Comparison between intranasal dexmedetomidine and intranasal midazolam as premedication for brain magnetic resonance imaging in pediatric patients: A prospective randomized double blind trial

Ayushi Gupta, Naina Parag Dalvi, Bharati Anil Tendolkar
Department of Anesthesiology, Lokmanya Tilak Municipal Medical College and Lokmanya Tilak Municipal General Hospital, Sion, Mumbai, Maharashtra, India

Abstract

Background and Aims: Preprocedural preparation of children scheduled for magnetic resonance imaging (MRI) is challenging. This prospective, randomized trial compared intranasal midazolam with intranasal dexmedetomidine as premedication for children scheduled for brain MRI.

Material and Methods: In total, 60 children, aged 1–8 years, scheduled for elective brain MRI, were randomly assigned to the intranasal dexmedetomidine (1 µg/kg; Group D) or intranasal midazolam (0.2 mg/kg; Group M) group. We compared hemodynamic and respiratory parameters, onset, level, sedation quality, and successful parental separation. All patients received intravenous propofol as an induction and maintenance agent for MRI.

Results: No significant differences were observed in demographic, hemodynamic, and respiratory parameters. Group D (14.3 ± 3.4 min [10–20 min]) had a longer time of sedation onset than Group M (8.7 ± 3.7 min [5–15 min]; P < 0.001). The median and mean sedation scores were lower in Group D (3 and 3.7 ± 0.8, respectively) than Group M (4 and 4.3 ± 1.2, respectively; P = 0.055). Group D (80%) had a higher percentage of children achieving satisfactory sedation at the time of induction than did Group M (53.3%; P = 0.0285). Parental separation was successful in 73.3% of patients in Group D compared with 46.7% of patients in Group M (P = 0.035).

Conclusion: Intranasal dexmedetomidine results in more successful parental separation and yields a higher sedation level at the time of induction of anesthesia than intranasal midazolam as premedication, with negligible side effects. However, its onset of action is relatively prolonged.

Key words: Dexmedetomidine, midazolam, intranasal, magnetic resonance imaging

Introduction

The success of magnetic resonance imaging (MRI) as a diagnostic tool has led to its increased use in patients of all age groups; however, children undergoing MRI often require sedation because the magnetic field creates a sound of a very high decibel and to minimize motion artifact. Anxiety and fear in children lead to increased catecholamine levels in the body, thereby leading to tachycardia, hypertension, and tachypnea and increased difficulty in gaining intravenous access, separation from parents, and induction of anesthesia. Premedication facilitates overcoming these difficulties, with midazolam being the most commonly used agent. However, midazolam is associated with the risk of respiratory depression.

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and has no analgesic action. Contrastingly, dexmedetomidine, a selective α₂ agonist, has analgesic and sedative action with no risk of respiratory depression and has been used as premedication.

However, few studies have reported on the intranasal use of dexmedetomidine in radiological procedures. In this prospective, randomized, double-blind study, we compared intranasal midazolam (0.2 mg/kg) and intranasal dexmedetomidine (1 μg/kg) in terms of hemodynamics; parental separation anxiety; and onset, level, and sedation quality at the time of patient induction.

**Material and Methods**

After obtaining approval from the institutions’ Ethics Committee, written, informed, and valid consent was obtained from the parents of the patients after explaining the study protocol to them. This study included 60 American Society of Anesthesiologists (ASA) Grades I and II patients who were aged 1–8 years and were scheduled for brain MRI.

Patients aged < 1 and > 8 years, with parents’ refusal, ASA Grades III and IV, congenital heart disease, upper respiratory tract infection, and body mass index > 35; being administered digoxin or beta blockers; and requiring emergency MRI were excluded from the study.

Preanesthetic assessment included medical and surgical history; general and systemic examination; airway examination; and investigations, such as complete hemogram and renal function tests, conducted on an outpatient basis. On the day of MRI, the nil by mouth status was confirmed, and parental consent was obtained.

Baseline saturation (SpO₂) and heart rate (HR) were monitored using a pulse oximeter. Electrocardiogram and respiratory rate (RR) were monitored using a respiration strap, and blood pressure (BP) was measured using a noninvasive BP cuff. The sedation level was assessed using the Observer’s Assessment of Alertness/Sedation (OAA/S) scale, a 6-point sedation scale. The patients were randomly allocated to two groups. To avoid bias, observers and attending anesthesiologists were blinded to the study drug. Group M received intranasal midazolam (0.2 mg/kg) and Group D received intranasal dexmedetomidine (1 μg/kg). The intranasal drug was dripped into both nostrils using a 1-mL syringe, with the patients in the recumbent position. The time of dosage was noted, and the observer recorded SpO₂, HR, systolic BP (SBP), diastolic BP (DBP), RR, and the sedation level at 5-min intervals for 30 min following drug administration.

The onset of sedation was defined as an increase in the sedation level compared with the baseline −1 (change in the OAA/S score from 6 to 5). Adequate sedation was defined as the time taken to achieve an OAA/S score of 4 and was the time when the patients allowed intravenous cannulation without crying.

Within 15 min of cannulation, the patients underwent MRI. The behavior of the patients while entering the MRI room was monitored, and the OAA/S score at the time of induction was noted.

At the time of induction, an OAA/S score between 1 and 4 represented satisfactory sedation and of 5 or 6 represented unsatisfactory sedation. Time of induction was noted, and whether parental separation at the time of induction was successful was recorded. Sedation was considered successful when the patients were calm and sedated, were not crying and agitated, and allowed smooth induction. For induction, an intravenous bolus of 0.5 mg/kg propofol was administered for 2–3 min, and the infusion was started at 100 μg/kg/min and increased to a maximum of 350 μg/kg/min, provided HR > 60 beats/min, fall in SBP was <20% of the baseline value, and respiratory depression was absent (SpO₂ < 95). SpO₂, HR, BP, and RR were noted at the time of induction, for every 5 min for the first 15 min and then for every 15 min until the end of brain MRI, which lasted for a maximum of 60 min.

**Statistical analysis**

Sample size was calculated based on the results of a previous study using the formula for quantitative statistical analysis with confidence level of 95% and an allowable error of 5%. Parametric data were analyzed using the unpaired t-test. Repeated measurements data were analyzed using the paired t-test, and binary data were analyzed using Chi-squared test. P < 0.05 was considered statistically significant.

**Results**

The demographic profile was comparable between the two groups [Table 1]. Furthermore, the mean HR [Figure 1] and other hemodynamic parameters, such as BP [Figure 2], were comparable between the groups.

Sixteen of 30 children (53.3%) in Group M and 24 of 30 children (80%) in Group D achieved satisfactory sedation at the time of induction (i.e., OAA/S score ≤ 4), which was statistically significant (P < 0.0285) [Figure 3]. Median sedation scores for Groups M and D were 4 and 3, respectively [Figure 4]. Fourteen children (46.7%) in Group M and 22 (73.3%) in Group D showed successful parental separation, with a statistically significant difference (P < 0.035) [Table 2].
Discussion

Premedication is required to alleviate anxiety and fear, allow smooth separation from parents, and allow easy acceptance of needle prick for intravenous cannulation and anesthesia induction. In addition, premedication has analgesic, amnesic, antisialagogue, antiemetic, and vagolytic effects. Various drugs are available for premedication, with midazolam being the most commonly used. However, midazolam is associated with respiratory depression and an increased incidence of adverse postoperative behavioral changes, hiccups, and paradoxical reactions.\cite{3} Clonidine, a $\alpha_2$ agonist, has also been suggested for premedication, but it has a slow onset of action (1–3 h). Dexmedetomidine is a newer $\alpha_2$ agonist with more selective action.

Table 1: Demographic data

| Parameters (number of cases) | Group M ($n=30$) | Group D ($n=30$) | $P$ |
|-----------------------------|------------------|------------------|-----|
| Age (years)*               | 3.7±1.7          | 3.6±1.6          | 0.82|
| Sex (%)                     |                  |                  |     |
| Male/female                 | 16 (53.3)/14 (46.7) | 18 (60.0)/12 (40.0) | 0.794|
| Weight (kg)*                | 12.7±4.0         | 12.3±3.9         | 0.6454|
| Mean duration of scan (min)*| 35.3±7.1         | 36.3±6.9         | 0.582|
| ASA I/II                    | 30/0             | 30/0             | -   |

*By Student’s t-test, #By Chi-squared test. ASA = American Society of Anesthesiologists

Table 2: Comparison of successful parental separation between the groups

| Successful parental separation | Midazolam, $n$ (%) | Dexmedetomidine, $n$ (%) | $P$ |
|--------------------------------|--------------------|--------------------------|-----|
| Yes                            | 14/30 (46.7)       | 22/30 (73.3)             | 0.035*|
| No                             | 16/30 (53.3)       | 8/30 (26.7)              |     |

*By Chi-squared test. *Significant

Figure 1: Comparison of mean heart rate between the two groups

Figure 2: Comparison of mean systolic blood pressure between the two groups

Figure 3: Comparison of level of sedation between the groups at the time of induction

Figure 4: Comparison of median sedation score between the groups
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on α₂-adrenergic receptors and a shorter half-life. Increasing evidence has shown that dexmedetomidine is an effective and safe sedative in children scheduled for radiological procedures.\[4,5\] Dexmedetomidine has analgesic and antishivering properties and does not cause respiratory depression.

Intranasal application is a relatively noninvasive, convenient, and easy route of administration and results in a faster onset of action as well as reduces first-pass metabolism.\[6,7\] Hence, we administered midazolam intranasally. Dexmedetomidine is only available in an intravenous formulation; intravenous preparation has been used through oral, transmucosal, and intranasal routes. Dexmedetomidine has been extensively studied intranasally in both children and adults. Investigations conducted by Yuen et al. have shown that intranasal dexmedetomidine produces significant sedation in healthy adults and in children aged between 2 and 12 years.\[8-10\]

In this study, the time of onset of sedation is 8.7 ± 3.7 min (5–15 min) in Group M compared with 14.3 ± 3 min (10–20 min) in Group D. The difference in onset time was statistically significant with early onset in midazolam. Sheta et al. reported similar results regarding the onset of sedation between the two groups.\[11\]

In our study, 80% of patients in Group D achieved satisfactory sedation (OAAS score ≤4) compared with 53.3% of patients in Group M, which was statistically significant (P = 0.028) [Figure 3]. Sheta et al. and Sundaram and Mathian have reported similar findings in patients undergoing dental treatment.\[2,11\]

We observed successful parental separation in 73.3% of patients in Group D compared with 46.7% of patients in Group M. The difference was clinically as well as statistically significant (P < 0.035) [Table 2]. In another study by Mostafa and Morsy comparing the use of dexmedetomidine, midazolam, and ketamine as intranasal premedication, the percentage of children who achieved child–parent separation score Grade 1 was 93.8%, 87.5%, and 68%, respectively.\[12\] Sundaram and Mathian reported similar results.\[2\]

No significant change was observed in Sp\textsubscript{O\textsubscript{2}} between the groups until the end of 30 min. None of the patients in both groups had Sp\textsubscript{O\textsubscript{2}} <95% at any point of time during patient monitoring. Similarly, Sp\textsubscript{O\textsubscript{2}} was comparable in two studies comparing intranasal dexmedetomidine and midazolam, and none of the patients had Sp\textsubscript{O\textsubscript{2}} <95% at any point of time.\[2,13\]

The baseline HR was comparable between the groups [Figure 1]. Dexmedetomidine is known to decrease sympathetic outflow and circulating catecholamine levels. HR, SBP, and DBP decreased from baseline after premedication, as expected. Sundaram and Mathian reported similar results.\[2\]

None of the children in both groups had untoward complications, such as bradycardia, hypotension, hypertension, and respiratory depression, after premedication. Similar findings regarding side effects were noted in other studies.\[9,11\] Nasal irritation and stinging in addition to paradoxical reactions, such as restlessness and euphoria, are major disadvantages of the intranasal administration of midazolam and could be deterrents in its use as premedication. Several studies have reported these unwanted side effects in children.\[14,15\] Our study did not specifically observe the concerns of patients’ acceptance of the drug.

Contrastingly, dexmedetomidine does not cause any transient nasal burning or irritation, paradoxical reaction, hiccups, and respiratory depression. It acts on the locus coeruleus and produces an unusually cooperative form of sedation, in which the patient is calmly and easily aroused from sleep to wakefulness and subsequently quickly falls back asleep when not stimulated, which is similar to natural sleep. Therefore, children who had received dexmedetomidine had a tendency to awaken during transfer from parents’ lap to the MRI table but were quiet, calm, and cooperative.

**Conclusion**

We observed that intranasal dexmedetomidine (1 µg/kg) results in more successful parental separation, better hemodynamics, higher sedation level, and more satisfactory sedation at the time of induction than intranasal midazolam (0.2 mg/kg) as premedication, with negligible side effects in MRI.

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**Conflicts of interest**

There are no conflicts of interest.

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