"COMPARATIVE EVALUATION OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN UNDERGOING ANAESTHESIA." A ONE YEAR DOUBLE BLIND RANDOMISED CONTROLLED TRAIL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARATIVE EVALUATION OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN UNDERGOING ANAESTHESIA." A ONE YEAR DOUBLE BLIND RANDOMISED CONTROLLED TRAIL** is a bonafide research work done by **REG NO. BA0114003.**

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ABBREVIATIONS

α	-	Alpha
ASA	-	American society of Anaesthesiologists
AV node	-	Atrioventricular node
BT	-	Bleeding time
c- AMP	-	cyclic Adenosine Mono Phosphate
CNS	-	Central nervous system
CT	-	Clotting time
CVS	-	Cardiovascular system
DBP	-	Diastolic blood pressure
ECG	-	Electrocardiography
FDA	-	Food and drug administration
GABA	-	Gama Amino Butyric Acid
GI	-	Gastrointestinal system
Hb	-	Hemoglobin
HR	-	Heart Rate
hrs	-	Hours
ICU	-	Intensive care unit
i.m	-	Intramuscular
IV	-	Intravenous
Kg	-	Kilogram
OR	-	Operating room
MAS	-	Mask acceptance scale
mcg(μg)	-	microgram

mg	-	milligram
min.	-	minutes
ml	-	milliliter
mm Hg	-	millimeters of mercury
MRI	-	Magnetic resonance imaging
PACU	-	Post Anaesthesia Care Unit
pKa	-	pH of dissociation constant of acid
PSAS	-	Parental separation anxiety scale
P Value	-	Probability value
RBS	-	Random Blood Sugar
SA node	-	Sino atrial node
SBP	-	Systolic blood pressure
SPO	-	Oxygen saturation
VAS	-	Visual analogue score
V_d	-	Volume of distribution
Viz	-	Which is
vs	-	Versus
Wt	-	Weight
Yrs	-	Years

ABSTRACT

INTRODUCTION:

Children undergoing surgical procedures can experience significant anxiety and distress during the perioperative period. The use of sedative premedication may help to reduce anxiety, minimize the emotional trauma and facilitate a smooth induction of anaesthesia. Midazolam is most commonly used as a premedication agent in children. However adverse effects such as post-operative behavioral changes, hiccups and paradoxical hyperactive reactions have been observed. Dexmedetomidine, which is a highly selective alpha-2 agonist, has sedative properties. Hence in this study we made an effort to compare intra-nasally administered midazolam and dexmedetomidine for premedication in paediatric patients.

AIMS AND OBJECTIVES:

This study was conducted to compare the efficacy of intranasal dexmedetomidine (1µg/kg) and intranasal midazolam (0.2 mg/kg) for premedication in paediatric age group in terms of:-

Primary objective :- 1) Parental separation anxiety

2) Acceptance of anaesthesia mask

Secondary objective: Occurrence of adverse events like bradycardia and desaturation.

MATERIALS AND METHODS:

This prospective randomised controlled study was carried out in the Department of Anaesthesiology at KLE'S Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehrunagar, Belagavi which included 60 ASA grade I and II patients between 1 to 10 years of age who underwent lower abdominal and lower limb surgeries under caudal epidural anaesthesia with sedation from January 2015 to December 2015. After obtaining ethical committee clearance and informed consent, the patients were randomly allocated into two groups (30 in each) by computer generated randomisation table to receive 0.2mg/kg intranasal Midazolam (up to a maximum 5 mg) using 1ml tuberculin syringe with atomiser in Group M and 1µg/kg Dexmedetomidine intranasally using 1ml tuberculin syringe with atomiser in Group D. The parental separation anxiety was assessed using the parental separation anxiety scale(PSAS) while shifting the patient to operating room and mask acceptance was assessed by the attending anaesthesiologist using mask acceptance scale (MAS) in operating room who is blinded to the drug given. Heart rate (HR) and oxygen saturation(SpO_2) were monitored till the end of procedure.

RESULTS:

Demographic characteristics were comparable in both groups and there was no statistically significant difference ($P > 0.05$) between the groups. The mean parental separation anxiety scale (PSAS) was 1.2 ± 0.40 in dexmedetomidine group and 1.6 ± 0.56 in midazolam group which is statistically significant with P value of 0.003. The mean mask acceptance scores (MAS) at the time of induction was 1.7 ± 0.59 in dexmedetomidine group and 2.1 ± 0.58 in midazolam group which is statistically

significant(P=0.020). Only 2(6.6%) children in dexmedetomidine group had MAS > 2 when compared to 6(20%) children in midazolam group.

CONCLUSION:

We conclude that intranasal dexmedetomidine 1 μg/kg is an effective and safe alternative for premedication in children undergoing lower abdominal surgeries under caudal epidural anaesthesia and it resulted in lower anxiety levels, allowed better parent separation and resulted in better mask acceptance at the time of induction when compared with intranasal midazolam 0.2 mg/kg without causing much side effects or post-operative complications.

KEYWORDS: Dexmedetomidine, Midazolam, Intranasal, Pre-operative Anxiety, Premedication, Atomiser.

CONTENTS

S. No	TOPIC	PAGE NO.
1.	INTRODUCTION	1-3
2.	AIMS AND OBJECTIVES	4
3.	REVIEW OF LITERATURE	5-19
4.	PHARMACOLOGY OF MIDAZOLAM	20-27
5.	PHARMACOLOGY OF DEXMEDETOMIDINE	28-37
6.	MATERIALS AND METHODS	38-42
7.	RESULTS	43-53
8.	DISCUSSION	54-62
9.	CONCLUSION	63
10.	SUMMARY	64
11.	BIBLIOGRAPHY	65-72
12.	ANNEXURE I – CONSENT FORM	73-77
13.	ANNEXURE II – PROFORMA	78-83
14.	ANNEXURE III – PHOTOGRAPHS	84-85
15.	ANNEXURE IV – ETHICAL COMMITTEE CLEARANCE CERTIFICATE	86
16.	ANNEXURE V – MASTER CHART	

LIST OF TABLES

TABLE NO.	DESCRIPTION	PAGE NO.
1	Demographic data	43
2	Preoperative mean SpO_2	45
3	Preoperative mean HR	47
4	Intraoperative mean HR	49
5	Intraoperative mean SpO_2	51
6	PSAS & MAS:	53

LIST OF GRAPHS

GRAPH NO.	DESCRIPTION	PAGE NO.
1	Demographic data	44
2	Sex distribution	44
3	Preoperative mean SpO_2	46
4	Preoperative mean HR	48
5	Intraoperative mean HR	50
6	Intraoperative mean SpO_2	52
7	PSAS & MAS	53

LIST OF IMAGES

IMAGE NO.	DESCRIPTION	PAGE NO.
1	**Structure of Midazolam**	20
2	**Structure of Dexmedetomidine**	28
3	**Physiology of alpha 2 receptors**	29

LIST OF PHOTOGRAPHS

FIGURE NO.	DESCRIPTION	PAGE NO.
1	Dexmedetomidine ampule	84
2	Midazolam ampule	84
3	Tuberculin syringe with atomiser	85
4	Anaesthesia work station	85

INTRODUCTION

Children undergoing surgical procedures can experience significant anxiety and distress during the perioperative period. They are usually uncooperative, fearful, anxious or physically resistant particularly during times of parent separation, mask application and venipuncture.[1] Pre-operative anxiety can have negative psychological and physiological effects on a child.[2] Various interventions used to allay anxiety of a child during peri-operative period are pre-operative preparation programs, parental presence during induction and sedative premedication.[3,4]

Procedural psychological preparation of the patient by use of educational booklets, movies, slideshows and reinforcement of information by the anaesthesiologist can relieve procedure related anxiety. But it is not possible in all the children. Sedation in pre-operative room remains one of the widely used methods for decreasing anxiety in young children. The use of sedative premedication may help to reduce anxiety, minimize the emotional trauma and facilitate a smooth induction of anaesthesia.[1]

Many drugs and many routes of administration have been tried and used successfully as premedication. Oral trichlofos used as premedication gave adequate sedation but has longer onset of action. Trimeprazine when used in children provide good sedation and has mild antisialogogue effect but it is associated with more chances of post-operative restlessness. Opioids are also used for premedication but are associated with side effects like nausea, vomiting, cardiovascular and respiratory depression. Ketamine is also used as premedication orally. It has faster onset of action and provides adequate sedation but its use is associated with side effects like

increase in salivary and bronchial secretions, unpleasant and vivid dreams both in the recovery room and occasionally for long period afterwards.[5]

Benzodiazepines are the most commonly used group of drugs for premedication. Midazolam is a water soluble, short acting gama-amino-butyric acid (GABA) receptor inhibitor which is used by multiple routes of administration viz: oral, nasal and rectal. Administered nasally it has a faster onset of action. Thus it gained popularity as a premedication agent in children.[6] It provides effective sedation, anxiolysis and varying degrees of anterograde amnesia. However adverse effects such as post-operative behavioral changes, hiccups and paradoxical hyperactive reactions have been observed.[7] Clonidine, a centrally acting alpha-2 agonist and has been used as a premedicant after noticing its sedative effects, decreased requirement of anaesthetic drugs during induction, decreased rescue analgesic requirement post-operatively and decreased incidence of post-operative shivering.[8] But oral clonidine has delayed onset of action and is not a selective alpha-2 agonist. Dexmedetomidine, which is a highly selective alpha-2 agonist has faster onset of action than clonidine with analgesic, sedative properties and devoid of respiratory depressive action which became available in 1999 and has been used as a premedication. Dexmedetomidine is used for premedication by oral, intranasal and intravenous routes.

Oral route is most commonly used route for medication as it has good acceptance by children and can be given by unskilled person. However it has a longer onset of action and less bioavailability due to first pass metabolism. Unpalatable drugs cannot be given by this route. Intravenous and intramuscular routes are painful and frightening to the child. Also rectal and sublingual routes have fewer acceptances by children. Intranasal application is a relatively noninvasive, convenient and easy

route of administration, not requiring much of patient co-operation as would be the case for swallowing the medication or retaining it sublingually. Intranasal administration also reduces first pass metabolism. The rich vascular plexus of the nasal cavity provides a direct route in to the blood-stream leading to fast onset of action.

Midazolam administered nasally is an irritant to the nasal mucosa causing burning and stinging. Hence in this study we made an effort to compare intra-nasally administered midazolam and dexmedetomidine as premedicant in paediatric patients.

AIMS AND OBJECTIVES

To compare the efficacy of intranasal dexmedetomidine (1µg/kg) and intranasal midazolam (0.2mg/kg) as premedication in paediatric age group in terms of:-

Primary objective :- 1) Parental separation anxiety

2) Acceptance of anesthesia mask

Secondary objective: Occurrence of adverse events like bradycardia and desaturation.

REVIEW OF LITERATURE

The transfer of reluctant children from the ward to the operating suite may cause long-term psychological trauma. Furthermore, forced induction of anaesthesia may lead to personality and behavioral changes in 17% to 57% of children including sleepwalking, bed-wetting and irritability. Effective communications, premedication and anaesthetic induction with parental presence help to reduce preoperative anxiety in children. Premedication is common, but there is no widely accepted drug regimen.[9]

In 1976, Fryer and Walser synthesized the first clinically used water soluble benzodiazepine, midazolam.[10] Midazolam is most commonly used premedication in children and has been administered by various routes. We have extensive literature on use of midazolam as premedicant.

J. M. Malinovsky et al (1995) performed a double blind randomised study in children aged between 2- 5 years with similar duration of surgical procedure to compare time and plasma drug concentration necessary to achieve a similar state of sedation after midazolam premedication given by various routes.[11] They randomised the patients into three groups receiving midazolam 0.2mg/kg intranasally, 0.5mg/kg orally, 0.3mg/kg rectally. Sedation was measured regularly until IV cannulation was possible. Adequate sedation occurred sooner with intranasal (7.7±2.4min) than oral (12.5±4.9min) or rectal (16.3±4.2min). The initial blood levels were lower when drug was given by alimentary route despite higher doses (146±51 ng/ml in 11.5±3.9 min: 104±34 ng/ml in 21±6 min; 93±63 ng/ml in 23.1±3.5 min for intranasal, oral and rectal routes respectively). Hence intranasal midazolam is an excellent alternative for rapid premedication.

Geldner et al (1997) performed a double blind randomised study in 47 children assigned to 3 different groups, all receiving midazolam transmucosally.[12] Group N received 0.2mg/kg nasally; Group R 0.5mg/kg rectally and Group S 0.2mg/kg sublingually. In all three groups the plasma levels of midazolam 10 min after premedication were higher than 70ng/ml (accepted as a sedative level). All three trans mucosal applications are safe and well accepted, although nasal application was rejected by two of the children as caused nasal irritation.

Kogan et al (2002) performed a double blind randomised study in children undergoing minor elective surgery in the age group of 1.5 -5 years (n=119).[13] They randomised the patients into four groups. Group I received intranasal midazolam 0.3mg/kg, Group II received oral midazolam 0.5mg/kg, Group III received rectal midazolam 0.5mg/kg and Group IV received sublingual midazolam 0.3mg/kg. Satisfactory mask acceptance was 77% in sublingual, 80% in intranasal, 83% in oral and 86% in rectal route. Though intranasal route provided faster onset of action (22.4 ± 5.6 minutes), it caused nasal irritation, 77% of the children from this group cried after drug administration. They concluded that all four routes are equally effective.

Tschirch F. T. et al (2007) conducted a study to assess prospectively the potential of low-dose intranasal midazolam as compared to oral midazolam in claustrophobic patients undergoing routine body magnetic resonance imaging.[14] 72 Adult claustrophobic patients referred for body MRI were randomly assigned to one of two treatment groups (TG1 and TG2). The 36 patients of TG1 received 7.5mg midazolam orally 15 min before MRI, whereas the 36 patients of TG2 received one (or if necessary two) pumps of a midazolam nasal spray into each nostril immediately prior to MRI (in total, 1 or 2mg). Patients' tolerance, anxiety and sedation were

assessed using a questionnaire and a visual analogue scale immediately before and after MRI. Image quality was evaluated using a five-point-scale. MRI image quality was rated higher among patients of TG2 compared to TG1 (P<0.001). They concluded that low-dose intranasal midazolam is an effective and patient-friendly solution to overcome anxiety in claustrophobic patients for MRI. Its anxiolytic effect is superior to that of the orally administrated form.

There are various studies to find the ideal dose of intranasal midazolam for premedication in children. Davis et al (1995) conducted a randomised double blind trial in 88 ambulatory surgical patients 10-36 months of age undergoing myringotomy and tube insertion.[15] All patients were randomly assigned into 3 medication groups. Group A received 0.2mg/kg intranasal midazolam; Group B received 0.3mg/kg intranasal midazolam and Group C received intranasal saline drops. After preanaesthetic medication, the children were evaluated for ease of separation and induction of anaesthesia. Both midazolam groups were similar in age (19.1±6.9 months vs. 19.9±7.9 months), weight (11.8±1.8 kg vs. 11.6±1.7 kg), duration from pre-medication to parental separation (26.8±20.6 min vs. 27.4±13.3 min), duration of anaesthesia (9.2±3.7 min vs. 10±2.5 min), time in the PACU (12±10.3 min vs. 13.7±11 min), time until hospital discharge (30.6±12.7 min vs. 31.7±13 min), percentage of satisfactory separation (91% vs. 90%) and induction scores (60% vs. 80%). The patients receiving midazolam had significantly better separation and induction scores than the patients who received saline. Hence, Groups A (0.2 mg/kg) and B (0.3 mg/kg) are comparable in terms of easing up parental separation anxiety and induction score.

Bhakta et al (2007) performed a study involving 45 paediatric patients of 2-5 years of age belonging to ASA I & II, scheduled for minor elective surgery.[16] Patients were divided in 3 equal groups to receive normal saline (Group I), 0.2mg/kg midazolam (Group II) or 0.3mg/kg midazolam (Group III) intranasally. Vital parameters and level of sedation (using a sedation scale) were assessed before administering the drug and at every 5 min interval up to induction of anaesthesia. A statistically significant change in the level of sedation (group II at 5 min and at 10 in in group Ill), parental separation (20% in group 1 versus 80% in group 2 and 3) and mask acceptance rate (33% in group 1 versus 80% in group 2 and 3). There was no statistical difference in recovery parameters in any group. No major adverse effect was seen in any midazolam group. No major advantage was found with higher dose of midazolam.

Initially intranasal preparation was not available for midazolam and hence intravenous (IV) preparation was used. There are studies which compared the administration of intravenous formulation of midazolam (5mg/ml) intranasally as drops and commercially available midazolam spray. Griffith N. et al (1998) conducted a randomised controlled trial in 44 children aged 1-8 years undergoing elective day surgery.[17] Patients were allocated into two groups. Group D: Midazolam 0.2mg/kg as drops in a 1ml syringe and Group S: midazolam 0.1mg/kg as spray. Behavior was recorded on a four point scale and coefficients obtained representing change in behavior score. It was observed that there was no significant difference in method of administration ($P = 0.39$) and midazolam by either method was equally effective.

Primosch et al (2005) conducted a retrospective review of 64 records of 2 and 3 year old dental patients who received intranasal midazolam either as drops or as spray and Compared the behavioural outcomes observed for agent acceptance during administration and agent efficacy during parental separation by using Frankl scale and OSBRS(Ohio State Behavioural Rating Scale).[18] Improvements in the Frankl behavioural rating score was observed during sedation but no statistically significant difference between the drops and the spray group was measured using the OSBRS. However, the spray group demonstrated a statistically significant reduction (P=0.025) in aversive behavior when compared to drops as measured by the OSBRS. This study suggested that the use of commercially available atomiser improved patient acceptance of intranasal administration but did not influence agent efficacy compared to drops administration.

Intranasal midazolam has already been studied in the context of sutures, peripheral venepunctures and echocardiograms with no occurrence of adverse respiratory or cardiovascular events with a high success rate in surgical procedures. It has been recently studied as a pre-anaesthetic medication and has been gained prominence for sedation in radiological procedures with children.

Following are studies where intranasal midazolam is compared with placebo to identify its sedative, amnesic, anxiolytic and other properties. Fishbein M et al (1997) conducted a prospective, randomised, double-blind study in 40 children, aged 2 to 12 years, who were undergoing eosophago-gastro-duodenoscopy (EGD).[19] Patients in group I were premedicated with intranasal placebo (0.9% NaCl) followed 10 minutes later by intravenous midazolam (0.05mg/kg) and intravenous meperidine (1mg/kg). Patients in group II were premedicated with intranasal midazolam

(0.2mg/kg) followed by intravenous placebo (0.9% NaCl) and intravenous meperidine (1mg/kg). Anxiolysis and sedation were scored by a blinded observer who identified minor and major negative behaviors during four observation periods: intranasal drug administration, separation from parents, venepuncture and EGD. Premedication with intranasal midazolam significantly reduced negative behaviors during separation from parents ($P < 0.05$); however, no difference between regimens was noted during venepuncture or EGD.

Kawanda et al (2012) conducted a study in which 80 children (median age 3 years) were recruited and 140 surgical procedures were performed.[20] Intranasal midazolam was used at a dose of 0.5 mg/kg in 52 children and the control group consisted of 28 children. As clinical outcomes, patients' behaviour and sedation level were noted along with ease of performing surgical procedure. For both clinical outcomes there was a statistically significant difference among children's behaviour (shouting, crying and struggling parameters) ($p < 0.001$). The mean score of the ease of completing the procedures was significantly different among the 2 groups ($P < 0.0001$).

Midazolam has been compared with other drugs also for paediatric premedication. Ketamine is also one of the commonly used premedicant. Midazolam has been compared with ketamine and also combination of midazolam and ketamine. Khatavkar S. et al (2014) conducted a comparative study in 60 children aged 1-12 yrs posted for intermediate and major surgery.[21] Group A - midazolam (0.2mg/kg), Group B - midazolam (0.15mg/kg) + ketamine (1mg/kg). Both groups received drug intranasally 30 min before surgery in recovery room with monitored anaesthesia care. Onset of sedation, sedation score, emotional reaction, intravenous cannula acceptance

and mask acceptance were studied. Acceptance to IV cannulation was without cry in 13.3% in Group A while it was 43.3% in Group B. Face mask acceptance was without cry in 50% in Group A while it was 52.70% in Group B.

In patients receiving clonidine as antihypertensive agent it was noticed that there is marked sedative effect and reduction in anaesthetic drug requirement. Its use as a sedative and premedicant was investigated further. Clonidine is not a selective alpha(α)-2 agonist and also because of its delayed onset of action it is less commonly used for premedication. In 1999 dexmedetomidine was introduced in clinical practice which is highly selective α-2 agonist(α-1: α-2 = 1600:1) and is fast acting compared to clonidine. Various studies have been done using dexmedetomidine as premedicant.

Aantaa et al (1990) conducted a study to know anaesthetic requirements, hemodynamics and plasma catecholamine levels in 20 healthy ASA I women scheduled for uterine dilatation and curettage after dexmedetomidine premedication.[22] Four doses of IV dexmedetomidine were used (0.167, 0.33, 0.67, and 1.0μg/kg) with five subjects at each dose level. Fearfulness, anxiety and alertness decreased and mental clouding increased after dexmedetomidine administration as measured by VAS. Dexmedetomidine induced a clear and statistically significant increase ($F = 20.75$ and $P< 0.0001$) in mouth dryness. This effect lasted until the end of the study. The time needed to regain consciousness after termination of nitrous oxide administration was dose dependently decreased by dexmedetomidine (from 6.8 ± 3.8 min after 0.167μg/kg of dexmedetomidine to 2.4± 2.1 min after 0.67μg/kg). After the highest dose (1.0μg/kg), the duration of recovery was again longer (5.0±1.9 min) than after the two intermediate doses (0.33 and 0.67μg/kg). Only one patient in the

0.33µg/kg dose group required analgesic supplementation (Oxycodone 5 mg intravenously and 5 mg intramuscularly) for lower abdominal pain.

Mason KP et al (2006) conducted a prospective pilot study in 62 patients with a mean age of 2.8 years (SD = 1.8, range 0.5-9.7) posted for radiological imaging studies.[23] Patients received IV dexmedetomidine administered as a 2µg/kg loading dose over 10 minutes followed by repeat boluses of 2µg/kg over 10 minutes until target of Ramsay Sedation Score 4 (RSS) was achieved. Patients were then maintained on 1µg/kg/hr infusion until imaging was completed. Repeated-measures ANOVA indicated that compared to pre-sedation values, the heart rate and mean arterial blood pressure decreased by an average of 15%during bolus, infusion and recovery ($P < 0.01$). No significant changes were observed in respiratory rate or end-tidal CO_2. Mean recovery time was 32±18 minutes. Hence they concluded that dexmedetomidine may provide a reliable and effective method of providing sedation in radiological procedures.

Sakurai et al (2010) performed a prospective study with 40 children undergoing inguinal or umbilical hernia repair.[24] Twenty children received dexmedetomidine buccally at 3-4µg/kg (Dex Group) and 20 children received a diazepam suppository at 0.7mg/kg (Diazepam Group) as preanaesthetics. The Ramsay score of the Dex Group was significantly higher than that of the Diazepam Group at all times. The mean serum dexmedetomidine concentration at induction in patients with a Ramsay score of 5 or greater (75 ± 50 pg/ml) was significantly higher than in those with a Ramsay score less than 5 (34 ± 36 pg/ml, $P < 0.05$). These results suggest that the buccal administration of dexmedetomidine (3-4µg/kg) 1 hr before the operation can be used safely and effectively for premedication.

Mason KP et al (2012) conducted a study involving 65 children who received consecutive intramuscular dexmedetomidine injection to achieve sedation for MRI and CT of children.[25] A single or repeated doses of 1-4μg/kg i.m. (intramuscular) dexmedetomidine was administered to achieve a minimum Ramsay sedation score of 4. There was no statistically significant relation between the total dose of dexmedetomidine received, mean time to achieve sedation (13.1-13.4 min), or time to meet discharge criteria after arrival in the recovery unit (17.1-21.9 min). Nine patients (14%) experienced hypotension, defined as a decrease in blood pressure of less than 20% of the age-adjusted awake normal value. Hence the study concluded that the intramuscular route is an alternative approach to dexmedetomidine delivery for paediatric sedation. However larger studies are warranted to evaluate the efficacy, safety and hemodynamic outcome associated with the intramuscular use of dexmedetomidine in the care of children.

Yuen et al (2007) conducted a double blind crossover study to assess the sedative and analgesic effects of intranasal dexmedetomidine in 18 healthy volunteers between ages of 18- 38 yrs.[26] The study was double-blind and there were three treatment groups: A (placebo), B (intranasal dexmedetomidine 1μg/kg) and C (intranasal dexmedetomidine 1.5μg/kg). Both 1 and 1.5μg/kg doses equally produced significant sedation and decreases in bispectral index, SBP, DBP and HR when compared with placebo ($P<0.05$). The onset of sedation occurred at 45 min with a peak effect at 90 — 150 min. The maximum reduction in SBP was 6%, 23%, and 21% for Groups A, B, and C respectively.

Yuen et al (2008) performed a prospective, randomised double blind controlled trial in 96 children of ASA 1 or 2 scheduled for elective minor surgery.[27]

Patients were randomly assigned to one of three groups. Group M received midazolam 0.5 mg/kg in acetaminophen syrup and intranasal placebo. Group D0.5 and Group D1 received intranasal dexmedetomidine 0.5 and 1μg/kg, respectively and acetaminophen syrup. There were no significant differences in parental separation behaviour score at induction and wake-up behaviour score. When compared with group M, patients in group D0.5 and D1 were significantly more sedated when they were separated from their parents (P = 0.001). Patients from group D1 were significantly more sedated at induction of anaesthesia when compared with group M (P = 0.016). Intranasal dexmedetomidine produces more sedation than oral midazolam but with similar and acceptable cooperation.

Yuen et al (2010) performed a prospective, randomised, double-blind controlled trial in 100 children of ASA physical status I or II, aged between 1 and 12 years, undergoing elective surgery to determine the optimal timing of dosage of intranasal dexmedetomidine for premedication.[28] Twenty patients were randomly allocated to each of the treatment groups A, B, C, D and E. Children from groups A, B, C and D had an attempt at intravenous cannulation by a paediatric anaesthetist at 30, 45, 60 and 75 min, respectively, after 1μg/kg intranasal dexmedetomidine. In group E twenty children received intranasal placebo (0.9% normal saline) of equivalent volume and cannulation attempt was done after 45 minutes. More children from groups A to D achieved satisfactory sedation at the time of intravenous cannulation when compared to group E (P < 0.001). 74 out of the 79 children (93.7%) who received intranasal dexmedetomidine had satisfactory sedation at some time during the premedication period. The median onset time of satisfactory sedation was 25 min (95% CI 25-30 min); median duration of sedation was 85 min (95% CI 55-100 min). At 45 min after intranasal dexmedetomidine, 91 % (95% Cl 85— 98%) of the

subjects had achieved satisfactory sedation. At the time of parental separation, significantly more children from groups A-D achieved satisfactory sedation compared to those receiving placebo (62% vs. 14.3% respectively, P < 0.001). Similarly, significantly more children from groups A-D achieved satisfactory sedation at the time of anaesthetic induction when compared to placebo (57% vs. 9.5% respectively, P < 0.001).

Yuen et al (2012) conducted a prospective randomised trial in children aged between 1 and 8 years scheduled for elective surgery.[29] Children were assigned to receive either intranasal dexmedetomidine 1μg/kg(Group 1) or 2μg/kg(Group 2). 31 (53%) patients from Group 1 and 38 (66%) patients from Group 2 were satisfactorily sedated at the time of anaesthetic induction. Logistic regression showed a significant interaction effect (P = 0.049), with the odds ratio between Group 2 over Group 1 estimated as 1.1 (95% CI 0.5-2.7) for the 1-4 year age group and 10.5 (95% CI 1.4-80.2) for the 5-8 year age group. Both doses produced a similar level of satisfactory sedation in children aged 1-4 years whereas 2μg/kg resulted in a higher proportion of satisfactory sedation in children aged 5-8 years without causing adverse hemodynamic effects suggesting that the higher dose is more appropriate in this age group.

Gyanesh P. et al (2014) conducted a double blind randomised placebo controlled trial in 150 children aged 1 - 10 years.[30] Patients were divided randomly into 3 groups as dexmedetomidine group(DXM), ketamine group(K), and normal saline group(S). For blinding, every child received the intranasal drugs twice; syringe S1, 60 min before and syringe S2, 30 min before intravenous (IV) cannulation. For children in group DXM, S1 contained DXM (1 μg/kg) and S2 was plain saline.

Children in group K received saline in S1 and ketamine (5 mg/kg) in S2 whereas children in group S received saline in both S1 and S2. 90.4 % of the anaesthesiologists in the DXM group and 82.7 % in the ketamine group were satisfied with the conditions for IV cannulation whereas only 21.3 % were satisfied in the saline group. Children in group DXM and group K had earlier awakening and discharge than those in group S. DXM and ketamine were equally effective, by the intranasal route, as premedication in children undergoing MRI.

Surendar M.N. et al (2014) conducted a randomised triple blind comparative study of 84 children aged 4 -14 years undergoing dental procedures.[31] All the children were randomised to receive one of the four drug groups: Dexmedetomidine 1 µg/kg(D1), 1.5µg/kg (D2), Midazolam 0.2mg/kg (M1) and Ketamine 5mg/kg (K1) through intranasal route. The onset of sedation was significantly rapid with M1 and K1 as compared to D1 and D2 ($P < 0.001$). The overall success rate was highest in D2 (85.7%) followed by D1 (81%), K1 (66.7%) and M1 (61.9%), however the difference among them was not statistically significant ($P > 0.05$).

Dexmedetomidine and midazolam by intranasal route has been compared in many studies. Sundaram et al (2011) conducted a prospective, randomised, and double-blind controlled trial in 90 children aged 2 - 9 years undergoing elective dental rehabilitation.[32] Patients were divided into two groups. Group M received 0.2mg/kg intranasal midazolam and Group D received intranasal dexmedetomidine 1µg/kg. The behavior and sedation status at separation from the parent and at induction of anaesthesia, SBP and HR changes, wake-up behaviour, and time until ready for discharge from the PACU were observed. The median sedation scores at separation from the parent were 6 and 1.5 for groups M and D respectively. 28.3% and 83% of

the children from groups M and D achieved satisfactory sedation at separation from parents. The median sedation scores at induction were 6 and 4 for groups M and D respectively. At induction of anaesthesia, 24.78% and 67.4% of the children from groups M and D respectively were satisfactorily sedated (P<0.004). Most children had satisfactory behaviour at induction of anaesthesia with no evidence of difference among groups (P= 0.137). SBP decreased significantly in group D when compared with group M (P = 0.004). HR decreased significantly with time in group D (P = 0.001). 85% of the children attained a satisfactory level of sedation after 1µg/kg intranasal dexmedetomidine. Moreover, 70.8% of these sedated patients allowed IV or inhaled induction without showing signs of distress or awakening. Hence children premedicated with intranasal dexmedetomidine attained more significant and satisfactory sedation at parental separation and at induction of anaesthesia than those patients who received midazolam.

Mostafa et al (2013) conducted a randomised double blind controlled trial in 96 children aged 2-8 years scheduled for bone marrow biopsy and aspirate.[33] They were divided into three groups 32 children in each one: (M group) were premedicated with intranasal midazolam 0.2mg/kg (D group) were premedicated with intranasal dexmedetomidine 1µg/kg and (K group) were premedicated with intranasal ketamine 5mg/kg. The degree of sedation was assessed every 5 min for 30 min by using a 4 point sedation scale. Child-parent separation was assessed and graded according to a 4 point scale at 30 min. It was observed that dexmedetomidine group achieved a faster sedation score less than 3 at 10 min (P < 0.05) then all groups achieved a comparable sedation score till 25 min. Both dexmedetomidine and midazolam groups had better sedation score than ketamine group at 30 min. Patients with child-parents separation

score grade 1 was significantly higher in dexmedetomidine group than midazolam and ketamine groups 30 (93.75%), 28(87.5%), 22(68%) respectively.

Akin et al (2012) conducted a prospective randomised double-blind controlled trial in children aged between 2 and 9 undergoing adenotonsillectomy surgery.[34] Group M (n = 45) received 0.2mg/kg of intranasal midazolam and Group D (n = 45) received 1μg/kg of intranasal dexmedetomidine 45 min before induction. Satisfactory mask induction was achieved by 82.2% of Group M and 60% of Group D (P = 0.01). There was no evidence of a difference between the groups in either sedation score (P= 0.36) or anxiety score (P = 0.56) upon separation from parents. They found that postoperative analgesic requirement was higher in the midazolam group (P= 0.045).

Sheta S.A et al (2014) conducted a prospective, randomised double-blind controlled trial in 72 children aged between 3 and 6 years undergoing dental rehabilitation.[35] Patients were divided into two groups: Group M received 0.2mg/kg intranasal midazolam and Group D received intranasal dexmedetomidine 1μg/kg. The patients' sedation status, mask acceptance and hemodynamic parameters were recorded until anaesthesia induction. The median onset of sedation was significantly shorter in group M 15min(10-25) than in group D 25min(20-40), (P = 0.001). Compared with patients in Group M those in Group D were significantly more sedated when separated from their parents(77.8% vs 44.4%)(P=0.002). Satisfactory compliance with mask application was 58.3% in group M vs 80.6% in group D (P=0.035). The incidence of postoperative agitation and shivering were significantly lower in group D as compared to group M. There were no incidences of bradycardia and hypotension in either of the groups.

Singla et al (2015) conducted a prospective, randomised double-blind controlled trial on 60 children, 3 to 10 years of age with ASA physical status I, scheduled for elective surgery.[36] These children were randomly divided into two groups, Group D patients received intranasal dexmedetomidine 1µg/kg and group M patients intranasal midazolam 0.2mg/kg, approximately 30 minutes before induction of anaesthesia in the form of a spray and they concluded that greater number of children in group D achieved a parental separation and mask acceptance when compared with group M but this was not statistically significant. Both parental separation score (P=0.0234) and mask acceptance score (P=0.0472) was significantly lower in group D. Hence intranasal dexmedetomidine is an effective and safe alternative and resulted in superior sedation.

BASIC SCIENCES

PHARMACOLOGY OF MIDAZOLAM

Fryer and Walser synthesized the first clinically used water soluble benzodiazepine, midazolam in 1976.[10] It is 3-6 times as potent as diazepam and has an affinity for benzodiazepine receptor that is approximately twice that of diazepam. Midazolam causes minimum venous irritation and has a short duration of action. These are the two main reasons for preference of midazolam over diazepam as sedative.

STRUCTURAL FORMULA:

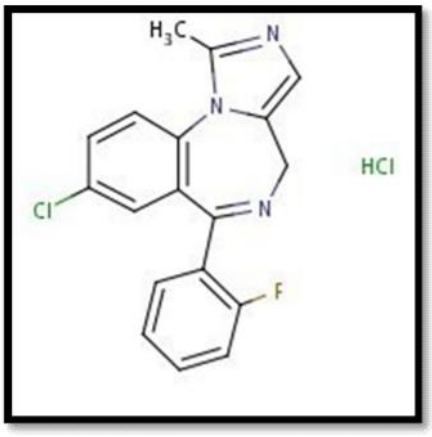


Image 1: Structure Of Midazolam

Physicochemical characteristics[10] :

Midazolam solution contains 1 or 5 mg/ml of midazolam with 0.8 percent sodium chloride and 0.01 percent disodium edetate, with 1 percent benzyl alcohol as a preservative. The pH is adjusted to 3 with hydrochloric acid and sodium hydroxide. Midazolam is highly lipid soluble but because of its pH dependent solubility, is water soluble as formulated in a buffered acidic medium (pH 3.5). The imidazole ring of it accounts for its stability in solution and rapid metabolism. The high lipophilic

property accounts for the rapid CNS effect, as well as for their relatively large volumes of distribution.

PHYSIOCHEMICAL CHARACTERISTICS OF BENZODIAZEPINES[10]

	Midazolam	**Diazepam**	**Lorazepam**
Molecular weight (D)	362	284.7	321.2
$pK_a(20^0)$	6.2	3.3	11.5
Water solubility	If pH < 4	No	Almost insoluble
Lipid solubility	If pH > 4	Yes	Yes

COMMERCIAL PREPARATION:

pKa of Midazolam is 6.2, which permits preparation of salts that are water soluble. 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 remain open at pH value of < 4 thus maintaining water solubility of the drug. The ring closes at pH >4, as when the drug is exposed to physiologic pH, thus converting Midazolam to highly lipid soluble drug.

Commercial preparations available for Midazolam are

1. IV/IM preparation 1mg/ml
2. IV preparation 5mg/ml (preservative free)
3. Oral preparation 0.5mg/ml
4. Nasal spray 5mg/ml (each metered dose of 100µl delivers 0.5mg).

PHARMACODYNAMICS

Central nervous system:

Midazolam has hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle relaxing properties like other benzodiazepines. Midazolam produces decrease in cerebral metabolic oxygen requirement ($CMRO_2$) and cerebral blood flow. But there is a ceiling effect for the decrease in $CMRO_2$. Cerebral vasomotor responsiveness to CO_2 is preserved.

Anterograde amnesia, produced by midazolam is dose related and often parallels the degree of sedation. As with other benzodiazepines, the amnesic effects of midazolam are more potent than its sedative effects. Thus, patients may be awake following the administration of midazolam but remain amnestic for events and conversations (postoperative instructions) for several hours. Induction of anaesthesia with midazolam does not prevent increase in ICP associated with direct laryngoscopy. Midazolam is a potent anticonvulsant, effective in treatment of status epilepticus. Midazolam produces adequate sedation and anxiolysis when used as premedicant but lacks the analgesic action.

Respiratory system:

Midazolam produces dose dependent decrease in ventilation. The peak onset of ventillatory depression with midazolam intravenously (0.13 to 0.2 mg/kg) is rapid (about 3 minutes), and significant depression remains for about 60 to 120 minutes. The rate of intravenous midazolam administration affects the onset time of peak ventillatory depression, the faster the drug is given, the more quickly this peak depression occurs. Patients with chronic obstructive pulmonary disease experience

even greater midazolam induced depression of ventilation. Midazolam also depresses the swallowing reflex and decrease upper airway reactivity.

Cardiovascular system:

Induction doses of Midazolam (0.2mg/kg IV) can produce decrease in systemic blood pressure and increase in heart rate. Cardiac output is not altered by midazolam suggesting that blood pressure changes are due to decrease in systemic vascular resistance. In presence of hypovolemia, administration of midazolam results in enhanced blood pressure lowering effects. There is ceiling effect for this decrease in systemic vascular resistance.

Pharmacokinetics:

Pharmacokinetics differs according to route of administration. In healthy children after administration of midazolam 0.15 mg/kg intravenously the volume of distribution at steady state, the elimination half-life, and the clearance were 1.29 L/kg, 70 minutes, and 9.1ml/kg per minute, respectively. There is a report on the kinetics of intravenous midazolam (0.5mg/kg) in 12 healthy Chinese children and noted that the kinetics were consistent with a three-compartment model with a volume of distribution of 1.9 L/kg, $t_{1/2}\beta$ of 107 minutes, and a clearance of 15.4ml/kg per minute.[37](5)

Midazolam undergoes rapid absorption from the gastrointestinal tract and prompt passage across the blood brain barrier. Only about 50% of an orally administered dose of Midazolam reaches the systemic circulation reflecting a substantial first pass hepatic effect. Commercially prepared solutions for oral midazolam are available. Literatures on the pharmacokinetics and pharmacodynamics

of oral midazolam have given different results, because studies have used different vehicles for administering the drug. Different vehicles affect drug absorption and, consequently, onset time and drug bioavailability. In addition, concurrent antacid use and grape fruit juice may increase the onset time and drug bioavailability of midazolam.

Nasal and sublingual transmucosal routes of administration have also been used for midazolam premedication. After administration of 0.1mg/kg of intranasal midazolam, peak plasma concentrations of midazolam occurred within 10 minutes after its administration, with peak plasma concentrations ranging from 43 to106 ng/mL. Plasma midazolam concentrations exceeded threshold sedation values for adults (40 ng/kg) as early as 3 minutes after its nasal administration and exceeded this level for as long as 30 minutes. Because intranasal midazolam can irritate the nasal mucosa, its use is limited by the volume of drug to be administered.[38]

The sublingual mucosa has a rich vascular supply and drugs are absorbed systemically, thereby eliminating hepatic first-pass metabolism. In a comparative study of intranasal and sublingual midazolam administration, it is noted that two routes to be equally effective but that the sublingual route of administration has better patient acceptance. Rectal administration of 0.3mg/kg midazolam for premedication resulted in satisfactory sedation levels, plasma concentration being 100ng/ml at the time of adequate sedation. In one dose finding study it has been shown that optimal dose for premedication by rectal route is 1 mg/kg.[39]

The protein binding of midazolam is extensive with a free fraction of only 3% to 6%. This binding is independent of the plasma concentration of midazolam. The short duration of action of a single dose of midazolam is due to its lipid solubility

leading to rapid redistribution from the brain to inactive tissue sites as well as rapid hepatic clearance.

Metabolism:

Midazolam undergoes extensive hydroxylation by hepatic microsomal oxidative mechanisms (Cytochrome P-450 3A) to form 1 hydroxy midazolam and 4hydroxy midazolam (smaller amounts). These water soluble metabolites are excreted in urine as glucuronide conjugates. These metabolites have pharmacological activity although it is less than that of parent compound. In contrast to diazepam, H receptor antagonists do not interfere with the metabolism of midazolam. But the drugs that inhibit cytochrome P-450 3A (erythromycin and Ca^{++} channel blockers) may decrease the hepatic clearance, resulting in CNS depression. Cytochrome P-450 3A also influences the metabolism of fentanyl. In this regard the hepatic clearance of midazolam is inhibited by fentanyl as administered during general anaesthesia. Overall the hepatic clearance rate of midazolam is five times greater than that of lorazepam and ten times greater than that of diazepam.

The elimination half-time of midazolam is 1-4 hours which is much shorter than that of diazepam. It may be doubled in elderly patients reflecting age related decrease in hepatic blood flow and possibly enzyme activity. The clearance of midazolam is more rapid than that of diazepam as reflected by the context sensitive half time. As a result of these differences, the CNS effect of midazolam would be expected to be shorter than those of diazepam.

The elimination half-time, V_d and clearance of midazolam are not altered by renal failure. This is consistent with the extensive hepatic metabolism of midazolam.

Comparative pharmacology of benzodiazepines[40]

Drug	Equivalent dose(mg)	Volume of distribution (lit/kg)	Protein binding (%)	Clearance (ml/kg/min)	Elimination (hrs)
Midazolam	0.15-0.3	1-1.5	96-98	6-8	1-4
Diazepam	0.3-0.5	1-1.5	96-98	0.2-0.5	21-37
Lorazepam	0.05	0.8-1.3	96-98	0.7-1.0	10-20

Clinical uses:

1. Preoperative medication in paediatric age group: Causes sedation, anxiolysis, and anterograde amnesia.
    a. 0.5 mg/ml oral,
    b. 0.05-0.1 mg/ml IM,
    c. 0.02-0.05 mg/kg IV,
    d. 0.2-0.3 mg/kg intranasal
    e. 0.75-1 mg/kg rectal.
2. Intravenous sedation
    a. Dose 1-2.5 mg IV for regional anaesthesia as well as for therapeutic procedures.
3. Induction of anaesthesia.
    a. Dose 0.1 — 0.2 mg/kg IV over 30 — 60 seconds.
4. Maintenance of Anaesthesia: Midazolam may be administered to supplement opioids, propofol, and/or inhaled anaesthetics during maintenance of

anaesthesia. Anaesthetic requirements for volatile anaesthetics are decreased in a dose-dependent manner by midazolam.

5. Nausea and vomiting prophylaxis: intravenous midazolam 0.05mg/kg can be usedto prevent nausea and vomiting

6. Postoperative Sedation: Intravenous midazolam is used for postoperative sedation. Also used in intensive care unit sedation.

7. Intrathecal use of midazolam: Preservative free midazolam is used to prolong the action of local anaesthetics. It is also used epidurally for postoperative pain relief.

Adverse effects:

Midazolam like other benzodiazepines cause dose dependent CNS depression ranging from mild sedation to stupor depending on dose used. Even with low doses used for sedation it can cause impairment of cognitive function, decreased motor coordination, anterograde amnesia which is accentuated by concomitant ingestion of alcohol. With concomitant use of other CNS depressants there will be synergistic effects. It causes hypotension, respiratory depression depending on dose and route of administration. Other uncommon side effects of midazolam are weakness, headache, blurred vision, vertigo, epigastric distress, and diarrhea.

PHARMACOLOGY OF DEXMEDETOMIDINE

Dexmedetomidine is a potent, highly selective and specific alpha-2 adrenoceptor agonist that has both sedative and analgesic effects. Dexmedetomidine was approved in the USA in 1999 for sedation and analgesia in the intensive care unit. Compared with clonidine, dexmedetomidine is about eight times more specific for alpha-2 adrenoceptors with alpha2:alpha1 ratio of 1600:1. These unique properties of dexmedetomidine make it an alpha-2 adrenoceptor full agonist agent with sedative and anxiolytic effects.

Chemical structure:

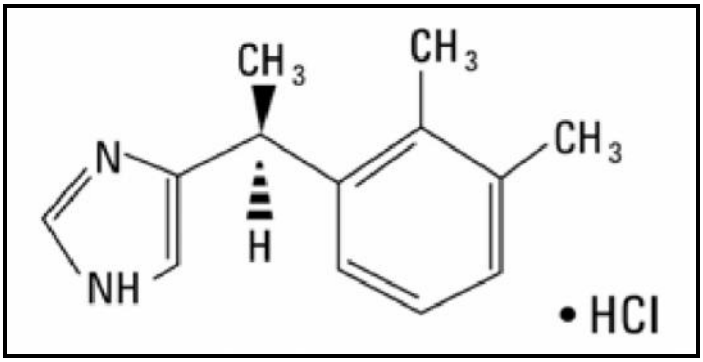


Image 2: Structure of Dexmedetomidine

Molecular formulae – $C_{13}H_{16}N_2$

Molecular weight : 200.13gm/mol

IUPAC name – 5-[1-(2,3-dimethylphenyl)ethyl]- 1H-imidazole

Physiology of alpha adrenergic receptors:

Adrenergic receptors were originally differentiated in to alpha and beta receptors on the basis of the rank order of potency of various natural and synthetic catecholamine's in different physiologic preparations. It was believed that activation of either alpha or beta adrenergic receptors produced excitatory effects in some tissues

and inhibitory effects in others. Later, a subclass of alpha adrenoceptors was discovered that regulates the release of neurotransmitters. Presynaptic α-2 receptors may be of the greatest clinical importance because they regulate the release of norepinephrine and adenosine triphosphate through a negative feedback mechanism. Alpha-2 adrenergic receptors are found in the peripheral nervous systems, central nervous systems, platelets, and a variety of organs, including the liver, pancreas, kidney, and eye. Physiologic responses mediated by alpha-2 adrenoceptors vary with location.

Clonidine is the prototypical alpha-2 agonist and has been studied for more than a decade. It has sedative and analgesic properties which reduce anaesthetic and analgesic requirements during perioperative period. The recently described dexmedetomidine has shorter half-life of 2-3 hours and is 8-10 times more potent for alpha-2 receptor. By virtue of this potency dexmedetomidine is considered to be full agonist at alpha-2 receptor.

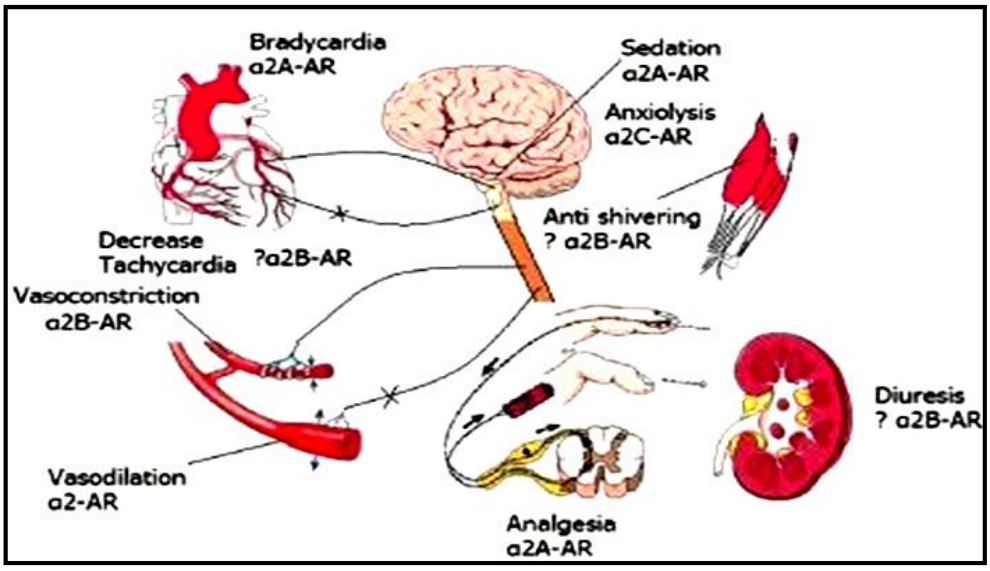


Image 3: Physiology of alpha 2 receptors

Mechanism of action:

The hypnotic effect of dexmedetomidine is mediated by the hyperpolarization of noradrenergic neurons located in the locus coeruleus, spinal cord is the principal site for analgesic action acting through alpha-2 adrenoreceptor. Dexmedetomidine acts through a G-coupled protein receptor that produces an inhibition of adenylcyclase and this result in decreased formation of cyclic AMP (c AMP) which is an important regulator of many cellular functions acting in various intracellular subsystems like the control of phosphorylation state of regulatory proteins. Other effects of alpha-2 adrenoreceptors agonists include activation of potassium ion channels causing efflux of potassium and an inhibition of calcium entry in to calcium channels of neuronal cell,[41] these effects lead to change in membrane ion conductance and produce alpha-2 adrenoreceptor agonist hyperpolarization of the membrane which suppresses neuronal activity. The main effect is an inhibition of noradrenaline release causing a reduction of excitation, especially in locus coeruleus. The locus coeruleus is small neuronal nucleus located bilaterally in the upper brainstem and is major site of noradrenergic innervations in the brain.[42] The locus coeruleus has also been implicated as adrenoreceptor agonist key modulator for alpha-2 adrenoreceptor agonist variety of important brain functions including arousal, sleep, anxiety and drug withdrawal associated with CNS depressant like opioids

Pharmacokinetics:

Absorption and Distribution:

Dexmedetomidine exhibits linear pharmacokinetics in the recommended dose range of 0.2- 0.7µg/kg/hr administered as an intravenous infusion over 24hrs. The distribution phase is rapid, with half-life of distribution of approximately 6 minutes

and elimination half-life of 2 hours.[43,44] The steady state of volume of distribution is 118 L. The average protein binding is 94% and is constant across different plasma concentrations and also similar in males and females. It has negligible protein binding displacement by drugs commonly used during anaesthesia and in ICU like fentanyl, ketorolac, theophylline, digoxin and lidocaine. Context sensitive half-life ranges from 4 minutes after a 10 min infusion to 250 minutes after an 8hr infusion. Oral bioavailability is poor because of excess first pass metabolism. However bioavailability of sublingually administered dexmedetomidine is high (84%), offering a potential role in paediatric sedation and premedication.

Metabolism and Excretion:

Dexmedetomidine undergoes complete biotransformation through conjugation (41%), N-methylation (21%), or hydroxylation followed by conjugation to inactive metabolites. Metabolites are excreted in urine (95%) and feces (4%). Dexmedetomidine has profound effects on cardiovascular variables and may alter its own pharmacokinetics. With large doses, there is marked vasoconstriction, which probably reduces volumes of distribution of the drug. Dose adjustment is required in patients with hepatic failure because of low rate of metabolism.

PHARMACODYNAMICS:

Cardiovascular system:

The haemodynamic effects of dexmedetomidine result from peripheral and central mechanism. Alpha-2 adrenoreceptor agonists show a biphasic dose dependent, blood pressure effect. At low doses the dominant action of α-2 adrenoreceptor agonist activation is a reduction in sympathetic tone, mediated by a reduction of

norepinephrine release at the neuroeffector junction and an inhibition of neurotransmission in sympathetic nerves. The net effect of dexmedetomidine action is a significant reduction in circulating catecholamines with a slight decrease in blood pressure and a modest reduction in heart rate. When dexmedetomidine is administered as a continuous infusion it is associated with an expected and stable haemodynamic response. Significant hypotension is only observed in patients with pre-existing hypovolaemia or vasoconstriction. The bradycardia frequently seen after the administration of dexmedetomidine may be due to the central sympatholytic action and partly by baroceptor reflex and enhanced vagal activity. This effect is frequently observed in younger patients with high levels of vagal tone. At higher doses dexmedetomidine produce a hypertensive action caused by the activation of α-2b, adrenoceptors located on vascular smooth muscle cells.

Respiratory System:

The alpha-2 adrenoreceptor agonists have minimal effects on ventilation. Although dexmedetomidine produces sedative, analgesic and anxiolytic effects, unlike other sedatives, it provides respiratory stability and does not cause ventilatory depression. This was shown in healthy volunteers in whom even very high doses of dexmedetomidine did not compromise respiratory function. Absence of respiratory depression was also observed in patients sedated with dexmedetomidine which was administered at infusion rates 10 to 15 times higher than maximally recommended. It was also demonstrated that combination of alpha-2 adrenoreceptor agonist with opioids does not lead to further ventilatory depression.

Central Nervous System:

Dexmedetomidine, like other alpha-2 adrenoreceptor agonists, provides sedation, anxiolysis and analgesia. The sedation produced by alpha-2 adrenoreceptor agonists does not depend primarily on activation of the gamma-amino butyric acid receptors like that produced by traditional sedatives such as Propofol or benzodiazepines.[41] The primary site of action of α-2 adrenoreceptor agonist is the locus coeruleus and not the cerebral cortex as would be the case with GABA-mimetic drugs. This should be the reason why this class of drugs produces a different type of sedation compared with benzodiazepines and Propofol. Sedation induced by dexmedetomidine has unique properties, it produces an unusually cooperative form of sedation in which the patient is calmly and easily roused from sleep to wakefulness to allow task performance and excellent communication and cooperation while intubated and ventilated and then quickly back to sleep when not stimulated. The unusual subcortical form of dexmedetomidine induced sedation is characterized by an easy and quick arousal, resembling natural sleep. With increasing doses of dexmedetomidine, profound anaesthetic actions have been demonstrated and this advocates that dexmedetomidine could be used as total intravenous agent.

Renal System:

Stimulation of alpha-2 adrenoreceptors in the kidneys results in diuresis and natriuresis possibly through an ability to reduce efferent sympathetic outflow to the kidney. In addition dexmedetomidine has shown to decrease the secretion of vasopressin and to antagonize its effect on renal tubules. Alpha-2adrenoreceptor agonists are also thought to increase the release of atrial natriuretic peptide resulting in natriuresis.

Endocrine System:

Action of alpha-2 adrenoreceptor agonists on endocrine system are mainly related to their action on sympathetic outflow and the decrease of catecholamines. This can attenuate the responses to stress by inhibiting the secretion of adrenocorticotropic hormone (ACTH) and cortisol.[45] In addition stimulation of alpha-2 adrenoreceptor agonists located on delta cells of the islet of Langerhans can cause direct inhibition of insulin release with concomitant detectable clinical hyperglycemia.

Analgesia:

Dexmedetomidine has been demonstrated to have significant analgesic effects and consistently reduce opioid requirements.[46] It is believed that the spinal cord isprobably the major site of analgesic action, where the activation of α2c-adrenoreceptor agonist subtype seems to increase the analgesic action of opiolds in lowering the transmission of nociceptive signals to brain centre. Dexmedetomidine also inhibits the release of substance P from the dorsal horn of the spinal cord, leading to primary analgesic effects.

Clinical Application of Dexmedetomidine:

1. **Premedication:** Dexmedetomidine is used as an adjuvant for premedication especially in patients susceptible to preoperative and perioperative stress because of its sedative, anxiolytic, analgesic and stable haemodynamic profile. Dexmedetomidine decreases oxygen consumption in intraoperative period (up to 8%) and postoperative period (up to17%).[47] Premedication dose is 0.33 to 0.67µg/kg IV given 15 minutes before surgery.

2. **Perioperative Use:** Dexmedetomidine may be a useful adjuvant during general anaesthesia to employ its sedative, hypnotic, analgesic and sympatholytic properties for the benefit of surgical patients by promoting haemodynamic stability and decreasing the doses of anaesthetics and analgesics.

3. **Regional Anaesthesia:** Highly liphophilic nature of dexmedetomidine allows rapid absorption into cerebrospinal fluid and binding to α-2 adrenoreceptor of spinal cord for its analgesic action. It prolongs both the duration of sensory and motor blockade induced by local anaesthetics irrespective of routes of administration (Epidural, caudal, spinal). It enhances both central and peripheral neural blockade by local anaesthetics.

4. **Sedation in ICU:** Dexmedetomidine has become popular sedative agent in the ICU because of its ability to produce cooperative sedation i.e. patients remain awake, calm and able to communicate, their needs. It does not interfere with respiratory drive or produce any agitation, hence facilitates early weaning from ventilator and discharge from ICU. Dexmedetomidine is currently approved by FDA for use in ICU for not more than 24 hrs. It has both sedative and analgesic sparing effects, reduced delirium and agitation, minimal respiratory depression and cardiovascular stability.[48]

5. **Procedural Sedation:** Dexmedetomidine is an attractive agent for short-term procedural sedation and has been safely used in transesophageal echocardiography, colonoscopy, awake carotid endarterectomy, shockwave lithotripsy, vitreoretinal surgery, elective awake fibreoptic intubation and in non-invasive radiological procedures like computed tomography and magnetic

resonance imaging. The usual dose of dexmedetomidine for procedural sedation is 1 μg/kg, followed by an infusion of 0.2 μg/kg/hr. Its onset of action is less than 5 minutes and the peak effect occur within 15 minutes. As the pharmacologic effects of Dexmedetomidine can be reversed by α2 adrenergic receptor antagonist atipamezole, Dexmedetomidine provides a titratable form of hypnotic sedation that can be readily reversed.

6. **Controlled Hypotension:** Dexmedetomidine is an effective and safe agent for controlled hypotension mediated by its central and peripheral sympatholytic action. It's easy administration, predictability with anaesthetic agents and lack of toxic side effect while maintaining adequate perfusion of the vital organs makes it a near- ideal hypotensive agent. Spinal fusion surgery for idiopathic scoliosis, septoplasty, tympanoplasty and maxillofacial surgery have been safely done with Dexmedetomidine-controlled hypotension.

7. **Analgesia:**Dexmedetomidine activates α-2 adrenergic receptor in the spinal cord reducing transmission of nociceptive signals like substance P. It has significant opioid sparing effect and is useful in intractable neuropathic pain.

8. **Other Uses:** Dexmedetomidine has been used successfully in the treatment of withdrawal from benzodiazepines, opioids, alcohol and recreational drugs.

Adverse Effects:

The various reported side effects are hypotension, hypertension, nausea, vomiting, dry mouth, bradycardia, atrial fibrillation, pyrexia, chills, pleural effusion, atelectasis, pulmonary edema, hyperglycemia, hypocalcaemia, acidosis, etc. Rapid administration of dexmedetomidine infusion may cause transient hypertension

mediated by peripheral α-2b adrenergic receptor vasoconstriction. But hypotension and bradycardia may occur with ongoing therapy mediated by central α- 2a adrenergic receptor, causing decreased release of noradrenaline from the sympathetic nervous system. Long-term use of dexmedetomidine leads to super sensitization and up regulation of receptors, so with abrupt discontinuation a withdrawal syndrome of nervousness, agitation, headaches, and hypertensive crisis can occur. Dexmedetomidine is not recommended in patients with advanced heart block and ventricular dysfunction. FDA has classified it as a category C pregnancy risk, so the drug should be used with extreme caution in women who are pregnant.

MATERIALS AND METHODS

SOURCE OF DATA

KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Nehrunagar, Belagavi -10.

In paediatric patients undergoing lower abdominal and lower limb surgeries under caudal epidural anaesthesia with sedation from January 2015 to December 2015.

a) Study design: A One year Prospective Double Blind Randomised Controlled Trial.

b) Sample size: A total sample size of **60** cases, 30 in Midazolam Group and the other 30 in Dexmedetomidine Group.

c) Sample size calculation:

The sample size was calculated by considering incidence of satisfactory mask induction of dexmedetomidine sedation as 53% and with that of incidence of satisfactory mask induction of midazolam sedation as 18%. [34]

With type I error rate $\alpha = 0.05$ and

type II error rate $\beta = 0.02$

with a power of 80% and using the formula -

$$n = \frac{2\,(Z\alpha + Z\beta)^2 pq}{(p_0 - p_1)^2}$$

n = number of samples in each group

$Z\alpha = 1.96$

$Z\beta = 0.84$

$P_0 = 18\%$

$P_1 = 53\%$

$$n = \frac{2\,(1.96+0.84)^2\,(35)(65)}{(35)^2}$$

$$n = \frac{2\,(2.8)^2(65)}{(35)}$$

$$n = 29.12$$

For ease of calculations sample size(n) has been taken as 30.

d) Place:

KLES Dr.Prabhakar Kore Hospital and Medical Research centre, Jawaharlal Nehru Medical College, Belagavi.

e) Selection Criteria:

Inclusion Criteria:

1. ASA physical status I and II.
2. Age between 1 to 10 years.
3. Patients undergoing lower abdominal and lower limb surgeries under caudal epidural anaesthesia with sedation.

Exclusion Criteria:

1. Known allergy or hypersensitive reaction to Dexmedetomidine or midazolam.
2. Cardiac arrhythmia.
3. Congenital heart disease.
4. Running nose.
5. Mental retardation.

f) Randomisation: A computer generated table of random numbers was prepared allotting equal number of patients in each group.

g) Methodology: After having met inclusion and exclusion criteria's and having obtained informed consent, children were randomly divided into two groups according to the computer generated randomisation table.

Group M- Intranasal Midazolam group and

Group D- Intranasal Dexmedetomidine group.

Group M received 0.2 mg/kg intranasal Midazolam (up to a maximum 5 mg) using 1ml tuberculin syringe with atomiser.

Group D received 1µg /kg Dexmedetomidine intranasally using 1ml tuberculin syringe with atomiser.

To avoid bias, drugs were administered by a blinded investigator. Observers and attending anaesthesiologist were blinded for study drug given. All the children were premedicated in pre-operative holding area in the presence of parent.

Intranasal drug was sprayed into both nostrils using 1ml tuberculin syringe and atomiser with child in recumbent position 45 to 60 min before shifting the patient to operating room(OR).

Base line heart rate (HR) and oxygen saturation(Spo2) were noted and monitored every 5min after administration until patient was transferred to operating room.

The parental separation anxiety was assessed while shifting the patient to operating room and mask acceptance was assessed by the attending anaesthesiologist in operating room who is blinded to the drug given.

Parental separation anxiety was assessed using the parental separation anxiety scale(PSAS), which is a 4 point scale.

1. Easy separation.
2. Whimpers but easily reassurable.
3. Cries and cannot be easily reassured but not clinging to parents.
4. Crying and clinging to parents.

A PSAS score of 1 or 2 are classified as an acceptable separation, score of 3 or 4 are considered as difficult separation.

The subject's ability to accept the anaesthesia mask during induction in the OR was measured using mask acceptance scale (MAS).

1. Excellent (unafraid, cooperative, accept mask readily).
2. Good (slight fear of mask, easily reassured).
3. Fair (moderate fear of mask, not calmed with reassurance).
4. Poor (terrified, crying or combative).

Subjects with score of 1 or 2 are considered as satisfactory acceptance of mask, scores of 3 or 4 are considered unsatisfactory.

Further the monitors were attached and patient was induced using inhalational agents and I.V. cannula secured. After induction all patients were given caudal epidural anaesthesia using a 24G needle and 1ml/kg body weight of 0.25%

bupivacaine, patient were maintained with O_2 + N_2O using face mask. The vital parameters and adverse events if any were noted till the end of procedure.

Statistical Analysis:

A Wilcoxon rank sum test was used to determine difference between the two groups for means of parental separation anxiety scale and mask acceptance scale. Quantitative data like HR and SpO_2 was analysed by using Student 't' test. P-value below 0.05 is considered statistically significant.

RESULTS

We compared intranasal dexmedetomidine 1µg/kg (Group D) with intranasal midazolam 0.2mg/kg (Group M) as premedication in children age between 1 to 10 years. Total of 60 cases were enrolled in the study with 30 cases in each group. All the children underwent below umbilical surgical procedures such as hernia repair, circumcision etc., under caudal epidural anaesthesia.

Demographic data

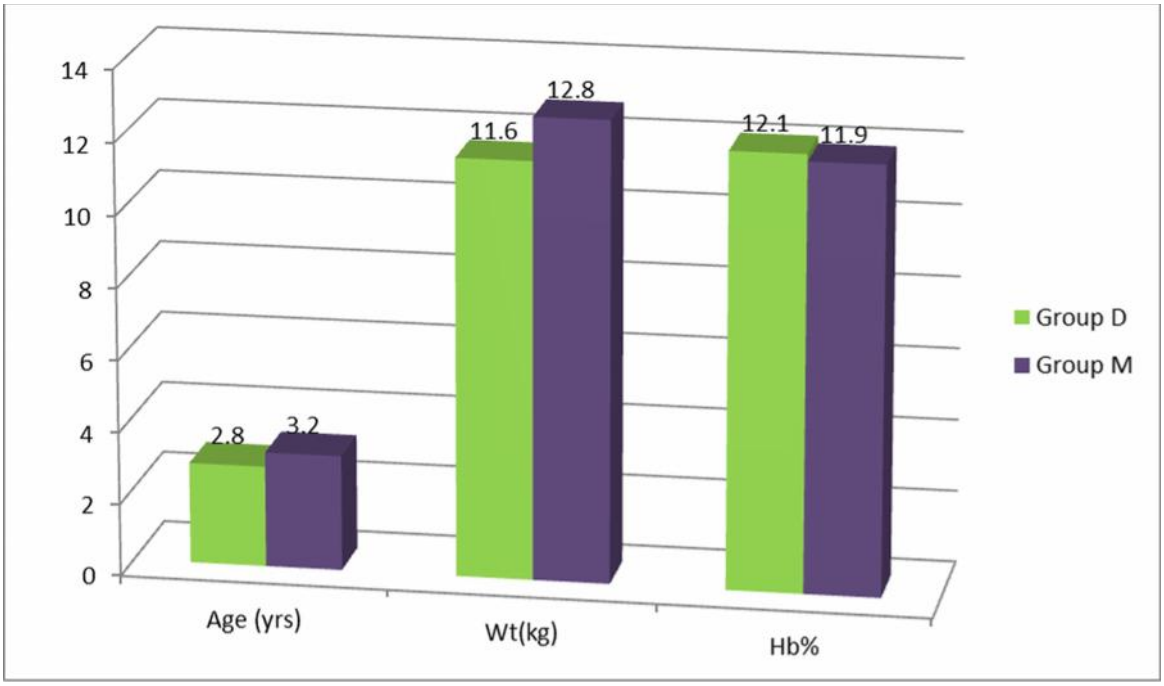
Demographic characteristics, i.e. age, sex, weight and Hb% were comparable in both groups and there was no statistically significant difference (P >0.05) between the groups (Table:1). Student 't' test was used to compare age, weight, and Hb%, Chi square test was used to compare sex of the patients.

Table 1: Demographic data

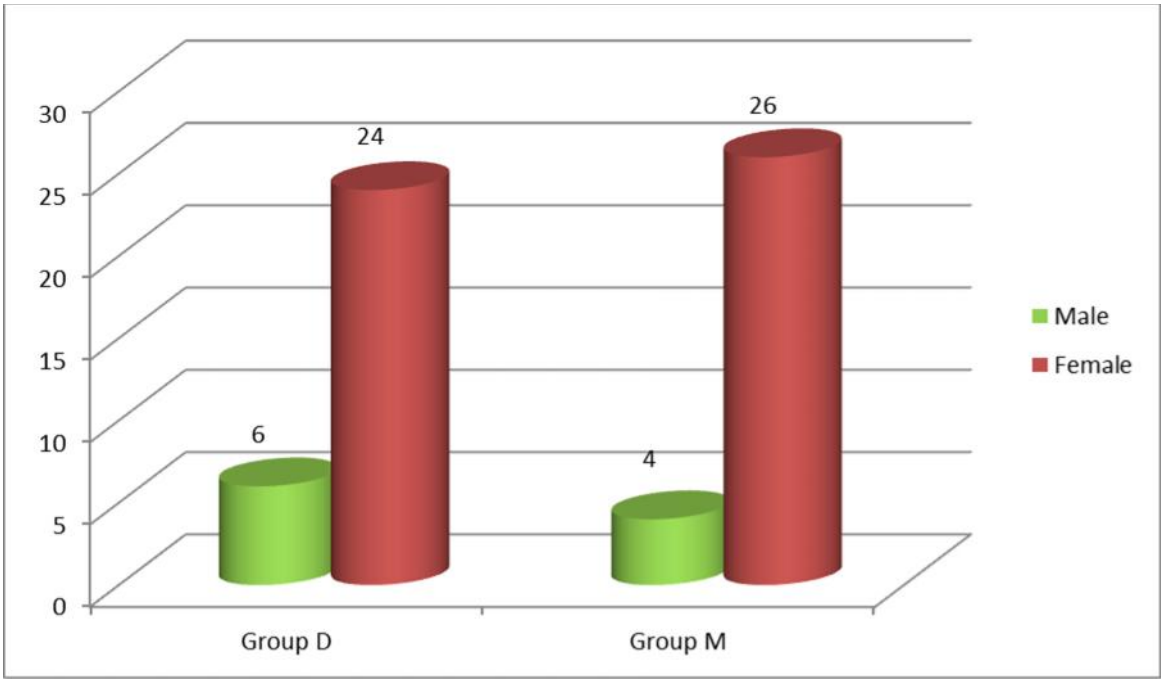
Parameters	Group D	Group M	P value
# Age (yrs)	2.8 ± 1.8	3.2 ± 2.22	0.435
@ Sex (M:F)	30(6 : 24)	30(4 : 26)	0.488
# Wt (kg)	11.6 ± 3.32	12.8 ± 3.99	0.217
# Hb%	12.1 ± 1.19	11.9 ± 1.48	0.518
No. of cases	N=30	N=30	

by Student 't' test @ by Chi square test

Graph 1: Demographic data



Graph 2: Sex distribution



Pre-operative mean SpO_2

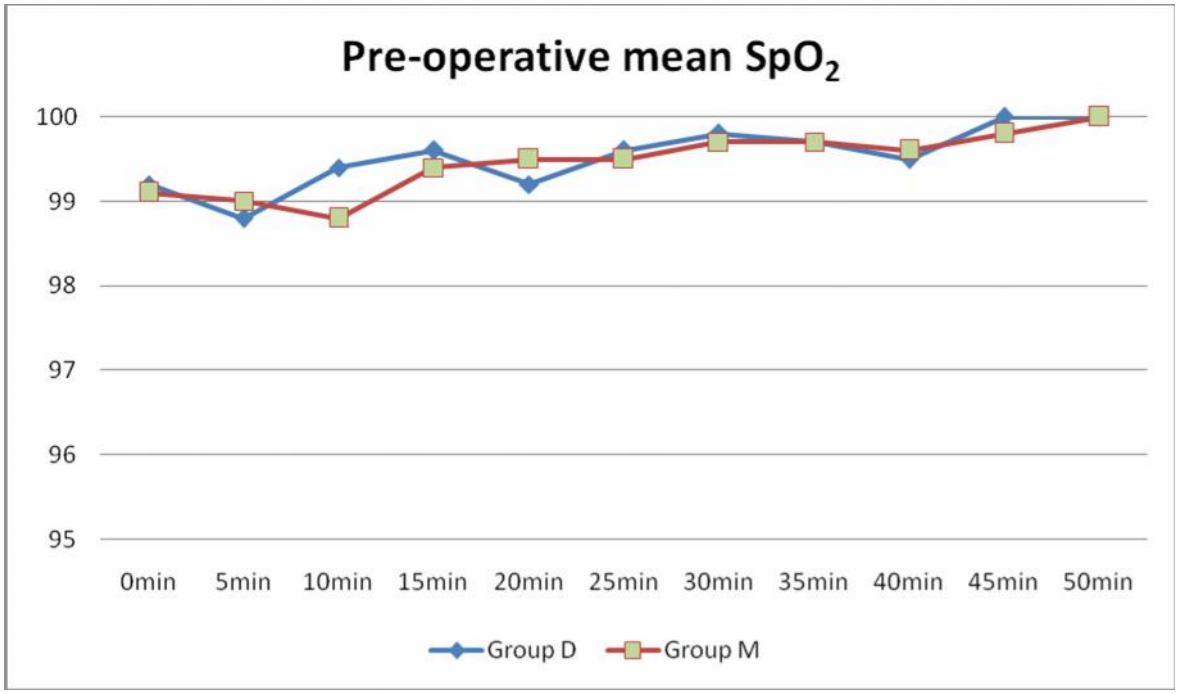
In our study the baseline mean oxygen saturation (SpO_2) and mean oxygen saturation (SpO_2) after administration of premedication were comparable in both the groups till end of 50min. (Table: 2)

The baseline mean SpO_2 was 99.1% in midazolam group which was comparable to 99.2% in dexmedetomidine and the difference was not statistically significant (P>0.05). No significant change was observed among both groups till the end of 50 min. None of the patients in both groups had SpO_2 less than 95% at any point of time during preoperative monitoring.

Table 2: Pre-operative mean SpO_2

	Group D	Group M	P value
0min	99.2 ± 1.12	99.1 ± 1.01	0.810
5min	98.8 ± 1.13	99.0 ± 1.01	0.475
10min	99.4 ± 0.93	98.8 ± 1.13	0.052
15min	99.6 ± 0.81	99.4 ± 0.89	0.549
20min	99.2 ± 0.99	99.5 ± 0.86	0.171
25min	99.6 ± 0.81	99.5 ± 0.81	0.875
30min	99.8 ± 0.61	99.7 ± 0.69	0.694
35min	99.7 ± 0.69	99.7 ± 0.69	1.0
40min	99.5 ± 0.86	99.6 ± 0.76	0.527
45min	100 ± 0	99.8 ± 0.51	0.161
50min	100 ± 0	100 ± 0	-

Graph 3: Pre-operative mean SpO_2



Preoperative mean Heart rate(HR)

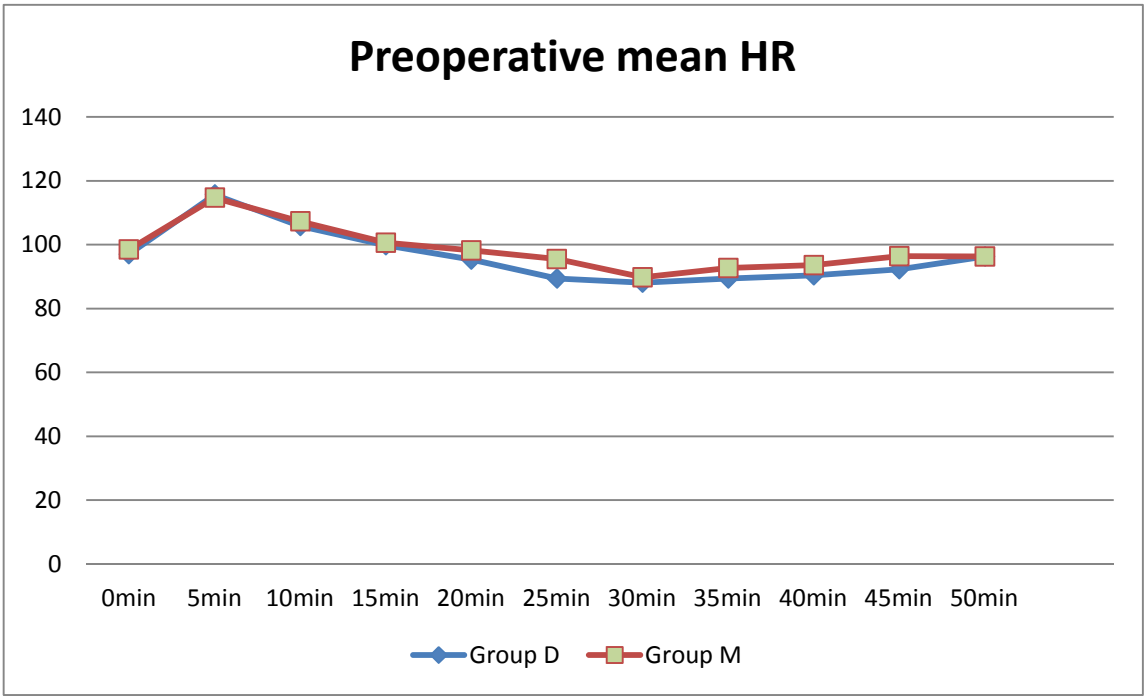
Pre-procedure mean heart rate(HR) was comparable in both the groups with no statistical significance(P>0.05) between the groups till end of 50min. (Table: 3)

In our study mean heart rate was decreased by 2% from baseline at 10 min and by 9.1% from baseline at 30 min after intranasal dexmedetomidine premedication. Similarly mean heart rate was decreased by 8.8% from baseline at 30min after intranasal midazolam premedication.

Table 3: Preoperative mean HR

	Group D	Group M	P value
0min	97.0 ± 10.95	98.5 ± 10.37	0.580
5min	115.7 ± 12.67	114.7 ± 13.96	0.773
10min	105.8 ± 11.45	107.3 ± 12.86	0.635
15min	99.8 ± 10.92	100.6 ± 10.87	0.759
20min	95.3 ± 11.60	98.2 ± 12.07	0.341
25min	89.4 ± 11.84	95.5 ± 13.54	0.070
30min	88.1 ± 10.01	89.8 ± 11.86	0.559
35min	89.4 ± 9.51	92.7 ± 9.98	0.191
40min	90.4 ± 10.37	93.6 ± 9.10	0.209
45min	92.3 ± 10.79	96.4 ± 8.31	0.107
50min	96.3 ± 6.26	96.3 ± 9.11	1

Graph 4: Preoperative mean HR



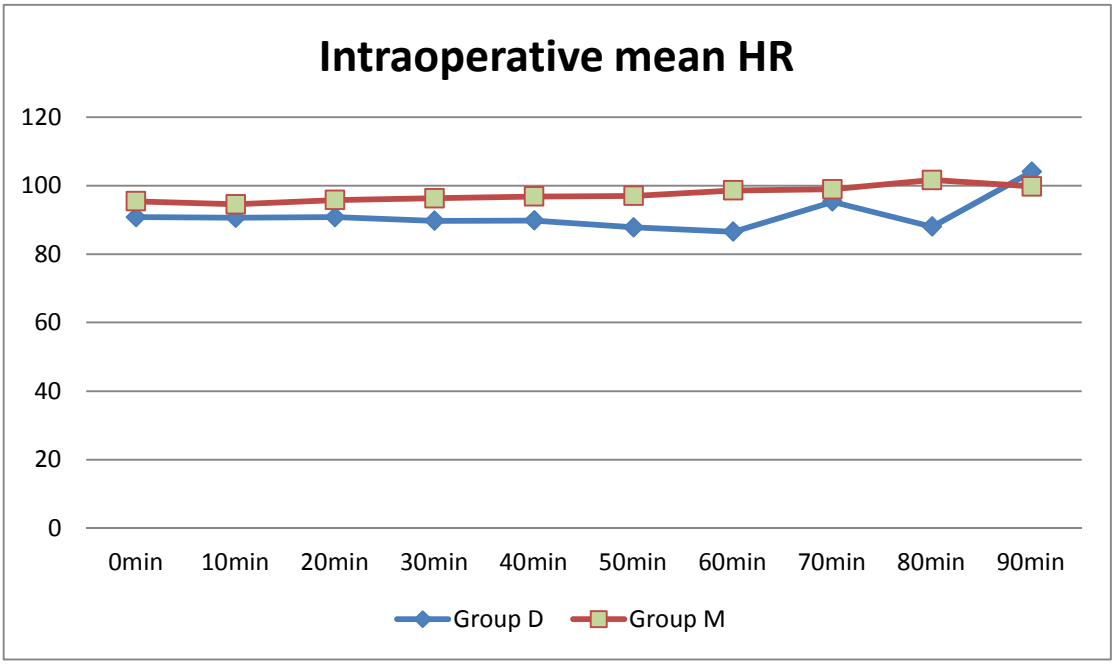
Intraoperative mean HR

Intra operatively the mean heart rate was comparable in both the groups with no statistically significant (P>0.05) difference between the groups at the time of induction (0min), 10min, and at 20 min, but was statistically significant (P<0.05) at 30, 40, 50, 60min with increase in heart rate from baseline in midazolam group and decrease form baseline in dexmedetomidine group. (Table: 4)

Table 4: Intra operative mean HR

	Group D	Group M	P value
0min	90.8 ± 9.40	95.4 ± 10.10	0.073
10min	90.6 ± 10.18	94.5 ± 10.42	0.145
20min	90.8 ± 10.09	95.8 ± 10.23	0.062
30min	89.7 ± 10.46	96.3 ± 10.52	0.027
40min	89.8 ± 11.87	96.8 ± 10.06	0.038
50min	87.8 ± 13.20	97 ± 9.11	0.022
60min	86.5 ± 15.25	98.6 ± 10.32	0.031
70min	95.3 ± 22.3	98.9 ± 10.51	-
80min	88.0 ± 25.45	101.6 ± 10.94	-
90min	104 ± 0	99.75 ± 10.23	-

Graph 5: Intraoperative mean HR



Intra operative mean SpO_2

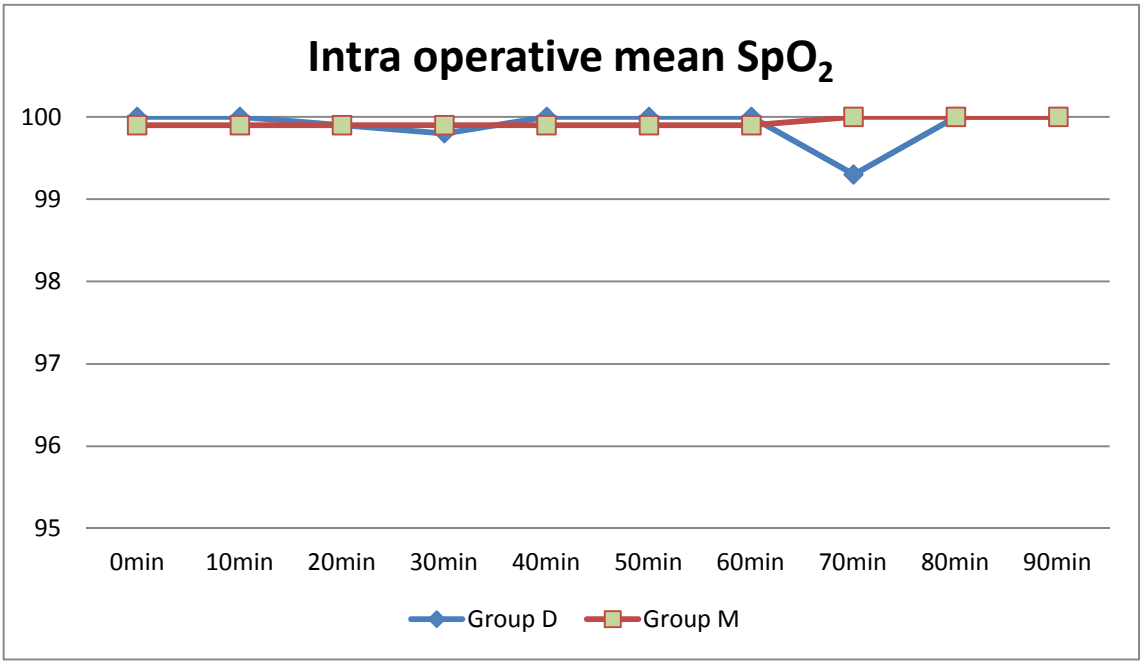
The intraoperative oxygen saturation was comparable in both the groups which is not statistically significant (P>0.05) till end of procedure.

In our study the baseline mean SpO_2 was 99.9% in midazolam group which was comparable to 100% in dexmedetomidine and the difference was not statistically significant (P>0.05) at starting of surgery. No significant change was observed among both groups till the end of surgery. None of the patients in both groups had SpO_2 less than 95% at any point of time during intraoperative monitoring. (Table: 5)

Table 5: Intra operative mean SpO_2

	Group D	Group M	P value
0min	100 ± 0	99.9 ± 0.18	0.326
10min	100 ± 0	99.9 ± 0.18	0.326
20min	99.9 ± 0.36	99.9 ± 0.18	0.656
30min	99.8 ± 0.53	99.9 ± 0.19	0.299
40min	100 ± 0	99.9 ± 0.20	0.377
50min	100 ± 0	99.9 ± 0.22	0.440
60min	100 ± 0	99.9 ± 0.25	0.492
70min	99.3 ± 1.5	100 ± 0	0.423
80min	100 ± 0	100 ± 0	-
90min	100 ± 0	100 ± 0	-

Graph 6: Intra operative mean SpO_2



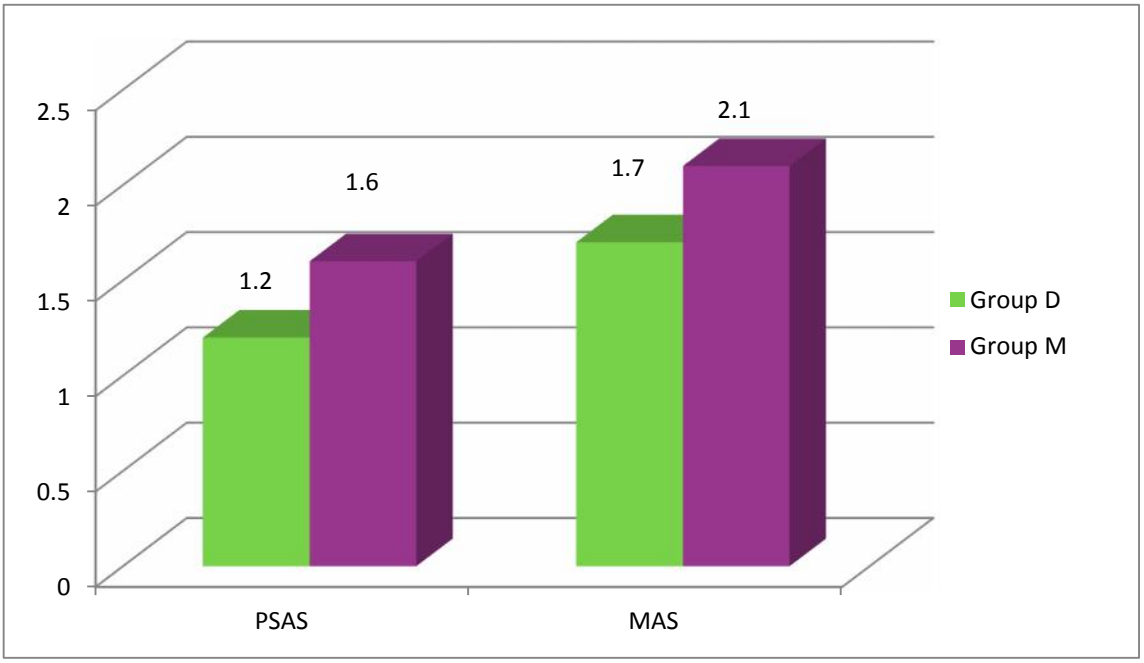
PSAS & MAS:

The mean parental separation anxiety scale(PSAS) was 1.2 ± 0.40 in dexmedetomidine group and 1.6 ± 0.56 in midazolam group which is statistically significant with P value of 0.003. The mean mask acceptance scores (MAS) at the time of induction was 1.7 ± 0.59 in dexmedetomidine group and 2.1 ± 0.58 in midazolam group which is statistically significant(P=0.020). Only 2(6.6%) children in dexmedetomidine group had MAS > 2 when compared to 6(20%) children in midazolam group (Table: 6).

Table 6: PSAS and MAS (were compared using Wilcoxon rank sum test).

	Group D	Group M	P value
PSAS	1.2 ± 0.40	1.6 ± 0.56	0.003
MAS	1.7 ± 0.59	2.1 ± 0.58	0.020

Graph 7: PSAS and MAS



DISCUSSION

Paediatric patients undergoing surgery can experience significant anxiety and distress during the perioperative period. They are usually uncooperative, fearful, anxious and physically resistant, particularly during times of parental separation, venipuncture and mask application.[1] And this preoperative anxiety can lead to negative response postoperatively. Kain demonstrated that 54% of their subjects had negative behaviour patterns at 2 weeks and 20% continued to have these patterns up to 6 months.[2]

The preprocedure period in paediatric patients can be made fearless either by psychological methods or by pharmacological methods. Premedication is required to allay anxiety and fear, allow smooth separation from parents, easy acceptance of needle prick and acceptance of mask at induction of anaesthesia. Additional advantages are analgesic, amnesic, antiemetic, anti-sialagogue and vagolytic effects.

The administration of medications in paediatric patients is not always an easy task. Several drugs have been tried to find the best premedicant and best route of administration for these drugs in children. Currently the drugs which are used routinely for premedication are midazolam, ketamine, fentanyl, with midazolam being the most commonly used. The beneficial effects of midazolam include sedation, anxiolysis and amnesia. But midazolam is associated with respiratory depression and lacks analgesic property. An increased incidence of adverse postoperative behavioural changes, hiccups and paradoxical reactions have also been observed.[6] Hence there is a need to search for a better premedicant.

Clonidine, an α-2 agonist is an another option for premedication in children. Its sedative effects and decreased requirement of anaesthetic drugs were noticed in patients receiving clonidine[7] but it has slow onset of action (1-3hrs). Dexmedetomidine is a newer α-2 agonist with a more selective action and a shorter half-life compared to clonidine. There is increasing evidence that dexmedetomidine is an effective and safe sedative in children and has analgesic and anti-shivering property.[23,25] It also reduces anaesthetic requirement and doesn't cause respiratory depression. Hence we decided to study dexmedetomidine as premedicant in comparison to midazolam.

Many studies have shown that intranasal route is an effective way to administer premedication and sedation to children. Midazolam has been used by various routes (oral, intranasal, rectal, sublingual, and intravenous, etc.) as premedicant. Intramuscular and intravenous routes are painful and require skill to administer. As children will be afraid of needle pricks these two routes make the child more anxious and uncooperative. Rectal route is distressing to some children and their parents. Sublingual route requires child's cooperation to retain the drug in the mouth. Oral route is most commonly used route for premedication. However it has longer onset of action and less bioavailability due to first pass metabolism. Intranasal application is a relatively non-invasive, convenient and easy route of administration, not requiring patient cooperation as would be the case for swallowing the medication in oral route or retaining it sublingually. Intranasal administration has faster onset of action and also reduces first pass metabolism.

Kogan et al compared four routes of administration of midazolam (oral, intranasal, rectal and sublingual) in young children and found satisfactory sedation

and found that anxiolysis was comparable in all four routes but intranasal route offered faster onset of action (22.4 ± 5.6 min).[13] Malinovsky et al found that onset of action with intranasal midazolam was 7.7±2.4min as compared to 12.5±4.9min with oral or 16.3±4.2min with rectal routes.[11]

Intranasal midazolam has been used in various doses (0.01mg/kg to 0.5mg/kg) as premedicant. Davis et al in a dose finding study of intranasal midazolam showed that percentage of satisfactory separation (91% vs. 90%) and induction scores(60% vs. 80%) were comparable in case of 0.2mg/kg and 0.3mg/kg dose.[15] Similar results were shown by Bhakta et al with statistically significant change in the level of sedation at 5 min with 0.2mg/kg and at 10 min in 0.3mg/kg.[16] In this study dose of 0.2mg/kg had faster onset of action and no major advantage with higher dose. Hence we decided to administer 0.2mg/kg midazolam as premedicant by intranasal route.

Griffith et al compared the administration of midazolam(5mg/ml) as used in our study intranasally as drops and commercially available spray and observed that there was no significant difference in method of administration(P= 0.39) and midazolam by either method was equally effective.[17] Similar results were observed by Primosch et al in a retrospective review of intranasal midazolam used either as drops or as spray and demonstrated a statistically significant reduction(P=0.025) in aversive behaviour with spray but no influence on agent efficacy compared to drops administration.[18]

Intranasal preparation for dexmedetomidine is not available and hence intravenous (IV) preparation was used intranasally in many studies. Intranasal dexmedetomidine has been used in doses ranging from 0.5µg/kg to 1.5µg/kg. In a comparative study by Yuen et al it was shown that 75% of the children in

dexmedetomidine 1µg/kg group had satisfactory sedation when compared to 59.4% in 0.5µg/kg group.[27] Yuen et al and Ghali et al showed that dexmedetomidine is effective and safe intranasally in 1µg/kg dose. Hence we decided to use 1µg/kg dexmedetomidine intranasally.[26,49]

Li B. L. et al compared intra nasal dexmedetomidine administered by atomiser or by drops in 279 children[50] and observed that the sedation rate was 82.5% and 84% for atomiser and drops respectively. They also concluded that in either mode of administration, dexmedetomidine was equally effective. Hence in our study we used an atomiser and administered the drug intranasally using a tuberculin syringe with an atomiser.

We also evaluated parental separation anxiety in children. Parental separation anxiety has been assessed by different scales by different authors. Yuen et al and Sundaram et al evaluated parental separation anxiety as whether successful or not.[27,32] Mostafa et al and Akin et al used 4 point scale at 30 min[33,34] Ghali et al used a 3 point scale[49] for parental separation anxiety. In our study we decided to assess parental separation anxiety scale(PSAS) using a 4 point scale. We considered it as successful for PSAS 1 and 2, and not successful for PSAS 3 and 4 as it is easy and simple.

Our results show that a dose of 1µg/kg of intranasal dexmedetomidine premedication is capable of producing a satisfactory PSAS when compared to 0.2 mg/kg intranasal midazolam. (P = 0.003). Which was similar to study done by Sheta et al who compared 72 children and found that in children in dexmedetomidine group were significantly more sedated than midazolam group when they were separated from their parents (77.8% vs 44.4%, respectively) (P = 0.002).

Yuen et al.[27] used 1µg/kg intranasal dexmedetomidine and 0.5 mg/kg oral midazolam for parental separation and at the time induction of anaesthesia and found both the drugs were comparable. In a subsequent study on one hundred children aged 1–12 years undergoing elective surgery, the author showed that 62% of the children who received 1µg/kg intranasal dexmedetomidine had satisfactory sedation at the time of intravenous cannulation.[28] Another study compared a higher dose of intranasal dexmedetomidine (2µg/kg) to oral midazolam (0.5mg/kg), which was administered 30–45 min before the surgery in children aged 1–18 years, and reported that both drugs were comparable in their sedation conditions at the time of anaesthesia induction.[51]

Recently, Akin et al.[34] conducted a study comparing intranasal dexmedetomidine and midazolam on children, aged between 2 and 9, undergoing elective adenotonsillectomy. Doses similar to that utilized in our study were utilized and administered approximately 45–60 min before the induction of anaesthesia. They reported that there was no evidence of a difference between the groups in either sedation score (P = 0.36) or anxiety score (P = 0.56) upon separation from parents.

Many authors have evaluated behaviour of the child while entering operation theatre and quality of mask acceptance.[34,35,49] We assessed acceptance of mask and behaviour under sedation. Sheta et al from a study conducted to compare midazolam and dexmedetomidine for premedication in children undergoing complete dental rehabilitation[35] observed that children in dexmedetomidine group were significantly more sedated and had satisfactory compliance with mask application[80.6% in dexmedetomidine group and 58.3% in midazolam group (P = 0.035)].

Faritus et al studied the effect of dexmedetomidine and midazolam on 60 children[52] and showed a better effect on the mask acceptance behaviour (mean mask acceptance score 2.58 ± 0.6 and 1.6 ± 0.67 for midazolam and dexmedetomidine, respectively; P< 0.05). Singla et al from a study[36] observed that Intranasal dexmedetomidine (1µg/kg) when used as premedication resulted in statistically significant parental separation and mask acceptance scores compared with midazolam. Our results show that the mean mask acceptance scores (MAS) at the time of induction in 1µg/kg intranasal dexmedetomidine group was 1.7 $\pm$ 0.59 when compared to 2.1 $\pm$ 0.58 in 0.2 mg/kg intranasal midazolam group which is statistically significant(P= 0.020). Hence we found that intranasal dexmedetomidine provides better mask acceptance score than intranasal midazolam in children.

Anaesthesia given was caudal epidural anaesthesia and patients were maintained with O_2 + N_2O using face mask in all children. We monitored Heart rate and peripheral Oxygen Saturation (SpO_2) till the end of surgery to assess effects of drugs on haemodynamics, and to monitor any adverse effects.

In our study we found that pre-procedure mean heart rate was comparable in both the groups with no statistically significant difference between the groups. Dexmedetomidine is known to decrease sympathetic outflow and circulating catecholamine levels and therefore would cause a decrease in heart rate. In a pharmacokinetic study of intravenous dexmedetomidine in children, it was shown that 0.66 to 1µg/kg IV dexmedetomidine, given over 10 min produced a significant reduction of HR > 15% compared with baseline.[52]

In our study heart rate was decreased by 2% from baseline at 10 min and 9.1% from baseline at 30 min after intranasal dexmedetomidine premedication. Similarly

heart rate was decreased by 8.8% from baseline at 30 mins after intranasal midazolam premedication. In a comparative study of intranasal dexmedetomidine with oral midazolam by Yuen et al, heart rate was decreased by 11.1% and 16.4% from baseline in patients who received 0.5 and 1µg/kg intranasal dexmedetomidine respectively during the first hour after the administration of the drug. However, these effects were clinically insignificant, and no intervention was required.[27] The study didn't mention heart rate variability in midazolam group. In another similar comparative study by Akin et al, reduction in heart rate of 6.7% from baseline in the intranasal dexmedetomidine and 7% from baseline in the intranasal midazolam group was noted.[34]

Sundaram et al, found 14.7% decrease in heart rate from base line only after 60 min of drug administration but by this time all our patients were shifted to OR.[32] Singla et al found Intranasal dexmedetomidine (1µg/kg) premedication resulted in statistically significant lower heart rate and blood pressure at 10, 20, and 30 minutes following administration compared with intranasal midazolam (0.2mg/kg) but it was clinically unimportant, which was similar to our study at 25,30,35 min.[36]

Hemodynamic disturbances, such as conduction abnormalities, bradycardia and severe hypotension were not observed in the children in our study who received 1µg/kg of intranasal dexmedetomidine. This finding demonstrates the safety of intranasal dexmedetomidine administration and is in accordance with the findings of several other studies that utilized the same dose[35], as well as with the findings in some studies that used higher doses of intranasal dexmedetomidine (2µg/kg).[51]

Dexmedetomidine has caused cardiovascular complications, including hypotension and bradycardia, in some adults and children. However, these

complications occurred in dissimilar situations and with different routes of administration.[54,55]

There was no evidence of oxygen desaturation, respiratory depression or apnea in our study which was similar to the study done by Singla et al on 60 children 3 to 10 years of age, which indicates that the doses used for both intranasally administered midazolam and dexmedetomidine are safe and comparable to the findings of other studies.[27,15]

In our study the baseline mean SpO_2 was 99.1% in midazolam group which was comparable to 99.2% in dexmedetomidine and the difference was not statistically significant. No significant change was observed among both groups till the end of 30 minutes. None of the patients in both groups had SpO_2 less than 95% at any point of time during preprocedural monitoring. Similarly in two comparative studies between intranasal dexmedetomidine and intranasal midazolam (Sundaram et al, Akin et al) SpO_2% was comparable and none of the patients had SpO_2< 95% at any point of time.[32,34]

In our study, from induction to the end of surgery, intra procedural heart rate in dexmedetomidine group was lesser compared to midazolam group. At induction mean heart rate was 90.8 $\pm$ 9.4 in dexmedetomidine compared to 95.4 $\pm$ 10.10 in midazolam group. From 30min to 60min the intra operative heart rate was significantly lower($P<0.05$) in dexmedetomidine group when compared to midazolam group. Intra procedural oxygen saturation was also comparable in both the groups and none of the patients in both groups had SpO_2 less than 98% at any point of time during intra procedural monitoring.

During the entire study we did not come across any significant side effects like nausea and vomiting. Similar findings regarding side effects were noted in other studies.[27,35] Nasal irritation and stinging along with paradoxical reactions like restlessness, euphoria are a major disadvantage of the intranasal administration of midazolam and these unwanted side effects have been reported in children in several studies.[56,57]

On the other hand, dexmedetomidine does not cause any transient nasal burning or irritation, paradoxical reactions, hiccups, respiratory depression. It acts on locus ceruleus and produces an unusually cooperative form of sedation in which the patient is calmly and easily roused from sleep to wakefulness and then quickly back to sleep when not stimulated, hence similar to natural sleep. Our study did not specifically address the issues of the patient acceptance of the drug. In a study done by Sundaram et al comparing intranasal midazolam and intranasal dexmedetomidine, seven children receiving midazolam were noted to become euphoric or restless after premedication, but none after dexmedetomidine.[32]

In our study we found that intranasal dexmedetomidine provides more successful parental separation, better sedation level for mask acceptance at the time of induction of anaesthesia, better preprocedural and intra procedural haemodynamic stability, when compared to intranasal midazolam 0.2mg/kg as premedication with negligible side effects.

CONCLUSION

We conclude that intranasal dexmedetomidine 1µg/kg is an effective and safe alternative for premedication in children undergoing lower abdominal surgeries under caudal epidural anaesthesia and it resulted in lower anxiety levels, allowed better parent separation and resulted in better mask acceptance at the time of induction when compared with intranasal midazolam 0.2mg/kg without causing much side effects or post-operative complications.

SUMMARY

In this prospective randomised controlled trial, 60 ASA grade I and II children were randomly divided into two equal groups of 30 each. After obtaining written and informed consent group D received 1µg/kg intranasal dexmedetomidine and group M received 0.2 mg/kg intranasal midazolam using 1ml tuberculin syringe with atomiser. The parental separation anxiety was assessed while shifting the patient to operating room and mask acceptance was assessed by the attending anaesthesiologist in operating room who was blinded to the drug given.

Demographic characteristics were comparable in both groups. The mean parental separation anxiety scale(PSAS) was 1.2 $\pm$ 0.40 in dexmedetomidine group and 1.6 $\pm$ 0.56 in midazolam group which is statistically significant (P= 0.003). The mean mask acceptance scores (MAS) at the time of induction was 1.7 $\pm$ 0.59 in dexmedetomidine group and 2.1 $\pm$ 0.58 in midazolam group which is statistically significant(P=0.020). The haemodynamic changes and oxygen saturation during the study period was comparable between the groups without any adverse events. Hence we conclude that intranasal dexmedetomidine 1µg/kg is an effective and safe alternative for premedication in children and it results in lower anxiety levels, allows better parent separation and better mask acceptance at the time of induction when compared with intranasal midazolam 0.2mg/kg without causing much side effects and complications.

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ANNEXURE-I - INFORMED CONSENT

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you to enroll your ward in study titled **"Comparative Evaluation of Intranasal Dexmedetomidine and Intranasal Midazolam for Premedication in Children undergoing Anaesthesia. A One year Double Blind Randomised Controlled Trial",** conducted by Dr. _____, Post Graduate in M.D. Anaesthesiology under the guidance of Dr. _____ .Professor, Department of Anaesthesiology, J.N. Medical College, Belagavi under KLE University, Belagavi.

Respected Sir/Madam We request you to enroll your ward to participate in our study as your ward is eligible for participating in the study. During the study you will be asked some questions regarding your ward's present complaint and you are supposed to answer to the best of your knowledge.

Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J.N.Medical College. If you decide to participate you are free to withdraw at any time.

Purpose of the study:

The purpose of research is to know whether intranasal dexmedetomidine is as effective as intranasal midazolam for premedication in children to reduce the stress and fear of treatment as well as to ease child-parent separation anxiety and promote a smooth induction of anaesthesia.

Procedure Involved:

If you agree to enroll your ward in my study, I will ask your ward's present past and family history. Then your ward will be clinically examined in detail and routine investigations like Hb, CT and BT will be done. Your ward will be allotted into one of the two groups randomly using computer generated software. One group will receive 0.2mg/kg intranasal midazolam (up to a maximum 5 mg) using 1ml tuberculin syringe with atomiser and the other group will receive 1µg/kg dexmedetomidine intranasally using 1ml tuberculin syringe with atomiser. This will be a double blinded procedure, neither you nor I will know as to which group your ward have been allotted to.

Risks:

There is almost no risk involved with use of 0.2mg/kg intranasal midazolam or 1µg /kg dexmedetomidine intranasally.

Benefits:

To alleviate the stress and fear of treatment as well as to ease child-parent separation anxiety and promote a smooth induction of anaesthesia. Intranasal administration is relatively easy and with high bioavailability than oral route.

Midazolam is the most commonly used drug for this purpose till now. Midazolam may not be the most suitable preoperative sedative and anxiolytic in all children and in all circumstances.

Clonidine, an α-2 agonist, has been suggested as an alternative. Dexmedetomidine is a more α-2 agonist with favorable pharmacokinetic properties than clonidine.

Voluntary Participation/Withdrawal: Taking part in the study is voluntary. You may choose not to enroll your ward in this study. Your decision will not change present or future health care services offered to you or your ward at K.L.E. hospital.

Alternatives: Even if you decline the participation in the study, your ward will get the routine line of management.

Privacy and Confidentiality: The only people to know that your ward is a research subject is you and members of the research team. No information about you, your ward or information provided by you during the research will be disclosed to others without your written permission except:

1. In emergency to protect your rights and welfare.
2. If required by law.

Authorization to Publish Results: When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with your identity remaining confidential.

Financial Incentives for participation: No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

Compensation: In the event of injury related to the study, treatment will be made available through KLES Hospital and MRC, Belagavi. There is no compensation or payment for such medical treatment by law. If your ward is injured you may contact Dr. _____at Department of Anaesthesiology, KLES Hospital and MRC.

Questions: In case you have any questions related to the study, in future or in case of study related injury or illness, you can contact Dr. _____Department of Anaesthesiology, KLES Hospital and MRC, Belagavi. Dr. _____ Professor, Dept. Of Anaesthesiology, KLES Hospital and MRC, Belagavi.

If you have any queries about your rights as a study subject, you may call Dr. _____, Professor, Department of Pathology and Chairman, J.N. Medical College Institutional Ethical Committee for Human Subjects Research, Phone number- _____, or extension 4052 at J.N. Medical College, Belagavi.

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

"COMPARATIVE EVALUATION OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN UNDERGOING ANAESTHESIA". A ONE YEAR DOUBLE BLIND RANDOMISED CONTROLLED TRAIL.

I, Mr/Ms/Mrs _____ voluntarily agree for the participation of my ward as a subject of study. By signing this consent form I am not giving up any of my legal rights, I may withdraw my ward from the study anytime. I am signing the consent form after having read or been read for me in vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name : _____

Parent/Guardian Name: _____

Signature or the Left Thumb Print of Subjects Parent/Guardian: _____

Date:

Witness Name:_____ Signature:_____

Investigators Name: _____ Signature:_____

Date:

Place : _____.

ANNEXURE-II - PROFORMA

"COMPARATIVE EVALUATION OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN UNDERGOING ANAESTHESIA". A ONE YEAR DOUBLE BLIND RANDOMISED CONTROLLED TRAIL.

Name & Address of the patient: _____

_____

_____

_____.

Age of the Patient: _____ IP. No: _____

Weight of Patient: _____ Sex: _____

Anaesthesiologist: _____ Surgeon: _____

PREANAESTHETIC EVALUATION:

Chief Complaints:

Past History:

History of Diabetes Mellitus/Hypertension/Asthma/Tuberculosis

Drug Therapy:

Previous Anaesthetic procedure/Previous surgeries:

History of renal disease, hepatic disease and neurological diseases.

Family History:

General Physical Examination:

Weight: Height: Pallor:

Cyanosis: Pedal Oedema: Clubbing:

Vitals:

Pulse : B.P: R.R: Temperature:

Airway Assessment:

Teeth:

Jaw Movements: M.P. Grading:

SYSTEMIC EXAMINATION:

Cardiovascular System:

Respiratory System:

Per Abdomen:

Central Nervous system:

Spine assessment:

INVESTIGATIONS:

Hb%: CT: BT: Other:

ASA STATUS: Grade 1 / 2

Diagnosis:

Proposed Surgery:

Inclusion Criteria:

1. ASA physical status I and II.
2. Age between 1 to 10 years.
3. Patients undergoing lower abdominal and lower limb surgeries under caudal epidural anaesthesia with sedation.

Exclusion Criteria:

1. Known allergy or hypersensitive reaction to dexmedetomidine or midazolam,
2. Cardiac arrhythmia
3. Congenital heart disease,
4. Mental retardation.

Methodology: After obtaining the approval of the Ethical committee and written informed consent, children were premedicated in pre-operative holding area in presence of parent. Intranasal drug was sprayed into both nostrils using 1ml tuberculin syringe with atomiser with child in recumbent position 45 to 60 min before shifting the patient to operating room(O.R.)

Base line heart rate and SpO_2 were noted and are monitored every 5min after administration until patient is transferred to operating room.

The parental separation anxiety was assessed while shifting the patient to O.R. and mask acceptance was assessed by the attending anaesthesiologist in O.R. who is blinded to the drug given.

Parental separation anxiety was assessed using the parental separation anxiety scale(PSAS), which is a 4 point scale

1- Easy separation

2- Whimpers but easily reassured

3- Cries and cannot be easily reassured but not clinging to parents

4- Crying and clinging to parents

A PSAS score of 1 or 2 is classified as an acceptable separation, score of 3 or 4 are considered as difficult separation.

The subject's ability to accept the anaesthesia mask was measured using mask acceptance scale (MAS).

1- Excellent (unafraid, cooperative, accept mask readily).

2- Good (slight fear of mask, easily reassured).

3- Fair (moderate fear of mask, not calmed with reassurance).

4- Poor (terrified, crying or combative).

Subjects with score of 1 or 2 were considered as satisfactory acceptance of mask, scores of 3 or 4 are considered unsatisfactory.

Further the monitors were attached and patient was induced using inhalational agents and I.V. cannula secured. After induction all patients received caudal epidural anaesthesia using a 24G needle and 1ml/kg body weight of 0.25% bupivacaine patient maintained with O_2 + N_2O using face mask. The vital parameters were noted till the end of procedure.

Observations:

Readings were recorded in the following manner:

Preoperative SpO_2 and HR:

IP no:	**SpO_2 :**	**HR :**
0 min		
5 min		
10 min		
15 min		
20 min		
25 min		
30 min		
35 min		
40 min		
45 min		
50 min		
55 min		
60 min		

PARENT SEPARATION ANXIETY SCALE :	**MASK ACCEPTANCE SCALE :**

Intraoperative SpO_2 and HR:

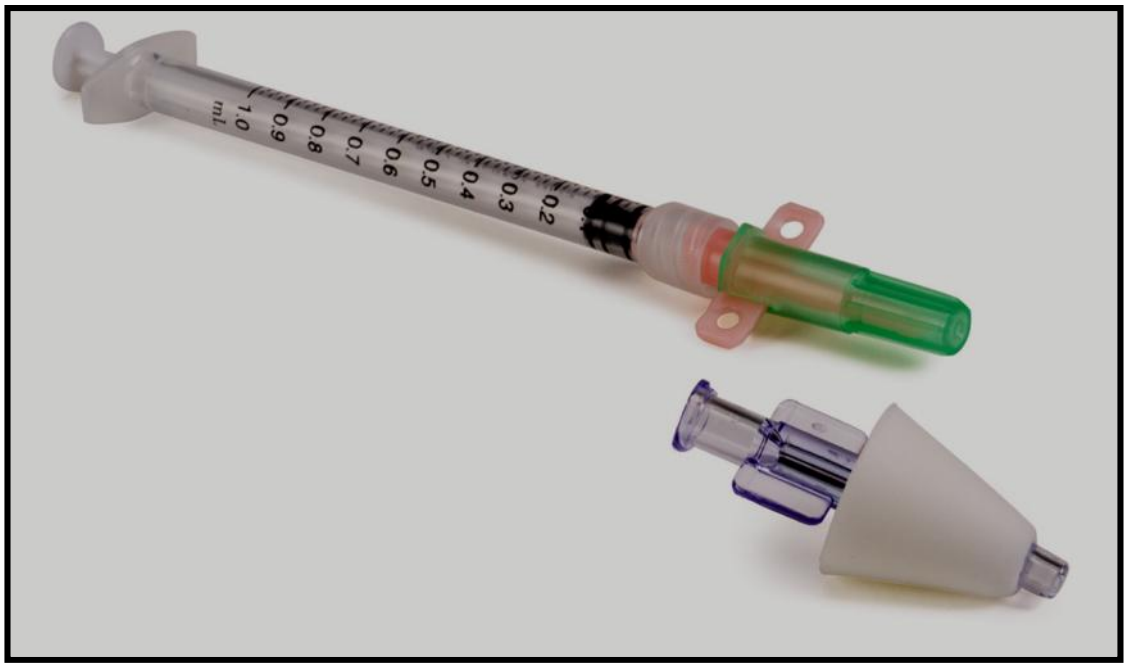
IP no:	**SpO_2 :**	**HR :**
0 min		
10 min		
20 min		
30 min		
40 min		
50 min		
60 min		
70 min		
80 min		
90 min		
100 min		
110 min		
120 min		

Side effects: Signature:

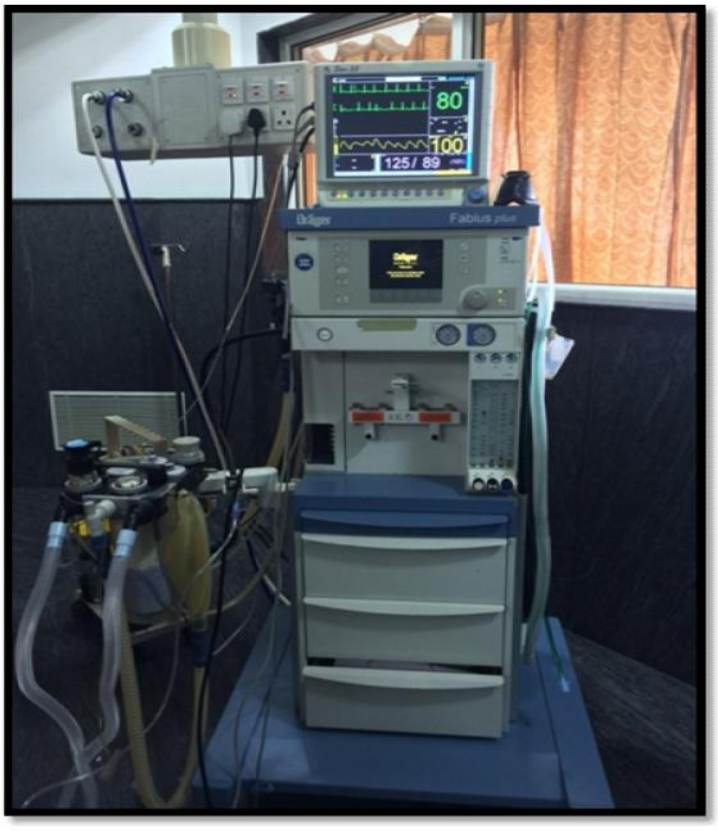
ANNEXURE III – PHOTOGRAPHS

Photograph :1. Dexmedetomidine ampule

Photograph :2. Midazolam ampule

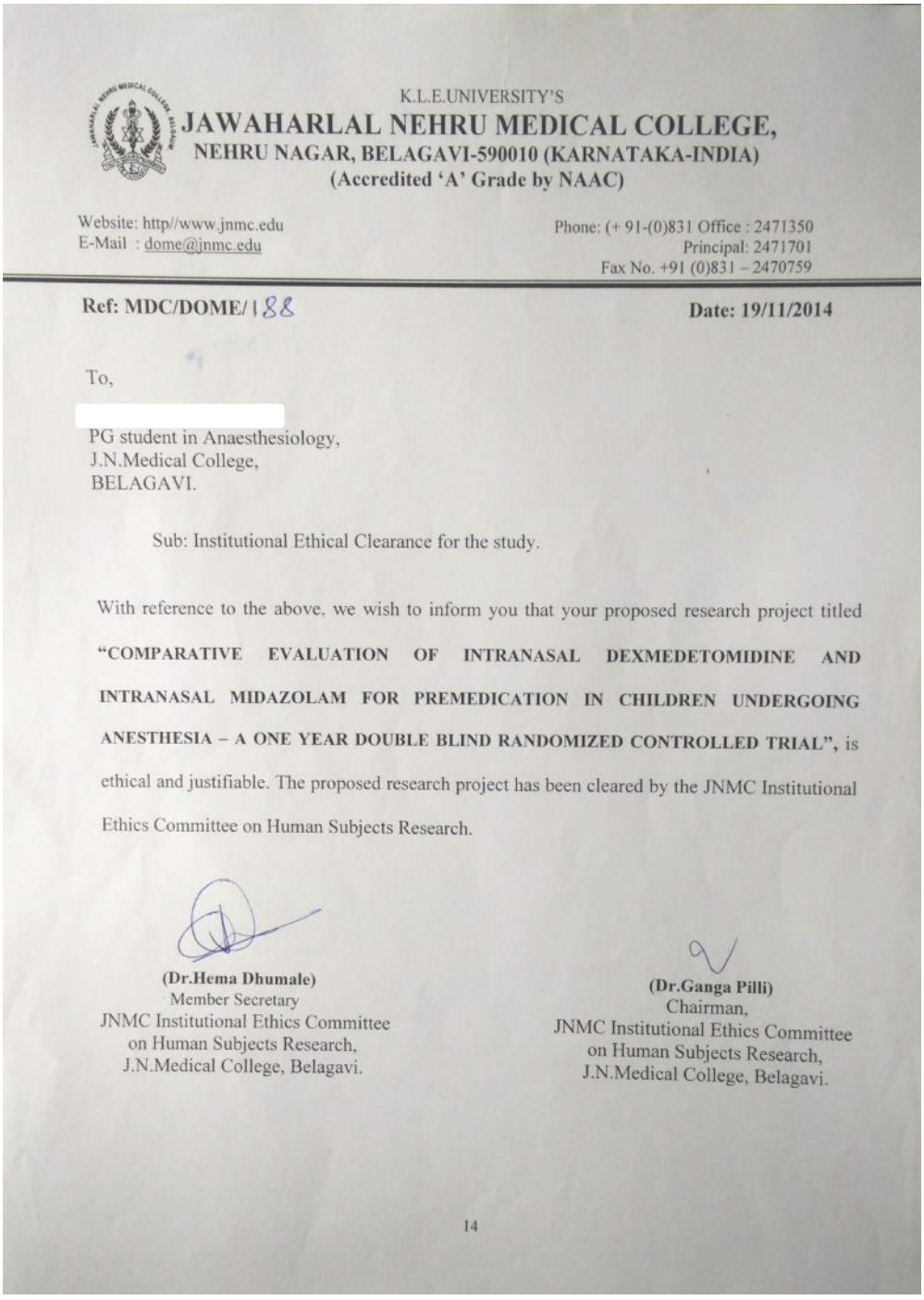


Photograph :3. Tuberculin syringe with atomiser



Photograph :4. Anaesthesia work station

ANNEXURE IV – ETHICAL COMMITTEE CLEARANCE CERTIFICATE



K.L.E.UNIVERSITY'S

JAWAHARLAL NEHRU MEDICAL COLLEGE,

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Ref: MDC/DOME/188 **Date: 19/11/2014**

To,

PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARATIVE EVALUATION OF INTRANASAL DEXMEDETOMIDINE AND INTRANASAL MIDAZOLAM FOR PREMEDICATION IN CHILDREN UNDERGOING ANESTHESIA – A ONE YEAR DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

(Dr.Hema Dhumale)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr.Ganga Pilli)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

14