Egyptian Journal of Anaesthesia (2013) **29**, 131–135

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Premedication with intranasal dexmedetomidine, midazolam and ketamine for children undergoing bone marrow biopsy and aspirate

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Received 5 August 2012; revised 11 October 2012; accepted 20 October 2012
Available online 21 November 2012

KEYWORDS

Dexmedetomidine;
Midazolam;
Ketamine;
Children;
Bone marrow biopsy and aspirate

Abstract *Background:* Preanesthetic medication in pediatrics is very helpful in relieving anxiety, fear, and psychological trauma due to maternal deprivation. Many drugs used in different routes aiming to alleviate stress and prevent psychological trauma. Of these drugs midazolam and ketamine are commonly used. We aimed in this work to compare both of them with dexmedetomidine which is α 2-agonist when used intranasally in children undergoing bone marrow biopsy and aspirate in sedation and premedication.

Methods: 96 children aged 2–8 years with ASA physical status II scheduled for bone marrow biopsy and aspirate were divided into three groups 32 child in each one: (M group) who were premedicated with intranasal midazolam 0.2 mg/kg, (D group) who were premedicated with intranasal dexmedetomidine 1 μg/kg, and (K group) who were premedicated with intranasal ketamine 5 mg/kg. The degree of sedation was assessed every 5 min for 30 min by using a 4 point sedation scale. Also, child–parent separation was assessed and graded according to a 4 point scale at 30 min.

Results: We found that dexmedetomidine group achieved a faster sedation score less than 3 at the point of 10 min, then all groups achieved a comparable sedation score till point of 25 min, both dexmedetomidine and midazolam groups had better sedation score than ketamine group at 30 min. Children achieved child–parents separation score grade 1 was significantly higher in dexmedetomidine group than midazolam and ketamine groups.

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

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http://dx.doi.org/10.1016/j.egja.2012.10.006

Conclusions: Midazolam, ketamine and dexmedetomidine produced adequate sedation with little side effects. So, we prefer to use midazolam due its efficacy and safety as well as availability and its low price in comparison to ketamine and dexmedetomidine.

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1. Introduction

Anxiety and the psychological trauma due to maternal deprivation are major challenges in pediatric anesthesia. Preanesthetic medication in children should aim at relieving this anxiety and psychological trauma parents and also to facilitate the induction of anesthesia without prolonging the recovery [1]. Several drugs have been tried to find the best sedative agent and the best route of administration of these drugs in children. So, a premedicant drug must have an acceptable, non-traumatic route of administration in order not add extra stress to the child. Currently the most commonly drugs are midazolam, ketamine, transmucosal fentanyl and/or meperidine. Many studies have shown that intranasal route is an effective way to administer premedication and sedation to children [2,3]. It is a relatively easy non-invasive route with high bioavilability and rapid onset of action comparable to that of IV administration because of the rich blood supply of the airway mucosa and bypassing the first pass hepatic metabolism. Also, this route is not painful and does not require trained personnel [4–6]. Midazolam is a water-soluble benzodiazepine known to have a rapid onset and short duration of action, as well as properties of amnesia and anxiolysis. Administered intranasally, midazolam is an effective option for conscious sedation [7,8]. Ketamine is a dissociative anesthetic that creates a trance-like state with properties of sedation, amnesia, analgesia, and catalepsy [9]. Dexmedetomidine is a newer alpha 2-agonist with a more selective action on the alpha 2-adrenoceptor and a shorter half-life [10,11] its bioavailability is (72.6–92.1%) when administered via the nasal mucosa.

The aim of this study is to compare the sedative effects of midazolam, ketamine and dexemedetomidine when administered intranasally as preanesthetic medication for children undergoing sternal puncture for bone marrow biopsy and aspirate from pubic bone.

2. Materials and methods

This study was carried out in the Department of Pediatric oncology in association with the Department of Anesthesiology after obtaining consent from guardians and official approval of the ethical committee. Exclusion criteria included known allergy to the studied drugs, organ dysfunction, cardiac dysrrhythmia and/or congenital heart disease, psychotropic medication use and mental retardation as well as any nasal disorder that may interfere with nasal administration of drugs as recurrent nasal bleeding or nasal masses. Also, the children who spit, sniffed or refused intranasal administration of medication were excluded. 96 children aged 2–8 years were selected for this randomized double blind controlled clinical trial in accordance with American Society of Anesthesiologists (ASA) physical status II scheduled for bone marrow biopsy and aspirate were divided into three groups: intranasal midazolam group **(M group)** ($n = 32$) 0.2 mg/kg (Dormicum®, 5 mg/mL; F. Hoffman La Roche Ltd., Basel, Switzerland), intranasal dexmedetomidine group **(D group)** ($n = 32$) (1 μg/kg) (Precedex, 200 μg per 2 mL; Abbott, USA) and intranasal ketamine group **(K group)** ($n = 32$) (5 mg/kg) (HIKMA Pharmaceuticals, Amman-Jordan). All study drugs were prepared by second researcher and packed in identical black plastic containers labeled with numbers that code its content. Observers and attending anesthesiologists were blinded to the given drug. Medications were administered 30 min prior to induction, in the pre-anesthesia area, with the parent(s) attendance. Intranasal drug was dripped into both nostrils using a 2-mL syringe with the child in the recumbent position. Inhalation induction was initiated by face mask with a mixture of sevoflurane 8% with O_2 100%. After loss of consciousness, intravenous line was inserted and when adequate depth of anesthesia was reached appropriate LMA was placed and the patient was left to breath spontaneously. The anesthetic level was delivered in a concentration that maintained a stable heart rate, blood pressure and respiratory rate (baseline ± 20%). Standard monitoring was done by using ECG, noninvasive blood pressure, respiratory rate, pulse oximetry and capnography. After the end of surgery anesthetic gases were discontinued to 0% and replaced with O_2 100% $\geqslant$4 L/min. LMA was removed when the patient was awake then the patient transferred to the recovery room for monitoring of vital signs till discharged to the ward.

2.1. Measurements

Baseline heart rate (HR), respiratory rate, oxygen saturation (SpO_2), and blood pressure (BP) were measured before and every 10 min after intranasal drug administration for 30 min until transfer to the operating room (OR). The degree of sedation was assessed every 5 min for 30 min by using a 4 point sedation scale. Sedation level: Agitated = 4, awake = 3, Drowsy = 2, Asleep = 1. A sedation score of 3 and above was considered as unsatisfactory while scores 1 and 2 were considered to be satisfactory. The response to the child–parent separation was assessed and graded according to a 4 point scale at 30 min. Separation score: Patient unafraid, cooperative, asleep = 1, Slight fear or crying, quite with reassurance = 2, Moderate fear, crying not quite with reassurance = 3, and Crying need for restraint = 4. Duration of anesthesia (time from start of anesthesia till discontinuation of all anesthetics) in minutes and duration of the procedure (bone marrow biopsy and aspirate) in minutes were recorded. Also, postoperative adverse effects as nausea, vomiting, increased secretion and bradycardia was reported.

2.2. Statistical methods

The statistical software used was SPSS 15.0 for Windows (SPSS, Chicago, IL). Data were expressed as mean ± SD or

number (percentages). Sedation and behavior scores were analyzed by Kruskal–Wallis test. When a significant result was obtained, the Mann–Whitney *U*-test was applied for post hoc pairwise comparisons. Hemodynamic variables including heart rate (HR), respiratory rate, oxygen saturation (SpO_2), and blood pressure (BP) were analyzed by ANOVA. When a significant result was obtained, the Tukey test was applied for post hoc pairwise comparisons. The changes of BP and HR from baseline among the three groups were tested by Kruskal–Wallis *t*-test. $p < 0.05$ was considered significant.

3. Results

Demographic data including age, weight, and sex were comparable in the three groups. Also, there was no statistical difference in the duration of anesthesia (time from starting anesthesia till discontinuation of all anesthetics) and duration of the procedure (bone marrow biopsy and aspirate) between three groups (Table 1).

Concerning the sedation score, we observed that dexmedetomidine group achieved a significantly faster sedation score less than 3 at the point of 10 min than that of midazolam and ketamine groups ($p < 0.05$). But we observed that all groups achieved a comparable sedation score at 15, 20, and 25 min. At 30 min both dexmedetomidine and midazolam groups had better sedation score than ketamine group (Table 2) (Fig. 1).

Number and percentage of children achieved child–parents separation score grade 1 was significantly higher in D group than M and K groups 30(93.75%), 28(87.5%), 22(68%) respectively (Table 2) (Fig. 1).

Overall, we did not observe any clinically significant effects of any of the studied drugs on SpO_2 below 95% during the observation period after premedication. There was no significant difference in heart rate, systolic blood pressure and respiratory rate between three groups while all these parameters at all groups were significantly decreased at 30 min value when compared with basal readings ($P < 0.05$) (Table 3). None of the children included in the study had significant nausea, vomiting or bradycardia.

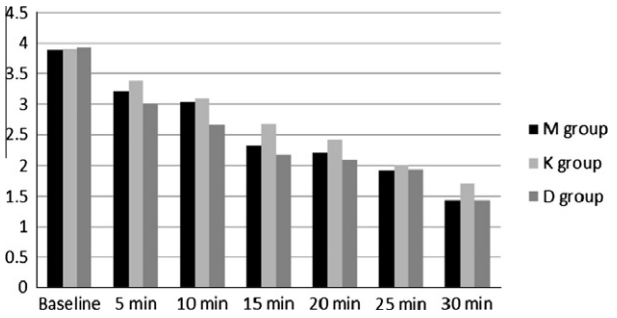

Figure 1 Sedation Score.

4. Discussion

The preoperative anxiety in children can lead to postoperative maladaptive behaviors in the form of eating problems, bad dreams, enuresis, increased fear of doctors and hospital, temper tantrums is well known [12,13]. Hence all pediatric patients should be premedicated in order to decrease preoperative anxiety, allow smooth induction, and prevent postoperative psychological insult and behavioral changes [14,15].

Our study evaluated the efficacy of intranasal midazolam, ketamine and dexmedetomidine as premedicant in pediatric

Table 1 Demographic data of patients included in all groups (mean ± SD).

	Midazolam group ($n = 32$)	Ketamine group ($n = 32$)	Dexmedetomidine group ($n = 32$)
Age (yr)	4.84 ± 0.44	4.93 ± 0.49	5.01 ± 0.40
Weight (kg)	18.33 ± 4.27	18.26 ± 4.12	18.95 ± 4.31
Duration of anesthesia (min)	25.21 ± 4.01	24.14 ± 3.73	24.44 ± 3.91
Duration of procedure (min)	18.52 ± 1.18	18.41 ± 1.12	19.02 ± 0.97

Table 2 Sedation and separation scores (mean ± SD).

	Midazolam group ($N = 32$)	Ketamine group ($N = 32$)	Dexmedetomidine group ($N = 32$)
Sedation score			
Baseline	3.89 ± 0.79	3.91 ± 0.74	3.93 ± 0.88
5 min	3.21 ± 0.50	3.39 ± 0.61	3.00 ± 0.73
10 min	3.03 ± 0.48	3.10 ± 0.50	2.66 ± 0.45*
15 min	2.32 ± 0.51*	2.67 ± 0.49*	2.18 ± 0.50*
20 min	2.21 ± 0.70*	2.41 ± 0.68*	2.10 ± 0.71*
25 min	1.92 ± 0.61*	2.01 ± 0.57*	1.94 ± 0.59*
30 min	1.43 ± 0.76**,[a]	1.71 ± 0.78**	1.44 ± 0.81**,[a]
Children achieved child–parents separation score grade I			
Number (percentage)	28 (87.5%)	22 (68%)	30[a] (93.75%)

* $p < 0.05$.
** $p < 0.01$ (within the same group in comparison to the base line).
[a] $p < 0.05$ (between all studied groups).

Table 3 Oxygen saturation and hemodynamic changes (mean ± SD).

	Midazolam group ($N = 32$)	Ketamine group ($N = 32$)	Dexmedetomidine group ($N = 32$)
Oxygen saturation (%) (SpO_2)			
Baseline	98.4 ± 1.11	98.3 ± 1.13	97.3 ± 1.20
10 min	98.4 ± 1.1	97.3 ± 1.2	97 ± 1.1
20 min	97.5 ± 1.6	98.3 ± 1.4	96.8 ± 1.9
30 min	97.2 ± 1.1	97.6 ± 1.5	97.4 ± 1.1
Systolic blood pressure (SBP) (mmHg)			
Baseline	97.5 ± 4.5	97.3 ± 3.6	98.1 ± 2.5
10 min	97.1 ± 4.3	97.4 ± 3.8	97.2 ± 1.3
20 min	94.4 ± 2.2	95.3 ± 3.6	94.2 ± 1.1
30 min	90.2 ± 2.1*	92.7 ± 3.1*	89.1 ± 0.7*
Heart rate (HR) (Beats/min)			
Baseline	110.2 ± 3.2	109.3 ± 2.2	110.2 ± 2.1
10 min	107.1 ± 1.9	107.2 ± 2.1	106.1.1 ± 1.1
20 min	100.3 ± 1.9	102.3 ± 3.3	100.3 ± 0.9
30 min	93.1 ± 1.1*	100.3 ± 2.2*	95.1 ± 0.2*0
Respiratory rate (RR) (Rate/min)			
Baseline	26.93 ± 4.3	27.25 ± 3.3	27.12 ± 3.2
10 min	26.82 ± 3.1	27.1 ± 3.2	26.3 ± 5.5
20 min	23.3 ± 2.2	24.92 ± 2.2	24.1 ± 3.3
30 min	22.2 ± 3.2*	23.3 ± 3.5*	22.8 ± 2.3*

* $p < 0.05$ (within the same group in comparison to the base line).

patient; we did not include placebo group as these drugs when compared with placebo the effectiveness was found to be superior to placebo in previous studies [16–20]. Many sedative analgesic agents and routes of delivery for facilitation of painful procedures have been studied, with varying degrees of patient acceptance, efficacy and safety [16]. The intranasal route may be irritating to nasal mucosa and drugs administered through it may traverse directly into the central nervous system through the cribriform plate by traveling along the olfactory nerves [17]. In our study, we selected children between 2 and 8 years where this age is most susceptible to the separation anxiety and their understanding is limited. The intranasal administration of midazolam 0.2 mg/kg, ketamine 5 mg/kg and dexmedetomidine 1 μg/kg produced effective and significant sedation which was seen at 10 min in dexmedetomidine group and at 15 min in midazolam and ketamine groups and this change was maintained in all groups at 20 min and at the time of induction of anesthesia and these results were comparable with the results of Naill et al. [18].

Malionovsky et al. [19] found that intranasal midazolam 0.2 mg/kg had produced more rapid sedation than when administered through other routes. Also, Lejus et al. [20] reported that intranasal midazolam 0.2 mg/kg is an effective and rapid route of premedication yet one that is poorly accepted by patients. Shashikiran et al. [21] found that on 40 children requiring conscious sedation, intranasal and intramuscular midazolam produced effective and comparable sedation with equal efficacy and safety profiles. But Lam et al. [22] proved that intramuscular midazolam produced better sedation and less movement at venipuncture than when used intranasally.

The variation in the onset of sedation in our results may be due to the site and mechanism of action of these drugs, as the site of action of midazolam and dexmedetomidine in the central nervous system in locus coeruleus where it induce electroencephalogram activity similar to natural sleep [23] but ketamine is a derivative of phencyclidine that creates trance like dissociative state characterized by sedation, amnesia, analgesia, and catalepsy. There are several reports about intranasal administration of ketamine (5–6 mg/kg) with good efficacy and no adverse effects for premedication and sedation in children [24,25].

Garcia-Velascop et al. [24] compared intranasal midazolam (0.25 mg/kg) and ketamine (5 mg/kg) in pediatric patients found that the nasal route of administration of the drugs is well accepted in both groups and midazolam and ketamine are equally effective as sedative premedication.

Wilton et al. [4] concluded that intranasal midazolam 0.2 mg/kg produced sedation comparable with a dose of 0.3 mg/kg and both were better than placebo. Ashu et al. [26] reported that intranasal midazolam 0.2 mg/kg produced a more rapid onset of sedation (average 4.8 min) and time of maximal sedation was only 12.7 min and this is not agreement of our study and this could be due age range in his study started from 6 month up to 6 years. Vivian et al. [27] reported that 75% of the children attained a satisfactory level of sedation after 1 μg/kg intranasal dexmedetomidine. Moreover, 70.8% of these sedated patients allowed IV or inhaled induction without showing signs of distress or awakening.

Our study showed that there was statistically significant change in heart rate, respiratory rate and systolic blood pressure in each group after 30 min and this may be due to increased level of sedation which is in agreement with Remadevi et al. [28]. Munro et al. [29] reported that the reduction of blood pressure and heart rate were <20% of baseline in children who were sedated with initial dose of 1 μg/kg IV dexmedetomidine but Vivian et al. [27] shown that 0.5 and

1 μg/kg intranasal dexmedetomidine reduces heart rate and blood pressure in healthy children during the first hour after drug administration.

Talke et al. [30] demonstrated that intranasal dexmedetomidine 1 μg/kg reduced HR and SBP during the preoperative sedation period and this may be due to dexmedetomidine is known to decrease sympathetic outflow and circulating catecholamine levels. This study support the data presented by Audenaert and colleges [31] who found that intranasal ketamine 5 mg/kg did not produce significant cardiovascular and respiratory side effects and this is agreement with our study.

In conclusion we found that midazolam, ketamine and dexmedetomidine produced adequate sedation with little side effects. So, we prefer to use midazolam due its efficacy and safety as well as availability and its low price in comparison to ketamine and dexmedetomidine.

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