

A COMPARISON OF
THE EFFICACY AND SAFETY OF
INTRANASAL SUFENTANIL/MIDAZOLAM
AND KETAMINE/MIDAZOLAM
FOR SEDATION AND ANALGESIA
IN A PAEDIATRIC POPULATION
UNDERGOING MULTIPLE DENTAL EXTRACTIONS



CHARL J DE LA HARPE

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ABSTRACT

This study was designed to evaluate the efficacy and safety of intranasal sufentanil/midazolam [S/M] and ketamine/midazolam [K/M] for sedation and analgesia in preschool children that require dental surgery [extractions].

Fifty children [ASA 1] aged 5 – 7 years, requiring six or more dental extractions under general anaesthesia, were allocated to two groups of 25 children to receive either ketamine 5 mg/kg or sufentanil 20µg intranasally, 20 minutes before induction of surgery in this randomised double-blind study. All the children in both groups in addition concurrently received nasal midazolam 0,3 mg/kg. For induction of anaesthesia, sevoflurane in nitrous oxide and oxygen, was used.

S/M was accepted significantly better as a nasal pre-medication [$p < 0.05$].

Both groups were equally sedated and a smooth mask induction of anaesthesia was experienced in the majority of children.

Recovery of children in both groups were similar; 82% of the S/M group were fully recovered 120 minutes post-operatively versus 80% in the K/M group [$p > 0,05$].

Effective postoperative analgesia for multiple extractions was provided.

For pain evaluation, children were divided into two groups, a non-responder group where all pain values over time were more than 40 and a responder group where pain values were equal to, or less than 40. Seventy two percent of children in the S/M group were responders as to fifty two percent in the K/M group [$p > 0,05$]. No adverse respiratory, cardiovascular or other effects were recorded.

This study showed that intranasal administration of sufentanil /midazolam or ketamine/midazolam, provides safe and effective sedation and analgesia in children aged 5–7 years undergoing multiple dental extractions.

DECLARATION

I hereby declare that the work contained in this thesis is my own work, and that it has not been submitted in its entirety or part for any degree or academic credit at any university or academic institution.

Signature



Date

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CHAPTER 1

INTRODUCTION

When children present for surgical procedures, several options are available;

- Local anaesthesia
- Local anaesthesia and behavioural management techniques
- Conscious sedation
- General anaesthesia

Whatever technique is chosen, children will have anxiety and fear. It is for us to decide which option will be the most suitable taking into consideration what is best for the child.

What we need to address is fear and anxiety. We can start by trying to find a definition for fear and anxiety.

Dental phobia is a term which can be used to describe both fear and anxiety. There is however a distinction between the two words.

Fear is a short-lived phenomenon to a known danger eg the local anaesthetic injection. This will result in the typical physiological reflex reaction of tachycardia, sweating, hypertension and tremors.

Anxiety however, is an emotional reaction. Its source is in the unconscious. It may occur as a learned response to a personal experience or one learned from another person. In dentistry, anxiety occurs at the thought of having treatment. Fear will usually occur when the patient is seated in the dental chair.

A combination of anxiety, general fear of the medical and dental fraternity and the procedures that might follow, their fear for pain, general discomfort and the unknown, most often make paediatric patients resist any intervention in various degrees of expression [Weinstein et al, 1988].

Various factors such as age, social background, intellect, physical handicaps, psychological factors and expression of different behavioural patterns, are all then important factors influencing the treatment possibilities of the ambulatory paediatric patient. The parent to child relationship [Ainsworth et al, 1978] and the conduct of the medical/dental staff [Sawtell RO et al, 1974] are also important contributaries to the behavioural reaction encountered or elicited. Past traumatic experiences will have a negative impact on the behaviour of children.

Local anaesthesia alone is suitable for many children. However, in the very anxious child, we may have to include other options. Behavioural techniques are available and should always be used but are not the only solution in all children. Conscious sedation, where inhalational agents and drugs are used, has gained renewed interest.

There are however, still children that require general anaesthesia for certain dental procedures. One of the biggest challenges facing paediatric anaesthesiologists in these circumstances, is a well controlled and atraumatic induction of anaesthesia, especially in children aged 3 – 7 years. By doing so, they minimise the incidence of psychological trauma to the child. This is extremely important for the future treatment of the child. Drugs play a prominent role in achieving this goal.

The administration of pharmacological agents to children to provide sedation, anxiolysis and analgesia are commonly used. A wide range of sedatives and analgesics, some used as single agents or in combination with others, have clinically been tried and tested to various degrees of efficacy.

The technique of conscious sedation has gained wide acceptance in treating children for dentistry. Various techniques are available. It is described as a minimally depressed level of consciousness in which the patient retains the ability to independently and continuously maintain an airway, respond appropriately to physical stimulation and verbal command and is produced by pharmacologic or non-pharmacologic methods or a combination thereof. Martens and Marks [2003], in their study recommend

conscious sedation together with behaviour management techniques, to facilitate treatment of dental fear or dental phobia.

Anxiety and pain control [conscious sedation] can be accomplished using many different routes of administration.

Inhalation sedation [IHS], utilising nitrous oxide/oxygen, has been a primary technique in the management of dental fears and anxieties for more than 150 years [Malamed and Clarke, 2003]. It is particularly suitable for children irrespective of age and the length of sedation. It has the advantage of rapid onset of action and a rapid recovery. It is claimed children need not fast. Duration can be controlled precisely and the safety of the technique has been proved. Studies suggest that IHS is effective for a large proportion of selected subgroups of children [>83 percent] who would have otherwise required dental general anaesthesia [DGA] [Blain and Hill,1998]. They did however state that young age, multiple dental extractions, predisposed to treatment failure. There are very few contra-indications to IHS, which makes this technique very attractive.

Comparing with DGA, IHS requires significant longer time per episode and more treatment sessions per patient. In academic dental hospitals however, staffing costs for IHS are estimated to be about one third cheaper compared to out-patient general anaesthesia [Laratzopoulos & Blain KM, 2003]

They also stated that IHS is particularly suitable for children requiring not more than four extractions. According to Paterson and Tahmassebi [2003], sedation for paediatric patients is an essential tool in anxiety management. Inhalation sedation with nitrous oxide /oxygen can be easily and safely administered to children in general dental practice.

The oral route may be the most frequently used means of drug administration as is supposed to be non-traumatic and simple. Children may however not willingly swallow medication. Some drug formulations have a bitter taste. Severe adverse effects are less common with oral

administration, but have been reported especially in drugs with long half-lives. Surprisingly, adverse effects have been reported with oral administration of short half-life drugs [Roelofse et al, 1997]

The major disadvantage of oral sedation, is the inability to titrate the drug dose to a desired endpoint. Another disadvantage is that prolonged recovery is possible after oral administration.

Prescription of medication per os, is and will remain a commonly used route of administration of drugs, but alternative routes have to be considered for drugs which are not absorbed well or have a high hepatic clearance [Ralley,1989]

Rectal administration is safe and relatively painless and a reasonably reliable method of administration of sedative/analgesic drugs [Roelofse et al, 1993, 1996]. The rectal route of administration is generally accepted by most children. It is however unpleasant and could be embarrassing to the older child and the medical staff involved. The problem of modesty is age related and is obviously not present in infants [Lejus et al,1997].

Rectal administration is however an effective way of administering drugs, especially with reference to nausea and vomiting in children. If for whatever reason intravenous access is not possible, rectal administration of drugs could be a viable option.

The sublingual route of administration has also been applied. A confounding factor encountered with this method, is that children tend to swallow the medication, which divide the dosage between sublingual [oral mucosa] and oral absorption. The sublingual route, restricted to those drugs available for absorption under the tongue, follows the same principles as for the oral route, except that one would expect a more rapid absorption and no first-pass metabolism from the liver.

The administration of drugs via the nasal route however, has several advantages to the oral route, which outweighs disadvantages eg burning sensation of the nasal mucosa which could be quite severe [Lejus C et al, 1997]. Drugs are rapidly absorbed from the nasal mucosa, an area with a rich blood supply, into the systemic circulation and bypasses the portal blood circulation. Intranasal administration has been successfully used for a variety of different drug groups used in anaesthesia. [Aldrete JA et al, 1987; Vercauteren et al,1988; Wilton NCT et al,1988; Zedie N et al,1996; Nishad Z et al,1996]

The nasal administration of lipophilic opioids, has been shown to be an effective method of administration that is devoid of major side-effects [Ralley, 1989; Helmers et al,1990; Ungerer et al,1990; Scholz et al, 1996; Dale, Hjortkjaer et al, 2002; Kendall and Latter, 2003].

Inhalational anaesthetic agents, eg sevoflurane, are also being used for conscious sedation in paediatric dentistry with excellent results. More research into this treatment modality will follow. Sevoflurane is a relatively new inhalation anaesthetic agent with exciting possibilities. It has less myocardial depressant effects than halothane [Hatakeyama, Ito et al,1993], is less soluble in blood [Malviya and Lerman,1990] allowing a more rapid recovery and it is not as extensively metabolised [Holaday and Smith,1981]. Furthermore, studies performed confirmed that sevoflurane in children has excellent induction characteristics and rapid emergence compared to halothane [Davis et al,1993; Kleinman et al,1992; Levine et al, 1993; Naito et al,1991]. In addition to its pharmacological advantages, it has a pleasant smell which makes it acceptable for inhalational induction of anaesthesia in children. Sevoflurane has a very low potency of airway irritation and respiratory complications are rare confirming good acceptance of the drug [Doi et al, 1993].

Several previous studies in both adults and children indicated that no significant differences in induction times were observed, while recovery was found to be significantly quicker with sevoflurane than with halothane or

isoflurane [Piat, dubois et al, 1994; Bacher, Burton et al, 1997; Levine Sarner et al, 1993; Frink, Malan et al,1992; Smith, Ding et al,1992]

With regards to paediatric anaesthesia, sevoflurane thus have several advantages over halothane. It is at least as effective as halothane in providing smooth induction of anaesthesia. Haemodynamically, it is better tolerated than halothane and recovery from anaesthesia is significantly more rapid. This indicates that sevoflurane has advantages over halothane in terms of induction and recovery suggesting that it could be the drug of choice for both induction and maintenance of anaesthesia in children for outpatient procedures.

General anaesthesia for dentistry remains an option in children, especially for young children and those traumatized by previous procedures. It is however becoming less important in the dentist's armamentarium, as costs and demands of third party medical aids place its availability at a premium.



An increasing number of children are undergoing outpatient surgery.

Children from 3 to 5 years of age may experience significant emotional upset as a result of hospitalisation, fear of separation from their parents and unfamiliar surroundings. Children in this age group may not be fully aware of the necessity of their surgical procedure.

The primary clinical need in children, is for well-tolerated effective sedative/analgesic drugs that is safe to use. There has been no direct comparison of the combination of intranasal sufentanil/midazolam and ketamine/midazolam to determine which combination is preferable for sedation and analgesia in preschool children.

The aim of this prospective, randomized, double blind study, is to evaluate the efficacy and safety of preoperative sedation and postoperative pain relief with intranasal sufentanil/midazolam when compared with intranasal ketamine/midazolam in children undergoing dental extractions under general anaesthesia.

CHAPTER 2

ANXIETY AND PAIN IN CHILDREN

ANXIOUS CHILDREN:

A BEHAVIOURAL MANAGEMENT CHALLENGE

To prepare anxious children for dental treatment is a challenge. We know that drugs enhance coping skills but are not a substitute for psychological support. Non-pharmacological techniques must be considered.

The development and assessment of various strategies to manage dental fear and anxiety in children therefore, remain an important part in our strategic planning. Research will have to be directed towards understanding fear and anxiety, leading towards acceptable and effective scientific methods of behavioural management.

Fearful, apprehensive children demand special dedication and expertise from the dental team and such actions usually are cumbersome, exhausting and time-consuming.

Traumatic dental experiences should at all cost be avoided, as this may lead to post-traumatic stress. The first contact of children with the dental surgery, staff and the procedures, as experienced, is critical. This could and most probably will be the determinant of future behavioural attitudes.

It should be the intent to exploit opportunities to establish a preventive orientation and demonstrate a safe, child-friendly environment, using appropriate fear-averting techniques. This is simply not always attainable. Developing behavioural management techniques is especially applicable in South Africa – almost seventy percent of the population is dependent on public dental services and the demand for these services, outstrips the supply.

It has been a personal observation during routine community dental clinics, arranged in rural areas, that children from the third world sector, tend to be more manageable in respect of dental interventions, than their first world counterparts. Strategies to enhance and support behavioural treatment techniques are usually more successful in the former group, the reason for this being unclear.

However, any young child requiring eg. multiple dental extractions, most often presents as a major treatment problem. Some form of pharmacological intervention to decrease anxiety and fear, when all other methods to establish co-operation have been exhausted, is therefore sometimes inevitable.

Phillip Weinstein and John E Nathan [1988], stated that through an understanding of child development and origins of fearful behaviour, there exists an opportunity to establish a preventive orientation and a friendly, safe child orientated environment. In this environment appropriate fear averting techniques can be used. Furthermore, if confronted with fear-related behavioural patterns, the children should be familiarised with a significant repertoire of non-aversive management techniques. The latter is diverse and should be practiced as to gain its full potential. This may be easier said than done.

Ideally, it should be the responsibility of clinicians to focus on their communication with children, rather than be occupied with the completion of the specific dental procedures. This alas, is not always attainable. [A practical model is presented at the end of this chapter - p16].

Child emotions have been ignored to a noticeable extent by many authors of journal articles, maybe because of the complexity of this subject. This may have supported the perspective to focus on inappropriate child management procedures to control problematic behavioural conduct/deviation.

Although not emphasized enough, it is recognized that fear underlies the expression of uncooperative child behaviour [Miller LC, 1983; Lenz, 1985; Lindsay et al, 1989].

CHILDHOOD FEAR

Fear is an inevitable part of development in children (Mark IM, 1978; Dupont,1983; Morris RJ et al, 1985). The average child has fears which are transitory and have to a great extent, little interference with their daily living activities. However, according to Weinstein and Nathan (1988) multiple childhood fears are commonplace. The average child exhibits several fears throughout his or her development. Such fears appear to be more prevalent in girls than boys with peak incidence rates occurring in pre-schoolers (age 2–4 years).

On the other hand, differences in the pattern of fears between children of different age groups are apparent. Ollendick et al [1985], found fear of the unknown to be more troublesome for younger children. In adolescents fears of lurking danger, death and physical disabilities are more disturbing. The context of fearful situations may be of significance. Lenz [1985], found that the fear for separation/abandonment as reported by younger children with mean ages 4½ years, differs from those of older children with mean ages 6 to 7 years.

In general, the following normative developmental trends have become acceptable in the classification of fearful children:

Children aged nine months to two years: fear of loud noise and separation from parents are overriding;

Children aged two to four years: fear of imaginary creatures, certain animals;

Children older than four years: fear of darkness and the unknown are common;

Children aged five to six years: social and school fears emerge

Children aged six years and up to adolescence; fear norms are constant and consist of injury and death related fears, natural events and social anxiety (Miller LC, 1983).

The Freudian position is that all fears are acquired during infancy and childhood. They occur largely as a result of a traumatic experience which is manifested in three ways:

reality anxiety, eg fear of physical harm, the dark, snakes etc.

neurotic anxiety, eg fear of some uncontrollable urge that will result in harm to oneself and

moral anxiety, eg fear of being punished for doing something contrary to what is morally acceptable.

This leads to the question – what is fear and anxiety? Can conditioning help us in managing these children which exhibits various expressions/levels of fear and anxiety.



The following definitions are universally used to explain fear and anxiety:

Fear is a unpleasant emotion caused by the threat of danger, pain, or harm in the external environment. Anxiety is a more general non-specific feeling of apprehension [Murray et al,1992]

Anxious feelings tell the personality to brave itself for something dreadful about to happen, the sufferer not usually knowing what it will be [Firestein S K, 1976]

From self-experience as a clinician, it can be stated that children do fear the possibility of physical harm and pain provoking procedures, or incidents in a clinical environment. In South Africa, a developing and industrialised third world country, poverty as a result of physical barriers and the struggle for existence, result in an ignorance towards oral care. The demand for pain and anxiety relief in grossly neglected oral environments are thus common practice. The Oral Health Centre of the University of the Western Cape is constantly inundated with endless

streams of paediatric and adult patients in need of multiple extractions. The patients randomly selected for this trial, came from this patient pool. Advanced dental pathology may necessitate invasive and painful dental procedures. This may lead to a pattern of avoidance which is often cyclic as a result of fear if other methods of treatment are not followed.

A child visiting a dentist, can either be fearful or anxious. The child may fear something specific eg an injection, or may be anxious about going to the dentist.

The level of fear can vary from mild apprehension to terror which prevents any clinical intervention. [Murray et al,1992]

“Is it going to hurt?”, is probably the most frequent question asked by children. This should be addressed by applying the most suitable non-pharmacological behavioural management techniques. It may however even be necessary to use pharmacological measures.

It is suggested that a child's pain experience does not only involve the direct physical sensation from trauma. It is claimed that the child's behavioural tendencies, emotional status and evaluative reactions, play an important role in a child's pain perception [Goldman et al,1991] This must always be kept in mind when trying to address fear and anxiety in dentistry.

Fear of the dental or medical fraternity, whether established as a consequence of aversive child management practices, or through negative experiences from others, may enhance the possibilities for traumatic dental experiences. The long-term consequences of the latter may influence the health and general welfare status of the child adversely. Post traumatic stress is not uncommon in the traumatised child.

According to Miller [1983], fear of the unknown eg bodily harm, pain, helplessness and death are central to the existence of fear.

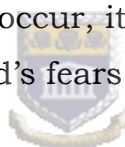
Children on their first visit to a dental surgery /clinic, usually will experience fear [of the unknown], as they do not know what to expect.

Many expressions of fear can be encountered. This can vary from child to child eg refusal to enter the operatory, or to sit in the dental chair, or to open their mouths and some may verbally express their opposition, disapproval and anxiety by screaming, crying or struggling.

Others may be less overt in their expression of fear. Traumatic dental experiences may lead to negative postoperative behavioural patterns like new onset enuresis, feeding problems, apathy, withdrawal and sleep disturbances. It is estimated that 60% of children may have this within fourteen days post-operatively[Kuttner,1989].

The question is, how best to handle the fearful child, as it is well known that successful management of dental fear may result in improved dental outcomes and may positively enhance the ability of a child to cope with general fearful situations [Nathan J, 1983]

Each clinician should assess the problem as accurately as possible, but if some error in judgement should occur, it is preferable that we err on the side of overestimation of the child's fears.



Non-pharmacological behaviour management strategies are extremely important when dealing with the anxious child. This should be in the armamentarium of every dentist treating children.

NON-PHARMACOLOGICAL BEHAVIOUR MANAGEMENT STRATEGIES

Enhancement of the Child's self-control:

One should never underestimate a child's potential to cope in stressful situations, however, time and patience are of paramount importance.

A feeling of control is enhanced by procedures that leaves options open to the child and also by acknowledging the child's experience.

When a multitude of small choices are given to a child, he or she is made to believe that their thoughts and judgements are of significance. This may be a slow process, but the child's ability to cope, is enhanced [Weinstein et al,1988]. The effort may just be worthwhile.

Examples:

“Would you like to control the buttons on the chair?”

Would you prefer that I peep at the top teeth first or should it rather be the bottom ones?

Can we fix that ugly black tooth in front today or should it rather be the one right at the back?”

The desires of pre-school children are usually met when we enhance their competence. They must however be allowed to manipulate dental objects in a surgery or to participate in the treatment. Older children on the other side feel that they are important and that their cooperation is voluntary and not the result of some form of conspiracy.

Recognition that a child is fearful and acknowledgement of the child's subjective experience, is extremely important and perhaps more so than doing anything else when the child feels distressed.

Talking to children about their feelings give them a sense of belonging and that they are cared for. To ask simple and unthreatening questions prior to, during, or after treatment, allows the child to cooperate and communicate and it creates a sense of belonging rather than that of an unwanted patient.

DENTAL SURGERY ORIENTATION

A number of studies on pre-exposing children to a positive, low stress dental experience, have been conducted since the 1960's on this subject. Evidence appears to favour separate pre-visits for young children to a dental surgery (Rosengarten 1961; Machen et al 1974, Sawtell 1974). They become familiar with the dental environment and learn appropriate dental patient behaviours. This is seen as the ideal - the problem is that the ideal is not always practical.

Staff attitude towards the young patient is of utmost importance. Friendly surgery staff who are understanding and sympathetic, will make an important contribution to alleviate anxiety and fear in children. This will make dental treatment more acceptable to them.

Other techniques may be necessary for the child that exhibits fear. These techniques allow the child to face fearful situations (i.e. dental procedures) in a supportive environment. They include behavioural treatments such as structured time, distraction, guided imagery, behaviour modification and pharmacologically based intervention techniques [Weinstein et al, 1988] Conscious sedation is one of the techniques used to support anxious and fearful children. Pharmacological options however cannot and must not replace psychological support.

A severely phobic child, could be referred to specially trained (professionals) individuals, fear clinics or psychologists. Alternatively, general anaesthesia may be the only option left to treat those children.

CREATING A FRIENDLY, SAFE AND CHILD ACCEPTABLE ENVIRONMENT

Creation of a safe, clinical environment for a child is an integral cornerstone to the successful management of child fear. The question is, how can we do this?

One can create a child-orientated and friendly environment providing child-size furniture, gadgets and toys. This is helpful as it provides a feeling of being welcome and being specially catered for. Children feel safe in an environment in which they can exert some self-sustaining influence or communicate their feelings. Of essential importance is the establishment and maintenance of trust between the clinician and the child – a sympathetic and caring attitude could pave the way to this ultimate goal.

In early treatment, the primary object should be to establish acceptable communication levels and rapport. However, rapport building is not an action which is applied for a short initial period. It is the recognition of the child's uniqueness as an individual which is brought about by ongoing successful levels of communication. Careful use of an appropriate vocabulary, especially at the first appointment which enhances trust, is essential.



We often recognise the need for adults to control events in their lives, but children are frequently treated denying them this consideration.

An individual who is denied this level of control, feels vulnerable, trapped, experience loss of self-control or feels victimized. This leads to suspicion, distrust and ultimately could elicit and aggravate fear.

Cooperation then becomes almost impossible.

Within a child-friendly, safe environment, a child is given the opportunity to exert freedom of expression and allow levels of self-control. The dental surgeon [and staff] should facilitate this. Alwin et al[1991], concluded in a study that the most common incident that contributed to child fear, was the “dentist’s manner”[75%], followed by procedures.

BEHAVIOURAL TREATMENT OPTIONS FOR ANXIOUS/FEARFUL CHILDREN

The practitioner who treats anxious children, has a variety of behavioural techniques which could be used. All of them can unfortunately not be discussed in detail.

Communicating with fearful children.

The following communication options are available:

The guidance-cooperation technique:

Three distinct models of doctor – patient communication possibilities were published by Szash and Hollander [1965];



(i) The active – passive model:

In this model the child will be completely passive as with surgery performed under general anaesthesia. This model is not advisable for anxious children.

(ii) The guidance-cooperation model:

In this model, the patient is not completely passive. The child is not permitted to participate with regards to dental treatment decision making, but communication is necessary and advisable.

(iii) The mutual-participation model:

Here the child fully participates with the practitioner in the decision making processes.

The guidance-cooperation model looks as the best option for dentist/child communication. The child is involved in the process. Here the child is expected to listen to the dentist. This is especially relevant for communication with young children.

Research done by the pediatric dental clinic at the University of Washington [Weinstein & Nathan, 1988] indicates that this model best leads to cooperative child behaviour, eg:

“Open your mouth as wide as you can, please – good boy/ girl”

Permissive behaviour on the other hand such as saying: “Are you ready so that I can start now” or begging “please” or coercive behaviour such as threats and scolding, results in substantial resistant and un-cooperative child behaviour [Wurster, 1979]

An interesting and informative study of how children are managed in dental surgeries was undertaken by Weinstein et al in 1982.

Identification of effective and ineffective patterns of communication between dentist/child and assistant/child were analysed from which the following results were obtained:



Anxiety related behaviours were lowest after the use of direction and reinforcement.

Specific feedback resulted in less anxiety-related behaviour than general feedback.

Direction was more effective than rules, which are general directions used before the anticipation of problematic behaviour.

Specific reinforcement eg “I like the way you keep your head still” is more effective than general reinforcement and appraisal like “Good boy/girl”.

Rhetorical questions such as “would you like to come and sit down now” which tend to have an undertone of leniency, were much less effective in decreasing fear-related behaviours than specific direction.

Rational discussion with three to five year old anxious children are usually ineffective.

It is also possible that anxious children sometimes question and encourage explanation to postpone or avoid anticipated clinical procedures.

Coercion and coaxing techniques, usually are ineffective management techniques which could be an indication that the clinician has lost control of the situation.

It was found that patting the child or a warm and friendly non-verbal gesture, is useful in reducing fear-related behaviour in young children (Weinstein, 1982).

Child management strategies such as directing, explaining, reinforcing, distracting and reassuring are more effective when the dentist is in working contact with the child. Interrupting dental procedures to manage child behaviour, is less effective and may inadvertently reinforce the child's anxiety-related behaviours eg the child is being rewarded for anxiety-related behaviours by the dentist stopping the treatment.

Many children perceive invasive medical/dental procedures such as injections , intra-venous lines and repetitive blood work, as their worst experience during hospitalisation [Eland J,1977, 1985]. Children with cancer report that procedures such as lumbar punctures and bone marrow aspiration are experienced worse, than the disease itself [Zeltzer et al, 1980]

It is stated by Sternbach [1978], that pain experience depends partly on previous learning. Due to hospitalisation and frequent painful procedures, children, particularly toddlers and preschoolers, have been observed to regress, withdraw and become fearful and uncommunicative [McGrath et al 1987; Ross et al, 1988; Kuttner L et al, 1989].

Kent and Blinkhorn [1991], supported this view. They believed that fears, including fear for dentistry, can be conditioned. A child may have felt distressed when given an injection in the past, so that injections have become associated with pain. A child might have been fearful when visiting a medical practitioner [someone else who gives injections and wears a white coat] and this fear could generalise to the dental setting. In this case, attempts to deconstruct negative associations could prove useful.

Moore [1991], reported the use of systematic desensitisation to break down maladaptive association between dental care and anxiety by using two techniques:

Video training and

Clinical rehearsals

Both were found to reduce anxiety levels, but no significant differences were found between the two techniques. This however, can be a useful tool in the hands of dental practitioners.

On the other hand, if classical conditioning is going to be useful in predicting dental anxiety in children, it still has to be explained why some children who have had traumatic experiences, do not develop dental anxiety subsequently, a matter beyond the scope of this study.

To summarise, evidence suggests that providing immediate direction and specific reinforcement are most consistently followed by a reduction in the child's fear-related behaviours.



DENTAL PAIN IN CHILDREN

Misconceptions about pain and the need for analgesia in paediatric patients have been shown to be wrong. This could have contributed to insufficient or inadequate post-surgical pain relief in children [Schechter NL, 1989]. It is now accepted that children feel pain and respond to pain analgesics in much the same way as adults [Acs et al, 1988; Drug Ther Bull, 1994; Roelofse et al 1999; Tate et al, 2002].

Levine and coworkers [1982], studied the relationship between levels of post-operative pain, number of teeth extracted and tissue injury. They found a positive correlation between tissue injury and the pain level. At that stage, this was rated as the first study which quantitatively evaluated the relationship between the tissue injury and the pain level.

Fung et al [1993], studied factors that may influence pain reported by children after dental extractions under general anaesthesia. Pain was reported by 57,5% of the children immediately after treatment. They suggested that the ages of the children and the extraction of primary rather than permanent teeth were influencing factors although not statistically significant. Although children having more than four teeth extracted seemed more likely to experience post-operative pain, no statistical significance was evident. However, significantly more children accompanied by their mothers, as opposed to someone else, complained of post-operative pain. They believed this phenomenon to be an empathetic bond between child and mother or a conscious or unconscious manipulation of the mother by the child. It also seemed that the greatest need for post-operative analgesia is immediately after the dental procedure, especially operations on young children undergoing multiple extractions.

Primosch et al [1996], studied risk factors associated with acute dental pain. Several variables such as the number of extractions, tooth position and osseous resorptive defects were found to be related to the prevalence of

pain. There was no relationship between pre-existing pain and the report of post-extraction pain.

This finding was supported by Mares et al [1997]. In a study of pain experience in children aged 6-14 years during dental treatment, they found the children's expectancy of dental pain to be more than it actually was. Their research could also not establish that children's feelings prior to a surgical procedure would signal in advance how unpleasant or painful the dental procedure would be.

Acs et al [1988], reported an incidence of severe post-extraction pain of 37,6% in children between the ages of 3 and 12. Although a parental questionnaire revealed a significant association between the number of teeth extracted and the incidence of post-extraction pain, the investigators believed that increased expectations of pain could have a confounding effect on their results.

Primosch et al [1996], could not find a relationship between several variables and pain as reported by parents. Their study included evaluations 48 hours before [pre-existing] and seven hours after extraction [post-extraction pain]. The variables studied included, age, sex, number of extractions, dental arch, tooth position, mobility, root length, osseous defects, soft tissue inflammation and history of pre-existing pain. Sixty-two children aged 2 – 10 years, were included in their study. Their results claimed that there was no relationship between pre-existing pain and the report of post-extraction pain.

They did however find a correlation between primary molars, osseous resorptive defects and pre-existing pain. Root lengths [complete root formation] and the presence of adjacent tissue lesion inflammation, were statistically significant for pre-existing pain.

Chronologic age was found to be the only variable that was associated with post-extraction pain in these children.

A study by Littlejohn et al [1996] found that when an average of >4 extractions per child [60 children, mean age 6years] were done, the pain experienced was such that treatment was necessary.

Atan et al [2004], studied the incidence of post-operative pain in children attending a day stay general anaesthetic unit for dental treatment. Sixty percent of individuals had at least one tooth extracted. As expected when local anaesthesia was used, post-operative pain was less. More pain was experienced when more teeth were extracted.

Although paediatric dental extractions as a day case procedure is a common phenomenon, the number of studies done on post-extraction pain in children are limited [literature review].

Payne and Roelofse [2000], investigated the effect of tramadol drops, an opioid analgesic, on post-operative pain in children aged 4 – 7 years.

Roelofse and Theologides [2000] also studied post-operative pain using a combination of midazolam/placebo or midazolam/tramadol in children aged 4 – 7 years. Both studies showed that six or more dental extractions caused significant pain in children.

Children often receive inadequate initial treatment for dental pain and may thus suffer unnecessarily [Mason C et al, 1997]. This may lead to post-operative behavioural problems. More emphasis should be focused in clinical practice on effective pain management in children.

MANAGEMENT OF PAIN IN CHILDREN

The idea of this part is not to look at the pharmacological options available in the management of pain in children – more emphasis will be placed on psychological support of children.

It is difficult to classify causes of pain in children but pain experiences could be considered as acute, chronic or recurrent. Tissue damaging stimuli such as trauma or burns or diseases such as sickle cell crises or cancer, cause acute pain. Medical interventions such as repeated venepuncture, investigations, therapeutic injections and surgical trauma, cause acute pain problems in a large group of children [Goldman and Lloyd Thomas, 1991].

Procedures of these nature which can cause trauma to the child and include dental procedures, eg extractions are particularly traumatic for young children of pre-school age, who still do not have the required understanding why the medical/dental procedure should take place. The situation is aggravated by the lack of verbal and communication skills [McGrath et al, 1988]. These procedures are sometimes perceived as punishment or considered a threat to their bodily integrity [existence] Factors most likely to result in psychological trauma for paediatric patients, were already identified by Gellert in 1958:

These were:

- Inadequate support received from parents
- Separation from parents, home and familiar places
- Unfamiliar routines, procedures and schedules
- Enforced dependency
- Misunderstandings and
- Physical constraint

Clinical observations have indicated that adequate preparation and management of children before and during painful procedures, considerably reduces hospital related problems.

A study of the literature, highlights the following concerns:

1. Conditioned anxiety responses to painful procedures and associated objects are rapidly developed by children [Katz et al,1980; Zeltzer et al, 1980; Kuttner et al, 1989]
2. There is evidence that over time, most children do not become inured to repeated procedures. Zeltzer and le Boron [1980] reported that 73% of their sample had considerable pain and anxiety during repeated bone marrow aspirations and lumbar punctures. Katz et al [1980] noted in their study, that the child's anxiety remained consistently evident for the procedure.
3. Frequent painful procedures and hospitalization of children, particularly toddlers and pre-school children, have caused them to regress, withdraw, become fearful and uncommunicative [McGrath PA, 1988; Ross and Ross, 1988; Kuttner et al 1989]. This increased sense of personal vulnerability places the child at risk for depression and sensitization to further procedures.
4. Anaesthesia has attendant risks like collapse and cardio-respiratory complications [Davies,1984]
The author believes sedation dulls the child's capacity to understand and cooperate during procedures, also tending to increase the child's sense of helplessness before or during pain provoking procedures. This can have paradoxical effects, exciting the child rather than having sedating effects. This however is difficult to accept as children have amnesia after procedures. What is difficult for them, is that they do not understand what happened.

Pain experienced in the past as recalled by patients, also plays a role in the pain experience, both for clinicians and researchers. In a study of dental anxiety, adults have been asked to report on the incidence of painful appointments which occurred in childhood [Hilgard, 1982; Eland 1985]. The observation that dentally anxious or phobic patients are more likely to report painful experiences in the past, has been taken as evidence of a learned link between pain and anxiety [Patterson et al, 1987]

Memory of dental pain is of particular interest in the study of dental anxiety. Experience of pain in the past is often cited as a reason for anxiety. It can be assumed that someone who has memory of pain during one appointment, could expect a similar degree of pain during another and therefore be anxious about visiting the dentist. It seems though, that many patients have unduly pessimistic expectations about the pain they will experience. When Kent [1985] asked patients before their appointments about the degree of pain they expected to feel and then compared the report with their post-appointment reports of pain actually experienced, a marked discrepancy occurred eg:

Patients who were more anxious expected more pain than they experienced, but nonanxious patients were accurate in their expectations. An explanation for this over-estimation as provided by the learning theory is, that patients who have had painful experiences in the past, tend to expect pain in the future. It may require many appointments, where patients experience less pain than expected, before these expectations are modified and the anxiety relieved.

According to such a view, pain is seen as a cause of anxiety. An alternative view is that patients' expectations of pain is not the cause of anxiety, but rather a result of it. That is, patients who are anxious may come to reconstruct their memory of the pain experienced at previous appointments so as to make it consistent with their already present anxiety.

Anxious patients may recall painful visits but the anxiety may have arisen first and any discomfort is subsequently exaggerated in memory.

Anxiety can be caused by a wide variety of experiences besides an anticipated painful dental appointment, such as their perceptions of the personality of the dentist, being 'captured' by someone else for a period of time or just a general view of the future [Butler et al,1983].

The idea that pessimistic expectations of pain can be associated with reconstructed memories, can be tested by asking patients about:

- i) their expectations of pain before the appointment
- ii) their actual experience pain during or after the appointment
- iii) their memory of that pain several months later.

If patients anxiety affects their memory of pain, then their remembered pain should be similar to their expected pain since both are subjects to the same reconstructive process. In fact, if patients' reports of past pain are based largely on their reconstructed memories thereof and these memories determine expectations, then pain remembered, should be more similar to the pain expected than to the pain actually experienced. Furthermore, the extent of reconstruction should be associated with patients' levels of anxiety. Hunter et al [1979], found that patients' memory for headache after 5 days were accurate but 5 of the 16 were 'shifters' – people whose recalled pain was quite different from their originally reported pain. They were more likely to have had high scores on the sensory, affective and evaluative scales of the McGill Pain Questionnaire [Melzack R, 1982; Reading A, 1982; Grushka et al, 1984; Cohen et al,1989]. The affective ratings of pain were more strongly associated with shifting than any other measure and the shifters remembered pain as being more severe on all scales. This led Hunter and coworkers to suggest that the high effect may have led to distortion and exaggeration of pain in memory.

PAIN REDUCTION TECHNIQUES

Psychological and physical methods that enables children to cope more successfully with anxiety-provoking and painful procedures are potentially time saving for medical and nursing staff. It provides immediate and long term benefits for children and parents as they reduce anxiety, establish skills to cope with negative experiences and increase self-efficacy (Jay et al, 1982; Patterson et al, 1987; Kuttner, 1989).

These techniques may be classified into three categories:

Kinesthetic,

Behavioural and

Imaginal (see table A below).

Kinesthetic refers to physical methods, behavioural refers to actions or responses that the child can make with external prompting and imaginal refers to techniques that are internal, cognitive or imaginative. These techniques can be organised according to developmental stages of children. Although these techniques were divided theoretically into 3 different categories, they may overlap when they are applied practically. It is not possible to discuss this all in detail in this thesis.

TABLE A

(Kuttner, 1989)

DEVELOPMENTALLY APPROPRIATE PAIN REDUCTION TECHNIQUES FOR CHILDREN:

| Age level | Pain Reduction Techniques | | |
|------------|---|---|--|
| | Kinesthetic | Behavioural | Imaginal |
| Infants | Rapid rocking and patting | Sucking (soother) | |
| Toddler | Rocking, ice/heat Parental presence | Bubble blowing, modeling Postprocedural play, music distraction | |
| Preschool | Parental presence, ice/heat stroking/blowing | Distraction (eg. pop-up books) Modeling, pre- and postprocedural play, bubble blowing | Imaginary involvement eg. favorite stories |
| School | Relaxation (eg Raggedy Ann), blowing, stroking, ice/heat | Distraction (eg. pop-up books, bubble blowing, procedural rehearsal. Modeling | Hypnosis Self-hypnosis |
| Adolescent | Relaxation (eg. pro- gressive, blowing, massage, ice/heat) | Distraction (eg. music on walkman) | Self-hypnosis Hypnosis |

The management of acute pain in procedures of children, often causes distress in staff and patients. It has been my experience that the younger the child, the more pronounced the feeling of distress. Interventions using the kinesthetic and auditory modalities, appear to be most effective in reducing the infant's distress (Elliot and co-workers, 1988). Holding and rapidly rocking the infant or child if possible during and acute pain episode can provoke quick reduction in distress. If a painful medical/dental procedure is being performed and rocking or holding the child is not possible, patting the child's back firmly, can help settle and comfort the child and reduce distress.

An auditory action eg talking, soothingly to the child, often enhances success.

DISTRACTION

Distraction as an example of a behavioural method, can be defined as diverting one's attention away from the sensation or experience of a noxious stimulus. The hypothesis that distraction will reduce pain, is based on the assumption that the pain experience depends on the cortical processing of information. Consequently, distractors that demand considerable attention, or a variety of distractors, may be most effective in reducing pain (Kuttner, 1989). Evidence however suggests that distraction may only be effective for low levels of pain (Mc Caul et al, 1984).

In studies with children, distractors have included: breathing exercises, asking the child to focus on objects in the room and using bubble blowing pop-up books to provide ongoing surprise and opportunities for diversion.

Research findings indicate that distraction with children significantly reduces pain but not anxiety (Zeltzer and le Baron, 1982). With children aged 3 – 6 years, distraction (only at the second intervention) was significantly more effective than the standard medical practice of providing support and encouragement, suggesting that more than one presentation is necessary for learning to occur (Kuttner,1989). This contrasts with children 6-10 years who were observed to be significantly less distressed at first intervention.

IMAGINAL METHODS: HYPNOSIS

Hypnosis, often, but not always, involves relaxation in which an individual develops a heightened concentration through which he/she is able to accept suggestion and optimisation. This will allow use and

optimisation of natural mental and physical skills to solve a problem or to maximise some potential (Gardner, 1981). Hypnosis with children, appear to depend on their capacity for imagination (Hilgard,1982). Hypnosis techniques should be applied in a flexible and informal manner as children 6 years of age and younger like to keep their eyes open. They may move around, may not wish to relax and can easily enter, leave and re-enter the trance state. Hypnosis may be of benefit in the sedated child, allowing pleasant thoughts enhancing relaxation and could possible reduce pharmacological intervention (Smith, 1987).

Children become highly suggestible during periods of acute pain and anxiety. Research has indicated hypnosis to be one of the treatments of choice for reducing pain and anxiety in children aged 3-6 year (Jay et al, 1982) and in school-aged children (Hilgard et al, 1982).

The pain reduction techniques mentioned do not exclude pharmacologic intervention eg. analgesics and sedative techniques. They may be additive or synergistic to these pain reducing methods.

ASSESSMENT AND MEASUREMENT OF PAIN IN CHILDREN

The objective assessment of the quality and the magnitude of pain in children, constitutes a challenge for parents and health professionals [McGrath, 1987]. This is especially important as pain is documented as being the most common complication following day surgery [Jonas DA, 2003]

The difficulties of pain assessment in children can probably be explained by their constantly changing state of perception, interpretation and expression of pain. This is related to age, developmental stage, previous pain experience and other environmental factors [Uyar M, 2004]

Children's pain measures may be classified as behavioural, physiological or psychological [McGrath, 1987]. The primary methods for assessing children's pain within these parameters, are as follows:

Behavioural: General physical behaviours, torso and limb movements, facial expressions, cry patterns and specific motor activity.

Physiological: Respiratory rate, heart rate, cortisol levels, palmar sweat and endorphins.

Psychological: Projective; colours, drawings and cartoons

Descriptive; Interviews, verbal description, interval scales and visual analogue scales.

MEASUREMENT VERSUS ASSESSMENT OF PAIN

The myth that children do not experience pain with the intensity of an adult because of an immature nervous system is refuted [Owens and Todd, 1984; Johnston and Strada, 1986; Dale JC, 1986]

Furthermore, a clear distinction between pain measurement and assessment is not always made in the literature.

Measurement is defined by McGrath and Unruh[1987] as the application of some metric to a specific element, usually intensity of pain.

Assessment is much broader. It encompasses not only the measurement of critical dimensions of pain eg location, intensity and quality, but seeks answers as to what precipitates, aggravates or eases the pain, the pattern of pain displayed and what factors influence how the pain is perceived by the child [Savendra and Tesler, 1989]. Assessment also involves awareness of the family's response style to pain and cultural differences.

Is it possible to identify the child who is faking pain from the child who is in pain? Increasing cognitive ability enables children to recognize that pain may bring reprieve from unlikeable activities. The assumption that pain is not present, as pathology or an adequate stimulus could not be identified, may lead to no or insufficient analgesia for the child [Savendra et al,1989]. Assessment also involves awareness of the family's response to pain and cultural differences.

The ability to assess pain in others, is an important human capacity [Deyo et al, 2004]. Post operative pain is an expected phenomenon but its passage beyond acceptable limits is a common and costly experience as is particularly the case in day surgery. This could be partly because of lack of knowledge about patients' experiences of post-operative pain and published research. The latter is mainly concerned with different interpretations of the phenomenon of pain that appeared to have led to a variety of often inappropriate pain measurement tools [Coll et al, 2004]

PAIN MEASUREMENT TOOLS

- Eland [1974] developed a strategy to assess pain using 8 colour crayons. Children were asked to select crayon colours that represented their pain experience.
- Behavioural tools such as the Children's Hospital of Eastern Ontario Pain Scale [CHEOPS], have components related to body position, protective touching and vocalization that can assist in assessing the location as well as the experience of pain[Mc Grath,1985]

- The Hester Poker Chip Tool [Hester NK, 1979], a type of numerical scale, uses four poker chips, one chip representing a “little hurt”, the last chip the “most hurt” possible. Children as young as 4 years can use the tool effectively.
- The Oucher six faces pain scale [Beyer JE, 1984; Beyer and Wells, 1989], is a two part scale with a numerical scale [0-100] on one side and six photographs on the other. It is designated for use with children 3-12 years of age. The happy-sad faces of a child are easily understood by children who have not yet learned to count to 100.
- The Visual Analogue Scale [VAS] is purported to be the most sensitive of the intensity scales [Scott et al, 1976 - White et al, 1985 - Savendra et al, 1989]. Happy-sad faces have been used to anchor the visual analogue scale. The number of faces in the scale usually ranges from 4-9. Variations of graphic rating scales include the pain ladder [Jeans et al, 1985] and a pain thermometer [Scott et al, 1976] Although the VAS is held to be the most sensitive of the intensity scales, children indicated that it was the least preferred [Savendra et al, 1989]
The VAS is often used in belief that the measurement continuum produces greater sensitivity than discreet points on the categorical scale [Collins et al, 1997].
- Word Graphic Rating Scale [WGRS]
Savendra et al[1989], suggested five levels of pain – no pain, little pain, medium pain, large pain and the worst possible pain as descriptors in the word graphic rating scale from their Adolescent Paediatric Pain Tool. They also warned not to use the word “moderate” to describe pain with children, as it is not readily understood. Medium pain was regarded as a more appropriate descriptor. They presented five scales [colour scale, VAS, word

graphic rating scale, a graded graphic rating scale and a magnitude estimation scale, 0-10], to children. While the colour scale was best liked, and considered “easiest to use”, by the majority of non-hospitalised children, hospitalized children in pain [n=175] when given the choice of the 5 scales, overwhelmingly selected the word graphic rating scale.

- Self-Report Measures [Goodenough et al,1997]

The Self -Report measures is indicated for children with communicative ability. Four levels of pain intensity are used from 0 = no pain [hurt] at all to 3 = most pain [hurt]. The value according to the child’s response is recorded. It is stated by Komarahadi et al [2004], that pain research is strongly dependent on the patient’s self-report.



Post-operative pain in this study was assessed by the following:

OUCHER FACIAL PAIN SCALE

[0 = no pain and 100 = extreme pain], as evaluated by the mother, the child and the observer/researcher;

WORD GRAPHIC RATING SCALE

Evaluated by the observer/researcher -

A modified version of the WGRS was used to simplify recordings eg four [in stead of five] levels of pain were recorded:

[A = no pain, B = little pain, C = moderate/medium pain and D = severe pain]

and the

HANNALAH OBJECTIVE PAIN SCALE [Hannalah et al,1987]

The Modified Hannalah Objective Pain scale is a behavioural-cardiovascular checklist on which a percentage is calculated according to six parameters: systolic blood pressure, crying, movement, agitation, posture and complaints of pain. The behavioural categories include crying, movement, agitation, posture and complaints of pain [verbalization].



ANXIOLYTIC AND ANALGESIC DRUGS

OPIATE ANALGESICS

Pain is a multidimensional phenomenon involving sensory, affective, motivational, environmental and cognitive components. The International Association for the study of pain has defined pain as:

An unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Pain is always subjective. Each individual learns the application of the word through experience related to injury in early life. It is unquestionably a sensation in a part of the body, but it is also unpleasant and therefore also an emotional experience. Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for physiological reasons. There is no way to distinguish their experience from that due to tissue damage, if we take this subjective report [International Association for the study of Pain, 1979].

The opioids are currently amongst the most commonly used and effective analgesics available for the management of moderate- to severe pain. They are known for their potency and speed of onset and they are often referred to as the primary analgesics.

Opioids are classified according to their:
receptor activity or chemical structure.

OPIOID RECEPTORS

The first definitive pharmacological evidence for opioid receptors was published by Martin and colleagues in 1976 [Simon and Gioanini, 1993]. In their pharmacological studies, they found that morphine and several of its analogs, differ in their pharmacological properties.

It was found that the protein receptors on membranes of certain cells in the central nervous system [CNS], nerve terminals in the periphery and cells of the gastro-intestinal tract, elicit stereo specific opioid interaction.

These results led Martin and co-workers in 1976 to postulate the existence of three different types of opioid receptors which they named for the prototypic drugs used in their studies: mu for morphine, kappa for ketocyclazocine, and sigma for SKF 10 047 [N-allylnormetazocine]. After the discovery of the enkephalins, Kosterlitz and co-workers [Lord et al, 1977], obtained evidence that these opioid peptides seem to bind to another type of opioid receptor. They named this site the delta receptor.

The four families of receptors designated by the Greek letters Mu (μ), Kappa (κ), Sigma [σ] and Delta (δ), each of which exhibits a different specificity for the drugs it binds, mediates the effects of the opioids. Analgesic properties of the opioids are primarily mediated by the μ receptors with contributions from the κ receptors in the dorsal horn. The enkephalins interact more selectively with the δ receptors in the periphery. The less specific σ receptor, may be responsible for the hallucinations and dysphoria which is intermittently associated with the use of opioids [Lippencotts 2nd Edit 1997] Recently a new opioid receptor N/OFQ [Nociceptin/Orphanin FQ] was discovered. It produces a complex behaviour profile including effects on drug reward and reinforcement [Devine et al, 2001]. Pain sensitivity studies have produced conflicting results [Pan et al, 2001] and more studies are needed to clarify its role.

DISTRIBUTION OF RECEPTORS

The five general areas of the central nervous system known to be involved in integrating information about pain, contains high densities of opioid receptors. These pathways descend from the peri-aqueductal gray matter through the dorsal horn of the spinal cord and have also been identified peripherally [Mansour et al, 1997]

Brainstem

Respiration, cough, nausea and vomiting, blood pressure, pupillary diameter and stomach secretion control are mediated by opioid receptors.

The Medial Thalamus

The medial thalamus mediates deep pain which is poorly localized and emotionally influenced.

Spinal Cord

Receives and integrates incoming sensory information leading to attenuation of painful afferent stimuli. This involves receptors in the substantia gelatinosa.

Hypothalamus

Receptors at this site affects neuro-endocrine secretion.



Limbic System

The amygdala contains the highest concentration of opiate receptors which probably do not exert analgesic action, but could influence emotional behaviour.

OTHER SITES

Periphery

Peripheral sensory nerve fibers and their terminals, provide sites to which opioids bind. Here, they inhibit calcium release of excitatory, pro-inflammatory substance (eg Substance P) from these nerve endings which has been suggested to contribute to the anti-inflammatory effects of opioids.

Immune Cells

The role of opioid binding sites (receptors) found on immune cells in nociception, has not been substantiated.

OPIOID ANALGESICS

[Goodman and Gilman, 2001]

Morphine

Crude opium contains morphine, the major analgesic drug which is the prototype agonist. Codeine is present in lower concentrations and is also less potent than morphine. The opioids, eg morphine, exert their effects by interacting with opioid receptors in the central nervous system and the gastro-intestinal tract. According to the classification by chemical structure, morphine belongs to the phenanthrene group of opioid analgesics.

It causes hyperpolarisation of nerve cells, inhibition of nerve firing and pre-synaptic inhibition of transmitter release. Morphine acts at the μ receptors in the lamina I and II of the substantia gelatinosa of the spinal cord and decreases the release of substance P, which modulates pain perception in the spinal cord.

As morphine is the prototype of opioid analgesics, a short discussion of its pharmacology follows:

Specific actions of morphine:

Analgesia:

The marked analgesic effect (without loss of consciousness) is brought about by raising the pain threshold at the spinal cord level and by altering the brain's perception of pain. Patients being treated with morphine are still aware of the presence of pain but the sensation is perceived as not too unpleasant.

Respiration:

A reduction of the sensitivity of the respiratory center neurons to carbon dioxide, causes respiratory depression. This occurs with normal morphine doses, but more so if the dose is increased.

Euphoria:

A powerful sense of contentment and well-being is produced by morphine which might be caused by stimulation of the ventral tegmentum.

Cough reflex depression:

Both morphine and codeine are able to depress the cough reflex by antitussive properties. Cough suppression usually does not correlate with the analgesic and respiratory depressant properties of opioid drugs, as different receptors appear to be involved.



Miosis:

Morphine stimulates the μ and κ receptors. It excites the Edinger Westphal nucleus of the oculomotor nerve which causes enhanced parasympathetic stimulation to the eye, resulting in characteristic pin-point pupils.

Emesis:

By stimulating the chemoreceptor trigger zone in the area postrema, morphine can cause vomiting which is not perceived by some as being unpleasant.

Gastro-intestinal Tract:

Morphine decreases mobility of smooth muscle and increases the tone thereof, it increases pressure in the biliary sphincter and increases the tone of the anal sphincter.

A common complaint from patients is constipation.

Cardio-vascular:

Bradycardia and hypotension is possible with higher doses of morphine, but at standard doses, no major effects on the blood pressure or heart rate are expected.

Histamine release:

Histamine is released from mast cells and can cause urticaria, sweating and vasodilation. It can also cause bronchoconstriction and should be carefully used in asthmatic patients.

Hormonal Activities:

Release of gonadotropin releasing hormone and corticotropin releasing hormone is inhibited and the concentration of luteinizing hormone, follicle stimulating hormone, adrenocorticotrophic hormone and β endorphin is decreased. It can also increase antidiuretic hormone, which can cause urinary retention.

MORPHINE PHARMACOKINETICS

[Goodman & Gilman, 2001]

Absorption

Absorption of morphine from the gastro intestinal tract is slow and erratic and the drug is seldom given per os. When orally administered to patients with severe pain, significant first pass metabolism of morphine occurs in the liver, reducing its potency two to sixfold. Intramuscular subcutaneous, intravenous and intra nasal administration, produce the most reliable responses.

Distribution:

Morphine rapidly enters all body tissues. Only a small percentage of morphine crosses the blood-brain barrier as it is the least lipophilic of the opioids.

Metabolism

Morphine is metabolised in the liver to glucuronides. The conjugates are primarily excreted in the urine and small quantities appear in the bile. Due to the low conjugating capacity in neonates, morphine should not be administered to them.

The adverse effects of morphine can include:

respiratory depression

nausea and vomiting

constipation

tolerance

dependence

pruritis



COMMONLY USED SYNTHETIC OPIOIDS AND THEIR THERAPEUTIC APPLICATION:

The major use of synthetic opioids, is to provide analgesia, not only preoperatively, but also during and after surgery.

Meperidine [Pethidine]:

Although some of its pharmacologic effects differ from the classic opioids (eg morphine), it binds to opioid receptors, particularly the κ -receptors and is mainly used for relieving acute pain. It is still in common use for analgesia, both in adults and in children.

Methadone:

It is a synthetic, orally effective opioid, with an analgesic activity equivalent to that of morphine. Methadone's greatest affinity is towards the μ -receptors, induces less euphoria and has a longer action than morphine.

Fentanyl:

It is chemically related to meperidine, but has 80 x the analgesic potency of morphine, is commonly used in anaesthesia and has a rapid onset and short duration of action. It is also commonly used during conscious sedation procedures for children.

Alfentanil:

Alfentanil has a rapid analgesic onset and time to peak effect as well as short distribution and elimination half-lives, depending on the duration of the infusion. The volume of distribution and total body clearance of this agent are smaller when compared with those of fentanyl and sufentanil.

Sufentanil:

Sufentanil, N-[4-(methoxymethyl)-1[2-(2-thienyl)-ethyl]-4-piperidinyl]-N-phenylpropanamide, is an opioid analgesic related to and about five to ten times more potent than fentanyl and over 1000 times more potent than morphine [van Deale et al, 1976].

It has hypnotic properties and given intravenously produces dose related attenuation of catecholamine release, particularly norepinephrine.

Plasma protein binding is approximately 80 to 92% of the administered dose, which after bio-transformation in the liver and intestine, is excreted within 24 hours.

Sufentanil can be administered as a primary anaesthetic agent with 100% oxygen or as an analgesic adjunct to nitrous oxide/oxygen. It is usually given intravenously, but can be used intranasally as in this study.

SUFENTANIL PHARMACOKINETICS

Compared to morphine, sufentanil has a relatively short onset and time to peak effect. In the table below [Scholz et al, 1996], the physiochemical and pharmacokinetic properties of sufentanil[S] are compared with alfentanil[A], fentanil[F] and morphine[M] after bolus administration as a single representative mean:

| | A | F | S | M |
|-------------------------------------|------|------|-------|------|
| Liquid solubility | 129 | 816 | 1727 | 1,4 |
| Non-ionised fraction at pH 7,4(%) | 89 | 8,5 | 20 | 23 |
| Plasma proteine binding at pH7,4(%) | 92,1 | 84,4 | 92,5 | 30 |
| Analgesic onset(min) | 0,75 | 1,5 | 1 | 7,5 |
| Time to peak effect(hrs) | 1,5 | 4,5 | 2,5 | 25 |
| Volume of distribution(L/Kg) | 0,75 | 4,0 | 2,9 | 3,2 |
| Distribution half-life(min) | 0,4 | 1.7 | 1,4 | 1,65 |
| Elimination half-life(min) | 94 | 219 | 164 | 177 |
| Total body clearance(L/h/Kg) | 0,48 | 0,78 | 0,762 | 0,9 |

Sufentanil was found to have the highest lipid solubility. The elimination half-life was found to be between those of fentanil and alfentanil. It is conceivable that the reduced volume of distribution [Vd] compared to fentanil, is at least in part responsible for the higher hepatic metabolism rate of sufentanil, resulting in a slightly reduced half-life.

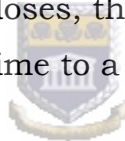
Sufentanil is metabolized by N-dealkylation at the piperidine and amide nitrogens as well as by O-demethylation and aromatic hydroxylation. Haynes et al [1993], found that intranasal sufentanil 2µg/Kg, given as nasal drops to children pre-operatively for pre-medication, produced analgesic plasma concentrations of >0,1 µg/L within 15 to 30 minutes. The highest measured plasma sufentanil concentration occurred 15 minutes

after intranasal administration in eight patients and at 30 minutes in the other seven patients in their trial. This shows that the maximum plasma concentration may be achieved between 15 – 30 minutes after administration. The plasma concentration of sufentanil at 150 minutes was $>0,08$ ng/ml.

These concentrations corresponded to the clinical observation of sedation, analgesia and pruritis. While the onset of sedation is rapid, the peak plasma sufentanil concentrations, associated with analgesia, persist well into the post-operative period.

The intranasal technique may therefore be inappropriate for short diagnostic procedures which are not associated with post-operative pain [Haynes et al, 1993].

For cases of brief duration, the context sensitive half-times for sufentanil, alfentanil and fentanyl are nearly identical. Therefore, when the opioid is administered by frequent small doses, there is no substantial difference amongst the three drugs in the time to a 50% decrease in concentration [Fisher DM, 1996].



FACTORS AFFECTING THE PHARMACOKINETICS [Scholz et al, 1996]

Age

The significance of age, has been researched in all age groups.

The elderly patient may be extremely sensitive to the action of opioids.

Obesity, a low plasma albumin concentration and a decrease in liver blood flow, from whatever cause, may play a role.

In premature infants and neonates, a reduced opioid clearance and prolonged elimination half-life are most likely due to a lower plasma protein content, decreased hepatic flow and immature enzyme systems. In older children a significant higher clearance [L/h/Kg] and shorter elimination half life have also been demonstrated in children compared with adults.

Bolus administration of opioid analgesics, can produce higher initial plasma concentrations in children than in adults, due to decreased initial

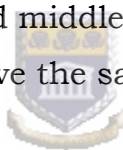
volume distribution. These concentrations, however, could decrease faster because of an increased clearance resulting in a shorter elimination half-life, which is clinically important.

Greeley et al [1987], observed a prolonged elimination half-life and reduced clearance for sufentanil only in neonates younger than 1 month. In the other age groups such as 1 to 24 months, 2 to 12 years and 12 to 18 years, it was not the case. Guay et al [1992], studied sufentanil

pharmacokinetics in children two to eight years and concluded that sufentanil is cleared faster in children [1,83 L/h/Kg] than in adults [0,76L/h/Kg]. This observation corresponded to those of Bovill et al [1984] and makes sufentanil an attractive proposition for analgesia in children.

On the other hand, Lehmann et al [1993], found no correlation between sufentanil half-life, volume of distribution, clearance and age.

From a clinical point however, it would appear that the elderly require less opioid analgesics than young and middle-aged adults, who in turn require less than small children to achieve the same result [Scholz et al, 1996]



Plasma Protein Content

Sufentanil binds to several plasma proteins including albumin, the lipoproteins and α_1 -acid glycoprotein. Approximately 50% of circulating sufentanil are bound to albumin. Sufentanil also binds to α - and β -globulins.

Decreases in α_1 -acid glycoprotein can occur in intensive care and trauma patients and other physiological related stresses [Meuldermans et al, 1982]. The content of this glycoprotein is markedly reduced and therefore the free fraction of the opioid analgesic sufentanil is markedly elevated in 19,5% of neonates and 7,8% of adults when opioids are administered.

Although changes in the α_1 -acid glycoprotein level have been demonstrated in some medical conditions as mentioned, the direct extrapolation of these changes to the clinical effects of opioids should be guarded against.

Acid Base Status

Changes in pH, influence the protein binding of sufentanil, fentanil and alfentanil. This result in an increase in protein binding with alkalosis and a decrease with acidosis. In other words, the unbound fraction of sufentanil increases with decreasing pH. Over the pH range of 5 to 12,5 the apparent solubilities are determined by the intrinsic solubility of the free base plus the concentrate of ionized drug necessary to satisfy the dissociation equilibrium at a given pH. Consequently, the drug concentrations of saturated aqueous solutions fall precipitously as the pH is raised and ionization is suppressed. [Roy et al,1989]

Intra-operative hyperventilation [arterial, pCO₂ 2,9 to 3,7kPa] during surgical procedures, can significantly influence the pharmacokinetics of sufentanil resulting in an increased Vd [5,4 ±1.9 vs 3,5± 1,1L/Kg]and a prolonged elimination half-life [232±60 vs 143 ±51 minutes]. The increased distribution of sufentanil with hyperventilation, could be caused by an increased proportion of opioids in the non-ionised state.

This observation could lead to speculation that an increased ionization of the opioid analgesic, could decrease the drug amount available for hepatic metabolism or renal excretion and lead to a prolonged duration of action. Whether intra-operative respiratory alkalosis and acidosis can result in a prolonged opioid effect and induce for example respiratory depression in the early post-operative phase, needs to be verified.

Obesity

The pharmacokinetics of sufentanil are altered in the obese. When compared with the non-obese, obese patients show an increased volume of distribution [9,098 vs 5,073 L/Kg] and a prolonged elimination half-life [208 vs 135 minutes]. The magnitude of the changes in these values, correlates with the severity of obesity. Although no definite conclusions

from the studies can be made, it would be wise to administer sufentanil on the basis of lean body mass.

Liver disease

In patients with liver disease, the degree of liver dysfunction and the ability of the drug to bind to plasma proteins are important variables to determine drug kinetics. Sufentanil, a drug with high hepatic extraction and clearance, is sensitive to changes in hepatic blood flow.

Inpatients undergoing abdominal aortic surgery, have shown a prolonged elimination half-life for sufentanil which seems to be due to a reduced hepatic flow.

It is important that liver disease be evaluated pre-operatively when opioids are to be administered.



Renal Insufficiency

Free-drug concentrations can be changed by altered protein binding which is a frequent finding with patients with renal disease. Sufentanil pharmacokinetics are not generally altered in renal insufficiency although greater variability exists in the clearance and elimination of half-lives of patients with impaired renal function [Davis JP et al, 1988] The renal clearance of sufentanil [0,6%], represents only a very small portion of total body clearance. Renal insufficiency does not appear to alter the fundamental pharmacokinetic properties of sufentanil following bolus administration. Renal insufficiency of the patient should nevertheless be considered when opioids have to be administered. This could lead to an increased duration of the effect.

OPIOIDS/PHARMACOKINETIC INTERACTIONS

As opioid analgesics are often used in combination with other agents, drug interactions are important with respect to changes in the pharmacokinetic and pharmacodynamic profiles.

It is also not the idea of this study to give a complete list of mechanisms and possible drug interactions, but a summary is necessary.

Propofol in clinically relevant concentrations, inhibits oxidative enzymatic degradation of sufentanil by microsomal systems from the human liver [Janicki et al, 1992]. Halothane administration has been shown to induce the activity of microsomal liver enzymes, which could have consequences for the metabolic pathway of opioid analgesics [Nimmo et al, 1981].

In this study sevoflurane was used – we are not aware of the effects on degradation of sufentanil.

Erythromycin can inhibit metabolism of several drugs. The clearance of alfentanil is reduced up to 50% by an impaired metabolism in patients receiving erythromycin whereas no effect on sufentanil clearance has been reported [Lemmens, 1995].

Phenothiazines, mono-amine oxidase [MAO] inhibitors and tri-cyclic antidepressants enhance the depressant action of morphine and other opioid analgesics [Goodman & Gilman, 2001]

From a theoretical point of view, many more pharmacokinetic and pharmacodynamic interactions of opioid analgesics with other drugs are conceivable, but detailed information is rare. The physician should be aware of the possibility of drug interactions with opioid analgesics.

OPIOID SELECTION

Although practical experience, convenience and costs influence the selection of opioid analgesics, pharmacokinetic and pharmacodynamic properties are important contributaries to choice. This is especially so in children undergoing outpatient procedures.

Opioids with rapid elimination half-lives like alfentanil and sufentanil, are often selected for brief procedures whereas opioids with longer elimination half-lives are considered for longer procedures.

However, simply comparing half-lives is not a rational method for selecting an opioid for specific procedures or requirements. The fast decay of concentrations after short duration intravenous administration is much more dependent on redistribution than drug elimination from the body. The most suitable drug, route and dose given, depend on the effects produced which are most important to the patient.

It seems that sufentanil may be the drug of choice for operations longer than 6-8 hours, when rapid decrease in the effect is desired after discontinuation of the infusion.

Although sufentanil has a longer distribution and elimination half-life than alfentanil, recovery from sufentanil infusions are more rapid than recovery from alfentanil infusions for longer operations. Fentanyl given as an infusion on the other hand, may be a very poor drug choice for surgical procedures longer than one hour. After the first hour, the time required for a 50% decrease in fentanyl concentrations, very rapidly increases to greater than 2 hours [Scholz et al,1996]

Precautions:

The severity (degree and duration) of respiratory depression is dose related and influenced by factors affecting the pharmacokinetics. A pronounced decrease in pulmonary exchange and respiratory arrest may occur. Patients should be under constant monitoring. Appropriate drugs and equipment should be available for resuscitation. Vital signs should be monitored routinely.

Conclusion:

The development of alfentanil and sufentanil after fentanyl, was an important step in analgesic management during and after surgical

procedures. Understanding the pharmacokinetic relationship between these and other drugs, will hopefully lead to effective application and increased safety in the management of pain and stress responses. It must however be emphasised that these drugs must be used carefully in the paediatric population by physicians trained in airway management.



BENZODIAZEPINE GROUP [BZD]

Various benzodiazepines are used in clinical practice today. For the purpose of this thesis, only the one used in this study, midazolam, will be discussed.

MIDAZOLAM

Midazolam, [8 chloro -6-(2-fluorophenyl)-1-methyl-4H imidazo(1,5a)(1,4)benzodiazepine] as the hydrochloride, is a derivative of the imidazobenzodiazepine group and is pharmacologically classified as a sedative and hypnotic.

PHAMACOLOGICAL ACTION:

Pharmacodynamics



Midazolam is a popular short acting benzodiazepine in common use for its hypnotic, sedative, anxiolytic, anticonvulsant, muscle relaxant, and amnestic effects. Anxiolysis at relatively low doses is postulated to be caused by elective inhibition of neuronal circuits in the limbic system of the brain. Spasticity of skeletal muscle is reduced, probably by increasing presynaptic inhibition in the spinal cord.

Pharmacokinetics:

High pressure liquid chromatographic retention places midazolam as the most lipid soluble benzodiazepine [Greenblatt et al,1982]

Absorption:

Peak serum concentrations of midazolam depend on the route of administration, eg several studies have shown that the peak serum levels and the bio-availability of benzodiazepines and synthetic opioids from the trans-mucosal route, are about the same or faster than those of the oral or intra- muscular routes (Kogan et al,2002]

Absorption of midazolam after intramuscular injection is rapid and complete and maximum plasma concentrations are reached within 30 minutes. Bio-availability after intra-muscular injection is over 90% [Roche brochure - Dormicum®]. When given orally, a peak plasma concentration is reached at 60 minutes, rectally at 30 minutes. De Santos and coworkers [1991] found no significant differences in the onset of sedation between intramuscular and intranasal premedication.



Distribution:

When injected intravenously, plasma concentrations show 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. Similar to other bezodiazepines, midazolam binds strongly to plasma proteins. Protein binding of 90–98% occurs. [Roche brochure-Dormicum®] [Greenblatt et al, 1982]

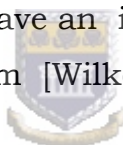
Metabolism:

Midazolam is completely metabolised with α -hydroxy-midazolam as the primary metabolite; 40 – 50 % is metabolized by the liver. Immediately after it's formation, this active metabolite conjugates with glucuronic acid (inactivation) and is then eliminated by the kidneys more rapidly than midazolam.

Elimination:

The route of hepatic biotransformation of the BZD's, appears to be important with respect to factors influencing drug metabolism. The three factors are oxidation, conjugation and nitro-reduction.

Midazolam is metabolised by oxidation and its clearance is dependent on hepatic flow as well as microsomal activity. Clearance may approach 50% of hepatic flow implying that clearance is dependent on hepatic flow as well as microsomal enzyme activity. The hepatic clearance of midazolam is higher than that of diazepam; a sound reason why midazolam is more commonly used today. Because of its high clearance, midazolam has a short half life of between 1,5 and 5,5 hours [in comparison to diazepam 20–70 hours]; plasma-clearance is in the region of 300–400 ml per minute. About 50–70% of midazolam is eliminated by the kidneys in the conjugate form (α -hydroxymetabolite). Factors that may alter hepatic flow and/or microsomal oxidising capacity, have an influence on the kinetic profile of all the BZD's including midazolam [Wilkenson GR et al,1975]



MIDAZOLAM AS THE BZD OF CHOICE

Midazolam has twice the potency of diazepam and has a rapid onset of action - the sedative end-point is reached much more quickly than with diazepam. Further increments must be given slowly and titrated to response. Care must be exercised when midazolam is given as significant respiratory and cardiovascular depression and an acute reduction of arterial oxygen saturation may follow. Clinical sedation should be achieved within 2 – 5 minutes, but a significant brain concentration is only reached after 12 minutes.

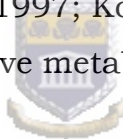
Midazolam is short acting and has a shorter half life (± 3 hours) than diazepam with a shorter duration of action and recovery is much quicker. Midazolam is an anticonvulsant, a muscle-relaxant and it provides anterograde amnesia [Sievers et al,1991]. This effect can be used to great effect in patients. Children who are apprehensive of dental procedures or

previously had been subjected to traumatic or painful procedures, will not readily be persuaded to attend follow-up appointments. The amnesiac properties of midazolam, can therefore be exploited to its most effective potential (within therapeutic limits), with children that requires pharmacological intervention.

Midazolam has a relatively high margin of safety. Its hypnotic and respiratory depressant effects is antagonised by flumazenil which is a GABA[gamma-aminobutyric acid] receptor antagonist, that can rapidly reverse the negative effects of benzodiazepines and adds to the safety of the drug. The fact that the effects of benzodiazepines can be reversed, make them excellent choices for sedation.

Midazolam has been extensively and successfully administered and researched via several routes e.g. orally, intravenously, intramuscularly, rectally and intranasally [Malinovsky et al,1993; Connors et al, 1994 Roelofse et al, 1996; Lejus et al, 1997; Kogan et al, 2002]

Midazolam does not produce active metabolites like diazepam – therefore recovery is much quicker.



ROUTES OP ADMINISTRATION

Midazolam is often used for pre-medication of children before general anaesthesia or for sedation. Different non-invasive routes of administration have been described. In a study, Tolksdorf and Erick C, [1991], compared the effects and acceptability of oral, nasal and rectal midazolam using standard dosages in 90 children. They showed that the children accepted the oral midazolam significantly better than the rectal and nasal route. The fastest onset of sedation was found after rectal application. Immediately after the nasal application, many children became euphoric. They showed that nasal administration make children more euphoric than sedated.

The effect of the oral midazolam was good in many children, but less predictable. They concluded that rectal midazolam had the fastest onset of

sedative and that nasal midazolam produced an almost immediate euphoric effect. Oral pre-medication was best accepted and nasal administration worst.

Malinovsky and co-workers [1995] compared the times oral, rectal and nasal midazolam took to reach an effective plasma concentration for sedation in children. Adequate sedation was achieved after 7,7 minutes SD 2,43 with intranasal; 12,5 minutes SD 4.9 with oral and 16,3 minutes SD 4,2 with rectal midazolam.

In an earlier study in 1993 by Malinovsky JM, Lejas C and co-workers, they compared plasma concentrations of midazolam after nasal or rectal administration in 45 children (2 – 9 years old). After nasal administration, the maximum midazolam concentration [C_{max}] reached was 182 (SD57)ngm/ml⁻¹ within 12,6 (5,9min) respectively. Rectal administration resulted in smaller plasma concentrations.

Connors and Tendrup [1994] studied the efficacy and safety of a single dose of midazolam given as an oral solution or nasal drops. They found that the oral route was associated with fewer administration problems. No significant differences were scored regarding effectiveness of the different dosage routes, but nasal irritation occurred in 5 out of 28 children.

Walbergh, Wills and Eckhert (1991), stated that nasally administered midazolam appears to be a useful method for achieving rapid sedation in children prior to induction of anaesthesia. They determined peak plasma concentrations after intra-nasal administration of midazolam and compared this to plasma concentrations achieved after intravenously administered midazolam in 18 children scheduled for open heart surgery. Intra-nasal midazolam achieved its peak plasma concentrations in 10,2 minutes ±2 . Ten minutes after the administration of nasal midazolam, the mean plasma concentration was 57 % of the concentration in the group receiving midazolam intravenously. These results confirm the clinical impression that intranasal administration of midazolam rapidly achieves

sedative plasma concentrations in children. This is exactly what was shown in this study.



KETAMINE

INTRODUCTION

Ketamine [C₁₃H₁₆ N₂ O HCl] produces dissociative anaesthesia characterised by a state of sedation, catalepsy, amnesia and marked analgesia which may persist into the recovery period [Martindale 20th Edit]. The commercially available racemic mixture [containing equal amounts of the two isomers], was approved for clinical use in 1970. Initial experience with ketamine as a sole anaesthetic agent led to unpleasant emergence reactions and cardiovascular stimulation effects, which limited its usefulness. However, supplementation with other drugs such as the benzodiazepines, have reduced these side effects. Evolving concepts of its mechanism of action, re-evaluation of its analgesic properties and the advantage of alternative routes of administration, leads to a changing role for ketamine in clinical anaesthesia.

BASIC PHARMACOLOGY

The ketamine molecule [2-(4-chlorophenyl)-2-methylamine cyclohexanone], structurally resembles phencyclidine [PCP] and cyclohexamine.

It has a molecular weight of 238 and a pKa of 7.5. The molecular structure contains a chiral centre at the C2-carbon of the cyclohexanone ring, so that two enantiomers or optical isomers exist: s[+] – ketamine and r[-] – ketamine. Racemic ketamine preparations contain equal concentrations of both.

PHARMACOKINETICS

Ketamine has a high bioavailability following intravenous[iv] or intramuscular[im] administration.

Because of first pass metabolism and lower absorption, higher doses need to be given by oral and rectal routes. Extensive biotransformation takes place in the liver.

Major pathway: N-demethylation of ketamine via cytochrome P-450 enzymes to form nor-ketamine, an active metabolite with an anaesthetic potency one third that of ketamine. Nor-ketamine is then hydroxylated and conjugated to water-soluble glucuronide compounds that are excreted in urine.

Minor pathway: Oxidative metabolism of the cyclohexanone ring.

Ketamine has a rapid onset of action, a relatively short duration of hypnotic effects and is ten times more lipid soluble than thiopental.

Within one minute following iv administration, peak plasma levels are achieved and within 5 minutes following intramuscular injection.

Ketamine is initially distributed to highly perfused tissue [including the brain and subsequently redistributed from vessel-rich tissues to less well-perfused tissues. Looking at a two-compartment model, the initial distribution phase of intra-venous ketamine from the central compartment [plasma] to peripheral tissue compartments occur with a half-life [$t_{1/2}$] of 7-11 minutes. The elimination phase, including both metabolic and excretory processes, occurs with a half-life [$t_{1/2}$] of 2-3 hours.

Duration of hypnosis is not affected by either the induction or inhibition of drug-metabolism enzymes or by decreased renal clearance.

This suggests that termination of the hypnotic or anaesthetic effects of ketamine is primarily due to redistribution from the brain to the tissues. Hepatic metabolism is important for the ultimate clearance of ketamine from the body and may be a factor in terminating posterior anaesthetic effects.

PHARMACODYNAMICS

The pharmacodynamic effect of ketamine is apparently due to the central nervous system [CNS] activity of the parent compound. As CNS levels decline by redistribution to the peripheral compartment, the CNS effects subside.

When ketamine anaesthesia is terminated, a large fraction of the drug administered [50-60%] remains in the body tissues in unchanged active form, producing significant plasma levels, which may lead to protracted emergence from anaesthesia in the recovery room. This may also be significant with respect to cumulative effects and the potential for drug interactions.

Chronic administration of ketamine to laboratory animals result in increased activity of hepatic drug-metabolising enzymes, including enzymes responsible for the metabolism of ketamine itself [cytochrome P-450]. These self-inductive effects could explain the occurrence of tolerance to the analgesic effects that occur in burn patients following repeated exposures to ketamine.

Pharmacodynamics are similar in children except for more rapid absorption after intramuscular administration and higher concentrations of nor-ketamine that are reached.

OPTICAL ISOMERS

A chiral centre at C2 of the cyclohexanone ring permits existence of two resolvable optical isomers of enantiomers, with absolute configurations of s[+]-ketamine hydrochloride and r[-]-ketamine hydrochloride, which differ in their pharmacological properties. The [+] enantiomer has been shown in rats to have a higher therapeutic index than the racemate, while at equi-hypnotic doses, the [+] enantiomer causes less stimulation of locomotor activity and less excitation. [+] -Ketamine is 3 times more potent

than [-]-ketamine as an analgesic and 1,5 times more potent in terms of its hypnotic effect. In a human study, more psychic emergence reactions occurred after administration of [-]-ketamine.

MECHANISM OF ACTION

The neuropharmacology of ketamine is complex. It interacts with multiple binding sites, including NMDA [N-Methyl-D-Aspartate] and non-NMDA glutamate receptors, nicotinic and muscarinic cholinergic receptors, monoaminergic- and opioid receptors. It also interacts with voltage dependent channels such as Na[sodium] and L-type Ca[calcium]-channels. All these interactions play a role in the pharmacological and clinical properties of ketamine.

NMDA [N-Methyl-D-Aspartate] Glutamate receptors:

NMDA receptor antagonism accounts for most of the analgesic, amnesic, psychotomimetic and neuroprotective effects of ketamine. The NMDA receptor is an inotropic receptor [ligand gated ion channel] that is activated by glutamate [a CNS excitatory neurotransmitter]. The channel is permeable to calcium and to a lesser degree to sodium and potassium. It requires glycine as an obligatory co-agonist and is inhibited by magnesium. NMDA receptors are involved in the so-called wind-up phenomenon which plays a major role in the development of chronic pain. Ketamine binds to the phencyclidine receptor in the NMDA channel and thus inhibits glutamate activation of the channel in a non-competitive manner. The channel must be in the open state to be blocked by ketamine.

NON-NMDA Glutamate Receptors

Several classes of non-NMDA glutamate receptors exist which are selectively activated by the agonists quisqualate [an excitotoxin], AMPA

[adenosine mono-phosphate aminase] or kainite and are inhibited by ketamine. The effects are mediated through the glutamate / NO / cGMP [guanosine mono-phosphate] system. NMDA and non-NMDA receptor activation stimulate NO synthesis. NO is known to play a role as a central and peripheral neurotransmitter and is linked to pain perception at spinal level. Thus, ketamine-induced NO-synthase inhibition, may be the mechanism for its analgesic effect and neuro-protective actions.

Opioid receptors

Ketamine has been reported to interact with mu[μ], delta[δ] and kappa[κ] receptors. The interaction is very complex.

Agonist actions of ketamine on opioid receptors play only a minor role in its analgesic effects. However, interaction with κ -opioid receptors may explain its psychomimetic side effects because κ -agonists induce similar effects. The affinity of ketamine for opioid receptors rank:

mu>kappa>delta but the affinity of ketamine for these receptors is 10 – 20 times less than for the NMDA channels, which suggests that the interaction is not of major clinical importance.

This is confirmed by findings that naloxone does not reverse the analgesic effect of ketamine in humans. Interactions with sigma receptors, might explain euphoric emergence reactions [the sigma receptors is no longer classified as an opiate receptor].

Cholinergic Receptors

Ketamine affects both nicotinic and muscarinic acetylcholine receptors and inhibits NMDA receptor-mediated acetylcholine release. The postsynaptic inhibitory effect on nicotinic acetylcholine receptors in skeletal muscle, is not necessarily noticeable clinically, as ketamine increases muscle tone by central mechanism. However, this effect can be uncovered by additional administration of muscle relaxants.

ADRENERGIC AND SEROTONERGIC MECHANISM;

Neuronal and intraneuronal uptake of noradrenaline is inhibited by ketamine leading to a prolonged response and increased transfer of noradrenaline into the systemic circulation.

Uptake of dopamine and 5-HT is similarly inhibited, which could lead to an increase in central dopaminergic activity. The 5-HT antagonist methysergide, antagonises the analgesic effects of intrathecal ketamine, implicating serotonergic mechanisms in ketamine analgesia. The mechanism may also explain ketamine-related emesis, as ondansetron inhibits this effect.

OTHER MECHANISMS

Inhibition of neuronal Na channels provide a modest local anaesthetic effect when high doses of ketamine are given. Ketamine has been used to produce adequate iv regional anaesthesia with complete sympathetic, sensory and motor block.

Non-competitive Ca channel blockade may be responsible for cerebral vasodilation.

PHARMACOLOGICAL EFFECTS OF KETAMINE:

CENTRAL NERVOUS SYSTEM [CNS] EFFECTS

Ketamine produces a so-called “dissociative” anaesthetic state: a functional and electrophysiological dissociation between the thalamo-neocortical and limbic systems. This is a state of catalepsy in which eyes remain open with a slow nystagmus, while light and corneal reflexes remain intact. Varying degrees of hypertonus and occasional purposeful movements unrelated to painful stimuli may occur in the presence of adequate anaesthesia.

ECG EFFECTS:

Early studies reported depression of thalamo-neocortical pathways and concomitant activation of the limbic system. Later studies demonstrated excitatory activity in both the thalamus and limbic system, without clinical evidence of seizure activity. Thus, although thalamic and limbic epileptiform patterns exist, there is no evidence that this seizure activity spreads to cortical areas, not that clinical seizures are likely to occur.

INTRA-CRANIAL PRESSURE [ICP]

Ketamine can increase ICP especially when ICP was increased before administration of the drug and when given in doses > 1 mg/kg iv.

Two possible reasons exist: during a period of impaired cerebrovascular autoregulation, cerebral blood volume may increase passively due to the increased arterial pressure; more importantly, ketamine-induced ventilatory depression may lead to an increase in arterial pCO₂. Studies have shown that when normocapnoea was maintained with controlled ventilation, ketamine did not raise the ICP. Although some studies have shown an ICP increase during normocapnoea after 2mg/kg iv ketamine, this could be avoided by mild hyperventilation or the administration of benzodiazepines.

EFFECTS ON CEREBRAL BLOOD FLOW [CBF]

Studies have shown that cerebrovascular effects of ketamine are related to the pre-existing cerebrovascular tone. The most likely mechanism determining CBF involves hypercapnia, regionally specific stimulation and inhibition of cerebral metabolic rate and direct vasodilation by Ca channel blockade.

NEUROPROTECTION

Cerebral hypoxia/ischemia initiates a cascade that leads to cell destruction and neuronal death. Activation of NMDA and non-NMDA receptors play an important role in this cascade: after stimulation of these receptors by high level of glutamate or aspartate, the resultant transmembrane flux and intracellular accumulation of Sodium [Na] and Calcium [Ca], lead to cell swelling and activation of pathways ultimately causing cerebral ischaemic damage. NMDA receptor antagonists, including ketamine, have neuroprotective potential.

POST ANAESTHESIA EMERGENCE REACTIONS AND PSYCHOTOMIMETIC EFFECTS

Classical side effects after ketamine anaesthesia include amnesia, altered short term memory, decreased ability to concentrate, decreased vigilance and altered cognitive performance. Other psychic sensations have been described as: alterations in mood state and body image, dissociative or extracorporeal experiences, floating sensations, vivid dreams or illusions and occasional frank delirium. The vivid dreams and visual illusions usually disappear immediately upon waking, although flashbacks have been reported after several weeks.

It seems that the psychic emergence reactions occur secondary to ketamine induced depression of auditory and visual relay nuclei, leading to misperception and/or misinterpretation of auditory and visual stimuli.

Loss of skin and musculoskeletal sensations result in decreased ability to feel gravity, thereby producing a sensation of bodily detachment. There is no evidence that covering the eyes or awakening the patient in a quiet area alters the incidence of emergence reactions. In fact, both pre-operative and post-operative discussions with the patient regarding expected effects and common side-effects are important.

The incidence of psychic disturbances following ketamine administration, range from less than 5 to more than 30 percent. Factors associated with a higher incidence include patients <16years, females, shorter operative procedures, large dosage >2mg/kg, rapid intravenous[iv] administration and a history of personal problems.

Benzodiazepines have proved the most effective adjuvant agents for prevention of these phenomena. Those insoluble in water with a long elimination half-life, produce a higher incidence of phlebitis and lead to prolonged recovery. Midazolam is water-soluble and shorter acting; it reduces ketamine's cardiovascular stimulation and emergence phenomena, is rapidly metabolized and does not have any active metabolites.

Ketamine is dispensed in an aqueous medium which is non-irritating as an iv injection. The combination of ketamine and midazolam leads to high patient acceptance, which never occurred with ketamine as a sole agent.



ANALGESIC ACTIONS:

Analgesia following ketamine administration outlasts the period of anaesthesia.

Suggested explanations for it's analgesic action:

- Ketamine blocks afferent signals associated with affective-emotional components of pain perception [the spinoreticular tracts] without significantly impairing the pathway related to localization of somatic stimuli [spinothalamic tract]
- Highly selective depression of nuclei involved in the transmission of impulses within the medial medullary reticular formation; this is a relay station for the transmission of the affective emotional components of nociception from the spinal chord to higher brain centra.
- Binding to opiate receptors

CARDIOVASCULAR [CVS] EFFECTS:

A major feature that distinguishes ketamine from other iv anaesthetics, is its stimulation of the cardiovascular system. Increases in heart rate, systemic arterial pressure, systemic vascular resistance, pulmonary arterial pressure and pulmonary vascular resistance have been reported.

Mechanism:

The mechanism of CVS effects of ketamine is not well understood. In vitro, ketamine produces a dose-dependent decrease in rate and force of myocardial contraction. In vivo, the direct negative inotropic effect is usually overshadowed by direct central sympathetic stimulation, Circulating catecholamine levels are increased by inhibition of reuptake.

Effects on rhythm

The effect of ketamine on cardiac rhythm is controversial. There is evidence to suggest sensitisation of the myocardium to the dysrhythmogenic effects of adrenergic agents. However, transient dose-related antiarrhythmic effects have also been demonstrated. Two cases of serious dysrhythmias were reported in plastic surgery cases who received 0,5 mg/kg of iv ketamine for sedation during infiltration of lignocaine solutions containing adrenaline.

Prevention of CVS Stimulation

Numerous drugs have been shown to block ketamine induced CVS stimulation including beta-blockers and the calcium channel blocker Verapamil, but the benzodiazepines are the most efficacious agents for this purpose. Midazolam is short acting and water-soluble and has become a common adjunct to ketamine anesthesia.

Ischaemic Heart Disease [IHD]

Ketamine directly dilates vascular smooth muscle [Ca channel blocking effect] while causing sympathetically mediated vasoconstriction. The net effect is that systemic vascular resistance [SVR] is not significantly altered. Even though ketamine increases coronary blood flow, it may be insufficient to meet metabolic demands of the myocardium produced by the increase in the rate-pressure product.

In patients with IHD, the cardiovascular stimulant effects might precipitate myocardial ischemia when used as a single agent. However, clinical studies of ketamine-diazepam anaesthesia in cardiac surgical patients indicate haemodynamic stability.

PULMONARY VASCULAR RESISTANCE [PVR]

Ketamine elevates pulmonary artery pressure and right ventricular stroke work secondary to increased PVR. Thus it is probably contra-indicated in patients with minimal right ventricular reserve.

CRITICALLY ILL PATIENTS

These patients occasionally respond to ketamine with an unexpected drop in blood pressure which may result from the inability of the sympathomimetic actions of ketamine to counterbalance its direct myocardial depressant and vasodilatory effects. Furthermore, general anaesthetics block the cardiovascular stimulation properties of ketamine so that significant cardio-vascular depression can be produced when used during volatile anaesthesia.

Ketamine should be used cautiously for shocked patients as severe hypotension may occur on induction of anaesthesia. This may result from loss of sympathoadrenal activity that accompanies loss of consciousness.

PULMONARY EFFECTS

Ketamine is a mild respiratory depressant: dose-related respiratory depression is demonstrated with incremental doses. The respiratory response to CO is maintained. The CO-response curve is shifted to the right but the slope of the curve is not altered. The respiratory depression is similar to that caused by opiates and opioid receptors play a role.

RESPIRATORY PATTERNS

Respiratory depression is usually only significant when it is given as a rapid iv infusion. When given at a slow rate [20µg/kg/m infusion rate after a bolus of 3 mg/kg iv] functional residual capacity, minute ventilation and tidal volume are maintained with an increase in the contribution of the intercostal muscles [relative to the diaphragm] to the tidal volume.



BRONCHODILATION:

Ketamine has bronchodilatation properties probably caused by circulating catecholamines [bronchodilatation effect is blocked by propanol]. It has been used in the treatment and emergency intubation of paediatric patients with status asthmaticus.

AIRWAY MAINTENANCE:

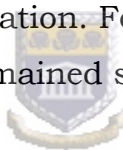
In clinical relevant doses, ketamine generally preserves the protective pharyngeal and laryngeal reflexes and maintains a patent airway. Nevertheless, there have been reports of pulmonary aspiration, prolonged apnoea and hypoxemia. Vigilant monitoring of a patent airway remains essential. Salivary and tracheo-bronchia secretions are increased and a

prophylactic antisialagogue is required. Glycopyrrolate and atropine are equally effective.

MISCELLANEOUS PHARMACOLOGICAL EFFECTS:

Ketamine produces an increase in skeletal muscle tone and occasionally muscle spasms, although it has been used safely in patients with myopathies and malignant hyperthermia. Through interfering with calcium binding or its fluxes, ketamine enhances the action of neuromuscular blocking drugs.

Ketamine has reportedly been used in patients with acute intermittent porphyria but can increase ALA [δ -aminolevulinic acid] synthetase activity in animals and should be used with caution in patients with porphyria. Recently it was found that intra-ocular pressure [IOP] decreased, after ketamine induction, before intubation. Following intubation, IOP returned to the pre-induction level and remained stable.



ANAESTHESIA FOR BURN PATIENTS

Ketamine has been used widely in burn units for dressing changes, debridements and skin grafting procedures. Low doses ketamine [1,5 – 2 mg/kg im] has a rapid onset of action to produce good operating conditions, amnesia and satisfactory analgesia. However, tolerance develops with repeated exposures [even after only two exposures] and the dose has to be increased progressively.

OUTPATIENT SEDATION – ANALGESIA

Ketamine's short duration of action and postoperative analgesic effects make it suitable for outpatient paediatric procedures and oral surgery, utilizing doses of 0,5 – 1 mg/kg iv or 1-3mg/kg im.

Different dosage regimens are recommended in the literature

Richard Kaplan [2002] recommends the following:

Intravenously; 0,25 – 0,5 mg/kg

Orally or rectally; 6-10 mg/kg

Intramuscularly; 2mg/kg

To avoid complications, it is recommended that intravenous ketamine be administered in acute cases only and that the dose be limited to 0,25 to 0,5 mg/kg boluses iv with a maximum of 2 mg/kg over 20 minutes.

Parker RI [1997] used a combination of iv midazolam and ketamine to provide conscious sedation for invasive or lengthy procedures in children 4 months to 17 years of age [lumbar punctures, bone marrow aspirations or biopsies, radiotherapy sessions and imaging studies]. Patients were sedated initially with midazolam [0,05 – 0,1 mg/kg iv; maximum single dose of 2 mg; maximum total dose of 4 mg], followed by ketamine [1-2 mg/kg iv]. During lengthy procedures, additional doses of ketamine [0,5mg-1mg/kg] were given as necessary. This sedative regimen was found to be safe and effective. It has reduced patient as well as parent anxiety for the procedures [Parker RI, 1997]

In a study comparing midazolam alone to the combination of midazolam and ketamine, it was found that both these techniques provided a safe and effective way to manage children for minor oral dental procedures under local anaesthesia. The children were between 2 and 7 years old and received either a combination of midazolam [0,35mg/kg] and ketamine [5mg/kg] or midazolam alone [1mg/kg] rectally 30 minutes before being taken to the dental operator. Both groups had reliable good anxiolysis and sedation without loss of respiratory drive or protective airway reflexes [Roelofse, 1996]

White [1982] reported that continuous infusions of ketamine [as a supplement to nitrous oxide] were preferable to bolus administration in outpatient anaesthesia.

In children, intramuscular ketamine 5 – 10mg/kg, can be used for diagnostic and minor surgical procedures , which do not require an intravenous canula or intubation [Wyant, 1971]. It has been used for

repeated radiotherapy, minor otolaryngological procedures [2mg/kg iv] and bronchoscopy [10mg/kg iv]. According to anecdotal reports, ketamine may produce 'hyperactive' airway reflexes, especially in the presence of inflammation of the upper respiratory tract.

Ketamine has been used for ocular examinations under anaesthesia. Although early clinical reports suggested there was an increase in intraocular pressure with ketamine, more recent studies have found this not to be the case.

Rectal ketamine 8-10mg/kg has been used successfully as an induction agent in paediatric anaesthesia. Loss of consciousness takes place after 7 – 15 minutes and peak serum concentrations are reached after 40 minutes.

Adjunct to local and regional anaesthesia:

During performance of a painful nerve block, the ideal adjunct drug would provide analgesia, sedation and amnesia without cardio-respiratory suppression.

Deng XM [2001], used midazolam and small-dose ketamine for sedation and analgesia during local anaesthesia. The study demonstrated that small-dose ketamine infusion in combination with midazolam provided satisfactory intra-operative sedation, analgesia and amnesia in healthy plastic surgery patients when used to supplement local anaesthesia. In the smaller-dose ketamine group [$<10\mu\text{g/kg/minute}$], less side effects were experienced.

ANAESTHESIA FOR THE AGED AND CRITICALLY ILL:

Ketamine has been used in critically ill patients with reports of good surgical anaesthesia with a greater margin of safety than 'conventional' anaesthesia and a low incidence of side-effects and post operative complications.

Ketamine's use in haemorrhagic shock is controversial. Ketamine induction in patients who were hypovolemic due to acute haemorrhage, displayed no change or a slight increase in blood pressure and heart rate. In patients who had been in borderline or actual shock for several days, it produced a marked depressor response. It is possible that prolonged pre-operative stress diminishes the usual cardiovascular stimulation produced in response to ketamine, thereby unmasking its myocardial depressant properties.

PRE-EMPTIVE ANALGESIA:

In small doses [0,1-0,5mg /kg], ketamine has noticeable analgesic action which can be used to supplement general, regional or local anaesthesia. Pre-emptive analgesia is the administration of an analgesic before the noxious stimulation occurs. The goal is to prevent or reduce the development of a "memory" of the pain stimulus in the CNS. When a massive amount of nociceptive impulses reach the spinal tract, a hyper excitable state of central nervous system sensitization known as 'wind-up' results. It seems that NMDA receptors are responsible for pain memory and their blockade can prevent the induction of central sensitization. The FDA has approved ketamine for this purpose. The administration of pre-emptive ketamine to prevent post operative pain requires small doses of the drug and the effect lasts for a relatively long period[>6 hours]. Pre-operatively administered ketamine, reduces the amount of narcotics required for post-operative pain control by 40 - 60%.

CONCLUSION

The indications for ketamine may have to be revised based on correct knowledge. The separation of the [+] and [-] enantiomers, has revealed the S[+] enantiomer to be a potentially valuable drug for modern iv anaesthesia. S[+] ketamine has been found to be a more effective

anaesthetic with less prominent side-effects than racemic ketamine. It's recent commercial introduction on the European market may lead to widespread clinical use and broadening of the indications for ketamine.
[Ketamine references – p121]



CHAPTER 3

PATIENTS, MATERIALS AND METHODS

The study was approved by the ethical research committee of the University of Stellenbosch's Health Sciences Faculty [before merging with the Dental Faculty of the University of the Western Cape] as a basic requirement before any research could be initiated. Parents signed written consent forms.

PATIENTS

Fifty healthy American Society of Anaesthesiologist [ASA] 1 children free from any naso-pharyngeal or respiratory problems aged 5 to 7 years, weighing 15–20 kg having six or more teeth extracted under general anaesthesia, were eligible for participation in this study.

A patient was accepted for the study when the following inclusion criteria were met:

- male or female patient aged between five and seven years
- classified as an ASA 1 patient
- six or more dental extractions required
- weight 15 – 20 kg

Exclusion criteria were as follows:

- the use of analgesics or central nervous depressants over the previous 24 hours
- an emergency procedure
- the use of anticoagulants

- history of sensitivity to opioids, benzodiazepines and ketamine, or any other drugs likely to cause drug interactions with the study drugs
- any medical condition leading to an ASA III or IV classification

At a pre-surgery visit, patients were evaluated for inclusion, using a medical history questionnaire and a clinical examination.

Children were randomly allocated before surgery according to a computer-generated randomization list, to one of two treatment groups. Children were fasted for 8 hours before the operation, with only sips of clear fluid allowed 3-4 hours pre-induction.

Baseline vital signs data were obtained from each child before surgery by means of a Dinamapp® adult/paediatric non-invasive blood pressure monitor, an Ohmedia Biox 3700® pulse oximeter for measuring oxygen saturation and a continuous electrocardiogram and heart-rate monitor.

In group A, 25 children received intranasal ketamine 5mg/kg and intranasal midazolam 0,3mg/kg [via a tuberculin syringe].

In group B, 25 children received intranasal sufentanil 20 micrograms [via a GO Medical® nasal spray] and intranasal midazolam 0,3mg/kg [via a tuberculin syringe]. Both groups received the premedication 20 minutes before induction of anaesthesia.

PREMEDICATION

Group A children

Nasal midazolam 0,3mg/kg [one nostril] with tuberculin syringe

Nasal ketamine 5mg/kg [other nostril] with syringe

Group B children

Nasal midazolam 0,3 mg/kg [one nostril] with tuberculin syringe

Nasal sufentanil 20 µg with Go Medical® nasal spray, other nostril.

All the children underwent more than six dental extractions.

General anaesthesia was induced with a sevoflurane in nitrous oxide and oxygen inhalational technique. After nasotracheal intubation, a throat pack

was inserted to protect the airway. Children were allowed to breathe spontaneously. No local anaesthesia was used.

When necessary, breathing was assisted to maintain an end-tidal carbon dioxide concentration of between 4 and 5%.

A blinded observer/researcher monitored parameters. The blinded observer/ researcher remained with the child from prior to drug administration until discharge from the recovery room and was unable to tell which drug combination was used. Patients were observed for adverse effects like nausea, vomiting, itching and excessive sedation.

Monitoring in theatre consisted of standard temperature, blood pressure [systolic, diastolic, mean], electrocardiogram, pulse oximetry and capnography. Children were postoperatively transferred to the recovery room where a trained research nurse monitored the parameters.



ASSESSMENTS

Monitoring consisted of a Dinamapp® adult/paediatric non-invasive blood pressure monitor, an Ohmedia Biox III® pulse oximeter for measuring oxygen saturation and a continuous electrocardiogram and heart rate monitor.

Blood pressure [systolic, diastolic, mean] pulse and respiratory rates and oxygen saturations, were recorded at the following time intervals:

1. Before the start of sedation
2. At 15 and 20 minutes after drug administration
3. At 30, 60, 90, and 120 minutes post-operatively

The same anaesthesiologist and the same dental surgeon carried out all the treatments and the independent observer/researcher made all the assessments.

The independent observer/researcher assessed the following:

ACCEPTABILITY OF THE NASAL SPRAY

This was assessed on a scale from 1-3 as follows:

- 1 = no defence action
- 2 = defence action/weeping
- 3 = refusing vehemently

ANXIETY SCORES

- 1= Very anxious
- 2= Alert, moderately anxious
- 3= Calm, indifferent, not anxious
- 4= Asleep

Anxiety levels were evaluated before administration of drugs and at 15 and 20 minutes after administration thereof.



SEDATION SCORES

[According to Ramsay M, 1980]

Sedation scores were evaluated by the same independent observer before and at 15 and 20 minutes after drug administration.

- 1= fully awake, orientated
- 2= drowsy
- 3= eyes closed. arousable to verbal command
- 4= eyes closed, arousable to shoulder shaking
- 5= eyes closed, unarousable to shoulder shaking

EASE OF MASK INDUCTION

Observed Scale:

- 1= no defense action
- 2= defense action/ weeping
- 3= refusing vehemently

POSTOPERATIVE ASSESSMENT

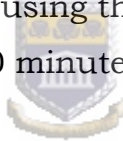
Children remained in the recovery room for 4 hours after surgery where recovery was assessed according to the Aldrete postanesthetic recovery score [Aldrete JA, 1970]

The score ranges from zero for an unresponsive, immobile child requiring airway maintenance, to 10 for a fully recovered child.

All the parameters were assessed on admission, after 15, 30, 60, 90 and 120 minutes.

PAIN ASSESSMENT

Postoperative pain was assessed using the following measurement techniques at 30, 60, 90 and 120 minutes post-operatively. The scales used were:



Oucher Facial Pain Scale (OFPS)

[Beyer and Wells, 1989]:

Value 0 (no pain) to 100 (extreme pain).

The OFPS pain scale was evaluated by the mother, child and observer/researcher. The OFPS comprises six faces showing increasing graduations of pain severity from “no pain” on the bottom face to “most pain” on the top face. The chosen faces were converted and assigned to a numerical visual analogue score [VAS] where 0 represents “no pain” and 100 represents “most possible pain”.

Word graphic rating scale [Modified]

[Savendra and Tesler, 1989] :

Category A – no pain,

B – little pain,

C – moderate pain and

D – severe pain.

Patients' responses were classified to these categories by their mother, child and observer/researcher.

A modified version using four levels of pain was used omitting the fifth level of pain "worst possible pain" used by Savendra et al[1989], to simplify application thereof.

Modified Hannallah Objective Pain Scale (HOPS)

[Broadman et al, 1988]:



The modified Hannallah objective pain scale is a behavioural-cardiovascular checklist on which a percentage is calculated according to six parameters [systolic blood pressure, crying, movement, agitation, posture and complaints of pain-[verbalisation]

Ranging from 0 – 2 were applied to each of the criteria monitored namely; systolic blood pressure (S.P), crying, movement, agitation, posture and complaints of pain , resulting in a reading from 0 –12 per patient.

Readings were recorded as indicated on the following table:

| |
|---|
| MODIFIED HANNALAH OBJECTIVE PAIN SCALE |
|---|

| | Criteria | Points |
|-----------------------------|---|---------------|
| Blood Pressure: Systolic | ± 10% preoperative | 0 |
| | > 20 % preoperative | 1 |
| | >30% preoperative | 2 |
| Crying | Quiet, none | 0 |
| | Crying stops with care | 1 |
| | Continuous crying /does not respond with care | 2 |
| Movement: | None | 0 |
| | Restless | 1 |
| | Thrashing around | 2 |
| Agitation: | Asleep, calm | 0 |
| | Mild | 1 |
| | Hysterical | 2 |
| Posture | No special posture | 0 |
| | Flexing limbs | 1 |
| | Holding mouth | 2 |
| Complaints of pain | Asleep/no pain | 0 |
| | Cannot localize | 1 |
| | Can localize | 2 |

Pain was also assessed using the HOPS on which a percentage is calculated according to the six parameters [severe / moderate / slight / no pain]

STATISTICAL METHODS

All tests of the significance of differences were two-tailed and a probability of 0,05 or less was accepted as significant. Various tests such as the chi-square, Kruskal Wallis and the Wilcoxon rank index, were applied.

All statistical modeling and significance testing were performed using the SAS statistical package [CMS version 5.18]

ETHICS

Approval to continue the study, was also obtained from the Ethics Committee of the University of the Western Cape [subsequent to the merger with the Dental School of the University of Stellenbosch] and it was completed without any deviation from the original University of Stellenbosch's approved protocol.

Parents of the children that took part in the study had to be informed that participation in the study was voluntary and without prejudice.

Informed consent had to be obtained from parents and documented for each one of the children that was included in the study.

Examples of the Patient Information- and Parent Consent forms that were used are shown on pages 83 and 84:

PATIENT INFORMATION

Your child is invited to participate in a clinical trial comparing two drug combinations [sufentanil/midazolam or ketamine/midazolam] for paediatric sedation and postoperative pain relief after dental extractions. Please read this leaflet which contains information on the trial carefully and ask the doctor to explain anything you do not understand. Your child will only be considered to participate in this trial, if completely healthy. Your child needs dental treatment under general anaesthesia. The drug combinations that will be compared, are commonly used every day to relieve anxiety and treat postoperative pain. The purpose of this trial is to compare the two drug combinations in a controlled clinical trial to see if they are equivalent in terms of effectiveness and side-effects. The study was approved by an independent Ethics Committee, a group of medical experts, who have made sure that your interests will be protected during its conduct.

You will make an important contribution to medical knowledge if you take part and follow the instructions carefully throughout the trial period. If you do agree to the trial, your child will be examined before treatment commences to make sure that he/she is suitable for the trial. On the morning of the operation, your child will be assigned a patient number, which will determine which of the two treatment combinations he/she will receive. The drug will be given intranasally 15 minutes before start of the procedure. At all times your child will be monitored and attended to. After the operation, your child will be kept in a recovery room, until we are satisfied that he/she can go home without any danger of any complications.

Drugs of this kind may cause some side-effects like drowsiness, vomiting, dizziness, nausea and depression of respiration is possible. All of these are reversible. You should report any side-effects immediately to the doctor.

If you do decide to participate [at no extra cost], you will be asked to sign a consent form which is required by the authorities to protect your rights. All information regarding your child will be kept in strict confidence. If you decide not to take part in this trial, or change your mind after first agreeing to do so, the most effective alternative treatment will be offered and your child will not suffer in any way.

PARENT CONSENT

I, _____, [print name],
 the parent [mother/father] or guardian of
 [name of the child _____]
 Address _____, give
 consent that my child may take part in this study.



I confirm that I have received and read the Patient Information leaflet, that the purpose of the study, the effects of the drugs and the content of the Patient Information leaflet, have been explained to me.

| | | | |
|-----------------|------|---------|------|
| Parent/Guardian | Date | Witness | Date |
| [Signature] | | | |

| | | | |
|-------------------|------|---------|------|
| Doctor/Researcher | Date | Witness | Date |
| [Signature] | | | |

CHAPTER 4

RESULTS

All the children [fifty], that entered the study, completed it.

The results of this study were used to evaluate the safety and efficacy of the drug combinations according to the set criteria in the protocol.

The following parameters were evaluated:

- Acceptance of nasal administration
- Behavioural [anxiety] changes
- Level of sedation
- Cardiovascular/ haemodynamic changes
- Respiratory rates
- Acceptance of mask induction
- Number of teeth extracted
- Pain intensity
- Postoperative recovery



Characteristics of the two trial groups.

All the children included in this study, met the predetermined criteria. Medical history and physical examination revealed no disease or evident psychological abnormalities. They were all classified as ASA 1 patients.

The children, all requiring multiple dental extractions of severely decayed teeth, [more than six], were randomly allocated to one of the two drug groups, which was administered 20 minutes prior to induction of general anaesthesia.

Throughout this study, the effects of the two drug groups were compared and evaluated:

Group A: Receiving intranasal ketamine and midazolam, referred to as the ketamine/ midazolam [K/M] group and

Group B: Receiving intranasal sufentanil and midazolam, referred to as the sufentanil/midazolam [S/M] group.

Children in the two groups were similar with respect to age, weight, number of teeth removed, heart rate, length of surgery and gender distribution.

[Table 1]

Table 1. Demographic Profile and Baseline Vital Signs in the Two Groups*

| | Group S/M* | K/M Group* |
|-------------------------------|---------------|----------------|
| | Mean ± SD | Mean ± SD |
| Age [year] | 5,87 ± 1,33 | 5,68 ± 1.31 |
| Weight [Kg] | 17,80 ± 2,72 | 17,17 ± 3,09 |
| Number of teeth | 10,68 ± 3,77 | 10,63 ± 4,26 |
| Heart rate [beats per minute] | 98,80 ± 20,29 | 105,16 ± 20,64 |
| Duration of surgery | 20,64 ± 6.60 | 19,96 ± 4,95 |
| Gender | | |
| Male | 15 | 12 |
| Female | 10 | 13 |

*S/M indicates sufentanil/midazolam and

*K/M, ketamine/midazolam

There were no significant differences in the physiological parameters, namely blood pressures [systolic, diastolic, mean arterial], heart rates, respiratory rates and oxygen saturation between the two groups at the various time intervals measured. [Table2]

Table 2. Physiological parameters in the two groups *

MEAN ± SD

| | | Baseline | 15 min post drug | 20 min post drug | 30 min post surg | 60 min post surg | 90 min post surg | 120 min post surg |
|--|------------|-----------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|------------------------------|
| Heart rate Beats/min | S/M | 98,8 ±20,29 | 95,00 ±15,86 | 97,7 ± 17,88 | 115,68 ±21,78 | 113,16 ±21,29 | 103,32 ±21,43 | 102,44 ±19,22 |
| | K/M | 105,16±20,64 | 104,21±18,97 | 104,68±22,70 | 114,44±25,26 | 111,80 ±22,03 | 107,44 ± 17,30 | 107,36 ±14,83 |
| Systolic BP [mm Hg.] | <u>S/M</u> | 112,89 ±12,10 | 104,84 ±10,28 | 100,08 ± 13,87 | 122,16 ± 17,64 | 120,80 ±20,04 | 120,84 ±16,30 | 115,48 ±15,18 |
| | <u>K/M</u> | 118,36 ±16,83 | 112,76 ±14,91 | 112,24 ±18,13 | 120,24 ±17,43 | 122,00 ±15,53 | 121,68 ± 16,50 | 119,84 ±11,08 |
| Diastolic BP [mm Hg] | S/M | 67,08 ±13,60 | 60,48 ±14,37 | 57,24 ±12,89 | 77,20 ± 15,87 | 72,56 ±16,30 | 75,36 ±15,79 | 71,00 ±15,31 |
| | K/M | 70,76 ±16,81 | 68,20 ±13,29 | 69,36 ±16,38 | 78,76 ±14,45 | 78,84 ±14,44 | 78,84 ±17,49 | 76,00 ±10,00 |
| Mean BP [mm Hg] | S/M | 82,72 ±13,47 | 76,60 ±12,47 | 71,36 ±12,69 | 92,52 ±15,8 | 88,35 ±19,16 | 90,57 ±16,37 | 87,85 ±14,68 |
| | K/M | 89,32 ±16,27 | 82,56 ±14,95 | 86,24 ±16,24 | 93,48 ±17,51 | 93,16 ±13,24 | 93,20 ±16,68 | 90,24 ±13,17 |
| Respiratory Rate Breath/min | S/M | 23,00 ±3,54 | 22,56 ±3,49 | 21,13 ±4,84 | 23,65 ±4,81 | 23,50 ±4,05 | 22,92 ±3,19 | 22,92 ±3,44 |
| | K/M | 23,56 ±2,74 | 23,20 ±3,06 | 21,57 ±3,67 | 23,38 ±3,80 | 23,13 ±2,97 | 21,79 ±2,32 | 22,00 ±2,50 |
| SpO2 | S/M | 97,72 ± 1,99 | 97,36 ±7,60 | 97,24 ±1,45 | 97,04 ± 1,70 | 97,60 ±1,26 | 97,92 ±1,35 | 97,76 ±1,20 |
| | K/M | 97,36 ±1,52 | 97,24 ±1,59 | 97,36 ±1,32 | 97,44 ±2,02 | 97,80 ±1,66 | 97,88 ±1,42 | 97,84 ±1,86 |

*S/M indicates sufentanil/midazolam; K/M, ketamine/midazolam

Figures 5, 6, 7 and 8, show the systolic blood pressure, oxygen saturation levels [SpO₂], pulse rates, and respiratory rates respectively.

Drug Administration

According to the study protocol, the drugs used were administered as follows:

| | |
|------------|------------|
| Midazolam | 0.3 mg/ kg |
| Ketamine | 5.0 mg/ kg |
| Sufentanil | 20 µg |

The mean doses of the different drugs used are shown in table 3. A standard sufentanil dose of 20µg was administered using the Go® Medical nasal spray .

Table 3

Mean doses of study medication administered

| | Ketamine | Sufentanil | Midazolam |
|---------|----------------|------------|--------------|
| Group A | 86.8mg/± 15.06 | | 3.43mg/±0,60 |
| Group B | | 20µg | 3,52mg/±0.52 |

No significant differences were found in the midazolam doses between the two groups [P=0.05]



Acceptance of Intranasal Spray

Significantly more patients in the sufentanil/midazolam group accepted the nasal premedication

[p= 0,021, Chi square test = 7,718]. Results are shown in table 4 & figure 1

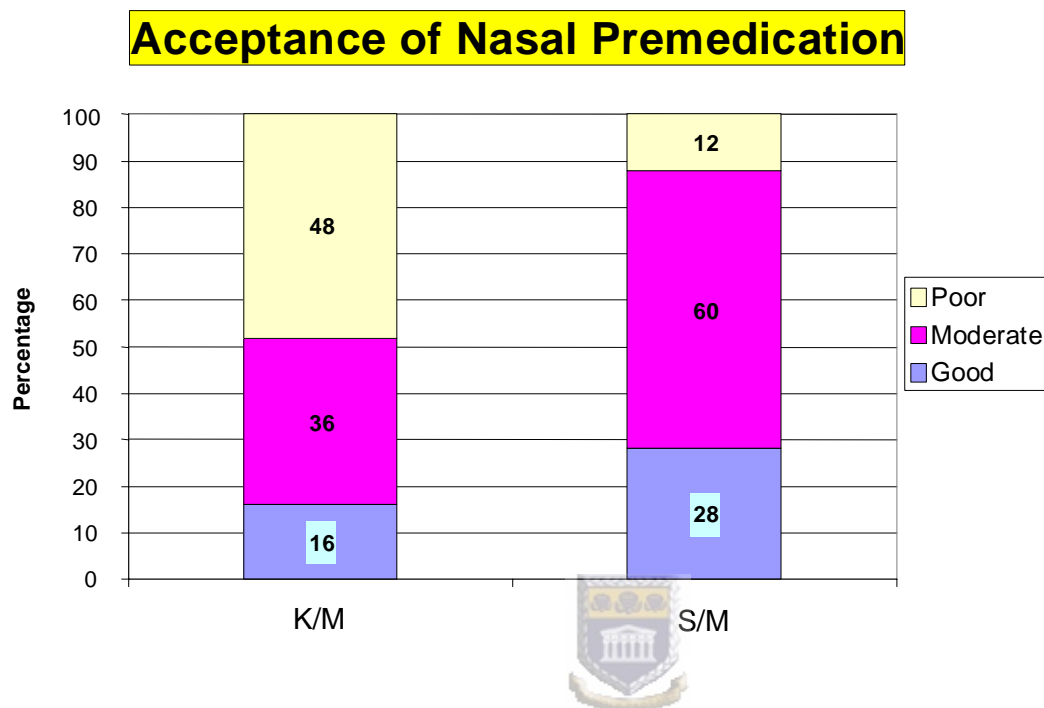
Table 4

Acceptance of intranasal spray

| Treatment group | Good | Moderate | Poor | Total |
|------------------------|---------|----------|---------|-------|
| Group A [K/M] | 4[16%] | 9[36%] | 12[48%] | 25 |
| Group B [S/M] | 7[28%] | 15[60%] | 3 [12%] | 25 |
| Total | 11[22%] | 24[48%] | 15[30%] | 50 |

Only three [12%] of the patients in the S/M group rated sufentanil/midazolam acceptance as poor, as to twelve [48%] of the patients in the ketamine/midazolam group [K/M group] [Figure 1]

FIGURE 1



Behavioural changes

Levels of Anxiety:

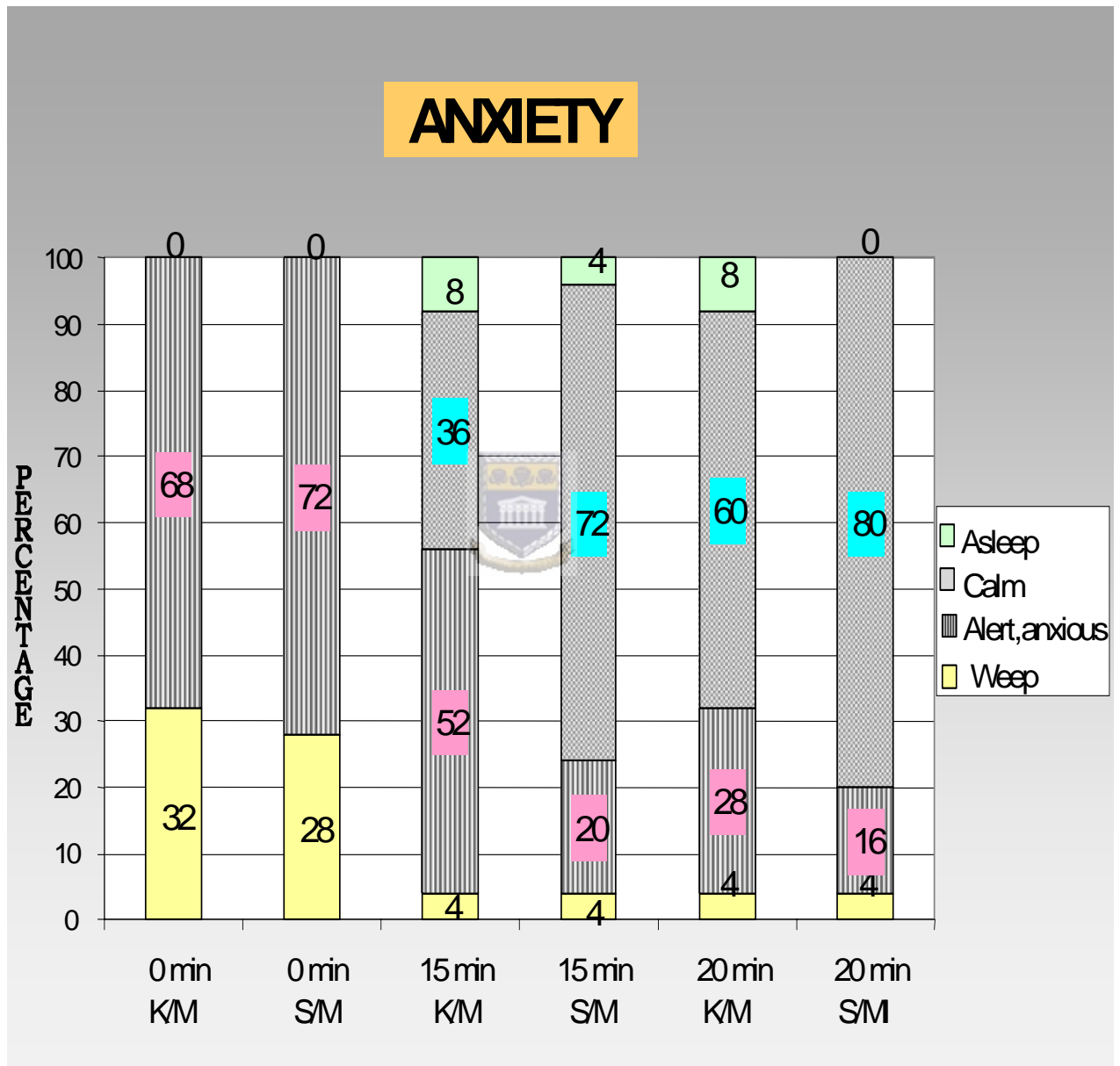
At baseline, all the children in both groups were classified as anxious; seventeen children [68%] were alert and anxious [not weeping] in the ketamine/midazolam group versus eighteen children [72%] in the sufentanil/midazolam group.

Fourteen of the children [56%] in the ketamine/midazolam group [K/M], were still alert, anxious or weeping 15 minutes after administration of premedication, as to six children [24%] in the sufentanil/midazolam group [S/M].

Immediately before induction, eight children [32%] in the K/M group were alert, anxious or weeping versus five children [20%] in the S/M group. Only one child

from each of the respective eight and five children, were still weeping. At the same time interval, twenty children [80%] in the sufentanil/midazolam group were calm [none were asleep] versus seventeen children [68%] in the ketamine/midazolam group - two children were asleep [p>0,05] [Figure 2]

FIGURE 2



0 minutes = preoperative

15 minutes = post drug

20 minutes = immediately before surgery

Levels of Sedation

Levels of sedation were measured preoperatively at 15 and 20 minutes post-drug administration [Figure 3].

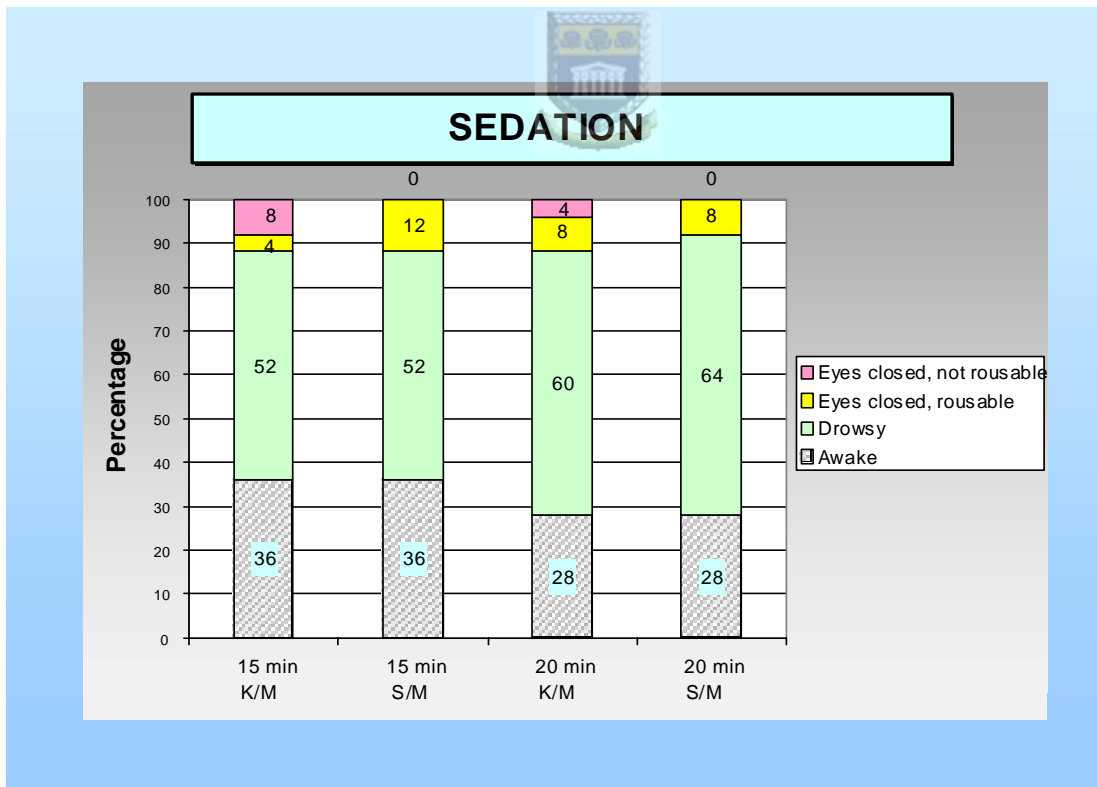
Table 5 shows the levels of sedation 20 minutes after drug administration:

Table 5

| Drug Group | Awake | Drowsy | Eyes Closed/ Rousable | asleep |
|------------|--------|---------|--------------------------|--------|
| K/M | 7[28%] | 15[60%] | 2[8%] | 1[4%] |
| S/M | 7[28%] | 16[64%] | 2[8%] | 0 |

With regards to the preoperative sedation and anxiety levels at the intervals post drug administration, no significant differences were found between the two groups. [$p > 0.05$] [Figures 2,3]

FIGURE 3



Acceptance of the Mask Induction [Table 6, p103]

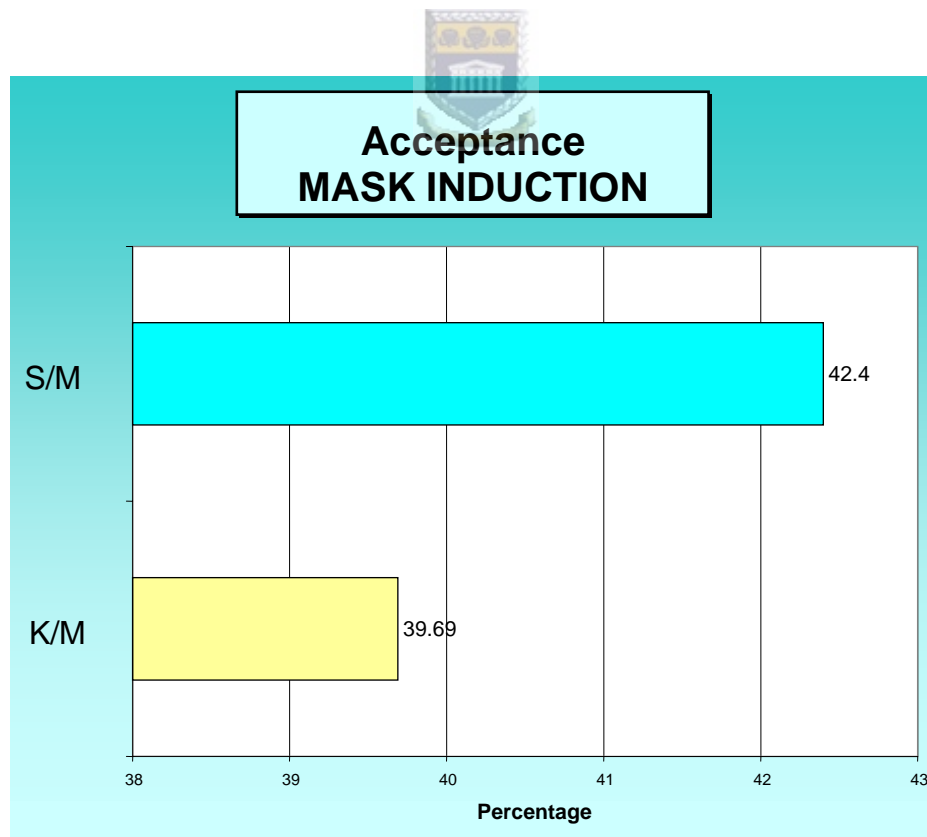
Acceptance of the mask induction was measured by the anaesthesiologist using 3 rating scales:

- 1 = no defense action
- 2= defense reaction/weeping
- 3 = refusing vehemently

The mask induction acceptance score in the S/M group was 42,40 and in the K/M group 39,69 [Table 6 – Figure 4].

No significant differences were found in the ease of mask induction [p= 0,05] as assessed by the anaesthesiologist.

FIGURE 4

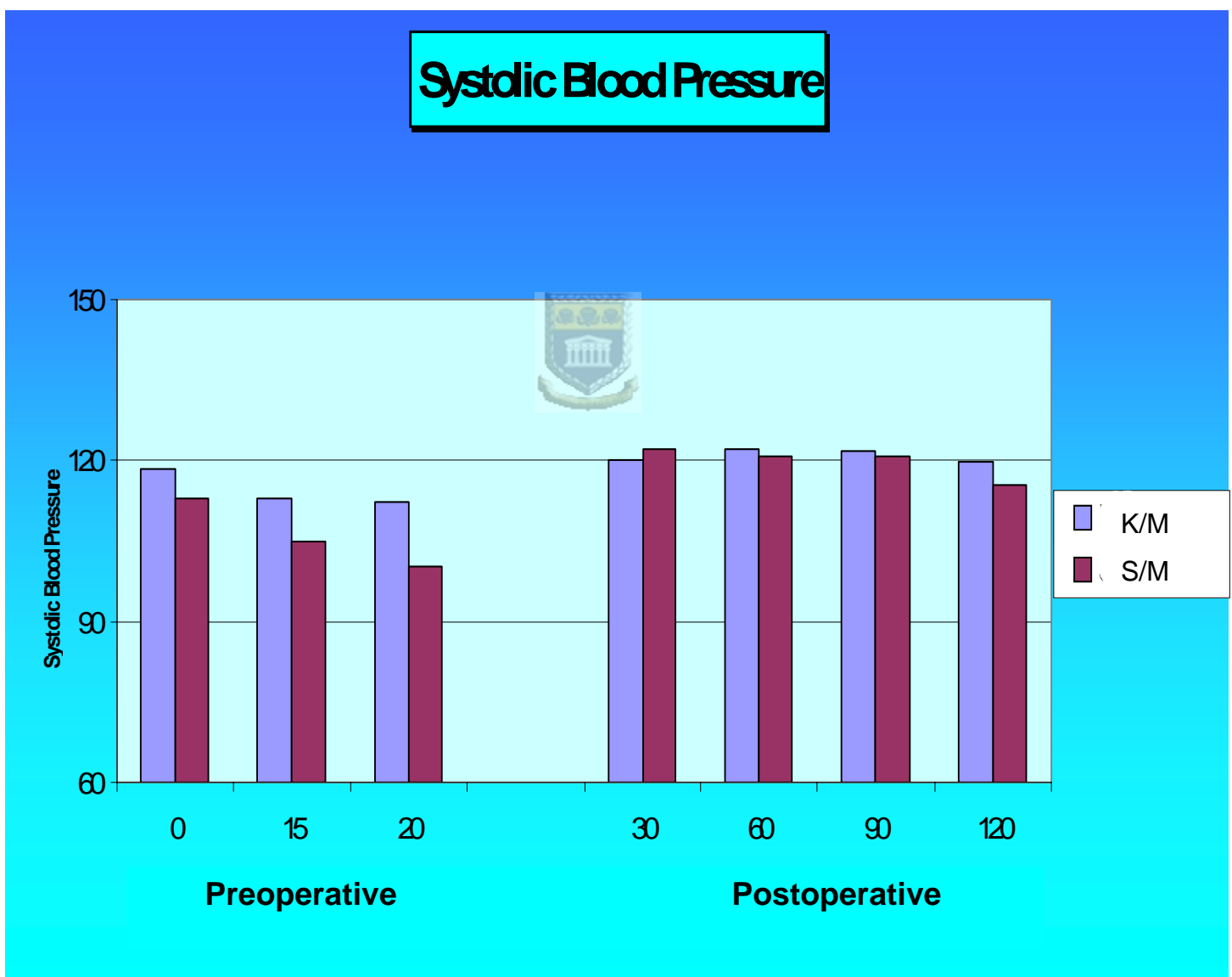


Systolic Blood Pressure [Table 2, p87]

As expected, the systolic blood pressures were higher in the ketamine/midazolam group with clinical differences at the 15 and 20 minute post drug administration intervals. Statistical significant differences were shown at both intervals [$p < 0.05$]

The postoperative systolic blood pressure evaluations at 30, 60, 90 and 120 minutes did not reveal any statistical significant differences (Figure 5).

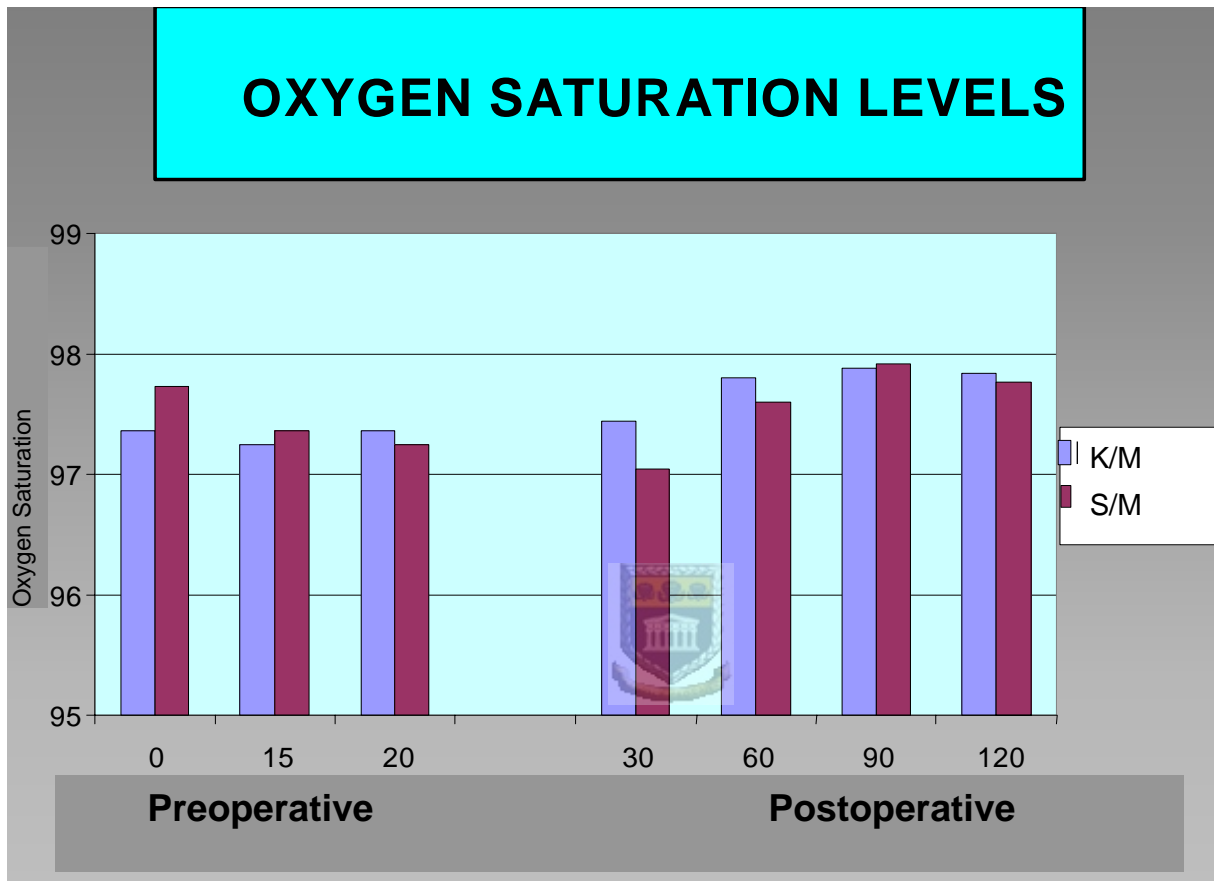
FIGURE 5



Oxygen Saturation Levels [Table2, p87]

The oxygen saturation levels after administration of premedication, as well as in the recovery room, are shown in figure 6.

FIGURE 6

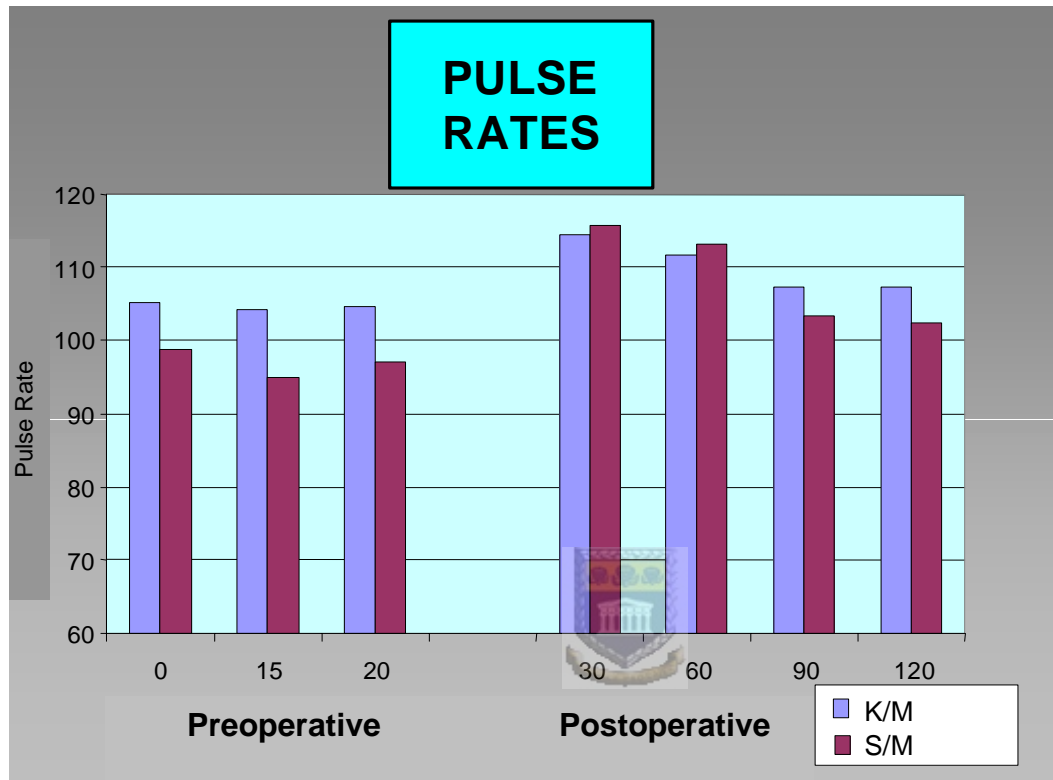


None of the patients experienced any oxygen saturation level drops below 97%. All the oxygen saturation levels were above 97% at all times. No statistical significance was found between the two groups [$p > 0,05$]

Pulse rate/minute [Table 2, p87]

The pre- and postoperative heart rates per minute are summarized in figure 7:

FIGURE 7

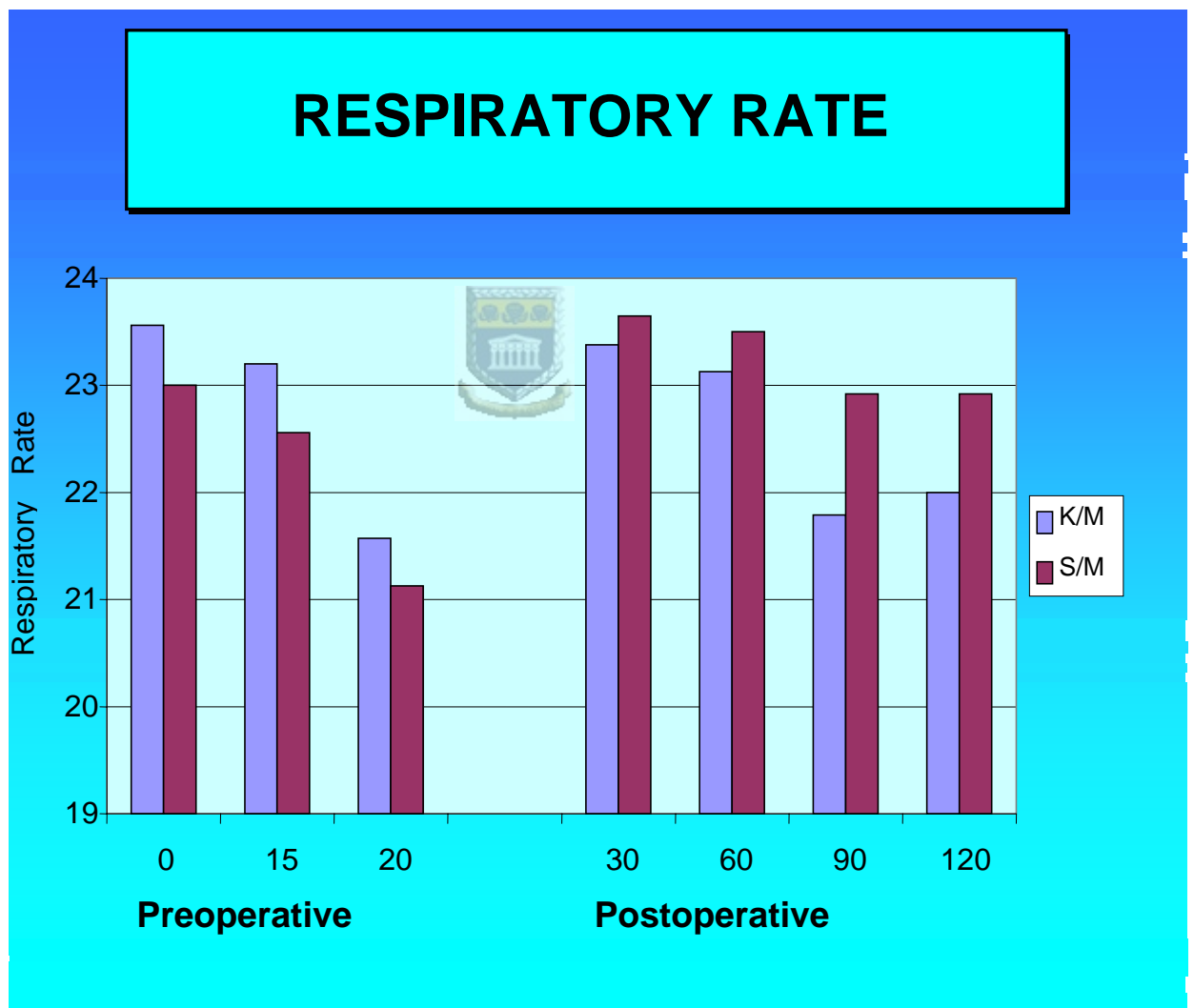


No significant differences were recorded between the two groups at all time intervals [$p > 0,05$]

Respiratory Rate [Table 2, p87]

Although the respiratory rates in both groups dropped [figure 8] after administration of the two drug combinations, no significant differences were found [p>0.05]

FIGURE 8



Pain

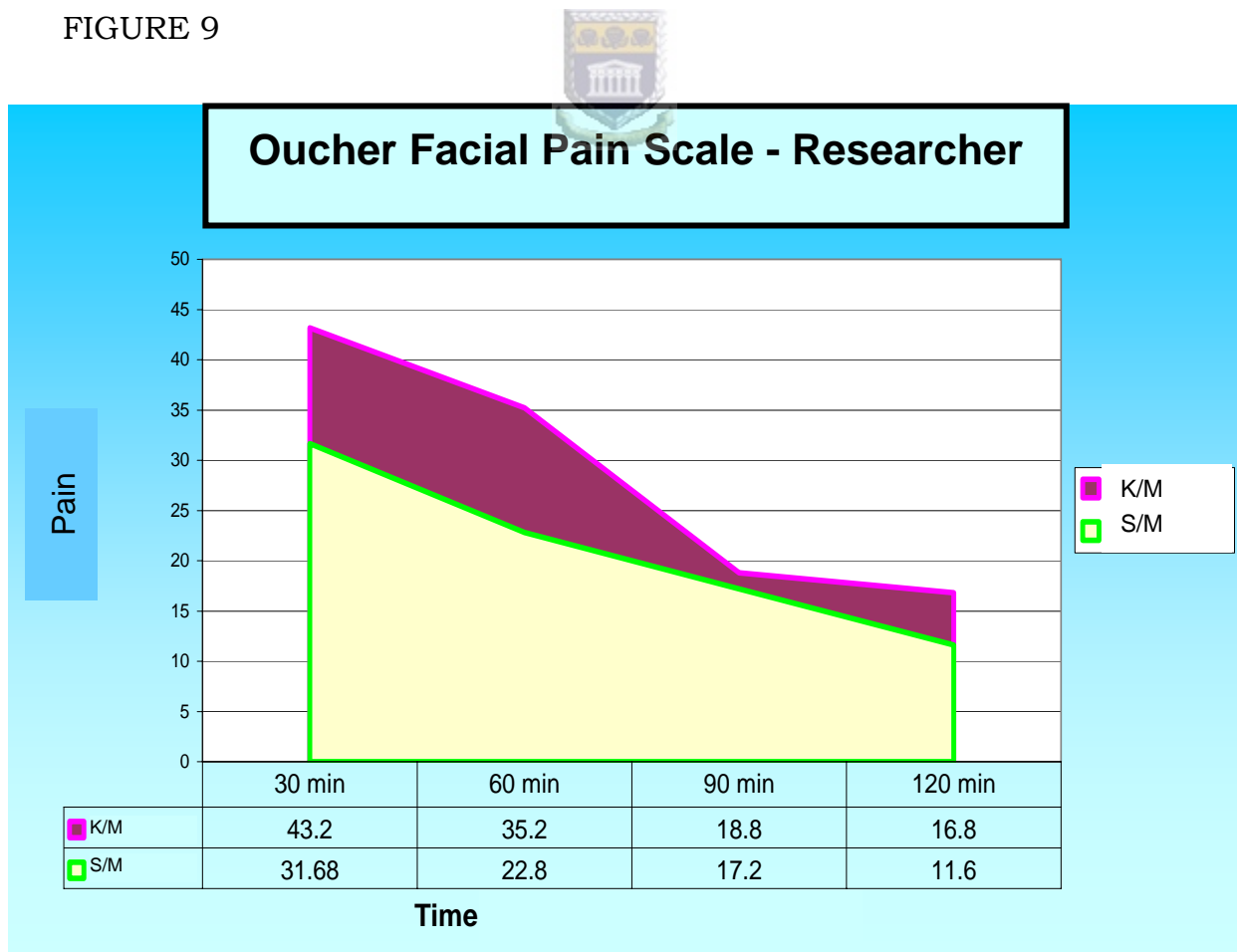
Pain was assessed with the Oucher facial pain scale, the word graphic rating scale and the modified Hannalah objective pain scale at 30, 60-, 90- and 120 minutes postoperatively.

The Oucher Faces Pain Scale [OFPS] [Bieri et al,1990]

The OFPS sum scores: child, mother and researcher [mean±SD] for the two groups, are summarized in Table 6, p103.

The OFPS showed that the sufentanil/midazolam group experienced less pain than those in the ketamine/midazolam group, although not statistically significant [$p>0.05$] [Figure 9]

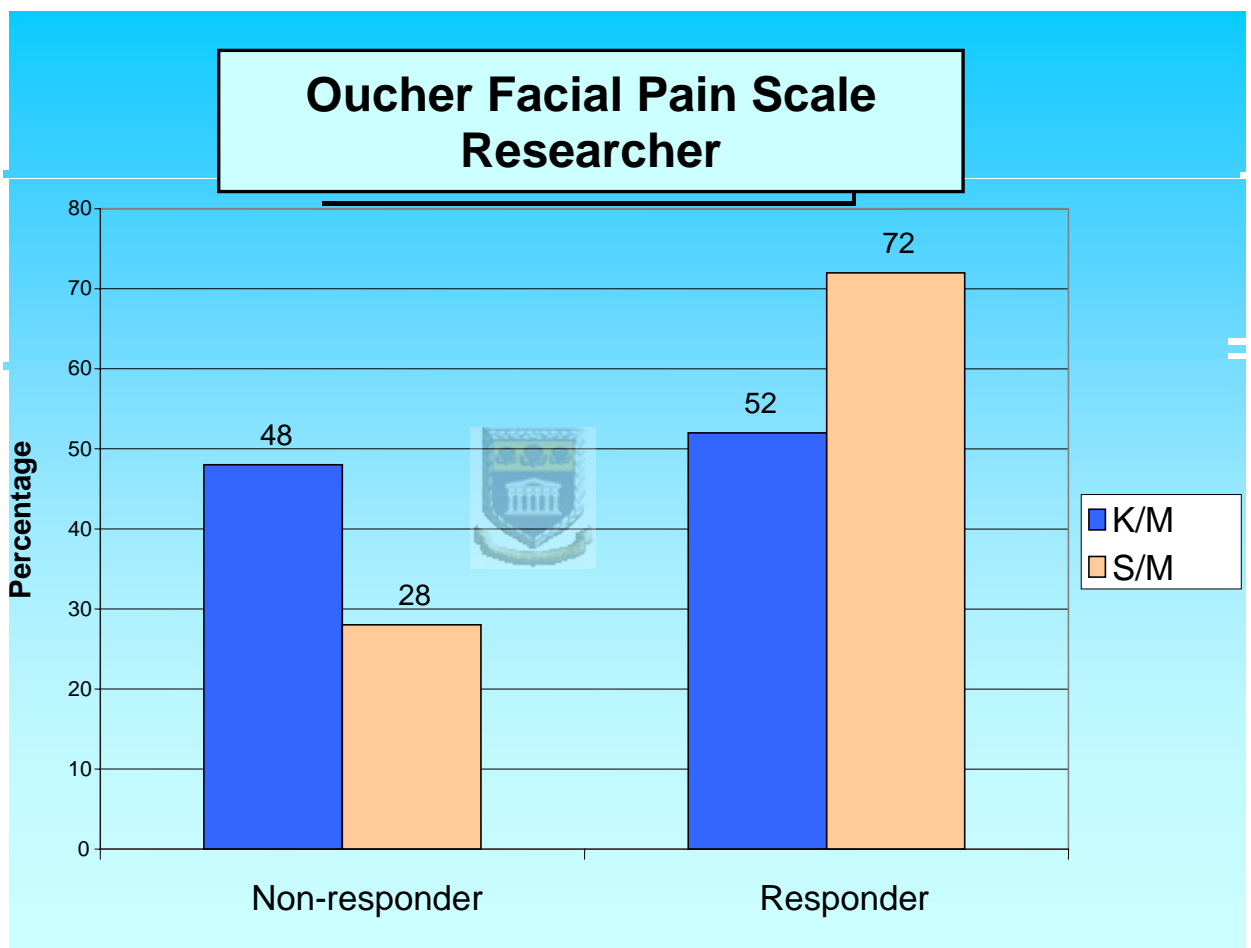
FIGURE 9



Responders / Non-Responders

Children with any pain value over time more than 40 mm on a 100 mm visual analogue scale, were classified as non-responders and those with any pain value over time equal or less than 40mm on a visual analogue scale, as responders [Figure 10].

FIGURE 10



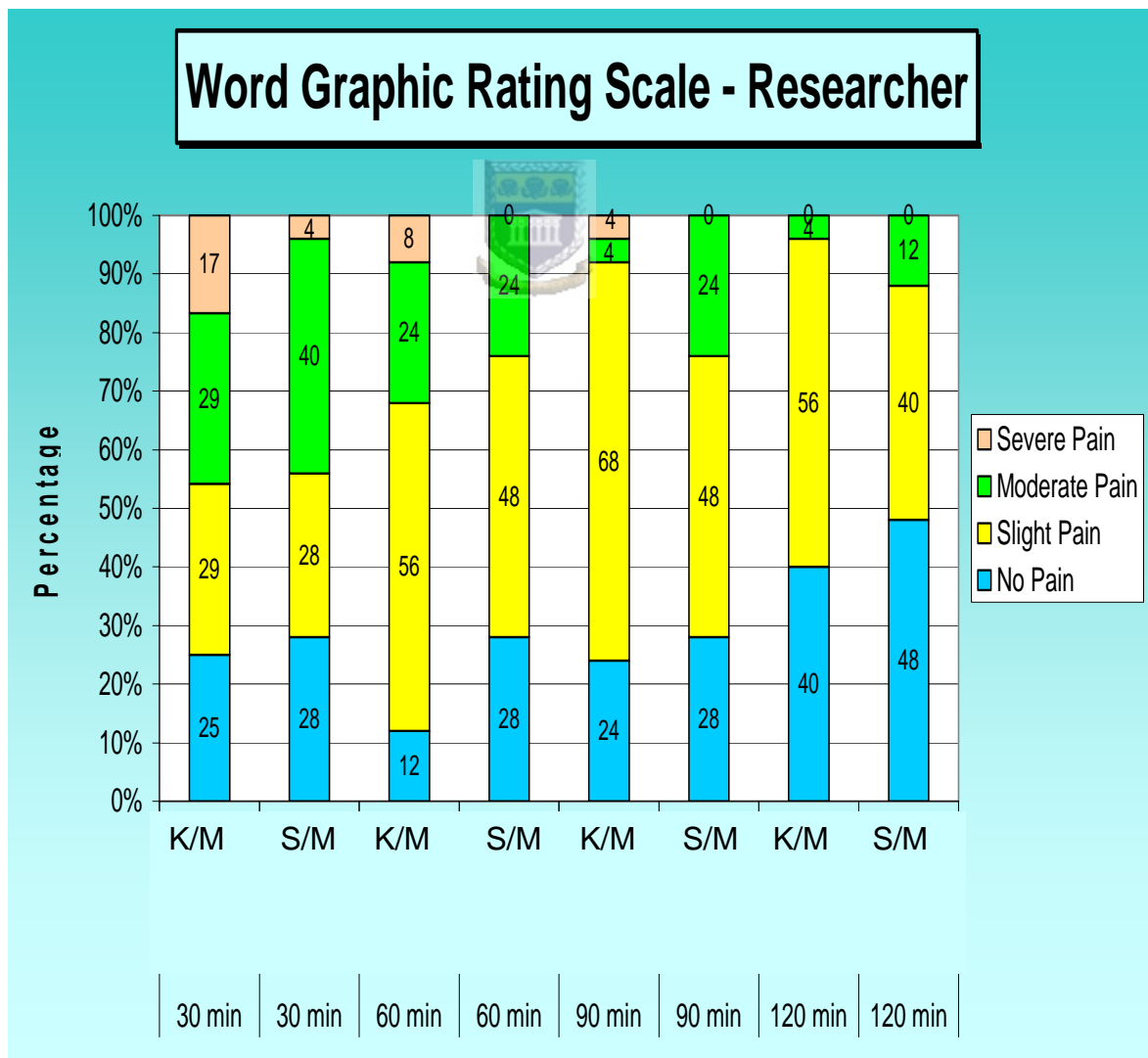
In the S/M group, 72% of the patients were responders as to 52% in the K/M group. The results however were not statistically significant [$p > 0,05$]

Word Graphic Rating Scale [Savendra & Tesler, 1989]

Pain was evaluated by the mother, child and researcher and classified according to the following categories [Figure 11]:

- A = no pain
- B = little pain
- C = medium pain
- D = severe pain

FIGURE 11



According to the word graphic rating scale for the observer/researcher at thirty minutes post-operatively, 17% of the ketamine/midazolam group had severe pain in comparison to the 4% in the sufentanil/midazolam group.

At sixty minutes, 8% of the children receiving ketamine/ midazolam had severe pain as to 0% in the sufentanil/midazolam group. At 90 minutes, 4% of children in the ketamine/midazolam group had severe pain as to 0% in the sufentanil/midazolam group. At 120 minutes, no severe pain was recorded. No significant differences were found between the two groups at the different time levels [$p>0,05$] [Figure 11]

Modified Hannalah Objective Pain Scale [Broadman et al,1988]

Postoperative pain was also assessed by using the modified Hannalah objective pain scale. This scale is a behavioural-cardiovascular checklist on which a percentage is calculated according to six parameters:

blood pressure, crying, movement, agitation, posture and complaints of pain.

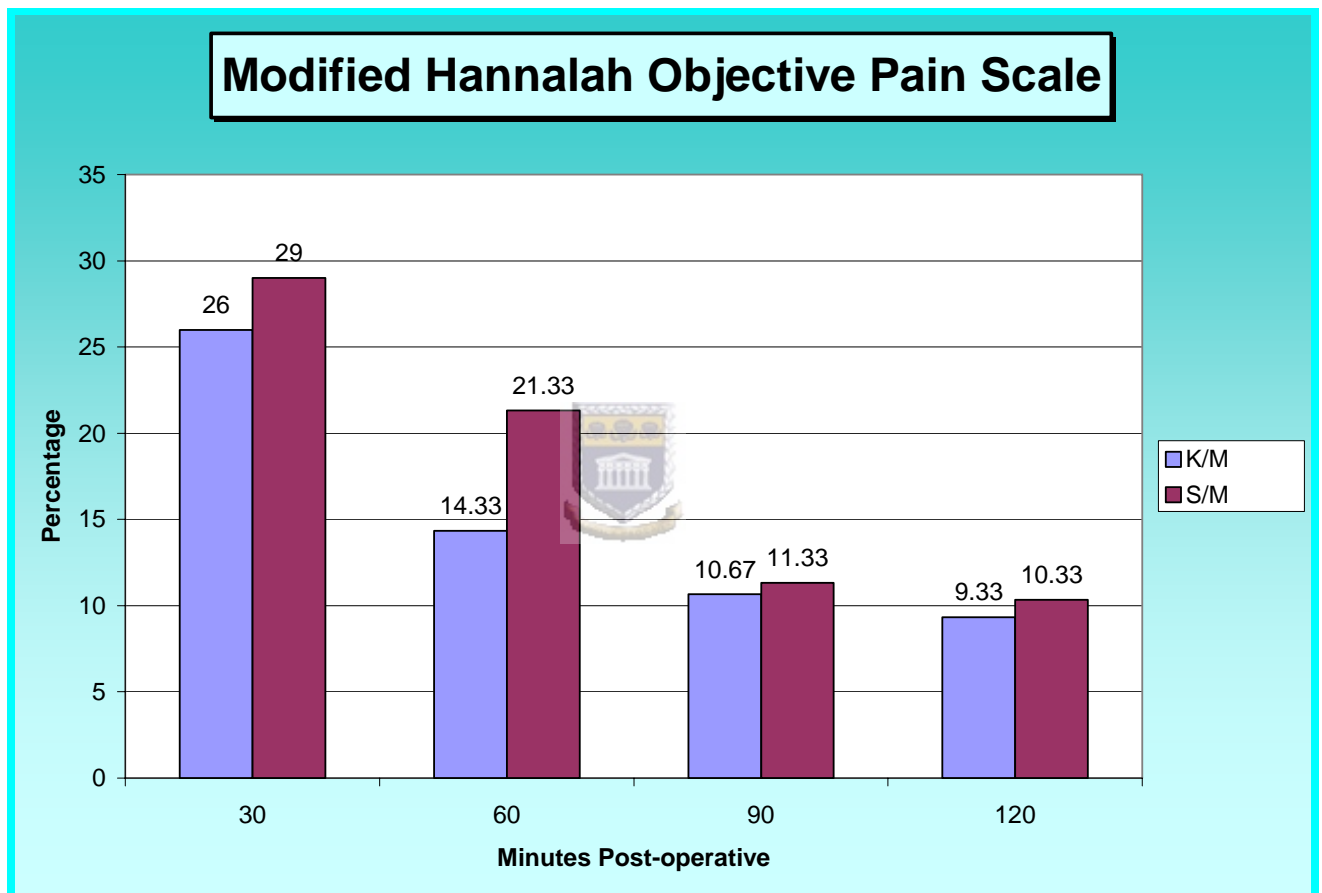


Calculations were based on measurements of these variable at 30,60,90 and 120 minutes postoperatively. Results as observed by the researcher are shown in Table 6 [p103] and Figure 12

Using both the word graphic rating scale and the modified Hannalah objective pain scale, no significant differences were observed between the two groups at the various time intervals measured postoperatively [$p=0,05$]

SUM OF HANNALAH OBJECTIVE PAIN SCALE - as scored at 30, 60, 90 and 120 minutes – [summarized in Table 6, p103] and shown in Figure 12:

FIGURE 12



Recovery Room Scores

Patients remained in the recovery room for 4 hours after surgery, where recovery was assessed according to the Aldrete postanesthetic recovery score.

The following were measured:

wakefulness

ventilation

movement

colour and

circulation

Recovery room scores are summarized in Table 6[p103] and Figure 13

The recovery room score when compared at the 30, 60, and 120 min intervals, revealed no significant differences [p>0.05]

FIGURE 13

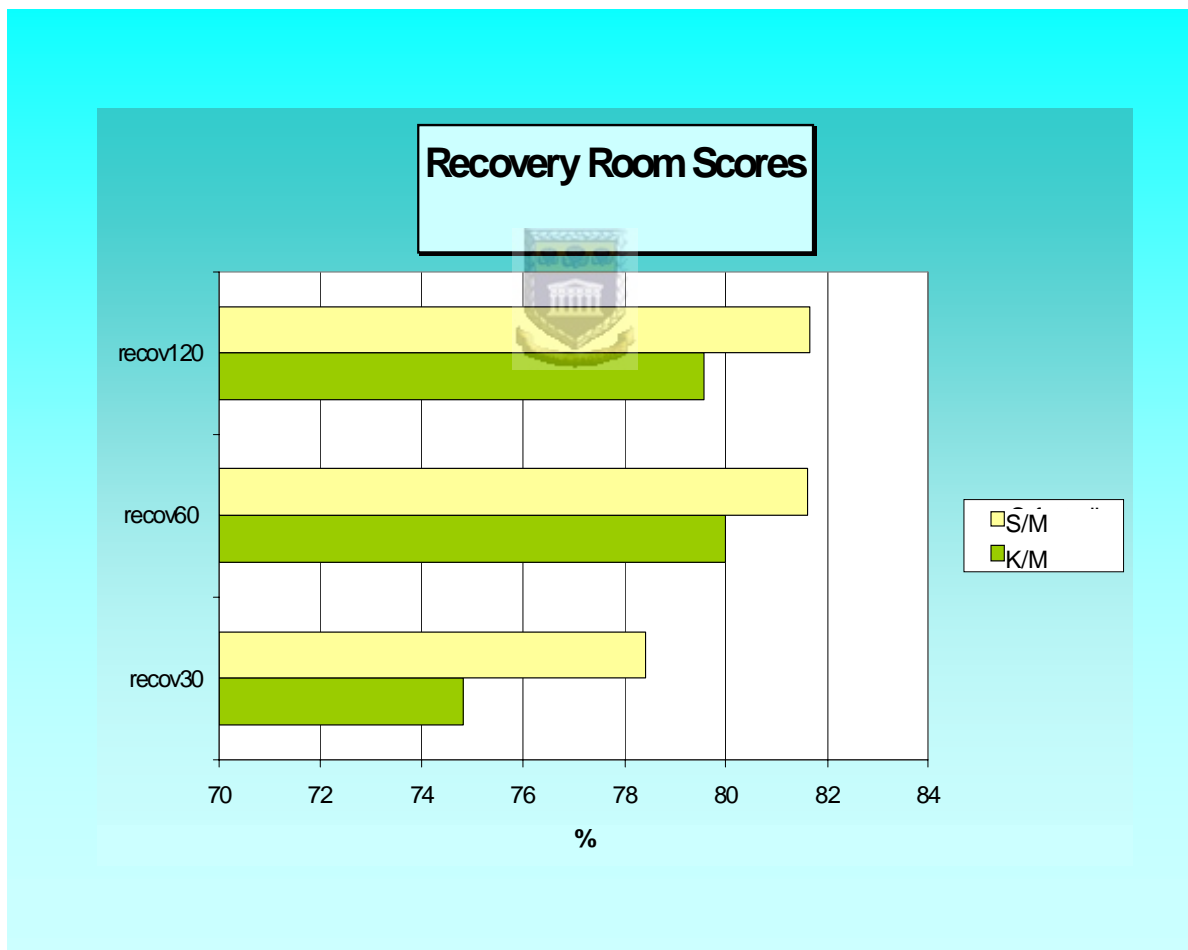


Table 6

MASK ACCEPTANCE SCORES, RECOVERY ROOM SCORES AND PAIN MEASUREMENTS
MEAN ± SD

| Mask induction | Mean ± SD |
|---|-------------|
| S/M Group - Mask induction acceptance score | 42,40 ±2,92 |
| K/M Group - Mask induction acceptance score | 39,69 ±7,49 |

| Recovery room scores | 30 minutes | 60 minutes | 90 minutes | 120 minutes |
|----------------------|--------------|-------------|------------|--------------|
| S/M Group | 78,40 ±15,46 | 81,60 ±8,50 | - | 81,67 ±6,37 |
| K/M Group | 74,80 ±13,88 | 80,00 ±7,64 | - | 79,58 ±10,42 |

| Sum of Hannalah Scale [%] | | | | |
|---------------------------|--------------|---------------|--------------|--------------|
| S/M Group | 29,00 ±25,36 | 21,33 ± 24,66 | 11,33 ±13,58 | 10,33 ±12,33 |
| K/M Group | 26,00 ±22,35 | 14,33 ±14,74 | 10,67 ±13,29 | 9,33 ±12,80 |

| Oucher sum | Child | Mother | Researcher |
|------------|----------------|----------------|---------------|
| S/M Group | 86,40 ±85,82 | 86,00 ±85,63 | 84,00 ±83,22 |
| K/M Group | 115,20 ± 89,36 | 115,60 ± 88,98 | 114,00 ±90,00 |

*S/M indicates sufentanil/midazolam ; K/M, ketamine/midazolam

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CHAPTER 5

DISCUSSION AND CONCLUSION

The aim of using sedative drugs in paediatric patients, is the control of pain, fear and anxiety, thereby creating behaviour that will facilitate the provision of quality medical and dental care. The fact that no single sedative drug has achieved universal acceptance, suggests that the ideal drug has not yet been found.

The search continues for a rapidly acting sedative tranquilizer, free of adverse effects and with a short duration of action. Particularly in outpatient and paediatric practice, such an agent would be beneficial. In the quest to establish a gold standard for methodology and drugs used, various routes of administration and various drugs or combinations of drugs have been scientifically studied by numerous researchers.

In a study of Roelofse et al [1996], the combination of ketamine and midazolam versus ketamine alone given rectally, were both found to be safe and effective for children 2 -7 years of age, as they provided good sedation and anxiolysis at the time of separation from their parents.

In a follow-up study by Roelofse et al [1998], whereby ketamine and midazolam were administered orally to children, requiring dental extractions under local anaesthesia, the combination was found to be safe and effective and a practical approach to manage fearful children before dental surgical procedures.

Intranasal administration of sedatives and analgesics is being explored as a possible alternative route, whereby sedatives and analgesics can be administered – this approach shows promise.

The efficacy and safety of nasally administered sufentanil or midazolam in children, have been demonstrated by research done by Henderson et al[1988] and Wilton et al[1988]. Wilton and coworkers concluded that the

rapid onset of the drug effects makes it particularly useful in the outpatient setting.

Diaz [1997] compared the outcome of intranasal ketamine premedication with a placebo in paediatric outpatients. His study showed that ketamine permitted pleasant and rapid separation of children from their parents, acceptance of monitoring and mask inhalation induction. Post-operative recovery and discharge home were not delayed.

Henderson et al [1988], studied the effect of nasally administered sufentanil in children. They concluded that dosages of 1,5 to 3,0 $\mu\text{g}/\text{Kg}$ intranasally, facilitates separation of children from parents, has minimal side-effects, may improve intubating conditions and provides effective postoperative analgesia.

Vercauteren, Boeckx et al [1988], also evaluated the effects of intranasal sufentanil as a short-acting and potent narcotic agent. They showed that sedation was of rapid onset, but limited duration. Side effects were minor and there appeared to be no difference in producing sedation between nose drops and nose spray. They also stated that a total dose of 5 micrograms appeared to be too low, while 10 or 20 micrograms was very effective in producing sedation.

Abrams et al [1993], researched the safety and efficacy of the intranasal administration of one of three sedative medications [ketamine 3mg/kg; midazolam 0,4mg/kg; sufentanil 1,5 or 1 $\mu\text{g}/\text{kg}$] in thirty children for urgent brief dental procedures.

They used the following sedation scale /score:

1 = hysterical /untreatable

5 = ideal sedation and

10= required airway assistance.

Intranasal midazolam administration resulted in acceptable sedation [mean score of 4] with no oxygen saturation below 90% as measured by pulse oximetry. A mean recovery room time of only 3 min ± 2 SD was observed.

Intranasal ketamine administration resulted in a mean sedation score of 4 and a short recovery period of $7 \text{ min} \pm 7$. However, two children experienced brief drops in oxygen saturation levels.

Intranasal sufentanil at a dose of $1,5 \mu\text{g}/\text{kg}$, produced much more heavily sedated children [mean score 7] with a high incidence of significant drop in oxygen saturation levels [80%]. A prolonged recovery period was observed [$58 \text{ min} \pm 40$]. The use of $1,0 \mu\text{g}/\text{kg}$ sufentanil intranasally, resulted in less sedation [mean score of 4] and a brief recovery time [$7 \text{ min} \pm 1$]. The oxygen saturation levels remained normal.

We know that when we combine a benzodiazepine [midazolam] and an opiate [sufentanil], respiratory depression is possible. Increasing the dose of the sedative agent may also be a contributing factor. Finding the correct dose that is safe and effective, is thus very important.

The intranasal route is one of the most permeable and highly vascularized sites for drug administration, ensuring rapid absorption into the systemic circulation and onset of therapeutic action. In general, it has been potentially explored as an alternative route for drugs with poor bioavailability and high molecular-weight compounds such as proteins, peptides, steroids and vaccines [Arora et al, 2003]

Direct systemic absorption bypasses the portal circulation [hepatic first-pass effect] and may increase the bioavailability of nasally absorbed drugs. Added absorption enhancers, such as cyclodextrins, phospholipids, bioadhesive powder systems and chitosan, improve nasal delivery [Davis SS et al, 2003]

Intranasal delivery devices include drops [eg dripped in using a tuberculin syringe], sprays, aerosols and microsphere formulations. Atomization of aqueous polymer solutions, is a key step in the formulation of several pharmaceutical products [Petersen FJ et al, 2004]. For example, in children, intranasal spray administered using an atomizer, has been found to be safe [Dallman et al, 2001].

Nasal drug delivery may be assessed by a variety of means, but high reliance is often placed on in vitro testing methodology [emitted dose, droplet or particle size distribution, spray pattern and plume geometry [Newman SP et al, 2004]. Spray patterns and plume geometry define the shape of the expanding aerosol cloud, while droplet size determines the likelihood of deposition within the nasal cavity by inertial impaction. Aerosols are deposited mainly in the anterior and turbinate regions while passing beyond the nasopharyngeal region. Spray droplets are deposited in spots of the middle and posterior portions of the turbinate region as well. Intranasal administration of sedatives and opioid analgesics provide a mechanism for more rapid onset of pain relief compared with oral dosing [Fitzgibbon et al, 2003].

Although the pharmacokinetics of intranasal sufentanil have not been worked out, lipophilic agents with a low molecular weight produce plasma levels similar to those achieved by the intravenous route [Manjushree R et al, 2002].

While previous work has demonstrated the efficacy and safety of premedication of children with intranasal sufentanil or midazolam, there has been no direct comparison of a combination of sufentanil/midazolam with ketamine/midazolam administered intranasally, to determine which drug combination is preferable for sedation and postoperative pain relief in preschool children. The GO® medical spray used in this study, is a portable 0,018 ml, patient controlled analgesic device, that is a hand activated spray. It incorporates a 3-minute fill time [during which another full dose cannot be delivered]. The spray is delivered in small-droplet form [80µg] and it is simple to use.

The 50 patients in this study had similar age and weight distributions: K/M group, mean = 17,17 kg and S/M group, mean =17,8 kg . The above results are important, as the drugs were administered according to the

weight of the patient. Bias according to these variables was therefore not introduced.

The presurgical behaviour was reflected in the baseline anxiety scale [Figure 2], in the preanaesthetic sedation [Figure 3] in which both groups were equally calm, drowsy and peaceful as well as in an uneventful and smooth mask induction [figure 4] of anaesthesia in the majority of children. The oxygen saturation measurements were of particular interest as opioids cause respiratory depression. Abrams et al [1993] found that sufentanil at 1,5µg/kg, resulted in a high incidence of significant drops in oxygen saturation levels in children. The combination of an opioid with a benzodiazepine, increases the risk for respiratory depression [Yaster et al, 1990].

No such event was detected in this study. Preanaesthetic and postanaesthetic oxygen saturation levels were the same for both groups [S/M and K/M, at mean levels of 97-98%. The study demonstrates that the drug combinations chosen had no negative effects on behaviour during the peri-operative period. There was also an absence of adverse effects such as nausea, vomiting and respiratory depression. No abnormal haemodynamic responses occurred during the perioperative period.

Respiratory rates in both the K/M and S/M study groups dropped after administration of the drug combinations preoperative and no significant differences [$p > 0,05$] between the groups were recorded [Fig 8]

The pre-operative pulse rate at 15 and 20 minutes post drug administration for both groups were stable. As expected it was raised intra- and post-operatively, dropping steadily. At the 120 minute interval, the pulse rates [Figure 7] dropped to almost the same base values that were measured at 0 minutes [$p > 0,05$].

The management of pain in children is controversial - it is not clear which drugs are the most suitable. One of the prime objects of this research, was to establish the effectiveness of pain relief with the two drug combinations used.

To evaluate the efficacy of the drug combinations for pain relief in this study, an acceptable pain model had to be available. The question is, do children have significant pain after dental extractions. We have to look at literature to see if there are studies done in this respect.

Single dental extractions are not usually associated with severe pain [Roelofse et al, 1999]. Littlejohn et al [1996], had a low incidence of pain after extractions of deciduous teeth in 60 children – this they claim was due to a small number of teeth extracted [<4]. Acs et al [1988], in their study reported a significant increase in the incidence of post-extraction pain when more than two teeth were extracted – 34,8% of children aged 6-9 years who had 1-2 teeth extracted, reported significant pain; when three teeth were extracted, 60,6% of children reported significant pain. They concluded that their study showed that the number of teeth extracted, is significantly associated with the severity of pain.

For inclusion in this study, it was a prerequisite that six or more extractions had to be performed. The mean number of teeth extracted was 10,68 in the S/M group, and 10,63 in the K/M group. This was considered as an ideal model to evaluate the efficacy of analgesic drugs in children.

Furthermore, ninety-two percent of patients in this study, had not received any previous dental surgery. Sufficient pain was therefore present to demonstrate the analgesic properties of the drug combinations used.

Although measuring pain and pain relief can be difficult in children, the pain assessment methods used have been validated [Paik HJ et al, 2002].

The Oucher facial pain scale is validated for use in children, as is a visual scale that children readily understand [Goodenough et al, 1997]

Seventy-two percent of the children in the S/M group [versus 52 % in the K/M group], were responders [Figure 10]. The Oucher facial pain scale

[Figure 9], showed the S/M group to experience less pain than those in the K/M group. Even though the S/M group showed improved clinical analgesia, this was not statistically significant [$p > 0,05$]. The analgesia provided was effective and reliable for pain due to multiple dental extractions. Using the modified Hannalah Objective pain scale [Table 6, Figure 12] as a behavioural-cardiovascular checklist, no significant differences were found between the two groups at various time intervals measured postoperatively [$p = 0,05$]. As the children had received no local anaesthesia, no significant differences reflected on the combination of drugs that were used.

Intranasal pharmacokinetic studies in volunteers are reported for fentanyl, alfentanyl, sufentanil, butorphanol, oxycodone and buprenorphine [Dale et al, 2002]. Mean times for reaching maximum serum concentrations vary from 5 to 50 minutes, while mean figures for bioavailability vary from 46% to 71%. Fentanyl, pethidine and butorphanol have been studied for postoperative pain. Mean onset time vary from 12 to 22 minutes and times to peak effect, from 24 to 60 minutes. There is considerable interindividual variation in pharmacokinetics and clinical outcome. This may partly be due to lack of optimization of nasal formulations. Patient-controlled intranasal opioid analgesia may be an effective alternative to intravenous patient-controlled analgesia. Adverse effect are mainly those related to the opioids themselves, rather than being due to nasal administration. Fewer patients with intranasal patient-controlled analgesia suffer opioid adverse effects such as episodes of vomiting, when compared with intravenous patient-controlled analgesia [Ward et al, 2002].

The use of oral midazolam as a premedicament in paediatric dentistry, preceded the use of the intranasal route and still needs to be compared to it [Jensen et al, 2002].

Using intranasal midazolam in healthy volunteers, the mean plasma concentration of midazolam of 71 [± 25] ng/ml is reached after 14 [± 5] minutes [Knoester et al, 2002]. Mean bioavailability following intranasal

administration is $0,83 \pm 0,19$. It has an elimination half- life of 4 hours. Intranasal midazolam [0,3 mg/kg, 0,4 mg/kg, 0,5 mg/kg] has been used in conscious sedation of young paediatric dental patients [al-Rakef et al, 2001]. There is a rapid onset of sedation, with the maximum effect occurring between 8 and 15 minutes. This sedation lasts for 25 – 40 minutes. All 3 doses of intranasal midazolam are effective in modifying the behaviour of the uncooperative child to accept dental treatment. Another recent study showed that, for premedication in young children, intranasal midazolam [0,3 mg/kg] achieves maximum sedation and anxiolysis at 20 minutes [Kogan et al, 2002]. Patient mask acceptance is good in the majority of children [more than 75%]. It does, however, cause significant nasal irritation. Most patients are satisfied with its use for premedication. In children, intranasal administration of low doses of ketamine produce plasma concentrations associated with analgesia [Malinovsky et al, 1996]. Intranasal ketamine permits pleasant and rapid separation of children from their parents, co-operative acceptance of monitoring and mask inhalation, induction and does not cause prolonged postanesthetic recovery or delayed discharge home [Diaz JH, 1997]. The bioavailability of the nasal spray is approximately 45%. The area under the curve [0 to 6 hours] of its metabolic, norketamine is low [approximately 100ng/ml in both enantiomers [Yanagihara et al, 2003]. Most reports demonstrate no or mild psychotomimetic effects when ketamine is dosed at subanaesthetic doses [Kronenberg RH, 2002]. This is further reduced by the use of the S-enantiomer of ketamine.

This study directly compared an intranasal combination of sufentanil/midazolam with ketamine/midazolam to determine which drug combination is preferable for sedation and postoperative pain relief in preschool children. This is to my knowledge the first time that a randomized double-blind study has been used in this way. The study demonstrated the safety and efficacy of both drug combinations. Key features were the ease of administration combined with rapid onset of

action. Both groups were equally sedated. A smooth mask induction of anaesthesia was experienced in the majority of children. Effective postoperative analgesia for multiple dental extractions was provided. However, these techniques may potentially still induce deep sedation and should not be attempted by operators unskilled in advance anaesthesia techniques.

CONCLUSION

The study of the intranasal route in children is still in its infancy. But the intranasal administration of drugs for sedation and analgesia has some promising features, especially in preschool children with fear of separation from parents and unfamiliar surroundings. Improvements of nasal spray devices may improve clinical outcome. Further adequately designed clinical studies are needed.



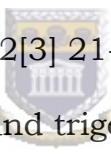
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