COMPARATIVE EVALUATION OF TWO DOSES OF KETAMINE WITH MIDAZOLAM, KETAMINE ALONE AND MIDAZOLAM ALONE AS ORAL PREMEDICATION IN CHILDREN

A study of 100 cases

DISSERTATION SUBMITTED FOR THE DEGREE OF

DOCTOR OF MEDICINE

ANAESTHESIOLOGY

(BRANCH – X)

SEPTEMBER 2006

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI

DEPARTMENT OF ANAESTHESIOLOGY

MADURAI MEDICAL COLLEGE

MADURAI

CERTIFICATE

This is to certify that the dissertation entitled **"COMPARATIVE EVALUATION OF TWO DOSES OF KETAMINE WITH MIDAZOLAM, KETAMINE ALONE, MIDAZOLAM ALONE AS ORAL PREMEDICATION IN CHILDREN",** is a bonafide record work done by **DR.N.SATHYAN**, in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

Professor and Head,

Department of Anaesthesiology,

Government Rajaji Hospital,

Madurai Medical College, Madurai.

DECLARATION

I, Dr. N. SATHYAN, solemnly declare that the dissertation titled "COMPARATIVE EVALUATION OF TWO DOSES OF KETAMINE WITH MIDAZOLAM, KETAMINE ALONE, MIDAZOLAM ALONE AS ORAL PREMEDICATION IN CHILDREN" has been prepared by me.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment of the regulations for the award of MD degree Branch [Anaesthesiology].

Madurai. **Dr. N. SATHYAN**

Date:

ACKNOWLEDGEMENT

I am deeply indebted to all the patients for submitting themselves for this study and I express my heartfelt gratitude to all of them.

It was with great trepidation and with a sense of unknown that I ventured into one of the novel and most advancing branches of Medicine Anaesthesiology. It is to the credit of my teachers that I managed to stay and began working on my dissertation.

If not for my Professor **DR.S.SUBBIAH,** MNAMS, DA., M.D., DCH., Chief and Head of Department of Anaesthesiology, Madurai Medical College, Madurai who gave invaluable guidance and inspiration, this study would not have consummated to its logical conclusions. I sincerely thank him for his encouragement and support at every stage of this study.

I express my gratitude to **DR.S.P.MEENAKSHI SUNDARAM**, MD., DA., Additional Professor of Anaesthesiology, for his able assistance and guidance in doing this project work.

I express my profound thanks to **DR.I.CHANDRASEKHARAN,** MD., DA., Additional Professor of Anaesthesiology for his constant support and guidance to perform this study.

I extend my special thanks to Prof. **DR.A.RAJA MANOHARAN,** MD., DA.., Head of Department of Anaesthesiology, Theni Medical College for his valuable assistance to this work.

My sincere thanks to **DR.S.AHANATHA PILLAI** MD., DA., and **DR.N.KRISHNAVENI** MD., DA., Former Professors of Anaesthesiology for their encouragement.

I am greatly thankful to all the Assistant Professors for their support and guidance

rendered towards this thesis.

My profound thanks to **THE DEAN**, Madurai Medical College, Madurai for permitting me to utilize the clinical materials of this hospital.

I also thank **MR.PARTHASARATHY**, Statistician, Department of Social and Preventive Medicine, Madurai Medical College for his support.

CONTENTS

INTRODUCTION

'At a time when Anaesthesia & Surgery has become safer and more effective than ever before, it is ironic that considerable number of patients remain fearful '.

"Patients may be afraid of not waking up again, not being put into sleep adequately, and the fear of unknown".

"The shift towards day care surgery has impeded the effective necessary premedications. As a consequence patient arrives at a day care facility in a markedly anxious state".

"Anaesthesiologists fail to recognize the fact that emotional stress often causes greater suffering than complications like nausea, vomiting and headache. A child who cries for weeks after leaving the hospital and who will not leave his mother's side is certainly suffering from an enviably severe insult.

- ROBERT.M.SMITH"

"Unpremedicated and anxious patients require larger doses of induction agents if awareness during instrumentation of airway has to be avoided".

"Premedication is the JOB of an anesthesiologist".

"The selection of drugs is important as it is said that anaesthesia begins when these drugs are given".

"The wise choice of medication can pave the way for an uncomplicated anaesthesia and post operative course where as an improper choice can lead to unsatisfactory experience to all concerned."

Claude Bernard observed that use of morphine before chloroform in a dog resulted in achieving anaesthesia in a smooth, rapid manner and with lesser dosage of chloroform. Ever since the realization of the importance of giving drugs before the induction of anaesthesia, the search for an ideal premedicant has been going on.

“ANAESTHESIA IS A SCIENCE BUT IT IS PRACTISED AS AN ART’.

AIM OF THE STUDY

To compare the efficacy of Two doses of ketamine with Midazolam and ketamine alone and midazolam alone as oral premedication in children. The quality of premedication was assessed by using parameters such as the level of sedation prior to induction, the level of anxiety at the time of separation from parents, anxiety levels at the time of intravenous cannulation and at the time of mask ventilation.

PREMEDICATION

I like to give a teaspoonful of brandy , without water, a few minutes before hand, but not so much as a tablespoonful . If wine be given or if the patient must have some water in the brandy then they should be given half an hour before inhaling, to allow time for absorption

- Clover JT , 1874

In the Pre-anaesthetic days, both wine and opium were given to mitigate the terrors of surgery. The word Premedication first appeared in print in an article by the American editor – anaesthetist Frank Hoeffer McMechan {1873 – 1930} in 1920.

Premedication can be defined as prescribing one or more drugs appropriately chosen in appropriate doses and administering it by the appropriate route in the right time before induction of anaesthesia, so as to have a beneficial effect on the systems of the patient preoperatively, intraoperatively, and post operatively.

THE OBJECTIVES OF PREMEDICATION ARE:

1. To produce sedation, allay anxiety and fear, reduce emotional upset [fear of unknown, fear of death, fear of not becoming conscious again].
2. To provide amnesia for the perioperative period while maintaining cooperation prior to loss of consciousness.
3. To relieve the pre-operative pain, if present.
4. To block the unwanted autonomic reflexes induced either by surgical manipulations or anaesthetic procedures.
5. To prevent excessive secretions in the airway.
6. To reduce the acidity and volume of gastric contents.
7. To decrease post-operative nausea and vomiting.
8. To reduce the stress response during perioperative period and facilitate induction of

anaesthesia.

9. To supplement anaesthesia and reduce the dose of drugs used in general anaesthesia.

6 A' S - ANXIOLYSIS , AMNESIA, ANTIAUTONOMIC, ANTACID, ANTIEMETIC, & ANALGESIC.

THE IDEAL PREMEDICATION :

- should be easily administered.
- should be well accepted by the patients.
- should not prolong emergence from anaesthesia.
- must act rapidly.
- must have few side effects.

ROUTES OF ADMINISTRATION OF PREMEDICATIONS :

1. ORAL
2. I NTRAMUSCULAR
3. I NTRAVENOUS
4. I NTRANASAL
5. ORAL TRANSMUCOSAL
6. RECTAL

There would not be any major difference between oral and intramuscular route in patients without gastro-intestinal problems.

ORAL PREMEDICATION

ADVANTAGES

1. Most commonly employed route for drug administration.
2. Easiest route.
3. More convenient for administration.
4. Economical.
5. Very safe.
6. Does not need assistance.
7. Non-invasive, often painless.
8. Need not be sterile.

DISADVANTAGES

1. Onset of action of the drug is slow and thus not suitable for emergencies.
2. Unpalatable drugs are difficult to administer; drug may be filled in capsules to circumvent this
3. May cause nausea and vomiting.
4. Reduced absorption of some drugs because of their physical characteristics.
5. Irregularity in absorption in the presence of food or other drugs.
6. Some drugs are destroyed by digestive juices.
7. Some drugs have increased hepatic first pass metabolism and reach blood in minimal concentrations
8. Irritation to the gastro-intestinal mucosa may cause emesis.

9. This route cannot be employed in unco-operative children and unconscious or a vomiting patient.

Oral ingestion is the oldest and commonest mode of drug administration. Both solid and liquid dosage forms can be given orally.

THREE PEOPLE AND THREE CONSIDERATIONS

Patient → Physical status, Physiological and Psychological conditions.

Surgeon → Requirements, Type of Surgery and Duration.

Anaesthetist → Technique, Skill and Knowledge.

PREMEDICATION IN CHILDREN

In 1938, Water published a monograph on premedication, in which he advised three types of approaches which holds good even today. He recommended

1. – Basal anaesthesia
2. - Sedation without depression
3. - No Medication.

Anxiety levels of children can be classified into different grades and premedication can be planned accordingly.

Enormous [time of] stress for the child occurs during their seperation from parents, in strange surroundings and during painful, frightening procedures. Children's anxiety also focus on issues such as fear of needles, a concern of change in bodily image, or not awakening at the

end of surgery or of survival.[26]

"I am allergic to needles-----" says a young patient

The entire family will undergo the psychological stress[26] of a child's surgery; with feelings of guilt, helplessness and inconvenience. Parental anxiety will be transmitted to young children.

The paediatric anaesthesiologist not only has to take care of the [safety of] child but also has to manage the parents.[26]

Premedication not only takes care of the child's anxiety, it provides emotional support and psychological preparation.

Parental anxiety is reduced if the child is calm and sedated, and decreases the desire of the parents to remain with the child during induction. Many studies[12] have proved that pre-operative sedation is superior to parental presence for decreasing anxiety during induction of anaesthesia and increasing the cooperation with inhalational induction.

Children sedated before coming to the operating room may have fewer stress related behavioural changes in the immediate postoperative period compared with groups of patients who received no sedation.

Thus Premedication helps to avoid a turbulent and stormy induction.

During the administration of Premedication the following factors have to be considered:-

1. Children fear needles and intensely dislike injections. Moreover, intramuscular injections are painful and is not a good way to induce tranquility.
2. The beneficial effect of Premedicant drug should not be negated by the side effect that increases the discomfort.
3. Children do remember past experiences and know what they like and do not like. All

one has to do is to spend enough time to ask them. Pre-anaesthetic premedication need to be individualised to the patient.

4. Timing of premedication is essential. Administering a fast acting agent for a procedure that will not take place for hours makes little sense. Conversely, administering a slow acting drug for a procedure that will begin immediately offers no benefit to the child.

Newer drugs offer some new horizons in paediatric premedications.[19]

PHARMACOLOGY OF MIDAZOLAM

HISTORY

→ Fryer & Walser in 1976 synthesized Midazolam as the first clinically used water soluble benzodiazepine.

→First Benzodiazepine that was produced primarily for use in anaesthesia.

STRUCTURE

8 – chloro – 6 [2– fluoro phenyl] 1- methyl-

4H – imidazol [1, 5a] [1,4] benzodiazepine

Midazolam solution contains 1 or 5 mg/ml of midazolam with 0.8% sodium chloride and 1% benzyl alcohol as preservative. Preservative free midazolam [5 mg / ml] is also available.

The imidazole ring in its structure accounts for its stability in solution and rapid metabolism. The parenteral solution of midazolam is water soluble and formulated in a buffered acidic medium with a PH of 3.5 .

Midazolam is characterised by a PH dependent ring opening phenomenon, ring remains open at PH < 4 thus maintaining water solubility; ring closes at PH > 4 making it highly lipid soluble.[20]

The molecular weight of midazolam is 362 and has a PK of 6.15.

METABOLISM

Midazolam undergoes extensive hydroxylation by hepatic microsomal oxidative mechanisms [cytochrome P450 3A] to form 1 – hydroxymidazolam and 4-

hydroxymidazolam. These metabolites have pharmacologic activity but are less potent than midazolam.[21] They are conjugated with glucuronic acid and excreted in urine more rapidly than midazolam. With normal hepatic and renal function these metabolites do not prolong the activity.

PHARMACOKINETICS

Midazolam is extensively bound to plasma proteins, 96-98%. Despite its prompt passage into brain, it has a slow effect-site equilibration time of 0.9 to 5.6 mints.[20]

Its volume of distribution is 1.1 – 1.7 L / kg and has a elimination half time of 1.7 – 2.6 hrs with a clearance of 6.4 – 11 ml / kg /minute. Plasma levels required for hypnosis and amnesia during surgery are 100 – 200 ng / ml, with awakening occurring at levels lower than 50 ng / ml.

The short duration of action is due to its rapid redistribution and rapid hepatic clearance. The elimination half life is prolonged in elderly patients and morbid obesity.

Midazolam is rapidly absorbed from the gastrointestinal tract but only about 50% of the dose reaches the systemic circulation, reflecting a substantial first-pass hepatic effect. Peak plasma concentration is achieved in 1 hr. Bioavailability is between 40 –50 %.

MECHANISM OF ACTION

Midazolam binds with the benzodiazepine receptor on gamma–2 subunit of GABA–A receptor [gamma amino butyric acid] with an affinity 3 – 6 times greater than diazepam. With activation, gating of the channel for chloride ions is triggered. The cell becomes hyperpolarized and therefore resistant to neuronal excitation.

Various effects of benzodiazepines is related to amount of receptor occupancy which corresponds to plasma concentration :[21]

Receptor occupancy of 20 % causes *Anxiolysis.*

Receptor occupancy of 30 – 50 % causes *Sedation*

Receptor occupancy of > 60 % causes *Unconsciousness.*

PHARMACOLOGIC ACTION

ONSET I V : 30 – 60 seconds.

Oral : 15 – 30 minutes.

DURATION I V : 30 – 60 minutes.

ORAL : 45 – 90 minutes.

EFFECTS ON ORGAN SYSTEMS

CENTRAL NERVOUS SYSTEM :

Midazolam produces sedation, hypnosis, anxiolysis, amnesia, and unconsciousness. It has an anticonvulsant effect and centrally produced muscle relaxation property. In a dose related manner it causes reduction in cerebral metabolic rate of oxygen consumption [$CMRO_2$] and cerebral blood flow [CBF]. It increases the seizure initiation threshold to local anaesthetics. Its cerebral protective effect against hypoxia is superior to diazepam but inferior to barbiturates.

RESPIRATORY SYSTEM :

Midazolam causes dose related ventilatory depression (greater than diazepam & other benzodiazepines). Depression of respiration is more marked following a rapid administration by intravenous route and is insignificant when given through oral route.[21]

It occurs rapidly with in 3 minutes & lasts longer for even 60 –120 minutes. Patients with chronic obstructive pulmonary disease experience greater midazolam induced respiratory depression.

The slope of ventilatory response curve to carbon-di-oxide is flatter than normal.[21]

Midazolam induction produces apnoea which is greater in old age, debilitated state & in the presence of opioids or other respiratory depressant drugs.

CARDIOVASCULAR SYSTEM :

Midazolam by decreasing the systemic vascular resistance, decreases the arterial pressure greater than other benzodiazepines but similar to thiopentone.

The plateau plasma level for midazolam is 100 ng / ml above which there is little change in arterial blood pressure. Heart rate, ventricular filling pressure and cardiac output are maintained after induction. Midazolam impairs baroreceptor reflex and also can decrease catecholamines. Thus, in combination with opioids midazolam can produce greater decrease in systemic blood pressure. [21]

FOETUS :

Less placental transfer than other benzodiazepines

Greater Neonatal depression than thiopentone and propofol.

DRUG INTERACTIONS

1. Erythromycin and calcium channel blockers inhibit cytochrome P450 3A, hence decrease the hepatic clearance of midazolam resulting in unexpected central nervous system depression.
2. Hepatic clearance of midazolam is inhibited by fentanyl [cyto P450 3A – metabolizes fentanyl]

3. Antifungal agents like itraconazole and ketoconazole increase the serum concentrations of midazolam.
4. Inhibition of oxidative enzyme function by cimetidine impairs the clearance of midazolam.
5. Habitual alcohol consumption, increases the clearance of midazolam.
6. Ethanol, barbiturates, opioids and other central nervous system depressants potentiates its effects.
7. It reduces the minimum alveolar concentration of volatile agents as much as 30%.

ROUTES OF ADMINISTRATION

Intravenous route commonly used. Other methods available are oral route for premedication. Intramuscular route for sedation and premedication. Intranasal and rectal routes for premedication in children.

DOSAGE

Oral : 0.5 - 0.75 mg/ kg.

Rectal : 0.25 - 0.5 mg/kg.

Intra nasal : 0.2 - 0.5 mg/kg.

Intramuscular: 0.05 – 0.15 mg/kg.

Intra venous : 0.05 – 0.15 mg /kg.

CLINICAL USE

1. Premedication:

Midazolam is an useful premedicant because of various available routes of administration. It provides reliable sedation, anxiolysis and amnesia in children without producing a delayed awakening.[25]

Oral formulation of Midazolam was approved by US Food & Drug administration in 1998, as a useful premedicant in children. Parenteral preparation can be administered orally but the problem of its bitter taste is negated by adding sugar solution.

Intramuscular route can also be used for premedication in adults. Transmucosal [sublingual] and intranasal midazolam are other novel routes for premedication in children.

2. IV sedation:

Midazolam 1 – 2.5 mg IV is effective for sedation during regional anaesthesia as well as for brief procedures. It is also useful in procedures like cardioversion and electroconvulsive therapy. It plays a major role in neuroimaging and radiological interventional procedures.

Synergistic effects with opioids permits a decrease in midazolam dose administered.

Midazolam scores over other benzodiazepines for the reasons : it is water soluble, no venous irritation, rapid onset, short duration, greater amnesia and less postoperative sedation.

At 4 mcg / kg / minute, it can be used as a continuous infusion or as patient controlled administration.

3. Induction of Anaesthesia :

Benzodiazepine of choice for induction. Usual induction dose between 0.05 and 0.3 mg/ kg over 30 – 60 seconds. Induction occurs less rapidly than thiopental [50 – 100% faster than midazolam] but amnesia is more reliable. End points of induction are unresponsiveness to command and loss of eyelash reflex.

Patients > 55 yrs and ASA more than or equal to III requires a 20% or more reduction in induction doses. Midazolam is used with other anaesthetic drugs [opioids / barbiturate / propofol] as coinduction in a dose of less than 0.1 mg/kg. Emergence occurs in about 15-17minutes.

4. Maintenance of anaesthesia :

Midazolam is used to supplement opioids, propofol or other inhalational agents. Though there is lack of analgesia it provides hypnosis and amnesia. Midazolam 0.6mg/kg lower the MAC of halothane by 30%.

Maintenance infusion of midazolam is between 0.25 – 1 mcg / kg / min.

Shorter context sensitive half time and greater clearance provides the advantage for midazolam in maintenance.

ADVERSE EFFECTS

Relatively high margin of safety compared with barbiturates.

Respiratory depression can occur when the drug is given for conscious sedation.

Loss of balance and loss of head control in children has been observed following premedication with midazolam. Some may also show dysphoric reactions like crying and disorientation following intranasal midazolam.

KETAMINE

HISTORY

Victor Maddox of Detroit synthesized phencyclidine and it was introduced into clinical use by Greifenstein and Johnstone in 1958.

Ketamine was synthesized in 1962 by Stevens and was first used in humans in 1965 by Corssen and Domino.

PHYSICOCHEMICAL CHARACTERISTICS

Ketamine is 2-0-chlorophenyl 2-methyl amino cyclohexanone hydrochloride. The molecular weight of 238 kd.[21] It is partially water soluble and forms a white crystalline salt with a pKa of 7.5. It is prepared in a slightly acidic pH of 3.5-5.5 and is available in 1%, 5% and 10% solutions containing the preservative benza thonium chloride. Ketamine occurs as two resolvable optical isomers or enantiomers, the commercial preparation being a racemic mixture of both isomers S (+) and R (-) in equal amounts.

[S (+) isomer produces more intense analgesia, more rapid metabolism and recovery, less emergence reaction.][21]

MECHANISM OF ACTION

Ketamine interacts with the following receptors.

A) N-methyl D- Aspartate receptor antagonism :

Non competitive antagonist of the NMDA – receptor calcium pore. It also binds to the

phencyclidine binding receptor site causing inhibition of the NMDA receptor activity (S(+) isomer more affinity)

B) Opioid receptors :

Ketamine may be an antagonist at mu receptors and an agonist at kappa receptors.

C) Mono aminergic receptors :

Antinociceptive actions may involve descending inhibitory monoaminergic pain pathways.

D) Muscarinic receptors :

Ketamine produces an antagonistic effect at these receptors. Anticholinergic symptoms are common.

E) Voltage sensitive calcium channels

PHARMACOKINETICS

The extreme lipid solubility of ketamine ensures its rapid transfer across the Blood - brain barrier (5-10 times that of thiopental). Peak plasma concentration occurs with in 1 minute after IV administration and 5 minutes after IM injection. Not significantly bound to plasma proteins.

Distribution half life	–	11 to 16 mintues.
Elimination half life	–	2 to 3 hours.
Large volume of distribution	–	3 L / kg.
Total body clearance	–	1.4 L / min.

Alterations in hepatic blood flow influences ketamine clearance rate .Eg. Halothane .

METABOLISM

By the hepatic microsomal enzymes cytochrome P – 450 . Major pathway is N-

demethylation to form nor – ketamine (20-30% activity) which is then hydroxylated to form hydroxy norketamine. These products are conjugated to water soluble glucuronide derivatives and are excreted in the urine.

Chronic administration of ketamine can stimulate the enzymes responsible for its metabolism (enzyme induction) and explain the observation of tolerance and dependance.

PHARMACOLOGY

Effect on the Central nervous system :

a) Dissociative anaesthesia :

A cataleptic state, with profound analgesia, the eyes remain open with a slow nystagmic gaze. Noncommunicative, though wakefulness appears to be present. Corneal, cough and swallowing reflexes are present but not protective. Varying degrees of hypertonus and purposeless movements can occur. The patient is amnesic.

In the thalamo neocortical projection systems, ketamine produces a functional disorganization of pathways and dissociation between the thalamo cortical and limbic system.

Plasma levels for anaesthesia are 0.6 to 2 mcg / ml in adults and 0.8 to 4 mcg / ml in children . Duration of action is 10 to 15 minutes and full orientation occurs in 15 to 30 minutes.

b) Ketamine produces an increase in the cerebral blood flow and cerebral metabolic oxygen requirement. With increase in cerebral blood flow and generalized increase in the sympathetic nervous system response, there is an increase in the intra cranial pressure.

Cerebro vascular response to carbon-di-oxide appears to be preserved with ketamine. Prior administration of thiopental, diazepam or midazolam can blunt the ketamine induced increase in cerebral blood flow and cerebral metabolic oxygen requirement.

c) Due to its excitatory central nervous system effects, the drug produces theta – wave activity

as well as petitmal seizure like activity in hippocampus. Theta activity signals analgesic activity. Onset of delta activity coincides with the loss of consciousness. Ketamine does not alter the seizure threshold in epileptic patients but it can produce a myoclonic and seizure like activity without cortical epileptic activity.

d) Emergence reaction :

Vivid dreaming, extracorporeal experiences (sense of floating) and illusions, may progress to delirium associated with excitement, confusion, euphoria and fear. This occurs in the first hour of emergence and usually abates within 1 to several hours.

Emergence delirium occurs secondary to ketamine induced depression of the inferior colliculus and medial geniculate nucleus leading to misinterpretation of auditory and visual stimuli. The loss of skin and musculo skeletal sensation results in decreased ability to perceive gravity producing a sensation of bodily detachment (floating in space).

Incidence 10 to 30 % . Factors that affect are i) age > 15 years ii) female gender iii) doses > 2 mg/kg IV iv) personality problems and psychologic susceptibility v) concurrent drugs – with inhaled anaesthetics.

Prevention – benzodiazepines especially midazolam is more effective; can be given 5 minutes before induction.Inclusion of thiopental or inhalation can decrease the incidence. Premedication with atropine or droperidol may increase the incidence of emergence delirium.

Effect on the Respiratory system :

Ventilatory response to carbon-di-oxide is maintained; transient decrease in minute ventilation (1-3 min) can occur after a bolus dose ; apnoea can occur after rapid IV or along with an opioid.

Respiratory depression can occur with the use of sedative and anaesthetic drugs. In children, it can cause respiratory depression.

Bronchodilator activity is used to treat bronchospasm and status asthmaticus. Mechanisms include increased circulatory catecholamine concentrations, inhibition of catecholamine uptake , voltage sensitive calcium channel block and inhibition of post synaptic nicotinic or muscarinic receptors.

Effect on the Cardio vascular system :

Sympathetic and pulmonary arterial blood pressure, heart rate, cardiac output and myocardial oxygen requirements are increased after IV ketamine.

Ketamine has a direct myocardial depressant effect (negative ionotropic) getting unmasked when the compensatory sympathetic nervous system activity is exhausted or following depletion of endogenous catecholamine stores.

Enhances the dysrhythmogenicity of epinephrine.

Mechanisms causing stimulation of sympathetic nervous system include: direct central nervous system stimulation and increased outflow, depression of baroreceptor reflex via N-methyl D-aspartate receptor, inhibition of norepinephrine uptake into post ganglionic sympathetic nerve endings and associated increase of plasma catecholamines.

Methods used to block ketamine induced sympathetic stimulation are use of alpha and beta adrenergic antagonist, vasodilators, clonidine, prior administration of benzodiazepines,inhalational anaesthetics, barbiturates, and droperidol.

DRUG INTERACTIONS

1. Ketamine in the presence of halothane causes hypotension, unmasking of the direct depressant effect by inhalation anaesthetics.
2. Ketamine causes a dose dependent decrease in minimum alveolar concentration of volatile anaesthetics.

3. Volatile anaesthetics prolong the duration of ketamine.
4. Ketamine enhances non depolarizing neuro muscular relaxants by interfacing with calcium ion binding .
5. With succinyl choline, ketamine can prolong the duration of action by inhibition of plasma cholinesterase
6. Pancuronium enhances the cardiac – stimulating effects.
7. Seizures have been reported in asthmatics receiving aminophyline following administration of ketamine:
8. Preservative chlorobutanol is neurotoxic and this precludes its use in subarachnoid or epidural space.
9. Ketamine with propofol is strictly additive and not synergistic, thus the dose of each should be reduced by about half .
10. Barbiturate & narcotics prolong the recovery time.

USES

I. INDUCTION AND MAINTENANCE :

IM induction in children and mentally retarded patients, for burn dressing changes , wound debridements and skin grafting procedures.[24]

Induction agent of choice in patients with reactive airway disease or bronchospasm or asthma. Its use as cardiac stimulant is advantageous in trauma victims with acute hypovolemia provided there is sufficient sympathetic reserve. Patients with septic shock also benefit from ketamine.

Ketamine anaesthesia is used for cardiac tamponade, constrictive Pericarditis & congenital heart disease with right to left shunt.

In patients with malignant hyperthermia and anterior mediastinal mass , ketamine use maintains spontaneous ventilation (inhalation contraindicated).

Diazepam 0.5mg /kg IV and ketamine 0.5 mg /kg IV followed by a continuous infusion of ketamine 15 to 30 μg/kg /mint can be used in patients with coronary artery disease. Low dose ketamine can be used as an analgesic following thoracic surgery.

Induction : 0.5 – 2 mg /kg IV

4 - 6 mg/ kg IM

Maintenance :

0.5 – 1 mg /kg IV

30 – 90 μg/kg /min IV

II. SEDATION :

Ketamine sedation is used for paediatric procedures like cardiac catheterization, radiation therapy[24], dressing changes and dental work.

0.2 - 0.8 mg/kg IV

2 - 4 mg/kg IM

Ketamine 0.5mg/kg IV combined with diazepam 0.15mg/kg IV is better accepted for supplementation of regional anaesthesia.

III. NEURAXIAL ANALGESIA :

Extra dural (30mg) and intrathecal (5mg) administration produces variable and brief analgesia.

ADVERSE EFFECTS

Increased Blood Pressure, tachycardia, tonic & clonic muscle movements, tremors and

vocalization, emergence reaction, visual hallucination, vivid dreams or illusions.

Less frequently bradycardia, hypotension, respiratory depression, apnoea, vomiting, cardiac arrhythmias, laryngo spasms and airway obstructions occur.

Rarely double vision, loss of appetite, nystagmus, skin rash (red skin) etc are noted.

CONTRAINDICATION

1. Severe Cardio vascular diseases.
2. Severe hypertension.
3. Recent myocardial infarction
4. Stroke
5. Cerebral trauma
6. Intra cerebral mass / Hemorrhage.
7. Congestive cardiac failure.
8. Tachyarrhythmias
9. Thyrotoxic state.
10. Increased intra ocular pressure and CSF pressure
11. Sensitivity to ketamine.
12. Alcohol / Drug abuse.

PREGNANCY

Crosses placenta, reported to cause birth defects in animals, secretion in breast milk is not known.

PAEDIATRICS

In neonates and < 4 months increased risk of respiratory complications.

REVIEW OF LITERATURE

1. Candian journal of anaesthesia, march 1994, vol 41, no:3.

Alderson, P J., MA MB BS; Lerman, J, BASc MD FRCPC

Compared the clinical characteristics of two oral premedicants, midazolam and ketamine; 40 healthy children, one to six years of age, scheduled for ambulatory dental surgery were assigned to receive either oral midazolam 0.5mg/kg or oral ketamine 5mg/kg in a double blind, randomized study. The study concluded that midazolam and ketamine offered similar clinical characteristics when used as oral premedicants for children, although the time to discharge from hospital may be more rapid after midazolam than after ketamine.

2. Anaesthesiology,jan 1992,vol 76, no:1

Gutstein, Howard B., M.D; Johnson, Kristen L., M.D; Heard, Maurine B., M.D; Gregory, George A., M.D.

The authors sought to define a dose of oral ketamine that would facilitate induction of anesthesia without causing significant side effects. Forty five children (ASA 1 and 2, aged 1-7 years) were assigned randomly in a prospective, double-blind fashion into three separate groups that received either ketamine 3 mg/kg or 6mg/kg or no ketamine mixed in 0.2 ml/kg cola flavored soft drink. They concluded that an oral dose of 6mg/kg ketamine is easily administered and well accepted in young children and provides predictable, satisfactory premedication without significant side effects.

3. Canadian Journal of Anaesthesia , July 1992,Vol 39,NO:6

McMillan, C. O., MD; Spahr-Schopfer, I. A., MD; Sikich, N., RN; Hartley, E., MD PhD FRCPC; Lerman, J., MD FRCPC

Eighty unpremedicated children were (ASA PS I or II, ages 1-6 years) randomly assigned to one of the four groups receiving midazolam 0.5, 0.75, or 1.0 mg Kg^{-1} or a placebo, 30 minutes before separation from parents. This double blind, placebo-controlled study concluded that oral midazolam 0.5mg/kg is a safe and effective premedicant and that 0.75 and 1mg/kg while offering no additional benefit, caused more side effects.

4. Pan AK, Rudra A, Ghosh M, Biswas BN, Sen A, Kar A.

Calcutta National Medical College and Hospital, Kolkata

Sixty children of ASA grade I and II, aged between 3 and 8 years were randomly enrolled in a observer – blinded fashion into 3 different groups in equal numbers. They found that midazolam 0.5mg/ kg or combination of midazolam 0.25 mg/kg plus ketamine 2.5mg/kg provided a better premedication in children than ketamine 5mg/kg when given orally 30 minutes before the induction of anaesthesia.

5. British Journal of Anaesthesia, Vol 84, Issue 3 335-340,

W Funk, W Jakob, T Riedl and K Taeger;

In a prospective, randomized double blind study it was observed that ketamine 3 mg/kg combined with midazolam 0.5mg/kg had significantly better anxiolysis and separation from parents than midazolam or ketamine alone. The duration of action and side effects of the combination were similar to those of midazolam alone.

6. Minerva Anaestesiol –2002 jul-aug ; 68 (7-8)

Astuto M, Disma N, Crimi E.

A clinical randomized and blind study on 120 patients, aged between 2 and 6 years showed that 2 mg/kg ketamine given orally with midazolam improved anxiolysis, sedation, achieved better parental separation and better acceptance of face mask for induction of anesthesia.

7. Journal of Anaesthesiology Clinical Pharmacology. 2000 Jan; 16(1): 23-28 Dept. of Anaesthesia, Maulana Azad Medical College, New Delhi

In a randomized, double blind, place controlled study, 60 children of 1-8 years ASA grade I or II scheduled for out patient surgery were assigned to three groups (n=20) receiving midazolam 0.5mg/kg or ketamine 5mg/kg or a placebo ie) apple juice, 30 minutes before separation from parents. There was statistically no significant difference between the ketamine and the midazolam groups in the time of onset of sedation, maximum sedation achieved, amnesia, induction time and recovery time.

8. Effects of a midazolam-ketamine admixture in human volunteers.

Morse Z, **Sano K**, **Kanri T**.

Ten ASA physical status I volunteers were administered loading doses of 0.07 mg/kg of midazolam followed by 0.7mg/kg of ketamine. The same amount of midazolam and ketamine was then infused constantly over 1 hour. The combined non narcotic, sedoanalgesic technique maintained spontaneous ventilation, stable cardio respiratory parameters and hence was suggested as an alternative to traditional conscious sedation or general anesthesia.

9. Anaesthesia and Intensive Care 2004;32:246-9.

Darlong V, Shende D, Subramanyam MS, Sunders R, NaikA.

The study showed that a combination of ketamine 3 mg/kg plus midazolam 0.25 mg/kg orally had a faster onset, better efficiency and more rapid recovery than the administration of oral ketamine 6mg/kg or oral midazolam 0.5 mg/kg alone.

METHODOLOGY

A clinical randomized, blind-prospective study was performed to assess the quality of premedication in children, following the administration of either of the two doses of oral ketamine with midazolam or midazolam alone or ketamine alone.

The clinical study was carried out in 100 patients, who got admitted in the paediatric surgery department of Government Rajaji Hospital, Madurai for elective surgeries during the period December 2004 to February 2006. This study was conducted after obtaining the approval from the hospital ethical committee and with the informed consent of the parents.

INCLUSION CRITERIA

- The age group of children selected for this study was between 1 and 12 years (both inclusive).
- Only patients belonging to American Society of Anesthesiologists (ASA) physical status I were chosen for the study. This was done to avoid the influence of associated diseases on the observation.
- Duration of the surgical procedures were not less than 30 minutes.
- Informed consent, from the parents was obtained.
- All the children were kept under overnight starvation prior to surgery.

EXCLUSION CRITERIA

- Patients on other sedative drugs, neuroleptic drugs, anticonvulsants and barbiturates were excluded from the study for fear of their possible influence on the effects of the

premedicant drug.

- Children, spitting out the drug following the administration of premedicants along with sugar crystals, were excluded from the study to avoid bias in results.
- Children, suffering from upper or lower respiratory infections were excluded.

PREANAESTHETIC EVALUATION

All the patients included in the study underwent a preanaesthetic assessment prior to the surgery, with due importance given to the following:

a. **History** – a detailed review of the past and present clinical conditions with history regarding previous surgeries and medications etc.,
b. **Clinical examination –** a thorough examination of the cardiovascular and respiratory systems.
c. **Investigation –** Hb%, blood urea, blood sugar, serum Creatinine, urine analysis, bleeding time and clotting time.

METHOD

The children were randomly allocated into four groups of twenty five each as per the premedications given.

Group A – ketamine 1 mg / kg combined with midazolam 0.3 mg / kg.

Group B – ketamine 2 mg / kg combined with midazolam 0.3 mg / kg.

Group C – ketamine 6 mg / kg alone.

Group D – midazolam 0.5 mg / kg alone.

In Group – A

Parenteral formulation of ketamine (50 mg per ml vial) in a dose of 1mg/kg was combined with parenteral formulation of midazolam (5 mg per ml ampoule) in a dose of 0.3 mg/kg.

This combination was then mixed with equal volume of sugar crystals using a stirrer. The prepared solution was given to the children to drink either from a tumbler or a palladai. Immediately after swallowing the drug, the child was offered 2-3 gms of sugar crystals to chew, inorder to avoid the bitter taste of the drug. This was given 30 minutes prior to the induction.

In Group – B

Parenteral formulation of ketamine (from 50 mg per ml vial) in a dose of 2 mg/kg was combined with parenteral formulation of midazolam (from 5 mg per ml ampoule) in a dose of 0.3 mg/kg. To the prepared mixture was added equal volumes of sugar crystals and dissolved using a stirrer. The prepared solution was then given to the children to drink from a tumbler or paladai. 2-3gms of sugar crystals were given to chew to avoid the bitter taste of the premedicant. This was done 30 minutes prior to induction.

In Group – C

Parenteral formulation of ketamine (from 50 mg per ml, vial) in a dose of 6 mg/kg, was taken alone and sugar crystals were dissolved in it. This was given to children to drink as a syrup. After swallowing the drug, the children were given 2-3 gms of sugar crystals to chew to avoid any bitter taste of drug. The premedication was administered 30 minutes before the induction.

In Group – D

Parenteral form of midazolam (5 mg per ml, ampoule) in the dose of 0.5mg/kg, was mixed with sugar crystals till it dissolved and was given orally 30 minutes prior to induction of anaesthesia. Following the drug 2-3 gms of sugar crystals were given to chew, to avoid the bitter taste of the drug.

CLINICAL STUDY

Thereafter the child was observed for any changes in mood, behaviour, sleepiness and appearance of any side effects like vomitting, increased salivation, hiccough, nystagmus etc.,

SEDATION

At 30 minutes following the oral premedication, the level of sedation was graded by evaluating the child's appearance with the help of a five point sedation score as below:

Score	Sedation level
1	Barely arousable [full sleep]
2	Eyes closed, light sleep
3	Eyes open but looks drowsy
4	Awake
5	Agitated

A sedation score of 3 or less, was considered as GOOD and scores of 4 & 5 as POOR.

ANXIETY

The emotional state of the child or the level of anxiety at the time of separation from the parents, was assessed using a four point anxiety score.

Inside the operating room, the level of anxiety at the time of intravenous cannulation and also the anxiety level on application of mask for preoxygenation were evaluated using the same four point anxiety score as below:

Score	Anxiety level
1	Calm, sleepy
2	Little apprehensive but withdrawn from surroundings
3	Crying
4	Agitated and difficult to control

ANAESTHETIC SEQUENCE

Intravenous cannulation was performed in all the children and injection atropine 0.02 mg/kg was given intravenously. All the children were preoxygenated, through face mask. Induction was done with 2.5% solution of injection thiopentone sodium 5 mg/kg followed by injection succinylcholine 2 mg/kg to facilitate tracheal intubation with an appropriate size uncuffed endotracheal tube. Anaesthesia was maintained with nitrous oxide – oxygen, injection pentazocine 0.6 mg/kg as opioid and injection atracurium 0.3 mg/kg as the non depolarizer. At the end of surgery the neuromuscular blockade was reversed with injection neostigmine 0.04 mg/kg and injection atropine 0.02 mg/kg in titrated doses. Any side effects or undue complications in the perioperative period were noted.

ANALYSIS

The observations were analysed and the data was compared between the groups by using students ‘t’ – test. A value of $p < 0.05$ was taken as a statistically significant difference. For continuous variables [age, weight] the analysis was performed as mean ± standard deviations.

OBSERVATIONS AND RESULTS

I. DEMOGRAPHIC PROFILE

Table 1

Criteria / Groups	Age (yrs)	Weight (kg)	Sex (M/F)
Group – A	4.92 ± 2.84	13.88 ± 4.37	19 / 6
Group – B	4.82 ± 2.54	13.48 ± 3.93	21 / 4
Group – C	6.93 ± 2.93	16.8 ± 4.67	22 / 3
Group – D	3.96 ± 2.66	12.56 ± 4.04	22 / 3

All the values are mean ± standard deviation except sex criteria.

All the four groups were comparable in age, sex and weight.

II. PH DETERMINATION

Table 2

Groups	Drugs	pH
Group – A	Ketamine 1 mg/kg plus Midaplam 0.3 mg/kg	4.7
Group – B	Ketamine 2 mg/kg plus Midazolam 0.3 mg/kg	4.96
Group – C	Ketamine 6 mg/kg	5.5
Group – D	Midazolam 0.5 mg/kg	3.8

The average weight distribution among each group was considered to calculate the dose and the drug so obtained was used to measure the pH. The pH was measured using the Merck pH indicator paper and was confirmed by the digital pH meter.

The pH of all these drugs were more than the most conservative pH limit of 2.5, thought to promote lung damage after aspiration of gastric contents.

III. INTENSITY OF SEDATION

Table 3

Score	Grade	No. of patients			
		Group A	Group B	Group C	Group D
1	Barely arousable, full sleep	2	0	1	2
2	Eyes closed, light sleep	4	9	5	4
3	Eyes open but looks drowsy	16	13	11	12
4	Awake	3	3	8	7
5	Agitated	0	0	0	0

When comparing Group A and Group B, the average sedation score for Group A was 2.8 ± 0.7483, and Group B was 2.76 ± 0.6499. When applying student 't' distribution, the 't'-value was 0.1977 and p value = 0.8441. The p value was >0.05 which is not significant. Comparing the average score, Group B appears to have a better score than Group A (the average score was less 2.76 vs 2.8) but the difference in the level of sedation achieved between the two groups was not statistically significant.

When comparing Group A and Group C, the average sedation score was 2.8 ± 0.7483 and 3.04 ± 0.8237 respectively. The 't' value was 1.0565 and p value = 0.2960, p >0.05 the difference was not significant. Though Group A has better average score than Group C the difference in the achieved sedation was not statistically significant.

On comparing Group A and Group D, the average score was 2.8 ± 0.7483 and 2.96 ± 0.8709 respectively. The 't' value 0.6827 and p = 0.4981, p>0.05 not significant. Though the average sedation score achieved by Group A was better than Group D (2.8 vs 2.96) their difference was not statistically significant.

Comparing Group B and Group C. the average score was 2.76 ± 0.6499 and 3.04 ± 0.8237 respectively. The 't' value 1.3074 and p = 0.1973, p >0.05 not significant. Thus the average score was better for Group B than Group C but the difference was not statistically significant.

Comparing the Groups B and D the average score was 2.76 ± 0.6499 and 2.96 ± 0.8709 respectively. But the t value of 0.9017 with a p = 0.3717, (more than 0.05) was not significant. Group B with a better average score than Group D has not produced a statistically significant

difference in the level of sedation.

Comparison of Group C and Group D showed an average score of 3.04 ± 0.8237 and 2.96 ± 0.8709 respectively. The 't' value was 0.3269 and the p of 0.7451 (more than 0.05) statistically insignificant. Hence Group D has a better average sedation score than Group C but the difference in level was not statistically significant.

Overall analysis of the level of sedation showed that all 4 Groups (A, B, C, D) provided a GOOD sedation score of 3 or less on the average:

Table 4

Sedation / **Groups**	**No. of children (percentage)**	
	Good score Score 3 or less	**Poor score Score 4 & 5**
Group – A	22 (88%)	3(12%)
Group – B	22 (88%)	3 (12%)
Group – C	17 (68%)	8 (32%)
Group – D	18 (72%)	7 (28%)

IV. ANXIETY LEVEL ON PARENTAL SEPARATION

Table 5

Score	Grade	No. of patients			
		Group A	Group B	Group C	Group D
1	Calm, sleepy	8	14	6	3
2	Little apprehensive, withdrawn from surroundings	15	10	18	16
3	Crying	2	1	1	6
4	Agitated and difficult to control	0	0	0	0

When comparing Group A with Group B by applying student 't' test, the average score was Group A 1.76 ± 0.5851 and Group B 1.48 ± 0.5741, t value was 1.6734 and p value = 0.1008, more than 0.05. The performance of both groups were similar with no statistically significant difference.

Comparing Group A and Group C the average scores were 1.76 ± 0.5851 and 1.8 ± 0.4899 respectively. 't' value was 0.2568 and p value = 0.7984, more than 0.05 and not significant. Hence, there was no statistically significant difference in the performance between Groups A and C during parental separation.

When comparing Group A and Group D the average score were 1.76 ± 0.5851 and 2.12 ± 0.5879 respectively. 't' value was 2.1263 and p value = 0.0386, which was less than 0.05 and statistically significant. Group A provides a better parental separation than Group D since the average score was less (1.76 vs 2.12) and the observed difference was statistically significant.

Comparison of Group B and Group C showed the average scores 1.48 ± 0.5741 and 1.8 ± 0.4899 respectively 't' value 2.0772 and p value = 0.0432 which was less than 0.05 and hence statistically significant. So, Group B provided a better control of anxiety on parental

separation than Group C (1.48 vs 1.8).

When Group B was compared with Group D, the average score was 1.48 ± 0.5741 and 2.12 ± 0.5879, respectively, t-test value was 3.8156 with a p of 0.0004, $p < 0.05$ which was statistically significant. Group B scores over Group D in alleviating the anxiety of parental separation (1.48 vs 2.12).

Finally comparing Groups C & D the average scores were 1.8 ± 0.4899 and 2.12 ± 0.5879 respectively. The 't' value was 2.0485 with a $p = 0.0460$ which is less than 0.05 and statistically significant. So, Group C has a better score and statistically significant difference than Group D (1.8 vs 2.12).

Further analysing the children who were either calm or crying at separation from their parents showed the following results:

Table 6

Anxiety / **Groups**	**No. of children (percentage)**	
	Calm Score 1 and 2	**Crying Score 3 & 4**
Group – A	23 (92%)	2 (8%)
Group – B	24 (96%)	1 (4%)
Group – C	24 (96%)	1 (4%)
Group – D	19 (76%)	6 (24%)

V. LEVEL OF ANXIETY AT INTRAVENOUS CANNULATION

Table 7

Score	Grade	No. of patients			
		Group A	Group B	Group C	Group D
1	Calm, sleepy	6	12	4	1
2	Little apprehensive, withdrawn from surroundings	14	12	13	11
3	Crying	5	1	8	13
4	Agitated and difficult to control	0	0	0	0

When comparing Group A and Group B, the average score was 1.96 ± 0.6621 and 1.56 ± 0.5713 respectively. The 't' value was 2.2408 and a p of 0.0297, $p < 0.05$ was statistically significant. Group B has a better average score (1.56 vs 1.96) than Group A and thus suppresses the anxiety level at intravenous cannulation in a statistically significant way than Group A.

Comparing Groups A and C, the average score was 1.96 ± 0.6621 and 2.16 ± 0.6741 respectively. The 't' value 1.0370 and p value 0.3050, $p > 0.05$ was statistically not significant, so the level of anxiety on intravenous cannulation were comparable between the Groups A and C.

On comparing Group A and Group D the average scores were 1.96 ± 0.6621 and 2.48 ± 0.5741 respectively. The 't' value 2.9070 with a p 0.0055, $p < 0.05$ was statistically significant. Group A has a better score than Group D since the average score was les (1.96).

Comparing Group B and Group C showed an average score of 1.56 ± 0.5713 and 2.16 ±

0.6741 respectively. The 't' value was 3.3265 with a p of 0.0017, $p < 0.05$ was significant statistically. Group B was better than Group C (1.56 vs 2.16) in keeping the child calm during intravenous cannulation.

Comparison of Group B and Group D revealed an average score of 1.56 ± 0.5713 and 2.48 ± 0.5741 respectively. They had a 't' value 5.5648 and p value 0.00001, $p < 0.05$ made the comparison statistically significant. Hence the anxiety level was significantly better in Group B than Group D (1.56 vs 2.48).

Comparing Group C and Group D average score were 2.16 ± 0.6741 and 2.48 ± 0.5741 respectively, with a 't' value 1.7705 and p value 0.0830 $p > 0.05$ was statistically not significant. There was no significant difference in anxiety level between the Groups C and D.

Further analysis of anxiolysis score showed the following data:

Table 8

Anxiety / Groups	**No. of children (percentage)**	
	Calm Score 1 and 2	**Crying Score 3 & 4**
Group – A	20 (80%)	5 (20%)
Group – B	24 (96%)	1 (4%)
Group – C	17 (68%)	8 (32%)
Group – D	12 (48%)	13 (52%)

VI. ACCEPTANCE OF FACE MASK FOR INDUCTON

Table 9

Score	Grade	No. of patients			
		Group A	Group B	Group C	Group D
1	Calm, sleepy	5	12	4	2
2	Little apprehensive, withdrawn from surroundings	15	12	15	9
3	Crying	5	1	6	14
4	Agitated and difficult to control	0	0	0	0

Comparing Group A and Group B it was seen to have an average score of 2 ± 0.6325 and 1.56 ± 0.5713 respectively with a 't' value 2.5291 and a $p = 0.0148$, i.e., $p < 0.05$ making it statistically significant. Thus Group B has a better score and statistically significant mask acceptance than Group A(1.56vs 2).

When Group A and Group C were compared average score was 2 ± 0.6325 and 2.08 ± 0.6274 respectively. They had a 't' value 0.4399 and p of 0.6620, $p > 0.05$ not significant. Though Group A had a better average score than Group C (2 vs 2.08) both the groups had a comparable mask acceptance without significant difference.

Comparing Group A and Group D their average scores were 2 ± 0.6325 and 2.48 ± 0.64 respectively. 't' value 2.6133 and p value = 0.0119, i.e., $p < 0.05$ statistically significant. Hence Group A showed statistically significant difference in accepting mask for induction better than Group D (2 vs 2.48).

Comparisons of Group B and Group C showed average scores as 1.56 ± 0.5713 and 2.08

± 0.6274 respectively, 't' value was 3.0022 and p value = 0.0042, $p < 0.05$ was statistically significant. Thus Group B fared better than Group C (1.56 vs 2.08) showing significant difference in mask acceptance.

When Groups B and D were compared their average were 1.56 ± 0.5713 and 2.48 ± 0.64 respectively. Their 't' value was 5.2536 and p value 0.00001, $P < 0.05$ and statistically significant. So, Group B reduces the anxiety level quite significantly than Group D during mask application.

Finally comparing Group C and Group D showed average scores as 2.08 ± 0.6274 and 2.48 ± 0.64 respectively. Their 't' value was 2.1865 and p value = 0.0337 which was less than 0.05 hence statistically significant. So, Group C had better score than Group D with a low average score (2.08 vs 2.48).

Analysing children who remained calm or cried on applying mask for oxygenation showed the following result:

Table 10

Anxiety Level / Groups	**No. of children (percentage)**	
	Calm Scores 1 and 2	**Crying Scores 3 & 4**
Group – A	20 (80%)	5 (20%)
Group – B	24 (96%)	1 (4%)
Group – C	19 (76%)	6 (24%)
Group – D	11 (44%)	14 (56%)

VII. ADVERSE EVENTS

In Group C, with ketamine alone, 8% children had nausea and vomiting, 16% showed increased salivations and secretions intraoperatively and a further 16% children were drowsy in the post operative period.

In Group D, with midazolam alone, 8% children had hiccoughs and another 8% of children showed a delayed recovery with post operative drowsiness.

In Group A and Group B no significant side effects were reported.

DISCUSSION

Fears of injection, operations, physicians and peculiar operation theatre environment where the children are separated from their parents prior to anaesthesia invariably produces traumatic experiences in the tender mind of the young children. An atraumatic premedication can minimise these problems when a calm separation from parents and a smooth induction of anaesthesia is achieved.

It has been a common practice to use oral midazolam and oral ketamine for anxiolysis and sedation in paediatric anaesthesia. Several studies have compared the efficacy of these two drugs as oral premedicants. In this study we have combined oral ketamine and midazolam in two different doses and have evaluated their synergistic action and compared their level of sedation and anxiolysis when either of the drugs were given alone.

STUDY DESIGN

McMillan et al and Lerman et al[15] using the parenteral preparation orally compared different doses of midazolam (0.5mg, 0.75mg, 1mg per kg) and concluded that oral midazolam in a dose of 0.5 mg/kg is safe and effective. We have used parenteral preparation of midazolam orally in the dose of 0.5mg/kg in this study (Group D).

Gutstein and Gregory George et al[8] after comparing different doses of ketamine and found that oral 6 mg/kg ketamine provides predictable and satisfactory premedication without significant side effects. Mehrotra et al reported similar results with 6 mg/kg oral ketamine. Hence in this study it was decided to use ketamine in the dose of 6 mg/kg orally (Group C).

Astuto et al[2] have used midazolam 0.3mg/kg with ketamine 1mg/kg or ketamine 2mg/kg

in his study. Funk et al[6] used ketamine 3mg/kg with midazolam 0.5mg/kg orally in combination. Hence with the idea of lowering the doses and providing an effective combination we arrived at the different dose combinations as ketamine 1 mg/kg with midazolam 0.3 mg/kg (Group A) and ketamine 2 mg/kg with midazolam 0.3 mg/kg (Group B).

Mishra and Gairola et al[16], have found that administering parenteral formulations as oral premedicants in paediatric age groups is more acceptable, effective and safe. Many of the previous studies have used sugar crystals[22] or apple juice[4], or strawberry syrup[6] or chocolate flavours[8] etc to mask the bitter taste of parenteral formulations. Considering all the above studies, we have used the parenteral formulations orally with sugar crystals added to it in this study. All the children accepted the preparations very well, except for one child who was given midazolam orally with sugar, spitted out the drug partially, this child was excluded from the study.

We did not administer oral atropine along with the test drug because it also imparts bitter taste and delays gastric emptying. So we decided to give atropine 0.02 mg/kg intravenously just prior to induction, which was also useful in preventing the pooling of secretions induced by ketamine during intubations.

The pH of the drugs used in this study remained above 2.5. According to Teabeut et al[23], the conservative pH limit thought to prevent lung damage after aspiration of gastric contents was more than pH 2.5. Further the premedicant volume used was kept at less than 0.4 ml/kg (John, Lockhart et al[11]), the minimal gastric volume to avoid aspiration pneumonitis (Anaesthesiology clinics of North American, Dec 1996)[9].

RESULT ANALYSIS

Suranjit Debnath and Yash Pand et al[22] have compared the parenteral formulations of ketamine 6 mg/kg and midazolam 0.5 mg/kg given orally mixed with sugar crystals and concluded that ketamine at 6 mg/kg orally provides better sedation and anxiolysis than midazolam. Anxiolysis for mask application was not studied.

Astuto et al[2] showed that midazolam 0.3 mg/kg with ketamine 2 mg/kg provides better sedation and anxiolysis than midazolam 0.5 mg/kg alone. No data on IV canulation is available. Funk et al[6] have found that ketamine 3 mg/kg with midazolam 0.5 mg/kg provided significantly better anxiolysis than with midazolam or ketamine alone. Acceptance of face mask had not been considered.

From the results of this study we see that all the four groups provide an equally effective ($P>0.05$) good level of sedation, 98% of children receiving the combined ketamine and midazolam premedications (both Group B and Group A) show a good acceptable sedation score. Comparatively it was only 72% among midazolam alone group (D) and 68% among ketamine alone group (C). We infer that, ketamine 1mg/kg with midazolam 0.3 mg/kg and ketamine 2 mg/kg with midazolam 0.3 mg/kg when given orally as premedicants provides a good and acceptable sedation similar to midazolam 0.5 mg/kg and ketamine 6 mg/ kg orally.

From the study of the anxiety level during separation from parents, we see that the children receiving ketamine 2 mg/kg with midazolam 0.3 mg/kg show better results with statistically significant difference ($p<0.05$) than those receiving midazolam 0.5 mg/kg alone and ketamine 6 mg/kg alone. The difference between ketamine 2 mg/kg with midazolam 0.3 mg/kg (96%) calm) and ketamine 1 mg/kg with midazolam 0.3 mg/kg (92% calm) is

insignificant ($p>0.05$). Ketamine 1 mg /kg with midazolam 0.3 mg/kg show better separation than midazolam 0.5 mg/kg alone ($p<0.05$) but the results are comparable with ketamine 6 mg/kg alone ($p > 0.05$).

With intravenous canulation, the dose of ketamine 2 mg/kg with midazolam 0.3 mg/kg achieve significant reduction in anxiety (96% calm) than all the other three groups ($p<0.05$). Ketamine 1 mg/kg with midazolam 0.3 mg/kg (80% calm) shows similar results ($p>0.05$) as ketamine 6 mg/kg (68% calm) but better than ($p<0.05$) midazolam 0.5 mg/kg (48%calm) during cannulation.

For acceptance of mask, ketamine 2 mg/kg with midazolam 0.3 mg/kg emerge more successful (96% calm) producing a significantly better anxiolysis ($p<0.05$) than all the other three groups. Anxiolysis of ketamine1 mg/kg with midazolam 0.3 mg/kg (80% calm) is comparable ($p>0.05$) with that of ketamine 6 mg/kg alone (76% calm) but both the groups are better than ($p<0.05$) midazolam 0.5 mg/kg (44% calm).

SUMMARY

A low dose combination of both ketamine and midazolam [both ketamine 1mg/kg with midazolam 0.3 mg/kg and ketamine 2 mg/kg with midazolam 0.3 mg/kg] when given orally as premedicants to children produce good and acceptable sedation comparable with that of ketamine 6 mg/kg alone and midazolam 0.5 mg/kg alone.

Two mg/kg of ketamine with 0.3 mg/kg of midazolam when given orally improves parental separation, achieve more success during intravenous cannulation and also shows better acceptance of face mask than ketamine 6 mg/kg alone or midazolam 0.5 mg/kg alone.

CONCLUSION

Combining both ketamine and midazolam and reducing their individual doses produces good sedation and better anxiolysis in children with no side effects.

Thus ketamine 2 mg/kg with midazolam 0.3 mg/kg has emerged as a more successful oral premedicant to calm a troubled child, ease the separation from parents and to facilitate the induction for a smooth conduct of anaesthesia.

BIBLIOGRAPHY

1. Alderson, P.J., Lerman, J: A comparison of ketamine and midazolam as oral premedicants for ambulatory anaesthesia in children. Canadian Journal of anaesthesia, March 1994, vol 41, No.3 : 221-226.
2. Astuto M, Disma N, Crimi E.: Two doses of oral ketamine, given with midazolam, for premedication in children. Minerva Anestesiol – 2002 Jul-Aug; 68 (7-8): 593-598.
3. Darlong V, Shende D, Subramanyan MS, Sundar R, Naik A: Oral ketamine or midazolam or low dose combination premedication in children. Anaesthesia and Intensive care 2004; 32: 246-249.
4. Department of Anaesthesia, Maulana Azad Medical College : Clinical evaluation of oral ketamine and oral midazolam for premedication in paediatric surgical outpatients. Journal of Anaesthesiology Clinical Pharmacology. 200 Jan; 16(1): 23-28.
5. Feld LH, Negus JB, White PF: Oral midazolam optimal dose for pediatric premedication. Anesthesiology of 1989, 71: A 1054.
6. Funk W, Jacob W, Riedl T and Taeger K: Oral preanaesthetic medications for children, a combination of midazolam and ketamine vs midazolam or ketamine alone. British Journal of anesthesia, vol 84, Issue 3; 335-340.

7. Goodman and Gilman's: The pharmacologic basis of therapeutics: eleventh edition, 2006 McGraw Hill; chapter 16:402-412; chapter 13: 351-352.
8. Gutstein HB., Johnson KL., Heard M.B., Gregory G: Oral ketamine preanaesthetic medication in children. Anaesthesiology Jan 1992, vol 76, No.1: 28.
9. James A, Greenberg, Peter J.D: Premedication and induction of anaesthesia in paediatric Surgical patients. Anaesthesiology clinics of North America. Dec 1996, vol 14; 781-801.
10. James CF, Modell MD : Pulmonary aspiration - effects of volume and pH in rats. Anaesthesia Analgesia 63; 655.
11. John E, Morrison JR, Clurles H, Lockhart : Preoperative fasting and medication in children. Anaesthesiology clinics of North America Dec 1991, Volu 9; No.4.
12. Kain ZN, Mayer LC, Wang SM, Cavanico L, Hofstadter MB : Oral midazolam more effective than parental presence or no intervention for managing child's anxiety. Anaesthesiology Nov 1998, Vol, No:5.
13. Levine MF, Hartley EJ, Macpherson BA, Lerman. J : Oral midazolam safe and effective alternative for premedicantion of children with cyanotic congenital heart disease. Canadian Journal of anaesthesia, Oct 93, Vol 40, No: 10.

14. Levine MF, Spahr Schopfer IA, Hartley E, Lerman J: Evaluation of time interval for onset of sedation following oral midazolam. Canadian Journal of Anaesthesia, 1993: vol 40, No:8.
15. McMillan C.O., Spahr-Schopfer I.A., Sikich N, Hartley E, Lerman J: Evaluation of different doses of oral midazolam as premedicant in children. Canadian Journal of Anaesthesia, 1992; Vol 39; No:6.
16. Mishra LD, Sinha GK, Bhaskar Rao P, Sharma V, Satya K, Gairola R: Injectable midazolam as oral premedicant in pediatric neurosurgery. Journal of Neurosurgical anesthesiology. October 2005, 17(4): 193-198.
17. Morse Z, Savo K, Kauri T: Effects of a midazolam-ketamine mixture in human volunteers.
18. Pan AK, Rudra A, Ghosh M, Sen A, Kav A: A comparison of midazolam, ketamine and midazolam plus ketamine.
19. Philip D. Bailey Jr and John L. Bastien et al; Preinduction techniques for paediatric anaesthesia. Current opinion in Anaesthesiology 2005, 18: 265-269.
20. Robert K, Stoelting, M.D., Text book of pharmacology and physiology in Anesthetic practice, third edition, 1999 by Lippincott–Raven publishers; Chapter 5: 128 - 132 and chapter 6: 148 - 154.
21. Ronald D, Miller M.D., Textbook of Anesthesia, sixth edition, 2005, Elsevier Churchill living stone; chapter 10: 334-342, 345-350 and

chapter 60: 2380 - 2383.

22. Suranjit Debnath, Yash Pad: Comparative study of oral premedication in children with ketamine and midazolam. Indian Journal of Anaesthesia, 2003; Vol 47 (1): 45 - 47.
23. Teabaut JR; Aspiration of gastric contents : An experimental study. Am J Pathol 28; 51 - 62.
24. Tobias JD, Phipps S, Smith B and Mulhern RK: Oral ketamine premedication to alleviate the distress of invasive procedures in paediatric oncology patients. American Academy of Pediatrics 1992, Vol 90, Issue 4: 537-541.
25. Wylie and Churchill Davidson's; A practice of anesthesia, seventh edition, 2003 Arnold; chapter 35: 575-577, and chapter 59:971.
26. Zeev N Kain: Perioperative psychological issues in children. Committee on pediatric anaesthesia.

PROFORMA

Name : Age: Sex: IP No: Wt:

Case : Plan:

ASA Risk: **Group:**

Pre – medication Drug: Dose: Time:

SEDATION SCORE :

SCORE	SEDATION LEVEL	OBSERVATION
1.	Barely arousable (Full Sleep)	
2.	Eyes closed (light sleep)	
3.	Eyes open but looks drowsy	
4.	Awake	
5.	Agitated	

ANXIETY SCORE :

SCORE	ANXIETY LEVEL	PARENTAL SEPARATION	IV CANNULATION	MASK ACCEPTANCE
1	Calm or Sleepy			
2	Apprehensive but withdrawn from surrounding			
3	Crying			
4	Agitated and difficult to control			

SIDE EFFECTS :

Nausea and Vomiting	
Increased Salivation and Secretions	
Hiccoughs	
Post Operative drowsiness	
Delay in Recovery	
Others	