IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 21, Issue 4 Ser.3 (April. 2022), PP 45-79
www.iosrjournals.org

"Comparison of Combination of Midazolam and Ketamine with Midazolam and Ketamine Alone As Oral Preanaesthetic Medication for Children"

P V SURYA PRASAD
G Vijaya Lakshmi, V Charishma, Manoj Kumar Gupta

Date of Submission: 02-04-2022 Date of Acceptance: 15-04-2022

I. Introduction

The preoperative period is a stressful event for the majority of individuals undergoing surgery. This is especially true in the paediatric patient and is related to a limited understanding of the nature of the illness and the need of surgery by young children. Pharmacological and behavioural interventions are used to treat preoperative anxiety in children and their parents.

Anaesthesia and surgery represent an immense time of stress for the child. The reasons for stress include primarily (i) separation from parents (ii) strange surroundings (iii) painful procedures (iv) frightening procedures and (v) survival.[1] They are unable to understand the necessity for their surgery, nor are they likely to be amenable to reasoned explanation.

Preanesthetic medication in paediatrics patients is a challenge for anaesthesiologists. It plays an important role in the anaesthetic care of infants and children by allaying anxiety, decreasing vagal stimulation and preventing postoperative psychological sequelae. A peaceful separation of the parent and the child is the definition of successful premedication.

Of the various aspects of paediatric anaesthesia, the most neglected part is premedication. In most of the busy paediatric surgical theatres, it is very common to find children in waiting area in various stages of anxiety and distress emitting various tones of crying. Most of the time, the anaesthetist will struggle with the child to start the intravenous line or induce inhalationally. Whenever we induce anaesthesia in a struggling adult patient, fearing hypertensive response, we never bother to properly sedate the paediatric patient before bringing the child to operation theatre.[3]

Extreme preoperative anxiety may prolong the induction of anaesthesia; may lead to new onset postoperative negative psychological effects such as nightmares, eating disturbance and enuresis[4, 5] .may cause arterial oxygen desaturation[6] and make subsequent contacts with health professionals more difficult.[7]

Therefore, an effective pre-anaesthetic medication for use in children undergoing surgery is required which will allay apprehension regarding anaesthesia and surgery; lessen the trauma of separation and facilitate induction of general anaesthesia without prolonging the post anaesthetic recovery period.[3]

A variety of premedications administered via various routes have been introduced.

The **ideal premedication** for procedures should be easy to administer, have a rapid and predictable onset and produce both amnesia and analgesia without significantly affecting cardiovascular and respiratory functions. Route of administration is another important factor for those patients who do not already have established venous access since starting intravenous access to administer sedation may be as traumatic as the procedure itself. Therefore an orally active agent could be especially welcome[8].

Oral Midazolam and Ketamine met these criteria with rapid onset, minimal side effects and rapid post-operative recovery.

Feld and co-workers [1] suggested that oral Midazolam 0.5 mg/kg 30 mins prior to induction was as effective as Midazolam 0.2 mg/kg I.M. for preanesthetic medication. They also suggested that administration of small amounts of fluid to children prior to induction of anaesthesia does not pose a significant risk.

Levine and co-workers [2] concluded that children may be separated from their parents as early as ten minutes after receiving oral Midazolam 0.5 mg/kg.

Gutstein and co-workers [3] had found that Ketamine 5 mg/kg provides predictable, satisfactory premedication without significant side effects.

The major problem with oral or sublingual administration is the strong after taste.[18]

Ketamine has well characterized sedative, anaesthetic and analgesic properties. It also has advantages over other sedative anaesthetic drugs because it stimulates the cardiovascular system, is usually associated with an

unobstructed airways and upper airway reflexes and cause minimum respiratory depression.[7] Ketamine has been tried with a high overall success rate without significant side effects. However it is widely acknowledged that ketamine IV or IM cause hallucinations in many patients. Even sub-anaesthetic concentration of ketamine produce psychedelic effects when given IV.[19] There is no such data in paediatric patients for oral administration, following which there is a high first pass metabolism. The metabolite norketamine causes sedation and analgesia also, but little is known of its side effects.[20]

The combination of oral ketamine 4-6 mg/kg, oral midazolam 0.5 mg/kg and oral atropine 0.02mg/kg provides a well sedated patient[18] .Studies have shown that a combination of midazolam plus ketamine provides better premedication than midazolam or ketamine alone.[21, 20, 22.]

Benzodiazepines augment the action of ketamine effects and attenuate emergence sequelae.[22]

In the present study, we have attempted to evaluate the scope of oral midazolam 0.5mg/kg, oral ketamine 6mg/kg and combination of midazolam 0.5mg/kg + ketamine 3mg/kg orally as a pre- medicant in paediatric age group.

AIMS AND OBJECTIVES OF THE STUDY

To compare the combination of midazolam and ketamine with midazolam or ketamine alone as oral pre-anaesthetic medication in children (2-10 years) with respect to the following parameters:

1) Sedation
2) Anxiolysis
3) Behaviour at parental separation
4) Side effects

PREMEDICATION

Anaesthetic management for patients begins with preoperative psychological preparation, and if necessary preoperative medication. Specific pharmacologic actions should be kept in mind when these drugs are administered before operation, and they should be tailored to the needs of each patient. Because it is part of and the beginning of the anaesthetic choice of premedication is based on the same considerations as the choice of anaesthesia including the patient's medical problems, requirements of the surgery and anaesthesiologist's skills.

Indications:

Children requiring premedication:

Young patients that may require premedication or sedation to obtain their Cooperation, include the following.

- ❖ Children who have had previous surgical experiences and who are only too aware of the impending discomforts related to the upcoming surgery and hospitalization;
- ❖ Preschool-age patients who will not easily separate from their parents and in cases in which the anaesthesiologist believes that parental presence would not be of benefit during induction;
- ❖ The patient in whom communication is limited due to physical disability (e.g.deafness, autism) and the parents cannot act as intermediaries to communicate with the child at the time of induction;
- ❖ Cases in which smooth anaesthetic induction with minimal crying or struggling is indicated (e.g. children with cyanotic heart disease). Caution should be exercised when premedicating these children, as they may become more cyanotic or develop hypercarbia;
- ❖ Adolescent patients who show a significant degree of anxiety. The adolescent is often fearful of loss of control, loss of body image and death, and may be quite anxious despite outward attempts of bravado.

The **ideal premedicant** for children scheduled for a surgical procedure should

1. Be available in a preparation that is readily accepted by children.
2. Have a relatively rapid and reliable onset.
3. Provide anxiolysis and mild sedative effects.
4. Ease separation from parents.
5. Have anxiolytic and sedative effects of sufficient duration to accommodate delays in operating room scheduling without delaying discharge.
6. Facilitate patient acceptance of face mask during induction of anaesthesia without prolonging emergence, cardio respiratory instability or post-operative delirium, nausea and vomiting.
7. Be free of side effects that would necessitate high levels of nursing supervision.
8. Provide for rapid recovery and return to alertness post operatively, thereby permitting early discharge from the recovery area.

Premedication in children prone to complications:

There are select groups of children who are at risk and in whom discretion should be used in the use of premedicant drugs. A specific history of upper airway obstruction, aspiration, in coordinate swallowing or coughing should be sought before any premedication is considered. A documented history of sleep apnea,

obstructive or central is an absolute contraindication. The following groups of children should be carefully assessed and premedicant drugs withheld or given in reduced dosages if deemed necessary.

- Adenoid hypertrophy
- Functional macroglosia
- Neurologically impaired children
- Muscular dystrophy
- Infants weighing less than l0 kgs
- Congenital airway abnormalities.

TABLE-1 Dose regimens of drugs used commonly for paediatric sedation – Premediction[23].

DRUG	ROUTE	DOSAGE MG/ KG
Benzodiazepines		
Diazepam	Oral	0.1-0.3
	I.V.	0.1-0.3
	I.M.	(not recommended)
	Rectal	0.2-0.3
Midazolam	Oral	0.25-0.75
	I.V.	0.05-0.15
	I.M.	0.05-0.15
	Rectal	0.5-1.0
	Nasal	0.2-0.3(not recommended)
	Sublingual	0.2-0.3
Opioids		
Morphine	Oral	0.2-0.5
	I.V.	0.05-0.2
	I.M.	0.1-0.2
	Rectal	(Not recommended)
Meperidine	Oral	1-2
	I.V.	0.5-2
	I.M.	1-2
	Rectal	(not recommended)
Fentanyl	Oral, transmucosal	0.005-0.015
	I.V.	0.001-0.003
Ketamine	Oral	4-6
	I.V.	0.5-2.0
	I.M.	1-2
	Rectal	3-10
	Nasal	4-6

Oral route:

This is usually the most acceptable route and widely used for drug administration. Issues of concern include medication palatability, volume required, onset time, duration, and behaviour during recovery, interaction with other medications and side effects.

The drug has to be absorbed from the gastrointestinal tract into the portal system and then pass through the liver before entering the general circulation. The absorption from GIT is governed by factors such as surface area for absorption, physical state of the drug and drug concentration at the site of absorption. Since most of the drugs are absorbed passively, absorption is favoured when the drug is in non-ionized and more lipophilic form. Weak acidic drugs are better absorbed in the stomach. Basic drugs are better absorbed in the intestine[18]. Any factor that accelerates gastric emptying will be likely to increase the rate of absorption, while any factor that delays gastric emptying will probably have the opposite effect.

Advantages of oral route of drug administration are:

- Convenience in administration.
- Better acceptance
- Economical
- More safe.

First pass metabolism is one limiting factor in achieving bio availability of an orally administered drug. The drug which is absorbed into portal system enters the liver. The liver can either metabolize this drug into inactive metabolites or it can excrete the drug unchanged into the intestines through the biliary system. Both these will limit the bioavailability of the drug.

At times the child may spit out an oral premedicant. This is usually due to the Uncooperative demeanour of the child and unpalatable nature of the premedicant.While an attempt can be made to repeat the oral dose, this will probably be futile, and an alternative route of administration should be considered.

A PALATABLE VEHICLE FOR MIDAZOLAM AND KETAMINE

Even though both midazolam and ketamine are used for oral sedation, neither is available as oral formations in India. The intravenous forms of these drugs are quite unpalatable and hence require a vehicle which can mask their taste. Several formulation including orange juice,[53] apple juice,[3,22] chocolate cherry syrup.[25,34] Cola,[9] flavoured gelatin with or without sugar, sugar syrup[20,21,27] has been tried with variable acceptance by children.

In our study, we used 5ml of orange juice which was well accepted. Administration of small amounts of fluid (e.g. 5-10ml) to children prior to induction of general anaesthesia has been shown not to pose a significant risk with respect to aspiration of abdominal contents.[3] The combinations of the drugs in the juice is chemically stable for 2-8 weeks.[20]

PHARMACOLOGY OF MIDAZOLAM18, 54-68

Midazolam is a water soluble benzodiazepine. It was first synthesized by Fryer and Walser in 1976. It was the first benzodiazepine that was produced primarily for use in anaesthesia. It has replaced diazepam as the most commonly administered benzodiazepine in the perioperative period for preoperative medication and intravenous "conscious" sedation. The five principal pharmacologic effects are: sedation, anxiolysis, anticonvulsant actions, spinal cord-mediated skeletal muscle relaxation and anterograde amnesia.

Chemistry:

The Molecular weight is 362 with a pKa of 6.2. The parenteral solution used clinically, is buffered to an acidic pH of 3.5. This is important because midazolam is characterized by a pH dependent ring opening phenomenon in which the ring remains open at pH values of less than 4, thus maintaining water solubility of the drug. The ring closes at pH values of more than 4, as when the drug is exposed to physiologic pH thus converting midazolam to a highly lipid soluble drug (Figure- 1).

Chemical structure:

Midazolam has a fused imidazole ring that is different from classic Benzodiazepines. The imidazole ring accounts for the basicity, stability of an aqueous solution and rapid metabolism. It is named 8-chloro-6(2 flurophenyl)-1 methyl-4H-imidazol (1, 5a) (1, 4) benzodiazepine maleate.

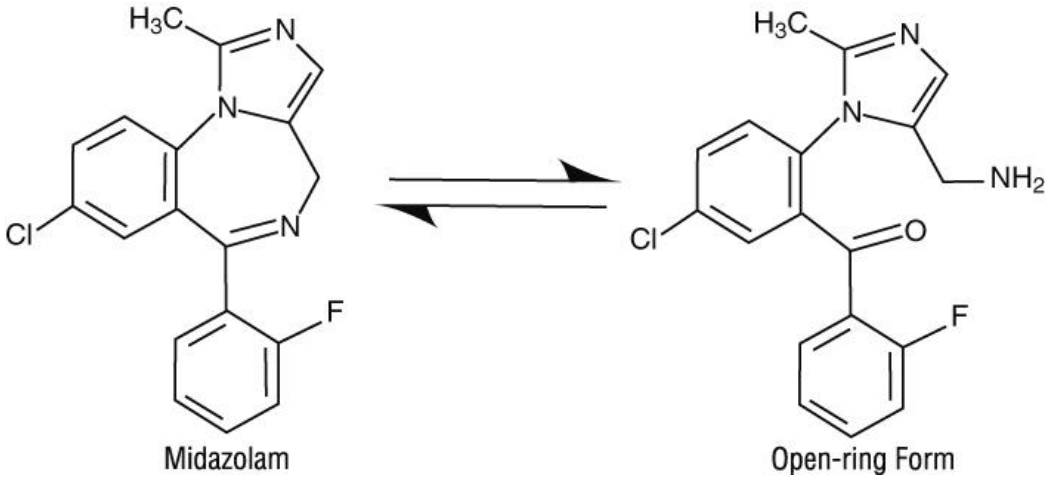


Figure-1: Reversible ring opening of midazolam above and below a pH of 4; the ring closes at a pH>4, converting midazoam from a water soluble to a lipid soluble drug.

a) The active lipid soluble ring configuration in blood.
b) The inactive water soluble configuration open ring.

Mechanism of action:

Midazolam and benzodiazepines in general appear to produce all their Pharmacologic effects by facilitating the actions of gamma amino butyric acid (GABA), the principal inhibitory neurotransmitter in the CNS. GABA-adrenergic Neurotransmission counterbalances the influence of excitatory neurotransmitters. The benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra, and inferior colliculus.

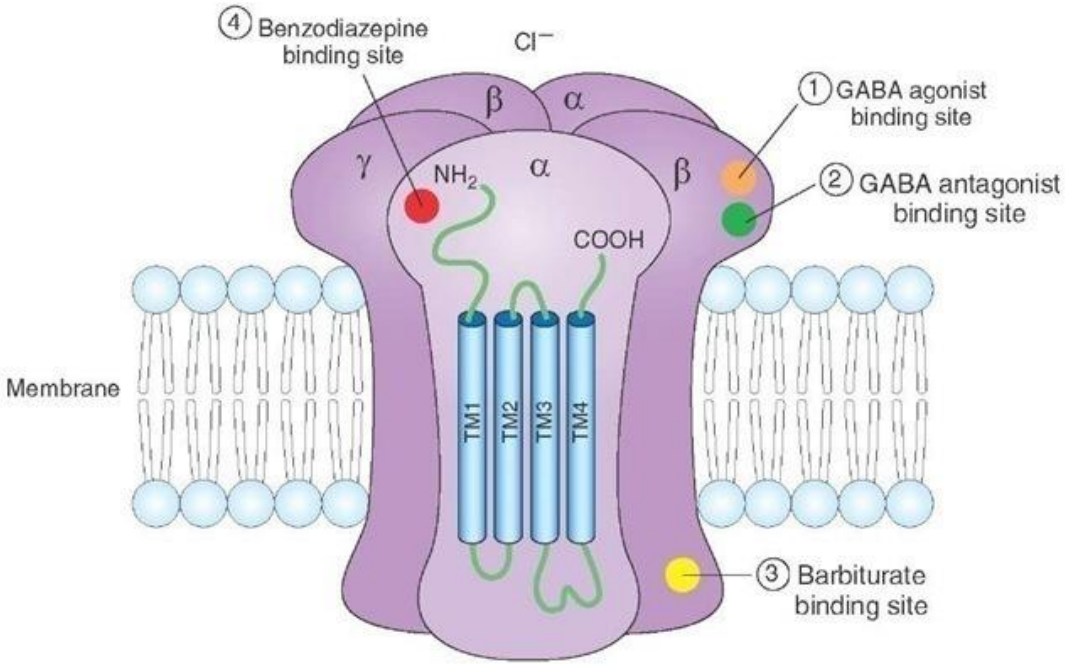


Figure-2: Schematic model of the $GABA_A$ receptor complex illustrating recognition sites for many of the substances that bind to the receptor.

Current data suggests a pentameric protein composed of α, β and subunits; the proposed arrangement of subunits is arbitrary. (Figure-2)

The GABA type A ($GABA_A$) is a receptor complex consisting of up to five Glycoprotein subunits. When the $GABA_A$ receptor is activated, transmembrane chloride conductance increases, resulting in hyper polarization of the postsynaptic cell membrane and functional inhibition of the postsynaptic neuron (Figure-3). Midazolam binds to a specific receptor site that is a part of the $GABA_A$ receptor complex. The binding increases the efficiency of the coupling between the GABA receptor and the chloride ion channel.

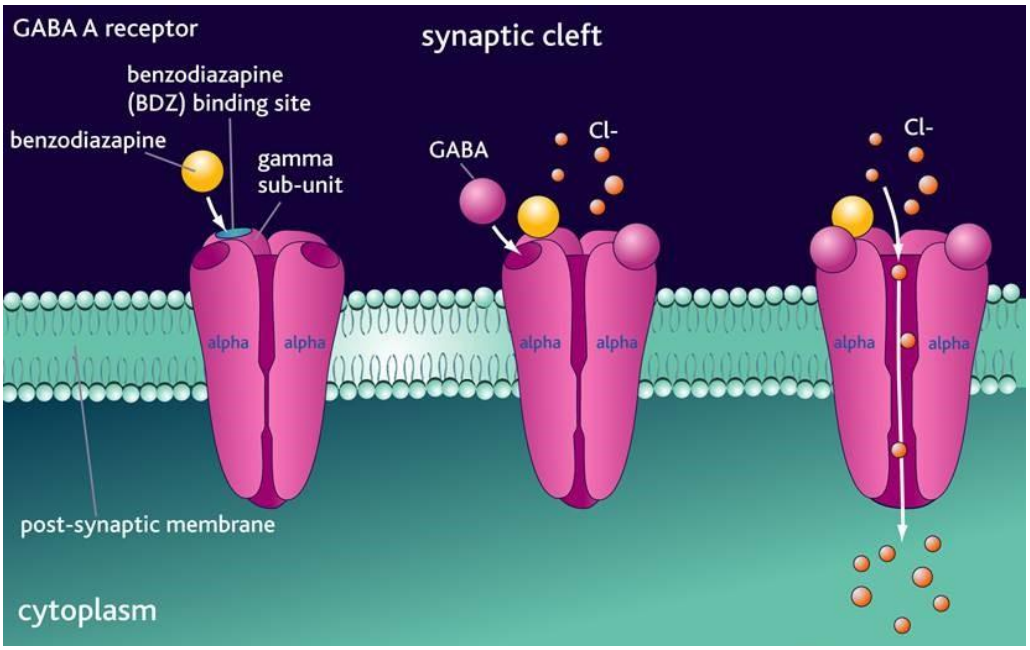


Figure-3: Mechanisms and sites of action of benzodiazepines.

PHARMACOKINETICS:

Midazolam blood levels decrease rapidly because of its high hepatic clearance, relatively shorter elimination half life ($t_{1/2}$) and rapid redistribution from the brain to inactive tissue sites. The termination of

action after single doses is caused both by distribution into peripheral tissues and by metabolic biotransformation. The context sensitive half time is shorter when compared to other benzodiazepines with a slow effect site equilibrium time. Most of the drug is metabolized in the liver by hydroxylation, followed by conjugation with glucoronic acid. Less than 0.5% is excreted unchanged in the urine. First pass metabolism is high. Clearance is also sensitive to hepatic blood flow.

Changes in pharmacokinetics:

Obesity: In morbidly obese subjects, those with greater than 120% of ideal body weight, there is a significantly increased volume of distribution resulting from enhanced distribution of the drug into peripheral adipose tissues.

Critical illness: In the critically ill patient, such as those with septic shock, multiple trauma, post cardiac arrest; and those with postoperative respiratory failure and or extensive re-explorations for surgical purposes, the pharmacokinetics of midazolam and its metabolites are altered. The elimination half life is significantly increased.

Congestive Heart Failure

- Volume of distribution is increased 2-3 fold
- Elimination half life is increased 2-3 fold
- Total body clearance is unchanged, therefore the dose should be reduced

Renal failure:

- There is no difference in volume of distribution, clearance or elimination half life.
- Free fraction of midazolam is almost doubled from 4-7% due to reduced albumin binding.

Therefore anaesthesia is induced more rapidly and patients may also sleep longer.

TABLE- 2 Pharmacokinetics of midazolam:

Distribution half life ($t_{½}$ alpha)	7-15 minutes
Elimination half life ($t_{½}$ beta)	1.7-2.6 hours
Protein binding	94%
Clearance	6.4-11 $ml.kg^{-1}$. Min^{-1}
Distribution volume at steady state (Vdss)	1.1-1.7$L.kg^{-1}$

Metabolism:

Midazolam undergoes extensive hydroxylation by hepatic microsomal oxidative mechanisms (cytochrome p-4503A4, p4503A3 and p450 3A5) to form α-hydroxymidazolam, the principal metabolite and small amounts of 4-hydroxymidazolam and even smaller amounts of α-4 dihydroxymidazolam (Figure 4). These water soluble metabolites are excreted in urine as glucoronide conjugates. Very little (<0.5%) unchanged midazolam is excreted by the kidneys. Plasma concentrations accumulate over the first 30 minutes after administration; reach the highest concentration in the first 2 hours.

Excretion:

Less than 1% of midazolam is excreted unchanged by the kidney. The metabolities are conjugated with glucoronic acid and all are excreted as glucoronides. The principal excretory product is the α-hydroxymethylmidazolam glucoronides.

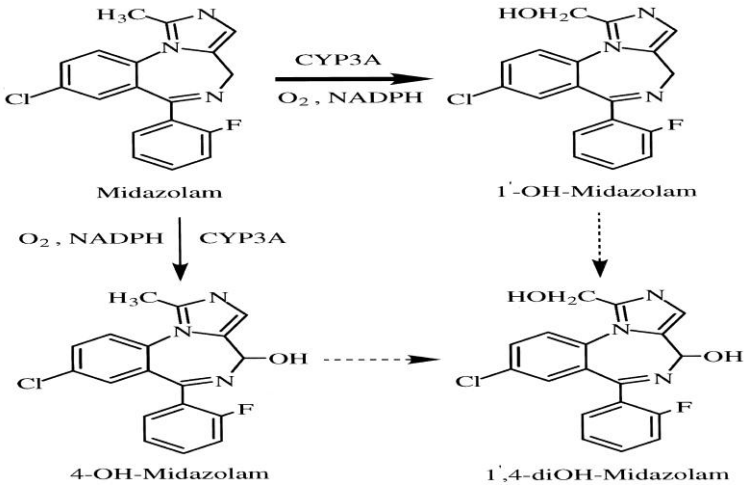


Figure-4: Metabolism of midazolam, with a-hydroxy midazolam occurring in the greatest quantity. All the hydroxylated metabolites are quickly excreted via the kidneys.

Pharmacodynamics:
Rising plasma concentrations correlate with clinical effects. Assessment of effects is carried out progressively as a steady state is achieved. The half life of equilibrium between plasma concentration of midazolam and its maximal EEG affect is only 2-3minutes, the time within which sedation is apparent. The therapeutic window to attain unconsciousness with midazolam is reported to be 100-200 ng/ml with awakening occurring at plasma concentration below 50ng/ml.

Effects on organ systems:
Central nervous system:
Midazolam like other benzodiazepines is a sedative-hypnotic and anxiolytic. It has been suggested that BZD receptor occupancy of 20% provides anxiolysis, while 30-50% receptor occupancy is associated with sedation and greater than 6O°% receptor occupancy is required for hypnosis (unconsciousness).

It decreases in a dose related manner both cerebral metabolic rate for oxygen ($CMRO_2$) and cerebral blood flow (CBF) maintaining a relatively normal ratio of CBF to $CMRO_2$. In contrast to drugs such as barbiturates and propofol, it is unable to produce a burst suppressive (isoelectric) pattern on the EEG, emphasizing that there is a "ceiling" effect with respect to the decrease in $CMRO_2$ produced by increasing doses of midazolam.

It also induces dose-dependent changes in regional cerebral perfusion in the parts of the brain that sub serve arousal, attention and memory. In patients with intracranial pathology, it decreases cerebral perfusion pressure (CPP) with little effect on intracranial pressure (ICP). It is also a potent anticonvulsant. Paradoxical excitement occurs in less than 1% of all patients receiving midazolam and is effectively treated with specific BZD antagonist `flumazenil'.

Respiratory system:
Midazolam produces dose dependent respiratory depression and in doses of 0.15mg/kg significantly reduces the ventilator response to CO_2 .In healthy patients; the respiratory depression associated with premedication is insignificant. However, the depressant effect is enhanced with chronic respiratory disease, and synergistic depressant effects occur when it is co-administered with opioid analgesics. Benzodiazepines also depress the swallowing reflex and decrease upper airway reflex activity. Transient apnea may occur after rapid injection of large doses of midazolam (> 0.15 mg/kg IV).
Cardiovascular system:
The predominant hemodynamic change is slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which midazolam maintains relatively stable haemodynamics involves the preservation of homeostatic reflex mechanisms. However the cardiovascular depressant effects are frequently "masked" by the stimulus of laryngoscopy and intubation.
Myocardial oxygen demand:
The myocardial oxygen demand is markedly decreased. But there is no alteration of myocardial contractility as evidenced by the maintained maximum velocity of shortening (v_{max}) · There is also a decreased left ventricular end diastolic pressure (LVEDP), reflecting a decreased preload.

Coronary haemodynamics:
Coronary vascular resistance is not altered. Coronary perfusion pressure is decreased, as reflected by a fall in diastolic artery pressure. Over all good stability is observed. Systolic and diastolic blood pressure and pulse rates are not significantly altered. Haemodynamic changes are more gradual and less pronounced than with equipotent doses of thiopental and are slightly but insignificantly greater than with diazepam.
Endocrinologic effects:
- Attenuates stress related epinephrine increases, which are minimal.
- Plasma cortisol levels decrease from approximately 12.5 to 7.5 pg/ml
- Adrenocorticotropic hormone (ACTH changes are minimal as midazolam prevents any significant endogenous increase in ACTH along with an unchanged response to exogenous ACTH.
- The course of β- endorphin plasma level is also similar to ACTH; minimal changes perioperatively.

Effects on memory:
Early studies established the anterograde amnesic action of IV midazolam which was maximal at 2-5 minutes after injection. Anterograde amnesia generally persists for 20-40 minutes after IV injection of a single dose. The durarion of anterograde amnesia following IM administration of midazolam is about 1 hour. The ability to produce a short period of anterograde amnesia is a useful feature of the efficacy of midazolam when used as a sedative for endoscopy and in dental procedures.

Skeletal muscle:
No influence on the neuromuscular junction has been determined.
Intraocular pressure:
Midazolam decreases intraocular pressure.
Clinical uses:
Midazolam is the most commonly used benzodiazepine for preoperative medication in paediatric patients, IV ("conscious") sedation and induction of anaesthesia. It is also used for maintenance of anaesthesia along with other drugs, and as an anticonvulsant.
1. **Preoperative medication:**

- Oral midazolam 0.5mg/kg, 30 minutes before induction provides reliable sedation and anxiolysis in children without producing delayed recovery. Intramuscular - 0.05 - 0.1 mg/kg is also effective but less well accepted by children.
- Transmucosal (sublingual) midazolam is as effective as and better accepted than intranasal route in a dose of 0.2 mg/kg.
- Jet injection (i.e. using compressed gas instead of a needle) 0.10-0.15 mg/kg produces effective and rapid sedation in children without emotional trauma associated with needle injections.

2. **Intravenous sedation:** Midazolam in doses of 1-2.5 mg IV is effective for sedation during regional anaesthesia as well as for brief therapeutic procedures. Compared with diazepam, it produces a more rapid onset, with greater amnesia and less post-operative sedation. Pain on injection and subsequent venous thrombosis are less likely with midazolam as it is water soluble.
3. **Induction of anaesthesia:** Midazolam is the benzodiazepine of choice for use in anaesthetic induction which is defined here as unresponsiveness to command and loss of eyelash reflex. In appropriate doses induction occurs less rapidly than with thiopental, but the amnesia is more reliable. Usual induction dose is 0.1 to 0.2 mg/kg or lesser (0.05-.15 mg/kg) in premedicated patients or when coinduced with other agents such as opioids, thiopental or propofol
4. **Maintenance of anaesthesia:** It is a useful hypnotic-amnestic during maintenance of general anaesthesia but cannot be used alone for the same. It is used with opioids, propofol and or inhaled anaesthetics. MAC of volatile anaesthetics is decreased in a dose dependent manner. It can also be used as an infusion in a dose of 0.25-1 mg/kg/ min.
5. **Anticonvulsant:** As an anticonvulsant for the treatment of grandmal seizures which may occur with systemic toxicity produced by local anaesthetics.
6. **Conscious sedation:** Midazolam is probably the only sedative to produce a true state of "conscious sedation". It provides relief of anxiety and anterograde amnesia when administered prior to

- Dental or minor surgical procedures
- Upper GI endoscopy
- Bronchoscopy
- Cardiac surgery
- Critically ill patients in ICU.

Adverse effects:

- Benzodiazepines are remarkably safe drugs in doses routinely used.
- Most significant problem with midazolam is respiratory depression when the drug is given for conscious sedation.
- When used as sedatives or for induction and maintenance of anaesthesia, they can produce an undesirable degree or prolonged interval of post operative amnesia, sedation and rarely respiratory depression. The residual effects can be reversed with flumazenil.
- Rarely loss of head control and balance, blurred vision and dysphoria may be seen.

Drug interactions:

- Alcohol, narcotics, sedatives and volatile anaesthetic agents potentiate CNS and circulatory depressant effects.
- Erythromycin, ranitidine, diltiazem, Fluconazole, grape fruit juice, verapamil and roxithromycin, increase serum levels and toxic effects.
- Serum levels are decreased by carbamazepine, phenobarbitone, phenytoin and rifampicin.
- It decreases MAC for volatile agents.
- Effects are antagonized by flumazenil.

Precautions:

- Reduce the dose in elderly, hypovolemic, high risk patients, and with concomitant use of other sedatives or narcotics.
- COPD patients are unusually sensitive to the respiratory depressant effect.
- It is contraindicated in acute narrow angle or open angle glaucoma.
- It is excreted in human milk; therefore caution should be exercised when it is administered to a nursing woman.

Advantages over Diazepam:

- Minimal discomfort or pain at injection site
- Absence of venous thrombosis
- More rapid onset of action
- Predictable dose
- Shorter duration of action
- Shorter time of distribution and of elimination
- More rapid body clearance

Role of oral midazolam for premedication in children:

Oral midazolam has a substantial first pass hepatic effect; thereby only about 50% of the administered dose reaches the systemic circulation. Its main disadvantage is its bitter taste which can be masked administering it with sweet syrup. It is found to be safe and effective without altering the cardiovascular or oxygen saturation values in the prepoperative or immediate postoperative periods. In the dose range of 0.4-O.6 mg/kg it produce good anxiolysis in older children (>5 year of age) allowing parental separation by 15-30 minutes. It also allows easy administration reducing the incidence of stormy induction providing amnesia, helping to prevent the fear of returning to the hospital or operating room and lowering the incidence of negative post operative behaviour.

PHARMACOLOGY OF KETAMINE[18, 32, 54, 59, 64-70]

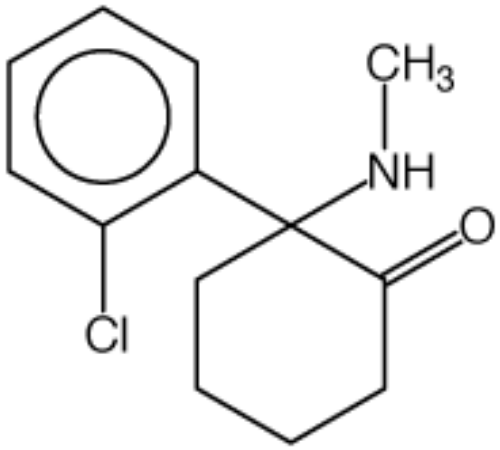


Figure: 5 Chemical Strucure of ketamine

Ketamine is a non-barbiturate anaesthetic agent. It belongs to the phencyclidine group of drugs. Chemically it is 2, 0-chlorophenyl-2 methylamino cyclohexanone which structurally resembles phencyclidine and cyclohexamine.

Ketamine was synthesised in 1963 by Stevens of Detroit and was tested on volunteers from state prison in Michigan in 1964. Domino and Corssen used it in anaesthesia in 1966.

The clinical state induced by ketamine was suggested to be called "Dissociative Anaesthesia", by Corsen et al in 1966.

Physical Properties: Ketamine hydrochloride is a white crystalline substance readily soluble in water forming a clear colourless solution. It is stable at room temperature and its solution has a pH of 3.5-5.5, molecular weight 238 and Pk of 7.5.

It exists as one of 2 optical isomers. The racemic mixture (containing equal amounts of two isomers) is approved for general clinical use. The drug is supplied as l0 mg or 50 mg of Ketamine per ml for l .V and I.M injections. These solutions are non-irritant on parenteral injection. The preservative used is Benzathonium chloride 1:10,000.

Pharmacokinetics: Ketamine is rapidly absorbed following parenteral administration. Peak plasma levels are achieved within one minute following intravenous administration and within 5 minutes following intramuscular injection.

First pass metabolism and lower absorption necessitate higher doses when ketamine is administered by oral or rectal routes. Ketamine pharmacokinetics follows a three term exponential decline. In unpremedicated patients, distribution half life is 24.1 seconds, redistribution half life is 4.68 minutes and elimination half life is 2.17 hours.

Ketamine is metabolised in the liver. A major pathway of bio transformation involves N-demethylation of ketamine via cytochrome P-450 enzymes to form norketamine (metabolite I) which in turn is conjugated to more water soluble glucuronide derivatives. Ketamine can also undergo ring hydroxylation without prior N-demethylation, but this pathway is of minor importance.

Following I.V. administration less than 4% of the dose can be recovered from urine as either unchanged drug or norketamine and only 16% as hydroxylated derivatives. Faecal excretion accounts for less than 5% of an injected dose of ketamine. Norketamine appears to be 1/5 to 1/3 as potent as ketamine as an anaesthetic.

PHARMACOKINETICS IN CHILDREN: After an I.V. injection in children there is a more rapid onset of action than in adults. Duration of action is also somewhat shorter. The clearance of ketamine is slightly more rapid than in adults, whereas steady state volume is smaller. In the studies by Grant, plasma norketamine concentrations were at all times greater in children. The higher norketamine concentrations in children probably reflect a faster N-demethylation of ketamine and perhaps, a slowing of metabolism of norketamine. After I.M injection in children, absorption is faster and predictable and recovery is also faster than adults.

Role of oral ketamine for premedication in children

Only 16% of ketamine is bioavailable orally, as opposed to 93% intramuscularly or intravenously. It also has been shown that oral ketamine doses equivalent to intramuscular doses produce peak plasma ketamine concentrations only one fifth as high as intramuscularly delivered concentrations and the time to reach peak plasma concentration is longer. However, the plasma concentration of norketamine, an active metabolite with one third the potency of ketamine, is twice as high after oral administration of Ketamine. This increased amount of norketamine relative to ketamine with oral administration may account for part of the sedative effect observed and possibly the reduced incidence of unwanted side effects with oral administration

Mechanism of action: The exact mechanism and site of action of ketamine have not been fully established. Unlike conventional anaesthetic agents, ketamine produces a selective sensory blockade of cortical association areas and thalamocortical projection system, without depressing the reticular activating system and limbic system. Sensory input reaches the cortical receiving areas, but fails to be perceived in some association areas because of blockade. Ketamine is a potent analgesic at subanaesthetic plasma concentrations and its analgesic and anaesthetic effects may be mediated by different mechanisms. The analgesia may be due to interaction between ketamine and central or spinal opiate receptors.

1. N-Methyl D-Aspartate Receptor Theory: N-Methyl D aspartate (NMDA) is an excitatory amine and its receptors in mammalian brain are blocked by phencyclidine and ketamine. The NMDA receptor may represent a subgroup of opiate receptors (the phencyclidine sites) that block spinal nociceptive reflexes.

2. Opiate Receptor Theory: Ketamine's affinity for opiate receptors is controversial, but this provides an attractive theory for its analgesic activity at central and spinal sites. Smith et al, showed that racemic ketamine displaced naloxone from rat brain opiate receptors in vitro and that (+), ketamine was about twice as potent as (-) ketamine for this purpose. Cross tolerance between the opiate and ketamine would also be expected if there is a common receptor. The opiate receptor theory would gain more credence if ketamine reversal by naloxone were proven in humans.

3. Monoaminergic Receptors: The antinociceptive action of ketamine may involve descending inhibitory monoaminergic pain pathways.

4. Miscellaneous Receptor Theory: Other neuronal systems may be involved in the antinociceptive action of ketamine, since blockade of noradrenaline and serotonin receptors attenuates the analgesic action of ketamine in animals. Interaction of ketamine with sigma opiate receptors might be a possible theory to explain dysphoric emergence reactions. Ketamine also interacts with muscarinic cholinergic receptors in CNS.

Pharmacodynamics: The pharmacodynamic effect of ketamine in humans is apparently due to CNS activity of parent compound.

Analgesia from ketamine is associated with a plasma concentration of 0.15 μ/ml following intramuscular administration and 0.04μ/ml following oral administration. The difference in analgesic concentration might be explained by a higher norketamine concentration following oral administration (probably from first-pass metabolism), which contributes to the analgesia. Awakening from ketamine anaesthesia takes place at plasma concentrations of 0.6 to1.12 μg/ml.

EFFECTS OF KETAMINE ON THE CENTRAL NERVOUS SYSTEM:

Ketamine produces a dissociative anaesthetic state that has been described as a functional and electrophysiological dissociation between the thalamoneocortical and limbic system. Early EEG studies reported that ketamine depressed thalamoneocortical pathways and concomitantly activated the limbic system. Subsequent studies demonstrated that ketamine produced excitatory activity in both thalamus and limbic systems. However, there was no clinical evidence that this seizure like activity spread to cortical areas.

Following an I.V dose of ketamine, onset of anaesthesia is rapid, in about 30 seconds to 1 minute. The patient appears to be wide awake, with eyes open with the appearance of vertical and horizontal nystagmus. The pupils become central and fixed in mid dilated position. Light reflex is diminished, but corneal reflex remains active.

Amnesia persists for an hour or more after apparent waking. Recovery is associated with a high incidence of emergence phenomena, which include dreams, hallucinations, irrational behaviour and restlessness.

Ketamine causes an increase in intracranial pressure. Even though ketamine is reported to have an anti-epileptic effect, it is generally contraindicated in patients with a history of epilepsy.

Analgesic Effect of Ketamine: Early observations suggested that analgesia following ketamine administration outlasted the period of anaesthesia and this analgesic effect occurred even at subanaesthetic doses of ketamine.

Stereospecificity of ketamine in binding to opiate receptors has been demonstrated (Phencyclidine sensitive sigma 1 receptors).

EMERGENCE PHENOMENON: The psychomimetic activity produced by ketamine can be disturbing to physicians and nurses and may upset other patients in the recovery room. Ketamine produces depressive action on the inferior collicular (a primary acoustic relay nucleus) and the medial geniculate (a visual relay nucleus) nucleus leading to misinterpretation of auditory and visual stimuli. It would appear that emergence reaction is secondary to this. Typically, the psychic sensations during emergence from ketamine anaesthesia are described as alterations in mood state and body image, extracorporeal (out of body) experiences, floating sensations, vivid dreams or illusions and occasional frank delirium.

The reported incidence of psychic disturbances following ketamine vary from <5% to >30%. Factors associated with higher emergence reactions include:

- Age > 6 years
- Sex-Female > males
- Subjects who dream frequently during sleep
- Large doses of ketamine - >2mg/kg. IV
- Rapid IV administration - > 40 mg/min.
- A history of personality problems.

Ketamine induced changes are short lived (< 24 hours).

Adverse reaction to ketamine can be minimised by informing the patient in advance of the likelihood of vivid visual imagery during the anaesthetic experience.

Several premedicants and adjuvant agents have been evaluated in preventing emergence reactions caused by ketamine. Atropine premedication before ketamine administration may increase the frequency of unpleasant dreams. Although droperidol was first reported to reduce the incidence of adverse emergence reactions when used as premedicant, others found that it could increase the occurence of vivid dreams. Furthermore, patients receiving droperidol tend to be significantly less responsive and more disoriented during recovery period.

Concomitant use of nitrous oxide significantly decreases the ketamine dose required for surgical anaesthesia, decreases the incidence of emergence reactions and shortens the recovery period.

Benzodiazepines appear to be the most effective drugs for attenuating the psychic actions of ketamine during emergence period. Diazepam (0. 15 to 0.3 mg/kg IV) has been reported to significantly decrease the incidence of dreams and to eliminate post-operative illusions when administered before or after induction of ketamine anaesthesia.

Of the currently available benzodiazepines; Lorazepam (2-4mg PO or IV) is reported to be the most effective in preventing unpleasant dreams and emergence sequelae after ketamine. Lorazepam enhanced effective and longer lasting amnesia than diazepam. Flunitrazepam (0.03 mg per kg IV), also attenuates the emergence sequelae associated with ketamine anaesthesia. Freunchen et al, found that combination of flunitrazepam and ketamine for induction, followed by ketamine infusion and nitrous oxide for maintenance of anaesthesia compared favourable to an inhalational anaesthetic technique. Midazolam, a more rapid and short acting water soluble benzodiazepine, also prevents unpleasant dreaming and emergence sequelae when used as an adjunct to ketamine for inducing general anaesthesia. Cart Wright and Pingel reported that midazolam was more effective than diazepam in preventing unpleasant dreams when used as an adjuvant to ketamine anaesthesia.

ELECTROENCEPHALOGRAPHIC EFFECTS:

Ketamine induces consistent changes in the EEG. There is a reduction in alpha wave activity, while beta, delta and theta wave activity increased, which are not altered by diazepam.

C.V.S. Effects: Following ketamine administration, there is an increase in both systolic and diastolic blood pressures, increase in heart rate and cardiac output. A rise in circulating catecholamines after ketamine injection has been seen, but the myocardium is not sensitised to them. Ketamine has a mild but demonstrable anti-arrhythmic effect. The pressor response has been considered to involve the sympathetic nervous system, but the postulated sites of action are diverse:

- Baroreceptor desensitisation
- Central sympathetic stimulation
- Increased efficacy of noradrenaline released from the adrenergic terminals as a result of blockade of neuronal reuptake.
- Release of catecholamines from the adrenal medulla.
- Release of corticosteroids from adrenal cortex.

Ketamine in vitro has negative inotropic effects. Numerous drugs have been shown to block the ketamine induced cardiovascular stimulation, including alpha and beta blocking agents and calcium channel blockers. The benzodiazepines are the most efficacious agents. The interaction with other anaesthetic agents, including the potent volatile agents either diminished or abolished ketamine's cardiovascular stimulant effects.

In patient with IHD, the cardiovascular stimulant effects of ketamine might precipitate myocardial ischemia. Laishley et al., found ketamine to be a safe induction agent in patients with cyanotic congential heart disease, although ketamine was associated with increased heart rate.

Respiratory system: Upon slow intravenous administration of a dose of 2mg/kg of ketamine, respiration is normal or moderately stimulated and minute volume increases. If the same dose is given rapidly, there may be transient apnea which usually follows a deep inspiration. A patent airway is maintained partly by virtue of unimpaired pharyngeal and laryngeal reflexes and partly by maintaining the tone of masseter muscles. However ketamine stimulates pharyngeal secretions, which may accumulate and trickle down and may precipitate laryngospasm and bronchospasm. Concomitant use of antisialogogues ensures airway patency during ketamine anaesthesia.

The presence of pharyngeal and laryngeal reflexes is thought to protect against aspiration during ketamine anaesthesia. But it has been demonstrated with the help of bronchographic studies after introducing dye in to the patient's mouth, that certain amount of the dye reaches the lower respiratory tract.

Blood gas studies do not show abnormality of respiratory function under ketamine anaesthesia. Ketamine dilates the bronchial tree. This is thought to be due to endogenous release of catecholamines, than due to a direct relaxant effect on the bronchial smooth muscle. Ketamine is thus beneficial in asthmatic patients.

Mankikian et al., administered IV ketamine 3mg/kg followed by an infusion of 20 μg/kg/min to patients who breathed spontaneously through endotracheal tubes. They reported maintenance of functional residual capacity, minute ventilation and tidal volume, with an increase in contribution of intercostal muscles to tidal volume. FRC is also preserved in young children during ketamine anaesthesia (Shulman et al., 1985).

Neuromuscular effects: An increase in skeletal muscle tone has been noticed during and after ketamine anaesthesia and occasionally muscle spasm may occur. These effects may be in part due to changes in calcium flux gradients and may also offer an explanation as to the ability of ketamine to increase neuromuscular blockade with both depolarizing and nondepolarizing muscle relaxants.

Metabolic and Endocrinal effects: The increase in metabolites found during ketamine anaesthesia is probably due to sympathetic stimulation and increase in muscle tone. Blood sugar and fatty acids are moderately increased. Renin, angiotensin and CPK do not increase. Plasma cortisol levels are elevated. Plasma T_4 levels are unaltered but T_3 is reduced.

Liver and Kidney: Ketamine has no effect on liver and kidney function.

Uterus and Placenta: Ketamine has no action on the contractility of the pregnant uterus. It crosses the placental barrier but there is no foetal depression.

Ocular effects: Ketamine increases intraocular tension. Nystagmus is transient during induction and both nystagmus and diplopia are uniform during emergence.

Dosage and Routes of Administration

Ketamine can be administered intravenously, intramuscularly, orally, nasally and rectally. The dose depends on the desired therapeutic effect and on the route of administration.

Dosage of Ketamine:

For Induction of General anaesthesia

0.5 - 2mg/kg IV

4-6 mg/kg IM

Rectal ketamine 8-l0mg/kg has been used successfully as an induction agent in paediatric anaesthesia. For maintenance of general anaesthesia

- 0.5 to 1mg/kg IV prn with N_2O 50% in O_2

- 15-45 µg/kg/min IV with N_2O 50 to 70% in O_2
- 30 µg /kg/min IV without N_2O

For sedation and analgesia

- 0.2-0.8 mg/kg IV over 2-3 min
- 2-4mg/kg IM
- 3-l0mg/kg orally

For sedation, ketamine may be given intramuscularly if the patient wishes to avoid awareness of intravenous catheter placement.

Lower doses are used if adjuvant drugs such as midazolam or thiopental are also given. Surgical anaesthesia is known to last for 5-10 minutes with 2mg/kg given I.V and 10-25 minutes with 10mg/kg given I.M.

Uses of Ketamine: It is used for premedication, sedation, induction and maintenance of general anaesthesia. It is specially indicated in

a) Poor risk patients who are in shock.
b) Severe anaemia.
c) Cardiac tamponade and constrictive pericarditis.
d) Asthmatics and patients with COPD.
e) Dressing changes in burns patients, wound debridement and skin grafting.
f) Paediatric anaesthesia - for brief diagnostic and therapeutic procedures.
g) As an adjuvant to local and regional anaesthetic techniques
h) Post-operative analgesia.
i) Obstetric analgesia: Ketamine is used in labour analgesia in dose of 0.2- 0.5 mg/kg intravenous.
j) Mass casuality, day care patients.
k) **Paediatric preanesthetic medication:** Ketamine is particularly suited for sedation of the paediatric patient. Paediatric patients have fewer adverse emergence reactions than adults, and this feature makes the use of ketamine in paediatrics more versatile. Ketamine is used for sedation and general anesthesia for the following paediatric procedures.Cardiac catheterization, radiation therapy, radiologic studies, dressing changes and dental work.

Advantages of ketamine over conventional agents such as meperidine, pentobarbital or the benzodiazepines include minimal effects on the cardiorespiratory system, which are thought to be related to its effects on the sympathetic nervous system with the release of endogenous catecholamines. Aside from its benefical effects on the cardiorespiratory system, ketamine possesses both analgesic and amnesic properties whereas more commonly used agents such as benzodiazepines have been shown in experimental animals to antagonize opiate-induced antinociception.

CONTRAINDICATIONS FOR THE USE OF KETAMINE:

A. Cardivascular diseases:

1. Poorly controlled hypertension
2. Intracranial, thoracic or abdominal aneurysms
3. Unstable angina or recent myocardial infarction.
4. Right or left heart failure.

B. Central nervous system disorders:

1. Cerebral trauma
2. Intracerebral haemorrhage
3. Intracranial tumours.

C. Opthalmic diseases

1. Open globe injury
2. Increased intraocular tension.

D. Surgical procedures involving larynx, pharynx and trachea

E. Thyrotoxic disease

F. Psychiatric disorders

Drug interactions:

1. Halothane has been shown to slow distribution and redistribution of ketamine and to inhibit its hepatic metabolism. Both these effects will contribute to prolongation of CNS effects.
2. Ketamine decreases minimum alveolar concentration of halothane even in subanaesthetic doses.
3. Diazepam prolongs elimination half life of ketamine and thus delays recovery. Intravenous diazepam causes increase in ketamine plasma level and a decrease in its clearance rate. These effects are presumed to be due to inhibition of hepatic metabolism of ketamine by the benzodiazepine.
4. Nitrous oxide has been shown to significantly reduce the dosage of ketamine required for surgical anaesthesia and to shorten the recovery period.

5. Chronic ketamine administration results in an increase in activity of hepatic drug metabolizing enzymes; including those responsible for metabolism of ketamine itself.
6. Ketamine maintains self administration behaviour in a manner similar to CNS depressant drugs and several cases of ketamine abuse have been reported.

II. Review Of Literature

Surgical intervention can be traumatic for children. Stormy inductions in children may be associated with arterial oxygen desaturation, besides vitiating a serene operation theatre environment. The screaming child requiring parental or nursing constraint to permit induction of anaesthesia may suffer psychological sequelae and is likely to view future hospitalization with a mixture of profound suspicion and terror. Hence despite reassurance and explanation, there remain some children who require a premedicant to allay anxiety and aid compliance with the induction.

Principles and objectives of premedication:

- Reduce apprehension, fear, anxiety, agitation and increase cooperation and permit easy separation.
- Control catecholamine and stress response.
- Control gastric acidity and volume
- Reduce metabolic requirements
- Reduce the anaesthetic dose requirements
- Achieve rapid recovery by avoiding over dose.

Midazolam, the benzodiazepine with the most favourable pharmacological profile, has been found to be an effective oral premedicant before anaesthesia for surgical procedures.

i) Feld LH, Negus JB, White PF, in 1990[3] studied in 124 children, aged 1-10 years who received oral midazolam, 0.25, 0.5 or 0.75 mg/kg and atropine 0.03 mg/kg p.o mixed with apple juice. The level of sedation, the quality of separation from parents and the degree of cooperation with an inhalation induction was compared.

Results: They concluded that midazolam 0.5-0.75 mg/kg po in combination with atropine 0.03 mg/kg po increased sedation, decreased separation, anxiety, and improved the quality of induction of anaesthesia. However 9-17% of the children who received this dose were still afraid, combative or crying.

ii) McMillan CO, Spahr-Schopfer IA,Sikich N,Hartley E, Lerman J,in 1992[24] compared four groups of children aged 1-6 years who received 0.5, 0.75 or l.0mg/kg midazolam or placebo 30 min before separation from parents. Heart rate, systolic blood pressure, arterial oxygen saturation, respiratory rate, sedation and anxiolysis scores were studied. Heart rate, systolic blood pressure, oxygen saturation and respiratory rate were unchanged during the study. Sedation and anxiolysis scores were greater in the midazolam treated groups than those in the placebo group.

Results: They concluded that oral midazolam 0.5 mg/kg is a safe and effective premedication and that doses of 0.75 and 1 mg/kg while offering no additional benefit, may cause more side effects such as loss of balance and head control, blurred vision and dysphoric reactions.

iii) Alderson PJ, Lerman J in 1992[25] Compared the clinical characteristics of two oral premedicants, midazolam 0.5 mg/kg and ketamine 5mg/kg. Sedation and anxiolysis scores before induction, cooperation at induction of anaesthesia, recovery times and complications were assessed. No important side effects were attributable to either premedication.

Results: Slightly higher percentage of patients became tearful on separation from their parents and when facemask was applied with ketamine. Over all both drugs offered similar chemical characteristics when used as oral premedicants, although the time to discharge from hospital was more rapid after midazolam than after ketamine.

iv) Malinovsky M, Poplaire C, Cozain A, Lepage JY, Lejus C, Pinaud Min 1995[27] conducted a study to determine the time and plasma drug concentrations necessary to achieve a similar state of sedation offered by midazolam premedication given by different routes in children 2-5 years old, 30 children were randomly assigned into three groups to receive midazolam 0.2mg/kg intranasally, 0.5mg/kg orally or 0.3mg/kg given rectally. Sedation was measured regularly until venepuncture was possible in a co-operative child. Blood sample for plasma concentration was taken, followed by another sample 10 minutes later. Anaesthesia consisted of IV propofol supplemented with regional analgesia. Adequate sedation occurred sooner (7.7 SD 2.4 min) with intranasal than oral (12.5 SD 4.9 min) or rectal (16.3 SD 4.2 min) midazolam. The initial blood levels were lower when the drug was given by the alimentary routes despite higher doses (146 SD 51 $ngml^{-1}$ in 11.5 SD 3.9min; - SD 34$ngml^{-1}$ in 21 ± 6 min and 93 SD 63 $ng.ml^{-1}$ in 23.1 SD 3.5 min for intranasal, rectal and oral routes respectively).

Results: They concluded that, oral and rectal administration of midazolam induced sedation in a similar time, but intranasal route shortened this onset time. Effect of tab midazolam orally and sublinguallv in a dose of 7.5 mg in one hundred ASA physical status I and II gynaecological patients posted for elective surgery was studied28. The sedation scores in the sublingual group were higher than in the oral group at 30 and 60 minutes

after drug administration. The main disadvantage of this method is related to the bitter taste of the tablet which is easier to mask in adults than the paediatric patient.

v) Kain Zeev N, Hofstadter Maura B, Mayes Linda C, Krivutza Dawn M, Alexander Gerianne, Wang Shu-Ming et al. (2000)[5] studied on the effects on amnesia and anxiety in children, premedicated with oral midazolam 0.5mg/kg was reported. Complete baseline memory testing was done using a validated series of picture cards on a group of children undergoing general anaesthesia and surgery. They were randomly assigned to 3 midazolam groups and a control groups. A second memory test using picture cards was done exactly 5, 10 or 20 minutes after receiving oral midazolam or 15min after receiving placebo. Anxiety of children was assessed during induction of anaesthesia along with postoperative recall and recognition for picture cards seen during baseline testing and postintervention testing. It was concluded that significant anterograde amnesia is produced with oral midazolam when given as early as 10 minutes and significant anxiolysis as early as 15 ± 4 minutes before a surgical procedure. **Sethi N, Dash, LK Madhusudanan TP in 2001** [29] compared 0.5 mg/kg oral midazolam with 6mg/kg oral ketamine as premedicants in 60 children, aged 1-7 years scheduled for elective surgery. They were evaluated preoperatively for acceptance of the premedicant, sedation and anxiolysis scores, separation from parents and cooperation at induction besides change in pulse, respiration and oxygen saturation. Postoperatively they were assessed for recovery time, vomiting and emergence phenomena. It was seen that 90% and 15% of children in midazolam group had satisfactory separation and became tearful on face mask application respectively as compared to 70% and 35% in ketamine group. They concluded that midazolam is a safe and more efficacious oral premedicant in children with shorter recovery time as compared to ketamine.

Efficacy, safety and taste acceptability of three doses (0.25, 0.5 and 1mg/kg of Commercially prepared midazolam HCL syrup in children stratified by age (6 month 2years, 2 to < 6 years and 6 to < 16years) was studied30 recently. All children were ASA class I-III scheduled for elective surgery. It was found that 95% of patients accepted the syrup. 88% satisfactory anxiety ratings at the time of attempted separation from parents and 86% had satisfactory anxiety ratings at face mask application. The youngest age group recovered earlier than the two older age groups. There was no relationship between the midazolam dose and duration of post anaesthesia care unit stay. It was finally concluded that the commercial oral midazolam syrup is effective in doses as small as 0.25 mg/kg with little advantage gained by doubling or quadrupling the dose.

It was demonstrated that oral midazolam with an antacid increases the speed of onset of sedation in children prior to general anaesthesia significantly by a difference of almost 30-40% (6-8 min).The proposed mechanism of action in rapid onset was attribute to imidazole ring closure of midazolam with an antacid such as sodium citrate due to a higher pH of the premedicant mixture and gastric contents.

vi) Gutstein Howard B, Johnson Kristein L, Heard Maurine B, Gregory George A, in1992[9] sought to define a dose of oral ketamine that would facilitate induction of anesthesia without causing significant side effects. 45 children (ASA physical status 1 & 2; aged 1-7 years) were assigned randomly in a prospective, doubleblind fashion to 3 separate groups.

- Group-1 patients received 3mg/kg of ketamine orally mixed in 0.2ml/kg of cola flavoured soft drink.
- Group-II –Received 6mg/Kg of ketamine mixed in cola drink.
- Group-III- received cola- flavored soft drink without ketamine.

Patients were evaluated for acceptance of oral ketamine as a premedicant reaction to separation from parents, emotional state and emergence phenomena. The 6mg/kg dose was well accepted; provide uniform, predictable sedation within 20-25 min and allowed calm separation from parents and good induction condition. The 3mg/kg dose did not always cause sedation and calm separation from parents. Neither dose of ketamine increased the incidence of laryngospasm, prolonged recover time or caused emergence phenomena. No episodes of respiratory depression, tachycardia or arterial Hb desaturation were detected before, during or after surgery.

vii) Alderson PJ, Lerman J in 1994[34] compared the clinical characteristics or oral ketamine and oral midazolam. 40 children 1-6 years of age who were scheduled for ambulatory dental surgery, were assigned to receive either oral midazolam 0.5mg/kg or oral ketamine 5mg/kg. They found that both drugs effectively sedated the children within 20 min of administration.No important side effects were attributable to either premedication. Discharge from the day surgery unit was slightly delayed in ketamine group compared with midazolam group.

viii) Sekerci S, Donmez A, Ates Y, Okten F in 1996[36] compared 3mg/kg and 6mg/kg doses of oral ketamine to a placebo control in paediatric premedication. 43 children aged 2-9 years were randomly allocated to receive either ketamine (3 or 6mg/kg) or placebo (cola 0.2mg/kg).Oral use of ketamine made separation from the families easier, gave an increased level of sedation, made acceptance of mask easier and improved the emotional state in the recovery phase. 3mg/kg dose of ketamine was found to be as effective as 6mg/kg but had a decreased incidence of side effects such as nystagmus and vomiting.

ix) Humphries Y, Melson M, Gore D in 1997[37] administered either ketamine oral suspension or 300 mg acetaminophen with codeine phosphate and diphenhydramine to 10 paediatric patiens with burns undergoing a

wound care procedure for analgesia and sedation. They demonstrated more than 400% reduction in pain and improved sedation by 360% with the use of ketamine.

x) Bachenberg Kenmeth L in 1998[38] reported successful use of oral ketamine as premedication in violent or uncooperative autistic adults on two occasions. In the first case, a 19 year old 118 kg autistic man with history of violent behaviour who came to the outpatient surgery department for removal of an infected toe nail was administered 5mg haloperidol and 600mg ketamine in a small amount of cocacola. The patients became sedate during the next 20 min. In the operating room the patient was managed with general anaesthesia combined with local anaesthesia. In the recovery room, patients remained cooperative and quiet during the two- hour recovery period.

In the second case, a 35 years old 60 kg male came to the outpatient surgery department for dental reconstruction and cleaning. He was agitated even after two doses of triazolam 0.25 mg. He was then administered 600mg of ketamine in cocacola. Within 20 min, patient was sedate and co-operative. In the operating room patient received general anaesthetia for three hours. Recovery was uneventful and no complications were noted.

xi) Raghu Raman TS & J in 1999[39] evaluated the efficacy of oral ketamine as a sedative in children undergoing painful invasive procedures and to determine the adequate dosage of ketamine. Ketamine was given orally diluted in 0.3ml/kg of 25% dextrose in a dosage ranging from 6 to 10 mg/kg.

- Group A (first 25 cases) received a dose of 6mg/kg.
- Group B (the second 25 cases) received a dose of 8 mg/kg.
- Group C (The last 25 cases) received a dose of 10 mg/kg.

Children given 10 mg/kg of ketamine showed no resistance to procedure as compared to children on either 6 or 8mg/kg of ketamine. The recovery time was independent of administered dosage of ketamine. There was no significant difference between the 3 groups in respect of side effects. The emergence phenomenon noted in 6 children was only moderate in the form of agitation and restlessness; none required any drug therapy. Children with hypersecretions remained capable of clearing the airway and responding appropriately throughout the procedure. 3 children had transient and mild increase in systolic BP, returning to normal without any medication. There were no other cardiovascular abnormalities and no cases in which hypoxia occurred clinically.

xii) Gupta PK, Deshmukh HB, Gurunath in 1999[40] studied on 60 children aged between 1 and 8 years (ASA I and II) posted for various operative procedures received a placebo or ketamine (6mg/kg) orally. It was observed that satisfactory sedation was rapidly achieved with oral ketamine and led not only to a calm separation of children from their parents but also a smooth induction of anaesthesia. In 60% patients IV cannulation could be achieved before induction of anaesthesia. No untoward cardiovascular or respiratory effects or any psychotomimetic effects were observed.

xiii) Auden SM, Sobezyk WL, Solinger RE, and Goldsmith LJ in 2000[41] compared I.M combination of meperidine, promethazine and chlorpromazine (DPT) to oral (PO) ketamine/midazolam in children having cardiac catheterization. 51 children, aged 9 months to 10 years were randomized in the double blind study. Ketamine/ midazolam given PO were better tolerated, had more rapid onset and provided Superior sedation. Heart rate and shortening fraction were stable. Oxygen saturation and mean arterial pressure decreased minimally in both groups. Parental satisfaction ratings were higher and amnesia was more reliably obtained with PO ketamine / midazolam. Two patients needed airway support after the premedication, as did two other patients when PO ketamine/midazolam was supplemented with IV propofol.

xiv) Young PA, Kendall JM in 2001[42] evaluated the efficacy of oral ketamine (10mg/kg) with oral midazolam (0.7 mg/kg) in providing sedation for suturing of lacerations was compared. They did a prospective, randomized, double blinded trial with 59 children aged 1 to 7 years with wounds requiring local anaesthetic (LA) injection or topical LA with an anxiety score more than one. Tolerance to LA injection was better with ketamine and tolerance to procedure after LA injection showed a trend towards being improved with ketamine. Time to reach a sedation score of less than 4 was faster with ketamine but times from dosing to discharge were similar. Dysphoria was not noted but vomiting was more common with ketamine but not significantly so. Oxygen desaturations were noted in both groups. Ataxia after discharge was seen in 2 patients in each group. 36% of children showed new behavioural disturbances in the 2 weeks after discharge, more commonly in the midazolam group.

xv) Horiuchi T, Kureharak, Kitaguchi K, Furuya H in 2001[43] Eavluated Lollipop containing ketamine (50mg) for premedication of 12 children aged from 1 year 7 months to 6 years. They received the lollipop and showed relatively good emotional state and no typical side effects.

xvi) Loken P, Bakstad OJ, Fonnelop E, Skogedal N, Hellsten K, Bjerkelund CE et al. In 1994[45] aimed to assess conscious sedation combined with local anaesthesia, as an alternative to general anaesthesia and further to evaluate the effects of addition of a low dose of ketamine to rectally administered midazolam, 24 children (aged 2-7 years) were given either midazolam 0.3mg/kg body weight or midazolam (0.3mg/kg bwt) plus

ketamine (1mg/kg bw). They found out that the feasibility of dental treatment was rated as excellent or good for 16 of 24 children when premedicated with midazolam and for 18 of 24 children when ketamine was added to midazolam amnesia and drowsiness were significantly increased and relief of anxiety and prevention of pain was better with combination. But there were large variations in the children's response to the drugs. Midazolam significantly reduced blood oxygen level, but not with ketamine added.

xvii) Roelofse JA, Joubert JJ, Roelofse PG in 1996[46] assessed the safety and efficacy of sedation technique for children having dental procedures under local anaesthesia, one hundred children aged 2 to 7 years were administered either a combination of midazolam (0.35mg/kg) and ketamine (5mg/kg) or midazolam alone (1mg/kg) rectally 30 minutes before removal to the dental chair. Satisfactory sedation and anxiolysis were achieved with both drugs used in the study. When evaluating post operative recovery, statistically significantly more children receiving midazolam alone were fully awake on admission to recovery room and 30 minutes later. Excessive salivation occurred in 26% of children receiving the combination of drugs compared with 14% receiving midazolam alone. 14% of children receiving the combination of drugs hallucinated, compared to 42% receiving midazolam alone. It was concluded that the use of a combination of midazolam and ketamine or midazolam alone is a safe, effective and practical approach to managing children for minor dental procedures under local anaesthesia.

xviii) Funk W, Jacob W, Riedl T, Taeger K in 2000 [20] investigated that addition of low dose oral ketamine 3mg/kg with midazolam 0.5mg/kg resulted in better premedication compared with oral midazolam 0.5mg/kg or ketamine 6mg/kg alone in a prospective, randomized double blind study. Here 120 children aged 2-10 years undergoing surgery of more than 30minutes duration was studied. After oral pre medication in the ward and transfer, the childs conduct in the induction room was evaluated by assigning 1-4 points to the quality of anxiolysis, sedation, behaviour at separation from parents and during venepuncture (transfer score). The transfer score was significantly better in combination group (12.5) than in the ketamine (10.6) or midazolam (11.5) groups. Success rates for anxiolysis and behaviour at separation were greater than 90% with the combination, approximately 70% with midazolam and only 51% with ketamine alone. Vertigo and emesis before induction were significantly more frequent after ketamine premedication. During recovery, there was no difference in sedation or time of possible discharge. After 1 week, parents reported nightmares–ketamine 5, midazolam 3 and combination 1, restless sleepketamine 5, midazolam 4, combination 4 or negative memories- ketamine 3, midazolam 4 and combination 1. It was concluded that significantly better anxiolysis; and separation from parents were observed with the combination. Duration of action and side effects of the combination were similar to those of midazolam

xix) Pan AK, Rudra A, Ghosh M, Biswas BN, Sen A, Kar A [47] evaluated sixty children of ASA grade I and II, aged between 3 and 8 years were enrolled randomly in observer blinded fashion into 3 different groups. Each group received midazolam 0.5mg/kg or ketamine 5mg/kg or combination of midazolam (0.25mg/kg) with ketamine (2.5mg/kg) po, 30 minutes before induction of anaesthesia. Children were evaluated preoperatively acceptance of premedication, sedation, separation from parents, response to intravenous cannulation and acceptance of face mask. It was found that the combination of midazolam plus ketamine provides good acceptability and predictable sedation within 30 minutes of administration. Smooth separation from parents was not found in the group. Intravneous cannulation was significantly uneventful with midazolam. Mask acceptance was better with midazolam or ketamine given alone. The incidence of side effects like nystagmus was higher with ketamine given alone. No respiratory distress, tachycardia or poor arterial saturation was noted perioperatively in all 3 groups. It was concluded that midazolam 0.5mg/kg or combination of midazolam 0.25mg/kg plus ketamine 2.5 mg/kg provides better pre medication in children than ketamine 5mg/kg when given orally 30 minutes before induction of anaesthesia.

xx) Turhanoglu S, Kasarmaz A, Ozyilmaz MA, Kaya S, Tok D in 2003 [48] defined the dose of oral ketamine that would facilitate induction of anaesthesia without causing significant side effects, 80 children undergoing elective surgery under general anaesthesia received oral ketamine 4, 6 or 8 mg/kg in a prospective randomized, double blind placebo controlled study. It was found that reaction to separation from parents, transport to the operating room, the response to intravenous cannula insertion and application of anaesthetic face mask was significantly calmer in the group receiving ketamine 8mg/kg and anaesthesia induction was more comfortable. Recovery from anaesthesia was however longer in this group.

Xxi) Vergheese ST, Hanallah RS, Patel RI, Patel KM in 2003 [49] studied the effects of intramuscular ketamine alone or combined with midazolam, on mask acceptance and recovery in young children who were uncooperative during induction of anaesthesia. It was concluded that ketaminemidazolam combination is not appropriate for preinduction of anaesthesia in paediatric ambulatory patients because of unacceptably prolonged recovery and delayed discharge times.

Xxii) Horuichi, Kawaguchi M, Kurehara K, Kawaguchi Y, Sasaoka N, Furuya H in 2005[51], the efficacy oral transmucosal ketamine (Lollipop) was compared with oral midazolam for premedication in children. Here 55 children, 2 6 years of age were randomized to receive orally either lollipop containing 50 mg of ketamine or

syrup containing 0.5mg/kg of midazolam before minor surgery. It was found that sedation, separation from parents and mask co-operation was significantly lower in ketamine group. It was concluded that, a relatively low dose of oral transmucosal ketamine premedication provides no benefits over oral midazolam in children.

xxiii) Ghai B, Grandhe RP, Kumar A, Chari Pin 2005 [52] compared the efficacy of oral midazolam alone (0.5mg/kg) with a low dose combination of midazolam (0.25mg/kg) with ketamine (2.5 mg/kg) orally concluded that both midazolam alone and the combination provide equally effective anxiolysis and separation characteristics. However the combination provided more children in awake, calm and quiet state who could be separated easily from parents.

xxiv) R Remadevi, P Ezhilarasu, L Chandrasekar, A Vasudevan in 2008 conducted a study on Comparison of Midazolam and Ketamine as Oral premedicants in pediatric patients.

Background: Preanesthetic medication plays an important role in the anesthetic care of children by allaying anxiety, decreasing vagal stimulation and preventing postoperative psychological sequelae. Midazolam and Ketamine are used by oral route as premedicants in pediatric anesthesia.

Materials and Methods: This study was undertaken to compare the two drugs. Fifty children in the age group of 1 to 7 years posted for elective surgical procedureswere randomly allocated to one of two groups – 'Group K' and 'Group M'. Group K received Ketamine 6 mg.kg-1 p.o. and Group M received Midazolam 0.5 mg.kg-1 p.o.Drug acceptance was noted.Heart rate, arterial pressure, respiratory rate, sedation score, anxiolysis score were notes before drug administration, 15 min and 30 min after drug administration. Parental separation score at 30 min and mask acceptance score were also noted. Sedation scores and anxiolysis scores between the groups were compared by MannWhitney test; Parental separation, drug acceptance and mask tolerance were analysed by Fisher's exact test. A 'p value' of < 0.05 was considered statically significant.

Results: Sedation score, anxiolysis score and mask acceptance score were significantly higher in Group-K than in Group-M (p<.05). Hemodynamic parameters, parental separation and drug acceptance were similar in both groups.Conclusion: Ketamine 6 mg.kg-1 p.o. is a better premedicant than Midazolam 0.5 mg.kg-1 p.o. in pediatric patients. Optimum time interval for parental separation is 30 minutes after administration of preanesthetic medication.

Xxv) Sreyashi Sen, Rajarshi G Thakurta, Sampa D Gupta in Preoperative anxiolysis in pediatric population: A comparative study between oral midazolam and oral ketamine effective infraumbilial and peripheral surgeries were randomized into two groups of 35 each to receive either midazolam (0.5 mg/kg) or ketamine (5 mg/kg) orally. They were assessed at an interval of 5 minutes up to 40 minutes at the time of parental separation, intravenous cannulation and application of face mask for ventilation.sedation was noted according to Ramsay sedation scale and anxiolysis was noted according to anxiolysisscores used in previous published studies elective infraumbilical and peripheral surgeries were randomized into two groups of 35 each to receive either mi dazolam.

PATIENTS AND METHODS

Study setting and design : The study was approved by the hospital ethical committee of GSL Medical College and Hospital. Informed consent was obtained from all the patients to take part of this study.

This study was conducted on patients admitted to G.S.L.Medical College and Hospital, Rajahmundry, during the period from November 2013 to October 2015, with co-operation from Departments of General Surgery, ENT and Orthopaedics.

150 patients of ASA grade I and II of either sex aged between 2-10 years were included in this study. Children undergoing surgical procedure between 20 minutes to 2 hours duration were selected for the study. The children were divided into three groups of 50 each randomly.

STATISTICAL ANALYSIS

Statistical analysis was performed by using SPSS software trial version 21.0 and MS Excel 2007. Descriptive statistical data was presented as mean ± standard deviation and percentages. Chi-square test was performed to assess the association among different categorical variables.

For all statistical analysis, $p<0.05$ was considered as statistically significant.

Children of group A received midazolam 0.5mg/kg orally

Group B received ketamine 6mg/kg orally and

Group C received midazolam 0.5mg/kg + ketamine 3mg/kg orally

The premedicant was prepared using orange syrup as a carrier 0.5ml/kg upto a maximum of 10ml. This was administered to children 30 minutes before induction.

Those children who refused to take the whole dose were excluded from further analysis. The child's condition was evaluated just before induction by the surgeons with a scale assigning a score of 1 to 4 to the quality of sedation, anxiolysis and behaviour at parental separation, while side effects were assessed by the anaesthetist

conducting the case. All observers including anaesthesiologists, surgeons and nurses were blinded about the contents of the oral premedicant.

Inclusion criteria:

- Patients coming for elective major or minor surgeries under general or regional anaesthesia
- Age 2-10 years
- ASA grade I and II.

Exclusion criteria:

- ASA grade III and IV
- Extremes of age
- Recent stressful life event
- History of prematurity and chronic illness
- History of developmental delay
- Increased intracranial pressure
- Increased intra ocular pressure
- Valvular heart disease
- Psychiatric disturbances

Drugs and dosage:

In the preoperative room, baseline recordings of heart rate, respiratory rate, systolic blood pressure and activity of child were noted.

In our study 150 cases were divided into three groups of 50 each.Group A received midazolam 0.5 mg/kg oral. Group B received ketamine 6mg/kg orally and group C received a combination of midazolam 0.5mg/kg and ketamine 3mg/kg orally. This was given with orange syrup 0.5ml/kg to mask the bitter taste of the drug, 30 minutes before induction of anaesthesia.

The children were evaluated for quality of sedation, anxiolysis and behaviour at parenteral separation; 30minutes after administration of the premedicant, side effects such as tachycardia, bradycardia, hypertension, hypotension, hypertonia, nystagmus, vomiting, involuntary movements, respiratory depression, apnoea, excitement, salivation, sweating and lacrimation were noted.

Children were observed for any signs of upper airway obstruction, respiratory Depression, apnoea and oxygen desaturation.

Pre-anaesthetic assessment:

All patients were visited and evaluated for fitness for the intended procedure and anaesthesia on the day prior to the surgery. During this visit, the procedure of the study planned was explained to the parents. An attempt was made to alleviate the anxiety of the patients. Parents were also instructed on the nil per oral guidelines. General clinical examination of the patient was performed including a general physical and systemic examination.

Laboratory investigations: The following laboratory investigations were performed on all the subjects in the Study.

Blood: Hb%, bleeding time, clotting time

HIV and HBsAg

Urine: Albumin, Sugar, and Microscopy

Chest x-ray: If required

Preoperative fasting:

No oral liquids upto 3 hours before the procedure

- Avoidance of milk or solids for 6 hours prior to the procedure.

Sedation was graded as follows –

Score 1: Alert

Score 2: Awake

Score 3: Drowsy

Score 4: Asleep

Anxiolysis was graded as follows –

Score 1: Panicky

Score 2: Moaning

Score 3: Composed

Score 4: Asleep, friendly

Behaviour at parenteral separation was graded as follows

Score 1: Combative, clinging to parents

Score 2: Anxious, consolable

Score 3: Calm

Score 4: Asleep

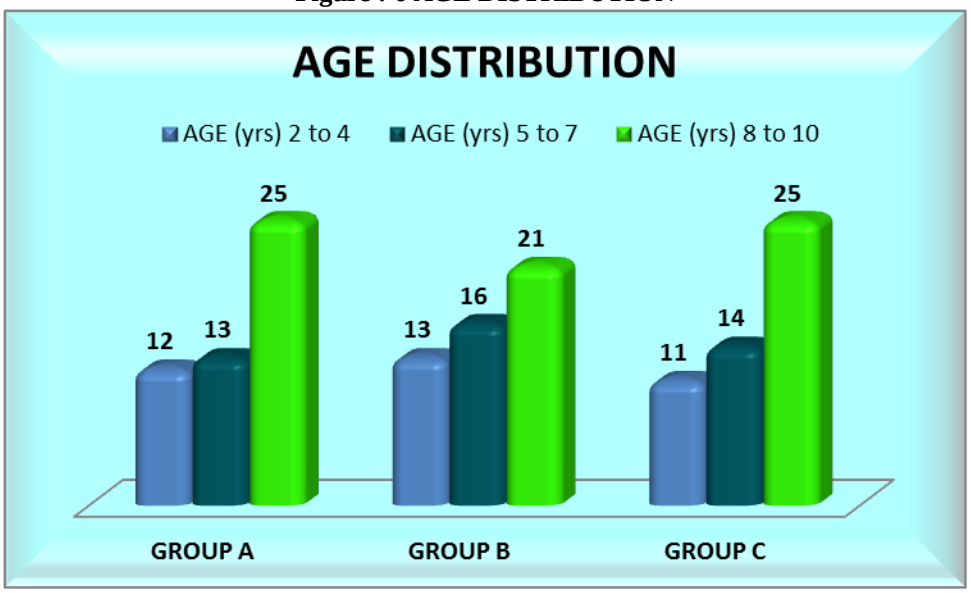
III. Observations And Results

A total number of 150 children were enrolled in this study. They were divided in to 3 groups of 50 each. Children in group A received oral midazolam 0.5mg/kg, while Children in group B received oral ketamine 6mg/kg and Children in group C received oral midazolam 0.5mg/kg and oral ketamine 3mg/kg.

Table-3 : AGE DISTRIBUTUION

AGE IN YEARS	GROUP A	GROUP B	GROUP C
2 to 4	12(33.3%)	13(36.1%)	11(30.6%)
5 to 7	13(30.2%)	16(37.2%)	14(32.6%)
8 to 10	25(35.2%)	21(29.6%)	25(35.2%)
TOTAL	50	50	50
MEAN±SD	6.81±2.79	6.46±2.62	6.77±2.47

Figure : 6 AGE DISTRIBUTION

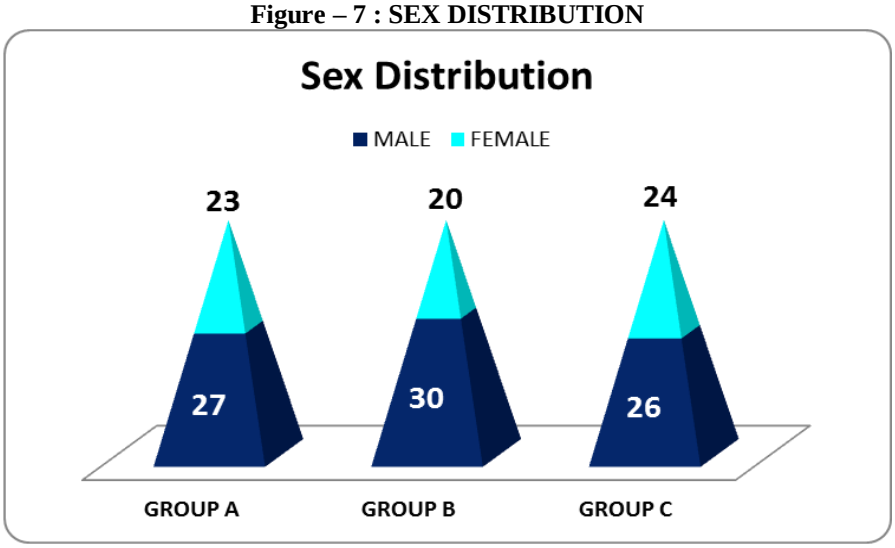


In group A there were 12(33.3%) children in the age group of 2-4 years, 13 (30.2%) children in the age group of 5-7 years, 25 (35.2%) children in the age group of 8-10 years. The mean age ±SD were 6.81 ± 2.79.
In group B there were 13 (36.1%) children in the age group of 2-4 years, 16(37.2%) children in the age group of 5-7 years and 21 (29.6%) children in the age group of 8-10 years. The mean age ± SD was 6.46 ± 2.62.
In group C, there were 11 (30.6%) children in the age group 2-4 years; 14 (32.6%) children in the age group of 5-7 years and 25 (35.2%) children in the age group of 8-10 yeas. The mean age ±SD was 6.77 ± 2.47.
There is no significant difference between the three groups with respect to age (p=0.918) as shown in table-3 and figure-6.

TABLE – 4 : SEX DISTRIBUTION

GENDER	GROUP A	GROUP B	GROUP C
MALE	27	30	26
FEMALE	23	20	24

Figure – 7 : SEX DISTRIBUTION

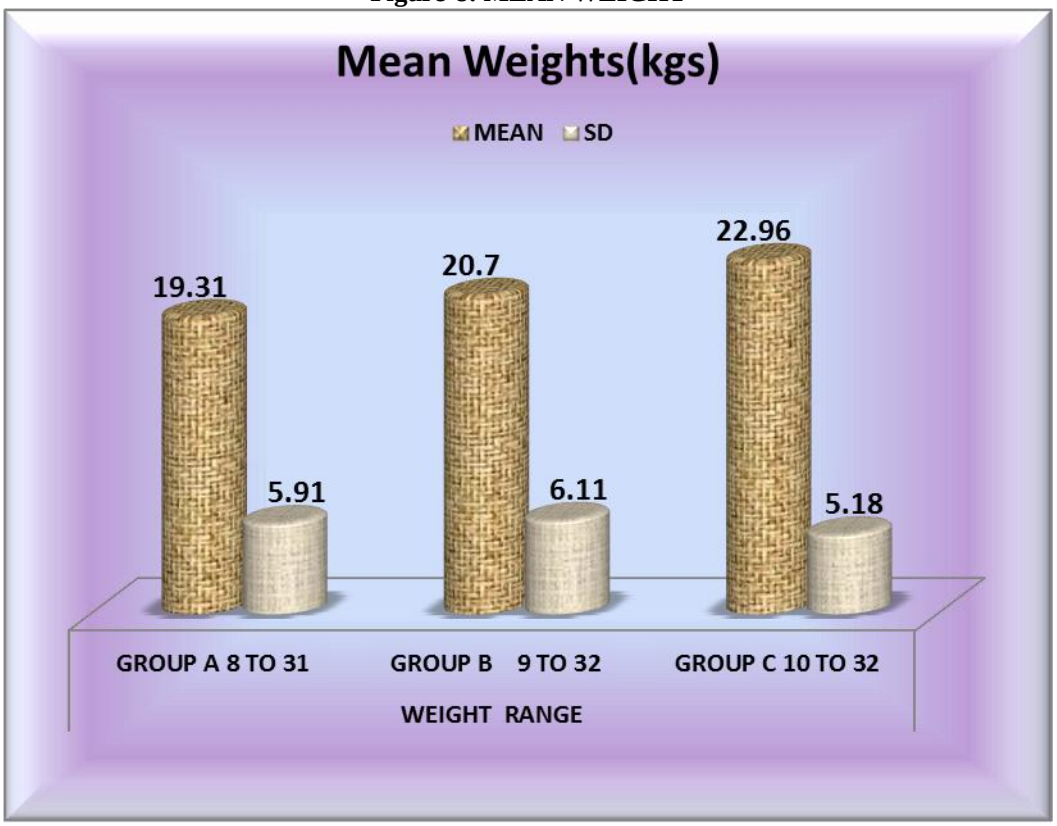


The three groups were comparable with respect to sex as shown in the table 4. Sex distribution is depicted as in the above figure-7.

TABLE-5 : WEIGHT

	GROUP A	GROUP B	GROUP C
RANGE	8 TO 31 kg	9 TO 32 kg	10 TO 32 kg
MEAN±SD	19.31± 5.91kg	20.7± 6.11 kg	22.96±5.18 kg

Figure-8: MEAN WEIGHT



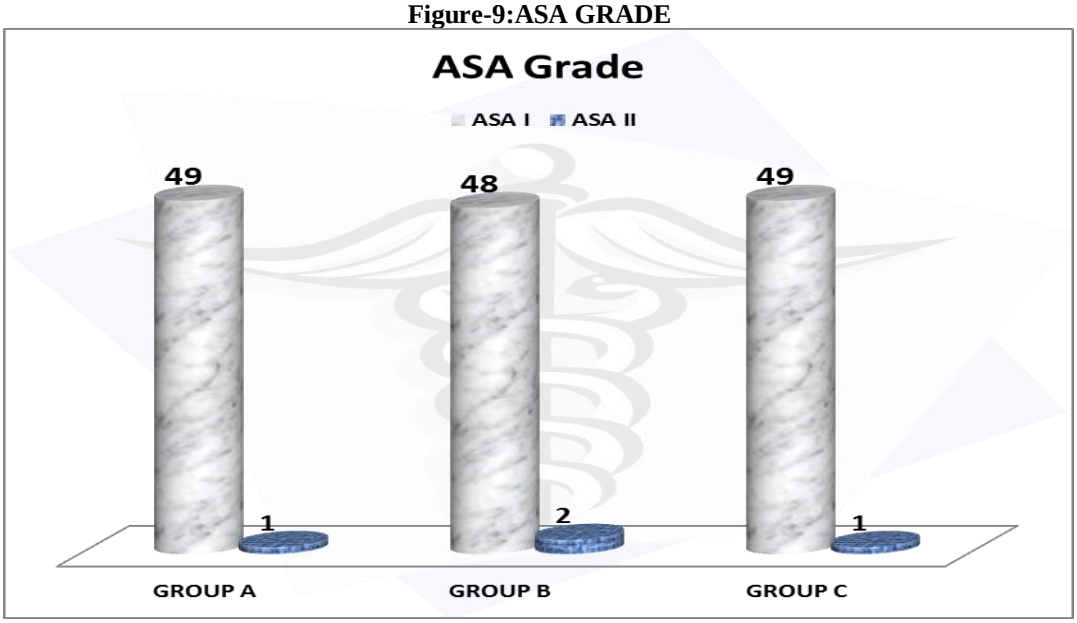
The weight of children ranged from 8-31 kgs in group A with mean 19.31±5.91.
Group B had children with weights between 9-32 kgs and mean of 20.7±6.11.
Group C also showed a range of 10-32 kgs with respect to weight with a mean of 22.96±5.18.

All the three groups show similar distribution with respect to weight.
Weight distributions of children in the groups are depicted as in the above table-5 and figure- 8.

TABLE-6 : ASA GRADE

ASA	GROUP A	GROUP B	GROUP C
I	49	48	49
II	1	2	1

Figure-9:ASA GRADE



Out of the total 150 children who were included in the study, 146 children belonged to ASA group I and 4 belonged to ASA group II.
Children belonging to ASA III and IV are not included in this study.
There is insignificant difference in ASA status of children among the groups, as shown in the table-6. The ASA distribution of children in the groups is depicted as in the above figure -9.

TABLE – 7 : COMPARISION OF SEDATION BETWEEN THE GROUPS

SEDATION SCORES	GROUP A	GROUP B	GROUP C
I ALERT	7(14%)	6(12%)	2(4%)
II AWAKE	13(26%)	19(38%)	12(24%)
III DROWSY	22(44%)	15(30%)	25(50%)
IV ASLEEP	8(16%)	10(20%)	11(22%)
TOTAL	50(100%)	50(100%)	50(100%)

TABLE : 8 COMPARISON OF ACCEPTABLE SCORES OF SEDATION BETWEEN THE GROUPS

SEDATION	GROUP A	GROUP B	GROUP C
ACCEPTABLE	30(60%)	25(50%)	36(72%)
UNACCEPTABLE	20(40%)	25(50%)	14(28%)

Figure-10: COMPARISION OF SEDATION BETWEEN THE GROUPS

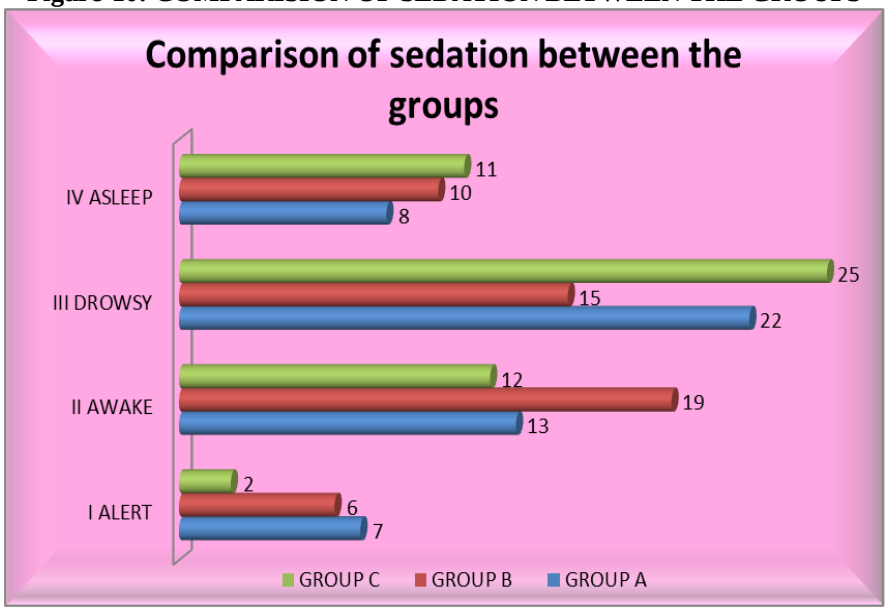
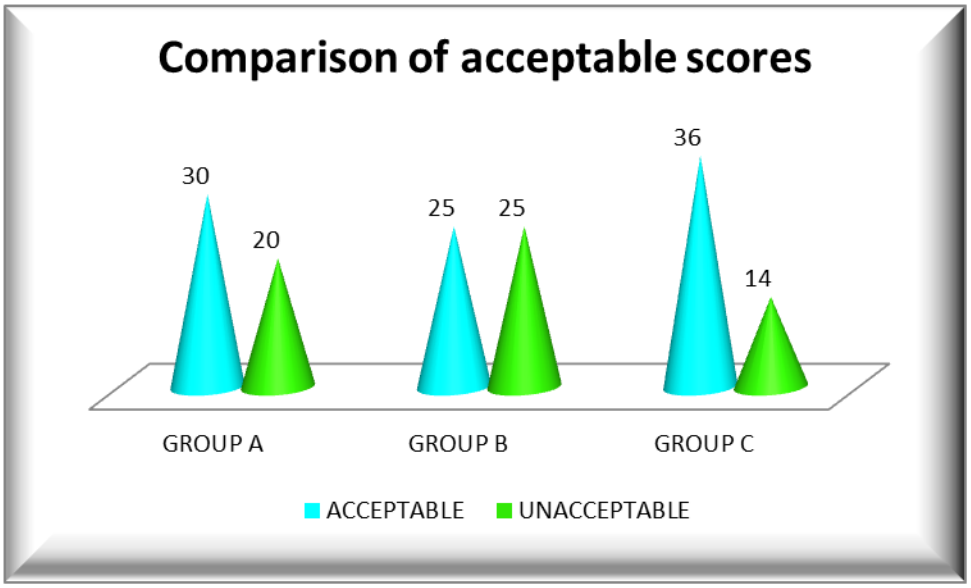


Figure-11: COMPARISON OF ACCEPTABLE SCORES OF SEDATION BETWEEN THE GROUPS



Sedation was assessed on a 4 point scale.
Score I was an alert child
Score II was an awake child
Score III was a drowsy child
Score IV represent a sleeping child.
In group A, a score of I was seen in 7 (14%) children while a score of II was seen in 13 (26%) children. A sedation score of III was seen in 22 (44%) patients while 8(16%) children showed a score of IV.
In group A, an acceptable sedation was obtained in 60% (30 of 50) children. Acceptability was defined as a score of III and IV.
In groups B, a sedation score of I was seen in 6(12%) children and a score of II in 19(38%) children .A score of III was seen in15(30%) children and 10(20%) showed a sedation score of IV.
In group B, an acceptable sedation was obtained in 50% (25 out of 50) children.
In group C, 2 (4%) children had a sedation score of I. 12 (24%) children had a sedation score of II and 25 (50%) children had a sedation score of III. A sedation score of IV was seen in 11(22%) children.
However, there is no significant difference between the three groups (p=0.254) as shown in the above tables 7, 8 and figures-10, 11.

TABLE-9: COMPARISION OF ANXIOLYSIS BETWEEN THE GROUPS

SCORE	GROUP A	GROUP B	GROUP C
PANICKY	5(10%)	8(16%)	1(2%)
MOANING	9(18%)	16(32%)	9(18%)
COMPOSED	32(64%)	22(44%)	26(52%)
ASLEEP	4(8%)	4(8%)	14(28%)
Total	50(100%)	50(100%)	50(100%)

TABLE- 10: COMPARISON OF ACCEPTABLE SCORES OF ANXIOLYSIS BETWEEN THE GROUPS

ANXIOLYSIS	GROUP A	GROUP B	GROUP C
ACCEPTABLE	36(72%)	26(52%)	40(80%)
UNACCEPTABLE	14(28%)	24(48%)	10(20%)

Figure-12: COMPARISION OF ANXIOLYSIS BETWEEN THE GROUPS

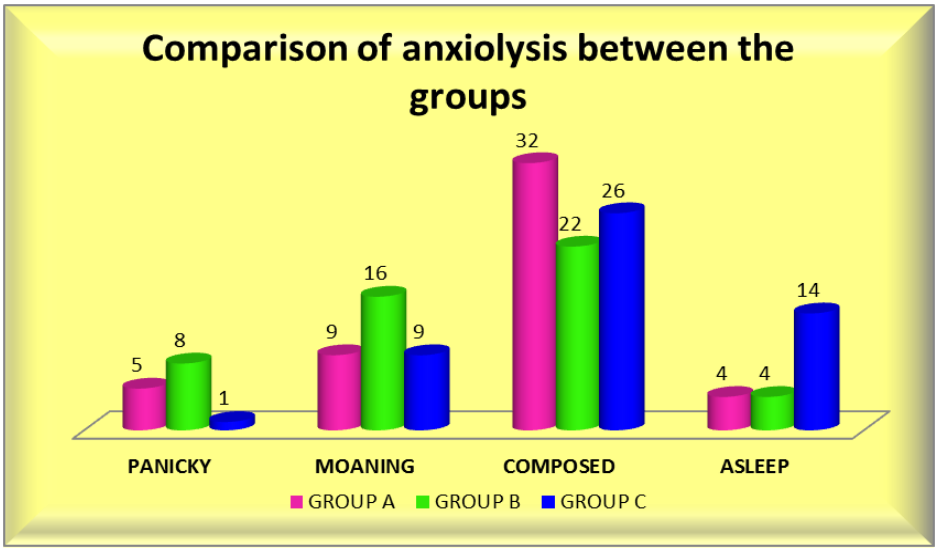
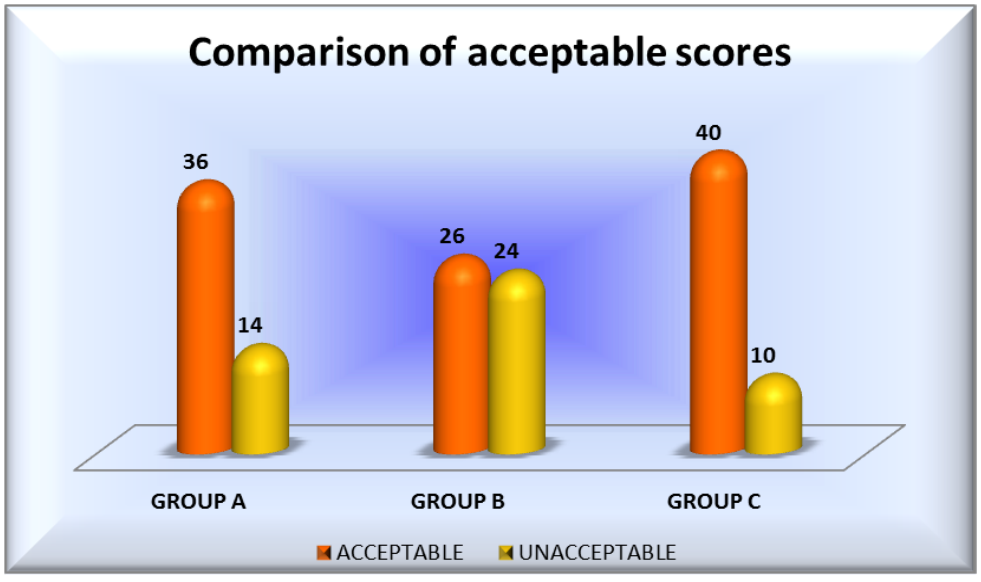


Figure-13: COMPARISON OF ACCEPTABLE SCORES OF ANXIOLYSIS BETWEEN THE GROUPS



Anxiolysis was similarly assessed on a 4 point scale.
Score I was a panicky child
Score II was child who was moaning
Score III was a composed child, while
Score IV was a steeping/ friendly child
In group A, an anxiolysis score of I was seen in 5 (10%) children a score of II Was seen in 9 (18%) children while a score of III was seen in 32 (64%) children. An anxiolysis score of IV was seen in 4 (8%) children.
In group A, acceptable anxiolysis was obtained in 72% (36 out of 50) children.
In group B, an anxiolysis score of I was seen in 8(16%) children while a score II was obtained in 16 (32%) children. 22 (44%) children had an anxiolysis score of III while only 4 (8%) children had a score of IV.
In group B, acceptable anxiolysis was obtained in 52% (26 out of 50) children.
In group C, 1 (2%) child had a score of I while 9 (18%) children had a score of II. 26 (52%) children had a score of III while 14(28%) children had a score of IV.
In group C, acceptable anxiolysis was seen in 80% (40 out of 50) children. Statistical studies show a significant difference between the three study groups (p=0.04) as a whole and between groups B and C, as shown in the above tables 9, 10 and figures-12, 13.

TABLE-11: COMPARISON OF BEHAVIOUR ON PARENTAL SEPERATION BETWEEN THE GOUPS

SCORE	GROUP A	GROUP B	GROUP C
I(Combative,clinging)	3(6%)	10(20%)	2(4%)
II(Anxious,Consolable)	14(28%)	15(30%)	7(14%)
III(Calm)	30(60%)	21(42%)	33(66%)
IV(Asleep)	3(6%)	4(8%)	8(16%)
Total	50(100%)	50(100%)	50(100%)

TABLE -12 COMPARISON OF ACCEPTABILTY OF BEHAVIOUR ON PARENTAL SEPARATION BETWEEN THE GROUPS

BEHAVIOUR	GROUP A	GROUP B	GROUP C
ACCEPTABLE	33(66%)	25(50%)	41(82%)
UNACCEPTABLE	17(34%)	25(50%)	9(18%)

Figure-14: COMPARISON OF BEHAVIOUR ON PARENTAL SEPERATION BETWEEN THE GOUPS

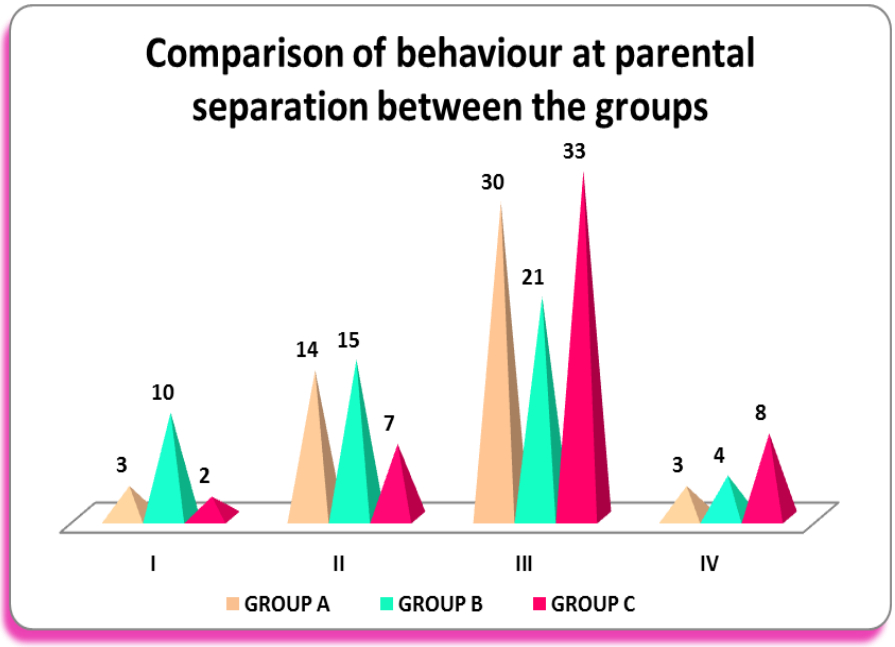
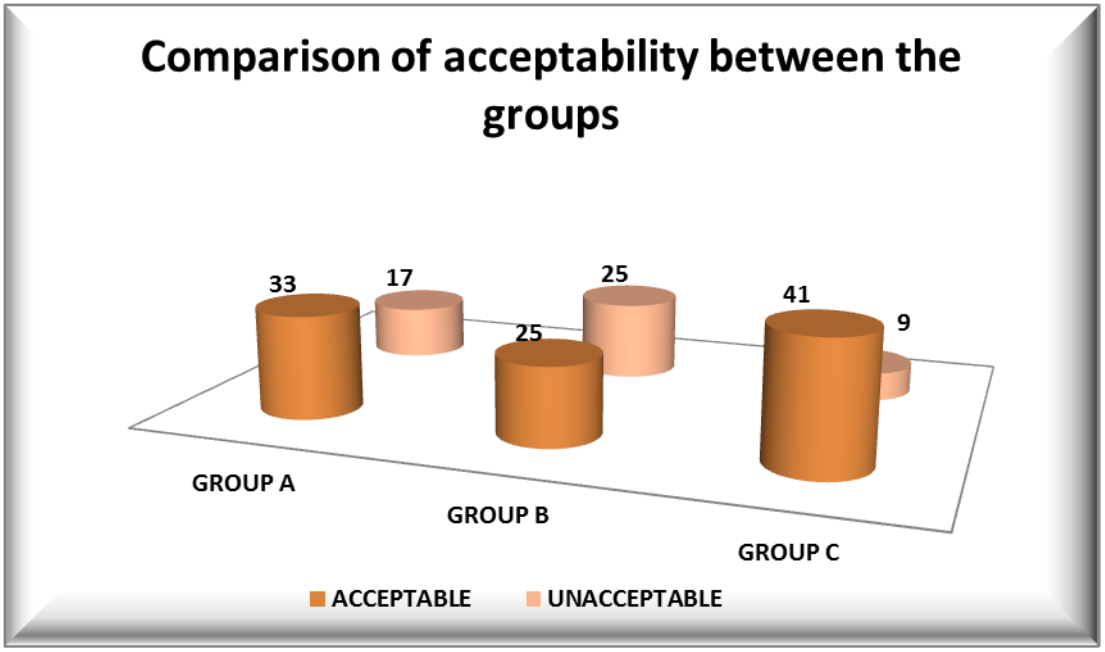


Figure-15: COMPARISON OF ACCEPTABILTY OF BEHAVIOUR ON PARENTAL SEPARATION BETWEEN THE GROUPS



Behavour at parental separation was also assessed by a 4 point scale.
Score I: A combative or clinging child, and
Score II: An anxious but consolable child
Score III: A calm child.
Score IV: A sleeping child.

In group A, 3 (6%) children had a score of I while 14 (28%) children had a score of II. A behaviour at parental separation score of III was seen in 30 (60%) of children. 3 (6%) had a score of IV.
In group A, an acceptable score for behaviour at parental separation was seen in 33 (66%) out of 50 children.
In group B, a behaviour at separation score of I & II was seen in 10 (20%) and 15 (30%) children respectively. .A score of III was seen in 21 (42%) children while a score of IV was seen in 4 (8%) children.
In group B, an acceptable score for behaviour at parental separation was seen in 25 (50%) children.
In group C, 2 (4%) children was having a score I while 7 (14%) children had a score of II. A score of III was seen in 33 (66%) children. 8 (16%) children had a score of IV.
In group C, an overall acceptable score for behaviour at parental separation was obtained in 41 (82%) children.
Significant difference on statistical analysis is seen between the three study groups (p=0.12) as a whole and between groups B & C as shown in the above tables 11, 12 and figure-14, 15.

TABLE -13: ADVERSE EFFECTS

ADVERSE EFFECTS			
	GROUP A	GROUP B	GROUP C
VOMITING	-	-	-
NYSTAGMUS	1	7	4
SALIVATION	4	3	4
TACHYCARDIA	3	6	5
BRADYCARDIA	1	-	-
EXCITEMENT	-	3	-
INVOLUNTARY MOVEMENTS	2	-	-
RESPIRATORY DEPRESSION	4	-	-

The side effects with midazolam, ketamine and the combination are shown in the above table 13.
Vomiting was not observed in any of the three groups. Nystagmus was seen in 7 children in group B while 1 children each in group A and 4 children in group C. salivation was also observed in 3 children in group B and 4

children in group A and group C. Tachycardia occurred in 6 children in group B while group A showed 3 and group C had 5 children with tachycardia. One child in midazolam group had bradycardia. Excitement was seen in 3 children in ketamine group. Involuntary movements were observed in 2 children in group A. 4 children in group A had respiratory depression which needed respiratory support for a short time.

IV. Discussion

Providing conscious sedation to facilitate parental separation in young children is often problematic. Many sedative analgesic agents and routes of delivery for facilitation of painful procedures have been studied, with varying degrees of patient acceptance, efficacy and safety but there is still no completely satisfactory way to pre-medicate children and ensure smooth induction of anaesthesia. Pre anaesthetic medication should relieve anxiety, reduce the trauma associated with separation from their parents and facilitate induction of anaesthesia without prolonging the recovery period.

The intravenous and intramuscular routes are traumatic. The disadvantages of intramuscular medications are that they are painful to administer and threatening to child, a sterile abscess may form and often the child remembers the shot they received.

The rectal route is marked by variable absorption, difficulty in predicting depth of sedation, and is often not well accepted by children. The absorption of drug through rectal route depends on the amount of faecal material present, the pH of medication administered.

The intranasal route is similarly marked by variable absorption, may be irritating to nasal mucosa and drugs administered may traverse directly into the central nervous system through the cribriform plate by traveling along the olfactory nerves.

Although various combinations of drugs and routes of administration have been used in children for preanaesthetic sedation, the oral route remains the least threatening method of drug administration[71]. The bioavailability of oral ketamine and oral midazolam are 10% -16% and 40% - 50% respectively due to extensive first pass hepatic extraction.

Both oral midazolam and oral ketamine fulfill many of the characteristics of ideal premedicants[34].

Studies have suggested that small amount of fluids given to children prior to general anaesthesia do not promote aspiration[9].

We did not administer oral atropine to reduce the salivary secretions because it imparts a bitter taste, delays gastric emptying and the time for peak decrease in salivation is 2 hours[72].

No placebo arm was included in our study since both midazolam[24,73] and ketamine[9] has been found to be superior to placebo for preanaesthetic sedation and anxiolysis and also because this was a comparative study to compare three different premedications.

Midazolam exerts a reliable dose dependent anxiolytic effect without oversedation and produces minimal cardiovascular and respiratory sideeffects. Also, the anterograde amnesia produced by midazolam should help to reduce the psychological effects of anaesthesia and surgery[74].

Ketamine also has well characterized sedative, anaesthetic and analgesic properties. It also has advantages over other sedative anaesthetic drugs, because it stimulates the cardiovascular system, is usually associated with an unobstructed airway and upper airway reflexes and cause minimum respiratory depression.

Age, Sex and Weight:

In the present study, children in the three groups were of 2-10 years of age with mean age of 5.7±2.6 years, weight of a mean of 19.12 kg with a male preponderance of 74%. This is in comparison; with studies conducted by W. Funk et al.20, who studied children in the age group of 2-10 years with a mean age of 5-7 years.

Prior studies have documented the effectiveness of 0.5mg/kg oral midazolam[3, 24]. Unfortunately, gastric absorption of midazolam is variable and results in large difference in the time it takes for different patients to become adequately sedated. The sedative effect of midazolam was found to be maximal at 30 minutes after oral administration in a study by Weldon BC et al[75]. McCluskey A et al[4], observed that oral midazolam 0.5mg/kg

promotes smooth and satisfactory induction of anaesthesia and reduces the psychological effects of hospitalization in children.

In another study[63], it was found that children given preoperative oral midazolam were less likely to cry and fight while being anaesthetized, and preoperative sedation was associated with increased incidence of adverse postoperative behaviour changes. McMillan Co. et al[24], compared three different doses of oral midazolam (0.5, 0.75 and 1mg/kg) and found all three to be equally effective in providing sedation and anxiolysis in children at the time of separation from parents 30 mts after premedication. Doses greater than 0.5mg/kg were found to be associated with more side effects.

Cote CJ[23] studied on preoperative preparation, premedication and various drugs and routes of administration stated that the dose of oral midazolam most commonly used is 0.5 - 0.75 mg/kg with a maximum dose of 15-20mg. This resulted in a satisfactorily sedated child in approximately 10-15 minutes with a peak effect occurring at approximately 20-30 minutes, with a minimal to no delay in recovery even for brief procedures.

Levine MF[26] evaluated the minimum time interval between oral midazolam premedication and a smooth separation from parents.30 children randomly assigned to 3 groups which differed only in time interval between drug administration and parental separation: 10, 20 or 30 minutes. Heart rate, systolic blood pressure, sedation and anxiolysis scores were assessed before premedication during separation and at induction of anaesthesia. Heart rate and systolic blood pressure changes were similar for all three groups throughout the study period. Sedation scores at separation did not differ among the three groups. Anxiolysis scores too did not differ from baseline values at any time for all three groups. The vital parameters, sedation and anxiolysis scores did not differ among the three groups. It was concluded that children may be separated from their parents as early as ten minutes after receiving oral midazolam 0.5 mg/ kg.

McCluskey A Meaken GH[4] Conducted a Study in 54 children aged 1-10 years who were prescribed either oral midazolam 0.5 mg/kg or a placebo preparation 30-60 minutes preoperatively. On arrival at the induction room, anxiolysis was satisfactory in 90% children who received midazolam compared with 44% who received a placebo ($P<0.001$). The time to early recovery from anaesthesia was longer in children premedicated with midazolam compared with controls ($P < 0.05$); so also, was the time to hospital discharge ($P< 0.01$).

The results indicate that midazolam premedication promotes smooth and satisfactory induction of anaesthesia, producing minimal cardiovascular and respiratory effects and reducing the psychological effects of hospitalization in children undergoing day care surgery.

TABLE- 14: Sedation scores with midazolam:

Study	Percentage of acceptable sedation
W. Funk et al[20]	58%
Suranjit Debnath et al[76]	36%
T.K. Howell et al[77]	81%
Marshall J, et al[61]	81%
Our study	60%

Satisfactory sedation we got in our study was 60% which corresponded well with that obtained by Funk W. et al[20] (58%) when 0.5 mg/kg midazolam was given.

TABLE- 15: Anxiolysis scores with midazolam:

Study	Percentage of acceptable anxiolysis
W. Funk et al[20]	75%
Y.C. Lin e tal[22]	66%
Lawrence H. Feld et al[3]	69%
Warner DL et al[35]	65%
Suranjit Debnath et al[76]	70%
P.J. Alderson et al[25]	80%
Our study	72%

W.Funk et al[20] in their study with 0.5mg/kg midazolam found to obtain an acceptable anxiolysis in 75% of children. Similarly studies by Lawrence H Field[3] et al and Warner DL et al[35] showed that 69% and 65% of

children were asleep or awake and calm at induction of anesthesia after receiving midazolam 0.5 mg/kg orally. We had a success rate of 72% which corresponds to the above studies.

TABLE- 16: Behaviour at Parental separation scores with midazolam:

Study	Percentage of acceptable parental separation
W Funk et al[20]	68%
PJ Alderson et al[25]	70%
Warner DL et al[35]	75%
Lawrence H Feld[3]	79%
YC Lin et al[22]	80%
Our Study	66%

Midazolam in the dose of 0.5mg/kg provided an acceptable behaviour at parental separation score in 72% of children in our study. W.Funk et al[20] in their study got a score of 68% for acceptable parental separation and PJ Alderson et al[25] also got a score of 70%.

Oral ketamine was used in the 1970's by dentists to facilitate the treatment of mentally handicapped children[20]. Only 16% of oral ketamine is bioavailable because of high hepatic first pass metabolism[21]. Parts of the clinical effects of oral ketamine are attributed to its metabolite nor-ketamine which has approximately one-third the potency, but reaches higher blood concentration. Gustein B et al[9] sought to define a dose of oral ketamine that would facilitate induction of anaesthesia without causing significant side effects. They compared oral ketamine in doses of 3mg/kg and 6 mg/kg with control.

They found that 6mg/kg dose was well accepted, provided uniform, predictable sedation, allowed calm separation from parents and provided good induction conditions. The 3mg/kg dose did not always cause sedation and calm separation from parents. Neither doses produced significant side effects.

Tohias et al[8] evaluated the efficacy of oral ketamine in alleviating procedure related distress in paediatric oncology patients. Ketamine 10mg/kg was administered orally to 35 children (mean age =6.5years).Procedure related distress was evaluated using parent/clinician ratings and the observational scale of behavioral distress (OSBD-R). 77% rated procedural distress as low and OSBD-R Scores were also low. Statistical comparison of OSBD-R scores of patients who received oral ketamine with those of his torical controls (using intravenous midazolam) showed significantly less distress during the procedure in children who received oral ketamine. No cardio respiratory side effects related to ketamine were noted. Majority of patients showed recovery from sedation within 2 hours following the procedure.

Increased nor-ketamine levels could explain the absence of emergence phenomena after oral administration, as compared to parenteral route. Serum ketamine levels necessary for analgesia is 150ng/ml. However, the peak serum ketamine level after ketamine is taken orally ranges from 35-55 ng/ml [14]. Nor-ketamine is the primary active metabolite of ketamine. It is one third as potent as ketamine. Due to high first pass hepatic metabolism, serum norketamine levels after oral ketamine are two to three times greater than those after parenteral ketamine. The peak analgesic effect of oral ketamine corresponds to the peak serum levels of nor-ketamine not ketamine. This suggests that nor-ketamine contributes significantly to the analgesic effects of oral ketamine. These increased amounts of norketamine relative to oral ketamine may account for part of the sedative effects observed and possibly the reduced incidence of side effects with oral administration. Thus oral ketamine appears to be better premedicant than oral midazolam in paediatric patients.

TABLE- 17: Sedation scores with ketamine:

Study	Percentage of acceptable sedation
W Funk et al[20]	47%
Navdeep Sethi et al[78]	75%
Joseph D Tobias et al[8]	77%
Suranjit Debnathet al[76]	77%
Our Study	52%

Funk W et al[20] in their study got an aceptable sedation score in 47% children who were given ketamine in dose of 6mg/kg. This corresponds well with our study in which we got an acceptable sedation score in 52% of children.

TABLE- 18: Anxiolysis scores with ketamine:

Study	Percentage of acceptable anxiolysis
W Funk et al20	54%
Warner DL et al35	42%
PJ Alderson et al25	65%
YC Lin et al22	73%
Our study	52%

Studies by Warner DL et al[35] showed an acceptable anxiolysis score in 42% of children while W Funk et al[20] had an acceptable score of 54% when 6mg/kg ketamine was given orally. This corresponds well with our result which showed an acceptable score in 52% of children with 6mg/kg ketamine orally.

TABLE- 19: Behaviour at Parental separation scores with ketamine:

Study	Percentage of acceptable behaviour sepration
W Funk et al [20]	50%
PJ Alderson et al[25]	65%
Navdeep Sethi et al[46]	70%
Our study	52%

Our studies showed an acceptable score for parental separation in 52% of children who were premedicated with 6mg/kg ketamine orally. This corresponds well with the studies by W Funk et al[20] and PJ Alderson et al[25] who got acceptable scores in 50% and 65% of children respectively.

The combination of ketamine and midazolam was described initially in 1992 by Bee be and coworkers[79] for rectal premedicatio n and in 1993 by Lin YC, et al[22] for oral administration. Both groups used a combination of midazolam 0.5mg/kg with ketamine 3mg/kg. In Beebe's study[79], separation was satisfactory with midazolam in 92%, cases and in 100% with the combination; but in only 60% with ketamine alone. Complications were low and similar between groups; but psychedelic side effects were not addressed. Lin YC, et al[22] reported no difference in separation with midazolam 0.75 mg/kg, ketamine 6mg/kg or the combination of 0.5 mg/kg and 3mg/kg respectively. Their success rates with combination were about 80% at separation, and the incidence of oral secretions and nystagmus was lesser as compared to ketamine. Warner et al[35] found the combination of midazolam 0.4 mg/kg and ketamine 4mg/kg to be significantly more effective than midazolam 0.5mg/kg or ketamine 6mg/kg alone. No psychological disturbances were noted in the immediate post operative period. The success rate for anxiolysis and separation was found to be >90% and only 70% for sedation with a combination of midazolam 0.5mg/kg and ketamine 3mg/kg by W Funk et al[20].

Young PA[42] conducted a clinical randomized and blind study on 120 patients aged between 2 and 6 years listed for minor surgery to assess the quality of premedication using oral ketamine with midazolam. Patients were divided into 3 groups.
Group MK 1 received midazolam 0.3mg/kg and ketamine 1mg/kg.
Group MK 2 received midazolam 0.3mg/kg and ketamine 2 mg/kg
Group M (control group) received 0.5mg/kg of midazolam.

More patients were successfully premedicated in MK2 group. This group accepted separation from parents and face mask for induction of anaesthesia more willingly. Side effects were observed in four MK2 group patients (nausea, vomiting and diplopia), but all these effects resolved spontaneously.

Roelofse [46] assessed the safety and efficacy of sedation technique for children having dental procedures under local anaesthesia, one hundred children aged 2 to 7 years were administered either a combination of midazolam (0.35mg/kg) and ketamine (5mg/kg) or midazolam alone (1mg/kg) rectally 30 minutes before removal to the dental chair. Satisfactory sedation and anxiolysis were achieved with both drugs used in the study. When evaluating post operative recovery, statistically significantly more children receiving midazolam alone were fully awake on admission to recovery room and 30 minutes later. Excessive salivation occurred in 26% of children receiving the combination of drugs compared with 14% receiving midazolam alone. 14% of children receiving the combination of drugs hallucinated, compared to 42% receiving midazolam alone. It was concluded that the use of a combination of midazolam and ketamine or midazolam alone is a safe, effective and practical approach to managing children for minor dental procedures under local anaesthesia.

Darlong V[50] conducted a randomized controlled trial to evaluate whether the combination of low dose oral midazolam (0.25mg/kg) or low dose oral ketamine (3mg/kg) provides better premedication than oral midazolam (0.5mg/kg) or oral ketamine 6mg/kg, seventy eight children of ASA I or II scheduled for elective ophthalmic surgery were randomly divided into three groups and given premedication in the holding area, 30 minutes before

surgery. It was found that – Onset of sedation was earlier in combination group at 20 mts 54% in combination, 21% in midazolam group and 16% in ketamine group. The mean time for best parenteral separation was significantly less with combination group. 19±8 min in combination group 28 ±7 min with midazolam and 29±7 min with ketamine group.Recovery was earlier with combination group 22±5 min than oral midazolam 36±11 min or ketamine 38±8 min. It was concluded that combination of oral ketamine 3mg/kg and midazolam 0.25mg/kg has minimal side effects, and given a faster onset and more rapid recovery than ketamine 6mg/kg or midazolam 3mg/kg for premedicated in children

TABLE- 20: Sedation scores with combination:

Study	Percentage of acceptable sedation
W.Funk et al[20]	70%
Ghai B. et al[52]	97.9%
Our study	68%

We got an acceptable sedation score in 68% children with a combination of midazolam 0.5mg/kg with ketamine 3mg/kg. This corresponds well with the studies of Funk W. et al20 who got an acceptable score in 70% children.

TABLE- 21: Anxiolysis score with combination:

Study	Percentage of acceptable anxiolysis
Y.C. Lin et al22	73%
Warner DL et al35	85%
W.Funk et al20	95%
Our study	82%

Y.C. Lin et al[22] in their study got an acceptable anxiolysis score in 73% of children while Warner DL et al[35] got an acceptable score in 85% of children. This corresponds well with our results (82%) when the combination of 0.5mg/kg midazolam was given with 3mg/kg ketamine.

TABLE- 22: Behaviour at parental separation score with combination:

Study	Percentage of acceptable parental separation
Ghai B. et al[52]	73%
Y.C. Lin et al[22]	80%
W.Funk et al[20]	90%
Our study	80%

We got an acceptable score for parental separation in 80% of children who were premedicated with the combination. This corresponds well with the studies of Ghai B et al[52] who got an acceptable behaviour at parental separation score in 73% of children. Lin et al[22] also got similar results in 80% of children.
In our study, there was no significant difference in sedation in the 3 groups, 30 minutes after receiving the study agents (p=0.254) as shown in table-7. This corresponds to the results obtained by Pan AK et al[47] and Funk W. et al[20] in their studies.

Also; both anxiolysis and behaviour at parental separation scores were significantly better in midazolam alone or in the combination group as shown in table 9 and 11 respectively. These results are similar to the results obtained by Funk W. et al[20] and Warner DL et al[35].

Side effects:
It has been suggested that oral, rather than intramuscular ketamine should produce less sideeffects because of different pharmacodynamics of its metabolite nor-ketamine.9 The sideeffects observed with orally administered ketamine in table 16 were of short duration and of minor significance.

However in our study, the incidence of preoperative nystagmus was 14% with ketamine and 2% each with midazolam alone and 8% with the combination. However, none of the children seemed distressed by the nystamgus. The reported incidence of nystagmus with ketamine ranged from 26% to 60%[9, 22] .An incidence of 13% for nystamgus with orally administered midazolam was mentioned by Lin et al[22].

Salivation was noted in 6% of ketamine group and 8% of combination group. However the observed salivation was not excessive to give an antisialogue with the premedication.

8% children in ketamine group developed hallucinations, which were alarming for parents. Such side effects were not noted in other groups. One child in ketamine group also developed involuntary movements. Addition of a minor transquillizer seems to be a logical answer to these problems and could at the same time broaden the pharmacologic profile. 10% children in combination group also showed tachycardia.

These sideeffects were similar to the results obtained by Pan AK et al[47] and were not clinically significant.

Limitations of our study were – (1) that our facility did not include specifically equipped child care area (2) only a few members of the anaesthesia team had long term experience in paediatric anaesthesia and (3) the scores used were similar and subjective.

Thus, the results of our study donot coincide with the previous studies which had found that adding a low dose ketamine to oral midazolam increased the success of premedication to more than 90% without increasing the side effects, or prolonging recovery. In our study, we found that the results produced by the combination of midazolam and ketamine were not significantly different from those of oral midazolam `alone with respect to behaviour at parental separation and anxiolysis. Although midazolam group showed lesser sedation as compared to the combination group it is no disadvantage as long as successful separation coincides with good anxiolysis.

V. Conclusion

The present study showed that oral premedication with midazolam 0.5mg/kg alone produces as good results as the combination of midazolam 0.5mg/kg and ketamine 3mg/kg in children. Although, midazolam 0.5mg/kg produced lesser sedation than the combination, it was no disadvantage as separation from parents was successful and coincided with good anxiolysis. The incidence of side effects was highest with ketamine 6mg/kg, especially nystagmus. The combination increased the cost factor, made preparation of premedication more complexes and produced higher incidence of tachycardia as compared to midazolam alone.
Even though, the combination did not produce statistically better sedation, anxiolysis or behaviour at parental separation than midazolam, the combination did produce distinctly better premedication characteristics than either midazolam or ketamine alone when given through oral route.

VI. Summary

This study entitled "Comparison of a combination of midazolam and ketamine with midazolam or ketamine alone as oral pre-anaesthetic medication for children", was intended to find out if addition of low dose oral ketamine to oral midazolam results in better premedication than either drugs given alone in children, presenting for various orthopaedics, ENT and general surgical procedures.
150 children of ASA grade I and II in the age group of 2-10 years were included in the study and were randomly divided into three groups of 50 each. All groups were comparable in age, weight and sex distribution.
Group A received 0.5mg/kg midazolam in 5ml orange syrup, group B received ketamine 6mg/kg while group C received a combination of oral midazolam 0.5mg/kg and oral ketamine 3mg/kg in orange syrup.
The main parameters studied were degree of sedation, anxiolysis and behaviour at parental separation after 30 minutes of giving premedication and preoperative side effects observed.
All parameters were studied using a 4 Point scoring system.
In group A, 60% children were adequately sedated and 72% children were having an acceptable anxiolysis and parental separatio n scores.
In group B, acceptable sedation, behaviour at parental separation was obtained in 50% children and 52% children had acceptable anxiolysis.
Group C shows an acceptable sedation in 72% children. Acceptable anxiolysis was observed in 80% of children. 82% children were calm with parental separation.
Side effects were mainly seen in ketamine group with 14% children showing nystagmus and 6% of children had excessive salivation. 8% children in ketamine group also developed hallucination.
Thus it was concluded that significantly better anxiolysis and separation were observed with a combination of ketamine and midazolam even in awake children, than with midazolam or ketamine alone.

References

[1]. Cravero Joseph P. and Jo Rice Linda.Paediatric anaesthesia. Chapter 44, In: Clinical anaesthesia, 4th edn, edt. Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting, 2001.p.1195.
[2]. Brzuskowicz Robert M, Nelson Dunkin A, Betts Eugene K, Rosenberry Kathleen R, Swedlow David B. Efficacy of oral premedication for paediatric out patient surgery. Anaesthesiology, 1984; 60: 475-77.
[3]. Feld LH, Negus JB, White PF. Oral midazolam preanaesthetic medication in paediatric out patients. Anaesthesiology, 1990; 73: 831-4.
[4]. McCluskey A, Meaken GH.Oral administration of midazolam as a premedicant for paediatric day-care anaesthesia. Anaesthesia, 1994; 49: 782-5.

[5]. Kain Zeev N, Hofstadter Maura B, Mayes Linda C, Krivutza Dawn M, Alexander Gerianne, Wang Shu-Ming et al. Midazolam effects on amnesia and anxiety in children. Anaesthesiology, 2000; 93: 676-84.
[6]. Morgan-Hughes JO and Bangham JA.Pre induction behaviour in children Anaesthesia, 1990; 427-35.
[7]. Tanaka M, Masayoshi S, Atsushi S, Toshiaki N.Re-evaluation of rectal ketamine premedication in children. Anaesthesiology, 2000; 93: 1217-1224.
[8]. Tohias Joseph D, Seanphipps, Bruce Smith, Raymond K. Mulhern.Oral ketamine premedication to alleviate the distress of invasive procedures in paediatric oncology patients. Paediatrics, 1992 Oct; 90(4): 537-41.
[9]. Gutstein Howard B, Johnson Kristen L, Heard Maurine B, Gregory George A. Oral ketamine pre-anaesthetic medication in children. Anaesthesiology, 1992; 76: 28-33.
[10]. Payne KA, Coetzee AR, Matheyse FJ.Midazolam and amnesia in paediatric premedication. Acta Anaesthesiol Belg, 1991; 42(2): 101-105.
[11]. Payne KA, Coetzee AR, Matheyse FJ, Dawes T.Oral midazolam in paediatric premedication. S.Afr Med J, 1991 Apr; 79(7): 372-5.
[12]. Parnis SJ, Foate JA, Van-der-Walt JH, Short T, Crowe CE.Oral midazolam is an effective premedication for children having day stay anaesthesia. Anaesthesia Intensive Care, 1992 Feb; 20(1): 9-14.
[13]. Payne KA, Coetzee Ar, Matheyse FJ, Heydenrynch JJ. Behavioural changes in children following minor surgery – is premedication beneficial? Acta Anaesthesiology Belg, 1992; 43(3): 173-179.
[14]. Patel D, Meakin G. Oral midazolam compared with diazepam, droperidol and trimeprazine as premedicants in children. Paediatr Anaesth, 1997; 7(45): 287-93.
[15]. Pywell Ca, Hung YJ, Nagelhout J. Oral midazolam versus meperidine, atropine and diazepam: a comparison of premedicants in paediatric outpatients. AANA J, 1995 Apr; 63(2): 124-130.
[16]. De-Witte JL, Alegret C, Sessler DI, Cammu G. Preoperative alprazolam reduces anxiety in ambulatory surgery patients: a comparison with oral midazolam. Anaesth Analg, 2002 Dec; 95(6): 1601-1606.
[17]. Singh N, Pandey RK, Saksena AK, Jaiswal JN.A comparative evaluation of oral midazolam with other sedatives or premedication in paediatric dentistry. J Clinic Paediatr Dent, 2002 winter; 26(2): 161-4.
[18]. 18. Cote Charles J.Paediatric anaesthesia.In Miller Ronald.D (editor), Miller's anaesthesia, 6th edn. NewYork: Churchill Livingstone, Vol.2, 2005 p.2367-2408.
[19]. Bowdle T. Andrew, Radant D. Allen, Cowley Deborah S, Kharasch Evan D, Strassman Rick J, Roy-Byrne Peter P. Psychedelic effects of ketamine in healthy volunteers. Anaesthesiology, 1998; 88: 82-8.
[20]. Funk W, Jacob W, Riedl T, Taeger K. Oral preanaesthetic medication for children double – blind randomized study of a combination of midazolam and ketamine Vs midazolam or ketamine alone. Br J Anaesth, 2000; 84 (3): 335-40.
[21]. Pan AK, Rudra A, Ghosh M, Biswas BN, Sen A, Kar A.Oral pre anaesthetic medication for children : A comparison of midazolam, ketamine and midazolam plus ketamine. J Indian Assoc Pediatr Surg, 2001; 6: 135-142.
[22]. Lin YC, Moynihan RJ, Hackel A comparison of oral midazolam, oral ketamine and oral midazolam combined with ketamine as pre anaesthetic medication for paediatric outpatients. Anaesthesiology, 1993; 70: A1177.
[23]. Cote CJ.Pre-operative preparation and premedication. Br J Anaesth, 1999; 83: 16-28.
[24]. McMillan CO, Spahr-Schopfer IA, Sikich N, Hartley E, Lerman J. Pre medication of children with oral midazolam. Can J Anaesth, 1992; 39(6): 545 50.
[25]. Alderson PJ, Lerman J A comparison of ketamine and midazolam as oral premedicants for ambulatory anaesthesia in children. Anaesthesiology, 1992; 77: A42.
[26]. Levine MF, Spahr-Schopfer IA, Hartley E, MacPherson B. Oral midazolam premedication in children: The minimum time interval for separation from parents. Can J Anaesth, 1993; 40(8): 726-9.
[27]. Malinovsky M, Poplaire C, Cozain A, Lepage JY, Lejus C, Pinaud M. Premedication with midazolam in children: effect of intranasal, rectal and oral routes on plasma midazolam concentrations. Anaesthesia, 1995; 50: 351-354.
[28]. Lim LW, Thomas E, Choo SM. Premedication with midazolam is more effective by the sublingual than oral route. Can J Anaesth, 1997; 44(7): 723-6.
[29]. Sethi N, Dash, LK Madhusudanan TP, Oral premedication for paediatric anaesthesia: a comparison of midazolam and ketamine. Ind J Anaesth, 2001; 45(3): 215.
[30]. Cote CJ, Cohen IT, Suresh S, Rabb M, Rose JB, Weldon BC, et al. A comparison of three doses of a commercially prepared oral midazolam syrup in children. Anesth Analg, 2002; 94: 37-43.
[31]. Lammers CR, Rosner JL, Crockett DE, Chhokra R, Brock-Utre JG.Oral midazolam with an antacid may increase the speed of onset of sedation in children prior to general anaesthesia. Pediatr Anaesth, 2002; 12: 26-28.
[32]. Grant IS, Nimmo WS, Clement JA.Pharmacokinetics and analgesic effects of IM and oral ketamine. Br J Anaesth, 1981; 53: 805-10.
[33]. Rosenberg Morton. Oral ketamine for deep sedation of difficult to manage children who are mentally handicapped: case report.Paediatric dentistry. 1991; 13(4): 221-23.
[34]. Alderson PJ, Lerman J. Oral premedication for paediatric ambulatory anaesthesia a comparison of midazolam and ketamine. Can J Anaesth, 1994; 41: 3: 221-6.
[35]. Warner DL, Cabaret J, Velling D.Ketamine plus midazolam, a most effective paediatric oral premedicant.Paediatr Anesth, 1995; 295.
[36]. Sekerci S. Donmez A, Ates Y, Okten F. Oral ketamine premedication in children (Placebo controlled double blind study).Euro J Anesth, 1996; 13: 606 11.
[37]. Humphries Y, Melson M. Gore D. Superiority of oral ketamine as an analgesic and sedative for wound care procedure in paediatric patient with burns. J Burn Care Rehabil, 1997 Jan-Feb; 18 (1pt 1): 34-6.
[38]. Bachenberg Kenmeth L. Oral ketamine for the management of combative autistic adult. Anaesthesiology, 1998; 89(2): 549-50.
[39]. Raghu Raman TS&J. Painless invasive procedures. Indian Paediatrics, 1999; 36: 1023-28.
[40]. Gupta PK, Deshmukh HB, Gurunath.Oral ketamine as pre-anaesthetic medication in children. Ind J Anaesth, 1999; 43: 39-41.
[41]. Auden SM, Sobezyk WL, Solinger RE. Goldsmith LJ. Oral ketamine midazolam is superior to intramuscular mepiridine, promethazine and chlorpromazine for paediatric cardiac catheterisation. Anesth Analg, 2000 Feb; 90(2); 299-305.
[42]. Young PA, Kendall JM. Sedation for children requiring wound repair : a randomized controlled double blind comparison of oral midazolam and oral ketamine. Emerg Med J, 2001; 18(1): 30-3.
[43]. Horiuchi T, Kureharak, Kitaguchi K, Furuya H. Ketamine lollipop for paediatric premedication. Masui, 2001 Apr; 50(4): 410-2.
[44]. Astuto M, Disma N, Crimi E.Two doses of oral ketamine given with midazolam for premedication in children. Minerva Anaesthesiol, 2002 Jul-Aug; 68(7-8): 5938.

[45]. Loken P, Bakstad OJ, Fonnelop E, Skogedal N, Hellsten K, Bjerkelund CE. et al. Continuous sedation by rectal administration of midazolam or midazolam plus ketamine as alternatives to general anesthesia for dental treatment of unco operative children. Scand J Dent Res, 1994; 102(5): 274-80.

[46]. Roelofse JA, Joubert JJ, Roelofse PG. A double blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of paediatric dental patients. J Oral Maxillo Fac Surg, 1996; 54(7): 838-44.

[47]. Pan AK, Rudra A, Ghosh M, Biswas BN, Sen A, Kar A. Oral preanaesthetic medication for children : A comparison of midazolam, ketamine and midazolam plus ketamine. J Indian Assoc Pediatr Surg, (6): 135-142.

[48]. Turhanoglu S, Kasarmaz A, Ozyilmaz MA, Kaya S, Tok D. Effect of different doses of oral ketamine for premedication of children. Eur J Anaesthesiol 2003; 20(1); 56-60.

[49]. Vergheese ST, Hanallah RS, Patel RI, Patel KM. Ketamine and midazolam is an inappropriate preinduction combination in unco-operative children undergoing brief ambulatory procedures. Pediatr Anaesth, 2003; 13(3): 228-32.

[50]. Darlong V, Shende D, Subramanyam MS, Sundeep R, Naik A. Oral ketamine or midazolam or a low dose combination for premedication in children.Anaesth Intensive Care, 2004; 32(2): 246-9.

[51]. Horuichi, Kawaguchi M, Kurehara K, Kawaguchi Y, Sasaoka N, Furuya H. Evaluation of relatively low dose of oral transmucosal ketamine premedication in children: A comparison with oral midazolam. Paediatr Anaesth, 2005; 15(8): 643-7.

[52]. Ghai B, Grandhe RP, Kumar A, Chari P. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Paediatr Anaesth, 2005 Jul; 15(7): 554-9.

[53]. Grant IS, Nimmo WS, Clements JA, Pharmacokinetics and analgesic effects of intramuscular and oral ketamine. Br J Anaesth, 1981; 53: 805-9.

[54]. Collins VJ. Principles of Anaesthesiology, 3rd edn, Philadelphia: Vol.1 & 2, 1993 .734-748pp.

[55]. Reves MD, Fragen RJ, Vinik R, Green BD. Midazolam: Pharmacology and uses, Saidman LJ (editor), Anaesthesiology, 1985; 62; 310-324.

[56]. Wardel C, Bocker R, Bohrer H, Browne A, Ringheiner E, Martin E. Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth, 1994; 73: 658-61.

[57]. Jones RDM, Chan K, Roulson CJ, Brown AG, Smith ID, Mya GH Pharmacokinetics of flumazanil and midazolam. Br J Anaesth, 1993; 70: 286-92.

[58]. Dundee JW, Wilson DB.Amnesic action of midazolam. Anaesthesia, 1980; 35: 459-61.

[59]. Stoeltin RK. Pharmacology and Physiology of Anaesthesia Practice, 3rd edn, Philadelphia: Lippincott-Raven, 1999; 126-139pp.

[60]. Chiu JW, Whtie PF. Non Opioid Intravenous Anaesthesia. In: Barash PG, Cullen BF, Stoelting RK, edt., Clinical anaesthesia, 4th Edn., Philadelphia : Lippincott, Williams and Wilkins, 2001 ; 327-343pp.

[61]. Marshall J, Rodarte A, Blumer J, Khoo KC, Akbari B, Kearus G. Paediatric pharmacodynamics of midazolam oral syrup.Paediatric Pharmacology Research Unit Network. J Clin Pharamacol, 2000 Jun; 40(6): 578-89.

[62]. Charney Ds, Mihic SJ, Haris RA.Hypnotics and sedatives. In: Hardman JG, Limbird LE, Gilman AG, edt. Goodman and Gilman's the pharmacological basis of therapeutics. 10th Edn, NewYork: McGrawhill, 2001; 399-427pp.

[63]. McGraw T, Kendrik A.Oral midazolam premedication and postoperative behaviour in children. Paediatr Anaesth, 1998; 8(2): 117-21.

[64]. Wayaman K, Shoemaker WC, Lippmann M.Cardiovascular effects of anaesthetic induction with ketamine. Anaesth Analg, 1980; 159: 35-40.

[65]. White PF, Way WL, Trevor AJ.Ketamine-its pharmacology and therapeutic uses. Anaesthesiology, 1982; 56: 119-36.

[66]. Bovill JG and Dundee JW. Alterations in response to somatic pain associated with anaesthesia: ketamine. Br J Anaesth, 1971; 43-46.

[67]. Frenchen I, Ostergaard J, Ohrt MB.Anaesthesia with flunitrazepam and ketamine.Br J Anaesth 1981; 53: 827-30.

[68]. Laishley RS, Burrows FA, Lerman J, Roy WL.Effects of anaesthetic induction regimens on oxygen saturation in cyanotic congenital heart disease. Anaesthesiology, 1986; 65: 673-77.

[69]. Smith DJ. Westfall DP, Adams JD.Ketamine interacts with opiate receptors as an agonist. Anaesthesiology 1980; 53: 55.

[70]. Cartwright PD, Pingel SM. Midazolam and diazepam in ketamine anaesthesia.Anaesthesia, 1984; 439-42.

[71]. Wilson KE, Welbury RR, Girdler NM.A randomized, controlled, cross over trial of oral midazolam and nitrous oxide for paediatric dental sedation. Anaesthesia, 2002; 57: 860-7.

[72]. Mirakur R K.Compartive study of the effects of oral and intramuscular atropine and hyoscine in volunteers. Br J Anaesth, 1978; 50: 591-8.

[73]. Mitchell V, Grange C, Black A, Train J.A comparison of midazolam with trimeperazine as an oral premedicant for children.Anaesthesia, 1997; 52: 416 21.

[74]. Suresh C, Kulshrenstha S, Jain A, Kohli P. Oral premedication for paediatric ambulatory anaesthesia : A comparison of midazolam and ketamine. Ind J Anaesth, 2000; 44: 41-46.

[75]. Weldon BC, Watcha MF, White PF. Oral midazolam in children: Effect of time and adjunctive therapy. Anesth Analg, 1992 Jul; 75: 1151-5.

[76]. Debnath S, Pande Y.A comparative study of oral premedication in children with ketamine and midazolam. Ind J anaesth, 2003; 47(1): 45-47.

[77]. Howell T K, Smith S, Rushman SC, Walker RWM, Radivan F.A comparison of oral transmucosal fentanyl and oral midazolam for premedication in children. Anaesthesia, 2002; 57: 798-804.

[78]. Sethi N, Dash LK, Madhusudanan TP.Oral premedication for paediatric anaesthesia: A comparison of midazolam and ketamine. Ind J Anaesth, 2001; 45(3): 215-9.

[79]. Beebe DS, Belani KG, Chang PN, Hesse PS, Schuh JS, Lia JC, et al.Effectiveness of preoperative sedation with rectal midazolam, ketamine or their combination in young children. Anesth Analg, 1992 Dec; 75(6): 880-4.

[80]. G. A. Finley, S. H. Stewart, S. Buffett-Jerrott, K. D. Wright, and D. Millington, "High levels of impulsivity may contraindicate midazolam premedication in children," Canadian Journal of Anesthesia, vol. 53, no. 1, pp. 73–78, 2006.

[81]. R. G. Cox, U. Nemish, A. Ewen, and M.-J Crowe, "Evidence-based clinical update: does premedication with oral midazolam lead to improved behavioural outcomes in children," Canadian Journal of Anesthesia, vol. 53, no. 12, pp. 1213–1219, 2006.

[82]. Kain ZN, MacLaren J, McClain BC, Saadat H, Wang SM, Mayes LC, et al. Ef
ects of age and emotionality on theeffectiveness of Midazolam administered preoperatively to children. Anesthesiology 2007;107:5 45-52.

[83]. R Remadevi, P Ezhilarasu, L Chandrasekar, A Vasudevan.Comparison of Midazolam and Ketamine as Oral premedicants in pediatric patients.The Internet Journal of Anesthesiology.2008 Volume 21 Number 2.

[84]. Damle S G, Gandhi M, Laheri V. Comparison of oral ketamine and oral midazolam as sedative agents in pediatric dentistry. J Indian SocPedodPrev Dent 2008; 26:97-101
[85]. Sheta SA, Alsarheed M. Oral midazolam premedication for children undergoing general anaesthesia for dental care. Int J Pediatr. 2009; 2009: 274380
[86]. Kumar A, Shah ZA, Anuradha, Garg R, Nath MP.Comparative evaluation of Ketamine, Midazolam andcombination of both as oral premedicant in children. J Anaesth Clin Pharmacol, 2009;25:449-53.
[87]. Sreyashi Sen, Rajarshi G Thakurta, Sampa D Gupta, Subir Bhattacharya, Sudakshina Mukherji12013