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Intranasal Dexmedetomidine Versus Oral Midazolam As Premedication In Anaesthesia In Children.

Purushotham R*, Devanand J, and Selvamani.

[1]Postgraduate, Dept of Anesthesiology, Sree Balaji Medical College & Hospital, Chennai, India.
[2]Postgraduate, Sree Balaji Medical College & Hospital,Chennai, India.
[3]Professor, Head of the Department, Sree Balaji Medical College & Hospital, Chennai, India.

ABSTRACT

In preanaesthetic days, substances like opium and wine were offered to the patient to minimize the fear of surgery. It was Claude Bernard who observed the smooth induction of anaesthesia with chloroform byusingmorphine as premedication. Mere thought of surgery itself produces stress to patients of any age and it is nevertheless for children. Hence premedication isessential for children undergoing surgery.
Keywords: Midazolam, dexmedetomidine, premedication, paediatric.

Corresponding author

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INTRODUCTION

In paediatric anaesthesia, Midazolam is commonly used preanaesthetic medication but in recent years, Dexmedetomidine an alpha-2 agonists has emerged as an alternative.

A number of clinical trials have been conducted to identify efficacy of dexmedetomidine versus midazolam. But consensus has not been achieved on which agent is superior to the other in terms of the overall benefit to patients. Therefore this study was conducted to compare the efficacy of Midazolam and Dexmedetomidine.

AIMS AND OBJECTIVES

To compare the efficacy & clinical effects of intranasal dexmedetomidine and oral midazolam as a preanaesthetic medication in children undergoing minor elective surgery.

REVIEW OF LITERATURE

The term premedication was first used in the 1920s. Administration of drugs before the induction and maintenance of anaesthesia is referred as preanaestheticmedication[2].

Aims[3,4,5] of Premedication are

- reduce anxiety and fear
- induce amnesia, sedation and analgesia
- facilitate rapid and smooth induction of anaesthesia
- reduce salivary and respiratory tract secretions
- reduce the volume of gastric contents and raise the pH for prevention of aspiration pneumonitis.
- minimize the undesirable adverse effects of anaesthetic agents and surgical procedures
-attenuate the sympathetic nervous system reflex activities.
- reduce the requirement of anaesthetic agents
- reduce the awareness during light anaesthesia
- protect the patient against the toxic effects of anaesthesia.

Properties of an ideal premedicantdrugs :

- fulfill the aims of premedication
- easy and safe to administer
- short duration of recovery from anaesthesia
- should not produce undue depression of cardiovascular,respiratory and central nervous systems.

Various routes of administration of premedication :

1) Intramuscular administration e.g. opioids, benzodiazepines, anticholinergics, H2 blockers
2) Intravenous administration e.g. opioids, benzodiazepines, anticholinergics, antiemetics
3) Oral administration e.g. clonidine, midazolam, triclofos, ketamine
4) Intra nasal administration e.gmidazolam, ketamine, sufentanil
5) Rectal eg. Methohexital, thiopentone sodium
6) Transmucosal administration eg Midazolam, transmucosalfentanyl citrate

Choice of premedicant drugs depends on the following factors.

1. Patient, age, body weight, physical condition, psychological status.
2. Proposed Surgery: Nature of procedure, site of surgery, posture during surgery and duration of surgery.
3. Availability of preoperative and post operative nursing care
4. Surgical and anaesthetic management available.

Commonly used routes of administration of premedication drugs are intravenous, intramuscular and oral.

Oral premedication has advantages of ease of administration, convenient to routinely use, economical and very safe. But has the disadvantages like slow onset of action, variable bioavailability, GIupset.This route cannot be employed in an unconscious patient and uncooperative patient.

Drug sensitivity is increased in conditions like adrenocortical, thyroid and pituitary insufficiency, hepatic or renal dysfunction and myasthenia gravis. Porphyria is a special condition in which barbiturates cause acute exacerbation resulting in abdominal pain, vomiting, haematuria, paralysis and even respiratory failure.

Premedication in children:

The goal of the premedication in pediatric surgery is the safe induction of anaesthesia with minimum stress and risk to the child. Factors to be addressed in children includes, increase in vagal activity, vomiting, aspiration, secretion, drug dosage and respiratory depression. The preanaesthetic medication and their routes of administration need to be individualized to the patient.

ANATOMY AND PHYSIOLOGY OF NASAL MUCOSA[7,8]

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

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

Nasal mucosal administration

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

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

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

PHARMACOLOGY OF DEXMEDETOMIDINE[8,9,10]

In 1960, alpha 2 adrenoceptor, clonidine was first synthesized as nasal decongestant. On its application, an unexpected adverse effect of prolonged sedation with cardiovascular depression was observed. Later, in 1999, FDA approved Dexmedetomidinefor use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit. It is used as a premedication, as an anesthetic adjunct for general and regional anesthesia, and as a postoperative sedative and analgesic.

Mechanisms of action

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α_2-adrenoceptor agonism. Inhibition of neuronal release, causing hypotension, bradycardia, sedation, and analgesia occurs with activation of the receptors in the brain

and spinal cord. On presynaptic activation of the $\alpha_2$adrenoceptor inhibits the release of norepinephrine, thereby terminating the propagation of pain signals. Postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Clinically, decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water; decreased intraocular pressure; and decreased insulin release are observed.

Combined, these effects can produce analgesia, sedation, and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multiagent therapies.One of the highest densities of α_2 receptors has been detected in the locus coeruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The hypnotic and sedative effects of α_2-adrenoceptor activation have been attributed to this site in the CNS. The locus coeruleus is also the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. In this region of the brain, α_2-adrenergic and opioidergic systems have common effector mechanisms, such that dexmedetomidine has a supraspinal site of action.

In addition to dexmedetomidine's action in the locus coeruleus of the brain stem, it has been shown to stimulate α_2 receptors directly in the spinal cord, thus inhibiting the firing of nociceptive neurons. The substantiagelatinosa of the dorsal horn of the spinal cord contains receptors which, when stimulated, inhibit the firing of nociceptive neurons stimulated by peripheral Aδ and C fibers and also inhibit the release of the nociceptive neurotransmitter substance P.

Pharmocokinetics

Dexmedetomidine undergoes almost complete biotransformation through direct glucuronidation and cytochrome P450 metabolism (hydroxylation, mediated by CYP2A6), all hepatic processes, with very little excretion of unchanged molecules in the urine (95%) or feces (5%). It shows dose dependent effect. Therefore, patients with liver faiure require dose reduction. The elimination half-life is approximately 2 hours.

Dexmedetomidine exhibits linear kinetics when infused in the recommended dose range of 0.2 to 0.7 µg/kg/hr for no more than 24 hours. The steady-state volume of distribution is 118 L, and the distribution phase is rapid, with a half-life of distribution of approximately 6 minutes.

The average protein binding of dexmedetomidine is 94%, with negligible protein binding displacement by fentanyl, ketorolac, theophylline, digoxin, and lidocaine, all drugs commonly used during anesthesia and in the ICU. There have been no significant sex- or age-based differences in the pharmocokinetic profile, even in elderly patients, and pharmacokinetics of the active dexmedetomidine molecule do not change in patients with renal failure.

Pharmacological actions:

Dosage [12,13] :
Intravenous -loading dose of 1 mcg/kg over 10 – 20 mins followed by a maintenance infusion in the range of 0.2 – 0.7 mcg/kg/hr. The rate of infusion can be increased in increments of 0.1mcg/kg/hr or higher.
Intramuscular – IM injection (2.5mcg/kg) of dexmedetomidine has been used for premedication.
Spinal – 0.1 – 0.2 mcg/kg
Epidural – 1- 2 mcg/kg
Peripheral nerve block – 1mcg/kg
Buccal – 1- 2 mcg/kg
Intranasal – 1 to 2 mcg/kg

Preoperative Effects

Because dexmedetomidine possesses anxiolytic, sedative, analgesic, and sympatholytic properties, it is useful adjunct for premedication, especially for patients susceptible to preoperative and perioperative stress.Dexmedetomidine attenuate sympathetic activation during induction of anesthesia and to provide a

more stable hemodynamic profile and was able to decrease oxygen consumption in the intraoperative period (up to 8%) and in the postoperative period (up to 17%). Dexmedetomidine potentiate the anesthetic effects of all intraoperativeanesthetics, regardless of method of administration.

Intraoperative Effects

Dexmedetomidine exerted anesthetic-sparing effects, increased hemodynamic stability, and reduced unwarranted responses to endotracheal intubation.

Opioid requirements in the intraoperative period and in the postanesthesia care unit (PACU) are reduced by dexmedetomidine .Dexmedetomidineadministration in patients allowed lower doses of anesthetics to be used, resulting in more rapid recovery from anesthesia and a reduced need for pain medication in the PACU, thereby reducing the length of stay.

Postoperative Effects

Thisα$_2$-adrenoceptor agonists is beneficial in the postoperative period because of itssympatholytic and analgesic effects without respiratory depression.All effects of dexmedetomidine could be antagonized easily by administering the α$_2$-adrenoceptor antagonist atipamezole, which reverses sedation and sympatholysis and has a half-life of 1.5 to 2 hours.

With dexmedetomidine, patients are able to return to their baseline level of consciousness when stimulated. It also provides intense analgesia during the postoperative period. Postoperative analgesic requirements were reduced by 50% in cardiac patients, and the need for rescue midazolam for sedation was diminished by 80%.

ADVERSE EFFECTS:

The adverse effects of dexmedetomidine include hypotension, hypertension, nausea, bradycardia, atrial fibrillation, and hypoxia. Overdose may cause first-degree or second-degree atrioventricular block. Most of the adverse events associated with dexmedetomidine use occur during or briefly after loading of the drug. By omitting or reducing the loading dose, adverse effects can be reduced.No study has described the long-term use of dexmedetomidine, but adaptive changes and withdrawal syndrome like those seen with the use of clonidine can be expected from dexmedetomidine.

Clinical utility[10]:

As Premedication:

Due to its sedative, anxiolytic, analgesic, sympatholytic and stable hemodynamics, Dexmedetomidine is used as premedication.

Intensive care unit sedation :

Dexmedetomidine is used for sedation during the initial intubation and mechanically ventilated patient in intensive care setting. Currently dexmedetomidine is approved by FDA for use in ICU not more than 24 hours. It is useful in postoperative patients as it decreases requirement of opiodsand high oxygen reqirements without or with minimal respiratory depression.

Procedural sedation :

It is indicated for sedation of non intubated patients prior to or during surgical and other procedures like transesophageal echocardiograph, colonoscopy, awake carotid endarterectomy, shockwave lithotripsy, vitreoretinal surgery, paediatric patients undergoing tonsillectomy.

As an adjuvant in local and regional techniques:

It is highly lipophilic, hence it is rapidly absorbed into CSF and binds at its site of action. It prolongs the duration of both sensory and motor blockade induced by local anaesthetics irrespective of route of administration. It enhances both central and peripheral neural blockade by local anaesthetics and has been used in regional anaesthesia.

- It produces controlled hypotension by its central and peripheral sympatholytic action
- Attenuates hemodynamic stress response to intubation and extubation by its sympatholytic property.
- It has anaesthetic sparing effect, when used intraoperatively in lower concentration. Tachycardia and incidence of myocardial ischemia is reduced. Therefore it can used during cardiac surgery [20, 23] and neurosurgery [19].
- It is a useful adjuvant in bariatric surgery and sleep apnea patients[21].
- High dose dexmedetomidine (3mcg/kg IV load over 10 mins with an infusion of 1 mcg/kg/hour) is used for sedation of children undergoing MRI[22].
- Awake intubation : for securing airway with fiberoptic intubation.
- It is used for sedation for monitored anaesthesia care in urology, gynecology cases and in burns, trauma patients.
- Postoperative analgesic requirements is drastically reduced with dexmedetomidine[17].
- It has opioid sparing effect and is used in treating cancer patients who are suffering from intractable pain, or delirium [18, 19].
- It is used in spine surgery, evoked potential study and head injury. It is also used in the management of tetanus and in treatment of alcohol and drug withdrawal.

PHARMACOLOGY OF MIDAZOLAM

It is the first clinically used water soluble benzodiazepine. Fryerand Walser synthesized it in 1976[13]. It was the first benzodiazepine that was produced primarily for use in anaesthesia[14].

Mechanism of action:

Midazolam, interaction with (GABA) a benzodiazepine receptor γ subunit,causes chloride channel opening which increases chloride ion conductance which causes hyperpolarization and therefore resistance to neuronal transmission.

Various effects of benzodiazepines is related to amount of receptor occupancy which corresponds to plasma concentration. If receptor occupancy is 20%, it causes anxiolysis . If receptor occupancy is 30-50%, it causes sedation. If receptor occupancy is > 60%, it causes unconsciousness.

Pharmacokinetics[15]:

Midazolam is extensively bound to plasma protein, about 95% bound to albumin. Its volume of distribution is 1.1 - 1.7 L/kg. Elimination half life is 1.7 - 2.6 hour. Clearance is 6.4 – 11 ml / kg / min.Plasma level required for hypnosis and amnesia during surgery is 100 – 200 ng/ml. Awakening usually occurs at a level lower than 50 ng/ml. Increased age and obesity prolong the elimination half life.It is rapidly absorbed from gastro intestinal tract and only 50% reached the circulation reflecting substantial hepatic first pass effect.In liver midazolam is biotransformed to 1 and 4 hydroxymidazolam by oxidative pathway by cytochronic P 450 (cyp 3A4 enzymes). These metabolites are active ones.The hydroxymidazolam is the principal metabolite and has half the activity of parent compound. But these are rapidly conjugated to glucuronic acid and excreted in urine more rapidly than midazolam. So there will be no prolongedsedation on single dose.

Pharmacological action:

Dosage:
Oral: 0.5 - 0.7 mg/kg
Rectum: 0.25 – 0.5 mg/kg
Intranasal: 0.2 – 0.5 mg / kg
Intramuscular: 0.05 – 0.15 mg/kg

Intravenous: 0.05 – 0.15 mg /kg
Sublingual: 0.1 mg / kg

Commonly used route is intravenous. Other available routes are intramuscular route for sedation, oral route for premedication, intranasal and rectal routes for premedication in children. Its time of onset is 15 – 30 mins and its action lasts for duration of about 45 – 90 mins.

Effect on Central nervous system:

Midazolam produces sedation, anxiolysis, anticonvulsant effect, muscle relaxation and unconsciousness. These effects are dose dependent according to percentage of receptor occupancy. It produces both anterograde and retrograde amnesia, dose related reduction in cerebral blood flow and CMRO2. Its cerebral protective effect is superior to diazepam but inferior to barbiturate. Cerebral vasomotor response to CO2 is preserved. It does not prevent increases in intracranial pressure following tracheal intubation. It's a potent anticonvulsant.

Effect on respiratory system:

Midazolam produces dose related ventilatory depression which is greater than with other benzodiazepines. It is more pronounced by intravenous route following fast administration along with opioids but insignificant when given through other routes (oral).Onset of respiratory depression is rapid within 3 minutes and the action lasts longer for even 60-120 minutes on intravenous administration.

Slope of ventilatory response curve to carbondioxide are flatter than normal.

Incidence of apnoea induction is similar as with thiopentone which is greater in old age, debilitated state, COPD patients and in presence of other respiratory depressants drugs.

Effect on cardiovascular system:

It decreases arterial pressure by decreasing systemic vascular resistance which is dose dependent and greater than with other benzodiazepines but similar to thiopentone.It produces variability in heart rate changes because it impairs baroreceptor and also decreases the vagal tone.

Effect on Fetus:

Midazolam has less placental transfer than other benzodiazepines but produces greater neonatal depression than thiopentone and propofol.

Drug interaction:

Erythromycin inhibits the metabolism of midazolam and causestwo to three fold prolongation and intensification of its effects.Antifungal agents like itraconazole,ketaconazole increases the serum concentration of midazolam. Calcium channel blockers inhibit cytochrome P450 enzymes leading to central nervous system depression. Clonidine inhibits metabolism of midazolam, but it is greater with diazepam than midazolam.

Ethanol, barbiturates and other central nervous system depressant drugs potentiate the sedative effects of midazolam. It reduces the minimum alveolar concentration of volatile agents as much as 30%. Hepatic clearance is inhibited by fentanyl

Hepatic clearance is 5 times greater than lorazepam and 10 times greater than diazepam.

ADVERSE EFFECTS :

Major side effect is respiratory depression, more common with fast intravenous route of administration along with opioids. Therefore it requires constant monitoring.

CLINICAL UTILITY[16]:

As Premedication :

Midazolam is an useful because of

- its various routes of administration
- its sedative anxiolyticamnestic action.
- useful in children, especially in the oral formulation, which was approved by the US food and drug administration in 1998, because of its easy administration, but it has bitter taste, which can be minimized by adding sugar solution.

As Intravenous sedation :

Midazolam is an effective intravenous sedative for therapeutic procedures and regional anaesthesia It is also useful in painless procedures like cardioversion and electroconvulsive therapy. Its advantages over other benzodiazepines are water solubility,less or no venous irritation, rapid onset, short duration and less postoperative sedation.

ForInduction and maintenance of anaesthesia :

It is the benzodiazepine of choice as an induction agent. Intravenous administration of midazolam in doses of 0.2 – 0.3 mg / kg over 30 – 60 sec will produce induction of anaesthesia which is 50-100% slower than with thiopentone.It is used to supplement opioids or inhaled anaesthetics during maintenance of anaesthesia. It reduces the anesthetic requirement of halothane by 30%.

Other Uses :

Paradoxical vocal cord motion (non organic upper airway obstruction &stridor) dose : 0.5 to 1 mg iv midazolam is an effective treatment.

Treatment of grandmal seizures which occurs with systemic toxicity due to local anaesthetics.

REVIEW OF LITERATURE

Corman et al[24] (1958) found about 80% patients were anxious using psychological questionnaire. Norris and Davis et al[25] (1967), observed that the anxiety level before anaesthesia is 40 – 60% in older children.

Lindgren, Saarnivaara, Himberg[26] (1980) conducted a pilot study with unpremedicated and premedicated children, observed the increased frequency of vaso-vagal attacks following lumbar puncture in unpremedicated children. The premedicated children showed better arterial oxygen saturationthan the unpremedicated children. They reported positive correlation between anxiolysis and ease of induction of anaesthesia

Male et al [26](1980), reported that premedication induced relief of apprehension reduces the hormonal and circulatory response to anaesthesia; thereby reducing the minimum effective dose of anaesthetic agents.

Finley et al [27](2006). Midazolam, though it is commonly used drug for premedication, it is not suitable in all circumstances especially in children with impulsive behavior.

Yuen et al[28] (2007), in a randomized, crossover evaluation of healthy adult volunteers, demonstrated that intranasal 1 & 1.5ug/kg dexmedetomidine produces sedation in 45 – 60 min and peaks in 90 – 105 min. In addition they observed only modest reduction in heart rate and arterial blood pressure. Also observed that there were no significant differences in parental separation acceptance, behavior score at induction and wake-

up behavior score. When compared with group M (midazolam), patients in group D (dexmedetomidine) 0.5 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 anesthesia when compared with group M (P = 0.016).

GhaliAM[29] (2011), observed intranasal dexmedetomidine to be a better choice for preanesthetic medication than oral midazolam in their study. Dexmedetomidine was associated with lower sedation levels, lower anxiety levels, and easier child-parent separation at the time of transferring patients to the operating room than children who received oral midazolam. Also noted that intranasal dexmedetomidine had better analgesic property than oral midazolam with discharge time from postanesthetic care unit similar to oral midazolam.

AL Sundaram et al [30](2011), observed that Children with 1ug/kg of intranasal dexmedetomidine attained more significant and satisfactory sedation at parental separation and at inductin of anaesthesia than those patients who received 0.2mg/kg of intranasal midazolam

Ambi US et al[31](2012), concluded that in an organized setting dexmedetomidine may be useful agent for sedation of children undergoing MRI studies. Use of meter-dozed Atomizer device or concurrent use of Benzodiazepines may enhance the success rate.

Mostafa et al [32](2013), found that dexmedetomidine group achieved a faster sedation score less than 3 at the point of 10 min, then all groups achieved a comparable sedation score till point of 25 min, both dexmedetomidine and midazolam groups had better sedation score than ketamine group at 30 min. Child–parents separation score grade 1 was noted significantly higher in dexmedetomidine group than midazolam and ketamine groups.

R. Adams (2013), systematically reviewed comparing the sedative qualities of dexmedetomidine and midazolam for adult patients. Concluded that overall, evidence for the sedative superiority of dexmedetomidine over midazolam is inconclusive.

Chuixian Zhou [35](2014), concluded the improved efficacy of dexmedetomidine or midazolam in premedication of sedation and analgesia.

Singla D et al [36](2015), observed intranasal dexmedetomidine (1 µg/kg) premedication resulted in statistically significant but clinically unimportant lower heart rate and blood pressure at 10, 20, and 30 minutes following administration compared with intranasal midazolam (0.2 mg/kg). They observed no episodes of hypotension or bradycardia. Children in group dexmedetomidine achieved better parental separation and mask acceptance scores compared with group Midazolam.

MATERIALS AND METHOD

This study was done to evaluate the efficacy of intranasal dexmedetomidine and oral midazolam as premedication in children. It is double blinded randomized study. This study was approved by the Institutional Ethical Committee. 60 patients who were taken up for surgeries at Sree Balaji Medical College & Hospital, Chennai, were studied during June 2014 – September 2016.

Inclusion criteria:

2 – 12 years old children of both genders
Posted for elective surgery
ASA I & II

Exclusion Criteria:

Less than 2yrs & above 12 years children
Posted for emergency surgeries
ASA III & IV

Children who refused to take the premedication or spit it out.
Children with nasal Infection or any nasal lesions
Patients on other sedative, neuroleptic drugs, barbiturates and other psychotrophic medications
Known allergy, or hypersensitivity reaction to dexmedetomidine or midazolam
History of CNS disorder or mental retardation

PREANAESTHETIC EVALUATION & PREPARATION

1. History
2. Clinical examination
3. Relevant investigations: Hb%, Urinalysis, Bleeding time,Clotting time, if needed blood urea, sugar, serum creatinine.

Written informed consent was obtained from the parents.All the children were kept nil oral for 4-6 hours prior to surgery .The sedation on the night before surgery was avoided.

Clinical study

The children were divided into two groups randomly as per premedication given

Group A: Intranasal dexmedetomidine 1 µg/kg body weight, 45 minutes prior to surgery. The dose was calculated and half of the dose was placed in each nostril with children in sitting position on their mothers' lap. Placing half the medication in each nostril reduced the volume while doubling the available area for absorption. Then the patient was kept in slightly head-down position for 2 minutes for easy absorption.

Group B: oral Midazolam 0.5mg/kg body weight in 10 ml apple juice 30 minutes before surgery. Any reaction to drug administration was evaluated.

Drugs were prepared by an unknown investigator; Observers and attending anaesthesiologists were blinded to the study in order to avoid bias.

Patient 'sblood pressure, heart rate, oxygen saturation was recorded at induction of aneasthesia. Sedation was assessed every 10 minutes with 6 point Modified observer's assessment of alertness / sedation scale. Scores 1, 2 was considered as good response, 3&4 as moderate response and 5 & 6 as mild response. Behavior assessed every 10 minutes with 4 point behavior scale; in which 1, 2 was considered as good response; score 2 & 3 as intermediate and 4 as inadequate or poor response to premedicated drug. Cooperation was assessed by acceptance of face mask and intravenous cannulation. Sedation and behavioural changes from parental separation to induction of anaesthesia was the primary end point. Secondary end point were hemodynamic changes, postoperative behavioral changes until the patient was shifted from post anaesthetic care unit.

Modified observer's assessment of alertness / sedation scale:

Score	Reaction
1	Does not respond to mild prodding or shaking
2	Responds only mild prodding or shaking
3	Responds only after name is called loudly
4	Lethargic response to name spoken in usual tone
5	Appear asleep but responds readily to name in usual tone
6	Appear alert and awake

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Behavior scores

Score	Reaction
1	Calm and cooperative
2	Anxious but reassurable
3	Anxious but not reassurable
4	Crying or resisting

In all children prior to induction preoxygenation was done for 3 minutes through face mask. The child's acceptance of mask was recorded. Mask acceptance score 1 as poor response; scores 2, 3 as intermediate response and scores of 4, 5 were regarded as successful response to premedication. Then intravenous cannulation was done and its response was recorded. Scores 1 was considered inadequate response, scores 2 & 3 as intermediate response to premedication whereas 4 scores as good response.

Mask acceptance:

Score	Reaction
1	Combative crying
2	Moderate fear of mask
3	Cooperative with assurance
4	Calm, cooperative
5.	Asleep

Reaction to intravenous cannulation :

Score	Reaction
1	Crying
2	Withdrawal of hand
3	Grimace
4	No response

After intravenous cannulation injection atropine 0.02 mg/kg was given intravenously and patient was induced with injection thiopentone 2.5% 5mg/kg followed by injection succinylcholine 2 mg / kg given to facilitate tracheal intubation. Patient was maintained with oxygen, nitrous oxide, analgesic and nondepolarizers. At the end of surgery neuromuscular blockade was reversed with injection neostigmine and injection atropine in titrated doses. Adverse effects like nasal irritation, nausea, vomiting, respiratory depression, laryngospasm or bronchospasm and other complications, in the perioperative period were noted.

After the surgery, the children were observed in the operating room for half an hour and then shifted to recovery room. Then the children's post operative agitation was assessed using the three point scale, in which score 3 was considered as satisfactory ; score 2 as intermediate and score 1 as unsatisfactory.

Post operative Agitation:

Score	Reaction
1	Agitated, crying
2	Crying but easily consoled
3	Calm or asleep

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Statistical Tools

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Statistical Programme for Scientific Student. Data was expressed in mean, standard deviation and standard error as numerical or percentage. To determine the differences within the groups and to compare the groups, tests of significance – chi square test &student 't' test was done. p value less than 0.05 was considered

OBSERVATION & RESULTS

This study was conducted in operation theatre complex, Department of Anaesthesiology, at Sree Balaji Medical College & Hospital, Chennai. The sample of 60 was taken for study. Test statistics used were Chi-Square test and't' test.The level of statistics significance was set up at $p < 0.05\%$

Demographic profile of the patients

Table 1: Age distribution comparison

Group	No. of patients	Mean (years)	Standard deviation	Standard error
Group A Intranasal dexnedetomidine	30	5.66	2.75	0.501
Group B Oral Midazolam	30	5.76	2.59	0.473

Significance of 't' test is 0.001. Significance of chi square is 0.073. p value is 0.787 (statistically insignificant). Hence Group A(Intranasal Dexmedetomidine) & Group B Oral (midazolam) are comparable.

Fig 1: Bar diagram of Age distribution in both groups

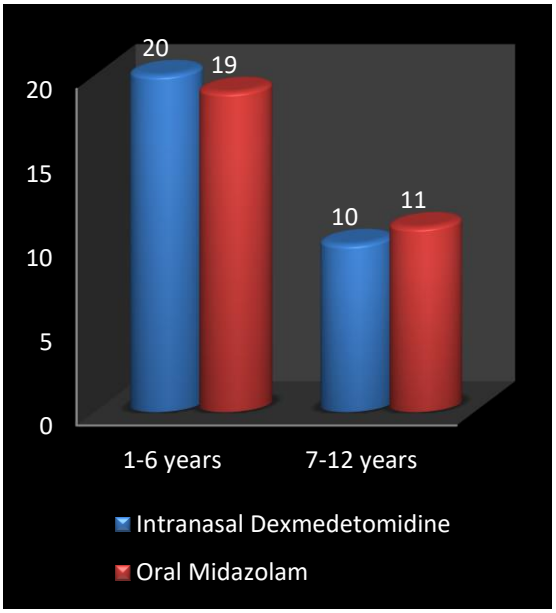

Table 2: Gender distribution comparison

GROUP	MALE	FEMALE	TOTAL
A (intranasal dexmedetomidine)	25	5	**30**
B (oral midazolam)	26	4	**30**
TOTAL	**51**	**9**	**60**

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Fig 2: Bar diagram of gender distribution

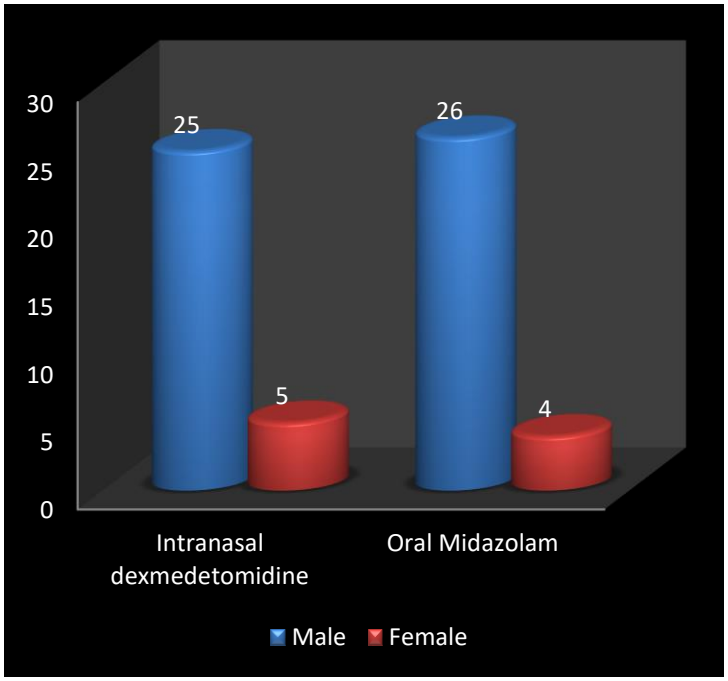

Table 3: Weight Distribution Comparison

Group	N	Mean	S.D.	Std Error Mean
A (intranasal dexmedetomidine)	30	16.00	2.67	0.487
B (oral midazolam)	30	16.34	3.20	0.584

Significance of 't' test is 0.438

Significance of chi square is 0.644. p value is 0.725 (statistically insignificant). Hence Group A (Intranasal Dexmedetomidine) & Group B Oral (midazolam) are comparable.

Fig 3: Bar diagram of weight distribution

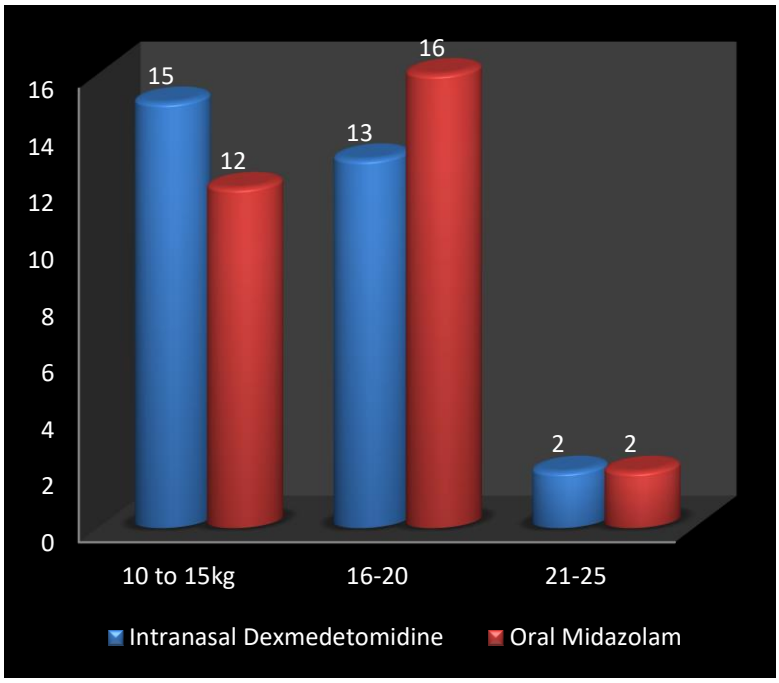

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Table 4: Types of surgery

SURGERY	Group A (intranasal dexmedetomidine)		Group B (oral midazolam)		Total	
Circumcision	1	4	1	5	**2**	**9**
Herniotomy	6		5		**1**	**1**
Orchidopexy	1		1		**2**	
Adenotonsillectomy	7		6		**1**	**3**
Tongue Tie Release	2		3		**5**	
TOTAL	**3**	**0**	**3**	**0**	**6**	**0**

Significance of chi square is 0.402. p value is 0.982(statistically insignificant). Hence Group A (Intranasal Dexmedetomidine) & Group B (Oral midazolam) are comparable by type of surgery

Table 5a: Comparison of Heart rate, systolic blood pressure & Oxygen saturation between Group A (Intranasal Dexmedetomidine) and Group B (Oral midazolam)

Groups	Group A (intranasal dexmedetomidine)			Group B (oral midazolam)		
	Statistical values	Baseline	OT	Statistical values	Baseline	OT
Heart rate	Mean	90.30	87.73	Mean	90.96	90.53
	S.D	3.58	5.41	S.D	2.95	2.80
	Standard error mean	0.654	0.988	Standard error mean	0.539	0.512
	P value	0.035 (statistically significant)		P value	0.562 (statistically insignificant)	
Systolic BP	Mean	94.8	94.2	Mean	93.86	93.20
	S.D	4.56	3.98	S.D	4.66	4.02
	Standard error mean	0.831	0.727	Standard error mean	0.852	0.734
	P value	0.589 (statistically insignificant)		P value	0.556 (statistically insignificant)	
O2 saturation	Mean	97.26	97.33	Mean	97.60	97.63
	S.D	1.68	1.49	S.D	1.49	1.32
	Standard error mean	0.307	0.273	Standard error mean	0.272	0.241
	P value	0.872 (statistically insignificant)		P value	0.928 (statistically insignificant)	

Table 5b: Comparison of Heart rate, systolic blood pressure & Oxygen saturation between Group A (Intranasal Dexmedetomidine) and Group B (Oral midazolam)

GROUP	Heart rate (beats/min)		Systolic Blood Pressure(mmHg)		Oxygen Saturation (%)	
	Baseline	At O.T	Baseline	At O.T	Baseline	At O.T
Group A (intranasal dexmedetomidine)	91 ± 6	86 ± 6	95 ± 7	94 ± 6	97 ± 3	96 ± 3
Group B (oral midazolam)	91 ± 5	90 ± 5	94 ± 7	93 ± 7	95 ± 5	94 ± 5

The baseline values of heart rate, systolic blood pressure & oxygen saturation were similar and iscomparable in both the groups. But while transferring to operation theatre, the heart rate of Group A(Intranasal dexmedetomidine) was significantly low on comparison with Group B(Oral midazolam). There was no statistically significant difference in systolic blood pressure and oxygen saturation between both groups on shifting to operation theatre.

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Fig 4: Sedation Score at 10 Minutes

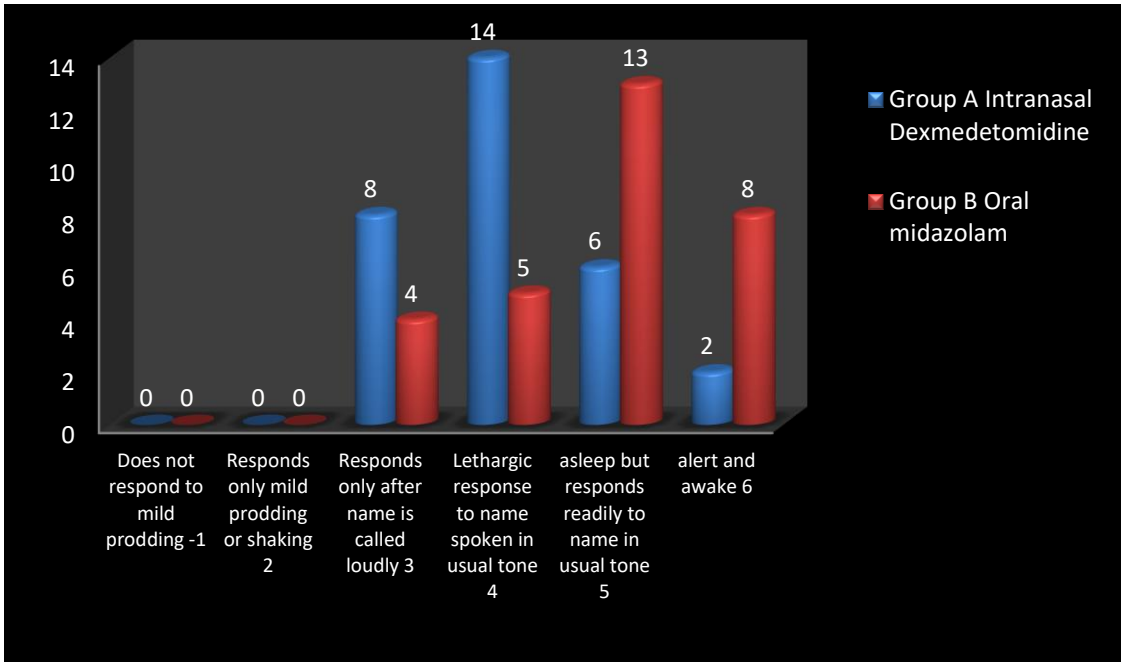

Table 6: Sedation Score at 10 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	4.06	0.868	0.158	3.181	0.002
Group B (oral midazolam)	30	4.83	0.985	0.179	3.181	0.002

The Chi – Square value is 11.75 ; p value is 0.0082(statistically significant)

Fig 5: Sedation Score at 20 Minutes

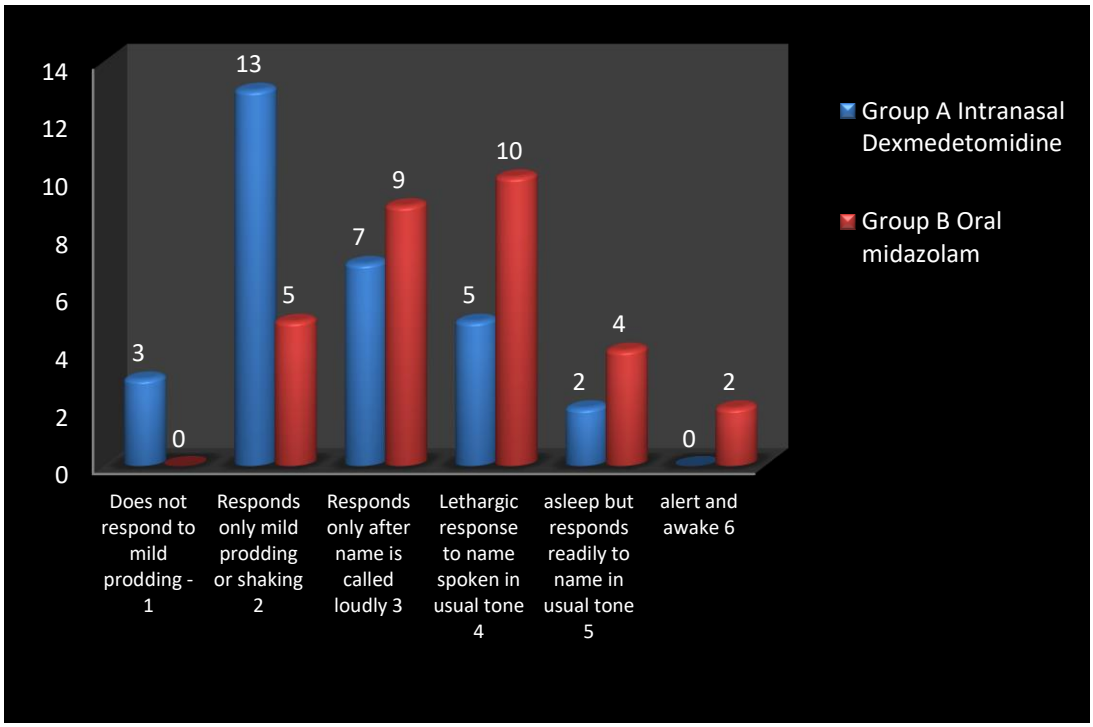

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Table 7: Sedation Score at 20 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	2.67	1.09	0.199	5.503	0.000
Group B (oral midazolam)	30	4.067	0.86	0.158	5.503	0.000

The Chi – Square value is 11.139; p value is 0.0487 (statistically significant)

Fig 6: Sedation Score at 30 Minutes

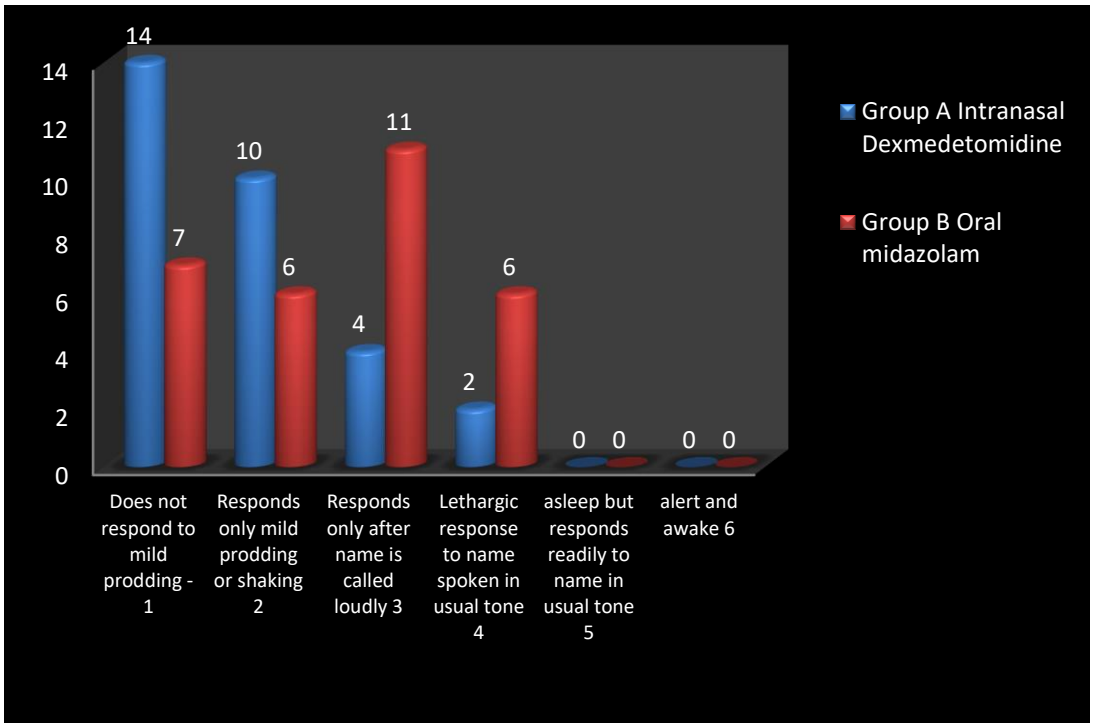

Table 8: Sedation Score at 30 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	1.80	0.924	0.196	2.82	.007
Group B (oral midazolam)	30	2.53	1.074	0.196	2.82	.007

The Chi – Square value is 8.6 ; p value is 0.0351 (statistically significant)

At 10, 20 , 30 minutes, Group A had faster onset of sedation than Group B.

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Fig 7 : Behaviour Score at 10 Minutes

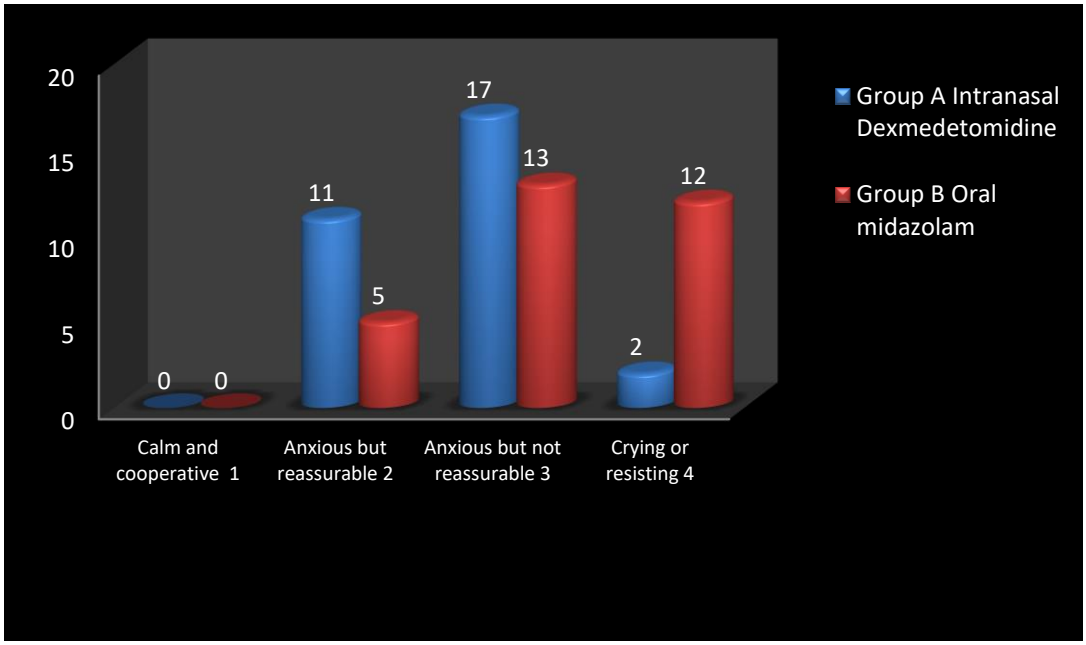

Table 9: Behaviour Score at 10 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	2.70	0.595	0.109	3.106	.003
Group B (oral midazolam)	30	3.23	0.728	0.133	3.106	.003

The Chi – Square value is 9.926 ; p value is 007 (statistically significant)

Fig 8: Behaviour Score at 20 Minutes

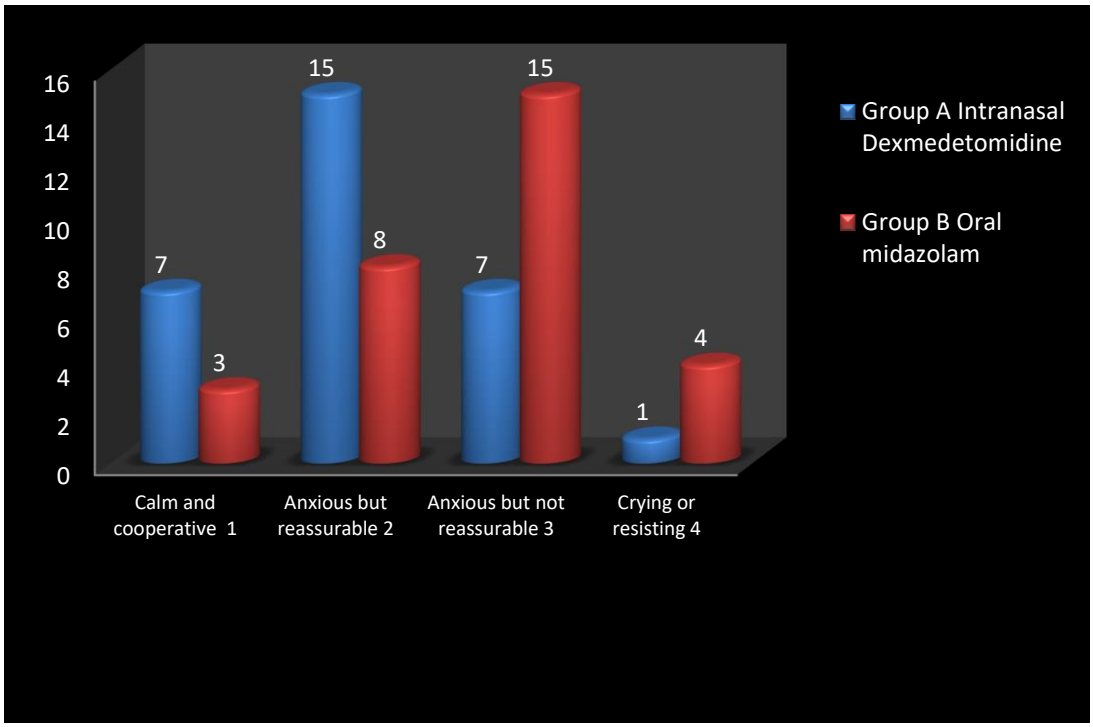

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Table 10: Behaviour Score at 20 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	2.06	0.78	0.143	2.85	0.006
Group B (oral midazolam)	30	2.66	0.84	0.154	2.85	0.006

The Chi – Square value is 7.878 ; p value is 0.0486 (statistically significant)

Fig 9: Behaviour Score at 30 Minutes

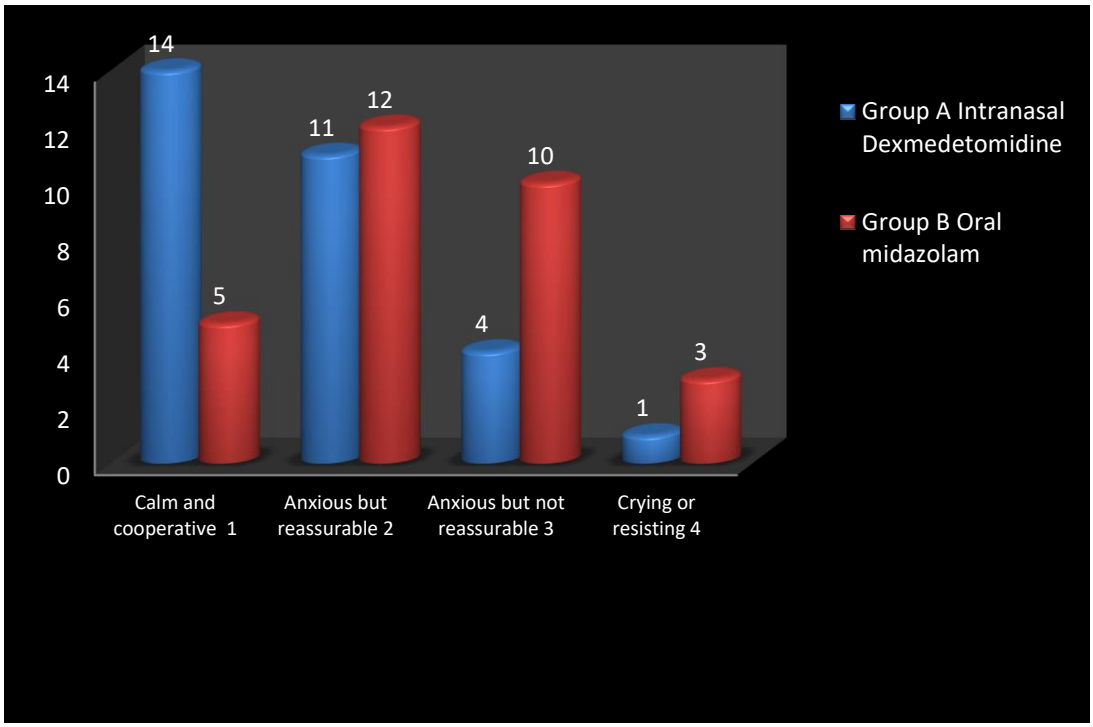

Table 11: Behaviour Score at 30 Minutes

GROUP	No	MEAN (mts)	S.D.	Std. Error. Mean	t	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	1.73	0.827	0.151	2.78	0.007
Group B (oral midazolam)	30	2.33	0.844	0.154	2.78	0.007

The Chi – Square value is 8.6 ; p value is 0.0351 (statistically significant)

At 10, 20, 30 minutes behavior score in Group A is better than Group B.

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Fig 10: Face mask acceptance score

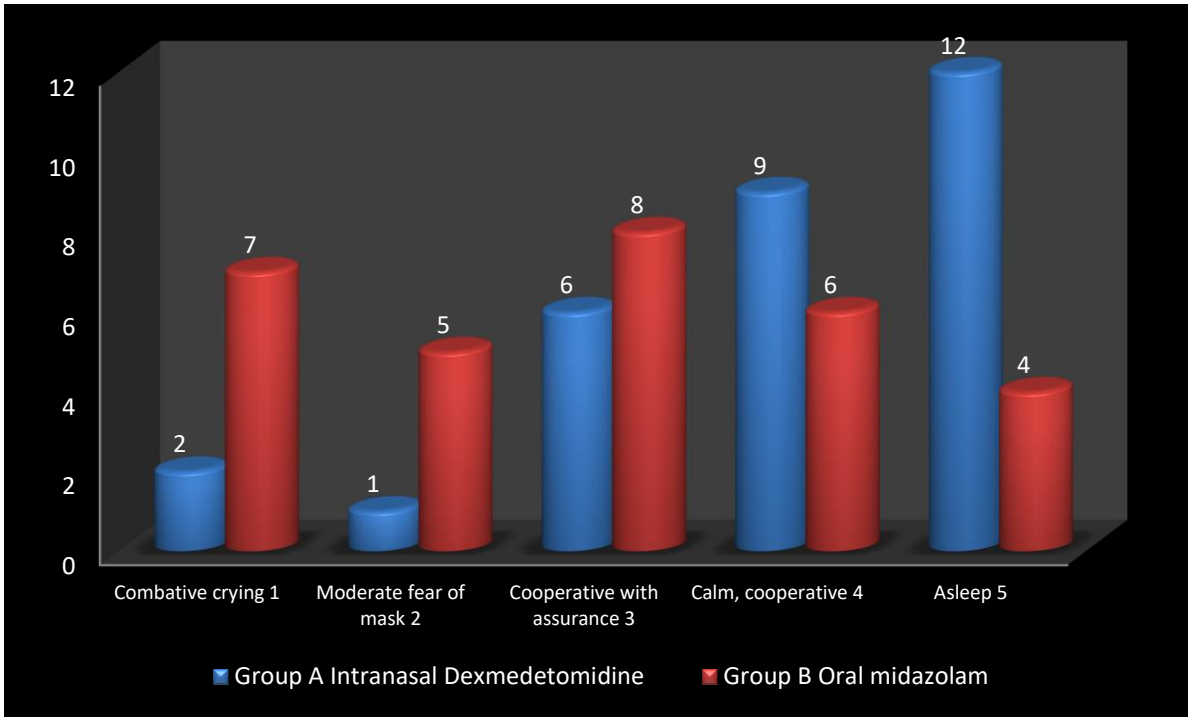

Table 12: Face mask acceptance score

GROUP	No	MEAN	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	3.93	1.172	0.214	3.3	0.001
Group B (oral midazolam)	30	2.83	1.36	0.249	3.3	0.001

The Chi – Square value is 10.3 ; p value is 0.0352 (statistically significant)
Group A showed better acceptance of face mask than Group B

Fig 11: Reaction to Intravenous canulation

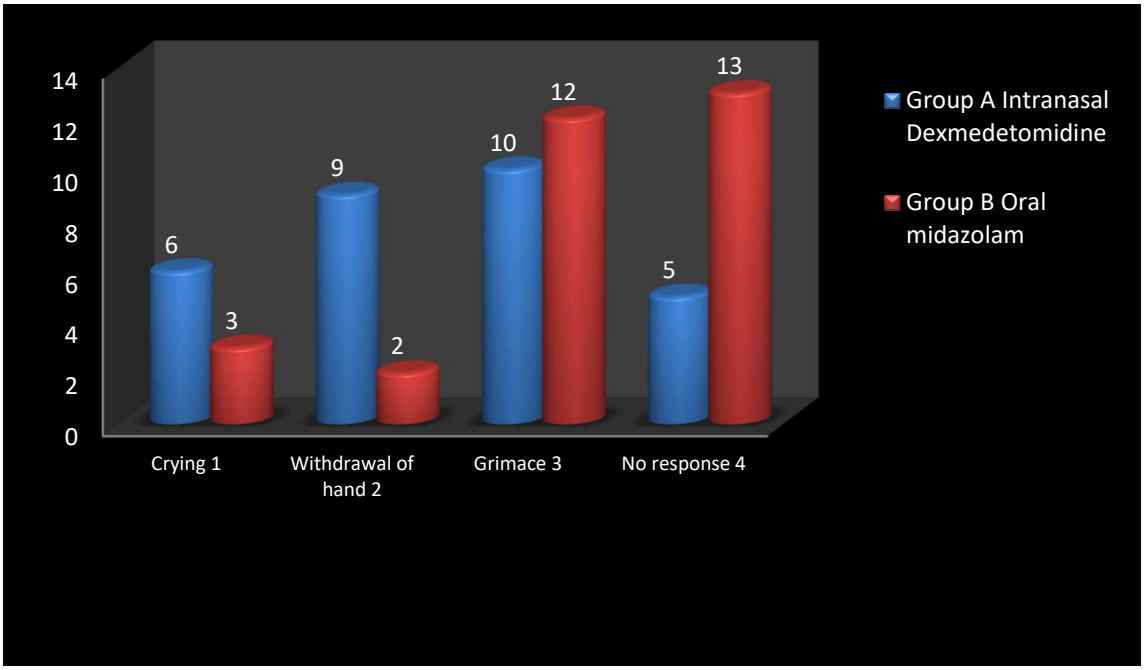

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Table 13: Reaction to Intravenous canulation

GROUP	No	MEAN	S.D.	Std. Error. Mean	t	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	3.16	0.949	0.173	2.78	0.007
Group B (oral midazolam)	30	2.46	1.008	0.184	2.78	0.007

The Chi – Square value is 9.192 ; p value is 0.0268 (statistically significant)

Group A showed better acceptance of intravenous cannulation than Group B.

Fig 12: Post operative agitation Score

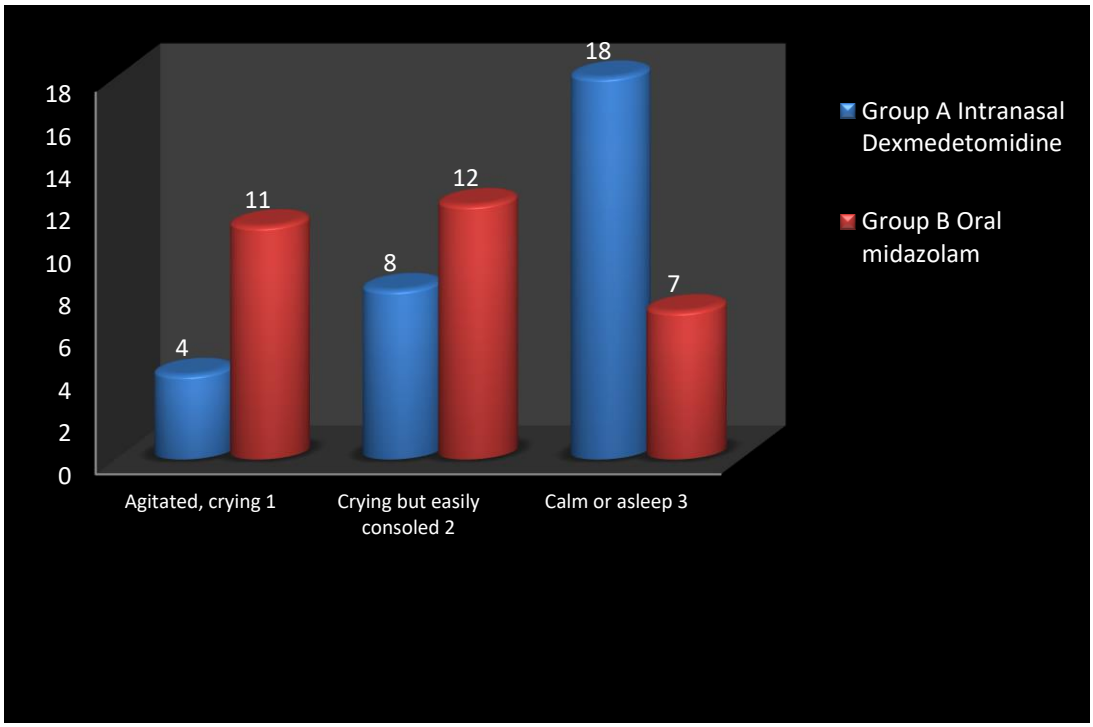

Table 14: Post operative agitation Score

GROUP	No	MEAN	S.D.	Std. Error. Mean	T	Sig (2tailed)
Group A (intranasal dexmedetomidine)	30	2.46	0.73	0.133	3.08	0.003
Group B (oral midazolam)	30	1.86	0.77	0.141	3.08	0.003

The Chi – Square value is 8.9; p value is 0.016 (statistically significant)
Group A showed less post operative agitation than Group B.

DISCUSSION

Children are generally uncooperative for taking medication and when it comes to surgery it is needless to mention about their anxiety and intolerance. To facilitate smooth induction of surgery, premedication is essential. It is required not only to produce sedation and analgesia but also to alleviate anxiety, increase tolerance and improve the outcomes of the interventions.

The medications used for inducing sedation and analgesia act on the nervous system. One such drug is Midazolam. This versatile drug is widely used in general anesthesia, since approved by FDA in 1986. It produces its effect by facilitating gamma amino butyric acid (GABA) receptor binding in the cerebral cortex which enhances the membrane conductance of chloride ions, which leads to alteration in the membrane

polarization that inhibits neuronal function. It may be administered in various routes. But it is not ideal drug for premedication because of its adverse effects of restlessness, paradoxical reaction, negative postoperative behavioural changes like delirium, amnesia and it has 70% acceptability rate only.

In recent days, dexmedetomidine a highly selective alpha 2 adrenoceptor agonist produces optimum sedation and analgesia without respiratory depression. It was approved by FDA in 1999. It acts on alpha 2 receptor at locus coeruleus and spinal cord to have negative feedback on the release of the neurotransmitter, norepinephrine and provides unique 'conscious sedation'.

In the present study total of 60 cases were included; of which 30 were in Group A for whom premedication with intranasal dexmedetomidine was used and 30 in Group B in which Oral midazolam was given as premedication.

This study is focused to identify an ideal premedication by comparing the efficacy & clinical effects of dexmedetomidine and midazolam as a preanaesthetic medication.

In our study, demographic profile (age, gender) of patients, weight distribution and type of surgeries underwent were statistically insignificant and is comparable in both groups (Table 1 – 4).

Children undergoing elective surgeries like circumcision, herniotomy, tonsillectomy, orchidopexy and tongue tie excision were included in the study. Children posted for emergency surgeries were excluded in order to not to interfere with routine operative schedule in such cases.

Only patients belonging to ASA I & II were chosen to avoid the influence of the associated diseases on the observation.

Haemodynamiceffects – heart rate, systolic blood pressure and oxygen saturation was monitored. There was mild reduction in heart rate after administration of intranasal dexmedetomidine compared to oral midazolam (Table 5a, 5b), which is attributed to decrease sympathetic outflow and circulating catecholamines levels. Yuen et al [28]& Munro et al[34] observed modest decrease in heart rate and systolic blood pressure. Normal SpaO2 was maintained in children of both groups.

Sedation score (Fig 4-6 & Table 6-8) of 3 and 4 were 73% in Group A (intranasal dexmedetomidine) at 10 mins, whereas 30 % in Group B (Oral Midazolam). At 20 mins, 60% were achieving score of 1 & 2 in Group A whereas 16% in Group B. at 30 mins, score 1 and 2 was about 80% in Group A and 43% in Group B. Children in Group A were well sedated than Group B at induction of anaesthesia and is statistically significant.Schmidt et al [33] found no difference between these groups, in sedation with premedication on parental separation of children. Discrepancy of the results could have been occurred from usage of non uniformity of sedation scale for assessment.

Behavior Scores (Fig 7-9 & Table 9-11) of 1 and 2 at 10, 20 30 mins in Group A were 37%, 74%, 83% and 17%, 43%, 57% for Group B respectively. The ease of separation of children from parents was better with Group A than Group B. This is in accordance with other studies conducted by Ghali et al[29] and Singla et al[36].

Cooperation was assessed on face mask application (Fig 10, Table12) and intravenous cannulation (Fig 11, Table13) and it was noted to be significantly better in Group A with p value of 0.035 and 0.027 respectively. Similar was observed by Mostafa[32] et al &Singla et al[36].

Postoperative agitation (Fig 12, Table14) was high with Group B (36%) children who were premedicated with Oral Midazolam than Group A (13%) children. Half life of dexmedetomidine is two hours which explains its post operative analgesic effect. Similarly, Schmidt et al[33] and Ghali[29] et al had observed the finding. During the study, we didn't encounter respiratory depression and any untoward effects in both the groups.

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SUMMARY

We compared the efficacy & clinical effects of intranasal dexmedetomidine and Oral midazolam as a preanaesthetic medication. This is double blinded randomized study. The efficacy and clinical effects of preanaesthetic drugs in causing sedation, behavioral changes, co-operation on parental separation, face mask application venepuncture and post operative agitation were compared with the help of separate scoring system.

In the present study, following were observed:

1. Age, Gender, weight distribution and type of surgery that the children in both groups underwent were comparable; no bias is noted and is statistically significant.
2. Heart rate was mildly reduced on shifting to operation theatre, in few children in Group 'A' (Intranasal dexmedetomidine) than Group 'B' (Oral midazolam). There was not much difference in systolic blood pressure and oxygen saturation levels in both groups.
3. The sedation scores at 10, 20 and 30 minutes are better with intranasal dexmedetomidine, which are statistically significant (p value is 0.0082, 0.0487 and 0.0351 respectively).
4. The behavioral scores at 10, 20 and 30 minutes are better with intranasal dexmedetomidine, which are statistically significant (p value is 0.007, 0.0486 and 0.0351 respectively).
5. The Cooperation scores for face mask application (p value is 0.0352) and venepuncture (p value is0.0268) are better with intranasal dexmedetomidine, which are statistically significant.
6. The post operative agitation was less with intranasal dexmedetomidine (P value is 0.016)than with oral midazolam.
7. Respiratory depression and other untoward incidents were not observed during the study in both groups.

CONCLUSION

We conclude that intranasal dexmedetomidine is an alternative anaesthetic adjunctive in children, instead of midazolam, as it is simple, has an easy route of administration, produces sedation, anxiolysis, facilitating better parental separation, smooth induction of surgery and with less or no post operative behavioural changes like agitation, amnesia and delirium .

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