Oral Midazolam as a Pre-Medication in Paediatric Patients

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Abstract

Introduction: In some medical circumstances, pediatric patients may need premedication for transferring to the operating room. In these situations, using oral premedication is preferred. We assessed the efficacy and safety of oral midazolam to reduce the anxiety and improve behavior in children undergoing general anesthesia. **Method:** In a double-blind randomized clinical trial, 90 children aged between 1-8 years were assigned to one of three oral premedication groups by random selection. Each group contained 30 children. Group I received 0.5 mg/kg oral midazolam Group II received 0.75 mg/kg oral midazolam both in 25% dextrose to a total volume of 5 ml. Group III or control group received 5 ml of 25% dextrose. To study its acceptility, onset and level of sedation, changes in vitals like pulse rate, blood pressure and emotional state before and after sedation, and post-op side effects. **Disscussion:** After premedication, difference in pulse rate, systolic blood pressure and respiratory rate between the three groups was not statistically significant sedation at 30 minutes after premedication was better in study group II as compared to study group I Emotional state was concluded to be better in study Group II (0.75 mg/kg) as compared to study group I (0.5 mg/kg) at the time of separation from parents. More post operative complications like nausea, vomiting, giddiness, headache with a dose of 0.75 mg/kg than with a dose of 0.5 mg/kg. **Conclusion:** So we conclude that oral midazolam in a dose of 0.5 mg/kg for premedication in pediatric patients at it provides good to excellent sedation at 30 minutes at the time of separation from parents, with better quality of separation, and stable emotional state at induction without significant hemodynamic changes with less postoperative

Keywords: Midazolam, Pediatric, Pre-medication

1. Introduction

Premedication is a term applied to the use of drugs prior to the administration of an anaesthetic agent, with the important object of making anaesthesia safer and mort agreeable to the patient.

Preoperative medication and preparation of the patient are vital aspects of the anaesthetic procedure. Patients about the undergo surgery may be frightened and apprehensive. What seems to be a minor procedure for the surgeon and anesthesiologist may represent a major ordeal for the patient. The incidence of clinically significant anxiety in patients awaiting operation has been variously reported to range from 60-80 %[1,2]. The most frequent causes of pre-operation anxiety relate to patients' concern about general health, the operation, leaving their family, uncertainty about their future, anaesthesia and fear of post operative discomfort[3].

In recent years, paediatric anaesthesia has evolved as a subspecialty because the needs of infants and young children are fundamentally different from those of adults. Premedication in paediatric age group deserves special attention given the child's inability to understand the nature of procedure besides anxiety and apprehension in the entire family about the outcome. Preparing the paediatric patient for the operating room can be a complex process because of many individuals involved[4,5]. Here parents of children less than 1 year of age and those children undergoing surgery for the first time is more apprehensive and anxious[6]. So preoperative counseling may be of great importance in paediatric patients. Egbert et al have likened the pre-operative visit to a barbiturate premedicant[7].

Leigh et al have reported lower anxiety levels in patients given pre-operative reassurance compared with a group given no premedication[8]. Nonetheless, in a

significant number of patents a pharmacological adjunct makes the transition to operating room less traumatic and more psychologically acceptable, hence the need for premedication. Moreover there is an increasing trend for out patient surgery in developed countries. These 'same day admission' procedures limits the time the anaesthesiologist has to interact with the child. Parental presence during induction of anaesthesia may completely eliminate the need for premedication in some children but some parents are upset by the process[9,10].

The objectives of premedication are[11]

- To produce sedation, allay anxiety and reduce emotional trauma.
- Block unwanted (vagal) autonomic reflexes.
- Reduce volume and acidity of gastric contents.
- Facilitate a smoother and safer induction of anaesthesia.
- To provide amnesia.
- Supplement anaesthesia and reduce need for general anaesthetic drugs.
- Prevention of post operative nausea and vomiting.

Premedication should be planned according to the developmental stage of the child. Infants less than 7 months of age will accept comforting from strangers but older infants and small children become concerned about parental separation and being held for the procedure by stranger.

The general fears of hospitalization in children are[12].

- Fear of separation from parents.
- Fear of physical harm and bodily injury.
- Fear of the unknown and unfamiliar.
- Fear of transgression and punishment-uncertainty about the limits on behaviour owing to hospital rules and regulations.
- Fear regarding loss of control, competence and privacy.

In the words of Lucida[13,14], 'the paediatric patient who is overwhelmed by irrelevant fears and is not amenable to logic of rational explanation, goes through an unpleasant ordeal before surgery. There is trauma of being separated from parents, the wait in pre-operative room and later when moved into operating room, anaesthetic apparatus, surgical instruments, operating lights and medical personnel moving about; without satisfactory premedication, the induction of anaesthesia can be a trying one.

Thus, undergoing surgery can be a traumatic experience for a child. Fear of physicians, nightmares and post operative behavioural abnormalities are common[15].

The aim of premedication in the paediatric age group is to produce sedation and anxiolysis, reduce emotional trauma and facilitate parental separation besides quiet and smooth induction of anaesthesia[18]. However, premedication may be associated with side effects such as drowsiness, restlessness, post-operative pain and dysphoria.

Premedication drug choice and its dose are determined by:
- Patient's age and weight.
- Physical status.
- Level of anxiety.
- Tolerance for depressant drugs.
- Previous adverse experience with premedicant drugs.
- Elective or emergency surgery.
- Inpatient of outpatient surgery[19].

The various drugs, tried for premedication are barbiturates, narcotics, benzodiazepines, butyrophenones, antihistamines, anticholinergics, H_2 receptor antagonists, antacids etc.

The ideal premedication for paediatric patients should have the following characteristics:
- Acceptable and a traumatic route of administration.
- Rapid and reliable onset.
- Minimum adverse effect.
- Rapid elimination.

Premedication in children can be administered through different routes (intramuscular, intravenous, rectal, sublingual or intranasal).

Although most of these routes of drug administration may be eventually effective, each has its own share if disadvantages[16].

Nowadays oral premedication is more widely used and there is an increasing tendency to avoid injections for premedication in children[17].

Recent studies have shown oral midazolam after oral administration is absorbed rapidly from GIT, peak plasma concentration is achieved easily and clinical effects are also rapidly obtained. It can be used as an effective premedicant in paediatric anaesthesia because of its bypnotic and sedative effects[20].

Therefore, the present study was undertaken to study the efficacy of oral midazolam as a premedication in children.

Also the acceptability of oral pre-medication in children, onset of sedation, level of sedation and anxiolysis, changes in vital parameters, emotional reaction of patients at the time of parental separation will be studied.

2. Aims and Objectives

- To study effectiveness of oral midazolam as premedication drug in children in doses of 0.5 mg/

kg, 0.75 mg/kg and control group without any premedication.

- To study the acceptability of oral premedication in children.
- Observation of onset of sedation after the premedication.
- Comparison of level of sedation after premedication.
- Comparison of changes in vital parameters like pulse rate, blood pressure and respiratory rate.
- Comparison of emotional state of patients at the time of
- Separation from parents.
- Holding mask.
- Comparison of post-operative complications like nausea, vomiting, restlessness, drowsiness, prolonged recovery etc.

3. Pharmacology of Midazolam Introduction

"Benzodiazepine"-First introduced as a sedative-bypnotic and anxiolytic agents have become extremely popular and extensively used medication in anaesthesia practice. Midazolam an imidazobenzodiazepine derivative is water soluble, short acting newer drug with excellent sedative, hypnotic, amnestic properties and stable cardiorespiratory response[21].

Fryer and Walser in 1976 synthesised midazolam, the first clinically used water soluble benzodiazepine. Midazolam was the first benzodiazepine that was produced primarily for use in anaesthesia.

3.1 Chemistry and Structures

Chemically it is 8-Chloro-6 (2-flurophenyl)-1-methyl-4H- imidazo (1,5-a) (1,4)-benzodiazepine.

Molecular weight: 362.

The unique chemical structure of midazolam confers a number of physiochemical properties that distinguishes it from other benzodiazepines in terms of its pharmacologic and pharmacokinetic properties. The imidazole ring is relatively basic, thus allowing the preparation of the salts, which are stable in aqueous solution. At pH below 4, part of drug in the solution has an open benzepine ring thus imparting water solubility. At physiological pH whole of the drugs is present in the 'ring closed from' and thus lipid solubility of the drug is increased.

Midazolam, an imidazobenzodiazepine derivative has a fused imidazole ring that is different from classic benzodiazepines[22]. The imidazole ring accounts for the rapid metabolism. The unique chemical structure of midazolam confers a number of physicochemical

properties that distinguish it from other benzodiazepine in terms of its pharmacologic and pharmacokinetic characteristics. Midazolam has molecular weight of 362. The pKa of midazolam is 6.15, which permits preparation of salts, which are water soluble. The parenteral preparation of midazolam used in clinical practice is buffered to an acidic pH (3.5). In acidic aqueous media, midazolam is water soluble, thereby allowing, parenteral formulation to exclude lipoidal constituents such as propylene glycol. On the other hand, at physiologic pH, midazolam becomes highly lipophilic and is one of the most lipid soluble benzodiazepines.(23) the high lipophilicity has a number of clinical consequences, which include rapid absorption from gastrointestinal tract and entry into brain tissue after intravenous administration. It is compatible with 5% dextrose normal saline, lactated Ringer's solution and can be mixed with acidic salts of other drugs. Midazolam with 0.8% sodium chloride and 0.01% disodium edetate with 1% benzyl alcohol as preservative.

Diagram:-Structure

Mechanism of action
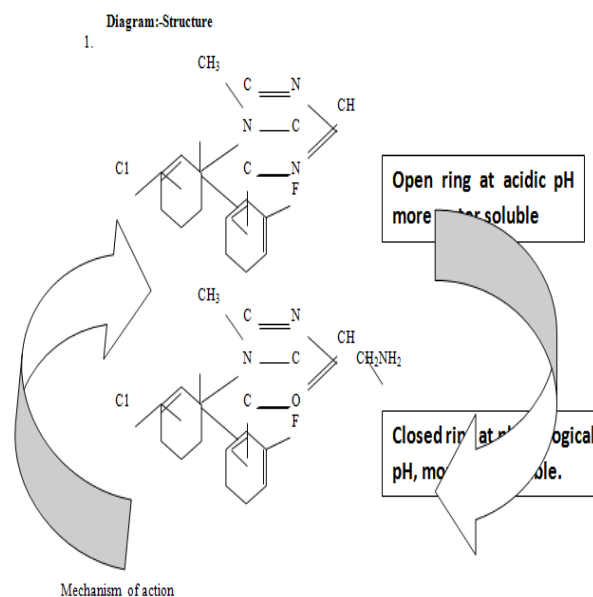
Benzodiazepines exert their general effect by occupying benzodiazepine receptors which modulate GABA (Gama amino butyric acid). The major inhibitory neurotransmitter in brain. (25) the benzodiazepine receptors are found in highest densities in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantia nigra and inferior collicus, with lower densities found in stratum, lower brain stem and spinal cord.

Although there are two GABA receptors, it appears that the benzodiazepine receptor is a part of $GABA_A$ receptor complex on the subsynaptic membrane of effector neuron. This receptor complex is made up of three protein subunits α, β and γ arranged as a pentameric

aerolic glycoprotein complex. These proteins contain the various ligand binding sites of $GABA_A$ receptor such as benzodiazepine, GABA and barbiturate binding sites. The benzodiazepine binding site located on γ2 subunit and β subunit is thought to contain binding site for GABA. With activation of $GABA_A$ receptor, gating of channel for chloride ions is triggered, the cells become hyperpolarized and therefore resistant to neuronal excitation. It is now postulated that hypnotic effects of benzodiazepines are mediated by alternation in a potential dependent calcium ion flux. The degree of modulation of GABA receptor function has inbuilt limitation and this explains the relatively high degree of safety with benzodiazepines.

By using plasma concentration data and pharmacokinetic simulation, it has been estimated that benzodiazepine receptor occupancy of less than 20% may be sufficient to produce anxiolytic effect. Sedation is observed with 30-50 % occupancy and unconsciousness requires 60% or higher occupation of benzodiazepine receptors.

Long term administration of benzodiazepines produces tolerance. Although mechanism of chronic tolerance is not fully understood, it appears that long term exposure causes down regulation of benzodiazepine $GABA_A$ receptor complex. After cessation of use there is up regulation of receptor complex, which could mean increased susceptibility to benzodiazepines[27].

3.2 Pharmacodynamics

Midazolam like all benzodiazepines has hypnotic, sedative, anxiolytic, amnestic, anticonvulsant and centrally produced muscle relaxant properties. The binding of benzodiazepines to their respective receptors is of high affinity with stereo-specificity and saturable in order of receptor affinity (potency). Midazolam is 3-6 times more potent than diazepam.

3.3 Effects on Central Nervous System

Midazolam, in a dose related manner, reduces the cerebral metabolic rate of oxygen consumption ($CMRO_2$) and Cerebral Blood Flow (CBF) but maintains a normal ration of CBF to $CMRO_2$. Brown et al.,[28] studied the EEG tracing after midazolam administration (10 mg IV) and showed the appearance of rhythmic beta activity at 22 Hz within 15-30 seconds of administration in healthy volunteers. Within 60 seconds, there was a second beta rhythm at 15 Hz, alpha rhythm started to appear within 30 minutes and after 60 minutes there was beta rhythmic activity. The EEG changes were not typical of light sleep, although patients were clinically asleep. Midazolam also increases seizure initiation threshold to local anaesthesia.

The reduction in $CMRO_2$ and CBF suggest that midazolam can protect against cerebral hypoxia and can be useful for patients who have increased Intracranial Pressure (ICP). This protection provided by midazolam is superior to diazepam but less than pentobarbital.

3.4 Effect on Respiratory System

Midazolam produces dose related central respiratory depression. The slope of ventilator response curve to carbon dioxide is flatter than normal, but not shifted to right as with opioids. Midazolam is five to nine times more potent than diazepam, taking into account plasma level and steepness of dose response curves. The peak onset of ventilatory depression with midazolam (0.13-02 mg/kg) is rapid (about 3 minutes) and significant respiratory depression remains for 60-120 minutes.

The rate of midazolam administration affects the onset of peak ventilatory depression, faster the drug is given, more quick is the depression. Respiratory depression is more pronounced in patients having chronic obstructive lung diseases. It is likely that benzodiazepines and opioids produced additive or supraaditive respiratory depression even though they act on different receptors.

Apnoea can occur after midazolam administration. The incidence of apnoea in patients induced by midazolam and thiopentone is similar[29]. Apnoea is related to does of midazolam and is more likely to occur in presence of opioids, old age and debilitating diseases. Other respiratory depressant drugs increase incidence and degree of respiratory depression and apnoea with midazolam.

3.5 Effects on Cardiovascular System

Midazolam used alone has a modest haemodynamic effect. The predominant change is slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The relatively stable haemodynamics after midazolam administration are due to preservation of homeostatic reflex mechanisms, but there is evidence that baroreceptor reflex is somewhat impaired by midazolam[30]. Midazolam cause more hypotension as compared to diazepam but is similar to thiopentone. The haemodynamic effect of midazolam is dose related, however there is a plateau plasma drug level above which little change in arterial blood pressure occurs. The plateau plasma level of midazolam is 100 mg/ml. Heart rate, ventricular filling pressure and cardiac output are maintained after induction with midazolam. In patients with raised left ventricular filling pressure,

midazolam produces a 'nitroglycerine like' effect by lowering filling pressure and increasing cardiac output[31].

The stress of endotracheal intubation and surgery is not blocked by midazolam, so opioids are generally used for the above purpose. The effect of combination of midazolam and opioids on hemodynamics is supra additive. The mechanism involved is probably related to a reduction in sympathetic tone.

3.6 Stress Response

Midazolam like other benzodiazepines reduces the adrenergic but not the cortisol or rennin response to the surgical stress. Premedication with midazolam decreases plasma concentration of the antidiuretic hormone just before anaesthesia compared with the placebo, an effect considered indicative of a reduced stress response[36].

3.7 Other Effects of Midazolam

Anxiolytic effect: Midazolam has an anxiolytic effect. In rats and squirrel monkeys, midazolam diminishes punished behaviour less than diazepam, apparently because of a more pronounced hypnotic component[32]. The mamillary body may be the site of anxiety, since bilateral injection of midazolam into the posterior hypothalamus mammilary bodies increased the punished response without a change in the unpunished response. It exerts its anxiolytic effect like other benzodiazepines by increasing the glycine inhibitory neurotransmitter. The affinity of the benzodiazepines for glycine receptors in the brain stem correlates with their antianxiety potency.

3.8 Hypnotic Effect

The hypnotic effect of midazolam is related to GABA accumulation and occupation of the benzodiazepine receptros. Specific benzodiazepine receptors are present mainly in the central nervous system possibly accounting for the relative lack of non CNS effects of the benzodiazepines. Midazolam has a relatively high affinity for the benzodiazepine receptor, two times that of diazepam.

The most widely accepted hypothesis for the hypnotic effect of benzodiazepine is that there are separate benzodiazepine and GABA receptor coupled to a common ionophore (chloride) channel. Occupation of both receptor produces membrane hyperpolarization and neuronal inhibition. Midazolam interferes with reuptake of GABA, causing its accumulation.

3.9 Anticonvulsant Effect

This is due to enhanced action of GABA on motor circuits in the brain.

3.10 Muscle Relaxant Effect

This effect is mediated through glycine receptors in the spinal cord. However, in anaesthetized humans, midazolam does not change the does of succinylcholine or pancuronium necessary to achieve and maintain muscle relaxation.

3.11 Antero Grade Amnestic Effect

The amnestic effect of an intravenous does of midazolam 5 mg, ranges from 20 to 32 min. Intramuscular administration may prolong it. The amnestic effect of midazolam may be more intense than diazepam but shorter lasting than lorazepam. Prolonged amnesia could be a problem in outpatients by interfering with their ability to recall oral instructions.

3.12 Antinociceptive Effect

Midazolam given by intrathecal or epidural injection can produce this effect. This could be GABA mediated because GABA has shown to have analgesic properties. Perhaps this is the mechanism by which midazolam decreases the MAC of halothane in humans[33].

3.13 Pharmacokinetics

The high lipophilicity of midazolam at physiologic pH causes it to have very rapid onset of action after intravenous administration, the equilibrium between plasma and CSF occurs within few minutes of intravenous administration. The high lipophilicity of midazolam, coupled with its very high metabolic clearance and rapid rate of elimination, cause it to have a short duration of activity. After intravenous administration of midazolam to healthy young humans, the disappearance of midazolam from plasma proceeds in at least two distinct phases, the initial phase of rapid disappearance is due to distribution of drug, while the final and slower phase of disappearance is mainly by biotransformation. In healthy individuals, volume of distribution averages between 1 to 205 1t/kg. It should be noted that midazolam is bound extensively to plasma proteins and volume of distribution estimated on basis of total drug in plasma (bound and free) underestimates the volume of distribution of unbound form that is pharmacologically active. After

the distribution equilibrium is achieved, elimination of midazolam proceeds rapidly, with half-life ranging from 1-4 hours. The total clearance of midazolam is approximately 50% of hepatic blood flow.

Thus midazolam is a widely distributed and very rapidly cleared benzodiazepine.

Table 1.   Comparison of pharmacokinetic variable

	Diazepam	Midazolam
T ½ α (min)	30-60	6-15
T ½ β(h)	24-57	1.7-4
Vd (1/kg)	0.7-1.7	1.1-1.7
Cl (ml/min/kg)	0.24-0.53	6.4-11.1

The major differences in pharmacokinetics of diazepam and midazolam can be seen in the above table. The distribution half life of midazolam (T ½ α) is at least one half that of diazepam and elimination half life (T ½ β) is tenfold less. The volume of distribution (Vd) is almost similar and the total body clearance (C1) of midazolam is much higher than diazepam. So midazolam is a short lived compound as compared to diazepam.

After oral administration, midazolam is absorbed rapidly from GIT, peak plasma concentration is generally achieved within 1 hour of ingestion and the clinical effects after oral administration are correspondingly rapid. Because of extensive first pass hepatic extraction, only 40-50% of orally administered midazolam reaches plasma. The elimination half-life of oral midazolam, on the other hand is similar to that observed after intravenous administration.

Factors known to influence pharmacokinetics of midazolam are age, gender, race, enzyme induction, hepatic and renal diseases[24]. Increasing age tends to reduce clearance of midazolam but to a lesser degree than diazepam. When administrated to obese individuals, the volume of distribution of midazolam include peripheral adipose tissue, this in turn causes a significant prolongation of elimination half-life but no change in the total metabolic clearance. However, dosing for continuous infusion in obese patient should be based on lean body weight because clearance is unaffected by weight.

3.14 Metabolism

Midazolam is bound extensively to plasma proteins, the degree of binding averages 96-97 % and is independent of the does and plasma concentration of midazolam.

Biotransformation of benzodiazepines occurs in liver. Metabolism of midazolam involves hydroxylation by hepatic microsomal oxidative mechanism. The fused imidazole ring is oxidized rapidly in the liver, much more rapidly than the methylene group of the diazepine of other benzodiazepines. This accounts for greater hepatic clearance of midazolam compared with diazepam. The principal metabolite is 1-hydroxyl midazolam, smaller amount of 4-hydroxyl midazolam is formed in parallel and even smaller amounts of 1-4 dihydroxy midazolam can be detected. These metabolites are excreted in urine as glucuronide conjugates. Very little drug is excreted unchanged in urine. The 1-hydroxyl and to l lesser extent 4- hydroxy metabolites of midazolam are present in the human blood in unconjugated form. The 1-hydroxy metabolite has a clinical potency of 20-30 % of the parent compound and can causes profound sedation in patients with renal impairment.

Diagram:

1-Hydroxy Methyl Midazolam Glucuronide

4- Hydroxy Midazolam Glucuronide
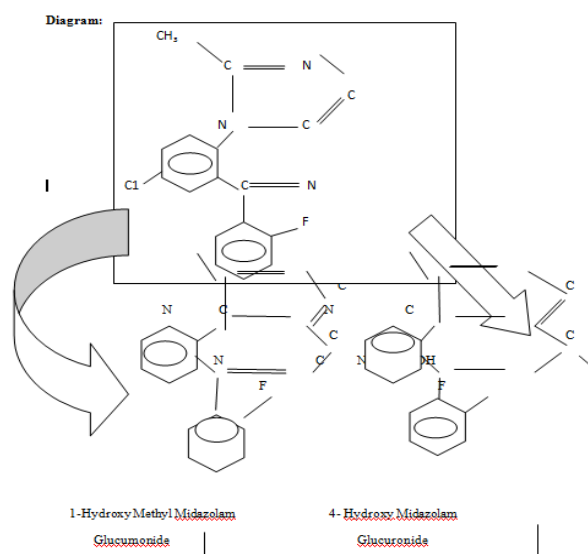
Routes of administration and dosages:
a) Preoperative sedation / Premedication:
Below 60 yrs.   0.07-0.08 mg/kg i. m.
                        0.15-0.35 mg/kg i. v.
                        0.5 mg/kg oral
                        0.3 mg/kg rectal
   b) Induction of anaesthesia: 0.15-0.5   mg/kg i.v.
   c) For i.v. Sedation: 0.03-0.3   mg/kg.

3.15 Uses /Indication

• Premedication

Midazolam, like other benzodiazepines, is well suited for premedication because of its anxiolytic and hypnotic properties. When midazolam 5 mg was given as an intravenous premedication, the hypnotic and anxiolytic effects appeared within 1-2 minutes and memory picture

shown at 4 minutes was not recalled by 78% of the patients. These effects persisted for 30 minutes. Midazolam has been used as a permedicant by intramuscular route. The intramuscular administration does not produce significant pain or local irritation. Oral midazolam for premedication has rapid onset and recovery and is being used for premedication in children, in a dose of 0.5 mg/kg. In adults 15 mg per oral dose of midazolam is shown to be superior to placebo.

- Induction and Maintenance of Anaesthesia

Faster onset of action and lack of pain and phlebitis after intravenous injection make midazolam a preferred induction agent among benzodiazepine. Induction of anaesthesia with midazolam is defined as unresponsiveness to commands and loss of eyelash reflex. Induction occurs less rapidly with midazolam but amnesia is more reliable as compared to thiopentone. Factors like dose, speed of injection, age, degree of premedication. American Society of Anaesthesiologist (ASA) physical status and concurrent anaesthetic drug administration influence the rapidly of induction with midazolam.

In a healthy, well premedicated patient midazolam 0.2 mg/kg given in 5-15 seconds will induce anaesthesia in 28 seconds. Patients above 55 years of age and those in physical statuses ASA III and above will require a 20% or more reduction in dose of midazolam for induction. Elderly patients require a lesser dose than healthy young patients. When midazolam is used with other anaesthetic drugs for induction (co-induction), there is a synergistic interaction, so that the induction dose of midazolam is reduced.

The emergence (defined as orientation to time and place) of young healthy volunteers who receive 10 mg midazolam IV occurs in about 15 minutes. Awakening after midazolam anaesthesia is due to redistribution of drug from brain to other less well perfused tissues. The emergence time is related to the dose of midazolam used and administration of adjuvant anaesthesia.

Double blind studies comparing midazolam and thiopentone as hypnotic show that midazolam is preferable because of better amnesia and smooth haemodynamic course. Midazolam (0.6 mg/kg) lowers the Minimum Alveolar Concentration (MAC) of halothane by 30% and probably has the same effect on other inhaled anaesthetics. Benzodiazepines do not have any analgesic properties but opioid requirements are less with midazolam. The amnesiac period following an anaesthetic dose of midazolam is 1-2 hours. A plasma level of 50 mg/ml when used with adjuvant opioids is achieved with a bolus loading dose of 0.05 to 0.15 mg/kg and a continuous infusion of 0.25 to 1 μg/kg/min. this

level of plasma concentration is sufficient to keep the patient amnesiac and asleep but easily arousable at the end of surgery.

- Intravenous Sedation

Midazolam is used for sedation pre-operatively as premedication, intra-operatively during regional or local anaesthesia, post operatively and in patients in ICU. The desirable actions are anxiolysis, sedation and elevation of local anaesthetic seizures threshold. There exists slight synergistic action of midazolam and spinal anaesthesia with respect to ventilation[34]. So respiratory monitoring is mandatory when used with regional anesthesia.

Midazolam should be given by titration for sedation, the end point being adequate sedation and dysarthria. The peak effect of midazolam is reached within 2-3 minutes of administration. There is often a disparity between the level of sedation as compared to amnesia (patients may be reasonably coherent and conscious but have amnesia for events and instructions). The degree of sedation and amnesia as well as preservation of respiratory and haemodynamic functions are better with benzodiazepine as compared to other sedatives and hypnotics.

- ICU Sedation

In critically ill patients, the main aim of sedation is to provide relief from anxiety and pain. Midazolam is safe and effective in these patients.

- As an Adjunct to Local/Regional Anaesthesia
- Other Uses

As an anticonvulsant especially in the treatment of refractory seizures- status epilepticus. It can be given intramuscularly when i.v. access if difficult to establish in emergency department.

3.16 Side Effects
Midazolam is remarkably free of side effects.
- Incidence of nausea, vomiting after general anaesthesia is 15-1%.
- Ventilatory depression-dose related and common after i.v. administration and seen after opiate premedication.
- Local complication like pain on injection and thrombophlebitis is negligible (upto 5%)
- Rare: hiccough, headache, bronchospasm and emergence delirium.

3.17 Drug Abuse and Dependence
Available data concerning drug abuse and dependence potential of midazolam suggest that its abuse potential is equivalent to that of diazepam.

3.18 Contraindications and Precaution

- Hypersensitivity to benzodiazepines.
- Acute narrow angle glaucoma.
- There may be impairment of psychomotor skills following midazolam sedation or anaesthesia. Hence, patients should not be allowed to operate hazardous machinery or a motor vehicle till the effects of midazolam, such as drowsiness and amnesia have subsided.
- Elderly patients require lower doses whether premedicated or not.
- Patients with chronic obstructive pulmonary disease are usually sensitive to the respiratory depressant effects of midazolam.
- Midazolam should not be administered unless the equipment for resuscitation and skilled personnel for the maintenance of airway are available.
- Midazolam is secreted in human milk, hence not recommended for use in nursing mothers.
- Paediatrics: No specific problem encountered till today.

3.19 Drug Interaction

- Sedation with midazolam is accentuated by premedication with morphine, meperidine and fentanyl.
- After i.m. administration as premedication, dose of pentothal required for the induction is less and hence should be titrated.
- Hypotensive effects may be potentiated when medication viz. Beta-blockers, Clacium-channel blockers, Diuretics, Angiotensin converting enzyme inhibitors, nitrates are used concurrently.
- I. V. administration of midazolam decreases the MAC of halothane required for general anaesthesia.

3.20 Over Dose and Its Treatment

The manifestation of midazolam over dose are expected to be similar to those observed with other benzodiazepines including sedation, somnolence, confusion, impaired co-ordination, diminished reflexes, coma and untoward effects on vital signs.

Treatment:
- Most important is the maintenance of airway and support of ventilation.
- Haemodynamic support.
- "Fulmanezil"-a specific benzodiazepine antagonist is indicated for reversal of the sedative effects of midazolam[26].

Fulmanezil has some intrinsic activity, but it competes with benzodiazepine agonist for receptors and reverses its depressant effect. It abolishes hypnogenic, psychomotor, cognitive and EEG effects of benzodiazepines.

After oral administration it is absorbed and then undergoes high first pass metabolism in liver, bioavailability is only 16%. On i.v. administration action starts in seconds and lasts for 1 to 3 hours. Elimination half-life is 1 hour.

- For reversal of benzodiazepine anaesthesia 0.3-1 mg/i.v.
- It allow more rapid discharge of patients after diagnostic procedures and facilitates post-anaesthetic management.
- Benzodiazepine over dose: 0.2 mg/min I.V. (maximum g mg).
- Patients usually respond within 5 minutes.

3.21 Side Effects

Agitation, discomfort, tearfulness, anxiety and rarely withdrawl seizures.

4. Review of Literature

The concept of premedication was well established by the end of nineteenth century. Shearer[37] in 1960 divided the history of premedication into two phases the period prior to 1920, when premedication was not considered an indispensable prerequisite to anaesthesia and the period after 120 when pre-medication really evolved. In preanaesthetic days both wine and opium were given to mitigate, the terrors of surgery. The word 'premedicantion' itself first appeared in print in an article by American editor-anaesthetist Frank Hoeffer McMechan in 1920[38] and in an annotation in Lancet[39]. It was recommended by Bellamy Gardner[40] and Dudly Buxton of University College Hospital in UK and rules determining whether or not 'preliminary medication' should be used were published in USA in 1911[41]. In 1914, it was stated that 'preliminary medication' was employed in 59% of hospitals in USA[42].

Morphine was the first drug to be used as a permedicant to allay anxiety by Bruno of Turin in 1850 and by Munich Surgeon JN Von Nussbaun (1829-1890) to reduce the amount of anaesthetic needed in 1864. Claude Bernard used morphine in animals before anaesthesia and this led to one of his pupil Guibert of St. Brieuc to use it clinically in an effort to reduce the amount of choloroform needed to produce deep anaesthesia. As combination of morphine and anaesthesia caused hypoventilation resulting in rigid abdomen, it failed to become a popular method but

pioneer neurosurgeon Sir Victor Rousely used it to reduce bleeding in1886[43]. Chloral hydrate was given to produce sleep and sedation by Forne[44].

Atropine was isolated by Louis Nicolas Vaquelin in 180. EH Embely showed experimentally in 1883 that occasional cardiac arrest caused by chloroform was due to vagal stimulation and could be blocked by full atropinization[45]. Thus, atropine was employed before chloroform anaesthesia. As ether gradually replaced chloroform, it was used for its drying effects on secretion. Schneiderlin in 1964 used scopolamine with morphine to treat acute mania and as a full anaesthetic. Later this combination became popular as premedication.

Pethidine was synthesized by Schaumann and Eisleb and first used as premedication by Schulungbaum et al as a supplement to nitrous oxide anaesthesia in 1949. A similar technique was also used by Mushin and Rendal Baker in 1949.

Dipps Eden Half and Vandam N in 159 used premedication to pave the way for a smooth anaesthetic and post operative course. Mushin WW in 1960 used premedication to prevent undesirable side effects of anaesthesia. Phenoperidone and morphine were recommended by Bailey et al in 1984 to decrease the stress response to general anaesthesia. Much of the rationale for premedication arose in the days when the most widely used anaesthetics were ether and cyclopropane, in order to minimize the sied effects of these drugs. Anaesthetists sought to bring patients to the operating room heavily sedated with a very dry mouth. However the goals of premedication have now expanded and include.

- Relief of apprehension before anaesthesia and surgery.
- To produce sedation.
- Produce amnesia.
- Provide relief from pain.
- As part of the anaesthetic technique to facilitate induction and smooth reversal of anaesthesia.
- Reduce secretions from trachea-bronchial tree and salivary glands.
- Prevention of vagal reflexes caused by surgical stimulation or associated with administered drugs.
- Prevent autonomic reflex response.
- Decrease minimum alveolar concentration of volatile anaesthetics.
- Prevent nausea and vomiting.
- As prophylaxis against allergic reactions.

In spite of availability and wide use of large number of premedicatnts, there has never been universal agreement on the optimal choice of permedicant for a particular patient. Traditional or institutional preference or both,

have long been the major factors when choosing a permedicant drug. Ideally the patients should enter the operation theatre without undue sedation or compromise of safety but with as much relief of anxiety as possible. Egbert et al in 1963 demonstrated that more patients were adequately prepared after a pre-operative interview alone than preoperative medication without an accompanying preoperative visit. But shortage of time and the fact that some patient problems do not lend themselves to reassurance might limit the value of preoperative interview and often indicate the need for premedication.

Despite the availability of large number of premedicatnts for paediatric age groups, there has been no universal agreement on the ideal permedicant and ideal route of drug administration. Oral premedication is more widely used and there is an increasing tendency to avoid injection in small children. Surveys of paediatric inpatients indicate that injections constitute one of the greatest fears in hospitalized children[46].

Recent studies have suggested that oral preanaesthetic medication can be as or even more effective than intramuscular premedication in paediatric inpatients. Nicholson et al.,[47] in a prospective, randomized double blind study compared pharmacological effects of oral verses intramuscular premedication in 67 paediatric inpatients more than 1 year of age. Children given oral medication (meperidine 3 mg/kg and pentobarbital 4 mg/kg) were more drowsy in the holding area (p<0.01) and more co-operative during induction than children who had been given intramuscular medication (morphine 0.1 mg/kg and pentobarbital 4 mg/kg). They concluded that oral premedication can be as or more effective than intramuscular injections for all but a few paediatric patients who cannot or refuse to swallow permedicant. Oral premedication prevents unpleasantness of placing a needle in a small child but may have the disadvantage of slower onset and lesser bioavailability of permedicant drugs.

Different drugs like phenothiazines, benzodiazepines, opioid analgesics, barbiturates etc have been used alone or in combination as premedicants in paediatric patients using different routes of administration. Midazolam, a water soluble benzodiazepine, has rapid onset of action and short elimination half life. Ketamine is a phencyclidine derivative, which has significant analgesic properties, compared to other induction agents. Both these drugs are frequently used as premedicants by different routes in paediatric patients. In 1974, Rita Lucida[48] and co-workers reported on the use of Ketamine in a dose of 2.5 mg/kg given intramuscularly for premedicating 60 children as compared to a control group who were premedicated

with pentazocine. They found that memory of unpleasant operating room experiences was prevented in 90% of children given Ketamine premedication and in only 10% of patients given pentazocine. The drawback of the use of IM Ketamine for paediatric pre-medication was the need for an anaesthesiologist or other responsible person to remain with the child to cope with untoward effects of the drug, viz. marked postoperative restlessness and high incidence of postoperative vomiting.

Rita et al.,[48] in a double blind study compromising of 90 children age 1-15 years compared sedative effect of intramuscular midazolam (0.08 mg/kg) and morphine (0.15 mg/kg). They concluded that children receiving intramuscular midazolam had smoother induction of anaesthesia compared to morphine or control group. They had shorter length of stay in recovery room and lower incidence of sleepiness and vomiting postoperatively.

Cranfield and Lyons in 1971[49] conducted a study of 150 children scheduled for otolaryngological surgery who were given Ketamine in a dose of 2.5 mg/Ib intramuscularly and compared then with a control group given routine preoperative medication. They observed that the children, who received Ketamine were unaware of their trip to the operating room, had a considerably shortened and smoother induction. However, they found a prolonged recovery time during which children had to be monitored closely. The adverse effects included respiratory irregularities and late laryngeal spasm occurring in 5% of the test group. Emergence phenomenon was not significant.

The advantages of intramuscular injections are more reliable effect and rapid onset. Disadvantages include the fact that they are painful and invariably frightening for a child, a sterile abscess may form at site of injection and usually the major adverse anaesthetic experience children remember is the 'shot' they received. Because of these reasons many institutions have switched away from this route for routine paediatric premedication.

Intravenous premedication and induction can be used in older paediatric patients and in patients who have an intravenous line in place. Before establishing intravenous access, EMLA cream, if available can be applied. Low dose IV midazolam (0.05-0.075 mg/kg) is used for sedation and anxiolysis in children. Intravenous Ketamine may also be used in low doses (0.25-0.5 mg/kg) for the same purpose. Intravenous injections can hurt and moreover it may be difficult to start an IV line in an uncooperative, agitated child.

Midazolam and Ketamine have both been used as a premedicant via intranasal route. Wilton et al.,[50] reported in a double blind study comprising of 45 preschool children, the effects of intranasal midazolam premedication. The children were allocated to 3 groups: group 1 received placebo, group 2 received intranasal midazolam 0.2 mg/kg, group 3 received 0.3 mg/kg intranasal. They concluded that intranasal midazolam is an effective anxiolytic and sedative and has a rapid onset of action. They recommended that a higher dose does not have any additional benefit and 0.2 mg/kg should be used for premedication. Though this route of drug administration is quite uncomfortable for the patients, it is reliable and rapid acting.

The efficacy of intranasal Ketamine as a paediatric premedicant was demonstrated by Weksler et al.,[51] who administered Ketamine 20-40 min before surgery. These children were compared with 60 others in whom 1 mg/kg each of promethazine and meperidine was injected intramuscularly. The researchers concluded that preanaesthetic nasal Ketamine is a viable alternative to intramuscular administration in children between 2-5 years of age.

An important concern with intranasal administration is that drugs, which are administered by this route, may traverse directly into the central nervous system through cribriform plate via the olfactory nerves. This route of administration is questionable until lack of neuro-toxicity is demonstrated with both midazolam and Ketamine besides their preservatives[52].

Midazolam has also been administered rectally in a dose of 0.5 mg/kg[53]. This generally results in a satisfactory level of sedation and anxiolysis in approx 15-20 minutes after administration. Lin[54] and others studied the effects of Ketamine hydrochloride Per Nasus (PN) or Per Rectum (PR) as premedication in 70 children aged 6 months to 6 years. Group A (n = 25) received no premedicant, while group B (n = 25) and group C (n = 25) received Ketamine 6 mg/kg PR and 3 mg/kg PN respectively. It was demonstrated that patients in group B and C accepted facemask during anaesthesia more willingly and peacefully than those in group A although their emergence from anaesthesia was delayed.

The major concern with rectal drug administration is that of irregular drug absorption[55] with some children having very rapid uptake and others having a delayed effect. This is as a result of several factors including how much faecal matter in present, the pH of drug administered, whether the child expels the premedication at time of administration and site in rectum where drug is administered[55]. In general, this route of drug administration is appropriate for children still in diapers but usually not accepted by older children.

Another method of midazolam administration is to

administer it sublingually in a dose of 0.2-0.3 mg/kg[56]. The oral mucosa provides a large vascular absorptive surface, which then results in rapid drug uptake comparable to nasal drug administration. The incidence of inadequate sedation is less compared to nasal drug administration. The incidence of inadequate sedation is less compared to nasal drug administration.

Ketamine has also been used by transmucosal route. Cioca et al.,[57] compared oral transmucosal Ketamine (5-6 mg/kg) with intranasal Ketamine (5-6 mg/kg). Oral Transmucosal Ketamine (OTK) provided effective sedation, facilitated IV injection and was accepted with pleasure by patients.

Sjonall et al [58] compared the effects of oral midazolam with those of intramuscular meperidine and atropine in children. They concluded that midazolam 0.2 mg/kg PO was as effective for anxiolysis as a combination of meperidine 1 mg/kg and atropine 0.01 mg/kg. Saarnivarra et al.,[59] reported a study involving children (1-9) receiving midazolam or chloral hydrate orally (in combination with atropine). Their investigations concluded that midazolam (0.4-0.6 mg/kg) PO provided only fair anxiolysis in children less than 5 years of age. In contrast midazolam 0.4-0.6 mg/kg PO produced good anxiolysis in older children (more than 5 years).

Feld et al.,[60] compared that effect of oral midazolam 0.25 or 0.5 mg/kg PO and midazolam 0.1 or 0.2 mg/kg IM. They concluded that midazolam 0.5 mg/kg PO was an effective alternative to IM injection for paediatric out patients requiring preanaesthetic medication.

Feld et al.,[60] studied effectiveness of three doses of midazolam in a randomized, double blind placebo controlled study. The study group included 124 children 1-10 years of age, undergoing ambulatory surgery, allocated randomly into four groups. Each group received 0.25 mg, 0.5 mg, 0.75 mg/kg of midazolam and placebo respectively with oral atropine 0.03 mg/kg mixed in apple juice. They concluded that oral midazolam in a dosage of 0.5-0.75 mg/kg was an effective preanaesthetic. Recovery time was not prolonged by midazolam atropine premedication.

Parnis et al.,[20] studied the effects of oral premedication in a double blind randomized trial of 200 children undergoing day stay anaesthesia. Midazolam 0.5 mg/kg, midazolam 0.25 mg/kg, diazepam 0.5 mg/kg or a placebo was given orally one hour prior to induction of anaesthesia. Patients who received 0.5 mg/kg midazolam per orally were more likely to be asleep or awake and calm at induction compared with other groups. They concluded that a high proportion of unsedated children were calm at induction of anaesthesia and that oral midazolam is an effective premedication for day stay anaesthesia.

Craig Weldon et al.,[61] studied oral preanaesthetic medication regimen in 15 healthy children, 1-8 years of age. Group A (placebo) received 5 ml of apple juice, the other five groups received medication with apple juice to a total volume of 5 ml. Group B received atropine (0.02 mg/kg), group C received midazolam (0.5 mg/kg), group D received midazolam (0.5 mg/kg) + atropine (0.2 mg/kg) + group E received meperidine (1.5 mg/kg) + atropine (0.02 mg/kg) + midazolam (0.5 mg/kg). The sedative effects of midazolam were maximal 30 minutes after oral administration. Ninety five percent of patients who were separated from their parents within 45 minutes after oral midazolam administration had satisfactory separation scores. Midazolam treated patients were more co-operative at mask induction of anaesthesia compared with non-midazolam treated children (83% Vs. 56%). They concluded that midazolam (0.5 mg/kg) given orally 30-45 minutes before induction of anaesthesia was safe and effective without delaying recovery after ambulatory surgery.

Levine et al.,[62] studied 30 children aged 1-6 years scheduled for elective cardiac surgery for congenital cyanotic heart disease. The children were randomly assigned to one of two groups, group I received oral midazolam 0.75 mg/kg 30 minutes before separation from their parents; group 2 received oral or rectal phenobarbitone 2 mg/kg at 90 minutes and morphine 0.2 mg/kg with atropine 0.02 mg/kg at 60 minutes before separation from their parents. They found improved anxiolysis and sedation but no difference in anxiolysis. Intramuscular morphine induced a transient decrease in mean SpO_3 (from 84% to 76%) that did not occur in midazolam group. They concluded that oral midazolam is a safe and effective premedication for children with CCHD undergoing cardiac surgery.

Anderson et al.,[63] in a double blind study consisting of 339 randomly selected children investigated the effects of several premedicants on preoperative and postoperative behavior of children who underwent day stay surgery. Patients were allocated to 2 groups; both groups received alprazolam 0.005 mg/kg, midazolam 0.3 mg/kg and placebo. In addition, Group I received chloral hydrate 40 mg/kg and Group II diazepam 0.25 mg/kg. Chloral hydrate produced superior conditions with more patients calm and asleep at induction of anaesthesia. The time to awaken postoperatively with diazepam was longer than placebo. Alprazolam and midazolam were unpalatable for children over four years and conferred no advantage over placebo.

Jones et al.,[64] studied 30 children 4-12 years of

age undergoing elective circumcision premedicated with midazolam 0.5 mg/kg and atropine 0.02 mg/kg by mouth. The children showed a significant decline in psychomotor performance 30 to 60 minutes after premedication compared to their best-unmedicated performance the previous evening. The decline in psychomotor performance was poorly related to serum midazolam concentration. They concluded that sedative and anxiolytic effects of midazolam provide a quiet environment for induction of anaesthesia.

Mitchell et al.,[65] compared midazolam and trimeprazine as an oral premedicants for children in a double blind randomized trial in 85 children undergoing tonsillectomy and of adenoidectomy. Orally administered midazolam (0.5 mg/kg) given 30 minutes preoperatively was compared with trimeprazine (2 mg/kg) and a placebo. Following premedication with midazolam none of the patients were anxious, crying or distressed leaving the ward compared with 2/18 in trimeprazine group and 5/28 in placebo group (p = 0.0007). More patients were calm and quiet on arrival in anaesthetic room following midazolam than following trimeprazine, with both premedicants comparing favorably with placebo. There was no significant difference between the three groups in the time to recovery or sedation score on discharge to ward. They concluded that oral midazolam is a safe and effective oral premedicants in children.

Vetter[66] in a prospective, randomized double blind study comprising o 75 children (1-6 years of age) undergoing outpatient surgery, compared midazolam, diazepam and placebo as oral preanaesthetic medication. Patients received randomly either midazolam (0.6 mg/kg), diazepam (0.3 mg/kg) or placebo orally. No significant differences in parental separation scores were observed. However, both midazolam and diazepam were observed to be superior to placebo in acceptance of mask. The author concluded that without premedication majority of children did not react to impending anaesthetic. Rather than implementing routine use of sedatives in children preoperatively, the challenge appears to be selective identification of likely candidates for preanaesthetic difficulties and psychological trauma.

Patel et al.,[67] studied 9 children who were assigned randomly to one of three groups for premedication, with oral midazolam 0.5 mg/kg, diazepam 0.25 mg/kg, droperidol 0.25 mg/kg or trimeprazine 2 mg/kg. on arrival in the anaesthetic room, anxiolysis was satisfactory in 26 out of 29 (90%) children in midazolam group compared with 23 out of 29 (79%) in diazepam and droperidol group and 18 out of 29 (62%) who received trimeprazine (p<0.05). At induction of anaesthesia these proportions

were 24 out of 29 (83%), 16 out of 29 (55%) and 11 out of 29 (40%) respectively (p<0.001). There were no significant differences in times to early recovery between the groups (25.4, 24.4, 28.5 min). Analysis of behavioural questionnaire completed two weeks after hospitalization showed a trend towards fewer postoperative behavioural disturbances in children who received midazolam and diazepam-droperidol compared with trimeprazine (47%) and (44% VS 75%). When results for the benzodiazepine containing premedicants were combined, the difference between these groups and trimeprazine was statistically significant (p<0.05).

Kain et al.,[68] compared parental presence during induction of anaesthesia with oral midazolam premedication in children undergoing anaesthesia. Children (n = 88) were randomly assigned to 3 groups, group 1 received 0.5 mg/kg oral midazolam, group 2 children had parental presence during induction of anaesthesia, group 3 was control group. Using multiple behavioural measures of anxiety, the effect of intervention in children and their parents was assessed. Observed anxiety in the holding areas (T_1), entrance to the operating room (T_2) and introduction of anaesthesia mask (T_3) differed significantly among the tree groups (p = 0.032). Children in midazolam group exhibited significantly less anxiety compared with children in the parental presence group of control group (p = 0.0171). Authors concluded that oral midazolam is more effective than either parental presence of no intervention for managing children and parental anxiety during the preoperative period.

Feld et al.,[60] studied the effectiveness of three different doses of oral midazolam administered in combination with atropine prior to ambulatory surgery. In this study, 124 children aged 1-10 years were assigned to one of four groups (31 each). They received midazolam, 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg po and atropine 0.03 mg/kg po mixed with apple juice 5 ml as a placebo. A blinded observer noted the child's level of sedation, the quality of separation from parents and the degree of co-operation with an inhalation induction of anaesthesia. Picture recall was used to assess the amnesic effect of midazolam in children over 5 years. Midazolam 0.75 mg/kg produced significant sedation at 30 minutes. After procedures lasting an average of 106-113 minutes, recovery was not prolonged by the oral midazolam-atropine combination. They concluded that oral midazolam 0.5-0.75 mg/kg is an effective preanaesthetic medication for paediatric outpatient.

Isabella A et al.,[69] studied the minimum time interval for separation from parents with oral midazolam in children as a premedication. 30 children were assigned

randomly to one of three groups (10 children per group). The groups differed only in the time interval between administration of midazolam and separation from parents: 10, 20 or 30 minutes. Heart rate, systolic blood pressure and sedation and anxiolysis score were assessed before midazolam premedication (baseline), at the time of separation from parents, and during the application of a face mask at the induction of anaesthesia. They found that heart rate and systolic blood pressure changes were similar for all three groups throughout the study period. Sedation scores at the time of separation from parents and on application of the mask for all three groups were greater than baseline values. Sedation scores at separation did not differ among he three groups. Anxiolysis values did not differ from baseline values at any time for all three groups. They concluded that children may be separated from their parents as early as ten minutes after receiving oral midazolam 0.5 mg/kg.

McCluskey and Meakin[70] studied 54 children aged 1-10 years scheduled for day-case anaesthesia. They were prescribed either oral midazolam 0.5 mg/kg or placebo preparation 30-60 minutes preoperatively on a double blind basis. On arrival at the induction room, anxiolysis was satisfactory in 23 out of 24 (96%) children who received midazolam compared with 12 out of 27 (44%) of those who received placebo (p<0.001); at induction of anaesthesia these proportions were 21 out of 24 (88%) and 9 out of 27 (33%) respectively (p<0.001). The time to early recovery from anaesthesia was somewhat longer in children premedicated with midazolam compared with controls (28.2 Vs 21.9 min) (p<0.05). Similarly, the time to hospital discharge was longer in midazolam group (244 Vs. 185min) (p<0.01). Analysis of behavioural questionnaires completed by parents 2 weeks after hospitalization indicated that there were fewer postoperative behavioural disturbances in children premedicated with midazolam compared with controls(p<0.5).

Mac Millan et al.,[71] in a randomized, double blind, placebo-controlled study, found the efficacy and feasibility of oral midazolam premedication in an ambulatory surgery unit. Eighty children (ASA PS I or II aged 1-6 years) were assigned to one of four groups receiving midazolam 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg and placebo distilled water in a chocolate syrup 30 minutes before surgery. Heart rate, systolic blood pressure, arterial O_2, respiratory rate, sedation and anxiolysis scores were studied before premedication and every 5 minutes for 30 minutes after they found that heart rate, systolic blood pressure, arterial O_2 saturation, respiratory rate were unchanged. Sedation and anxiolysis scores in midazolam treated groups were better than placebo group and that

anxiolysis and separation from parents was judged excellent 80-90 % of children who received midazolam. However, sedation and anxiolysis did not differ among the three midazolam groups. Mean times to discharge were similar in all four groups. The side effects, loss of balance and head control, blurred vision and dysphoric reactions were observed in 0.75 and 1.0 mg/kg groups. They concluded that oral midazolam 0.5 mg/kg is a safe and effective premedication and that 0.75 mg/kg and 1 mg/kg while offering no additional benefit may cause more side effects.

5. Materials and Methods

The present study was carried out in the department of anaesthesiology, General Hospital, Sangli after written informed consent of the parents. Approval of ethical committee of Government Medical College, Miraj was obtained. 90 children scheduled for elective surgery requiring general anaesthesia were included in the study. The inclusion criteria was:

- Children between 1-8 years of age nil by mouth.
- ASA physical status I.
- No known allergy to benzodiazepines or vehicle.
- No h/o any systemic disease, upper airway disease, CNS dysfunction, gastroesophageal reflux or dysmotility.

5.1 Selection of Patients

The children aged 1-8 years were assigned to one of three oral premedication groups by random selection. Each group contained 30 children.

Group I received 0.5 mg/kg oral midazolam and Group II received 0.75 mg/kg oral midazolam both in 25% dextrose to a total volume of 5 ml.

Group III or control group received 5 ml of 25% dextrose.

Routine investigations were done like hemoglobin percent, lecucocytes count, TC, DC, Urine albumin and sugar. Weight of patients was done.

Surgeries lasting approximately 30 minutes were selected in the study.

To make solution palatable the calculated doses of midazolam were mixed with 25% dextrose solution.

The premedication was administered orally to the patient 30-45 minutes before scheduled surgery time. Patients were encouraged to swallow the drug. Patients who refused to swallow or spitted or vomited the drug were excluded from the study. The drug was given in pre-operative room when the children were with their parents.

Baseline heart rate, systolic blood pressure and respiratory rate were measured before administering the premedication and at 5 minutes intervals there after upto 30 minutes after premedication.

Untoward effect such as apnea, airway obstruction was also recorded.

Efficacy and safety of oral midazolam were assessed during the 30 minutes. Clinical indices were used to quantitate the efficacy that is the degree of sedation during this period.

The level of sedation was measured at 10 minutes intervals on a 4 point Scale.

Score 1 = Alert /active
2 = Aware/Calm
3 = Drowsy / but responds to verbal/tactile stimulation
4 = Asleep

Children were separated from their parents after a period of at least 30 min after administration of premedication. The effectiveness of oral midazolam to minimize emotional responses at this time was assessed on the basis of a 4 point emotional state scale.

Score 1 = Tearful/Combative
2 = Anxious but easily reassured
3 = Asleep

On arrival in operation theatre anaesthesia was induced with oxygen, nitrous oxide and halothane with a facemask. Acceptance of mask was recorded using the same emotional state scale.

After inhalation induction and intubation with suitable muscle relaxants, anaesthesia was maintained with oxygen, nitrous oxide and halothane in a titrated concentration so as to maintain hemodynamic stability. Muscle relaxants were antagonized at the end of surgery. Postoperative side effects such as nausea, vomiting, giddiness, headache were recorded.

Proforma
Oral Midazolam as Premedication in Paediatric Patients

P. G. Teacher	P. G. Student
Dr. V. A. Kurhekar	Dr. J. K. Phaltankar
(M.D.)	(M.B.B.S.)
	DATE:18/06/2002
	STUDY Group :1
	Case No. : 2

Name of the patient: Omkar Jadhav
Reg. No.:2925
Age: 2 Yrs.
                    Weight: 13 Kg.

Sex: M
Operation: Circumcision
Pre-operative examination: ASA Grade I
Past medical / surgical history: Not contributory
Pre-operative investigations:
    Hb: 11 gm%
    TC: 8,600
    DC: P-62   L-37,   M-0,   E-1
    Urine: Albumin   -   Nil
                Sugar   -   Nil

I)

	Vital parameters	Time in minutes			
		0	10	20	30
1	Pulse Rate(Beats/Min)	122	122	114	114
2	Systolic Blood Pressure(mm Hg)	88	100	98	94
3	Respiratory Rate (Cycles / Min)	26	28	28	28

II) Level of Sedation

Time In Minutes	Score
0	1
10	1
20	1
30	2

III) Emotional State Scale   :   Score
a) At the time of separation from parents   :   2
b) On application of facemask in OT   :   2
IV) Postoperative Complications :   Nil

Proforma
Oral Midazolam as Premedication in Paediatric Patients

P. G. Teacher	P. G. Student
Dr. V. A. Kurhekar	Dr. J. K. Phaltankar
(M.D.)	(M.B.B.S.)
	DATE:23/10/2000
	STUDY Group :1
	Case No. : 5

Name of the patient: Nilesh Bhosale
 Reg. No.:17957
Age: 4 Yrs.
                    Weight: 13 Kg.
Sex: M
Operation: Postero-medial release for CTEV
Pre-operative examination: ASA Grade I
Past medical / surgical history: Nil
Pre-operative investigations:
    Hb: 9.2 gm%
    TC: 8,600

DC: P-64   L-32,   M-2,   E-2

Urine: Albumin   -   +

Sugar   -   Nil

I)

	Vital parameters	Time in minutes			
		0	10	20	30
1	Pulse Rate(Beats/Min)	120	125	125	122
2	Systolic Blood Pressure(mm Hg)	100	100	104	104
3	Respiratory Rate (Cycles / Min)	26	27	26	28

II) Level of Sedation:

Time In Minutes	Score
0	1
10	2
20	2
30	3

III) Emotional State Scale   :   Score

a) At the time of separation from parents   :   3

b) On application of facemask in OT   :   3

IV) Postoperative Complications :   Nil

Proforma

Oral Midazolam as Premedication in Paediatric Patients

P. G. Teacher   P. G. Student

Dr. V. A. Kurhekar   Dr. J. K. Phaltankar

(M.D.)   (M.B.B.S.)

DATE:23/10/2000

STUDY Group :1

Case No. : 5

Name of the patient: Saurabh Jadhav

Reg. No.:3386

Age: 2 Yrs.

Weight: 10 Kg.

Sex: M

Operation: Herniotomy

Pre-operative examination: ASA Grade I

Past medical / surgical history: Not Contributory

Pre-operative investigations:

Hb: 9 gm%

TC: 8,600

DC: P-64   L-32,   M-4,   E-0

Urine: Albumin   -   Nil

Sugar   -   Nil

I)

	Vital parameters	Time in minutes			
		0	10	20	30
1	Pulse Rate(Beats/Min)	120	130	124	122
2	Systolic Blood Pressure(mm Hg)	90	8	94	102
3	Respiratory Rate (Cycles / Min)	24	24	19	23

II) Level of Sedation

Time In Minutes	Score
0	1
10	1
20	1
30	1

III) Emotional State Scale   :   Score

a) At the time of separation from parents   :   1

b) On application of facemask in OT   :   1

IV) Postoperative Complications :   Nil

6. Observations

In the present study, a total of 90 patients were selected and randomly allocated into 3 groups, Group I, Group II and control group.

Only ASA grade 1 patients between the age of 1 to 8 years and posted for surgeries lasting no longer than 30-40 minutes were studied.

Study Group I (n = 30):

30 children randomly allocated in this group were administered midazolam 0.5 mg/kg of body weight orally in 25% dextrose upto a volume of 5 ml 45 minutes before scheduled time of surgery.

Study Group II (n = 30):

30 children randomly allocated in this group were administered midazolam 0.75 mg/kg of body weight orally in 25% dextrose upto a volume of 5 ml 45 minutes before scheduled time of surgery.

Control Group (n = 30):

30 children randomly allocated in this group were administered 3-5 ml of 25% dextrose orally.

After the oral doses, vital parameters as pulse rate, systolic blood pressure and respiratory rate were recorded at 0, 10, 20, 30 minutes.

The level of sedation was assessed at 0, 10, 20 minutes after the oral dose by using following scoring system.

1   =   Alert / Active

2   =   Awake / Calm

3   =   Drowsy but responsive to verbal / tactile stimulus

4   =   Asleep

30 minutes after premedication children were separated from their parents and emotional state was assessed at the time of separation from parents on the basis of a 4 points emotional state scale.

1   =   Tearful / Combative

2   =   Anxious but easily reassured

3   =   Calm

4   =   Asleep

The patients were shifted to the operating room and again emotional state was recorded at the time of application of a facemask by using same scoring system.

Postoperative complications, if any, were noted.

Table 2. Age distribution of patients

Age (Years)	Group I (0.5 mg/kg)	Group II (0.75 mg/kg)	Control Group
1-2	7 (23%)	7 (23%)	7 (23%)
3-4	6 (20%)	6 (20%)	6 (20%)
5-6	5 (17%)	5 (17%)	4 (13.3%)
7-8	12 (40%)	12 (40%)	13(43.3%)
Total	30	30	30

The difference in the ages of above three groups was not statistically significant. Hence, these three groups were comparable for age.

Table 3. Sex distribution of patients

Sex	Group I	Group II	Control Group
Male	19 (63%)	17 (57%)	18 (60%)
Female	11 (37%)	13 (43%)	12 (40%)
Total	30	30	30

In group I 63% was male and 37% were female.
In Group III 57% were male and 43% were female.
In Control Group 60% were male and 40% were female.
All the three groups were comparable for sex.

Table 4. Weight distribution of patients

Weight	Group I	Group II	Placebo Group
Mean $\pm$	16.4 $\pm$ 3.5	11.7$\pm$3.0	15.3$\pm$3.4

By applying the student's 't' text it was found that the difference in the weight of the patients in the 3 groups were not statistically significant. Hence, these three groups were comparable for weight.

Table 5. Mean changes in pulse rate in three groups

Time in minutes	Mean Pulse Rate (beats/min)		
	Group I	Group II	Control Group
0	111	112.2	111
10	110.2	113.2	110.4
20	109	112	110.2
30	110.3	111.6	109.4

The mean changes in pulse rate in the three groups were statistically not significant.
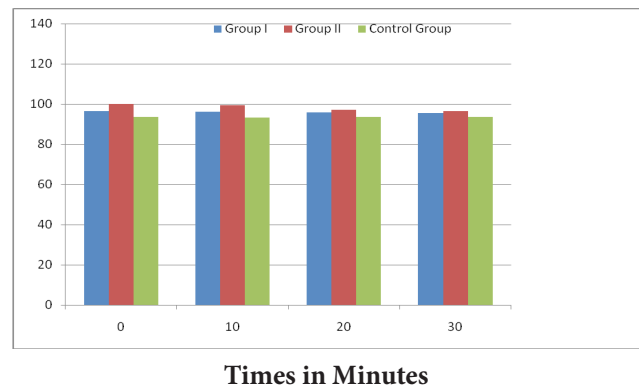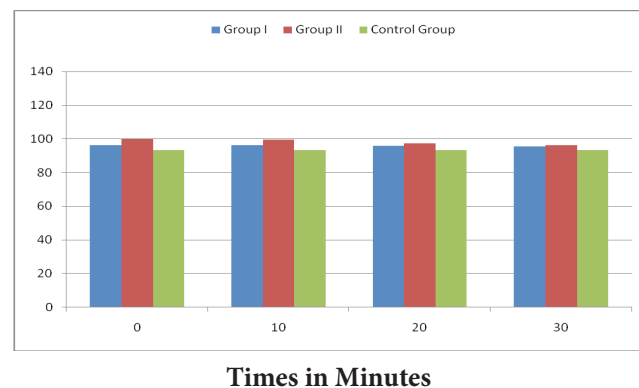

Graph 1. Graph showing mean changes in pulse rate.

Table 6. Mean changes in systolic blood pressure in the three groups

Time in minutes	Mean systolic blood pressure (mm Hg)		
	Group I	Group II	Control Group
0	96.4	100	93.5
10	96.3	99.5	93.2
20	95.8	97.2	93.5
30	95.4	96.4	93.5

Mean changes in systolic blood pressure in the three groups were statistically not significant.
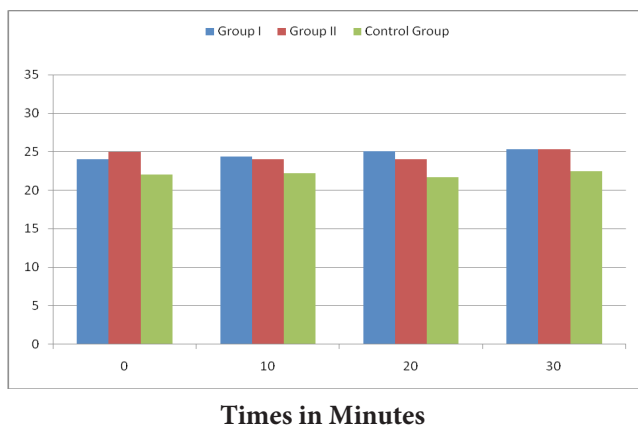

Graph 2. Graph showing mean changes in systolic blood pressure.

Table 7. Mean changes in respiratory rate in the three groups

Time in minutes	Mean Respiratory Rate (Cycles/Min)		
	Group I	Group II	Control Group
0	24	25	22
10	24.4	24	22.2
20	25.1	24	21.7
30	25.3	25.3	22.5

Mean changes in respiratory rate in the three groups were statistically not significant.

**Graph 3.** Graph showing mean changes in respiratory rate.

Table 8. Level of sedation [group I(0.5 mg/kg)(n=30)]

Time in minutes	Sedation Score			
	1	2	3	4
0	29(97%)	1(3%)	-	-
10	20(67%)	9(30%)	1(3%)	-
20	10(33%)	16(54%)	4(13%)	-
30	2(6%)	20(67%)	8(27%)	-

In group I at 10 minutes after premedication 67% of patients were alert and active 30% was awake but calm and 3% were drowsy but responsive.

At 20 minutes after premedication in this group 33% of the patient was alert and active 54% were awake and clam while 13% were drowsy but responsive.

At 30 minutes, 6% were alert and active, 67% were awake and calm while 27% were drowsy.
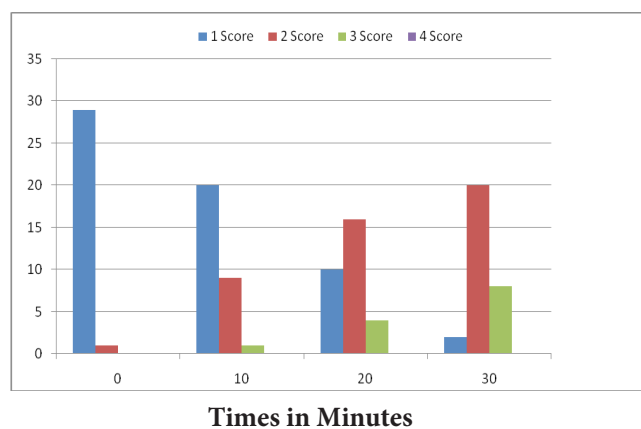
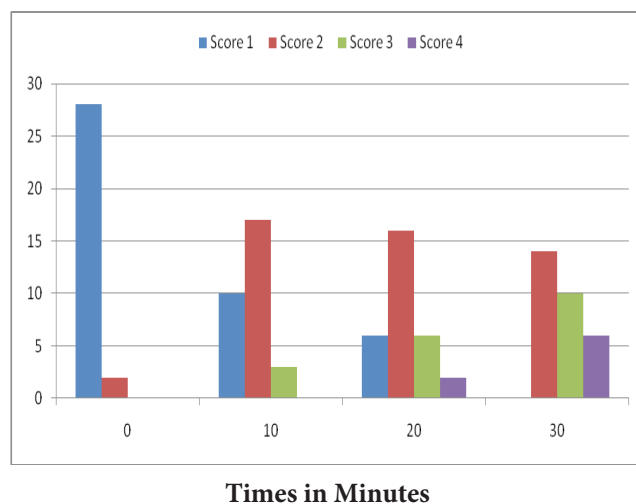**Graph 4.** Level of sedation (n=30) Group I-(0.5 mg/kg) oral midazolam.

Table 9. Level of sedation [Group II (0.75mg/kg) (n=30)]

Time in minutes	Sedation Score			
	1	2	3	4
0	28(93%)	2(7%)	-	-
10	10(33%)	17(57%)	3(10%)	-
20	6(20%)	16(53%)	6(20%)	2(7%)
30	-	14(47%)	10(33%)	6(20%)

In group II at 10 minutes after receiving premedication 33% of patients were alert and active 57% were awake but calm and 10% were drowsy but responsive.

At 20 minutes 20% were alert and active, 53% were awake and clam, 20% were drowsy while 7% were asleep.

At 30 minutes, 47% were awake but calm, 33% were drowsy but responsive and 20% were asleep.

**Graph 5.** Level of sedation (n=30) group II-(0.75 mg/kg) oral midazolam.

Table 10. Level of sedation [control group (n=30)]

Time in minutes	Sedation Score			
	1	2	3	4
0	29(97%)	1(3%)	-	-
10	24(80%)	6(20%)	-	-
20	15(50%)	15(50%)	-	-
30	13(43%)	17(57%)	-	-

In control group at 10 minutes after administering 25% dextrose 5 ml, 80% of the patients were alert and active while 20% were awake a=but calm.

At 20 minutes, 50% were alert and 50% were awake but calm.

At 30 minutes, 43% were alert and 57% awake but calm.
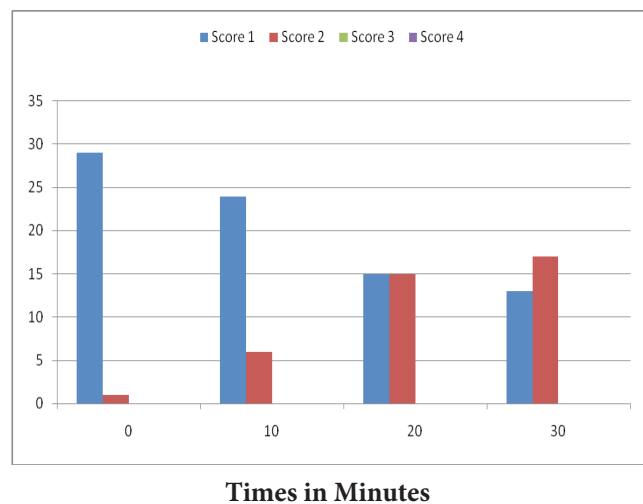
Graph 6. Level of sedation (n=30) control group.

At 30 minutes in control group, 43% of patients were alert and active and 57% were awake, whereas in study group (I), 6%) were alert and active, 67% were awake and calm while 27% were drowsy.

Also in study group (II), 47% were awake and calm, 33% were drowsy and 20% were asleep.

At the time of separation from parents, 83% patients in control were tearful and combative and 17% were anxious.

In study group I, 73% patients were calm and 20% anxious.

In study group II, almost 10% children were asleep and

83% were calm while only 7% were anxious.

Thus, at the time of separation from parents 93% children in group II and 67% children in group I were pacified as compared to the 83% children in control group who were tearful and combative.
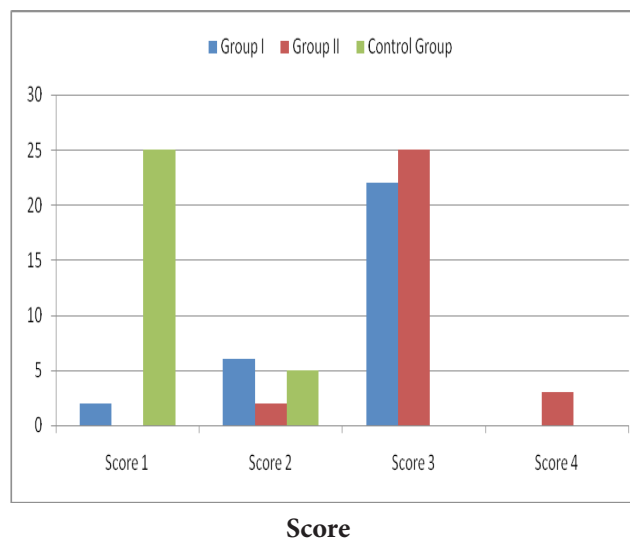
Graph 7. Graph showing emotional state scale at the time of separation from parents.
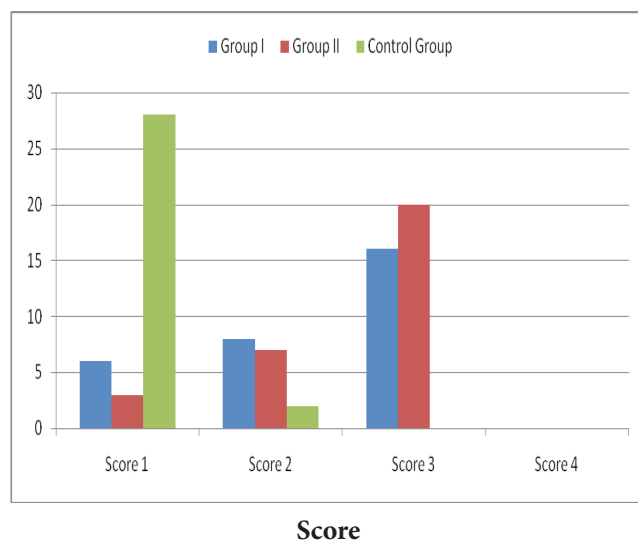
At the time of application of mask at the induction of anaesthesia, 93% children on control group were tearful and combative.

In study group I 53% were calm and 27% were anxious but easily reassured.

In study group II, 67% were calm and 23% were anxious but easily reassured.

Table 11. Comparison of level of sedation in three groups

Times In min	Group I(0.5mg/kg)				Group II (0.75mg/kg)				Control Group			
	1	2	3	4	1	2	3	4	1	2	3	4
0	29 (97%)	1 (3%)	-	-	28 (93%)	2 (7%)	-	-	29 (97%)	1 (3%)	-	-
10	20 (67%)	9 (30%)	1 (3%)	-	10 (33%)	17 (57%)	3 (57%)	-	24 (80%)	6 (20%)	-	-
20	10 (33%)	16 (54%)	4 (13%)	-	6 (20%)	16 (53%)	6 (20%)	2 (7%)	15 (50%)	15 (50%)	-	-
30	2 (6%)	20 (67%)	8 (27%)	-	-	14 (47%)	10 (33%)	6 (20%)	13 (43%)	17 (57%)	-	-

Table 12. Emotional state scale at the time of separation from parents

Group I(0.5mg/kg)				Group II (0.75mg/kg)				Control Group			
1	2	3	4	1	2	3	4	1	2	3	4
2 (7%)	6 (20%)	22 (73%)	-	-	2 (7%)	25 (83%)	3 (10%)	25 (3%)	5 (17%)	-	-

Table 13. Emotional state scale at the time of application of mask in operation theatre

Group I(0.5mg/kg)				Group II (0.75mg/kg)				Control Group			
1	2	3	4	1	2	3	4	1	2	3	4
6 (20%)	8 (27%)	16 (53%)	-	3 (10%)	7 (23%)	20 (67%)	-	28 (93%)	2 (7%)	-	-

Graph 8. Emotional state scale at the time of application of mask in operation theatre.

Table 14. Postoperative complications

Complications	Group I	Group II	Control Group
Nausea	4 (13%)	4 (13%)	-
Vomiting	-	2(7%)	-
Headache	-	1(3%)	-
Giddiness	-	1(3%)	-

In group I, 4 children had nausea.

In group II, 2 children had nausea & 2 had nausea & vomiting both.

Also in the same group 1 child complained of headache and another 1 of giddiness.

7. Discussion

Numerous regimens of paediatric premedication are in vogue. However in spite of extensive experience in this field, there is still no entirely satisfactory method to premedication children and ensure smooth induction of anaesthesia.

Many drugs have been tried through various routes of administration. Injections, nasal, sublingual or rectal administration of premedicant drugs can either be traumatic or difficult in children. In fact injections constitute one of the greatest fears in hospitalized children[46]. As oral premedication is atraumatic and less threatening to the child, we preferred the oral route of drug administration. Recent studies have suggested that oral premedication can be as or even more effective than intramuscular premedication in paediatric patients.

Nicholson et al., in 1989[47] in a study compared pharmacological effects of oral versus intramuscular premedication. Children given oral meperidine 3 mg/kg and pentobarbital 4 mg/kg were more drowsy and cooperative during induction than those who were given intramuscular (morphine 0.1 mg/kg and pentobarbital 4 mg/kg).

In the present study, 90 ASA grade I paediatric patients in the age group of 1 to 8 years undergoing elective surgery were randomly divided into three groups.

The patients in study group I (n = 30) received midazolam 0.5 mg/kg of body weight orally, patients in study group II (n = 30) received midazolam 0.75 mg/kg of body weight orally, both mixed with 25% dextrose solution upto a volume of 5 ml.

Study group III (n = 30) i.e., control group did not receive any premedication, but they were given 3-5 ml of 25% dextrose solution.

As midazolam possesses a bitter taste, we chose 25% dextrose as a vehicle for better acceptability of the drug in children 25% dextrose was chosen as a vehicle, because of easy availability in operation theatre greater than 2.5, the pH limit which may cause pulmonary damage after aspiration. The volume of solution administered orally in our study was 5 ml which was generally less than the residual gastric volume limit of 0.4 ml/kg. Moreover many studies have suggested that small amounts of fluid (5-10 ml) given to children prior to general anaesthesia do not promote aspiration. In the present study no children vomited during induction or displayed increased risk of aspiration.

Similarly, Anderson et al.,[63] in year 1990, in their study, found 55% of children less than 4 years and 85% of children more than 4 years of age to be calm at induction. In their study, the pre-theatre time of children was spent in the theatre reception area with their parents, where they were able to watch videos and have stories told. In our study, 7% of children receiving placebo had a satisfactory induction. The lower incidence may be attributable to

parents not accompanying children during induction and also no provision for recreation of children in the pre-anaesthetic room.

Mitchell et al in year 1997[65] compared midazolam and trimeprazine as an oral premedicant for children in a double blind randomized trial in 85 children undergoing tonsillectomy and or adenoidectomy.

Orally administered midazolam (05 mg/kg) given 30 minutes preoperatively was compared with trimeprazine (2 mg/kg) and a placebo. Following premedicantion with midazolam none of the patients crying, anxious or distressed leaving the ward compared with 7% in trimeprazine group and 17% in placebo group.

Thus, midazolam in a dose of 0.5 mg/kg orally produced satisfactory sedation in almost 100% children at 30 minutes after premedication.

Patel et al in year 197[67] studied 90 children who were assigned randomly to one of the three groups for premedication with oral midazolam 0.5 mg/kg, diazepam 0.25 mg/kg, droperidol 0.25 mg/kg or trimeprazine 2 mg/kg. At 30 minutes, sedation and anxiolysis was satisfactory in 26 out of 29 (90%) children in midazolam group compared with 23 out of 29 (79%) in diazepam and droperidol group and 18 out of 29 (62%) who received trimeprazine. Thus midazolam at 30 minutes produced satisfactory sedation and anxiolysis in 90% children in a dose of 0.5 mg/k.

Craig Weldon et al., in 1992[61] studied oral pre-anaesthetic medication regimen in 15 healthy children, 1-8 years of age. Group A (placebo) received 5 ml of apple juice, the other five groups received medication with apple juice to a total volume of 5 ml. Group B received atropine (0.02 mg/kg), group C received midazolam (0.5 mg/kg), group D received midazolam (0.5mg/kg) + atropine (0.2 mg/kg) + group E received meperidine (1.5 mg/kg) + atropine (0.02 mg/kg) + midazolam (0.5 mg/kg). The sedative effects of midazolam were maximal in 90% children at 30 minutes after premedication.

Feld et al., in year 160[60] studied the effectiveness of three different doses of oral midazolam administered in combination with atropine prior to ambulatory surgery. In this study, 124 children aged 1 -10 years were assigned to one of four groups (31 each). They received midazolam 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg orally and atropine 0.03 mg/kg orally mixed with apple juice 5ml as a placebo. A blinded observer noted the child's level of sedation, the quality of separation from parents and the degree of co-operation with an inhalation induction of anaesthesia. At 30 minutes after administration of premedication, 89% children receiving 0.5 mg/kg had good sedation whereas 90% had good and 7% had excellent sedation with 0.75 oral midazolam.

Mac Millan et al in year 1992[71] in a randomized, double blind, placebo-controlled study, found the efficacy and feasibility of oral midazolam premedication in an ambulatory surgery unit. 80 children (ASA I or II) aged 1-6 years were assigned to one of the three groups receiving midazolam 0.5 mg/kg, 0.75 mg/kg, 1 mg/kg 30 minutes before surgery. At 30 minutes after the premedication, 90% children receiving 0.5 mg/kg oral midazolam were calm while in children receiving 0.75 mg/kg oral midazolam 95% children were calm and had satisfactory anxiolysis.

McCluskey and Meakin in year 1994[70] studied 54 children aged 1-10 years scheduled for day-case anaesthesia. They were prescribed either oral midazolam 0.5 mg/kg or a placebo preparation 30-60 minutes preoperatively on a double blind basis. At 30 minutes, anxiolysis was considered satisfactory (score 3) in 23 out of 24 children who received 0.5 mg/kg midazolam (96%) compared with 12 out of 27 (44%) of those who received placebo (44%).

In our study, with oral midazolam in a dose of 0.5mg/kg in study group I we found 67% patients were calm (score 2) and 27% were drowsy (score 3). Thus 94% children had good to excellent sedation at 30 minutes after premedication with oral midazolam in a dose of 0.5 mg/kg.

In study group II receiving 0.75 mg/kg midazolam orally at 30 minutes after premedication 47% children were calm (score 2) 33% were drowsy (score 3) and 20% were asleep (score 4). Thus almost 100%patients had good to excellent sedation at 30 minutes with 0.75 mg/kg oral midazolam. In control group at 30 minutes only 57% children were calm.

Table 15. Sedation scores after 30 mins of oral midazolam

Author	Satisfactory sedation scores at 30 minutes	
	0.5 mg/kg	0.75 mg/kg
Mitchell et al	100%	-
Patel et al	90%	-
Craig Weldon et al	90%	-
Feld et al	89%	97%
MacMillan et al	90%	95%
McCluskey and Meakin et al	96%	-
Present study	94%	100%

Thus our findings which showed a satisfactory sedation and anxiolysis in 90-100% children with a dose of 0.5-0.75 mg/kg oral midazolam is consistent with those above.

Craig Weldon et al.,[61] 1992 studied the sedative effects of oral midazolam. They studied oral premedication regimen in 15 children 1-8 years of age. 5% children who

were separated from their parents within 45 minutes after oral administration 0.5 mg/kg midazolam had satisfactory separation scores. They concluded that midazolam 0.5 mg/kg given orally 30-45 minutes before induction of anaesthesia was safe and effective premedicant in facilitating easy separation from parents.

Feld et al., in 1988[60] studied various doses or oral midazolam in combination with oral atropine prior to ambulatory surgery. In the study 124 children aged 1-10 year were assigned to one of the 3 groups. They received oral midazolam 0.25 mg/kg, 0.5 mg/kg and 0.75 mg/kg. At the time of separation from parents emotional state was assessed. 79% children receiving 0.5 mg/kg oral midazolam had good to excellent separation. 91% children receiving 0.75 mg/kg had good to excellent separation from parents.

McMillan et al.,[71] 1992 in their study found the efficacy or oral midazolam premedication in 80 children age 1-6 years and assigned to one of 3 groups. They received midazolam 0.5 mg/kg and 0.75 mg/kg 30 minutes before surgery. At the time of separation from parents 90-95% children had satisfactory anxiolysis in a dose of 0.75 mg/kg oral midazolam and 70-75% had satisfactory anxiolysis in a dose of 0.5 mg/kg.

Mark Levine et al.[62], in 1993 found satisfactory separation from parents in 90% children with a dose of 0.75 mg/kg oral midazolam.

In our study we separated children from their parents at 30 minutes after per medication. At this time we studied the emotional state of the children on a four point scale. We found that in study group I receiving 0.5 mg/kg oral midazolam 73% children were calm i.e. they had a score of 3. In study group II receiving 0.75 mg/kg oral midazolam 83% children were calm (score 3) and 10% were asleep (score 4). Thus separation from parents was good to excellent in 73% patients in study group I (0.5 mg/kg) and 93% patients in study group II (0.75 mg/kg).

Table 16. Emotional state at the time of separation from parents

Author	Satisfactory emotional state	
	0.5 mg/kg	0.75 mg/kg
Craig Weldon et al	75%	-
Feld et al	79%	91%
MacMillan et al	75%	95%
Mark Levine et al	-	90%
Present study	73%	93%

Thus our findings which showed a satisfactory

separation from parents in 73% patients in a dose of 0.5 mg/kg and 93% patients in a dose of 0.75 mg/kg was consistent with above studies.

Patel et al.,[67] studied 90 children who were assigned randomly to one of three groups for premedication, with oral midazolam 0.5 mg/kg, diazepam 0.25 mg/kg, droperidol 0.25 mg/kg or trimeprazine 2 mg/kg. At the time of induction anxiolysis was satisfactory in 24 out of 29 (83%) children in midazolam group compared with 16 out of 29 (55%) in diazepam and droperidol group and in 11 out of 29 (40%) who received trimeprazine.

MacMillan et al.,[71] also studied the degree of anxiolysis in children at the time of application of face mask in operation theatre in 3 different doses i.e., 0.5 mg/kg, 0.75 mg/kg and 1 mg/kg of oral midazolam. They concluded that in the patients receiving 0.5 mg/kg oral midazolam 60% were calm (score 3). In those receiving 0.75 mg/kg or oral midazolam 60% were calm (score 3).

Craig Weldon et al.,[61] studed oral premedication in 15 children 1-8 years of age. 83% patients receiving 0.5 mg/kg of oral midazolam were more co-operative at mask induction of anaesthetic compared with 56% in non-midazolam treated group.

McCluskey and Meakin[70] studied 54 children aged 1-10 years scheduled for day case anaesthesia. They were premedicated with either oral midazolam 0.5 mg/kg or a placebo preparation 30-60 minutes preoperatively. At the time of induction that is at the time of application of face mask anxiolysis was satisfactory in 21 out of 24 (88%) children who received midazolam compared without of 27 (33%) of those who received placebo.

Feld et al.,[60] studied effectiveness of three doses of oral midazolam administered in combination with atropine prior to ambulatory surgery. The children received oral midazolam 0.25 mg/kg, 0.5 mg/kg, 0.75 mg/kg. In the group receiving 0.5 mg/kg 69% had good to excellent induction score compared with 78% in group receiving 0.75 mg/kg who had good to excellent anxiolysis at the application of face mask in operative theatre.

After separation from parents we induced patients on mask with oxygen, nitrous oxide and halothane. Now again we studied the emotional state of the children at the application of mask, on the basis of a 4 point scale. We found in study group I receiving 0.5 mg/kg oral midazolam 80% had good to excellent induction while in study group II receiving 0.75 mg/kg 90% had satisfactory induction. In control group 93% children were thrashing and tearful. Thus the application of face mask was accepted more readily in those who were given midazolam than those in control group.

Table 17. Emotional state at the time of application of mask

Author	Satisfactory scores at application of mask	
	0.5 mg/kg	0.75 mg/kg
Patel et al	83%	-
Macmillan et al	60%	60%
Craig Weldon et al	83%	-
McCluskey & Meakin et al	88%	-
Feld et al	69%	78%
Present study	80%	90%

Thus satisfactory induction in 80% of children receiving 0.5 mg/kg oral midazolam was consistent with the studies of Patel, Weldon, McCluskey[61,67,70].

The haemodynamic parameters like systolic blood pressure, respiratory rate and pulse was also studied. MacMillan et al.,[71] in his study evaluated heart rate, systolic blood pressure, respiratory rate, arterial oxygen saturation before premedication and every 5 minutes for 30 minutes. They found that these parameters were unchanged.

In our study group (0.5 mg/kg), oral midazolam I the mean baseline heart rate was 111/min. at 10 minutes it was 110.2/min, at 20 minutes 109/min and at 30 min it was 110.3/min. in group II (0.75 mg/kg), oral midazolam the mean baseline heart rate was 112./min, at 10 minutes 113.2/min, at 20 min 112/min and 30 minutes it was 111.6/min. Thus, there was no significant change in heart rate in the 2 groups.

Also the mean baseline systolic blood pressure in the study group I receiving 0.5 mg/kg midazolam was 6.4 mm Hg, after 10 minutes it was 96.3, after 20 minutes it was 95.8 and at 30 minutes 95.4 mm Hg. In study group II receiving 0.75 mg/kg midazolam, the baseline systolic blood pressure was 100, at 10 minutes 99.5, at 20 minutes it was 97.2 and at 30 minutes 96.4 mm Hg. Thus, there was no significant difference in the systolic blood pressure in the 2 groups.

The baseline respiratory rate in study group I was 24 cycles/min, it was 24.4/min, 25.1/min and 25.3/min at 10, 20, 30 minutes respectively. In study group II (0.75 mg/kg), the baseline respiratory rate was 25 cycles/min. it was 24/min, 24/min and 25.3.min at 10, 20, 30 minutes respectively. Thus the respiratory rate remained unchanged in the 3 groups.

Thus, in our study, we observed that the haemodynamic parameters like heart rate, systolic blood pressure and respiratory rate remained stable throughout the study in the 2 midazolam treated groups. These findings were consistent with the findings of Macmillan et al.

We studied the post-operative complications in the present study. We found 4 children in study group (0.5 mg/kg) had nausea. 2 children had both nausea and also vomiting in group II (0.75 mg/kg). Also in the same group I child each had giddiness and headache. Thus the complications in study group II (0.75 mg/kg) were definitely more (26%) than the (13%) complications in study group I (0.5 mg/kg).

Thus we concluded that oral midazolam in a dose of 0.5 to 0.75 mg/kg can be used as a premedicant in paediatric patients as if offers good to excellent sedation and satisfactory separation from parents along with satisfactory induction of anaesthesia. We prefer the dose of 0.5 mg/kg as it provide good to excellent sedation with excellent quality of separation and satisfactory induction with minimum incidence of side effects.

8. Summary and Conclusions

Women of the labour class used to give opium to lull their children to sleep while they were away on work. The same principle can be applied to the children who are about to undergo surgery. A child brought inside the operation theatre should be calm and quiet instead of crying and thrashing. This will be preferred not only by the anaesthesiologist but also by surgeon, nurse and other staff. Here a calm and sleepy child will make the anaesthesioloist' work such a securing an intravenous line, inducing the patient on mask etc. easy. Amongst the various routes of administering a premedicant drug, oral route appears to be more suitable for paediatric patients as hungry and thirsty child easily accepts it.

The present study was carried out in the Department of Anaesthesiolgy in General Hospital, Sangali attached to Govt Medical College, Miraj. In the study, 90 children of ASA grade I between the age of 1-8 years were studied. The patients undergoing elective surgery under general anaesthesia were divided into three groups-Study group I (n = 30), Study group I (n = 30) and Control group (n = 30). Patients in study group I received midazolam 0.5 mg/kg body weight orally mixed with 25% dextrose, study group II received 0.75 mg/kg midazolam mixed in 255 dextrose upto a volume of 5 ml, while control group receive 3-5 ml of 25% dextrose about 45 minutes before the scheduled time of surgery. All the three groups were comparable for age, sex and weight (Table 2, 3 and 4). The baseline pulse rate, systolic blood pressure and respiratory rate were recorded in the three groups. Thereafter, the vital parameters were recorded at 10, 20 and 30 minutes after oral premedication in the three groups. It was found that the differenced in pulse rate, systolic blood pressure and respiratory rate between the three groups was not statistically significant (Table 5, 6 and 7).

Level of sedation was assessed before the premedication

and thereafter at 10, 20 and 30 minutes in the three groups. The level of sedation increased with time in the three groups. At 30 minutes in control group 43% children were alert and active (score 1) while 57% were awake (score 2) (Table 10).

In study group I (0.5 mg/kg), 6% were alert and active (score 1), 67% were awake and calm (score 2) while 27% were drowsy (score 3) (Table 8).

In study group II (0.75 mg/kg), 47% were awake and calm (score 2), 33% were drowsy (score 3) and 20% were asleep (score 4) (Table 9).

Thus, sedation at 30 minutes after premedication was better in study group II as compared to study group I. (Table 11).

The children were separated from their parents 30 minutes after the oral premedication and their emotional state was evaluated on the basis of a 4 point scale.

It was found that in the control group 83% children were tearful and thrashing. (score 1).

In study group I (0.5 mg/kg), 73% children were calm (score 3) and 20% anxious but easily reassured (score 2). In study group II (0.75 mg/kg), 83% children were calm (score 3) 10% asleep (score 4) and only 7% anxious (score 2) (Table 12).

Emotional state was concluded to be better in study group II (0.75 mg/kg) as compared to study group I (0.5 mg/kg) at the time of separation from parents.

After separation from parents children were taken into the operating room and induced with oxygen, nitrous oxide and halothane on mask. The quality of induction was assessed on the basis of emotional state scale. At the time of application of mask, 93% children in control group were tearful, combative and thrashing (score 1).

In study group I (0.5 mg/kg), 53% were calm (score 3) and in study group II, (0.75 mg/kg) 67% were calm (score 3) (Table 13).

Thus, facemask at induction of anaesthesia was accepted more readily in the midazolam treated groups as compared to control group. The readily in the midazolam treated groups as compared to control group. The emotional states were not much different in study group I and study group II.

The incidence of postoperative complications like vomiting, nausea, giddiness and headache was also noted. (Table 14)

In study group I (0.5 mg/kg), 4 children nausea. In study group II (0.75 mg/kg), 2 children had nausea and vomiting, 1 child each had headache and giddiness.

So we like to conclude that oral midazolam in a dose of 0.5 to 0.75 mg/kg provide excellent sedation and good quality of separation from parents with stable emotional state at induction without significant haemodynamic changes.

We found more post operative complications with a dose of 0.75 mg/kg than with a dose of 0.5 mg/kg.

Thus we recommend oral midazolam in a dose of 0.5 mg/kg for premedication in paediatric patients at it provides good to excellent sedation at 30 minutes at the time of separation from parents, with better quality of separation, and stable emotional state at induction without significant hemodynamic changes with less postoperative complications.

Thus, oral midazolam would be a useful additive to the anaesthesiologist's armamentarium as a premedication in paediatric patients.

9. References

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