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A randomized study of midazolam versus dexmedetomidine for premedication in children via intranasal mucosal atomization device

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***Abstract*---**Many drugs have been tried for premedication in children [1] amongst which midazolam and dexmedetomidine are commonly used and are reportedly safe and effective for usage during both separation as well as induction of anaesthesia. Hence, we planned to carry out a study of midazolam versus dexmedetomidine for premedication in children via intranasal Mucosal Atomization Device. To compare the efficacy of midazolam and dexmedetomidine as premedication in children of 2 to 6 years of age via intranasal Mucosal Atomization Device. This randomized study was done at Dhiraj hospital, Piparia, Vadodara, Gujarat on 60 children belonging to American Society of Anaesthesiologists (ASA) physical status I or II of age 2-6 years of either gender undergoing elective surgeries under general anaesthesia. Children were separated into: Group M - Midazolam 0.2 mg/kg (preservative free) Group D - Dexmedetomidine 1µg/kg. Drug was administered 30 minutes prior to surgery and

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following parameters were assessed: Acceptance of drug, Sedation Score, behaviour during parental separation and mask acceptance. Dexmedetomidine was statistically significantly better in aspect of drug acceptance, sedation after 30 minutes of drug administration, parental separation and mask acceptance than midazolam. Intranasal dexmedetomidine is better than midazolam for premedication in children as it produces better sedation, parental separation and satisfactory ease of induction by successful mask acceptance.

***Keywords*---**dexmedetomidine, intranasal, midazolam, mucosal atomization device, paediatric.

Introduction

The preoperative period is a stressful time for children[2]. It has been observed that preoperative anxiety of parental separation predisposes children to sleep disturbances and behavioural changes postoperatively. Zeev N kain et al., suggested that the prevalence of preoperative anxiety was high and reported to range from 40 - 60% among young children before anesthesia induction and surgery[3]. This is a concern for anaesthesiologists. An ideal premedicant relieves anxiety, makes the children calm, reduces their fear, makes induction smooth, rapid recovery, provides good patient acceptance and parental separation[4]. In paediatric patients benzodiazepines are commonly used for premedication as they provide sedation, muscle relaxation, anxiolysis, hypnosis, amnesia and anticonvulsant properties. Midazolam is water soluble short acting gamma-amino butyric acid receptor inhibitor. It has faster onset of action. Thus gained popularity as premedication in children[5].

Dexmedetomidine has been explored extensively in the paediatric population. It is highly selective and specific agonist for α_2 adrenoceptor exhibits sedative, hypnotic, analgesic, anxiolytics and sympatholytic effect. It has minimal effect on respiratory drive. These properties render dexmedetomidine suitable for analgesia and sedation during preoperative period[6]. Children dislike forcible administration of injection which will lead to struggling and psychological impact. Intravenous and intramuscular routes cause more anxiety. Better acceptability of intranasal route is considered for premedication in children as it is non invasive route and its ease of administration. Large and well vascularized nasopharyngeal mucosal surface provided rapid absorption, early onset via intranasal route with high bioavailability[7].It had also the advantage of well tolerability, did not require children's cooperation as would be in case for drug swallowing or sublingual retention and did not have pungency or an unpleasant taste[8]. Atomization of drug intranasally by Mucosal Atomization Device (MAD) produced fine particles (30-100 micron in diameter) which was associated with less discomfort during administration and increase drug absorption[9]. So, we carried out a randomised study of midazolam versus dexmedetomidine for premedication in children via intranasal Mucosal Atomization Device.

Material and Methods

This randomised study was carried out in the department of Anaesthesiology at a tertiary health care Centre from 16th November 2019 to 31st May 2021 after obtaining approval from the institutional ethical committee. A total of 60 children of either sex of 2 – 6 years belonging to ASA I or II, scheduled for elective surgeries under general anesthesia were included in the study. Upper respiratory tract infections, any nasal pathology, any known allergy or sensitivity or any other form of reaction to benzodiazepines and α_2 adrenoceptor agonists, children with mental retardation, on anticonvulsant therapy or other sedative medications were excluded from the study.

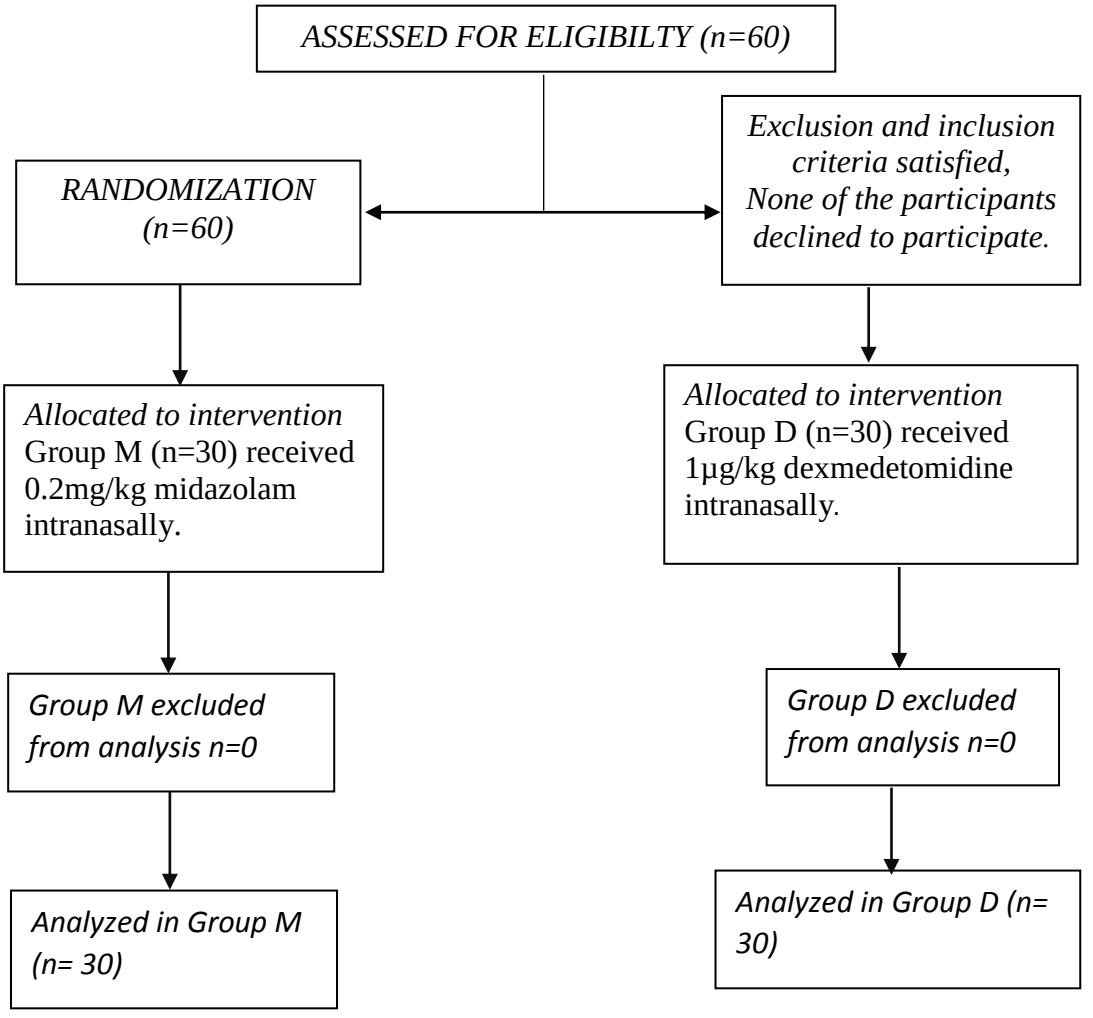
Detailed preanaesthetic history was taken a day prior to surgery. General examination, physical and systemic examination and thorough airway assessment were carried out. Children's weight were noted. All routine investigations were done. We explained the procedure, the device, drugs and details about their administration, their probable side effects to parents. Written parental informed consent was taken in their native language. Children were kept nil by mouth for solids about 6 hours and clear fluids were permitted upto 2 hours prior to the surgery. The children were kept in quiet, undisturbed area along with the parents. Primary parameters included were:

- Acceptance of the drug was assessed by using the Drug Acceptance Score (Parnis S.J. et al)10
  - Rejected entirely.
  - Accepted with grimace or complaint.
  - Accepted readily
- Sedation was assessed at 30 minutes after the administration of study drug by Four Point Sedation Score (Filos et al)11
  - Awake and alert,
  - Awake but drowsy, responding to verbal stimuli,
  - Drowsy but responding physical stimulus,
  - Unresponsive, not responding to physical stimulus.
- The behaviour at the time of separation from parents was assessed when the child was separated from parents to shift to operating room using the Parental Separation Score (Pandit UA et al)12
  - Excellent, happily separated,
  - Good, separated without crying,
  - Fair, separated with crying,
  - Poor, need for restraint.
- Acceptance of face mask was graded on Four Point Score (Mitchell V)13
  - Poor – afraid, combative, crying,
  - Fair – moderate fear of mask, not easily calmed,
  - Good – slight fear of mask, easily calmed,
  - Excellent – unafraid, cooperative, accepts mask easily.

Secondary parameters included baseline pulse rate, SpO_2 and monitored every 15 minutes till the end of surgery. Sample size had been estimated with the help of statistical software nMaster 2.0., sample size came out as 30 patients in each

group. They were divided equally into 2 groups. Children in Group M received a dose of 0.2 mg/kg midazolam (upto a maximum of 5mg) and children in Group D received dexmedetomidine in a dose of 1µg/kg (upto a maximum of 25 µg).

Figure 1



The half of the calculated dose of the drug was administered in each nostril 30 minutes before surgery in a recumbent position using mucosal atomization device by an experienced anaesthesiologist. Children were shifted to operation theatre and were premedicated with injection glycopyrrolate 0.004mg/kg intravenous and injection ondansetron 0.1mg/kg intravenous. They were preoxygenated with face mask with 100% oxygen for 3 minutes. Anaesthesia was induced by a standard technique of intravenous induction and maintained on O_2, N_2O, sevoflurane and atracurium. Intraoperatively children were monitored for pulse rate, SpO_2 every 15 minutes till end of surgery. At the end of surgery neuromuscular blockade was

reversed with inj.neostigmine (0.05mg/kg) and inj. glycopyrrolate (0.008mg/kg). Trachea was extubated after fulfilling the recovery criteria and children were shifted to recovery room. Postoperatively all children were watched for pulse rate, SpO_2, nausea, vomiting, rigor, bradycardia every hourly up to 4 hours and at 6 and 8 hours. Bradycardia was defined as pulse rate < 60/min and treated with IV atropine sulfate 0.6mg.

Statistical analysis

Data was collected, tabulated. Numerical variables were presented as mean and standard deviation (SD) while categorical variables were presented as frequency and percentage. As regard numerical variables, unpaired student – t test was used whenever appropriate between-group comparisons; while for categorical variables, chi–square test was used. A difference with significant level ($p<0.05$) was considered statistically significant.

Observation and Results

Demographically both the groups were comparable on the basis of age, gender, weight and ASA grading.

Table 1
Drug Acceptance Score between the groups

Drug Acceptance Score	Group M		Group D		p value
	No of pts.	%	No of pts.	%	
1- Rejected entirely	0	0.00%	0	0.00%	0.0337
2- Grimace or complaint	23	76.67%	14	46.67 %	
3- Accepted readily	7	23.33%	16	53.33%	
Total	30	100.00%	30	100.00%	

Based on the above results it was found that the Drug Acceptance Score in Group D (dexmedtomidine 1µg/kg) was statistically significantly good as compared to Group M (midazolam 0.2mg/kg) ($p=0.0337$). None of the children in any group rejected the drug.

Graph 1. Drug Acceptance Score between the groups

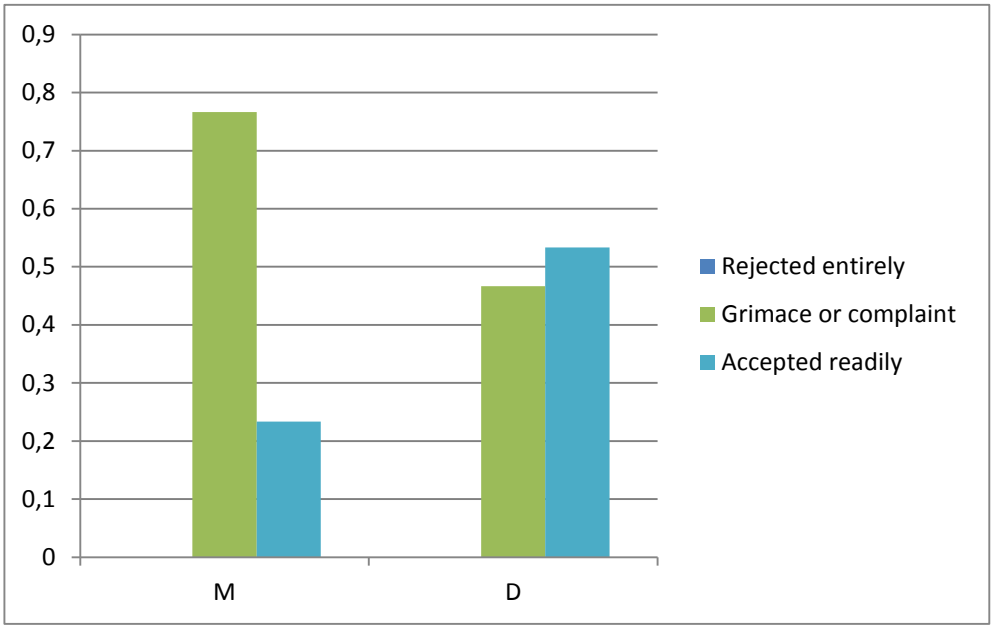


Table 2
Sedation Scores between the groups

Four Point Sedation Score	Group M		Group D		p value
	No of pts.	%	No of pts.	%	
1- Awake and alert	7	23.33%	2	6.67%	0.0347
2- Awake but drowsy,responding to verbal stimuli	8	26.67%	13	43.33%	
3- Drowsy but responding physical stimulus	9	30.00%	14	46.67%	
4- Unresponsive	6	20.00%	1	3.33%	
Total	30	100.00%	30	100.00%	

Based on the various studies we had compared Sedation Score at 30 minutes after administration of the study drug. The Sedation Score was statistically significant in Group D when compared to Group M (p=0.0347).

Graph 2. Sedation Scores between the groups

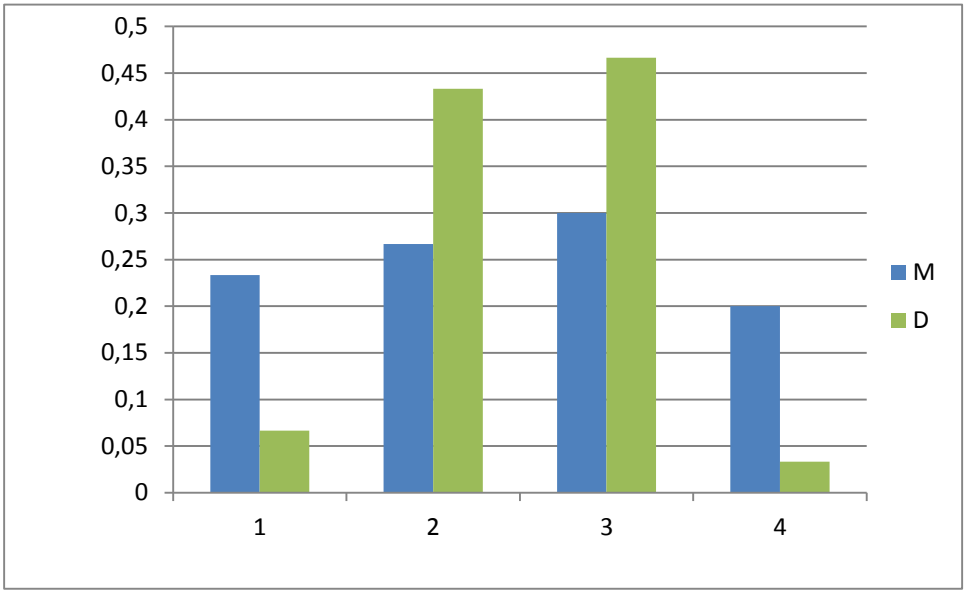


Table 3
Parental Separation Score between the groups

Parental Seperation Score	Group M		Group D		p value
	No of pts.	%	No of pts.	%	
1- Excellent, happily separated	8	26.67%	15	50.00%	0.0288
2- Good, separated without crying	9	30.00%	11	36.67%	
3- Fair, separated with crying	13	43.33%	4	13.33%	
4- Poor, need for restraint	0	0.00%	0	0.00%	
Total	30	100.00%	30	100.00%	

In the present study overall Parental Separation Score was statistically significantly good to excellent in dexmedetomidine group as compared to midazolam group (p = 0.0288). None of the children in any group were needed to be restrained.

Graph 3. Parental Separation Score between the groups

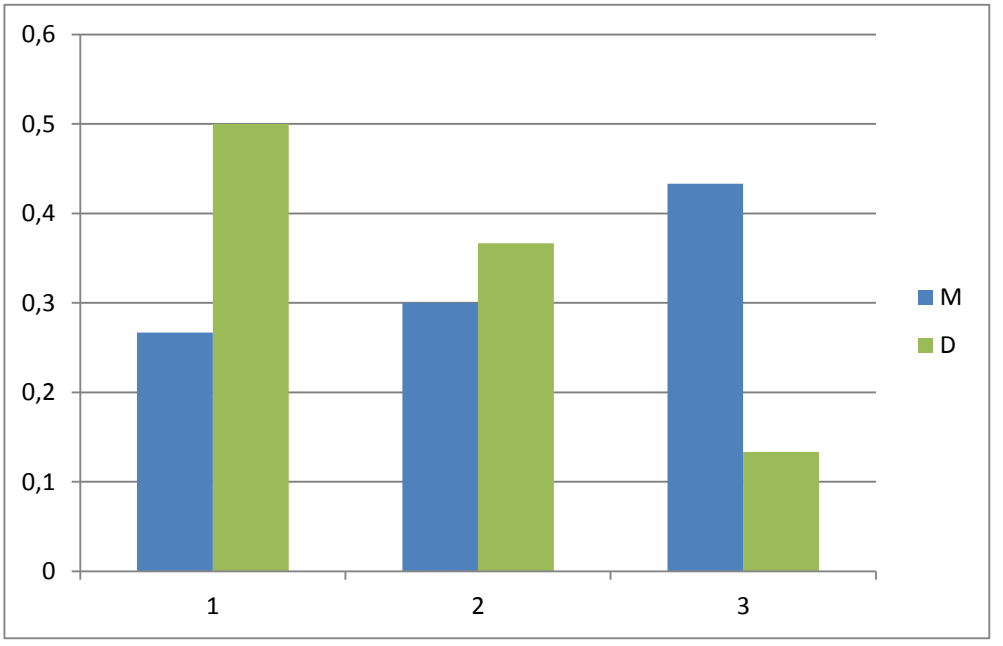
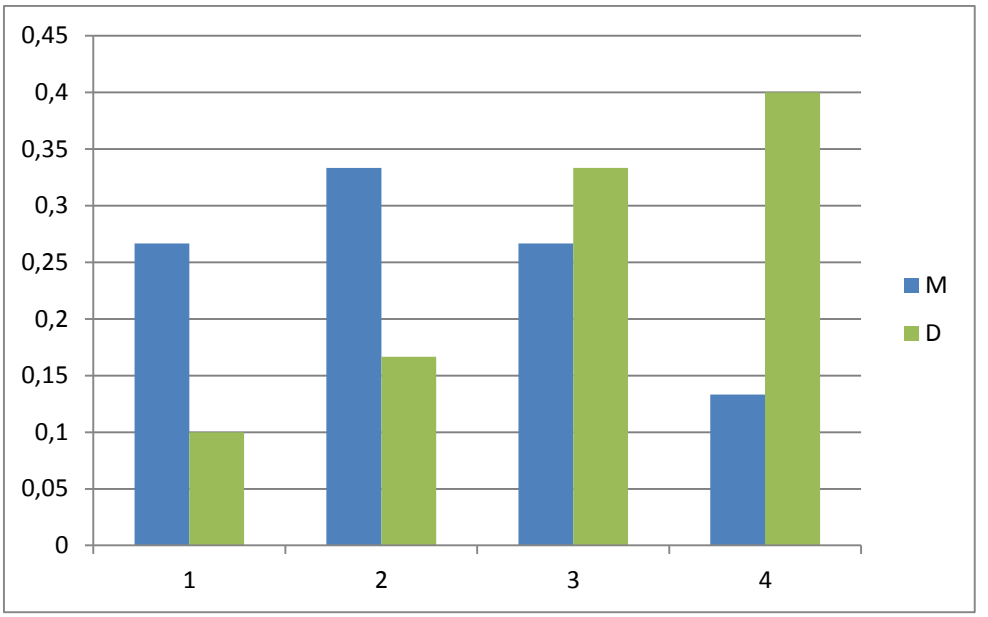


Table 4
Behaviour during mask acceptance between the groups (FOUR POINT SCORE)

Acceptance of Face Mask	Group M		Group D		p value
	No of pts.	%	No of pts.	%	
1- Poor	8	26.67%	3	10.00%	0.0428
2- Fair	10	33.33%	5	16.67%	
3- Good	8	26.67%	10	33.33%	
4- Excellent	4	13.33%	12	40.00%	
Total	30	100.00%	30	100.00%	

In the operation theatre the acceptance of mask (Four Point Score) was compared as it has an impact on induction. The overall Mask Acceptance Score was statistically significantly good to excellent in Group D as compared to Group M (p value = 0.0428).

Graph 4. Behaviour during mask acceptance between the groups



In both the groups intraoperative and postoperative heart rates were found to be statistically insignificant ($p>0.05$). No medical intervention was needed in either group. Nasopharyngeal irritation was not seen in any patients in our study. No significant change was observed in SpO_2 between both the groups intraoperatively as well as postoperatively. None of the patients in both groups had $SpO_2 < 98\%$ at any point of time during study period. In our study none of the children in both groups had complications such as bradycardia, hypertension and hypotension both during intraoperative and postoperative period.

Discussion

Paediatric patients undergoing surgical procedures can experience significant anxiety and distress during perioperative period. They are usually uncooperative, anxious or physically resistant particularly during the times of parental separation, mask application and venipuncture[4]. Various interventions were used to allay the anxiety of a child during perioperative preparation. Sedation in preoperative room remained one of the widely used method and helped to reduce anxiety, minimized the emotional trauma and facilitated a smooth induction of anaesthesia[14].

The intranasal application of pre anaesthetic drugs is a preferred route of administration and is an effective way to administer sedatives to children. It doesn't require cooperation and it is convenient, noninvasive, well tolerated. Child would not be having an unpleasant taste or pungency. The Mucosal Atomization Device is safe simple metered dose delivery system and painless way to deliver medications as it is needle free. Atomization can be done in any position. The soft conical plug on the tip forms a seal with the nostril, preventing expulsion of drug.

Atomised nasal medications are the optimal size for rapid absorption across mucosal membranes into the blood stream, avoiding first pass metabolism[15]. We compared the intranasal administration of midazolam (0.2mg/kg) and dexmedetomidine (1µg/kg) and as premedication in children undergoing elective surgeries under general anaesthesia using MAD. Midazolam which is a water soluble benzodiazepine has emerged as a widely used pre medication due to its fast onset of action and short elimination half life[3]. It binds to $GABA_A$ receptor triggering chloride channel and hyperpolarization of cells thus causing resistance to excitation of neuron, hence producing sedation. Intranasal administration of midazolam was better tolerated than oral and has the advantage of no first-pass effect with rapid absorption directly into the systemic circulation and a bioavailability of 55-83%[16]. Dexmedetomidine is a α_2 agonist which produces cooperative sedation and no respiratory depression. It produces its hypnotic and sedative effects by neuronal hyperpolarisation via activation of α_{2A} adrenoceptor on the predominant noradrenergic nucleus in the brain, locus coeruleus. Intranasal dexmedetomidine administration had a high bioavailability of 35-93% (65%)[17]

Table 5

Publication Author	Type of study	Study population number and age.	Drugs and Method	Results
Malineni N. et al (2017)[1]	Randomised controlled trial, double blind study	60 children. 1-10 years.	- Midazolam 0.2mg/kg. - Dexmedtomidine 1µg/kg. - Administered with 1ml tuberculin syringe intranasally to assess parental seperation anxiety and acceptance of anaesthesia mask.	Parental seperation and mask acceptance at time of induction was better in dexmedetomidine when compared to midazolam.
Kumar A. et al (2017)[18]	Prospective, randomised, double blind study	60 children 2-12 years.	- Oral midazolam 0.5mg/kg - Intranasal dexmedetomidine1µg/kg - 0.2ml drug dripped into both nostrils using 1 ml syringe to assess sedation scores at seperation from parents and at induction of anaesthesia.	Sedation scores were superior with dexmedetomidine group at separation and induction.
Xie z. et al (2017)[19]	Randomised study	106 children 2-5 years.	Dexmedetomidine 2µg//kg in 20µl//kg of Normal saline is given as	Dexmedtomidine by MAD offered better sedation effects to

			drops via syringe or spray using MAD to assess response to venous cannulation by FLACC scores (faces, legs, activity, cry and consolability) after 30 minutes of administration.	reduce responses to venous cannulation than by drops without any significant complications.
Gupta A. et al (2017)[20]	Prospective, randomised, double blind study	60 children 1-8 years.	- Midazolam 0.2mg/kg. - Dexmedetomidine 1µg/kg - Administered intranasally using 1ml syringe to assess time of onset, level, sedation quality upon separation from parents.	Dexmedtomidine resulted in more successful parental separation and yielded a higher sedation level than midazolam.
Naik Shilpa S. et al (2018)[21]	Longitudinal study	30 children 1-5 years.	- Midazolam spray intranasally 0.5mg/kg . - Dexmedtomidine instillation intranasally 1µg/kg. - To assess compliance to intravenous cannulation, separation from parents and induction score, sedation score, postoperative recovery score.	Dexmedetomidine spray gave gives better sedative condition, response to i.v. cannulation, separation and induction as compared to midazolam.
Medhat MM. et al (2018)[14]	Prospective, randomised, double blind study	60 children 3-6 years.	- Midazolam 0.2mg/kg - Dexmedetomidine 1µg/kg - By drop instillation intranasally using 2ml syringe to assess sedation score, anxiety score and child- parent separation	Dexmedtomidine attained satisfactory and significant sedation and lower anxiety level with better parental separation than intranasal midazolam.

			score.	
Diwan G.et al (2020)[22]	Prospective, randomised, double blind study	60 children 2-12 years.	- Midazolam 0.1mg/kg - Dexmedetomidine 1µg/kg - Administered intranasally using 1ml syringe comes to assess sedation score, anxiety score and child- parent separation score.	Dexmedtomidine was associated with lower sedation levels, anxiety levels and easier child parent seperation when shifting to operating room when compared to midazolam group.

Conclusion

We conclude that administration of intranasal dexmedtomidine 1µg/kg is better than intranasal midazolam 0.2mg/kg for premedication in children between ages of 2 and 6 years via Mucosal Atomization Device as it produces satisfactory ease of drug acceptance, sedation, parental separation and induction by successful mask acceptance without causing any complications.

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