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RESEARCH

Comparison of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery: a double-blind, randomised study

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Objective: The aim of this study was to compare the effect of dexmedetomidine with midazolam for intranasal premedication in children posted for elective surgery.
Trial design: This was a prospective, randomised, double-blinded clinical study.
Method: 60 children, 3 to 10 years of age, with American Society of Anaesthesiologists (ASA) physical status I, scheduled for elective surgery, were randomly divided into two groups, group D (dexmedetomidine) and group M (midazolam). Group D patients received intranasal dexmedetomidine 1 µg/kg and group M patients intranasal midazolam 0.2 mg/kg, approximately 30 minutes before induction of anaesthesia, in the form of a spray.
Outcome: Preoperative effects on heart rate, blood pressure, sedation and anxiety including parental separation and mask acceptance were assessed.
Results: 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). There were no episodes of hypotension or bradycardia. Children in group D achieved better parental separation and mask acceptance scores compared with group M.
Conclusion: Dexmedetomidine resulted in better parental separation and mask acceptance scores than intranasal midazolam. Thus it would seem to offer some advantage compared with midazolam.

Keywords: dexmedetomidine, intranasal, midazolam, paediatric patients

Introduction

Most paediatric patients have varying degrees of anxiety during the preoperative period, which may be due to separation from parents, or fear of injections or the operating theatre.[1] This leads to stress, tachycardia, agitation or excessive crying, which make the management of such patients difficult during induction of anaesthesia. Preoperative anxiety is therefore an important concern for paediatric anaesthesiologists.[2] Many anxiolytic medications have been tried with varying results. Of the benzodiazepines, midazolam has become the most frequently used premedication[2,3] due to its fast onset and short duration of action.

Intranasal midazolam as premedication in preschool children was first studied by Wilton and colleagues.[4] The intranasal route has a slower onset of action compared with the intravenous route; however, it is not as painful as the intramuscular route, and it is absorbed directly into the systemic circulation, avoiding first-pass metabolism.[5,6] However, midazolam is also though rarely associated with side effects such as respiratory depression, cognitive impairment and excessive sedation.[7]

Recently α2-agonists have emerged as alternative anti-anxiety premedication in children. Dexmedetomidine is a centrally acting selective α2-agonist, which has an anxiolytic and sedative effect and is devoid of respiratory depression.[8] It is odourless and does not cause mucosal stimulation, making it suitable for intranasal administration in paediatric patients.[9,10]

Objective

The aim of this study was to compare the effect of dexmedetomidine versus midazolam for intranasal premedication in children posted for elective surgery on preoperative anxiety, sedation, heart rate and systolic blood pressure as well as postoperative analgesic requirements.

Material and methods

This double-blind equally randomised (1:1) parallel group clinical study was carried out in Bhagat Phool Singh Govt Medical College and Hospital for Women after obtaining clearance from the ethical committee of the institute (No. BPSGMCW/RC78/IEC/15).

A total of 63 paediatric patients, 3 to 10 years of age, with American Society of Anaesthesiologists (ASA) physical status I, scheduled for elective surgery, were considered for this study. Children with ASA physical status 2 or more, runny nose or upper respiratory tract infection, any central nervous system disorder, refusal for intranasal administration or history of allergic reaction to dexmedetomidine or midazolam were excluded. In total 63 children undergoing minor surgical procedures such as tonsillectomy, hernia repair, squint surgery or minor orthopaedic procedures were considered for this study. Of these, parents of 3 patients declined to give consent for the study; a total of 60 children were enrolled.

All patients were fasted overnight and clear fluids were allowed up to 4 hours prior to induction. In the morning, on the day of surgery, children were taken into the preoperative room with one parent allowed to accompany them. After informing the parent about the benefits of intranasal anti-anxiety premedication written consent was obtained from those willing to participate in the study. The children were randomly divided into two groups, group D and group M, using a computer-generated sequence.

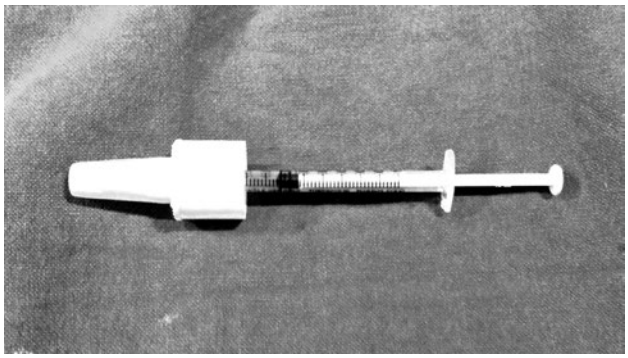

Figure 1: Syringe assembly used for the intranasal spray.

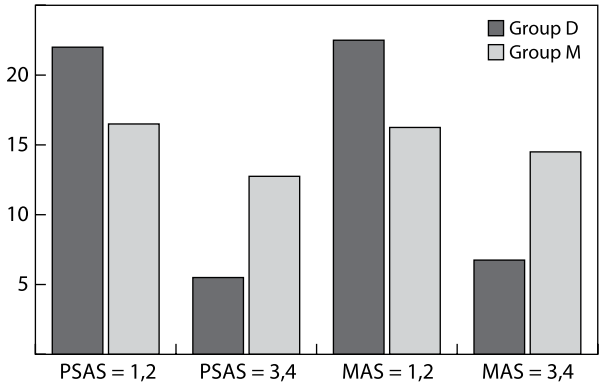

Figure 2: Parental separation anxiety scale and mask acceptance scale in groups D and M.

Group D patients received intranasal dexmedetomidine (1 µg/kg) and group M patients were given intranasal midazolam (0.2 mg/kg) approximately 30 minutes before induction of anaesthesia, in the form of a spray. Both the drugs used were free of any kind of preservative. Children were made to lie on one side (lateral position) and the calculated dose of drug diluted to a total volume of 1 ml was administered, 0.5 ml in each nostril, with the help of a spray device fitted on the top of a syringe (Figure 1). The investigator (anaesthesiologist) involved in preparing and administering the drug was different from the one (anaesthesiologist) responsible for further assessment and management of the patient.

Vital signs (heart rate, blood pressure, oxygen saturation) were recorded before administering the intranasal drug and again at an interval of every 10 minutes, for 30 minutes. The Modified Observers Assessment of Alertness/Sedation Scale (MOAA/S) (Table 1)[11] was used to assess sedation. Also the response to parent separation was assessed at 30 minutes and was graded on a four-point

Table 1: Modified observer's assessment of alertness/sedation scale

Scale item	Score
Agitated	**6**
Responds readily to name spoken in normal tone (alert)	5
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Does not respond to mild prodding or shaking	1
Does not respond to deep stimulus	0

Table 2: Parental separation anxiety scale

Behaviour of the child during separation from parents	Criteria	Score
Excellent	Patient unafraid, cooperative, or asleep	1
Good	Slightly afraid/crying, quiet with reassurance	2
Fair	Moderately afraid and crying, not quiet with reassurance	3
Poor	Crying, need for restraint	4

Parental Separation Anxiety Scale (PSAS) (Table 2).[12–14] Thirty minutes after premedication children were taken into the operating room and acceptance of a mask was assessed using the Mask Acceptance Scale (MAS) (Table 3).[12–15] Children were transported to the operating room where mask induction was carried out with 4–5% sevoflurane in oxygen via a Jackson Rees circuit.

Statistical analysis

Data were analysed using SPSS® version 16 (Statistical Packages for the Social Sciences, Chicago, IL, USA). Results were expressed as mean ± standard deviation (SD) or numbers (percentages). Quantitative data were compared using one-way analysis of variance (ANOVA) and unpaired *t*-test; qualitative data were analysed using a chi-square test. A *p*-value of < 0.05 was considered statistically significant.

Results

A total of 60 children were randomly divided into two groups with 30 patients each. Demographic characteristics of both groups, i.e. age, sex and weight, were comparable. Children underwent minor surgical procedures such as tonsillectomy, hernia repair, squint surgery or minor orthopaedic procedures like K-wiring etc. The duration of anaesthesia and surgery was similar in both groups (Table 4). No local or regional anaesthesia was administered to these children apart from general anaesthesia.

There were no significant differences between groups in baseline preoperative heart rate, blood pressure and oxygen saturation prior to premedication. After premedication, heart rate and systolic blood pressure were significantly lower in children who received dexmedetomidine, at 10, 20 and 30 minutes (Table 5); there was no significant difference in oxygen saturation between groups. The MOAA/S scores were comparable in both groups before premedication. However, group D had a significantly lower MOAA/S (Table 5) score at the time of transfer to the operating theatre (*p*-value 0.003). A greater number of children in group D achieved a parental separation and mask acceptance of 1 or 2 when compared with group M but this was not statistically significant (Table 6). Both parental separation score (*p*-value 0.0234) and mask acceptance score (*p*-value 0.0472) was significantly lower in group D (Figure 2, Table 7). None of the children in either group had any undesirable effects like hypotension, bradycardia, vomiting, excessive sedation, nasal irritation etc.

Discussion

Midazolam is the most commonly used anxiolytic premedication in young children. It facilitates gamma amino butyric acid (GABA) receptor-mediated chloride conductance, which has an inhibitory effect on neurons in the cerebral cortex. It has been successfully used through various routes, e.g. intravenous, intramuscular, oral

Table 3: Response to induction (mask acceptance scale)

1	Combative, crying
2	Moderate fear of mask, not easily calmed
3	Cooperative with reassurance
4	Calm, cooperative

and intranasal.[2] A study by Malinovsky et al.[16] also showed that intranasal midazolam 0.2 mg/kg has a faster onset of sedation compared with other routes. Recently, α2-receptor agonists such as dexmedetomidine have also been found to be useful for premedication in children. These drugs act on central α2 receptors located at the presynaptic terminal where they mainly cause inhibition of release of noradrenaline.[17] The site of action of dexmedetomidine is in locus coeruleus where it causes EEG activity similar to normal sleep. This results in anxiolytic effects, sedation and analgesia without excessive drowsiness.[18] The intranasal route was used in our study as it is non-invasive, unlike intravenous and intramuscular routes, and produces a more rapid onset of action than the oral route.

Our study confirms other reports comparing dexmedetomidine with midazolam premedication that found a stable heart rate and blood pressure, and better parent separation and mask acceptance, with comparable sedative effects. Previous studies[10,19,20] have found dexmedetomidine to be highly effective compared with midazolam. Mustafa et al.[19] compared intranasal dexmedetomidine with intranasal midazolam and ketamine and found that dexmedetomidine achieved faster sedation and better child–parent separation scores. In a study by Yuen et al. intranasal dexmedetomidine was found to produce more sedation than oral midazolam.[21]

The dose of intranasal dexmedetomidine of 1 µg/kilogram has been shown to have a time of sedation onset of approximately 25 minutes and median duration of approximately 85 minutes.[21] However, Telon et al. reported that with a dose of 2 µg/kg onset time of intranasal dexmedetomidine was 15 minutes when administered with a metered dose atomizer.[22] Also it has been shown that bio-availability of an intranasal drug is greater when used in the form of a spray.[23] In our study both midazolam and dexmedetomidine were administered in the form of a spray and children were observed for 30 minutes before induction. Therefore the MOAA/S was significantly less at 30 minutes after intranasal dexmedetomidine. This also resulted in easier child–parent separation and better mask acceptance.

Table 4: Demographic data of patients

Item	Midazolam group (n = 30)	Dexmedetomidine group (n = 30)
Age (years)	5.91 ± 0.46	5.86 ± 0.40
Sex (M:F)	14:16	17:13
Weight (kg)	18.25 ± 4.28	17.92 ± 4.18
Duration of anaesthesia (min)	34.54 ± 4.01	33.89 ±3 .28
Duration of procedure (minutes)	26.43 ± 3.96	25.71 ± 4.09

Table 5: Comparison of preoperative vitals and modified observer's assessment of alertness/sedation scale in midazolam group and dexmedetomidine group

Factor		Time interval (minutes)	Midazolam group (n = 30)	Dexmedetomidine group (n = 30)	p-value
Heart rate	Before premedication	0	112.76 ± 7.14	113.07 ± 6.78	0.434
	After premedication	10	108.43 ± 6.71	101.43 ± 9.77	0.002
		20	106.03 ± 5.11	99.2 ± 6.905	0.001
		30	99.93 ± 5.71	94.23 ± 9.33	0.006
Systolic blood pressure	Before premedication	0	107.43 ± 6.15	107.5 ± 7.06	0.969
	After premedication	10	107.63 ± 6.020	104.17 ± 5.712	0.0258
		20	107.8 ± 6.69	103.7 ± 7.32	0.0273
		30	106.67 ± 6.92	102.83 ± 6.54	0.0315
Oxygen saturation	Before premedication	0	98.5 ± 1.106	98.23 ± 1.07	0.347
	After premedication	10	98.3 ± 1.022	98.77 ± 1.10	0.095
		20	98.6 ± 1.1.163	98.83 ± 1.085	0.425
		30	97.93 ± 1.048	97.9 ± 0.84	0.892
Modified observer's assessment of alertness/ sedation scale	Before premedication	0	4.8 ± 0.99	4.86 ± 1.008	0.797
	After premedication	10	3.43 ± 0.89	3.33 ± 1.03	0.689
		20	3.53 ± 1.14	2.93 ± 1.143	0.352
		30	3.23 ± 0.82	2.4 ± 0.855	0.003

Table 6: Comparison of parental separation anxiety scale and mask acceptance scale in midazolam group and dexmedetomidine group

Factor		Midazolam group (*n* = 30)	Dexmedetomidine group (*n* = 30)
Parental Separation Anxiety Scale	No separation problems (score = 1 or 2)	17	24
	Separation problems (score = 3 or 4)	13	06
Mask Acceptance Scale	Good acceptance (score = 1 or 2)	16	23
	Poor acceptance (score = 3 or 4)	14	07

Table 7: Parental separation anxiety score and mask acceptance score in midazolam group and dexmedetomidine group at the time of transfer to the operating theatre

Mean ± SD	Midazolam group (*n* = 30)	Dexmedetomidine group *(n = 30)*	*p*-value
Parental Separation Anxiety Scale (PSAS)	2.333 ± 0.9942	1.800 ± 0.7611	0.0234
Mask Acceptance Scale (MAS)	2.333 ± 1.028	1.833 ± 0.8743	0.0472

Our study showed that dexmedetomidine reduces both pulse rate and systolic blood pressure in the preoperative period, though clinically significant hypotension or bradycardia was not observed in children in group D. Children who received intranasal dexmedetomidine premedication had lower anxiety levels, and better mask acceptance and parental separation compared with intranasal midazolam. However, the statistical significance of the analgesic-sparing effect could not be determined due to the small sample size. Our study was designed to compare the efficacy of two drugs for premedication in children. So a sample size just adequate for this purpose was calculated and studied. Therefore, further studies with higher sample size are required to establish the usefulness of intranasal dexmedetomidine as perioperative anxiolytic in children.

Conclusion

In conclusion, premedication with intranasal dexmedetomidine 1 µg/kg resulted in lower anxiety levels, and better parent separation and mask acceptance as compared with intranasal midazolam 0.2 mg/kg and would seem to offer some advantage.

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