

A Comparison of Intranasal Dexmedetomidine and Intranasal Midazolam for Premedication in Children Undergoing Elective Surgeries

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Abstract: *Relieving pre-operative anxiety is an important concern for anaesthesiologists in case of children and it is a challenging problem. If not managed in a considered and structured fashion, it can lead to distress for the child, parents, and the operating theatre staff involved. Midazolam has been the most widely used sedative agent, with a long history of safety and efficacy. But it has side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia, and respiratory depression. Paradoxical reactions can result in a restless and agitated child. Dexmedetomidine is a new potent and highly selective α -2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties, which has been described as a useful and safe adjunct in many clinical applications. It provides a unique "conscious sedation" (patients appear to be asleep, but are readily roused), analgesia, without respiratory depression. In our study children who were premedicated with intranasal Dexmedetomidine (1 μ g/kg) were more significantly sedated at the time of parental separation, at mask acceptance as compared to Midazolam (0.2mg/kg), and was comparable at venipuncture.*

Keywords: intranasal, dexmedetomidine, premedication, venipuncture, children

1. Introduction

Relieving pre-operative anxiety is an important concern for anaesthesiologists in case of children and it is a significant and challenging problem. If not managed in a considered and structured fashion, it can lead to distress for the child, parents, and the operating theatre staff involved. The link between preoperative anxiety in children and an increased incidence of adverse postoperative clinical outcomes is of considerable concern. Pre-induction techniques in paediatric anaesthesia are primarily focused on relieving the pre-operative anxiety of the child; however consideration of parental anxiety is also important.(1)

Children from 6 months of age to 4 years of age have previously been reported to experience the greatest negative postoperative behaviour changes and benefit from premedication. Premedication is commonly used to reduce preoperative anxiety, to facilitate separation from parents and to promote acceptance of mask induction.(2)

A variety of drugs have been used as premedication in paediatric patients. To name a few:- Chloral hydrate (3), Phenothiazines (4), Diazepam (5), Midazolam (5), Fentanyl (1), Ketamine(6), Clonidine(7), Dexmedetomidine(8).

Midazolam has been the most widely used agent, with a long history of safety and efficacy. It produces adequate sedation with fast onset, and limited duration of action and despite having these beneficial effects, it is far from an ideal pre-medicant as it has side effects such as restlessness, paradoxical reaction, cognitive impairment, amnesia, and respiratory depression. Paradoxical reactions can result in a restless and agitated child and are most common after IV administration. (1)

Dexmedetomidine is a new potent and highly selective α -2 adrenoceptor agonist with sympatholytic, sedative, amnestic, and analgesic properties, which has been described as a useful and safe adjunct in many clinical

applications. It provides a unique "conscious sedation" (patients appear to be asleep, but are readily roused), analgesia, without respiratory depression.(9)

Several reports are now available for IV Dexmedetomidine for both non-invasive and invasive procedural sedation in infants and children. An interesting future for Dexmedetomidine is oral or nasal administration for paediatric sedation.

In our study we are evaluating the sedative and anxiolytic effect of Dexmedetomidine as compared to Midazolam administered via intranasal route for paediatric sedation. The hemodynamic stability after administration of both Midazolam and Dexmedetomidine is also being evaluated.

2. Material and Methods

In this randomised double blind study we compared intranasal Dexmedetomidine and intranasal Midazolam for premedication in paediatric patients posted for elective surgeries in our institute. This study was conducted on 60 paediatric patients of age 2 to 9 years of American Society of Anaesthesiologists Physical Status of I and II after approval of institutional ethics committee for conduct of the study. Exclusion Criteria were Known allergies or hypersensitivity to Dexmedetomidine or Midazolam. Any nasal pathologies, surgeries, upper respiratory tract infections, h/o central nervous system disorder, mental retardation, cardiac arrhythmias or congenital heart disease, organ dysfunction. Children who do not allow complete dose administration. Children on drugs causing nausea, vomiting. Parents refusal.

A pre-operative visit was made one day prior to elective surgery. Main motive of the pre-operative visit was to gain the confidence of the child and his/her parents and to get them familiar with the procedure to be done next day and also explain the importance of premedication to the parents. This would help the child to be less anxious and more

acceptable to the medication and their parents to be more comfortable prior to surgery. All patients were fasted overnight with clear fluids allowed until 4 hours pre-operatively. Patients were randomly divided in two equal groups. Randomization with permuted blocks was used to achieve balance between the treatment groups, i.e. 30 patients in each treatment group. GROUP D (n=30): to receive (1 µg/kg) intranasal Dexmedetomidine one hour prior to surgery. GROUP M (n=30): to receive (0.2mg/kg) intranasal Midazolam one hour prior to surgery.

Intranasal Dexmedetomidine was prepared from the 100 µg per ml parenteral preparation, in a 1ml syringe with saline to make a final volume of 0.5 ml. Intranasal Midazolam was prepared from preservative free injectable preparation and the concentration of the drug was 5 mg/ml. This helped in limiting the drug volume, which has major pharmacokinetic importance in intranasal route

Child was placed in recumbent position in the lap of one of the parents and intranasal drug was dripped into both the nostrils using a 1ml syringe (without needle). Drugs were administered as drop by drop to avoid wastage of the drug through anterior and posterior nostrils.

Baseline heart rate, oxygen saturation and blood pressure, respiratory rate were recorded before the administration of the study drug and every 10 minutes after that until the child was transferred to operating room.

Sedation and anxiety levels were assessed before administration of the study drug and every 10 minutes after that till the child was transferred to operating room.

Sedation status was assessed with 6-point sedation scale, which was modified from the Observer Assessment of Alertness and Sedation Scale(8)(Table 1) and behaviour was assessed every 10 minutes with 4-point Behaviour Score(8) (Table2).

Those children who were not satisfactorily sedated were given rescue sedation with intramuscular Ketamine and taken into the operating room.

The study drug was prepared by an anaesthetist who did not participate in the collection of data and the observing anaesthetist and the anaesthetist conducting the case were blinded to the drug given.

After transferring of the patient to operation theatre, standard monitors were attached and heart rate (HR), oxygen saturation (SpO₂), non-invasive blood pressure (NIBP), respiratory rate (RR) were recorded. Sedation score was recorded on arrival in operating room.

An intravenous line was secured after the patient arrived in the operating room. At the time of venipuncture children were assessed for response to venipuncture using the behaviour scale (Table 2). Intravenous fluid was started according to weight of the child. Induction was done by inhalation method with the use of mask, and at that time mask acceptance was assessed using a mask acceptance score(10).(Table 3)

Table 1

| Sedation Score | | |
|----------------|---|----------------|
| Score | | |
| 1 | Does not respond to mild prodding or shaking | Satisfactory |
| 2 | Responds only to mild prodding or shaking | |
| 3 | Responds only after name is called loudly or repeatedly | |
| 4 | Lethargic response to name spoken in normal tone | |
| 5 | Appears asleep but responds readily to name spoken in normal tone | Unsatisfactory |
| 6 | Appear alert and awake, responds to name in normal tone | |

Table 2

| Behaviour Scale | | |
|-----------------|----------------------------|----------------|
| Score | | |
| 1 | Calm and cooperative | Satisfactory |
| 2 | Anxious but reassuring | |
| 3 | Anxious and not reassuring | Unsatisfactory |
| 4 | Crying, or resisting | |

TABLE 3:

| Mask Acceptance Score | | |
|-----------------------|------------------------------|----------------|
| Score | | |
| 1 | Combative and crying | Unsatisfactory |
| 2 | Moderate fear of mask | |
| 3 | Cooperative with reassurance | Satisfactory |
| 4 | Calm | |
| 5 | Asleep | |

Statistical Methods

The demographic data on patients treated with Dexmedetomidine and Midazolam was obtained and summarized in terms of numbers and percentages. Descriptive statistics like mean, standard deviation, range and median were obtained for parameters like heart rate, systolic BP, SPO₂ and respiratory rate for patients in two groups at different time points. The significance of difference in the mean values of parameters at different times was determined using t-test for independent samples. Also, the analysis was performed longitudinally to determine the significance of change in the mean levels of each parameter with time independently in two treatment groups. One-way repeated measure analysis of variance (ANOVA) was used to determine the significance of difference across time points. The sphericity assumption was assessed for each parameter using Mauchly's sphericity test and accordingly the F-value and the corresponding p-value was used to conclude about significance. The sedation score at different time points was summarized in terms of above statistical measures for both the treatment groups. The significance of difference in the distribution of scores in two groups was determined using Wilcoxon rank sum test. The behaviour score between two groups at different time points was also assessed using Wilcoxon rank sum test. The mask acceptance between the groups was evaluated for significance of difference using t-test for independent samples. The descriptive statistics for above study parameters at venipuncture were evaluated for significance of difference between groups using t-test for independent samples and Wilcoxon rank sum test. All the analyses were performed using SPSS 18.0 (SPSS Inc.) software and the level of significance was tested at 5%.

3. Results

The demographic characteristics of the patients in the two groups, group D, group M, were comparable with respect to age, gender, weight, and ASA status. The basal hemodynamic parameters i.e. heart rate, systolic blood pressure, respiratory rate and oxygen saturation of the two groups were comparable.

The mean sedation score at separation from parents was 2.47 in Dexmedetomidine group and 4.27 in Midazolam group. The difference in sedation at parental separation was statistically significant. ($p < 0.05$)

We compared the anxiety with a pre-decided 4 point behaviour score. In the Midazolam treatment group, the initial mean score was 2.73. With time it decreased and attained the lowest of 1.87 at 20th min. Subsequent to that, it increased to 2.27 at 50 min. and continued till 60th min.

In the Dexmedetomidine group, the mean behaviour score at baseline was 2.63. Subsequently, with time, the mean score reduced and attained the lowest of 1.47 at 40 min. Later at 50th min, the mean score marginally increased to 1.53 and continued till 60th min. The difference in the behaviour scores between two groups was evaluated at each time point for statistical significance. It is evident that up to 10 min, the difference of behavioural scores between two groups was insignificant, while at later times, the scores in Dexmedetomidine group was significantly lower than that of Midazolam group as indicated by p-values < 0.05 .

In Dexmedetomidine group at the time of parental separation children were less anxious as compared to the Midazolam group as behaviour score was lower in the Dexmedetomidine group which was statistically significant.

The statistical significance of difference between the mean heart rate of two groups at different time points was evaluated. The heart rate at baseline in both the groups was comparable. It dropped after 10 min. of pre-medication till the 50 min. The mean heart rate in Midazolam group was significantly higher than that of Dexmedetomidine group at these time points.

The drop in both the groups was statistically significant at regular intervals with ($p < 0.05$). and bradycardia can be explained on the basis of adequate sedation in both the groups more so in the Dexmedetomidine group. The heart rate analysis was performed across times in each treatment group independently. In the Midazolam treatment group, test resulted into a p-value of 0.0274 ($p < 0.05$) indicating significant variability across time points in the group, implying significant difference in the mean heart rate across time points in this treatment group. Pair wise comparison of mean heart rate revealed significant change in first 20 min. However, at later times the change was insignificant till 50 min. At 60th min, there was significant increase in the mean heart rate as indicated by p-value of 0.0133 ($p < 0.05$). which corresponds to the point of parental separation.

Similarly, in Dexmedetomidine group, the test resulted into a p-value of 0.0132 ($p < 0.05$) indicating significant

variability of heart rate across time points. This implied statistically significant difference of mean heart rate across time points in this group. It shows that the mean heart rate decreased significantly at consecutive time points till 50 min ($p < 0.05$). At 60th min, the change in the heart rate was statistically insignificant as indicated by p-value of 0.5632 ($p > 0.05$).

At baseline in Midazolam treatment group, the mean systolic BP was 99.07 mmHg and in Dexmedetomidine group, the mean systolic BP of patients was 100.27 mmHg. and the values were comparable ($p > 0.05$). At subsequent time points, the mean systolic BP dropped down to lowest of 92.7 mmHg till 40 min and then showed a marginal increase at 60 min. in Dexmedetomidine group whereas in Midazolam group the blood pressure remained more or less near the baseline values. The difference in mean blood pressure was statistically significant after 30 min. in between the groups. ($p < 0.05$)

In both Midazolam and Dexmedetomidine groups, the mean SpO₂ was consistently close to 98% till 60 min. This data shows that oxygen saturation is maintained in both the groups. SpO₂ reduction was never $< 95\%$ in any of the groups. In Midazolam and Dexmedetomidine group, the baseline respiratory rates were comparable however after 30 min. the mean difference was statistically significant between the groups. The respiratory rate remained more stable in Dexmedetomidine group however the variation in Midazolam was clinically irrelevant as no fall in oxygen saturation below 95% was seen.

Behaviour scores at venipuncture; in Midazolam treatment was 2.03 where as in Dexmedetomidine treatment it was 2.00. The difference in distribution of behaviour scores between groups was statistically insignificant with p-value of 0.7568 ($p > 0.05$).

In our study though the sedation score in the operating room was more in Dexmedetomidine group, the behaviour at venipuncture in both the intranasal Dexmedetomidine and intranasal Midazolam group was comparable. The degree of sedation reduces on interventions, such as venipuncture and mask application, which goes along the lines of the unique feature of easy arousability on stimulation that is characteristic of Dexmedetomidine.

In Midazolam group, mask acceptance score was 2.93 and in Dexmedetomidine treated group, the mean mask acceptance score was 3.3. The difference between two means was statistically significant with p-value of 0.0013 ($p < 0.05$).

Table 4: Distribution of patients according to age for two treatment groups

| Age interval (years) | Dexmedetomidine [No. (%)] | Midazolam [No. (%)] |
|----------------------|---------------------------|---------------------|
| 2-3 | 8 (26.67) | 7 (23.33) |
| 4-5 | 5 (16.66) | 7 (23.33) |
| 6-7 | 9 (30.00) | 10 (33.34) |
| 8-9 | 8 (26.67) | 6 (20.00) |
| Total | 30 | 30 |

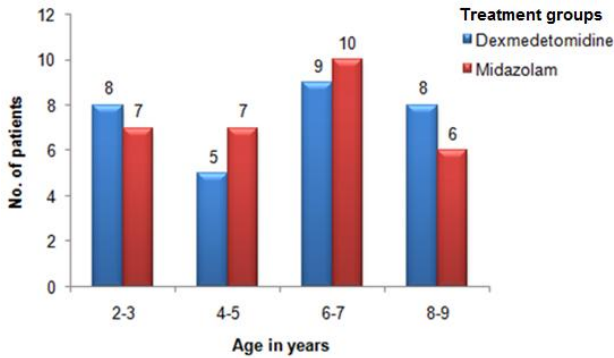


Figure 1: Bar chart showing the distribution of patients as per age for Dexmedetomidine and Midazolam treatment groups

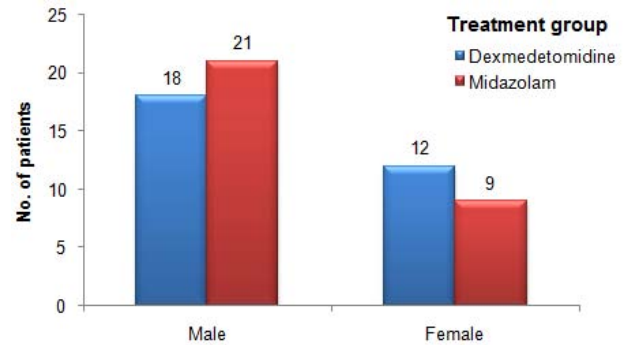


Figure 2: Bar chart showing the distribution of patients as per gender for Dexmedetomidine and Midazolam treatment groups

Table 5: Distribution of patients as per gender in two treatment groups

| Gender | Dexmedetomidine [No. (%)] | Midazolam [No. (%)] |
|--------|---------------------------|---------------------|
| Male | 18 (60) | 21 (70) |
| Female | 12 (40) | 9 (30) |
| Total | 30 | 30 |

Table 6: Distribution of weight in both the groups

| Weight of the children (kg) | | P- value |
|-----------------------------|----------------|----------|
| Dexmedetomidine | Midazolam | |
| 15.067(2.935) | 15.033 (2.710) | 0.9637 |

Using *chi-square* test

Table 7: Descriptive statistics for sedation scale according to different time points for Dexmedetomidine and Midazolam treatments

| Time (min) | Sedation scale - Dexmedetomidine | | | | Sedation scale - Midazolam | | | | P-value* |
|------------|----------------------------------|------|-------|--------|----------------------------|------|-------|--------|----------|
| | Mean | SD | Range | Median | Mean | SD | Range | Median | |
| 0 | 6.00 | 0.00 | 6 - 6 | 6 | 6.00 | 0.00 | 6 - 6 | 6 | - |
| 10 | 5.33 | 0.55 | 4 - 6 | 5 | 6.00 | 0.00 | 6 - 6 | 6 | < 0.0001 |
| 20 | 3.40 | 1.52 | 1 - 5 | 4 | 5.00 | 0.00 | 5 - 5 | 5 | < 0.0001 |
| 30 | 3.00 | 1.44 | 1 - 4 | 4 | 4.60 | 0.50 | 4 - 5 | 5 | < 0.0001 |
| 40 | 2.13 | 1.31 | 1 - 4 | 1 | 4.00 | 0.00 | 4 - 4 | 4 | < 0.0001 |
| 50 | 2.13 | 1.46 | 1 - 5 | 1 | 3.40 | 0.50 | 3 - 4 | 3 | 0.0001 |
| 60 | 2.47 | 1.31 | 1 - 5 | 2.5 | 4.27 | 0.45 | 4 - 5 | 4 | < 0.0001 |

* Using *Wilcoxon rank sum test*

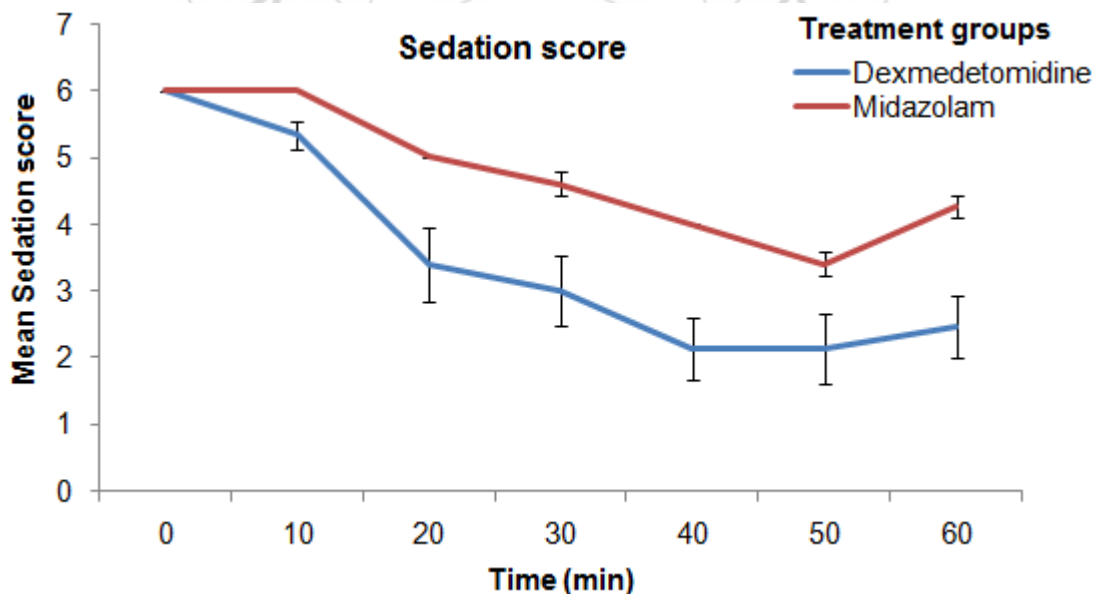


Figure 3: Line chart with error bars showing the mean sedation score according to different time points for Dexmedetomidine and Midazolam treatment groups

Table 8: Descriptive statistics for behaviour score at different time points for two treatment groups

| Time (min) | Behaviour Scale - Dexmedetomidine | | | | Behaviour Scale - Midazolam | | | | P-value* |
|------------|-----------------------------------|------|-------|--------|-----------------------------|------|-------|--------|----------|
| | Mean | SD | Range | Median | Mean | SD | Range | Median | |
| 0 | 2.63 | 0.67 | 2 - 4 | 3 | 2.73 | 0.45 | 2 - 3 | 3 | 0.3355 |
| 10 | 2.60 | 0.67 | 2 - 4 | 3 | 2.47 | 0.51 | 2 - 3 | 2 | 0.5525 |
| 20 | 1.60 | 0.62 | 1 - 3 | 2 | 1.87 | 0.35 | 1 - 2 | 2 | 0.0265 |
| 30 | 1.57 | 0.63 | 1 - 3 | 2 | 2.00 | 0.74 | 1 - 3 | 2 | 0.0222 |
| 40 | 1.47 | 0.63 | 1 - 3 | 1 | 2.13 | 0.63 | 1 - 3 | 2 | 0.0002 |
| 50 | 1.53 | 0.73 | 1 - 3 | 1 | 2.27 | 0.45 | 2 - 3 | 2 | < 0.0001 |
| 60 | 1.53 | 0.73 | 1 - 3 | 1 | 2.27 | 0.45 | 2 - 3 | 2 | < 0.0001 |

* Using *Wilcoxon rank sum test*

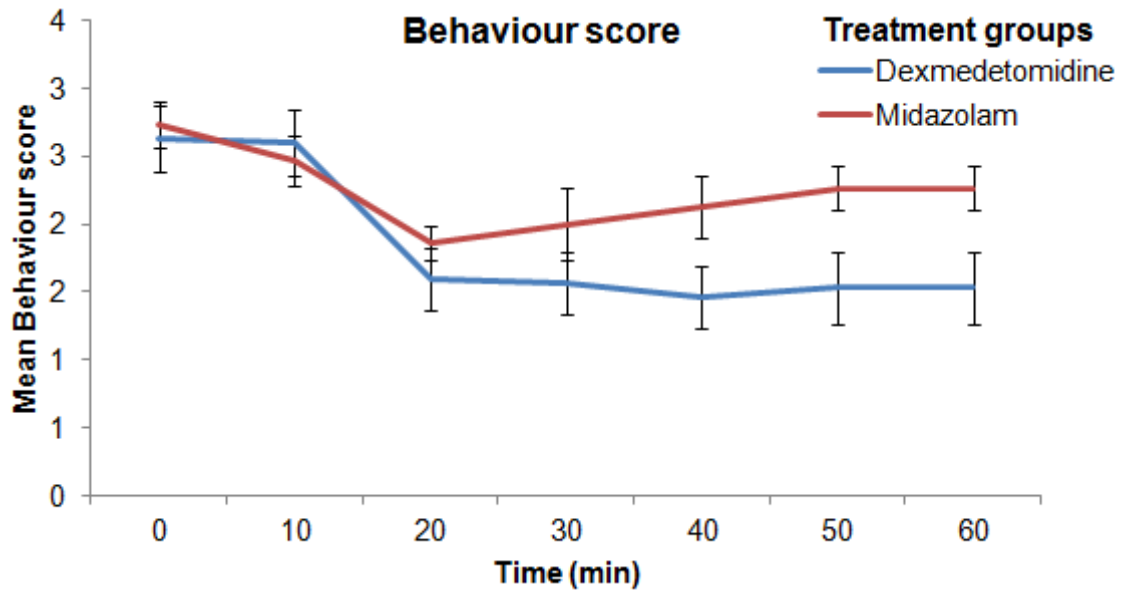


Figure 4: Line chart with error bars showing the mean behaviour scale according to different time points for Dexmedetomidine and Midazolam treatments.

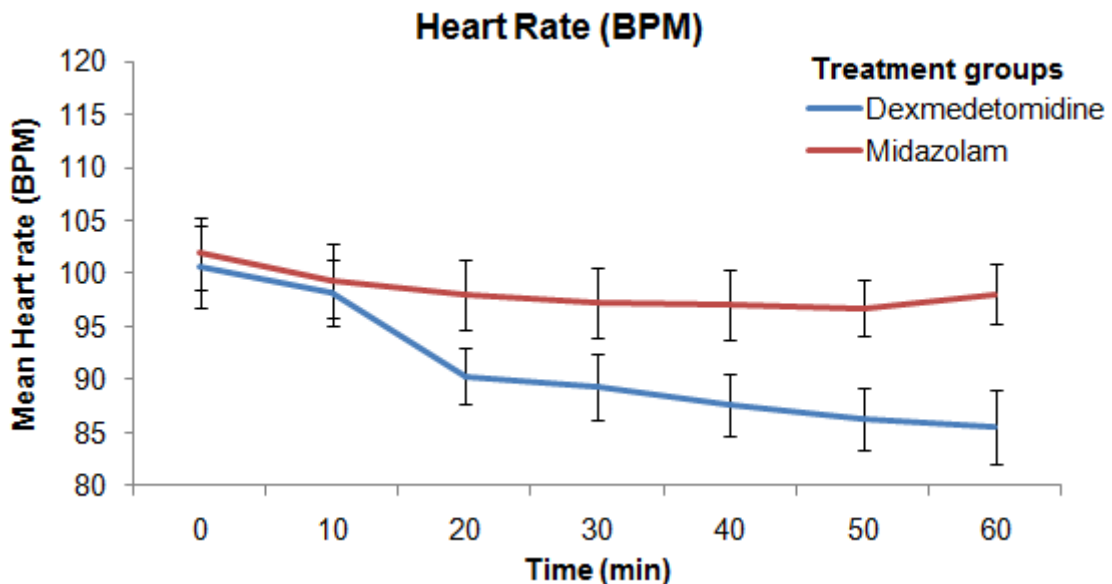


Figure 5: Line chart showing the mean heart rate of patients in two treatment groups according to time

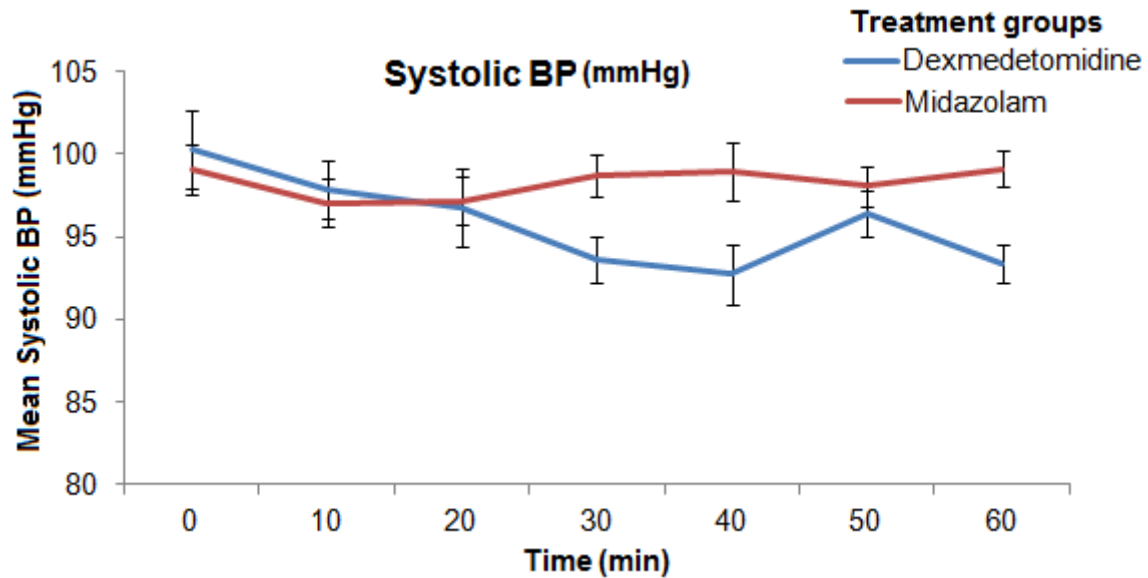


Figure 6: Line chart with error bars showing the mean systolic BP according to different time points for Dexmedetomidine and Midazolam treatments.

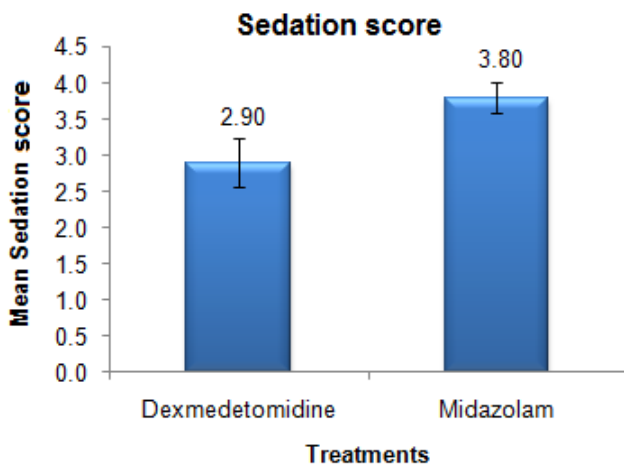


Figure 7: Bar chart with error bars showing the mean sedation scale (Intra-Operation) according to treatment groups.

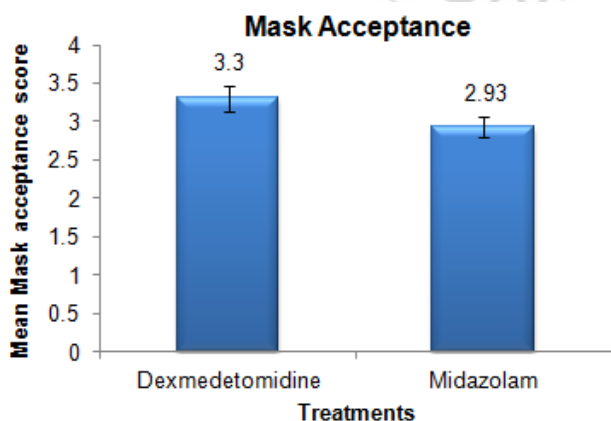


Figure 8: Bar chart showing the mean mask acceptance score (Intra-Operation) according to treatment groups

4. Discussion

This prospective, double-blind, randomized, controlled trial compared intranasal Dexmedetomidine and Midazolam as

premedication in healthy children between 2 and 9yrs of age. Children premedicated with intranasal Dexmedetomidine attained more significant and satisfactory sedation and were less anxious at parental separation and at mask induction than those patients who received Midazolam. The behaviour at venipuncture in both the groups was comparable. Most children tolerated the intranasal administration of drugs. Previous studies have shown that intranasal administration is an effective way to administer premedication and sedation to children. The advantages of intranasal delivery are considerable. It is both rapid and non-invasive. It bypasses the blood brain barrier and targets the central nervous system, reducing systemic exposure and thus systemic side effects.(11)

In our study it was observed that the level of satisfactory sedation in Dexmedetomidine group was achieved within 20 min. whereas in Midazolam group it was achieved at 30 min. The mean sedation score at separation from parents was 2.47 in Dexmedetomidine group and 4.27 in Midazolam group. The difference in sedation at parental separation was statistically significant.(p <0.05).

In Dexmedetomidine group at the time of parental separation children were less anxious as compared to the Midazolam group as behaviour score was lower in the Dexmedetomidine group which was statistically significant.

An ideal pre anaesthetic medication should ease separation from parents and our study suggests that intranasal Dexmedetomidine is better than intranasal Midazolam to allay the anxiety at parental separation. In Dexmedetomidine group 4 children had unsatisfactory scores whereas 8 children in Midazolam group had similar unsatisfactory scores for sedation and anxiety.

All these patients were administered complete medication successfully, however did not have satisfactory sedation and anxiolysis. Hence, they were labelled as failure of sedation and were administered rescue medication in the form of intramuscular Ketamine. The literature discusses various

reasons for failure of intranasal drug administration. One of the reasons for failure is volume of drug more than 1ml, as it can lead to spillage easily(12). Another possible reason would be excessive nasal secretions due to nasal pathology and recent upper respiratory tract infection such patients were excluded from our study. Drugs in our study were prepared in less than 1ml volume in all cases, so we feel that the possible reason of failure could be individual variation in response by the patients.

In our study it was observed that the mean heart rate and systolic blood pressure decreased across different time points in both the group but the fall in heart rate and systolic blood pressure was much more in Dexmedetomidine group owing to its property of pronounced α -2 agonist activity.(13)

In our study oxygen saturation is maintained in both the groups. Oxygen saturation reduction was never $<95\%$ in any of the groups. In case of respiratory rate it remained more stable in Dexmedetomidine group however the variation in Midazolam was clinically irrelevant as no fall in oxygen saturation below 95% was seen. Despite profound sedative properties, Dexmedetomidine is associated with only limited respiratory effects, even when dosed to plasma levels up to 15 times of those normally achieved during therapy, leading to a wide safety margin. Hypercapnic arousal is preserved, and the apnea threshold is actually decreased.(13)

Eight children in Midazolam group and four in Dexmedetomidine group required rescue drug. The difference in the proportion of children requiring rescue drug in two groups was statistically insignificant with p-value of 0.3329. Accordingly, the intra-op comparisons for sedation and behaviour were performed using samples of 22 and 26 for Midazolam and Dexmedetomidine groups respectively.

We also studied the effects of the both drugs at venipuncture which is a very painful and distressing process for a child and their parents, it was observed that the behaviour at venipuncture in both the intranasal Dexmedetomidine and intranasal Midazolam group was comparable. The degree of sedation reduces on interventions, such as venipuncture and mask application, which goes along the lines of the unique feature of easy arousability on stimulation that is characteristic of Dexmedetomidine. We have not come across any previous studies which compare the effects of both the drugs for venipuncture using intranasal route.

After venipuncture induction was done with the inhalation method with mask. Occasionally a child describes an excessive fear even to anaesthesia facemask, hence, premedication is used to facilitate a smoother induction and mask acceptance. In our study it was observed that mask acceptance was much easier in children premedicated with Dexmedetomidine as compared to Midazolam.

There are a few limitations to our study:-
We have administered the drug with the help of a needle less syringe; it is possible to use atomiser for this purpose. Midazolam atomiser is available but it is not available for Dexmedetomidine. If we would have used only Midazolam atomiser the process of blinding would have been adversely affected in our study.

Another limitation of our study is that we have not studied recovery characteristics after intranasal premedication with study drugs. An ideal premedication should not adversely affect recovery from anaesthesia. For this purpose, the duration of surgery and conduct of anaesthesia should be comparable. Our study ended with mask acceptance. Different Surgeries with variable duration were included and conduct of anaesthesia was left to the discretion of the attending anaesthesiologist.

Hence, we did not evaluate effect of premedication on intraoperative anaesthetic and analgesic requirements and post-operative recovery characteristics.

5. Conclusion

From our study we conclude that Dexmedetomidine as premedication in paediatric patients gives better sedation and anxiolysis at parental separation, venipuncture and mask acceptance without hemodynamic instability.

Hence, we feel that intranasal Dexmedetomidine is a better alternative for Midazolam („gold standard“) as premedication in paediatric patients.

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