INTRANASAL DEXMEDETOMIDINE VS. INTRANASAL MIDAZOLAM FOR PREMEDICATION OF PAEDIATRIC SURGERY PATIENTS

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ABSTRACT

AIM

Preoperative anxiety is one of the most common problems faced by anyone practising paediatric anaesthesia. Various drugs have been used in various routes to get a calm but cooperative child before induction of anaesthesia. Midazolam and dexmedetomidine have already proved their value in paediatric premedication. This study was conducted to compare the effects of these two drugs given intranasally.

MATERIALS AND METHODS

100 children falling under the inclusion criteria were assigned to groups of 50 each. They received either intranasal midazolam 0.2 mg/kg (group M) or intranasal dexmedetomidine 2 mcg/kg (Group D) as premedication. They were compared with regards to the sedation status, anxiety levels and cardiovascular status every 10 minutes, at parental separation and at face mask application.

RESULTS

The mean sedation score obtained at all-time intervals, at parental separation and more importantly at mask induction were much lower for the midazolam group compared to the dexmedetomidine group. The mean anxiety levels, in general, were lower in the midazolam group, but they attained statistical significance only at 10 minutes and at mask induction. The heart rate measured up to 20 minutes after drug administration did not show much difference between both groups, but at 30 minutes, 40 minutes and at parental separation, heart rate was found to be lower in the dexmedetomidine group.

CONCLUSION

Intranasal dexmedetomidine and intranasal midazolam are equally effective in providing satisfactory parental separation, but intranasal midazolam produced superior conditions for mask acceptance than intranasal dexmedetomidine.

KEYWORDS

Intranasal, Midazolam, Dexmedetomidine, Paediatric, Premedication.

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INTRODUCTION: Preoperative anxiety is one of the most common problems faced by anyone practising paediatric anaesthesia. Anxiety felt by the child's parent may be reflected onto the child as well.[1] Extreme preoperative anxiety can prolong the duration of induction, and lead to negative psychological effects postoperatively like nightmares, nocturnal enuresis and eating disturbances.[2] Therefore, effective premedication should be formulated to overcome these problems and facilitate a smooth induction of anaesthesia. Various pharmacological agents were tried as premedicants in children of which the most commonly used agent these days is midazolam, a gamma amino butyric acid (GABA A) receptor inhibitor.

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It offers excellent anxiolysis, amnesia and sedation, but was shown to have various side effects like paradoxical aggressive behaviour and hiccups.[3] Dexmedetomidine is a newer more selective alpha-2 agonist and has a shorter half-life than clonidine. It has anxiolytic, analgesic, sedative properties with an anaesthetic sparing effect. It is also tasteless, odourless and painless.[4] A non-invasive method of premedication is preferable because most of the children exhibit an exaggerated psychological response towards the needle. Oral and rectal are not ideal because it is difficult to titrate the dose and there is considerable delay in onset. Intranasal route is preferable because they are associated with a faster onset and minimal first pass metabolism. Here, we decided to compare the effects of dexmedetomidine with that of midazolam both drugs administered intranasally. The objectives of the study were to compare the effect of these two drugs on parental separation, haemodynamic changes during premedication and face mask acceptance during induction of anaesthesia.

MATERIALS & METHODS: After obtaining clearance from the ethical committee of the institution, a prospective cohort study was undertaken at Amala Institute of Medical Sciences over a period of 19 months (Jan 2014 to July 2015) on paediatric patients, aged between 2-12 and falling in ASA grade 1 and 2 classification, who are posted for elective surgeries.

The sample size of the study was taken at 100 after examining the results of similar studies done earlier. Children who had allergy to either midazolam or dexmedetomidine were excluded from the study. After a detailed pre-anaesthetic evaluation, the parents of the children participating in the study were informed of the procedure and consent obtained. The baseline pulse rate, blood pressure and oxygen saturation by pulse oximetry were recorded. 50 Children then received intranasal midazolam 0.2 mg/kg (M group) and 50 children received intranasal dexmedetomidine 1 mcg/kg (D group) as premedication. Children were separated from parents by 50 minutes and were anaesthetised by inhalation induction with a face mask. The following parameters were then monitored at premedication, thereafter every 10 minutes, at parental separation and at mask induction.

1. Sedation status by 6-point Observer assessment of Alertness and Sedation scale (OAA/S).
2. Anxiety levels by a 4-point scale (1=Calm, 2=Anxious but could be re assured, 3=Anxious but cannot be reassured, 4=Crying/Resisting). Anxiety levels at mask induction was measured by a 3-point scale (1=Calm, cooperative or asleep, 2=Moderate fear of mask, 3=Crying or Combative).
3. Pulse rate, blood pressure and oxygen saturation by pulse oximetry.
4. Patients were monitored for any other complications also.

6	Appears alert and awake, responds readily to name spoken in normal tone.
5	Appears asleep but responds readily to name spoken in normal tone.
4	Lethargic response to name spoken in normal tone.
3	Responds only after name is called loudly or repeatedly.
2	Responds only after mild prodding or shaking.
1	Does not respond to mild prodding or shaking.
0	Does not respond to noxious stimulus.

Table 1: Modified Observer's Assessment of Alertness/Sedation

All data collected were coded and entered in Microsoft Excel sheet and analysed using SPSS software. Statistical test was done using Mann Whitney and student T-test. A p value of <0.05 was taken as significant.

RESULTS:

Demographic Data: Patients were well matched with regard to age, weight, sex and ASA physical status (Table 2).

Variable	Group Dexmedetomidine	Group Midazolam
Age (Years)	6.65±2.8883	6.6 ±2.2767
Weight (KG)	19.86±7.2139	19.64±5.3861
Sex (M/F)	27/23	26/24
ASA Grading (1/2)	47/3	47/3

Table 2: Demographic Data

Hemodynamic Variables: The heart rate measured up to 20 minutes after drug administration did not show much difference between both groups, but at 30 minutes, 40 minutes and at parental separation, heart rate was found to be lower in the dexmedetomidine group and this was found to be statistically significant (p< 0.05). There was no need for any rescue medications. Systolic and diastolic pressures were found to be lower in midazolam group during mask induction, probably because of increased sedation in children of this group. Prior to mask induction, systolic and blood pressure values were lower in dexmedetomidine group, but it was not found to be statistically significant. There was no difference in the oxygen saturation among the two groups (Diagram: 1).

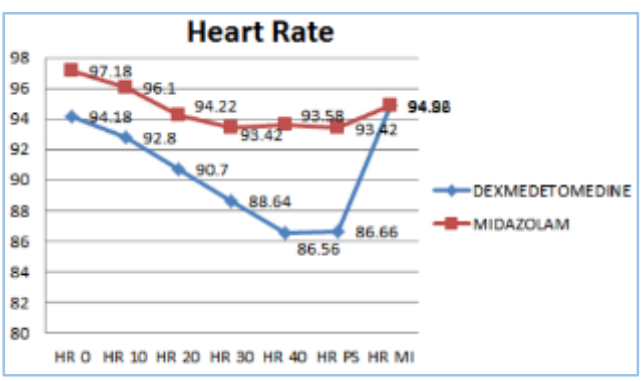

Diagram 1: Heart Rate at Various Time Intervals

The mean sedation score obtained at all-time intervals, at parental separation and more importantly at mask induction were much lower for the Midazolam group compared to the dexmedetomidine group. These differences were statistically significant too. (Table 3)

Sedation Score (Time in Minutes)	Group		P value
	Dexmedetomidine (50)	Midazolam (50)	
SED 0	6.0±0.0	6.0±0.0	-
SED 10	5.38±0.602	4.72±0.454	0.0001
SED 20	4.30±0.735	3.94±0.512	0.005
SED 30	3.92±0.566	3.46±0.503	0.0001
SED 40	3.68±0.513	3.18±0.388	0.0001
SED PS	3.64±0.485	3.26±0.600	0.001
SED MI	5.18±1.004	3.66±1.062	0.0001

Table 3: Comparison of Sedation Scores at Various Time Intervals

The mean anxiety levels, in general, were lower in the midazolam group but they attained statistical significance only at 10 minutes and at mask induction. The anxiety level at parental separation was higher in the midazolam group but it was not statistically significant. (Table 4).

Anxiety Score (Time In Minutes)	Group		P value
	Dexmedetomidine (50)	Midazolam (50)	
ANX 0	2.22±0.465	2.32±0.741	0.421
ANX 10	1.68±0.587	1.44±0.501	0.030
ANX 20	1.06±0.240	1.02±0.141	0.312
ANX 30	1.0±0.0	1.0±0.0	-
ANX 40	1.0±0.0	1.0±0.0	-
ANX PS	1.0±0.0	1.10±0.364	0.055
ANX MI	1.98±0.845	1.52±0.762	0.005

Table 4: Mean Anxiety Scores at Various Time Intervals

DISCUSSION: Premedication in children is a challenging step to reduce anxiety and provide a calm and cooperative child for smooth induction. It can be administered via various routes, but in children a needle less approach is preferred. These include oral, intranasal, buccal and rectal routes. Of these, transmucosal routes like intranasal and buccal have a faster onset of action and a better bioavailability than oral or rectal routes. We chose the intranasal route because it offers rapid onset of action and the bitter taste associated with the drugs, especially midazolam could be avoided.

Midazolam is one of the most commonly used drugs for premedication. Yildirim SV[5] et al, while administering midazolam for echocardiography in infants, have shown that intranasal route is better tolerated than the oral route. Dexmedetomidine has also gained popularity for premedication in paediatric patients and the intranasal routes have been studied by Yuen et al.[6] Even though there are studies.[7] which have shown that intranasal midazolam at 0.3 mg/kg is safe and achieves faster sedation and better separation scores as compared to 0.2 mg/kg, we decided to go ahead with a dose of 0.2 mg/kg for safety reasons. On similar grounds, we decided to go ahead with a dose of 1 mcg/kg of dexmedetomidine for premedication even though Yuen V M et al[8] in their study have shown that dexmedetomidine in a dose of 2 mcg/kg produced more satisfactory sedation in children of age 5-8 than 1 mcg/kg.

We thought it would be fair to the drugs only if we compare them in equivalent doses. One of the main drawbacks of intranasal premedication is the time needed to get optimal effects of the individual drugs. Drugs should be reasonably quick to act and undue prolongation for time of optimal sedation will have a negative effect on both the anaesthesiologist and the parent. There are studies.[9] which have reported greatest sedation at 90-150 minutes for intranasal dexmedetomidine. Intranasal midazolam is slightly quicker to give optimal sedation. Kogan et al[10] while comparing four different routes of premedication with midazolam has shown the peak effect of sedation for intranasal midazolam at around 20 minutes.

They were; however, using a dose of 0.3 mg/kg. Hence we decided to compare these drugs at an intermediate period, parental separation at 50 minutes and mask acceptance at 60 minutes. Both groups were comparable with regard to age, sex weight and ASA status. The baseline pulse rate, blood pressure and oxygen saturation were also comparable.

After administration of the drugs, there was a lowering of the heart rate in both the groups at 10 minutes and 20 minutes. But this fall was not statistically significant when the two groups were compared.

However, at 30 minutes, 40 minutes and at parental separation, the fall in heart rate in the Dexmedetomidine group was statistically significant ($p < 0.05$). This fall in heart rate did not require any interventions. However, there was no difference at mask induction. This significant drop in heart rate after 30 minutes may be explained by the peaking of the effect of drug at that time. The systolic and diastolic blood pressure was on the lower side in the Dexmedetomidine group. However, this was not significant. At mask induction, the blood pressure was lower in the midazolam group when compared to the dexmedetomidine group. This may be because of better sedation in the midazolam group at mask induction. There was no fall in the oxygen saturation in either of the groups. Dexmedetomidine as premedication is known to produce a fall in heart rate and blood pressure.[11] A systematic review and meta-analysis by Ke Peng et al[12] have shown a lower heart rate in patients receiving dexmedetomidine. Singla et al[13] noted clinically insignificant lower heart rate and blood pressure at 10, 20 and 30 minutes after drug administration.

However, a study by Sheta et al[14] did not find any fall in heart rate or blood pressure. The fall in heart rate may be due to a direct alpha 2 activity or as a sequelae of sedation. In our study, we found that the sedation scores were significantly lower in the midazolam group at all the time intervals. The values were highly significant statistically too. Intranasal dexmedetomidine provided satisfactory sedation at parental separation but not satisfactory at mask acceptance (60% achieved satisfactory mask acceptance).

Intranasal midazolam was effective during parental separation as well as mask acceptance (84% satisfactory mask acceptance). There are studies showing better mask acceptance with dexmedetomidine than midazolam.[15] but the dose of midazolam used was 50% of our dose while the dose of dexmedetomidine was double. Study by Singla et al[13] had found, at doses used by us, dexmedetomidine better than midazolam at both parental separation and mask acceptance. Whether an intranasal spray (as used by them) has any advantage over the traditional intranasal instillation (as used by us) needs further analysis. Akin et al[16] compared intranasal dexmedetomidine and intranasal midazolam in children undergoing elective adenotonsillectomy.

The results obtained were similar to that of our study. They also used an IV preparation mixed in saline for intranasal administration. The patient population in their study was also similar to our study. It was seen in our study that midazolam group had lower anxiety scores at 10, 20 and 30 minutes than dexmedetomidine which was clinically insignificant. This could be explained by the faster peak onset time of intranasal midazolam. During parental separation, both dexmedetomidine and midazolam offered good anxiolysis. Midazolam was found to be better at the

time of mask acceptance since it had significantly lower anxiety scores than dexmedetomidine (P=0.005).

The major limitation in this study would be the issue of optimal timing of parental separation after drug administration. It could have been possible that the peak effect of midazolam would have passed at the time of parental separation. The peak effect of dexmedetomidine may not have been achieved at the time of parental separation or mask induction, which could explain the unsatisfactory anxiety scores at mask induction.

The study also can't guarantee that equivalent doses of the drugs were compared. The inclusion of 3-point scale for anxiety evaluation was also very subjective and could have interfered with the results. Other problems of intranasal administration like itching in the nose and possible side effects like nausea and vomiting were also not evaluated.

CONCLUSION: Intranasal dexmedetomidine and intranasal midazolam are equally effective in providing satisfactory parental separation, but intranasal midazolam produced superior conditions for mask acceptance than intranasal dexmedetomidine.

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