Original Research Article

Study of two doses of intranasal dexmedetomidine (1mcg vs. 2mcg) for premedication in children

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Abstract

Background: Dexmedetomidine is a highly selective α2-adrenoceptor agonist with sedative, analgesic and anxiolytic effects. It is well tolerated by intranasal route without having unpleasant sensation. In the present study, we aimed to evaluate and compare the sedation score to assess onset and quality of sedation, behaviour score at the time of parental separation and hemodynamic stability between two doses of intranasal dexmedetomidine (1 mcg and 2 mcg) for premedication in children. **Methods:** The present prospective, randomized, double-blind study was conducted in 100 paediatric patients, weighing up to 20 kg, aged between 2-9 years with ASA physical status I at Institute of Kidney Disease and Research Centre and Dr. H. L. Trivedi Institute of Transplantation Science, Ahmedabad. The subjects were randomly divided into 2 groups, 50 patients in each group. Group1. Group-1 received 1 mcg/kg intranasal dexmedetomidine while Group-2 received 2 mcg/kg intranasal dexmedetomidine 60 minutes prior to surgery. **Results:** Heart rate was gradually reduced 12.7% and 12.2% from baseline in group 1 and in group 2 respectively. (p value > 0.05). Sedation score was 3.4, 3.5 and 3.3 at the time of 30, 45 and 60 minutes in group 2 which was significantly higher as compared to (2.9, 2.9 and 2.8 at time of 30, 45 and 60 minutes) group 1. ($p < 0.05$) Behaviour score at 30, 45 and 60 minutes were exactly same in both two groups. **Conclusion:** We concluded that intranasal dexmedetomidine in a premedication dose of 2 mcg/kg resulted in excellent sedation in children. It proved excellent sedation, good parentral separation and better intravenous cannulation acceptance when compared to 1 mcg/kg. It also provides stable hemodynamics with minimal side effects.

Key Word: intranasal, dexmedetomidine, premedication, children

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INTRODUCTION

Apprehension and fear of operation, injections, parental separation and operation theatre environment are all traumatizing experiences in young children consequential to postoperative maladaptive behavioural change.[1] Aim of premedication prior to anaesthesia is to provide anxiolysis and to facilitate separation from parents as well as to ensure smooth induction of anaesthesia. Route of administration of premedication is very significant to avoid extra stress to the child. Hence, routine clinical practice frequently makes use of non-parenteral routes of administration like oral or intranasal routes. Oral midazolam is a gold standard premedication in children.[2] Midazolam has a number of beneficial effects when used

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as premedication in children like sedation, reduction of vomiting, fast onset and limited duration of action. Midazolam is unpleasant tasting even with a flavoured vehicle and as a result, patient acceptance is sometimes poor.[3] New drugs, such as the α2- agonists, have developed as replacements for premedication in paediatric anaesthesia. Dexmedetomidine is a highly selective α2-adrenoceptor agonist with sedative, analgesic and anxiolytic effects. It enables parental separation and help improve conditions for induction of general anesthesia, while maintaining airway reflexes.[4] It is well tolerated by intranasal route without having unpleasant sensation. The primary site of action of dexmedetomidine is the locus ceruleus rather than the cerebral cortex. Therefore, its induced sedation is considered by quick and easy arousal from sedation similar to natural sleep. Bioavailability of sublingually administered dexmedetomidine is high (84%), proposing a prospective role in pediatric sedation and premedication.[5] Group A received intranasal dexmedetomidine (1 mcg/kg) and Group B received intranasal dexmedetomidine (2 mcg/kg) as a premedication 60 minutes prior to surgery. As there are very few studies related to use of intranasal dexmedetomidine in India, we aimed to evaluate and compare the sedation score to assess onset and quality of sedation, behaviour score at the time of parental separation and hemodynamic stability between two doses of intranasal dexmedetomidine (1 mcg and 2 mcg) for premedication in children.

MATERIALS AND METHODS

The present prospective, randomized, double-blind study was conducted in 100 paediatric patients, weighing up to 20 kg, aged between 2-9 years with ASA physical status I. They were selected by sealed envelope method. They were scheduled for various urological surgeries and diagnostic procedures under general anaesthesia during the year 2015 to 2016 at Institute of Kidney Disease and Research Centre and Dr. H.L. Trivedi Institute of Transplantation Science, Ahmedabad. The study protocol was approved by the Ethics Committee of our institution and informed consent was obtained for each patient from at least one of the parents or a legal guardian. The day before surgery, all patients underwent thorough pre-anaesthetic check- up which included routine history, general as well as systemic examination. Necessary investigations were obtained in indicated cases. Patients were kept nil orally for at least 6 hours for solid food. The patients were randomly divided into two equal groups of 50 using a computerized random number generator.

- **Group-1:** Who received intranasal dexmedetomidine 1 mcg/kg 60 minutes prior to surgery.
- **Group-2:** Who received intranasal dexmedetomidine 2 mcg/kg 60 minutes prior to surgery.

Children received intranasal premedication in the preoperative holding area at approximately 45–60 min before induction of anesthesia in the presence of one parent in a full resuscitation facility. The study cases were arranged whenever possible to be scheduled at the first cases in the operative list in a way to lessen the interference of the premedication time with the OR list. The prepared drug solution was divided in two aliquots and administered cautiously in both nostrils using a tuberculin 1-ml syringe as drop by drop to avoid wastage of the drug through anterior and posterior nostrils. The child was positioned on the parent's lap in a recumbent position during drug administration and was allowed to sit up or assume a more comfortable position 5 min later. Heart rate (HR), oxygen saturation (SpO2), respiratory rate were measured before (baseline) and 5, 10, 15, 30, 45 and 60 minutes after administration of medication. Sedation Score was considered for assessment of sedation. Sedation status at separation from the parent was considered the primary endpoint. Behaviour status of the children were assessed regularly until induction of anaesthesia. After securing venous access, glycopyrrolate 0.04 mg/kg and fentanyl 2.0mcg/kg were given. The patient was induced with thiopentone sodium 5 mg/kg followed by succinylcholine 1.5mg/kg to facilitate intubation or LMA insertion. Patient was maintained with N_2O $\pm O_2$ ± inhalational anaesthetic agent like isoflurane or sevoflurane and muscle relaxant (atracurium) given as per need of surgery. Pulse rate and systolic blood pressure was measured at 15 minutes interval intraoperatively. At the end of surgery, patient was successfully reversed with neostigmine 0.05mg/kg and glycopyrrolate 0.08mg/kg where relaxant was used. Patient was successfully extubated and shifted to recovery room where patient was assessed for hemodynamics and side effects like nausea, vomiting, shivering. Children with a known allergy or hypersensitive reaction to either dexmedetomidine, any nasal pathology, organ dysfunction, cardiac arrhythmia, congenital heart disease, or hemodynamic or respiratory instability, cardiopulmonary disease, or any treatment with sedatives or anticonvulsants were excluded from the study.

Statistical Analysis: All statistical calculations were carried out using computer program SPSS version 15 (Statistical Package for the Social Science; SPSS Inc., Chicago, Illinois, USA) for Microsoft Windows. Data were statistically described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate. Student's t-test was used to compare normally distributed continuous variables

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between the two groups and Mann–Whitney U-test for independent samples. For comparing categorical data, $\chi 2$-test was conducted. P-values less than 0.05 were considered statistically significant. $P<0.05$ considered to be statistically significant difference. $p<0.01$ considered to be statistically highly significant difference.

OBSERVATION AND RESULTS

In our study total 100 ASA Grade I paediatric patients with <20 kg of body weight which were included and they were posted for various urological surgeries and diagnostic procedures. Patients were divided equally into two groups, 50 patients in each group. Group 1 received intranasal dexmedetomidine (1 mcg/kg) and Group 2 received intranasal dexmedetomidine (2 mcg/kg) as a premedication 60 minutes prior to surgery. Both the groups are comparable according to age, gender and body weight. (Table 1)

Table 1: Demographic data of study population

	Group 1	Group 2	p value
Age(yrs)	5.3 ± 2.1	5.1±1.7	0.57
Male	36 (72%)	29 (58%)	0.17
Female	14 (28%)	21 (42%)	
Weight (kg)	14.7±5.8	14.1± 4.0	0.93

Table 2: Comparison of heart rate between Group 1 and Group 2

	Time (Mins.)	Base line	5	10	15	30	45	60
Group 1	Mean	113.7	115.5	111.3	107.2	103.5	101.5	99.1
	± SD	12.8	10.9	10.2	8.9	8.3	6.9	5.2
Group 2	Mean	111.8	113.3	108.7	105.8	102.6	99.5	97.8
	± SD	5.491	5.7	7.0	7.8	5.7	4.4	3.42
p value		0.81	0.11	0.24	0.59	0.65	0.07	0.22

Heart rate was gradually reduced 12.7% and 12.2% from baseline in group 1 and in group 2 respectively. It was not statistically significant (p value > 0.05). We did not observe clinically significant fall in SPO_2 which remained > 95% in both groups.

Table 3: Comparison of onset of sedation between Group 1 and Group 2

Variables	Group 1 Mean ± SD	Group 2 Mean ± SD	p value
Onset of sedation (Minutes)	25.7 ± 6.9	19.9 ± 4.1	< 0.005
Duration of sedation (Minutes)	43.0 ± 10.7	71.3 ± 21.6	< 0.005

The assessment of sedation was done at 5, 10, 15, 30, 45 and 60 minutes by Sedation Score. Onset of sedation was 25.7 ± 6.9 min in group 1 and 19.9 ± 4.1 min in group 2 which was statistically significant ($p<0.005$). Difference between mean duration of sedation in group 1 and group 2 was statistically significant ($p < 0.05$). (Table 3)

Table 4: Comparison of onset of sedation and duration between 2 to 5 year and 6 to 9 year

Variables	Group 1 Mean ± SD	Group 2 Mean ± SD	P value
Onset of sedation (Minutes)			
2 to 5 year	23.8 ± 5.8	19.6 ± 3.9	0.07
6 to 9 year	27.7 ± 7.3	20.2 ± 4.3	< 0.005
Duration of sedation (Minutes)			
2 to 5 year	44.4 ± 12.3	72.3 ± 22.1	< 0.005
6 to 9 year	41.8 ± 8.6	70.5 ± 21.5	< 0.005

In lower age group (2 to 5 year) onset of sedation was earlier than in higher age group (6 to 9 year) in group 1 patients. Onset of sedation was earlier in group 2 (2 mcg/kg) as compared to group 1 (1 mcg/kg). It may be due to higher dose of dexmedetomidine. In both age group duration of sedation was longer in higher dose receiving group, which was significant.

Table 5: Comparison of Sedation score between Group 1 and Group 2

	Time (Mins.)	5	10	15	30	45	60
Group 1	Mean	1.1	1.4	2.3	2.9	2.9	2.8
	± SD	0.3	0.8	1.0	0.8	0.9	0.8
Group 2	Mean	1.1	1.4	2.5	3.4	3.5	3.3
	± SD	0.3	0.8	0.5	0.5	0.5	0.5
p value		1.00	1.00	0.39	0.001	0.001	0.005

Sedation score was 3.4, 3.5 and 3.3 at the time of 30, 45 and 60 minutes in group 2 which was significantly higher as compared to group 1 ($p < 0.05$). Maximum sedation was achieved during 30 to 60 minutes. (Table 5)

Table 6: Comparison of Behaviour score between Group 1 and Group 2

	Time (Mins.)	5	10	15	30	45	60
Group 1	Mean	2.0	2.7	3.4	3.5	3.6	3.7
	± SD	1.0	0.9	0.8	0.6	0.7	0.6
Group 2	Mean	1.9	2.8	3.5	3.5	3.6	3.7
	± SD	1.0	0.8	0.6	0.6	0.6	0.6
p value		0.83	0.92	0.93	0.58	0.89	0.83

There was no any significant difference observed between two groups. All the patients were calm 15-20 minutes after giving premedication. (Table 6) Side effect was not reported in any groups like hypotension, bradycardia, nausea, vomiting.

DISCUSSION

Premedication is intended to relieve anxiety, apprehension and resistance to anaesthesia. The benefit of using sedative drugs in peadiatric patient is to control pain, fear and anxiety, thus forming a behaviour that will ease the provision of quality medical care.[1] Intranasal administration of drug is chosen as it works for a widespread range of drugs and is available, non-invasive and easy because of child cannot resist or spit it out. The intranasal route has a important benefit of a non-invasive, quicker onset of action and relatively less or delayed side effects.[6] Presently the most common paediatric pemedicants are midazolam, ketamine, clonidine and dexmedetomidine. Midazolam recognized as the gold standard method of preoperative anxiolysis against which other preinduction strategies are compared.[7] Clonidine is an alpha 2 agonist has been recommended as alternative for premedication in children and previous studies have revealed it to be equally as effective as midazolam.[8] Dexmedetomidine is a newer alpha 2 agonist with a more selective action on the alpha 2 adrenoreceptor and short half-life.[9] Children premedicated with intranasal Dexmedetomidine attained more significant and satisfactory sedation at parental separation and at induction of anaesthesia than those who received Midazolam. Most children tolerated the intranasal administration of drug. It is an effective way to administer premedication and sedation to children, it is relatively easy and noninvasive route with a high bioavailability.[10] Intranasal dexmedetomidine decreased heart rate and systolic blood pressure during preoperative sedation period in comparison to baseline HR and SBP. Children in both groups maintained normal SpO2 values. Heart rate was progressively decreased 12.7% and 12.2% from baseline in group 1 and in group 2 respectively. It was not statistically significant (p value >0.05) Karim Kamal et al[11] and Zub et al[12] have done study with similar dose of dexmedetomidine (3 mcg/kg) they found them to be safe without any hemodynamic side effect. Similar results were reported by Yuen et al[13] and concluded that Dexmedetomidine is known to reduce sympathetic outflow and catecholamine levels and therefore it is expected to cause a decrease in HR and SBP. Munro et al.[10] described that the reduction of blood pressure and heart rate were < 20% of the baseline who were given initial dose of dexmedetomidine 1 mcg/kg iv. Aantaa et al.[14] stated that use of dexmedetomidine can be linked with some cardiovascular side effect including hypotension and bradycardia. The sedation onset time was defined as time from drug administration to the observed onset time of satisfactory sedation. This study demonstrated that onset of sedation was faster in group 2 (2 mcg/kg) than group 1 (1mcg/kg). (19.9 ± 4.1 vs 25.7 ± 6.9, $p<0.005$). In higher age group (older children) (6 to 9 year) onset of sedation was earlier in group 2 (2 mcg/kg) as compared to group 1 (1 mcg/kg) [20.2 ± 4.3 vs 27.7 ± 7.3, $p < 0.05$]. Yuen VM et al.[13] compared two different dose of intra nasal dexmedetomidine (1 and 1.5 mcg/kg doses) in 36 subjects. The onset of sedation occurred at 45 mins with a peak effect at 90-150 min. In our study, duration of sedation was defined as the time from sedation onset to the time the patient woke up naturally or by stimulation (with sedation score of 2 or below) e.g

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from being transferred to the operation theatre, canulation or application of facemask. Duration of sedation was longer in group 2 as compare to group 1 (71.3 ± 21.6 vs 43.0 ± 10.7, $p < 0.05$). Sedation score was 3.4, 3.5 and 3.3 at the time of 30, 45 and 60 minutes in group 2 which was significantly higher as compared to (2.9, 2.9 and 2.8 at time of 30, 45 and 60 minutes) group 1. ($p < 0.05$) In 2 to 5 year age group duration of sedation in group 2 was significantly longer than group 1 (72.3 ± 22.1 min. vs 44.4± 12.3 min , $p < 0.05$). Same result observed in 6 to 9 year age group. Yuen and his colleagues observed that duration of sedation was 85.1 ± 15.1 min. in higher dose receiving group (2 mcg /kg) and it was longer than low dose receiving group (1 mcg /kg) [80.2± 10.3] which was not significant. In their study adequate sedation at the time of induction was attained in 53% of the children in lower dose group versus 66% in higher dose group ($p = 0.049$).[13] In our study, adequate sedation at 45 minutes was achieved in 72% of the children in group 1 versus 98% in group 2 ($p = 0.52$) and at 60 minutes, adequate sedation was achieved in 74% of the children in group 1 versus 99% in group 2 ($p = 0.54$). The assessment of Behaviour score was done at 5, 10, 15, 30, 45 and 60 minutes**.** There was no any significant difference observed between two groups. Same result was observed in Yuen VM study. All the patients were calm when they were shifted to operation theatre.[13]

CONCLUSION

We concluded that intranasal dexmedetomidine at a dose 2 mcg/kg resulted in excellent sedation in paediatric patients. The intranasal route proves to be an effective alternative to other invasive routes. It proved excellent sedation, good parentral separation and better intravenous cannulation acceptance when compared to 1 mcg/kg. It also provides stable hemodynamics with minimal side effects. Dexmedetomidine in doses of 1 mcg/kg and 2mcg/kg administered as intranasal drops produced a similarly satisfactory sedation in children aged 2–5 years. In children aged 6–9 years, 2 mcg/kg was associated with higher proportion of satisfactory sedation than 1 mcg/kg without causing adverse hemodynamic effects, suggesting that the higher dose 2 mcg/kg is more appropriate in this age group.

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