, confusion, hallucinations and irrational behaviour. Children and elderly patients appear to be less sensitive. Patients may also experience increased muscle tone, sometimes resembling seizures.
Blood pressure and heart rate may be temporarily increased by ketamine; hypotension, arrhythmias, and bradycardia have occurred rarely.
Respiration may be depressed especially during too rapid intravenous injection. Apnoea and laryngospasm have occurred. Diplopia and nystagmus may occur. Nausea and vomiting, lachrymation, hypersalivation, and raised intra-ocular and cerebrospinal fluid pressure have also been reported. Transient skin rashes and pain at the site of injection may occur.
Special Precautions
The necessary equipment for airway support, intubation and resuscitation should always be readily available.
Special caution should be taken when administering ketamine to patients with a history of epilepsy, psychiatric illnesses or porphyria. Cardiac function should be monitored in patients with mild hypertension or cardiac decompensation.
Patients should be intubated if there is a risk of aspiration as laryngeal reflexes are not necessarily maintained.
Incompatibility exists with soluble barbiturates, and these should not be combined in the same syringe. It is also not recommended that ketamine be combined with ergometrine.
Verbal, tactile and visual stimuli should be kept to a minimum during recovery in an attempt to reduce the risk of emergence reactions.
Dosage may need to be decreased in the event of renal and liver impairment.

11. **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**
Respiratory depression. Supportive ventilation and resuscitation equipment should always be available when general anaesthesia is administered. Treatment is symptomatic and supportive.

12. **IDENTIFICATION**
A clear, colourless solution in amber vials.

13. **PRESENTATION**
Ketamine-Fresenius 10 mg/1 ml in 20 ml amber vials packed in tens and singles.
Ketamine-Fresenius 50 mg/1 ml in 10 ml amber vials packed in tens and singles.
Ketamine-Fresenius 100 mg/1 ml in 10 ml amber vials packed in tens and singles.

14. **STORAGE INSTRUCTIONS**
Store below 25ºC
KEEP OUT OF REACH OF CHILDREN.

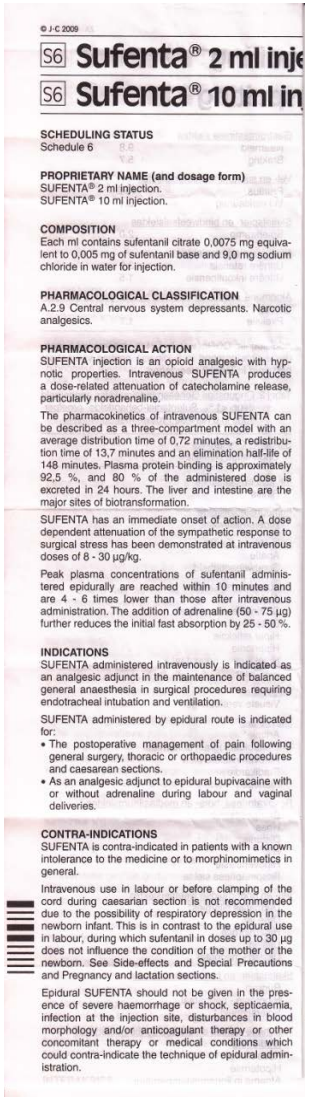
15. **REGISTRATION NUMBER**
Ketamine-Fresenius 10 mg/1 ml - Y/2.1/373
Ketamine-Fresenius 50 mg/1 ml - Y/2.1/273
Ketamine-Fresenius 100 mg/1 ml - Y/2.1/274

16. **NAME AND BUSINESS ADDRESS OF THE APPLICANT**
BODENE (PTY) LIMITED trading as Intramed, 6 Gibaud Road, Port Elizabeth, 6001, South Africa

17. **DATE OF PUBLICATION OF THIS PACKAGE INSERT**
MAY 1992.

12-067/11/02
PRO.PRINT

ANNEXURE O: Sufentanil



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S6 **Sufenta® 2 ml inje**

S6 **Sufenta® 10 ml in**

SCHEDULING STATUS
Schedule 6

PROPRIETARY NAME (and dosage form)
SUFENTA® 2 ml injection.
SUFENTA® 10 ml injection.

COMPOSITION
Each ml contains sufentanil citrate 0,0075 mg equivalent to 0,005 mg of sufentanil base and 9,0 mg sodium chloride in water for injection.

PHARMACOLOGICAL CLASSIFICATION
A.2.9 Central nervous system depressants. Narcotic analgesics.

PHARMACOLOGICAL ACTION
SUFENTA injection is an opioid analgesic with hypnotic properties. Intravenous SUFENTA produces a dose-related attenuation of catecholamine release, particularly noradrenaline.

The pharmacokinetics of intravenous SUFENTA can be described as a three-compartment model with an average distribution time of 0,72 minutes, a redistribution time of 13,7 minutes and an elimination half-life of 148 minutes. Plasma protein binding is approximately 92,5 %, and 80 % of the administered dose is excreted in 24 hours. The liver and intestine are the major sites of biotransformation.

SUFENTA has an immediate onset of action. A dose dependent attenuation of the sympathetic response to surgical stress has been demonstrated at intravenous doses of 8 - 30 µg/kg.

Peak plasma concentrations of sufentanil administered epidurally are reached within 10 minutes and are 4 - 6 times lower than those after intravenous administration. The addition of adrenaline (50 - 75 µg) further reduces the initial fast absorption by 25 - 50 %.

INDICATIONS
SUFENTA administered intravenously is indicated as an analgesic adjunct in the maintenance of balanced general anaesthesia in surgical procedures requiring endotracheal intubation and ventilation.

SUFENTA administered by epidural route is indicated for:

- The postoperative management of pain following general surgery, thoracic or orthopaedic procedures and caesarean sections.
- As an analgesic adjunct to epidural bupivacaine with or without adrenaline during labour and vaginal deliveries.

CONTRA-INDICATIONS
SUFENTA is contra-indicated in patients with a known intolerance to the medicine or to morphinomimetics in general.

Intravenous use in labour or before clamping of the cord during caesarian section is not recommended due to the possibility of respiratory depression in the newborn infant. This is in contrast to the epidural use in labour, during which sufentanil in doses up to 30 µg does not influence the condition of the mother or the newborn. See Side-effects and Special Precautions and Pregnancy and lactation sections.

Epidural SUFENTA should not be given in the presence of severe haemorrhage or shock, septicaemia, infection at the injection site, disturbances in blood morphology and/or anticoagulant therapy or other concomitant therapy or medical conditions which could contra-indicate the technique of epidural administration.

INTERACTIONS
Barbiturates, benzodiazepines, neuroleptics, halogenic gases and other non-selective central nervous system depressants (e.g. alcohol), may potentiate the respiratory depressive effects of SUFENTA. When patients have received central nervous system depressants, the dose of SUFENTA required will be less than usual. Likewise, following the administration of SUFENTA, the dose of other central nervous system depressants should be reduced.

Sufentanil is metabolised mainly via the human cytochrome P450 3A4 enzyme. However, no *in-vivo* inhibition by erythromycin (a known cytochrome P450 3A4 enzyme inhibitor) has been observed.

Although clinical data are lacking, *in-vitro* data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (eg. fluconazole, ketoconazole, itraconazole, ritonavir, diltiazem and cimetidine) may inhibit the metabolism of sufentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of SUFENTA.

Mono-amine oxidase (MOA) inhibitors must be discontinued 2 weeks prior to the administration of SUFENTA.

PREGNANCY AND LACTATION
Safety in pregnancy and lactation has not been established.

SUFENTA added to epidural bupivacaine in total doses up to 30 µg has no detrimental effect on the mother or the newborn, but intravenous use is not recommended in labour.

An antidote for the child should always be at hand, however.

It is not known whether this drug is excreted in human milk. Caution should be exercised when SUFENTA is administered to a nursing woman.

DOSAGE AND DIRECTIONS FOR USE
The dosage of SUFENTA should be individualised. Factors to be considered in determining the dose are age, body mass, physical status, underlying pathological condition, use of other medicines, type of anaesthesia to be used and duration of the surgical procedure.

In obese patients, the dosage of SUFENTA should be determined on the basis of standard body mass.

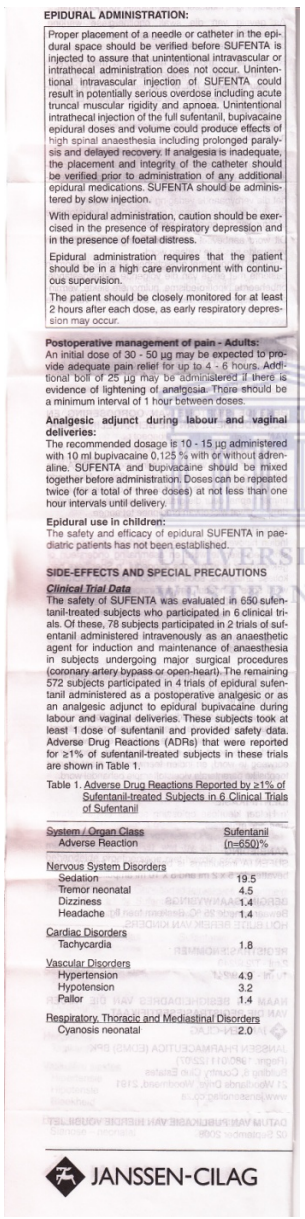
Compatibility:
If desired, SUFENTA may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. They should be used within 24 hours of preparation.

ADMINISTRATION AS AN ANALGESIC ADJUNCT TO NITROUS OXIDE/OXYGEN
Droperidol may be given to reduce the incidence of nausea and vomiting.

INTRAVENOUS ADMINISTRATION - ADULTS:
Initial dose: 1 - 8 µg/kg administered with nitrous oxide/oxygen. The duration of action is 1 - 8 hours depending on the dose.

Maintenance dose: 0,1 - 0,5 µg/kg as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

Supplemental dosages should be individualised, and adjusted to the remaining operative time anticipated.



EPIDURAL ADMINISTRATION:

Proper placement of a needle or catheter in the epidural space should be verified before SUFENTA is injected to assure that unintentional intravascular or intrathecal administration does not occur. Unintentional intravascular injection of SUFENTA could result in potentially serious overdose including acute truncal muscular rigidity and apnoea. Unintentional intrathecal injection of the full sufentanil, bupivacaine epidural doses and volume could produce effects of high spinal anaesthesia including prolonged paralysis and delayed recovery. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to administration of any additional epidural medications. SUFENTA should be administered by slow injection.

With epidural administration, caution should be exercised in the presence of respiratory depression and in the presence of foetal distress.

Epidural administration requires that the patient should be in a high care environment with continuous supervision.

The patient should be closely monitored for at least 2 hours after each dose, as early respiratory depression may occur.

Postoperative management of pain - Adults:
An initial dose of 30 - 50 µg may be expected to provide adequate pain relief for up to 4 - 6 hours. Additional boli of 25 µg may be administered if there is evidence of lightening of analgesia. There should be a minimum interval of 1 hour between doses.

Analgesic adjunct during labour and vaginal deliveries:
The recommended dosage is 10 - 15 µg administered with 10 ml bupivacaine 0,125 % with or without adrenaline. SUFENTA and bupivacaine should be mixed together before administration. Doses can be repeated twice (for a total of three doses) at not less than one hour intervals until delivery.

Epidural use in children:
The safety and efficacy of epidural SUFENTA in paediatric patients has not been established.

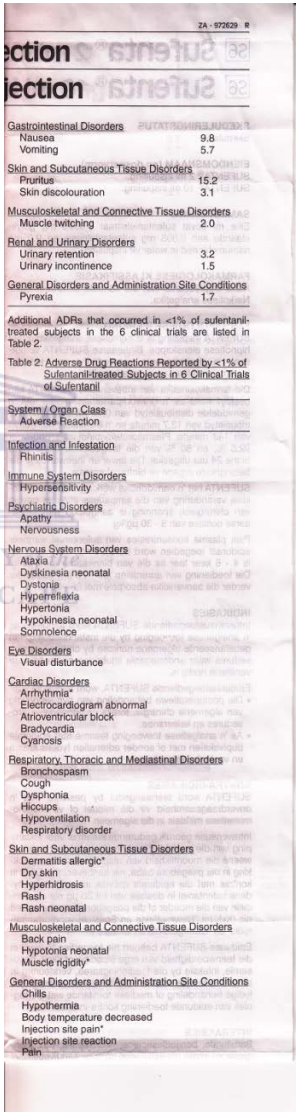
SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Clinical Trial Data
The safety of SUFENTA was evaluated in 650 sufentanil-treated subjects who participated in 6 clinical trials. Of these, 78 subjects participated in 2 trials of sufentanil administered intravenously as an anaesthetic agent for induction and maintenance of anaesthesia in subjects undergoing major surgical procedures (coronary artery bypass or open-heart). The remaining 572 subjects participated in 4 trials of epidural sufentanil administered as a postoperative analgesic or as an analgesic adjunct to epidural bupivacaine during labour and vaginal deliveries. These subjects took at least 1 dose of sufentanil and provided safety data. Adverse Drug Reactions (ADRs) that were reported for ≥1% of sufentanil-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥1% of Sufentanil-treated Subjects in 6 Clinical Trials of Sufentanil

System / Organ Class Adverse Reaction	Sufentanil (n=650)%
Nervous System Disorders	
Sedation	19.5
Tremor neonatal	4.5
Dizziness	1.4
Headache	1.4
Cardiac Disorders	
Tachycardia	1.8
Vascular Disorders	
Hypertension	4.9
Hypotension	3.2
Pallor	1.4
Respiratory, Thoracic and Mediastinal Disorders	
Cyanosis neonatal	2.0

JANSSEN-CILAG



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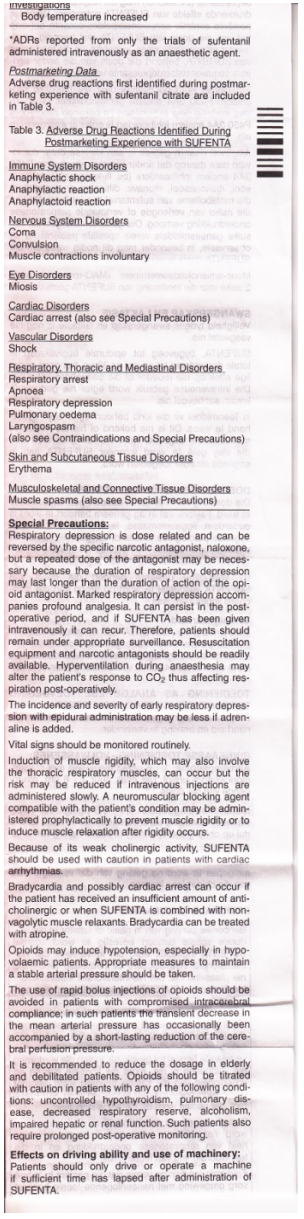
Gastrointestinal Disorders	
Nausea	9.8
Vomiting	5.7
Skin and Subcutaneous Tissue Disorders	
Pruritus	15.2
Skin discolouration	3.1
Musculoskeletal and Connective Tissue Disorders	
Muscle twitching	2.0
Renal and Urinary Disorders	
Urinary retention	3.2
Urinary incontinence	1.5
General Disorders and Administration Site Conditions	
Pyrexia	1.7

Additional ADRs that occurred in <1% of sufentanil-treated subjects in the 6 clinical trials are listed in Table 2.

Table 2. Adverse Drug Reactions Reported by <1% of Sufentanil-treated Subjects in 6 Clinical Trials of Sufentanil

System / Organ Class Adverse Reaction
Infection and Infestation
Rhinitis
Immune System Disorders
Hypersensitivity
Psychiatric Disorders
Apathy
Nervousness
Nervous System Disorders
Ataxia
Dyskinesia neonatal
Dystonia
Hyperreflexia
Hypertonia
Hypokinesia neonatal
Somnolence
Eye Disorders
Visual disturbance
Cardiac Disorders
Arrhythmia*
Electrocardiogram abnormal
Atrioventricular block
Bradycardia
Cyanosis
Respiratory, Thoracic and Mediastinal Disorders
Bronchospasm
Cough
Dysphonia
Hiccups
Hypoventilation
Respiratory disorder
Skin and Subcutaneous Tissue Disorders
Dermatitis allergic*
Dry skin
Hyperhidrosis
Rash
Rash neonatal
Musculoskeletal and Connective Tissue Disorders
Back pain
Hypotonia neonatal
Muscle rigidity*
General Disorders and Administration Site Conditions
Chills
Hypothermia
Body temperature decreased
Injection site pain*
Injection site reaction
Pain



Investigations
Body temperature increased

*ADRs reported from only the trials of sufentanil administered intravenously as an anaesthetic agent.

Postmarketing Data
Adverse drug reactions first identified during postmarketing experience with sufentanil citrate are included in Table 3.

Table 3. Adverse Drug Reactions Identified During Postmarketing Experience with SUFENTA

Immune System Disorders
Anaphylactic shock
Anaphylactic reaction
Anaphylactoid reaction
Nervous System Disorders
Coma
Convulsion
Muscle contractions involuntary
Eye Disorders
Miosis
Cardiac Disorders
Cardiac arrest (also see Special Precautions)
Vascular Disorders
Shock
Respiratory, Thoracic and Mediastinal Disorders
Respiratory arrest
Apnoea
Respiratory depression
Pulmonary oedema
Laryngospasm
(also see Contraindications and Special Precautions)
Skin and Subcutaneous Tissue Disorders
Erythema
Musculoskeletal and Connective Tissue Disorders
Muscle spasms (also see Special Precautions)

Special Precautions:
Respiratory depression is dose related and can be reversed by the specific narcotic antagonist, naloxone, but a repeated dose of the antagonist may be necessary because the duration of respiratory depression may last longer than the duration of action of the opioid antagonist. Marked respiratory depression accompanies profound analgesia. It can persist in the postoperative period, and if SUFENTA has been given intravenously it can recur. Therefore, patients should remain under appropriate surveillance. Resuscitation equipment and narcotic antagonists should be readily available. Hyperventilation during anaesthesia may alter the patient's response to CO_2 thus affecting respiration post-operatively.

The incidence and severity of early respiratory depression with epidural administration may be less if adrenaline is added.

Vital signs should be monitored routinely.

Induction of muscle rigidity, which may also involve the thoracic respiratory muscles, can occur but the risk may be reduced if intravenous injections are administered slowly. A neuromuscular blocking agent compatible with the patient's condition may be administered prophylactically to prevent muscle rigidity or to induce muscle relaxation after rigidity occurs.

Because of its weak cholinergic activity, SUFENTA should be used with caution in patients with cardiac arrhythmias.

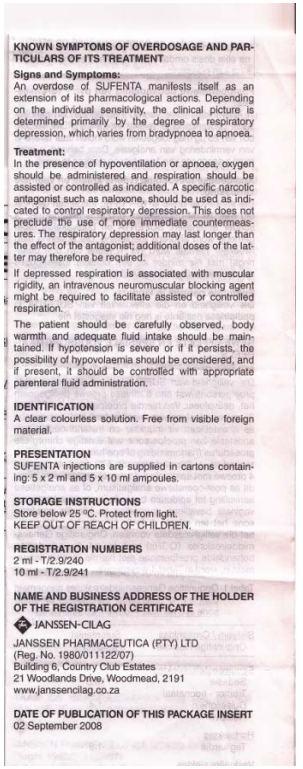
Bradycardia and possibly cardiac arrest can occur if the patient has received an insufficient amount of anticholinergic or when SUFENTA is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

It is recommended to reduce the dosage in elderly and debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism, pulmonary disease, decreased respiratory reserve, alcoholism, impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

Effects on driving ability and use of machinery:
Patients should only drive or operate a machine if sufficient time has lapsed after administration of SUFENTA.



KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Signs and Symptoms:
An overdose of SUFENTA manifests itself as an extension of its pharmacological actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnoea to apnoea.

Treatment:
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific narcotic antagonist such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.

If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.

The patient should be carefully observed, body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolaemia should be considered, and if present, it should be controlled with appropriate parenteral fluid administration.

IDENTIFICATION
A clear colourless solution. Free from visible foreign material.

PRESENTATION
SUFENTA injections are supplied in cartons containing: 5 x 2 ml and 5 x 10 ml ampoules.

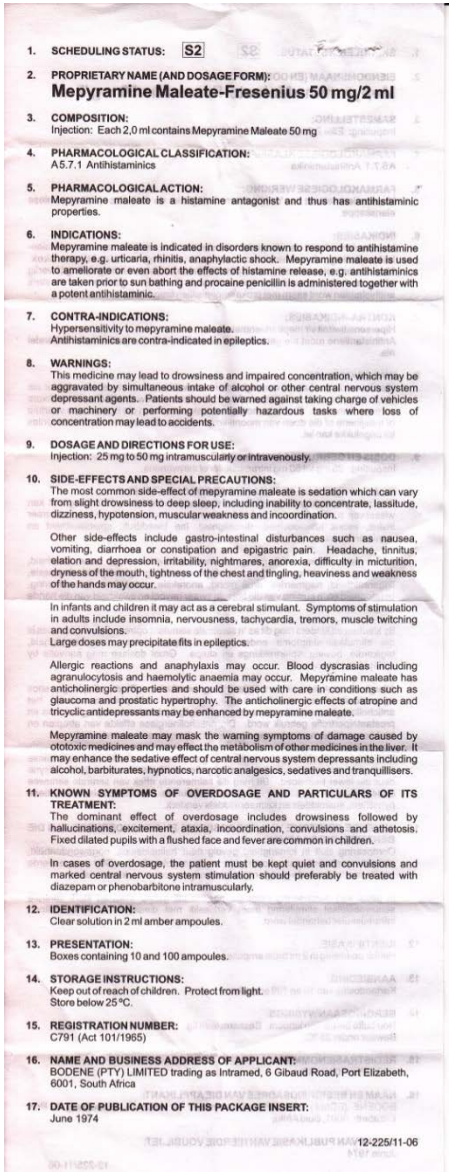
STORAGE INSTRUCTIONS
Store below 25 °C. Protect from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS
2 ml - T/2.9/240
10 ml - T/2.9/241

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE REGISTRATION CERTIFICATE
JANSSEN-CILAG
JANSSEN PHARMACEUTICA (PTY) LTD
(Reg. No. 1980/011122/07)
Building 6, Country Club Estates
21 Woodlands Drive, Woodmead, 2191
www.janssencilag.co.za

DATE OF PUBLICATION OF THIS PACKAGE INSERT
02 September 2008

ANNEXURE P: Mepyramine maleate



1. **SCHEDULING STATUS:** S2
2. **PROPRIETARY NAME (AND DOSAGE FORM):**
   Mepyramine Maleate-Fresenius 50 mg/2 ml
3. **COMPOSITION:**
   Injection: Each 2,0 ml contains Mepyramine Maleate 50 mg
4. **PHARMACOLOGICAL CLASSIFICATION:**
   A.5.7.1 Antihistaminics
5. **PHARMACOLOGICAL ACTION:**
   Mepyramine maleate is a histamine antagonist and thus has antihistaminic properties.
6. **INDICATIONS:**
   Mepyramine maleate is indicated in disorders known to respond to antihistamine therapy, e.g. urticaria, rhinitis, anaphylactic shock. Mepyramine maleate is used to ameliorate or even abort the effects of histamine release, e.g. antihistaminics are taken prior to sun bathing and procaine penicillin is administered together with a potent antihistaminic.
7. **CONTRA-INDICATIONS:**
   Hypersensitivity to mepyramine maleate.
   Antihistaminics are contra-indicated in epileptics.
8. **WARNINGS:**
   This medicine may lead to drowsiness and impaired concentration, which may be aggravated by simultaneous intake of alcohol or other central nervous system depressant agents. Patients should be warned against taking charge of vehicles or machinery or performing potentially hazardous tasks where loss of concentration may lead to accidents.
9. **DOSAGE AND DIRECTIONS FOR USE:**
   Injection: 25 mg to 50 mg intramuscularly or intravenously.
10. **SIDE-EFFECTS AND SPECIAL PRECAUTIONS:**
    The most common side-effect of mepyramine maleate is sedation which can vary from slight drowsiness to deep sleep, including inability to concentrate, lassitude, dizziness, hypotension, muscular weakness and incoordination.

    Other side-effects include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea or constipation and epigastric pain. Headache, tinnitus, elation and depression, irritability, nightmares, anorexia, difficulty in micturition, dryness of the mouth, tightness of the chest and tingling, heaviness and weakness of the hands may occur.

    In infants and children it may act as a cerebral stimulant. Symptoms of stimulation in adults include insomnia, nervousness, tachycardia, tremors, muscle twitching and convulsions.
    Large doses may precipitate fits in epileptics.

    Allergic reactions and anaphylaxis may occur. Blood dyscrasias including agranulocytosis and haemolytic anaemia may occur. Mepyramine maleate has anticholinergic properties and should be used with care in conditions such as glaucoma and prostatic hypertrophy. The anticholinergic effects of atropine and tricyclic antidepressants may be enhanced by mepyramine maleate.

    Mepyramine maleate may mask the warning symptoms of damage caused by ototoxic medicines and may effect the metabolism of other medicines in the liver. It may enhance the sedative effect of central nervous system depressants including alcohol, barbiturates, hypnotics, narcotic analgesics, sedatives and tranquillisers.
11. **KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**
    The dominant effect of overdosage includes drowsiness followed by hallucinations, excitement, ataxia, incoordination, convulsions and athetosis. Fixed dilated pupils with a flushed face and fever are common in children.

    In cases of overdosage, the patient must be kept quiet and convulsions and marked central nervous system stimulation should preferably be treated with diazepam or phenobarbitone intramuscularly.
12. **IDENTIFICATION:**
    Clear solution in 2 ml amber ampoules.
13. **PRESENTATION:**
    Boxes containing 10 and 100 ampoules.
14. **STORAGE INSTRUCTIONS:**
    Keep out of reach of children. Protect from light.
    Store below 25 °C.
15. **REGISTRATION NUMBER:**
    C791 (Act 101/1965)
16. **NAME AND BUSINESS ADDRESS OF APPLICANT:**
    BODENE (PTY) LIMITED trading as Intramed, 6 Gibaud Road, Port Elizabeth, 6001, South Africa
17. **DATE OF PUBLICATION OF THIS PACKAGE INSERT:**
    June 1974

12-225/11-06

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