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ORIGINAL ARTICLE

Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial

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Abstract
Introduction Providing anesthesia to children undergoing MRI is challenging. Adequate premedication, administered noninvasively, would make the process smoother. In this study, we compare the efficacy of intranasal dexmedetomidine (DXM) with the intranasal administration of ketamine for procedural sedation in children undergoing MRI.
Methods We studied 150 children, between 1 and 10 years of age, divided randomly into three groups (DXM, K, and S). For blinding, every child received the intranasal drugs twice; syringe S1, 60 min before, and syringe S2, 30 min before intravenous (IV) cannulation. For children in group DXM, S1 contained DXM (1 μg/kg) and S2 was plain saline. Children in group K received saline in S1 and ketamine (5 mg/kg) in S2 whereas children in group S received saline in both S1 and S2. The child's response to drug administration, ease of IV cannulation, the satisfaction of the anesthesiologist and child's parents with the premedication, and the total propofol dose required for the satisfactory conduct of the procedure were compared. We also compared the time to awakening and discharge of the child as well as the occurrence of any side effects with these drugs.
Results Both DXM and ketamine were equally effective as premedication in these patients. Most of the children accepted the intranasal drugs with minimal discomfort; 90.4 % of the anesthesiologists in the DXM group and 82.7 % in the ketamine group were satisfied with the conditions for IV cannulation whereas only 21.3 % were satisfied in the saline group. The total dose of propofol used was less in the study groups. Furthermore, children in group DXM and group K had earlier awakening and discharge than those in group S.
Conclusion DXM and ketamine were equally effective, by the intranasal route, as premedication in children undergoing MRI.

Keywords Intranasal premedication · Dexmedetomidine · Ketamine · MRI sedation · Intravenous cannulation

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Introduction

Children undergoing magnetic resonance imaging (MRI) frequently require sedation. They do not understand the need of undergoing the diagnostic procedure and are apprehensive of lying down in a dimly lit, noisy "tunnel." They are afraid of skin pricks and cannot be reassured with explanations. Sedating these children is technically difficult. The agents used should have minimum effects on hemodynamics and respiration and should allow rapid recovery and early discharge of the child without any side effects. Different methods have been tried to achieve these aims [1–5]. Serafini et al. [6] published a review of the anesthesia protocols for MRI in pediatric patients.

Most of these techniques involve intravenous (IV) administration of drugs to sedate the child. Securing a peripheral line is difficult in an anxious, agitated and sometimes fighting child. Painful IV cannulation, with the use of restraints, may have long-term psychological consequences in the children, making them afraid of

subsequent contacts with healthcare professionals [7, 8]. Children with psychological, developmental, or behavioral disorders, who most often must undergo diagnostic MRI scans, may be combative or aggressive from the outset and require deeper levels of sedation or restraint. Commonly, the procedure has to be carried out in the MRI waiting hall or reception area, in the presence of the child's parents and other patients. This requirement further adds to the stress of the child and the anesthesiologist.

Various drugs have been used as premedicant to decrease the discomfort of IV cannulation [9, 10]. Intranasal premedication avoids the need for securing a venous access in combative children. Intranasal administration of the drugs is well tolerated, effective, and fast acting. This site is highly vascularized and very permeable for drug administration, ensuring rapid absorption into systemic circulation [11].

This study aims to compare intranasal DXM with intranasal ketamine in children undergoing diagnostic MRI. The ease of IV cannulation, propofol dose requirements, and time to awakening and discharge is compared across the groups. We also evaluate the quality of the MRI, and the satisfaction of the anesthesiologist as well as parental satisfaction with the drug and procedure.

Materials and methods

The study was started after obtaining approval from the institute ethics committee and after registering in the clinical trial registry (CTRI/2012/11/003146). After proper explanation of the procedure and written parental consent, 150 children, aged between 1 and 10 years, undergoing MRI were included in this randomized and prospective study. Patients with heart and lung disease, airway abnormalities, expected difficult intravenous cannulation, and patients with known allergies to the study drugs were excluded from the study.

Standard pediatric fasting guidelines were followed. Presedation behavior was assessed on a 4-point scale (1 = calm, cooperative; 2 = anxious but reassurable; 3 = anxious and not reassurable; 4 = crying or resisting) by an anesthesiologist (A1) who was blinded to the group of the child. Baseline hemodynamic values were recorded upon the arrival of the unpremeditated child to the preparation room.

According to computer-generated random numbers, the children were allocated to receive either DXM (group DXM) or ketamine (group K) or saline (group S). Previous studies have shown that the onset time of adequate sedation after intranasal DXM is 45 min, with a peak effect at 60–90 min, whereas the onset of action for intranasal ketamine is within 5–10 min, with an duration of action of about 60 min [12–15]. For the purpose of blinding, we had to administer the drugs twice to each child, as described below.

An independent investigator (A2), not involved with observation or providing anesthesia to the child, prepared two tuberculin syringes, each containing the study drug and diluted to 1 ml, for each child and labeled them S1 and S2. The contents of the syringes were as follows:

Group DXM: S1 contained DXM (1 μg/kg prepared from parenteral preparation of DXM 100 μg/ml) and S2 was saline.
Group K: S1 was saline and S2 contained ketamine (5 mg/kg prepared from ketamine 50 mg/ml).
Group S: Both S1 and S2 contained plain saline

A1 then premeditated the child with the study drugs. Syringe S1 was administered at 60 min and syringe S2 at 30 min before IV cannulation. All the drugs were given intranasally in both nostrils, with the child in recumbent position, after proper explanation to the child and his parents, and the concentration of drugs was made such that the volume of the drug was 1 ml. The child's response to the drug was noted on a 3-point scale (1 = refusing vehemently, 2 = defensive action/weeping, 3 = no defensive action).

Intravenous cannulation was attempted after a lapse of 30 min from the second instillation. Ease of cannulation scores were noted at three stages by the score used by Beebe et al. [10] when the child's hand is held, when the child is approached with the needle, and when the skin is punctured. A1 rated the child's response at each step on a scale of 4 (1 = fights with success, 2 = fights without success, 3 = minor resistance, 4 = no reaction). Children in whom securing the IV access failed after three attempts were considered as dropouts for our study. Their peripheral access would be secured by an expert and they would not be considered for further statistical analysis for the purpose of this study.

Based on the ease of cannulation score, the anesthesiologist ranked the drug in a scale of 1–5 (1 = extremely unsatisfactory and 5 = highly satisfied). A score ≤ 3, given by A1, was considered as unsatisfied and ≥ 4 as satisfied.

After peripheral venous access was secured, all patients were injected with IV midazolam 0.03 mg/kg and IV glycopyrrolate 4 μg/kg. Children were then transferred and positioned on the scanning table. After noting the hemodynamics, all patients were given 1 mg/kg IV propofol. Once the patients were immobile, the procedure started. A rescue dose of 0.5 mg/kg propofol was given if the patient moved during the procedure.

Mean arterial blood pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2), and respiratory rate (RR) were monitored continuously. Patients were allowed

to breathe spontaneously through an oxygen facemask during the procedure. Ventilatory function was assessed by observation of respiratory activity. In case of desaturation (SpO_2 level below 93 % for 30 s) or apnea (no respiratory movement for 30 s), the imaging process was planned to be interrupted and the patient taken out of the MRI tunnel. The anesthesiologist would then assess the airway patency and respiration of the child and manage accordingly.

Quality of the MRI was evaluated by a radiologist using a 3-point scale (1 = no motion, 2 = minor movement, 3 = major movement necessitating the repetition of sequence) [4].

We noted the time required to conduct the procedure and the dose of propofol required for each child. Recovery time was accepted as the interval between completion of procedure and spontaneous eye opening. Discharge time was defined as the time between completion of the procedure and meeting the discharge criteria as recommended by the American Academy of Paediatrics and the American Academy of Pediatric Dentistry (Appendix) [16].

Complications if any were noted and managed. Expected complications were bradycardia, hypotension, and desaturation. Side effects such as nausea, vomiting, and delayed recovery were also recorded.

All the patients were observed for 3 h after completion of the procedure. The parents and the anesthesiologist were then asked to rate the premedication provided on a scale of 5 depending on the child's acceptance of the intranasal drug, the ease of IV cannulation, the success of the diagnostic procedure, the time to awakening and discharge and any complication. A score of 1 depicted extreme dissatisfaction whereas 5 meant highly satisfied.

Statistical analysis

In a previous study using rectal ketamine, 52 % of anesthesiologists found the conditions for IV cannulation to be unsatisfactory in children [10]. To increase the satisfaction for IV cannulation by 50 %, we needed to study 90 experimental and 45 control subjects to be able to reject the null hypothesis that the failure rates for the study and control subjects are equal with probability (power) of 0.8. The α error associated with this test of this null hypothesis is 0.05.

All data were analyzed with SPSS 16 software for Windows. Demographic data were analyzed with the chi-square test and Student *t* test. Hemodynamic variables were compared with one-way analysis of variance (ANOVA) with Bonferroni correction. Kruskal–Wallis test was used for evaluating the sedation level, child acceptance of the intranasal drug, ease of IV cannulation scores, and for the parent, anesthesiologist, and the quality of MRI. When a significant result was obtained, Mann–Whitney *U* test was used for post hoc pairwise comparison with protection for type 1 error with Bonferroni adjustment of the α level.

Results

We evaluated 200 patients for enrollment into the study. Children whose parents did not give consent ($n = 30$), children having expected difficult IV cannulation ($n = 9$), and children with expected difficult airway ($n = 5$) were excluded from the study. Thus, 156 children received the study drugs after randomization. All the groups were comparable with regard to the demographic variables (Table 1). The peripheral venous access of 4 patients in the control group and 1 each receiving ketamine and DXM could not be obtained after three attempts; these patients were considered as dropouts. The IV access of 5 of these patients was secured by an expert. Even the expert could not cannulate the peripheral vein of the remaining child, and his right external jugular vein was cannulated for the procedure.

Heart rate and blood pressure were measured before drug administration, at the start of the procedure, every 5 min during the procedure, at the end of the MRI, and every 15 min post procedure for 3 h. All the three groups had comparable hemodynamics at presentation, and the heart rate and blood pressure remained similar throughout the procedure and for 3 h after the completion of MRI.

We measured the child's sedation/agitation, before the start of the procedure, on a four-point scale. Most of the children were anxious and afraid of the procedure. Only 23.07 % children were calm and cooperative at presentation. Although 5.76 % where crying, the majority were anxious and not reassurable (41.6 %) or anxious but reassurable (29.48 %). All the three groups were comparable in terms of the child's anxiety at presentation ($p = 0.257$).

Most of the children accepted the nasal drug with minimal discomfort. Although 54 % of the children exhibited no defensive action, 32.7 % wept when the drug

Table 1 Sex, age (in years), and weight (kg) distribution between groups

Group	Saline ($n = 46$)	Ketamine ($n = 52$)	DXM ($n = 52$)	*p* value
Sex (male/female)	29/21	36/17	36/17	0.480
Age (years) (mean ± SD)	5.0 ± 2.4	4.9 ± 2.4	5.1 ± 2.8	0.926
Weight (kg) (mean ± SD)	15 ± 5	14 ± 5	15 ± 5	0.879

Table 2 Child's acceptance of nasal drug administration

Group of the child	Child's response nasal drug administration			*p* value
	Refusing vehemently (%)	Defense action/ weeping (%)	No defense action (%)	
Saline	3.3	11.3	16.0	0.076
Ketamine	4.0	11.3	19.3	
Dexmedetomidine	6.0	10.0	18.7	
Total	13.35	32.65	54.0	

The majority of patients tolerated the drug instillation with minimum discomfort

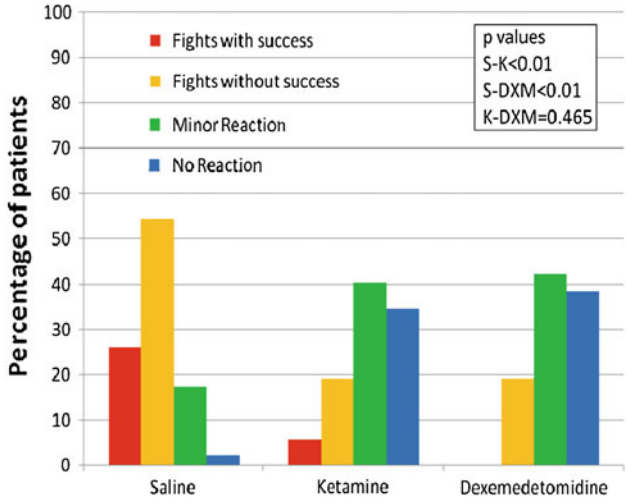

Fig. 1 Venipuncture scores between the groups. The children in ketamine and dexmedetomidine groups tolerated the procedure better than those in the saline group [*p* values between saline and ketamine groups (S–K), saline and dexmedetomidine groups (S–DXM), and ketamine and dexmedetomidine groups (K–DXM)]

was instilled into the nostrils. Only 13.3 % of the children fought actively against the drug administration (Table 2). All the three groups were comparable with regard to the child's acceptance of nasal administration ($p = 0.076$).

The child's response to needle placement was studied at three points: when his hand was held, upon approach with the needle, and when the skin was punctured. Kruskal–Wallis test revealed a significant difference in the child's response between the three groups ($p < 0.01$ at all three stages). The Mann–Whitney *U* test was used for post hoc comparisons between the groups. The corrected *p* value was 0.016 after Bonferroni correction. In comparison to the saline group, most of the children in the ketamine group ($p < 0.01$) and DXM group ($p < 0.01$) exhibited minor or no withdrawal reaction to IV cannulation. However, children in group S fought against all three steps. Both ketamine and DXM were equally effective in this context, and there was no significant difference between group K and group DXM ($p > 0.05$ for all three stages) (Fig. 1).

The anesthesiologist performing the procedure ranked the ease of IV cannulation in each child. The satisfaction of the anesthesiologist with the conditions for cannulation provided by intranasal ketamine (82.7 %) and DXM (90.4 %) was significantly greater than with the saline group (21.7 %) [χ^2 60.95 ($n = 150$, $F = 2$), $p < 0.01$]. Although the satisfaction in group DXM was higher than that in group K, this difference was not found to be statistically significant ($p = 0.253$).

We also assessed the parent's satisfaction with the drug. Higher numbers of parents were satisfied (scale ≥ 4) with the use of ketamine (92.4 %) and DXM (97.3 %) than with intranasal saline (41.6 %), and this difference was statistically significant (Kruskal–Wallis $H = 23.49, 2\,df, p < 0.05$]. There was no significant difference between ketamine and DXM ($p = 0.212$).

The duration of the procedure was similar in all three groups. However, there was a significant difference in the amount of propofol used among the groups. The requirement of propofol was significantly higher in group S than in group DXM and group K ($p < 0.02$) (Table 3).

The duration of awakening was also longer in the control group than the other two groups. The children receiving intranasal saline met the discharge criteria later than those receiving intranasal DXM and ketamine. However, the difference in the propofol dose requirements, the duration of awakening, and the time to discharge was not significantly different between ketamine and DXM. One-way ANOVA with Bonferroni correction was used to compare this variable between the groups (Table 3).

The radiologists rated the procedure on a 3-point scale. The quality of MRI was significantly higher with intranasal ketamine and intranasal DXM than with the control group ($H = 19.72$, 2 *df*, $p < 0.05$). There was no difference between ketamine and DXM groups in terms of the MRI quality ($p = 0.13$).

The incidence of side effects was similar among the three groups ($p = 0.137$). Two patients in group D had bradycardia (heart rate <20 % of baseline) that did not require treatment with atropine. Three patients in group C, five patients in group K, and two patients in group DXM had an episode of nausea and vomiting that was treated with injected ondansetron (0.08 mg/kg).

A1 rated the study drug on a scale of 5: this was dependent on the ease of cannulation, the duration of awakening and discharge, and the incidence of side effects.

Table 3 Comparison of duration of procedure, propofol dose requirements, duration of awakening, and discharge between groups

Parameter (mean ± SD)	Saline	Ketamine	DXM	*p* value (groups)		
				S–K	S–DXM	K–DXM
Duration of procedure (min)	19 ± 6	18 ± 6	18 ± 5	1.000	0.554	1.000
Propofol dose (mg)	31 ± 18	20 ± 10	19 ± 8	<0.01	<0.01	>0.5
Duration of awakening (min)	6 ± 4	4 ± 2	3 ± 4	<0.01	<0.01	0.675
Duration to discharge score (min)	18 ± 7	12 ± 5	10 ± 7	<0.01	<0.01	0.618

There was no significant difference in the duration of procedure between the groups, but the amount of propofol used and the duration of awakening and discharge were significantly higher in the saline group [*p* values between saline and ketamine (S–K), saline and dexmedetomidine (S–DXM), ketamine and dexmedetomidine groups (K–DXM)]

Kruskal–Wallis analysis revealed significant difference in the satisfaction levels among the three groups ($H = 27.06$, 2 *df*, $p < 0.05$). Mann–Whitney analysis showed that the satisfaction with both ketamine and DXM was significantly higher than with the control group ($p < 0.01$). Satisfaction between group K and DXM was not significantly different ($p = 0.021$; corrected $p = 0.016$).

Discussion

The primary aim of our study was to assess the ease of IV cannulation in children undergoing MRI under sedation. Secondary objectives were to evaluate the propofol dose requirements, the MRI quality, and the time to awakening and discharge.

In children undergoing MRI, the use of intranasal ketamine (5 mg/kg) or intranasal DXM (1 μg/kg) premedication significantly increased the ease of IV cannulation. Children receiving the study drugs (ketamine or dexmedetomidine) required a lesser amount of propofol for sedation, had fewer movements during MRI, woke up earlier after the procedure, and could be discharged earlier than those receiving plain saline. The radiologist, child's parents and the anesthesiologist were, therefore, more satisfied in groups K and DXM as compared to the group S.

Children presenting to the MRI suite are frequently anxious. In our study, only 23 % of the children were calm at presentation to the MRI. Securing an IV access for the administration of anesthetic drugs and contrast, in these children, is a difficult procedure. We found the intranasal administration of DXM (1 μg/kg) or ketamine (5 mg/kg), to be very effective in providing adequate conditions for the placement of the IV cannula. Although most of the children in the saline group fought against all the three steps of the procedure, children receiving the study drugs were significantly more comfortable; this led to higher satisfaction for the parents and considerably reduced the anesthesiologist's stress. Most of the children accepted the intranasal instillation of the drugs with minimum discomfort. Hence, the initial interaction between the child, the parents, and the anesthesiologist was smoother and more successful with the use of intranasal DXM or ketamine.

Propofol is commonly used for procedural sedation in MRI [1, 2]. It can cause hypotension and may lead to hypoventilation and decreased oxygen saturation. Use of DXM and ketamine decreased the dose of propofol required for the successful conduct of the procedure. Although none of our children in the control group experienced hypotension or desaturation, the decreased amount of propofol used in the study groups allowed earlier awakening and discharge. Lesser movement in the study group increased the quality of the MRI.

A concern with the use of DXM was the possibility of bradycardia in the children. Two of our patients in group DXM did have a decrease in the heart rate, but they did not require any treatment for this. Use of intranasal drugs, therefore, increased the comfort of the child as well as the anesthesiologist and increased their satisfaction levels.

We did not find any significant difference between the effectiveness of ketamine and DXM as premedicants in children undergoing MRI. The use of DXM led to a higher satisfaction with the IV cannulation and earlier awakening and discharge than ketamine, but this difference was not statistically or clinically significant. However, intranasal DXM does have a longer time of onset, and it may not be feasible to wait for 1 h after premedication in a busy MRI suite. Ketamine has the advantage of having a quicker onset and being almost as effective as DXM.

One limitation of this study was the need for second intranasal administration of drugs; this was done for blinding purposes. However, children receiving DXM were more sedated at the time of the second instillation than those receiving saline in syringe S1. This finding might have given some hint about the group of the child to the anesthesiologist performing the case, and might have led to bias. In addition, we used a dose of 1 μg/kg of DXM. Studies with higher doses of DXM administered intranasally have been conducted [17, 18]. Yuen et al. found no difference in

the sedation levels and hemodynamic effects of 1 μg/kg and 1.5 μg/kg DXM. Higher doses may allow DXM to be used as the sole agent for MRI, but its side-effect profile should be compared with the standard techniques. Similarly, the dose of intranasal ketamine used in previous studies ranged from 3 to 9 mg/kg [19]. Roelofse et al. [20] used 5 mg/kg and we used a similar dose for our study.

Another limitation may lie with the method of intranasal drug delivery. We instilled the study drugs with the use of tuberculin syringes. Sprayed or atomized intranasal medication delivery is a more recent technique. This method has improved usability issues as well as better bioavailability data [21, 22]. Use of these methods of drug delivery may lead to more bioavailability and higher satisfaction with the use of intranasal medications in children.

Conclusion

Large numbers of children and their parents are unsatisfied with the anesthesia protocol in the absence of adequate premedication. The authors, therefore, strongly recommend the use of drugs to decrease the discomfort of the child and to allay their anxiety. Intranasal administration is pain free and more acceptable to children and their parents. Both DXM and ketamine are effective by this route. DXM, however, has to be given at least an hour before the procedure, which may pose problems in the busy schedule of the MRI suites. Ketamine is as effective as DXM for this purpose.

Conflict of interest None.

Appendix 1: Recommended discharge criteria

1. Cardiovascular function and airway patency are satisfactory and stable.
2. The patient is easily arousable, and protective reflexes are intact.
3. The patient can talk (if age appropriate).
4. The patient can sit up unaided (if age appropriate).
5. For a very young or handicapped child incapable of the usually expected responses, the presedation level of responsiveness or a level as close as possible to the normal level for that child should be achieved.
6. The state of hydration is adequate.

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