DISSERTATION ON COMPARISON OF INTRANASAL MIDAZOLAM WITH ORAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN

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CERTIFICATE

This is to certify that the dissertation titled "**COMPARISON OF INTRANASAL MIDAZOLAM AND ORAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN**" is a bonafide original work of **Dr. A. CAROLIN VON MULLAI** in partial fulfillment of the requirements for M.D. (Anaesthesiology-Branch -X) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in March 2010. The period of the study was from April 2008 to March 2010.

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INTRODUCTION

Surgery and anaesthesia induce considerable emotional stress and psychological consequences in children. This stress may remain in the child's psyche long after the hospital experience has passed, and it was first described by Duputyren in 1834.

Age, parental anxiety level, previous hospital experiences and type of surgery are factors that can influence a child's anxiety level and psychological well being.

Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. These reactions reflect the child's

- fear of separation from parents and home environment
- fear of physical harm
- fear of unfamiliar routines
- fear of surgical instruments and procedures

The preoperative interventions directed towards reduction of anxiety can be grouped into psychological and pharmacological methods. The introduction of new drugs and alternative routes of administration like transmucosal route in last decade by avoiding painful intramuscular injections, the most horrifying experience for a child, has facilitated a more rational approach to premedication for paediatric patients.

In paediatric anaesthesia, premedication needs to be in an acceptable form, to have a rapid onset with minimal hangover effect and without side effects. Midazolam, a sedative with all the desirable properties of a benzodiazepine was introduced into clinical practice in 1980s.

Midazolam, a water soluble benzodiazepine, may be administered by various routes. Oral and rectal routes are used widely and provide effective sedation. However, there are concerns about the wide bioavailability when given by these routes , ranging from 18% to 44% with an appreciable first pass effect. Intramuscular administration is painful and the sublingual route has poor compliance.

The intranasal route for midazolam has been used since 1988 and has the advantage of rapid absorption directly into the systemic circulation with no first pass effect and a bio- availability of 55-83%

Intranasal midazolam is absorbed from an area rich in blood supply and avoids the disadvantage of passing through the portal circulation, thus increasing the bio-availability of the drug. Tolerance to midazolam is good, and the duration of action is shorter and more predictable than other benzodiazepines. Intranasal midazolam has all the advantages of intravenous administration without the disadvantages of pain and fear associated with intramuscular and intravenous injections.

AIM OF THE STUDY

The aim of the study is to compare the effectiveness of Intranasal and oral midazolam used as a premedication in paediatric patients undergoing minor elective surgical procedures.

PREMEDICATION IN CHILDREN

Finding a suitable premedicant for children and the best route of administration is something that has been investigated for a long time.

An ideal paediatric premedication should

- allay anxiety and fear
- be easily available and affordable
- produce the desired clinical effect
- enable smooth separation from parents
- abolish any preoperative pain
- facilitate smooth induction
- reduce the dose of anaesthetic
- maintain vital functions
- maintain airway reflexes
- offer rapid postoperative recovery
- easily acceptable by parents
- have minimal hangover effect
- should produce amnesia of transfer and entry into the operating room

The advantages and disadvantages of various routes of administration are as follows.

Sl. No.	Route of Administration	Advantages	Disadvantages
1	Oral	Painless	Variable onset and depth of sedation, prolonged effect, Nausea
2	Intramuscular	Reliable, Rapid onset, better absorption, greater predictability of the duration of action	Painful, threatening, risk of infection, abscess formation, required skilled personnel
3	Rectal	Reliable, Rapid onset	Distressing procedure, defaecation, irregular absorption, first pass effect
4	Intravenous	Most Reliable, Rapid onset	Painful, threatening, risk of infection, requires skill
5	Nasal	Rapid, Reliable onset of action, No first pass effect, No risk of infection	Objection, coughing, sneezing, swallowing
6	Sublingual	Painless, No first pass effect, No risk of infection	Nausea and vomiting, slower onset

Transmucosal routes

Drug absorption through a mucosal surface is generally efficient because mucosal surfaces are usually rich in blood supply, providing the means for rapid drug transport to the systemic circulation and avoiding degradation by first-pass hepatic metabolism.

The amount of drug absorbed depends on the following factors

- drug concentration
- vehicle of drug delivery
- mucosal contact time
- venous drainage of the mucosal tissues
- degree of the drug ionization and
- pH of the absorption site
- size of the drug molecule
- relative lipid solubility

Distribution of the drug depends on the following factors

- Formulation
- Dilution
- Particle size
- Lipid solubility
- Site of administration

MIDAZOLAM PHARMACOLOGY

Midazolam is a short-acting, water soluble benzodiazepine and central nervous system depressant that was introduced into clinical practice in 1980s. It is two to three times as potent as diazepam.

Structure

Chemically Midazolam is composed of a benzene ring fused to a 7 membered benzodiazepine ring. It has a molecular formula of $C_{18}H_{13}Cl\ FN_3$ and a calculated molecular weight of 325.8

Midazolam is 8-chloro-6-(2-flourophenyl)-1-methyl- 4H-imidazo (1,5-a) (1,4) benzodiazepine.

Ring Opening Phenomenon

The pK of midazolam is 6.15, which permits the preparation of salts that are water soluble. The parenteral solution of midazolam used clinically is buffered to an acidic pH of 3.5 . This is important because midazolam is characterized by a pH dependent Ring Opening phenomenon in which the ring remains open at pH values of < 4, thus

maintaining water solubility of the drug. The ring closes at pH values of >4, as when the drug is exposed to physiologic pH, thus converting midazolam to a highly lipid soluble drug. The imidazole ring in its structure accounts for stability in aqueous solutions and rapid metabolism.

Pharmacodynamics

Midazolam has the following six principal pharmacological actions.

- Anxiolysis
- Sedation
- Anticonvulsant
- Skeletal muscle relaxation
- Anterograde amnesia
- Hypnosis

The pharmacological effects of midazolam results from reversible interactions with the Gamma-Amino Butyric Acid (GABA) benzodiazepine receptor, the major inhibitory neurotransmitter in the central nervous system.

Pharmacokinetics

Midazolam undergoes rapid absorption from the gastrointestinal tract and prompt passage across the Blood Brain Barrier.

Absorption of midazolam is rapid, peak plasma concentrations being achieved within 20 to 60 minutes of administration depending on the route. Only about 50% of an orally administered dose of midazolam reaches the systemic circulation, reflecting a substantial first-pass hepatic effect.

Midazolam is extensively bound to plasma proteins. (96-98%). This binding is independent of the plasma concentration of midazolam.

The elimination half time of midazolam is 1- 4 hours, which is much shorter than that of diazepam. The short duration of action of midazolam is due to its lipid solubility, leading to rapid redistribution from the brain to inactive tissues and rapid hepatic clearance.

The volume of distribution (Vd) of midazolam is 1.0-1.5 l/ kg.

Metabolism

Midazolam is rapidly metabolized by hepatic and small intestine cytochrome p-450 (CYP3A4) enzymes to active and inactive metabolites .

The principal metabolite of midazolam, 1–hydroxy midazolam has approximately half the activity of the parent compound. This active metabolite is rapidly conjugated to 1-hydroxy midazolam glucuronide and is subsequently cleared by the kidneys. The other pharmacologically active metabolites like 4 hydroxy midazolam is not present in detecteble concentratoions in the plasma.

Metabolism of midazolam is slowed in the presence of drugs such as Cimetidine, Erythromycin, Calcium channel blockers, antifungal drugs that inhibit cytochrome p-450 enzymes resulting in unexpected CNS depression.

Hepatic clearance rate of midazolam is 5 times greater than that of lorazepam and 10 times greater than that of diazepam.

Clinical uses

- Prepoperative medication
- Conscious sedation
- Induction of maintenance
- Maintenance of anaesthesia
- Postoperative sedation
- Grandmal seizures
- Febrile seizures

ANATOMY AND PHYSIOLOGY OF THE NASAL MUCOSA

Although, phylogenetically, the olfactory function of the nose is of major importance, physiologically the nasal structure and function in humans relate primarily to humidification, warming and filtration of inspired air. The nose is richly vascularised with numerous microvilli and a relatively large surface area for these functions. The nasal cavity and septum are lined by simple ciliated columnar epithelium.

The subepithelial capillaries are lined with fenestrated endothelium, which possesses porous basement membrane. It appears that nasal vascular bed is designed for the passage of fluids and dissolved substances from the blood vessels to tissues and vice versa. This property of nasal mucosa is favourable for intranasal drug administration. Moreover, drugs absorbed through the nasal vasculature avoids the first pass effects through the liver and degradation in the luminal fluids of the gastrointestinal tract .

Nasal muosal administration

Nasal mucosa is the only location in the body that provides a direct connection between the central nervous system and the atmosphere. Drugs sprayed into the olfactory mucosa rapidly traverse through the cribriform plate into the CNS by 3 routes.

1. Directly by the olfactory neurons.
2. Through the supporting cells and the surrounding capillary bed
3. Directly into the cerebrospinal fluid

Transneuronal absorption is generally slow, whereas absorption by the supporting cells and the capillary bed is rapid.

Intranasal midazolam has been successfully used in

1. dental procedures
2. endoscopic procedures
3. cardiac catheterization
4. accident and emergency cases
5. minor surgical procedures
6. change of dressings and suturings
7. febrile seizures

MIDAZOLAM NASAL SPRAY (INSED ATOMISER)

Insed Atomiser is a metered dose inhaler available for intranasal administration containing 50 metered doses of midazolam. Each metered dose of 100 μl of Insed Atomiser delivers 0.5 mg midazolam.

Intranasal midazolam has been used for over a decade now for sedating children before anaesthesia, due to its unique property of a good premedicant because of its sedative and anxiolytic properties. Insed atomiser can be used instead of rectal and intravenous drugs for the emergency of seizures, both in and out of hospital.

Intranasal administration of midazolam results in bio-availability of 50% to 83% when compared to the IV administration. The variation in bioavailability depends on the method of administration, with atomisation demonstrating higher levels than dropper application.

Nasal midazolam has a faster onset of action and 1 to 3 times higher peak plasma levels than rectal and oral midazolam.

REVIEW OF LITERATURE

1. J.-M.Malinovsky et al.,[17](British Journal of Anaesthesia 1993) compared plasma concentrations of midazolam after nasal, rectal and intravenous administration in forty five children aged two to nine years, weighing between ten and thirty kgs who were undergoing minor urological surgery. Children were allocated randomly to receive midazolam 0.2 mg/kg by the nasal, rectal or intravenous route. Venous blood samples were obtained before and up to 360 minutes after administration of the drug. Plasma concentrations of midazolam were measured by gas chromatography and electron detection. After nasal and rectal administration, midazolam Cmax was 182ng/ml within 12.6 minutes, and 48 ng/ml within 12.1 minutes. Rectal administration resulted in smaller plasma concentrations. In the nasal group, a plasma concentration of midazolam 100 ng/ml occurred at about 6 minutes. After 45 minutes, the concentration curves after intravenous and nasal midazolam were similar.

2. N.Griffifth, S.Howell and D.G.Mason[7] (British Journal of Anaesthesia 1998) Compared two methods of administering midazolam intranasally in 44 surgical day-care children allocated randomly to

receive midazolam 0.2 mg/kg as drops or midazolam 0.1 mg/kg from an intranasal device. Behaviour was recorded on a four-point scale by the parent, nurse and anaesthetist. They found that there was no significant difference in the method of administration and midazolam by either method was equally effective.

3. Gustaf L.Jungman et al.,[8] (pediatrics Vol.105 Jan 2000) investigated whether intranasal midazolam given before insertion of a needle in a subcutaneously implanted central venous port could reduce anxiety, discomfort, pain and procedure problems. Forty-three children with cancer participated in this randomized, double-blind, placebo–controlled crossover study in which nasal administration of midazolam spray, 0.2 mg/kg body weight, was compared with placebo. Children, parents and nurses completed a Visual Analog Scale questionnaire to evaluate efficacy. Parents and nurses reported reduced anxiety, discomfort and procedure problems for children in the midazolam group and would prefer the same medication at next procedure. They also reported pain reduction.

4. H.AL-Rakaf et al., [9] (International Journal of Paediatric Dentistry 2001) compared the effects of three different doses of intra-nasal midazolam in the conscious sedation of young paediatric dental patients.

Thrity-eight uncooperative young children aged 2-5 years were randomly assigned to one of three groups.

- Group A – Intranasal midazolam 0.3 mg/kg
- Group B – Intranasal midazolam 0.4 mg/kg
- Group C – Intranasal midazolam 0.5 mg/kg

There was rapid onset of sedation with the maximal effect between eight and fifteen minutes. This sedation effect lasted for twenty five to forty minutes in Group A and B and for sixty minutes in Group C. They concluded that all 3 doses of intranasal midazolam were effective in modifying the behaviour of the uncooperative child to accept dental treatment.

5. Singh N; Pandey RK[24] (Journal of clinical Paediatric Dentistry 2002) evaluated the safety and efficacy of orally administered midazolam in children as a sedative agent and to compare it with two other older agents, triclofos and promethazine. The study was conducted on ninety children between three and nine years, requiring short dental procedures. The patients were randomized into three study groups on the basis of the drugs to be administered.

- Group I – Midazolam
- Group II – Triclofos
- Group III – Promethazine

After administration of drugs in each group, the effects were evaluated in terms of onset of action, sedative effect, ease of treatment completion, recovery time and postoperative amnesia. Midazolam was found to be the best drug among the three to produce conscious sedation in children.

6. Kogan, Alexander MD et.al.,[14] (Paediatric Anaesthesia, Oct.2002) studied the effects of four routes of administration on the efficacy of midazolam for premedication in 119 unpremedicated children between one and five years, scheduled for minor elective surgery. They were randomly assigned into one of four groups.

- Group I – Intranasal midazolam 0.3 mg/kg
- Group II – Oral midazolam 0.5 mg/kg
- Group III – Rectal midazolam 0.5 mg/kg
- Group IV – Sublingual midazolam 0.3 mg/kg.

A blinded observer assessed the children for sedation and anxiolysis every five minutes prior to surgery. Quality of mask

acceptance for induction, postanaesthesia care unit behaviour and parents' satisfaction were evaluated. There were no significant differences in sedation and anxiety levels among the four groups. Average sedation and anxiolysis increased with time, achieving a maximum at 20 minutes in group I and at 30 minutes in groups II-IV. Mask acceptance was good for more than 75% of the children. They concluded that intranasal, oral, rectal and sublingual midazolam produces good levels of sedation and anxiolysis. Mask acceptance for inhalation induction was easy in the majority of children, irrespective of the route of drug administration.

7. Charles J.Cote et al.,[3](Anesth Analg 2002)examined the efficacy, safety and taste acceptability of three doses (0.25, 0.5 and 1.0 mg/kg upto a maximum of 20 mg) of commercially prepared versed syrup (midazolam Hcl) in children stratified by age (6 months to 2 yrs, 2 to < 6 yr, and 6 to < 16 yrs.). There was no apparent relationship between dose and onset of sedation and anxiolysis. 88% had satisfactory anxiety ratings at the time of attempted separation from parents, and 86% had satisfactory anxiety ratings at face mask application. They concluded that oral midazolam syrup was effective for producing sedation and anxiolysis at a dose of 0.25 mg/kg with minimal effects on respiration

and oxygen saturation even when administered at doses as large as 1.0 mg/kg as the sole sedating medication to healthy children.

8. Christy Lam et al.,[4](Anesth Prog 2005) compared the effectiveness of intramuscular and intranasal midazolam used as a premedication before intravenous conscious sedation. The study was conducted on twenty-three children from 2 to 9 years who were scheduled to receive dental treatment under intravenous sedation.

The sedation level, movement and crying were evaluated at the following time points: 10 minutes after drug administration and at the time of parental separation, nitrous oxide nasal hood placement, local anesthetic administration and initial venepuncture attempt. Intranasal midazolam was found to be as effective as intramuscularl midazolam in providing a better sedation level and less movement at the time of venepuncture.

9. Asif Pervez Kazemi et.al.,[2](Pakistan J Med Science 2005) compared the sedative effect of ketamine and midazolam administered nasally as premedication. 130 children aged two to five years were randomly allocated in three groups and 20 minutes before surgery received either 0.2 mg/kg midazolam or 5 mg/kg ketamine or 2 ml

normal saline, intranasally. At the time of separation and at the time of intravenous line insertion, they received a sadation score based on Sury and Cole sedation score.

According to statistical analysis, at the time of separation from parents 90% of patients were sedated in midazolam group,89% were sedated in ketamine group, while in placebo group 47.5% showed sedation. At the time of intravenous line insertion, in midazolam group 86% were sedated, in ketamine group 80% were sedated while in placebo group 22.5% showed sedation. They concluded that midazolam 0.2 mg/kg and ketamine 5 mg/kg administered intranasally in children aged 2-5 years was equally effective for easier separation of children from their parents and obtunding their response to venepuncture.

10. Daniel P. Wermeling et al.,[5](Anesthesia & Analgesia 2006) evaluated the bioavailability of a novel intranasal midazolam formulation and compared the pharmacodynamic effects on psychomotor performance and subjective reporting of drug effect after single five mg doses of midazolam via intranasal, intramuscular and intravenous routes of administration in twelve healthy volunteers. The intranasal formulation, a nonaqueous solution containing 25mg/ml provided 2.5 mg of midazolam in 0.1 ml spray from a modified version of a commercially available unit-dose spray pump. Blood samples were

taken serially from 0 to 12 hr after each dose. Plasma midazolam concentrations were determined by liquid chromatography/mass spectrometry. The mean midazolam bioavailabilities and % coefficient of variation were 72.5 and 93.4 after the intranasal and intramuscular doses respectively. They concluded that intranasal midazolam was a therapeutic alternative for aconvenient, noninvasive and rapidly acting sedative and the novel formulation was rapidly and reliably absorbed.

11. Parag Gharde, Sandeep Chauhan, Usha Kiran[22](Annals of cardiac Anaesthesia 2006) compared the efficacy of intranasal midazolam, ketamine and their mixture as premedication in children with Tetrology of Fallot (TOF) undergoing intracardiac repair using bispectral index (BIS), sedation score and separation score at the time of separation from parent. Sedation score at the time of intravenous cannulation was also measured. Sixty children with TOF were randomly divided into three equal groups.

- Group A – Intranasal Ketamine (10 mg/kg)
- Group B – Intranasal midazolam (0.2 mg/kg)
- Group C – Intranasal mixture of Ketamine (7.5 mg/kg) and midazolam (0.1 mg/kg)

After thirty minutes of premedication, sedation and separation scores were noted. BIS values were recorded at 5 minute intervals. A four point scale for sedation, separation and acceptance of intravenous cannulation was used. They found out that sedation was good in midazolam group and concluded that the mixture of ketamine and midazolam intranasally was better than midazolam alone.

12. Lee-Kim,S.J.S.Fadavi, et al.[16](J Dent child 2004) evaluated and compared intranasal and oral midazolam for effect on behaviour, time of onset, efficacy and safety for patients requiring dental care. Forty anxious subjects were sedated randomly with either intranasal(0.3 mg/kg) or oral(0.7mg/kg) midazolam. They concluded that mean onset time was approximately three times faster with intranasal administration compared to per oral administration. Overall behaviour under oral and intranasal was similar. All vital signs were stable throughout the procedures with no significant differences between the two groups.

13. Levent V.Karabas et al.,[29](Journal of Paed Ophthal and Strabismus 2006,vol.43) investigated the effectiveness of topical anesthesia with sedation using intranasal midazolam in patients with symptomatic congenital nasolacrimal duct obstruction undergoing probing. 74 patients were divided into two groups, probing was

performed with general anaesthesia in 30 cases and with topical anesthesia using intranasal midazolam (0.3 mg/kg) in 44 cases. They concluded that probing under topical anaesthesia with intranasal midazolam was cost-effective, safe and comparable in efficacy to probing under general anaesthesia but with less risk.

14. Shashikiran ND, Reddy Subba[21] (J Indian Soc Pedod Prev Dent 2006) evaluated midazolam as a Paediatric conscious agent and compared its efficacy and safety when administered by intranasal and intramuscular routes, at a dosage of 0.2mg/kg body weight. These children were randomly assigned to two groups consisting of 20 subjects each. Group M received midazolam intramuscularly, while Group N received midazolam intranasally. Both the intranasal and intramuscular groups showed highly significant decrease in crying levels, motor movements and sensory perception levels. Though both the routes almost matched each other in their efficacy and safety profiles, the intranasal route showed a significantly faster pharmacodynamic profile in terms of faster onset, peak and recovery times. They concluded that midazolam could be safely and successfully employed by intranasal and intramuscular routes for Paediatric conscious sedation

in a routine dental setup with basic facilities at a dosage of 0.2 mg/kg body weight.

15. PradiptaBhakta, B.R.Ghosh, Manjushree Roy[23](Indian Journal of Anaesthesiology 2007) evaluated the efficacy of intranasal midazolam for preanaesthetic medication in paediatric patients. Forty five patients of two to five years of age belonging to ASA I and II, scheduled for minor elective surgery for this study. Patients were divided into three equal groups.

- Group I - Normal saline intranasally
- Group II - 0.2 mg/kg midazolam intranasally
- Group III - 0.3 mg/kg midazolam intranasally

Vital parameters and level of sedation using a sedation scale were assessed before administering the drug and at five minutes intervals up to induction of anaesthesia. A statistically significant change in the level of sedation was found at 5 minutes in group II and at ten minutes in group III compared to control group. Parental separation was easier in midazolam groups. Mask acceptance rate was found to be higher in midazolam groups. They concluded that intranasal midazolam in a dose of 0.2 mg/kg is an effective premedication for producing effective

sedation and anxiolysis in paediatric patients without any untoward side effect and no added advantage was found in 0.3 mg/kg dose.

16. SunnyAlex, Barbara Coelho, Ambareesha M[(25)](J Anaesth Clinical Pharmacology 2008) Compared the efficacy of nasal and oral midazolam as premedicant in preschool children. Sixty paediatric patients in the age group of one to six years scheduled for elective surgeries were included in this study. The children were randomly allocated into two groups I and II

- Group I - Oral midazolam 0.5 mg/kg with oral atropine0.04 mg/kg
- Group II - Nasal midazolam0.3 mg/kg with oral atropine0.04mg/kg

The drug used orally was the injectable preparation 5 mg/ml ampoule. The drug was mixed with sugar to mask the bitter taste before administration. The same preparation was used nasally. The calculated dose was taken in syringe and half dose administered into each nostril. The children were evaluated for baseline anxiety, time of onset of action of drug, time of onset of action of drug , time for satisfactory sedation, levels of sedation on a five point score, levels of anxiety on a four point

score, co-operation at the time of mask application. The mean time for onset of sedation and satisfactory sedation were 14.03 minutes and 18.3 minutes respectively for the oral midazolam group and 8.63 and 11.3 minutes for nasal midazolam group.

They concluded that both oral and nasal midazolam were effective as premedicants in preschool children, oral tolerated better than nasal and onset of sedation and satisfactory sedation were faster for intranasal route.

17. Lane, Roni D, Schunk, Jeff E [15](J of Pediatric emergency care, May 2008) performed a retrospective chart review of children who received intranasal midazolam sedation in the pediatric emergency department from April 1,2005 through June 30,2005. All children aged one to sixty months who received intranasal midazolam as the initial means of sedation were eligible for the study. A Mucosal Atomizer Device(MAD) was used to administer midazolam intranasally.The atomizer was attached to an one ml syringe and sprayed at a dose of 0.4 mg/kg with a maximum of 10 mg while the child was sitting upright. Onset of sedation, degree of sedation, NPO status, additional medications given and adverse events were recorded.

The majority of patients in this study achieved a level of mild to moderate sedation using atomized intranasal midazolam. Ninety-five percent of children did not require an additional sedative agent to complete the procedure. They concluded that atomized intranasal midazolam was effective in providing anxiolysis to children undergoing minor procedures in the paediatric emergency department. They also found that no adverse events occurred with the use of intranasal midazolam alone despite relatively short fasting times.

18. McCormick, A.S.M.,Thomas, V.L. Berry,D. [19] (British Journal of Anaesthesia 2008) compared two potential methods of administering midazolam by the nasal and nebulized routes. Midazolam (0.2 mg/kg) was given by both nebulizer and nasally by liquid instillation to ten healthy volunteers . Plasma concentrations of midazolam, Ramsay sedation score, visual analogue scores and parameters of cardiovascular and respiratory function were measured over 60 minutes. They found that nasal instillation was associated with higher plasma concentrations and caused more sedation than nebulized administration. They concluded that a higher dose might be needed for adequate pre-anaesthetic medication when midazolam was given by nebulizer.

MATERIALS AND METHODS

Seventy paediatric patients belonging to ASA physical status I and II scheduled for elective minor surgical procedures were included in the study.

Children belonged to age group of 2 to 8 years of both sexes.

The children were randomly allocated into 2 groups with 35 patients in each group. (Group N and Group O). It was a comparative study.

The study was approved by the Institutional Ethical Committee and parents provided written informed consent before premedication of their children.

Inclusion Criteria

- ASA I and II physical status
- Age group 2-8 yrs
- weight < 20 kgs

EXCLUSION CRITERIA

- ASA III and IV
- Nasal Infection
- Nasal Pathology
- Nasal Allergy and URI
- Children with Seizure disorder
- History of adverse reactions to benzodiazepines
- patient taking other sedative drugs**.**

MATERIALS

- Nasal midazolam spray (Insed atomiser)
- Oral midazolam

PREPARATION OF THE PATIENT

Written informed consent from the parent obtained.

All patients fasted as per NPO guidelines.

Demographic data including age, weight and sex of the children were recorded.

The children were given premedication 30 minutes before surgery orally or nasally. The reaction of the children to the premedication was noted.

- Group – N – received intranasal midazolam at a dose of 0.2mg/kg using Insed atomiser midazolam Nasal spray containing 100 micro litre / metered dose which delivers 0.5 mg/dose. The dose was calculated and divided equally into each nostril with the children in sitting position on their mothers' lap. Half of the dose was placed in each nostril .Placing half the medication in each nostril reduced the volume while doubling the available area for absorption. Then the patient was kept in slightly head-down position for 2 minutes for easy absorption.

Dosing guidelines of Nasal Spray

Age (years)	Approximate Wt	Dose (mg)	Metered Doses in each nostril
1-2	6-8	1.2 – 1.5	1-2
2-5	8-15	1.5 – 3.0	2-3
5-10	15-30	7.5 – 10	6-8

- Group – O – received oral midazolam at a dose of 0.5 mg/kg. The drug used was the injectable preparation which contains preservative free midazolam one ml (5mg/ml) in an ampoule. The drug was mixed with apple juice to mask the bitter taste before administration.

- After premedication, the children were observed carefully in the premedication room. Pulse oximeter was connected to the children and pulse rate and saturation were observed.
- The onset of sedation, levels of sedation and anxiolysis at 10, 20 and 30 minutes were noted. The reaction of the children at the time of separation from parents were noted and graded as per the co-operation score.
- After bringing the child to the theatre, an intravenous cannulation was done and child's response to venepuncture was noted and scored.
- Standard Monitors such as ECG, Pulse Oximeter, Non-invasive BP, Precordial Stethescope were attached.
- Anaesthesia was induced and response of the child to mask application was noted and scored before surgery was started.
- The children were kept in the recovery position after the surgery was over and observed in the operating room for 30 minutes and shifted to the recovery room.

OBSERVATIONS

- Time of Onset of Sedation
- Sedation Score at various points of time (10 minutes intervals for 30 minutes)
- Anxiolysis score at various points of time (10 minutes intervals for 30 minutes)
- Co-operation score at the time of separation from parents
- Co-operation score at the time of mask application
- Co-operation score at the time of venepuncture.

The presence or absence of the following side effects and complications from the time of instillation to 24 hours postoperatively, were noted.

- Nasal irritation
- Postoperative – nausea and vomiting
- Respiratory depression
- Laryngospasm/ Bronchospasm
- Other complications

SEDATION SCORE

Criteria	Grade	Score
Moving, physical or verbal display of apprehension	Alert /Active – agitated	1
Tearful, clinging to mother	Upset/ Worried	2
Calm, responding readily to commands	Relaxed	3
Easily arousable	Drowsy	4

ANXIOLYSIS SCORE

Criteria	Grade	Score
Afraid and crying, restrained	Poor	1
Fearful, moderate apprehension	Fair	2
Slightly fearful	Good	3
No fear or apprehension	Excellent	4

CO-OPERATION SCORE

Criteria	Grade	Score
Strongly refuses intervention	Poor	1
Considerable effort required to achieve intervention	Fair	2
Accept intervention reluctantly	Good	3
Accept intervention readily	Excellent	4

OBSERVATION AND RESULTS

The study was conducted in Paediatric Surgery operation theatres, New Paediatric block, Government Stanley Medical college hospital.

TYPES OF SURGERIES

SURGERY	GROUP N	GROUP O	TOTAL
Herniotomy	7	10	17
PV sac ligation	4	4	8
Circumcision	17	10	27
Others	7	11	18

ASA GRADE

All patients of both groups belonged to ASA Grade I and II

DEMOGRAPHIC PROFILE

The sample of 70 was taken for study. Test statistics used were Chi-Square test and 't' test.

The level of statistics significance was set up at $p < 0.05\%$

TABLE-1

Comparison of Age distribution

Group	N	Mean (Years)	S.D	Std.Error mean
Nasal	35	3.59	1.54	0.260
Oral	35	3.80	1.38	0.233

Chi – Square value is 1.645, p value = 0.649

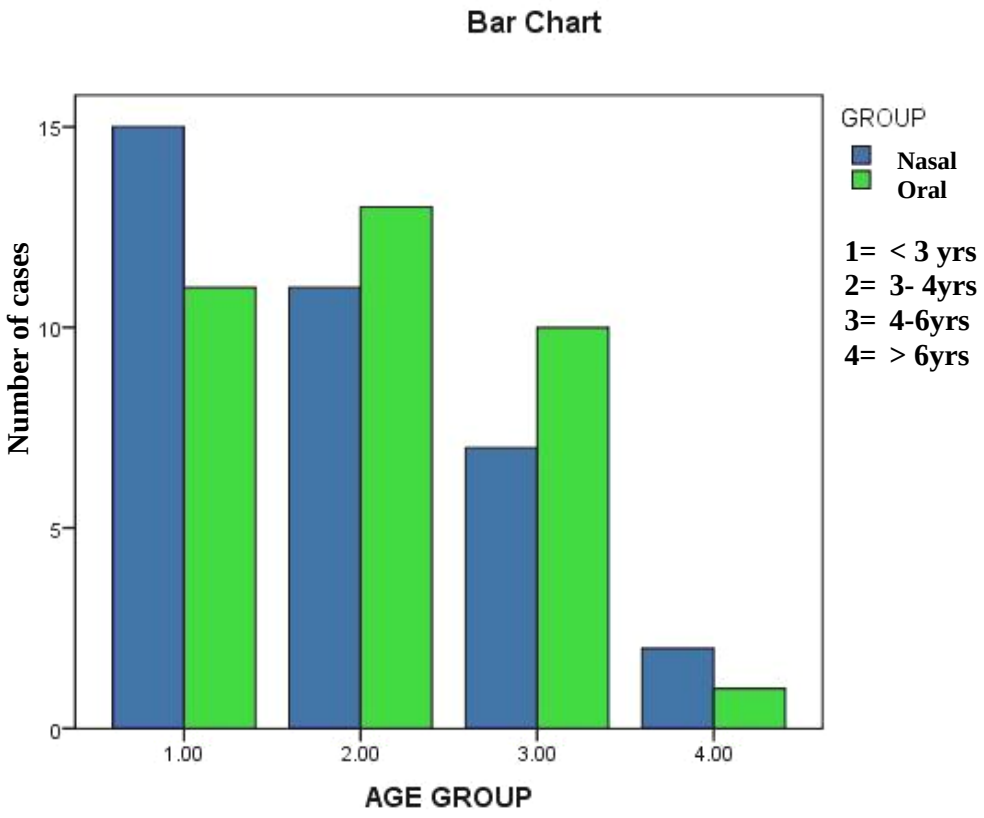


Figure : Bar Diagram Compares the age distribution of Nasal and Oral group

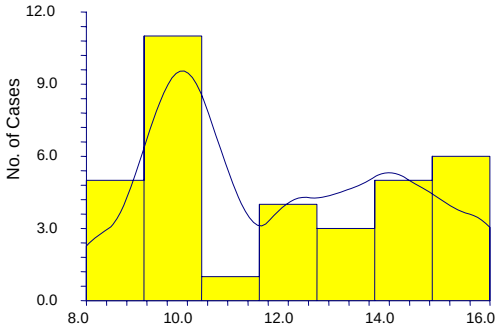
The mean age in nasal midazolam group is 3.5 years and in oral midazolam group is 3.8 years. The data is statistically insignificant ($p>0.05$) and thus both groups are comparable in terms of age.

TABLE-2

Comparison of weight distribution

GROUP	N	Mean (Kgs)	S.D	Std. Error mean
Nasal	35	11.82	2.43	0.410
Oral	35	12.17	2.46	0.417

Histogram of Weight – Nasal



Histogram of weight-Oral

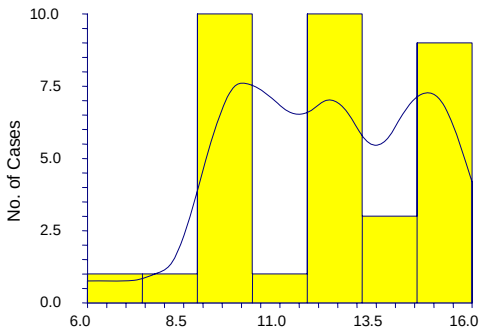


Figure : Histogram compares the weight distribution of Nasal and Oral group

The mean weight in Nasal group is 11.82 kg and in oral group is 12.17 kg. The data is statistically insignificant ($p>0.05$) and thus both groups are comparable in terms of weight.

TABLE - 3

Comparison of Sex Distribution

Group	Female	Male	Total
Nasal	5	30	35
Oral	6	29	35
Total	11	59	70

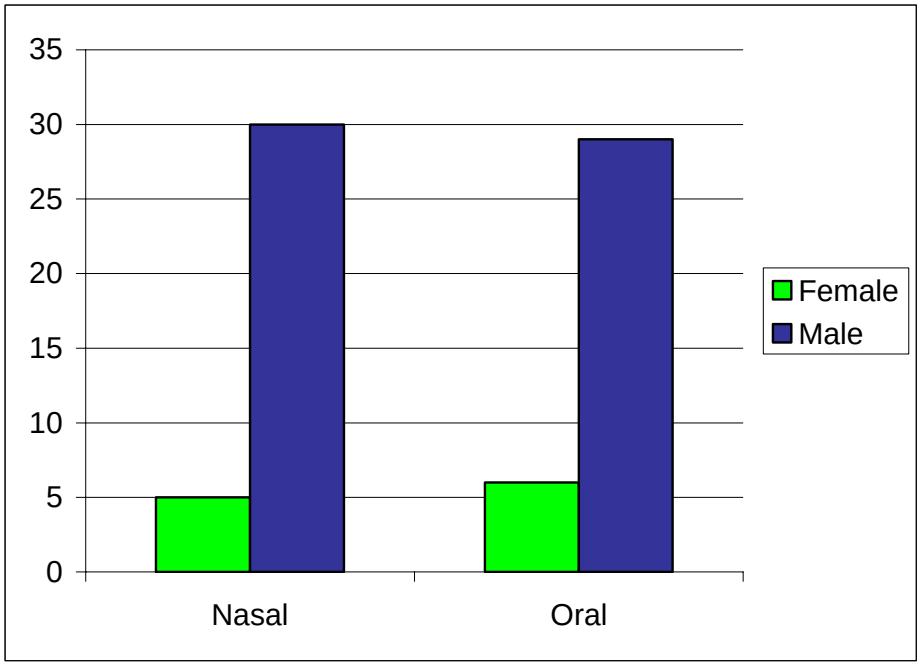


Figure : Bar Diagram shows Sex Distribution of Nasal and Oral group

TABLE-4

Comparison of time of onset of sedation

Group	No	MEAN (mts)	S.D	Std. Error mean
Nasal	35	8.42	2.07	0.350
Oral	35	15.82	2.73	0.462

Independent Samples Test

Time of onset of sedation

	Levene's Test of Variances		T-test for Equally of Means						
	F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error difference	95% Confidence Interval of the difference	
								Lower	Upper
Equal variances assumed	2.578	.113	-12.739	68	**.000**	-7.4000	.58089	-8.559	-6.240
Equal variances not assumed			-12.739	63.381	**.000**	-7.4000	.58089	-8.556	-6.239

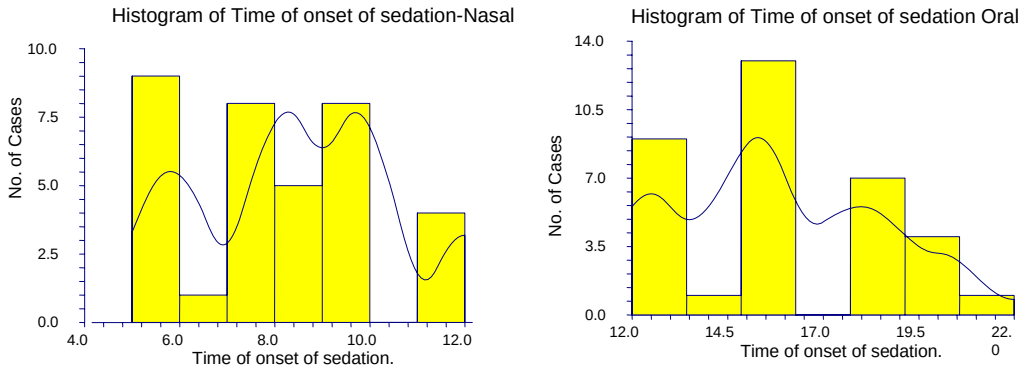


Figure : Hisogram compares the time of onset of sedation in Nasal and Oral groups

The mean time of onset of sedation in nasal midazolam group is 8.42 minutes and in oral midazolam group is 15.82 minutes. The data is statistically highly significant (p= 0.000).

TABLE -5

Sedation Score at 10 Minutes

Cross table					
			GROUP		
			Nasal	Oral	Total
Sedation Score 10 Minutes	1.00	Count	0	30	30
		% within Group	.0%	85.7%	42.9%
	2.00	Count	18	5	23
		% within Group	51.4%	14.3%	32.9%
	3.00	Count	16	0	16
		% within Group	45.7%	.0%	22.9%
	4.00	Count	1	0	1
		% within Group	2.9%	.0%	1.4%
	Total	Count	35	35	70
		% within Group	100.0%	100.0%	100.0%

Chi – Square value is 54.348, P value = 0.000

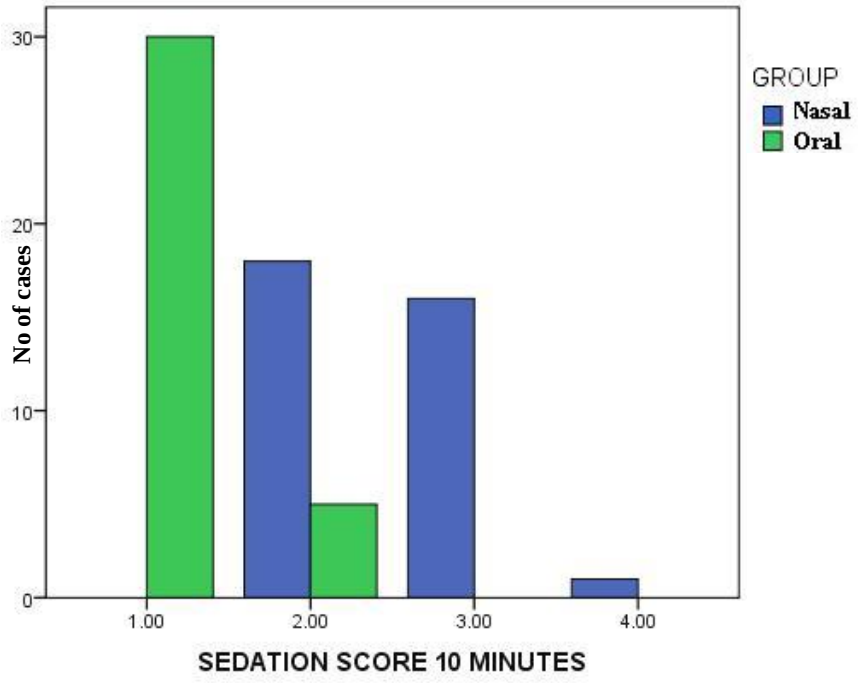


Figure : Bar diagram Compares Sedation score at 10 minutes in Nasal and Oral Groups

The sedation score in 10 minutes is statistically significant with a P value of 0.000<0.05

TABLE -6

Sedation Score at 20 Minutes

Cross table					
			GROUP		
			NASAL	ORAL	Total
Sedation Score 20 Minutes	1.00	Count	0	4	4
		% within Group	.0%	11.4%	5.7%
	2.00	Count	0	15	15
		% within Group	.0%	42.9%	21.4%
	3.00	Count	26	14	40
		% within Group	74.3%	40.0%	57.1%
	4.00	Count	9	2	11
		% within Group	25.7%	5.7%	15.7%
	Total	Count	35	35	70
		% within Group	100.0%	100.0%	100.0%

Chi – Square value is 27.055, P value = 0.000

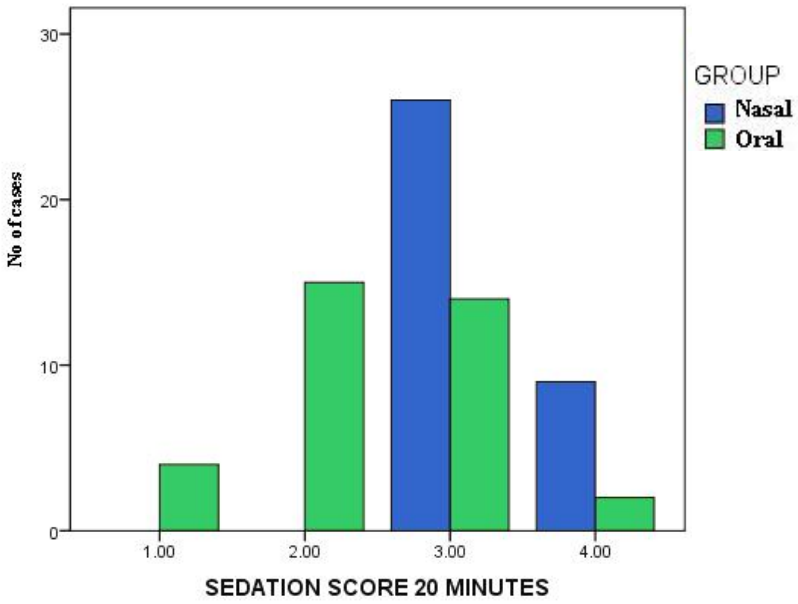


Figure : Bar diagram Compares Sedation score at 20 minutes in Nasal and Oral Groups

The Sedation score in 20 minutes is highly statistically significant with a P value < 0.05

TABLE -7

Sedation Score at 30 Minutes

Cross table					
			GROUP		
			Nasal	Oral	Total
Sedation Score 30 Minutes	2.00	Count	0	1	1
		% within Group	.0%	2.9%	1.4%
	3.00	Count	7	20	27
		% within Group	20.0%	57.1%	38.6%
	4.00	Count	28	14	42
		% within Group	80.0%	40.0%	60.0%
	Total	Count	35	35	70
		% within Group	100.0%	100.0%	100.0%

Chi – Square value is 11.926, P value = 0.003

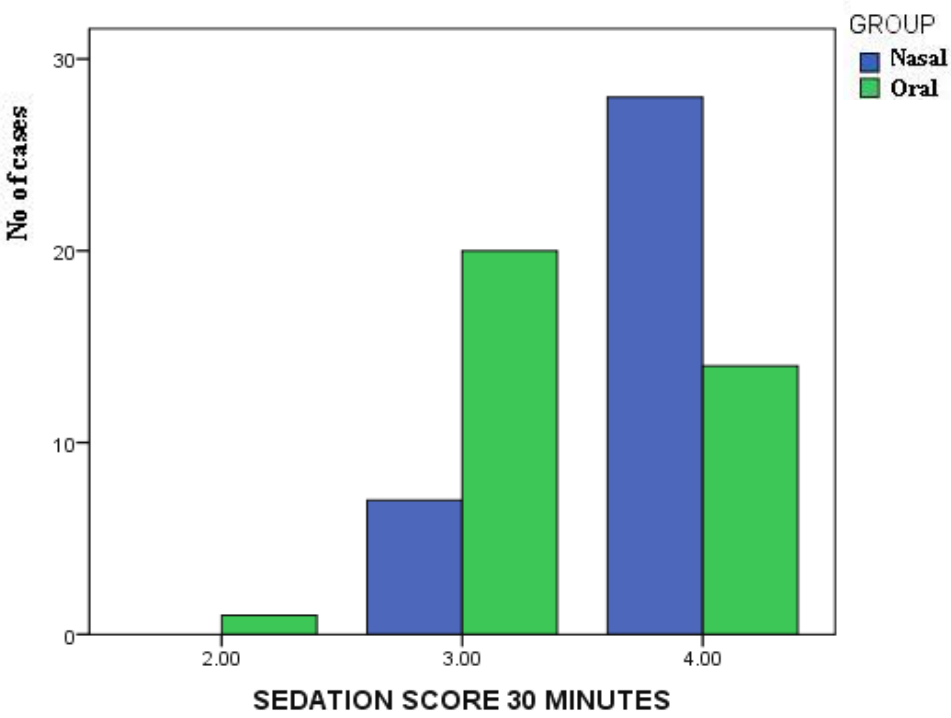


Figure : Bar diagram Compares Sedation score at 30 minutes in Nasal and Oral Groups

Sedation score in 30 minutes is statistically significant with a P value of 0.003 < 0.05

TABLE -8

Anxiolysis at 10 Minutes

Cross table				
Anxiolysis 10 Minutes		GROUP		
		Nasal	Oral	Total
1.00	Count	0	6	6
	% within Group	.0%	17.1%	8.6%
2.00	Count	13	17	30
	% within Group	37.1%	48.6%	42.9%
3.00	Count	20	9	29
	% within Group	57.1%	25.7%	41.4%
4.00	Count	2	3	5
	% within Group	5.7%	8.6%	7.1%
Total	Count	35	35	70
	% within Group	100.0%	100.0%	100.0%

Chi – Square value is 10.906, P value = 0.012

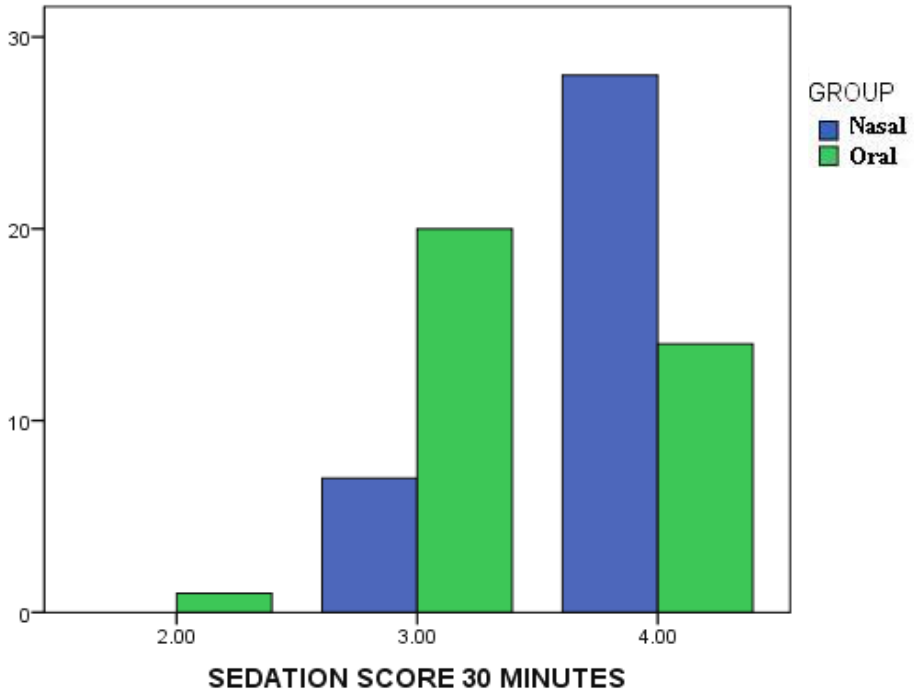


Figure : Bar diagram Compares Anxiolysis at 10 minutes in Nasal and Oral Groups

Anxiolysis score in 10 minutes is statistically significant with a P value of 0.012<0.05.

TABLE - 9

Anxiolysis at 20 Minutes

Cross table				
Anxiolysis 20 Minutes		GROUP		
		Nasal	Oral	Total
2.00	Count	1	4	5
	% within Group	2.9%	11.4%	7.1%
3.00	Count	23	18	41
	% within Group	65.7%	51.4%	58.6%
4.00	Count	11	13	24
	% within Group	31.4%	37.1%	34.3%
Total	Count	35	35	70
	% within Group	100.0%	100.0%	100.0%

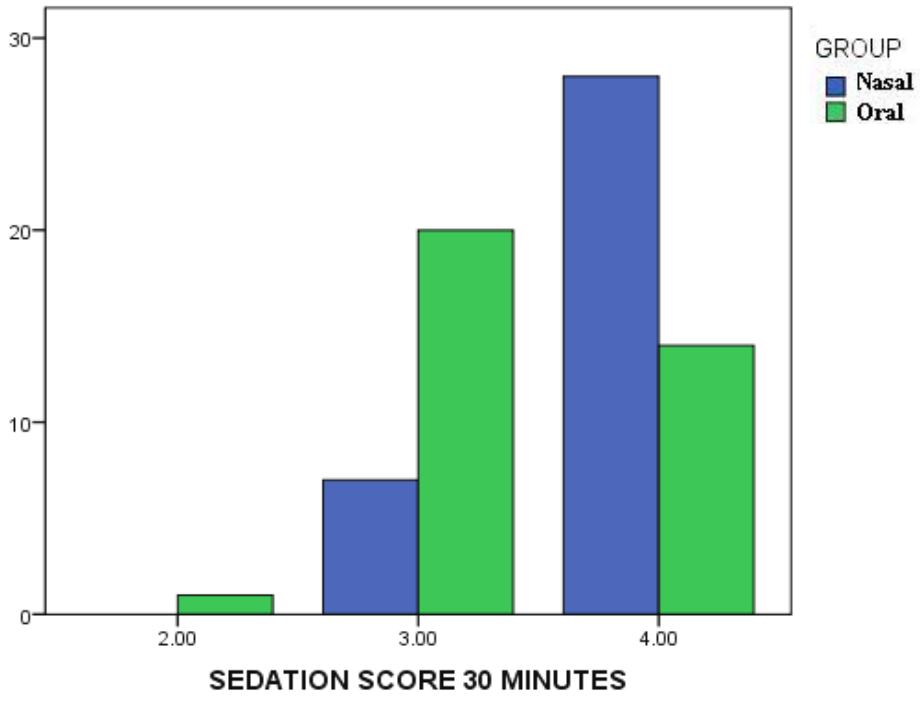


Figure : Bar diagram Compares Anxiolysis at 20 minutes in Nasal and Oral Groups

P value is 0.276

TABLE - 10

Anxiolysis at 30 Minutes

Cross table				
Anxiolysis 30 minutes		GROUP		
		Nasal	Oral	Total
3.00	Count	6	15	21
	% within Group	17.1%	42.9%	30.0%
4.00	Count	29	20	49
	% within Group	82.9%	57.1%	70.0%
Total	Count	35	35	70
	% within GROUP	100.0%	100.0%	100.0%

Chi – Square value is 5.510, P value = 0.019

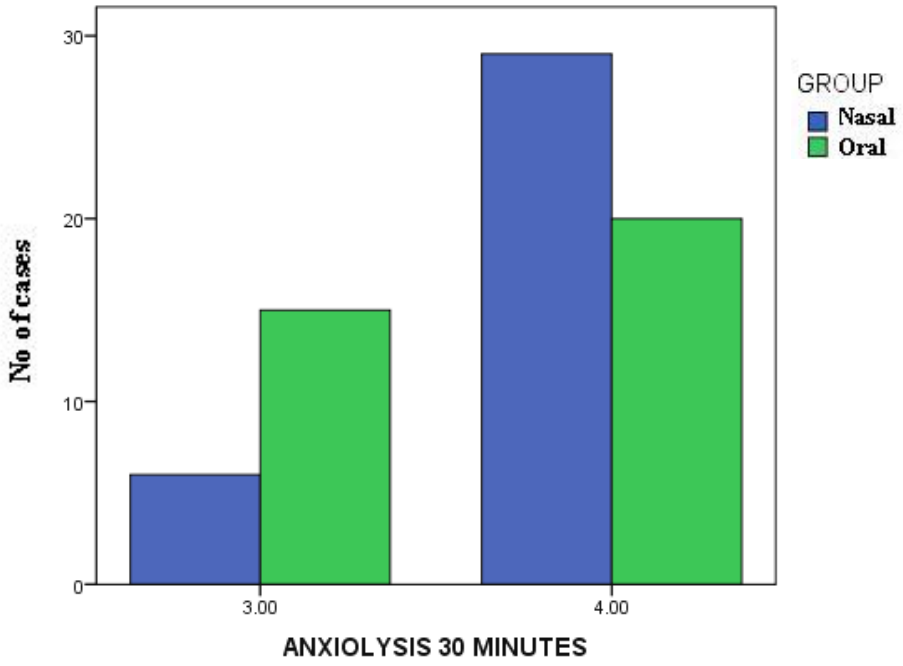


Figure : Bar diagram Compares Anxiolysis at 30 minutes in Nasal and Oral Groups

Anxiolysis in 30 minutes is statistically significant with a P value of 0.019(<0.05)

TABLE - 11

CO-OPERATION SCORE-PARENTAL SEPARATION

Cross table				
Co-Operation Score-Parental Separation		GROUP		
		Nasal	Oral	Total
2.00	Count	2	4	6
	% within Group	5.7%	11.4%	8.6%
3.00	Count	25	17	42
	% within Group	71.4%	48.6%	60.0%
4.00	Count	8	14	22
	% within Group	22.9%	40.0%	31.4%
Total	Count	35	35	70
	% within Group	100.0%	100.0%	100.0%

Chi – Square value is 3.827, P value = 0.148

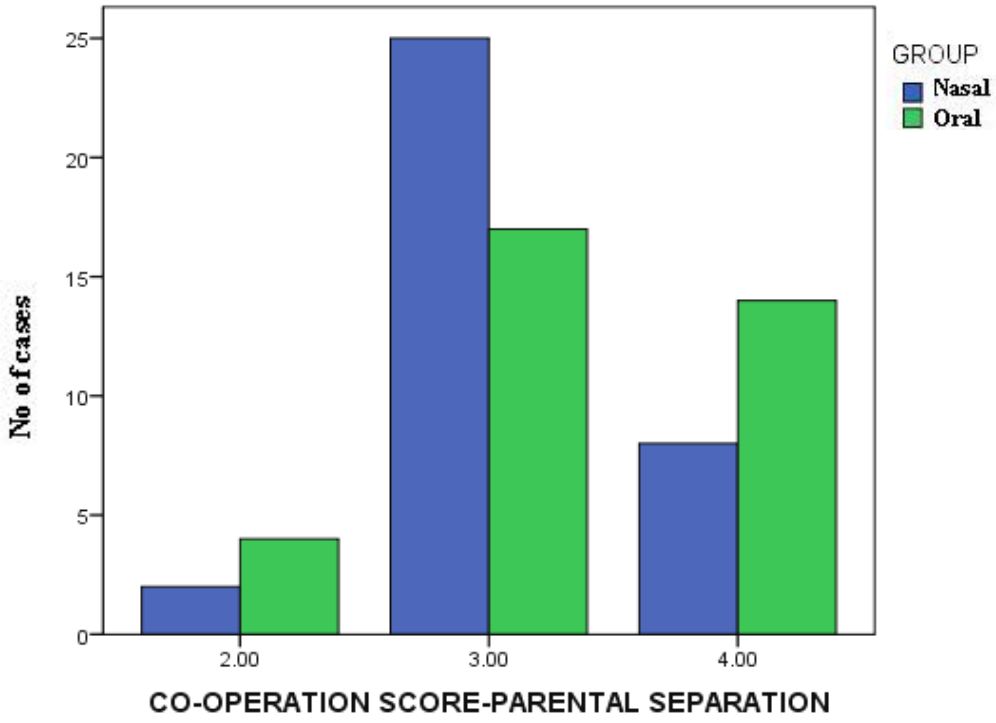


Figure : Bar diagram Compares co-operation score for parental separation in Nasal and Oral Groups

The data is statistically not significant as the P value is 0.148(>0.05)

TABLE - 12

CO-OPERATION SCORE - VENE PUNCTURE

Cross table				
VENE PUNCTURE		GROUP		
		Nasal	Oral	Total
2.00	Count	0	3	3
	% within Group	.0%	8.6%	4.3%
3.00	Count	17	20	37
	% within Group	48.6%	57.1%	52.9%
4.00	Count	18	12	30
	% within Group	51.4%	34.3%	42.9%
Total	Count	35	35	70
	% within Group	100.0%	100.0%	100.0%

Chi – Square value is 4.443, P value = 0.108

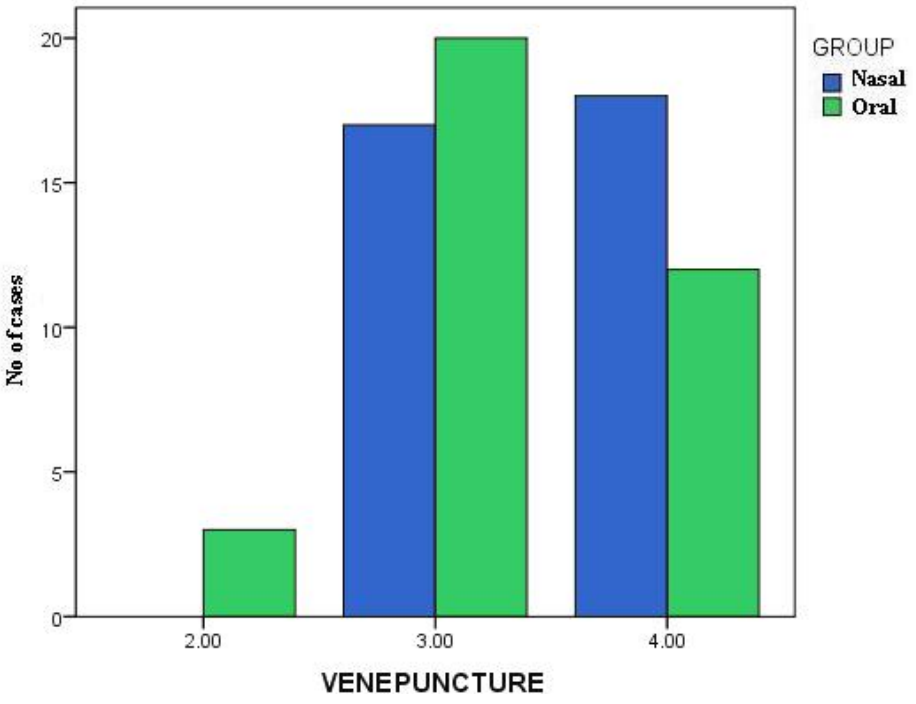


Figure : Bar diagram Compares co-operation score for Venepuncture in Nasal and Oral Groups

The data is statistically not significant as the P value is 0.108(>0.05)

TABLE - 13

CO-OPERATION SCORE FOR MASK APPLICATION

Cross table				
MASK APPLICATION		GROUP		
		Nasal	Oral	Total
3.00	Count	12	10	22
	% within Group	34.3%	28.6%	31.4%
4.00	Count	23	25	48
	% within Group	65.7%	71.4%	68.6%
Total	Count	35	35	70
	% within Group	100.0%	100.0%	100.0%

Chi – Square value is 0.256, P value = 0.607

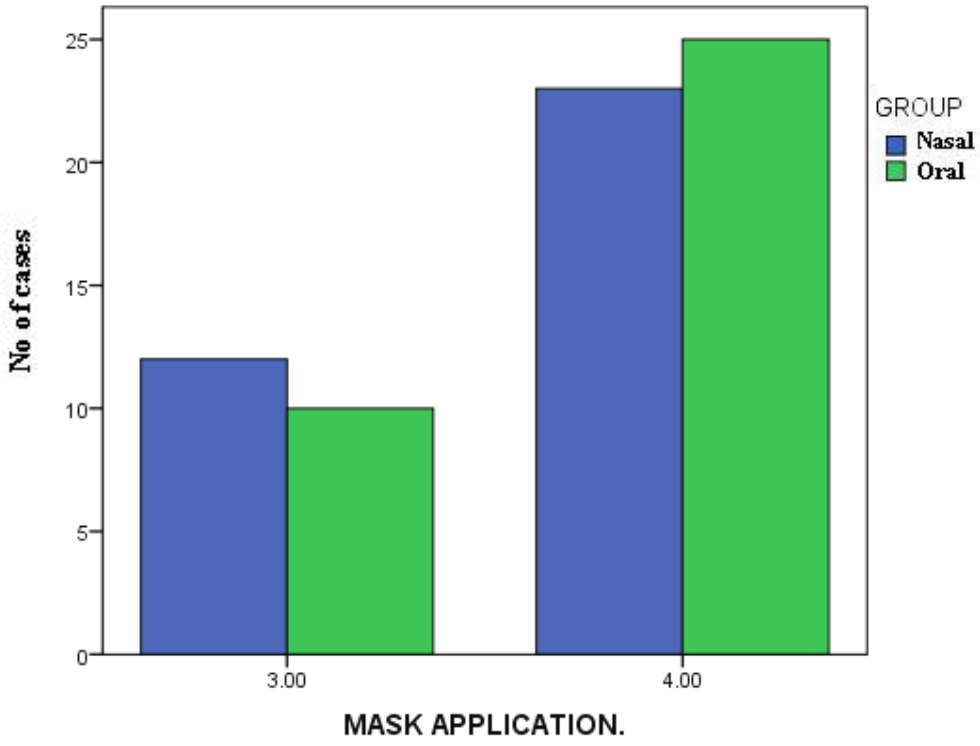


Figure : Bar diagram Compares co-operation score for Mask Application in Nasal and Oral Groups

The data is statistically not significant as the P value is 0.607 (>0.05)

DISCUSSION

Wilton NCT[27], Karl HW[12] and many others have searched for the ideal paediatric premedicating agent and also for the best route of administration. A paediatric premedicant must have an acceptable, atraumatic route of administration in addition to other characteristics needed for such a drug.

Midazolam has been extensively used in anaesthetic practice since 1982, and its pharmacodynamics and pharmacokinetics are well known. Midazolam is used frequently for premedication in children, preferably by non-parenteral routes.

Nasal administration of various drugs such as ketamine and midazolam has been recommended previously for premedication in children. Oral midazolam remains the commonly used premedication in paediatric outpatients.

Intranasal midazolam for premedication in preschool children was first described and advocated by Wilton and colleagues[27].

Midazolam has many desirable properties as a premedicant in children undergoing surgery. Midazolam exerts a reliable dose dependent anxiolytic effect without oversedation and provides minimal cardiovascular and respiratory effects. The anterograde amnesia produced by midazolam help reduce the psychological trauma of anaesthesia and surgery. Its elimination half life is 1.5 -2 hrs which is considerably shorter than that of diazepam. The elimination half life of intranasal midazolam is similar to that when the drug is given intravenously and no significant complications have been reported when it is given by the intranasal route.

As midazolam has many of the properties of an ideal permedicant drug, this comparative study was undertaken to compare the efficacy of this drug when given by oral and intranasal routes.

Most studies have used midazolam in a dosage of 0.1 to 0.3 mg/kg intranasally and several pharmacokinetic studies have examined plasma concentrations and effect at varying intranasal doses.

Intranasal midazolam has generally been administered in the form of drops, which in the awake patient are difficult to keep in the nose and may be swallowed and subjected to first pass metabolism in the liver.

Twersky and colleagues used a Devilbiss 286 atomizer to deliver 0.2 mg/kg. Bjorkman, Rigemar and Idvall[30] used a spray bottle in adults and found the procedure acceptable. Midazolam has also been given to adults by nebulizer with good acceptability.

It has been shown that the fine aerosol would allow greater contact with the absorbing surface and that application would be less unpleasant than drops. Bio-availability with nasal spray has been shown to be high (83%) with virtually complete absorption.

N. Griffifth et al., [7]compared two methods of administering midazolam intranasally in 44 day-care children and used midazolam 0.2 mg/kg as drops or midazolam 0.1 mg/kg from an intranasal spray device.

Behaviour was recorded on a four point scale and co-efficients were obtained representing the change in behaviour score. There was no significant difference in the method of administration (coefficient 0.13, p=0.39). midazolam by either method was equally effective but acceptability of the premedication was poor in nasal drops group.

Intranasal midazolam in the form of a spray was used in this study. Each metered dose of 100 microliter of atomiser delivered 0.5 mg of midazolam.

Oral midazolam used in this study was the preservative free injectable preparation (5 mg/ml) in an ampoule. The drug was mixed with the apple juice to mask the bitter taste and to increase the acceptability.

Sunny Alex et al., [25] used intranasal midazolam at a dose of 0.3 mg/kg and oral midazolam in a dose of 0.5 mg/kg in their study.

Charles J.Cote et al.,[3]studied 306 patients, using 3 different doses of oral midazolam syrup 0.25, 0.5,1.0 mg/kg. Overall 97% of patients achieved satisfactory sedation (score>3) after treatment. The difference between the 0.25 and 0.1 mg/kg dosage was significant.($p<0.01$).

There was no difference between the 0.5 and 1.0 mg/kg groups or between the 0.5 and 0.25 mg/kg groups. After study medication, 99% maintained satisfactory sedation scores and 97.5% achieved a satisfactory anxiolytic response(score>3). There was a positive association between dose and onset of anxiolysis($p=0.01$); a larger

proportion of children achieved satisfactory anxiolysis within 10 minutes at the higher doses. >90% maintained satisfactory anxiolysis for upto 45 minutes.

No child experienced respiratory complications before induction, two experienced nausea and three vomited before induction. The proportion of subjects experiencing an adverse event was slightly larger in the 1.0 mg/kg.

Hence it was decided to use oral midazolam in a dose of 0.5 mg/kg for all children in the oral group in this study and none of them experienced respiratory depression, nausea, vomiting or any adverse effect.

Asif Pervez et al.,[2]compared the effect of intranasal midazolam with intranasal ketamine and used intranasal midazolam in a dose of 0.2 mg/kg.

In a study performed by Garcia-Velasco P et al.,[28] intranasal midazolam was used in a dose of 0.25 mg/kg and it compared it with ketamine (5mg/kg) nasally and found that the nasal route of administration of the drug was well accepted in both groups and midazolam and Ketamine were equally effective as sedative premedication.

Gustaf L jungman et al.,[8]conducted a double blind, placebo controlled, crossover study in which nasal administration of midazolam spray 0.2 mg/kg was compared with placebo.

Sunny Alex et al.,[25]used a five point score for level of sedation, four point score for level of anxiety and a four point score for co-operation at the time of parental separation.

Sedation score at 10, 20, 30, 40 minutes and at the time of separation from parents were evaluated and compared between the oral and nasal midazolam groups.

In our study, mean time for onset of sedation, time for satisfactory sedation, level of sedation at 10 minutes, 20 minutes, and 30 minutes, level of anxiety at 10 minutes, 20 minutes, 30 minutes in both the groups were compared. In addition, co-operation at the time of separation from parents, co-operation at the time of venepuncture and co-operation at the time of mask application were scored and compared.

A four point scale for sedation score, five point scale for anxiolysis score and a four point scale for co-operation score were used to compare the groups in this study.

In our study, the mean time for onset of sedation in nasal midazolam group was found to be 8.42 minutes and in oral group it was 15.8 minutes. Thus the onset time in oral group was almost twice that of nasal group.

Sunny Alex et al.,[25] found that the mean time for onset of sedation and satisfactory sedation were 8.63 minutes and 11.3 minutes respectively for the nasal midazolam group and and 14.03 minutes and 18.3 minutes for the oral midazolam group with P value of 0.001 which was very highly significant.

Christy Lam et al.,[4]compared the effectiveness of intramuscular and intranasal midazlolam as a premedication before intravenous conscious sedation. The patients ranged in age from 2-9 yrs (mean age 5.13 yrs) and received a dose of 0.2 mg/kg of midazolam via intramuscular or intranasal administration. They studied 23 patients and reported that patients who were given intramuscular midazolam were more deeply sedated than those receiving intranasal midazolam.

Karl HW et al., [12] showed that the rich blood supply of the nasal mucosa allows rapid absorption of drugs directly into the systemic circulation. Absorption depends on the time that the drus is adjacent to the mucosal surface (Resident time), local pH (6-7), presence of

secretions (respiratory tract infections), physicochemical properties of the drug and physicochemical properties of route of the administration of the drug.

The method and technique of administration also affect the drug absorption. The aqueous solubility of midazolam at acidic pH (3.5) allows this drug to maintain a high concentration in nasal mucosa (pH 6-7). The pK_a of midazolam 6.15 which is close to local pH. Both ionized and nonionized forms are absorbed from nasal mucosa.

Kogan et al.,[14] studied the effects of oral, rectal and nasal midazolam. The children accepted oral route significantly better compared to nasal or oral routes. The fastest onset of sedation was found after rectal route. The effect of oral midazolam was good in many children but less predictable.

Asif Pervez et al.,[2] conducted the study on paediatric surgical patients in 2-5 yr age group. Our study was conducted on patients between 2-6 yrs.

In the study conducted by Sunny Alex et al.,[25]sedation scores were slightly better in the nasal group upto 20 minutes after premedication with P value of 0.006 which was highly significant at 10 minutes, and P value of 0.028 which was significant at 20 minutes. At

30 minutes , 40 minutes and at the time of separation from parents sedation scores were comparable between two groups with p value of >0.05 which was statistically insignificant.

In our study, statistical analysis showed that sedation score at 10 minutes was better with the nasal group with a P value of <0.001 which is statistically highly significant.

Sedation score at 20 minutes after premedication was better with nasal midazolam with a P value of < 0.001 which is again statictically significant. Sedation score at 30 minutes was better in the nasal group with a P value of 0.003 which is statistically significant.

In our study, anxiolysis scores were better with the nasal group with p value of 0.012 at ten minutes and twenty minutes and a P value of 0.019 at thirty minutes which are statistically significant. But this contradicts the study of Sunny Alex et al.,[25] who found the anxiolysis score to be similar in the two groups (nasal and oral) throughout the study period with a p value of >0.05 which was not significant statistically.

In our study, co-operation scores at the time of parental separation are comparable in both groups with a P value of 0.148 which is

statistically not significant. This result can be correlated with the study of Sunny Alex et al., who had similar results.

Co-operation scores at the time of venepuncture are found to be similar in both groups with a P value of 0.108 which is not statistically significant. This also correlates with the study of Sunny Alex et al.,[25] who had the same results.

The co-operation for mask application is comparable in both groups with a P value of > 0.05 which is not statistically significant.

In both groups no patient had coughing, gagging, vomiting, laryngospasm or respiratory depression.

SUMMARY

We compared the efficacy of midazolam as a paediatric premedication when used in two different routes.

Midazolam was used as premedication in intranasal and oral routes in children undergoing minor surgical procedures and the efficacy of the drug in producing preoperative sedation, anxiolysis and co-operation during separation from the parents, venepuncture and face mask application was compared using separate scoring systems.

The following observations were made during the study.

There are no significant differences between the two groups in demographic data.

The time of onset of sedation is 8.42 minutes with intranasal midazolam and 15.82 minutes with oral midazolam.

We observed that intranasal midazolam has more rapid onset of action compared to oral midazolam, which is statistically significant.

The sedation scores are better with intranasal midazolam than oral midazolam at 10 minutes, 20 minutes and30 minutes which are statistically significant.

The anxiolysis is better with nasal midazolam group with statistical significance.

There is no significant difference in the co-operation score for venepuncture, separation from the parents and mask application between the two groups.

No patient was oversedated or drowsy postoperatively. No complications were observed in both the groups.

CONCLUSION

In conclusion, Intranasal midazolam when used as a premedication in children, in a dose of **0.2 mg/kg** has more rapid onset of action with satisfactory sedation and anxiolysis than oral midazolam. The rapid onset of action of nasal midazolam makes it an ideal route for premedication in children.

PROFORMA

Name :
Age :
Sex :
Weight :
IP No.
ASA Physical Status :
Diagnosis :
Procedure :
Duration of Surgery :
Baseline Anxiety :

Oral	Nasal

I. Time of onset of sedation (minutes) :

II. Sedation score at various points of time

Time	Group N	Group O
10 Minutes		
20 Minutes		
30 Minutes		

IV. Anxiolysis score at various points of time :

Time	Group N	Group O
10 Minutes		
20 Minutes		
30 Minutes		

V. Co-operation score:

Time	Group N	Group O
Parental Separation		
Venepuncture		
Mask Application		

VI. Complications if any :
Respiratory depression, Salivation, Laryngospasm, Others

SEDATION SCORE

Criteria	Grade	Score
Moving, physical or verbal display of apprehension	Alert /Active – agitated	1
Tearful, clinging to mother	Upset/ Worried	2
Calm, responding readily to commands	Relaxed	3
Easily arousable	Drowsy	4

ANXIOLYSIS SCORE

Criteria	Grade	Score
Afraid and crying, restrained	Poor	1
Fearful, moderate apprehension	Fair	2
Slightly fearful	Good	3
No fear or apprehension	Excellent	4

CO-OPERATION SCORE

Criteria	Grade	Score
Strongly refuses intervention	Poor	1
Considerable effort required to achieve intervention	Fair	2
Accept intervention reluctantly	Good	3
Accept intervention readily	Excellent	4

Sno	Name	IP no	Age (yrs)	Sex	Wt (kgs)	Surgery	Time of onset of sedation (mts)	Sedation score			Anxiolysis			Co-operation score			Compications
								10 mins	20 mins	30 mins	10 mins	20 mins	30 mins	Parental seperation	vene puncture	Mask application	
1	Hariharan	060966	2	M	8	circumcision	5	2	3	4	2	3	4	3	4	4	
2	Gowtham	060958	2.5	M	10	circumcision	8	3	3	4	2	3	3	3	3	4	
3	Henry	060957	4	M	14	hypospacdias repair	6	3	3	4	2	4	4	3	4	4	
4	Kalaivani	060915	6	F	16	preauricularsinusexcision	5	3	3	4	3	3	4	3	3	4	
5	Jennifer	060771	4	F	14	tongue tie release	5	4	3	4	2	3	4	4	4	3	
6	Roshan	060869	2 1/2	M	10	circumcision	6	2	3	3	2	3	3	3	3	4	
7	Monesh	060870	2	M	10	circumcision	10	2	3	4	2	3	4	3	4	4	
8	Sachin	060871	7	M	16	rt.pvsacligation	8	2	4	4	3	3	4	3	4	4	
9	Santhosh	060614	2	M	8	circumcision	6	3	3	4	2	2	4	3	3	4	
10	Iyyapan	060618	2 1/2	M	9	circumcision	9	2	3	4	2	3	4	3	4	4	
11	Manohar	060617	3 1/2	M	12	circumcision	10	3	3	4	3	3	4	3	3	4	
12	Kumaran	060615	2 1/2	M	11	circumcision	10	2	3	3	2	3	4	3	3	4	
13	Saravanan	067613	4	M	12	circumcision	8	3	3	4	3	4	4	4	4	4	
14	Mahalaxmi	060742	3 1/2	F	12	rt.herniotomy	10	2	3	3	2	3	4	3	3	3	
15	Manivannan	060743	6	M	14	circumcision	9	2	4	4	3	4	4	3	4	4	
16	Ravi	60684	5	M	14	circumcision	10	3	3	4	3	3	4	4	4	3	
17	Kishore	60696	2 1/4	M	10	circumcision	8	2	3	4	3	4	4	4	3	4	
18	Karthikeyan	60700	3 1/2	M	13	circumcision	12	3	4	4	3	3	4	4	4	4	
19	Gowtham	60777	2	M	10	circumcision	10	2	3	3	3	3	4	3	3	3	
20	Saravana Kumar	60768	2	M	10	circumcision	12	2	3	3	2	3	3	3	4	3	
21	Rithish	66774	2 1/2	M	14	rt.pvsacligation	8	3	3	4	3	3	4	4	3	4	
22	Saikanth	60770	6	M	16	rt.pvsacligation	10	3	3	4	2	3	4	3	4	3	
23	Sira	62298	5	M	13	umblical h repair	9	2	3	3	2	3	3	3	4	3	
24	Bhuvanesh	62301	2	M	10	orchidopexy	9	2	4	4	3	4	4	4	3	3	
25	Hemesh Kumar	62306	3	M	9	herniotomy	10	3	3	4	3	4	4	3	4	4	
26	Susainathan	62229	2 1/2	M	10	circumcision	12	2	3	3	3	3	3	2	3	3	
27	Akash	62305	2 1/2	M	12	herniotomy	8	3	4	4	4	4	4	3	4	4	
28	Dhinakaran	62303	3	M	10	circumcision	6	3	4	4	3	4	4	2	4	4	
29	Hemanth	63289	3	M	10	tongue tie release	8	3	3	4	3	4	4	3	3	3	
30	Priyan	63282	2 1/2	M	10	rt.pvsacligation	6	3	4	4	3	3	4	3	3	4	
31	Vishwa	68288	7	M	15	l.herniotomy	12	2	3	4	3	3	3	3	4	4	
32	Manickam	63322	3	M	9	r.herniotomy	6	3	4	4	3	3	4	4	3	3	
33	Keerti	63319	5	F	15	tongue tie release	8	2	3	4	3	3	4	3	3	4	
34	Naveen	62353	4	M	13	herniotomy	7	2	3	4	3	4	4	3	3	3	
35	Pavithra	62352	6	F	15	herniotomy	9	2	4	4	4	4	4	3	4	4	

GROUP 'O'																	
Sno	Name	IP no	Age (yrs)	Sex	Wt (kgs)	Surgery	Time of onset of sedation (mts)	Sedation score			Anxiolysis			Co-operation score			Compications
								10 mins	20 mins	30 mins	10 mins	20 mins	30 mins	Parental seperation	vene puncture	Mask application	
1	Shadik	62243	2 1/2	M	13	prominent coccyx excison	15	1	3	4	1	4	4	3	3	3	
2	Sasi	62355	2 1/2	M	10	circumcision	18	1	2	3	1	3	3	3	4	4	
3	vignesh	62351	3	M	10	circumcision	20	1	1	3	1	3	3	3	4	4	
4	alisha	62356	5	M	12	circumcision	15	1	2	3	1	2	3	4	4	4	
5	Sarath babu	60495	2	M	10	r.herniotomy	12	2	3	3	1	3	3	3	3	4	
6	Vennila	60660	6	F	14	r.herniotomy	15	2	2	3	2	3	3	3	4	4	
7	Renuka devi	60655	5	F	12	mucus cystlip excision	13	1	1	2	1	3	3	4	4	4	
8	Mahadevan	60653	2	M	10	circumcision	12	1	2	3	2	4	4	4	3	4	
9	Vetrivel	60652	5	M	15	circumcision	16	1	2	3	2	4	4	4	3	4	
10	Muthuvel	60682	6	M	16	r.pvsl	18	1	4	4	2	4	4	4	4	4	
11	Mariam Sihana	63543	7	F	16	elective appendicecpomy	14	1	2	4	2	2	4	4	3	4	
12	Ajith	63522	6	M	15	elective appendicecpomy	12	1	1	4	2	3	4	4	3	4	
13	Yuvendran	63582	2 1/2	M	9	l.orchidopexy	15	1	2	4	2	4	4	3	3	3	
14	Yuvan	63584	2 1/2	M	10	r.pvsl	13	1	3	3	2	3	3	3	4	4	
15	Hemanth	63587	3 1/2	M	12	r.pvsl	15	1	3	4	2	3	3	4	3	4	
16	Madesh	63586	2 1/2	M	10	r.herniotomy	13	1	4	4	2	4	4	4	3	4	
17	Vinoth kumar	63581	3	M	11	r.herniotomy	12	2	2	3	3	4	4	3	4	4	
18	Niranjan	63583	2 1/2	M	10	circumcision	15	2	3	4	3	4	4	3	3	4	
19	Prashanth	63483	4	M	12	r.herniotomy	13	2	3	4	3	3	3	3	3	4	
20	Lenin	63580	4	M	14	r.herniotomy	12	1	3	3	2	3	3	3	3	3	
21	Anandhi	62865	5	F	15	sub mandibular sinus excison	18	1	2	3	3	4	4	3	4	4	
22	Puviarasu	63287	6	M	15	orchidectomy	20	1	3	4	3	3	4	4	4	4	
23	Mohammed	63286	5	M	13	r.pvsl	16	1	3	3	4	4	4	4	4	4	
24	Yathish	63283	3	M	10	r.herniotomy	15	1	3	3	4	4	4	3	3	4	
25	Vignesh	63299	3	M	12	tongue tie release	20	1	2	3	3	4	4	4	3	4	
26	Sanjay	64201	4	M	13	elective appendicecpomy	18	1	3	4	3	3	4	4	4	4	
27	Adhilaxmi	64238	5	F	15	demoid excision	18	1	2	4	4	4	4	3	3	4	
28	Jeeva	64234	2 1/2	M	8	r.herniotomy	16	1	2	3	3	3	4	3	3	3	
29	Monisha	64241	2	F	6	r.herniotomy	22	1	1	3	3	3	3	3	2	3	
30	Naveen	64240	4	M	15	tongue tie release	18	1	3	3	2	3	3	3	2	3	
31	Vijayakumar	64248	3	M	12	circumcision	16	1	3	4	2	3	4	4	3	4	
32	Chanakya	64247	3 1/2	M	12	circumcision	18	1	2	3	2	2	3	2	3	3	
33	Pradheen	64243	2 1/2	M	10	circumcision	16	1	2	4	2	3	4	2	3	3	
34	Praveen	64244	4	M	14	circumcision	20	1	2	3	2	2	3	2	3	3	
35	Vikram	63323	4	M	15	r.orchidectomy	15	1	3	3	2	3	3	2	2	3	

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6. Stoelting's Pharmacology and Physiology in Anaesthesia- 4th edition

7. Grant's Atlas of Anatomy- 12th edition

Stanley Medical College, Chennai - 1
Ethical Committee

CERTIFICATE FOR APPROVAL OF ETHICAL COMMITTEE

To
Dr.A.Carolin Von Mullai PG in MD(Anes)
Dear **Dr.A.Carolin Von Mullai PG in MD(Anes)**
The Institutional Ethics Committee reviewed and discussed your application for approval of the project entitled

"Comparison of Intranasal and Oral Midazolam as premedication in Children "

The following members of the ethics committee were present at the meeting held on 24.02.2009 at the Modernised Seminar Hall, Stanley Medical College, Chennai-1 at 12.00 Noon

Dr.C.B.Tharani, Director of Pharmacology,
Madras Medical College, Chennai-3 Chairman of the Ethics Committee
Dr.A.Sundaram, Vice-Principal,
Stanley Medical College, Chennai - 1 Member Secretary of the Ethics Committee

Members

Dr. Jayanthi
Prof. of Medical Gastroenterology
Dr. Madhavan
Prof. of Pharmacology
Dr. Rengaramani
Prof. of Biochemistry
Dr. Madhan
Prof. of Aneasthesiology
Dr.Thenmozhivalli
Prof. of Microbiology
Dr.V.Ruckmani
Prof.of Medicine
Dr.P.Dhileepan
Prof.of Surgery
Tmt. T. Mary Ramola
Administrative Officer
Thiru. A. Senthil Manoharan
Advocate

We approve the project to be conducted in its presented form.
The Institutional Ethics Committee/Independent Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

Yours sincerely,

Member Secretary,
Ethical Committee

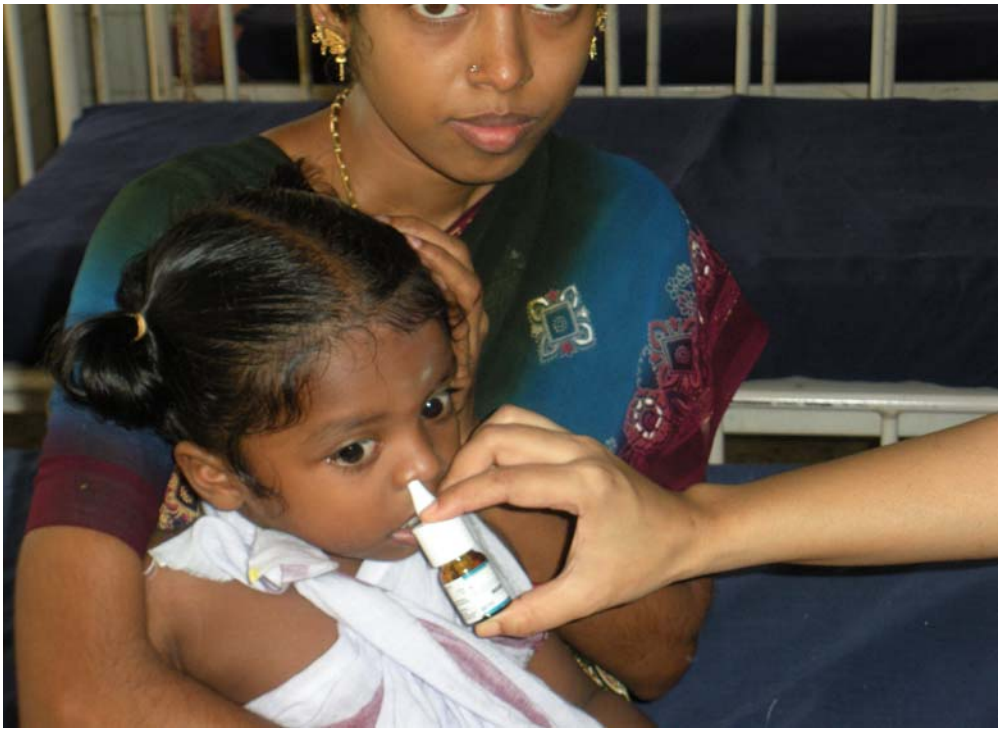
STANLEY MEDICAL COLLEGE ★ CHENNAI-600 001. ★
24 FEB 2009

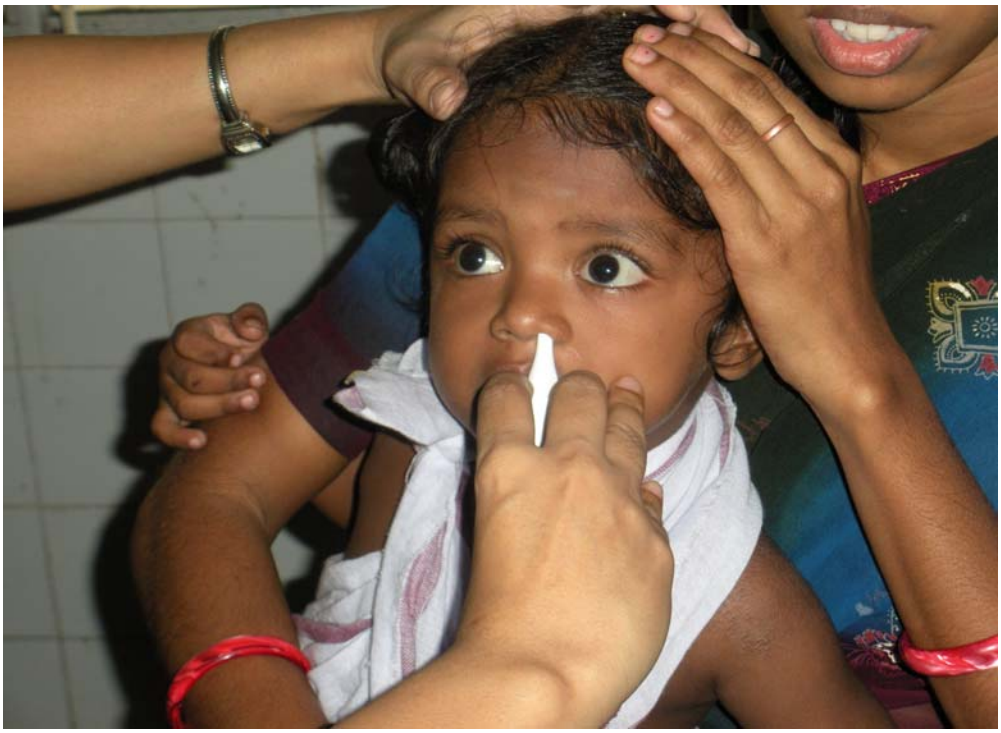
INFORMED CONSENT FORM

I Mr./Mrs._____ was informed by Dr. _____ that it was important to make my child calm and quiet before shifting him / her into the operating theatre for surgery. I was told that it was easier to make my child asleep by instilling the drug in the form of 2 -3 nasal drops than by giving injection.

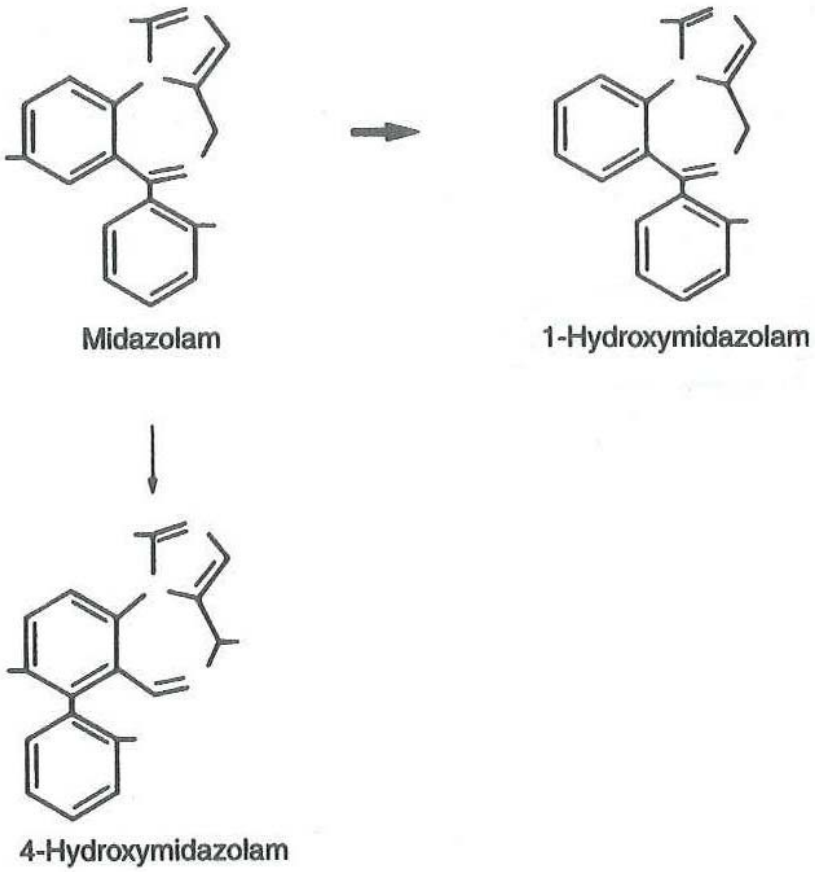
I clearly understand that this method is painfree and without side effects. As my child is not allergic to any drug, I willingly give my consent to make my child asleep by this method.

Signature of the Parent

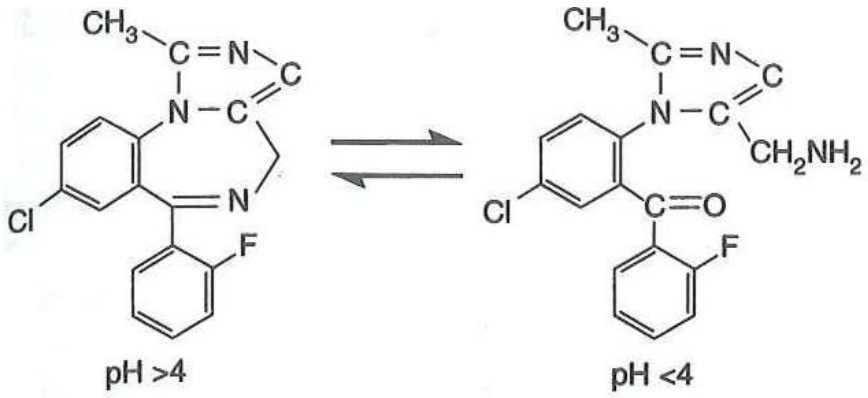




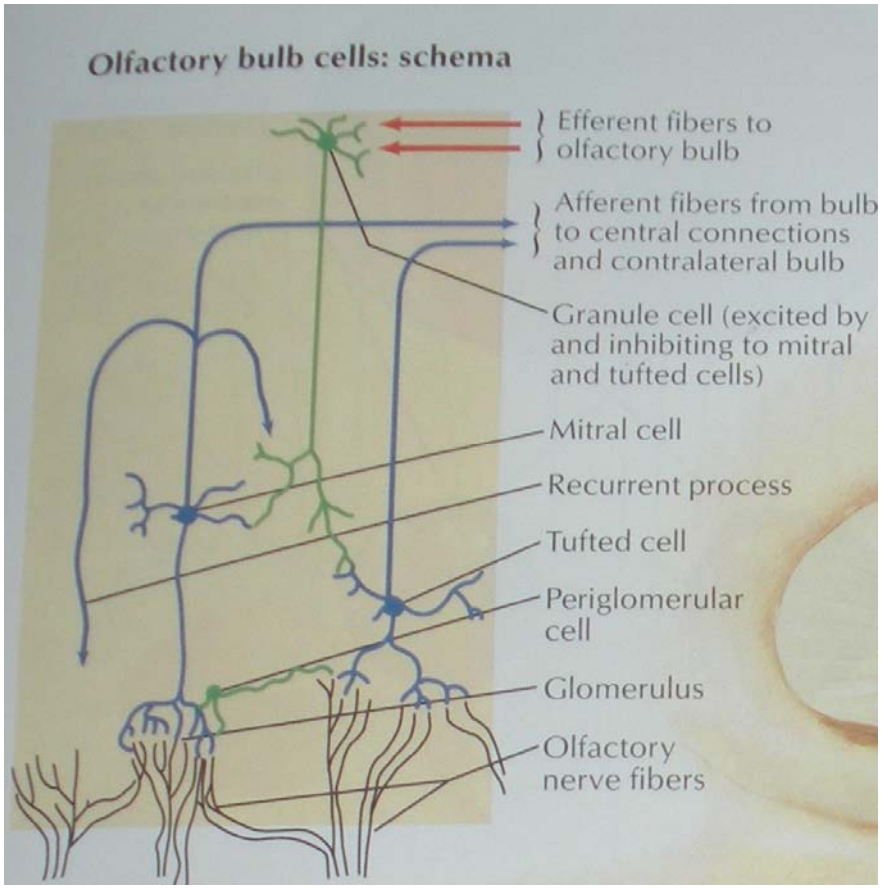
The picture shows the child being premedicated with nasal midazolam spray

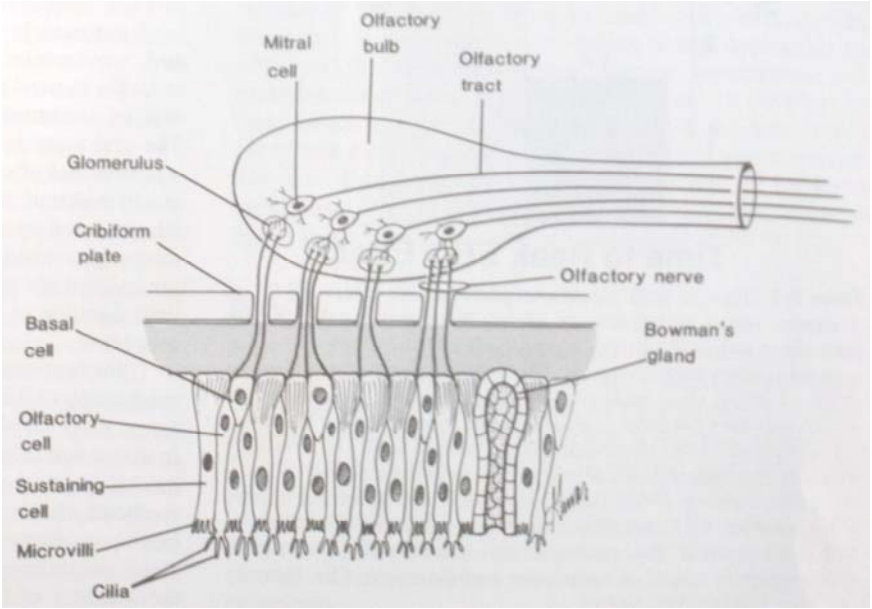


Structure and Metabolism of midazolam



Reversible ring opening of midazolam above and below a pH of 4

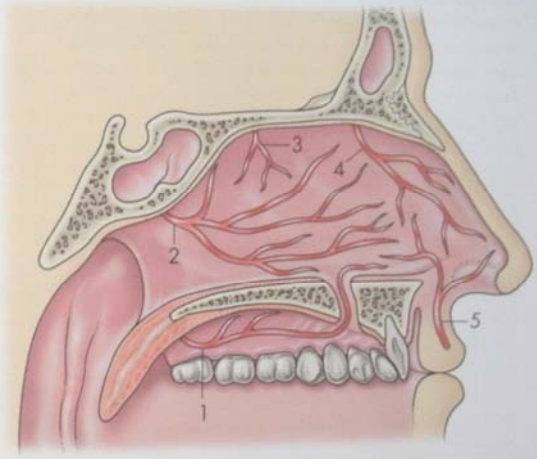


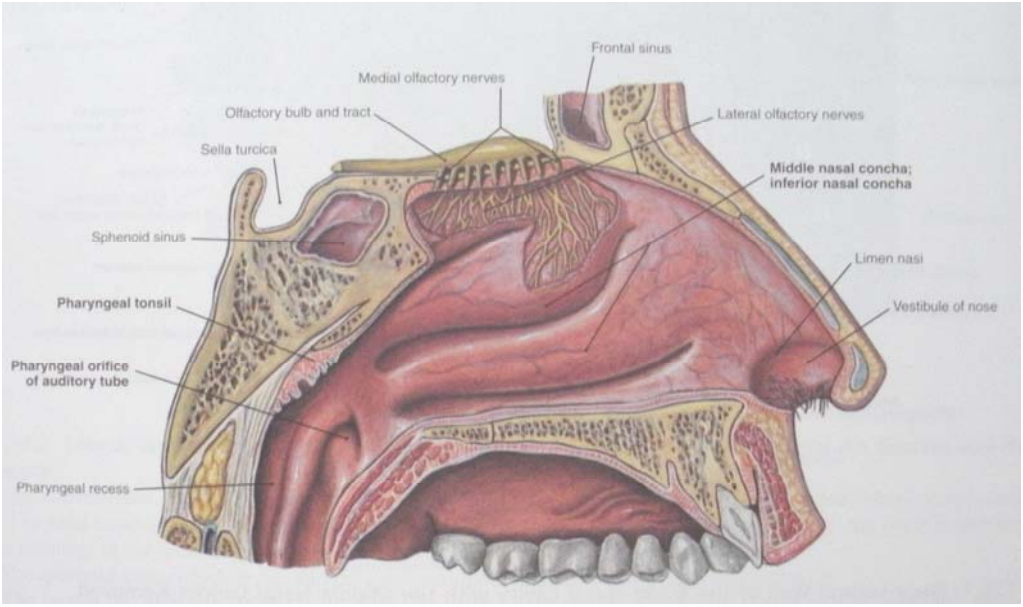


Anatomy of the nasal mucosa-cribriform plate interface

6.13 The vasculature of the nasal septum

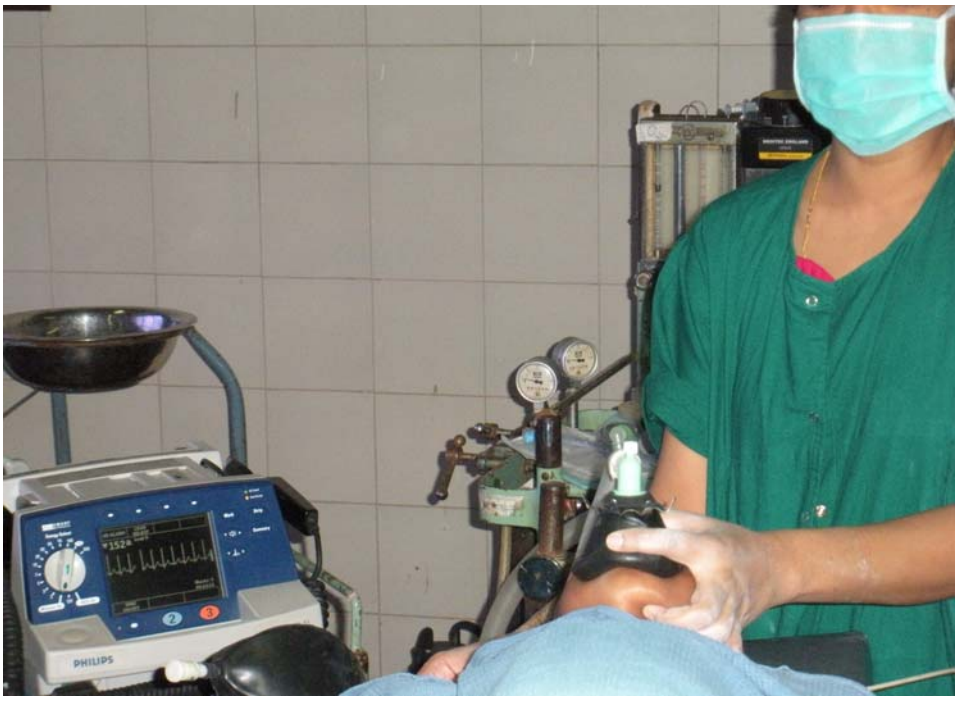
1 Greater palatine artery
2 Sphenopalatine artery
3 Posterior ethmoidal artery
4 Anterior ethmoidal artery
5 Superior labial artery (septal branch)

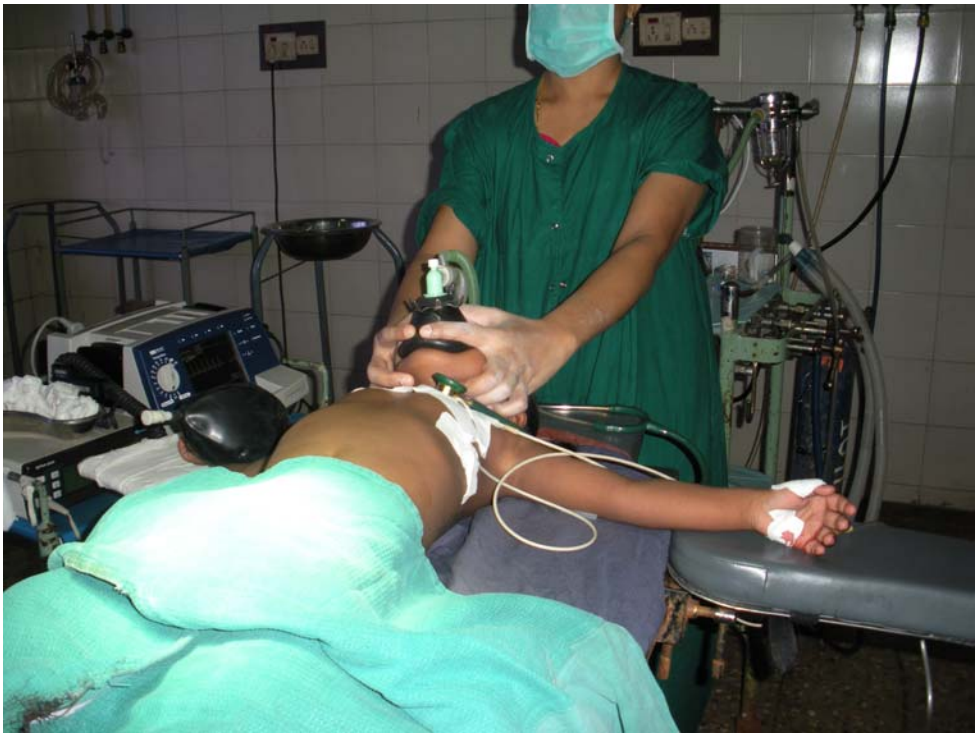




Lateral wall of the left Nasal Cavity showing the Olfactory Nerves

Nasal midazolam spray





This pictures shows the child at induction