Research Article

BJMP 2011;4(4):a441

Dexmedetomidine versus ketamine combined with midazolam; a comparison of anxiolytic and sedative premedication in children

Mohamed A. Daabiss and Mohamed Hashish

ABSTRACT

Background: Preanaesthetic medication plays an important role in the anaesthetic care of children by allaying anxiety, decreasing vagal stimulation and preventing postoperative psychological sequelae. This study was undertaken to evaluate the efficacy of dexmedetomidine when administered orally as a hypnotic and anxiolytic compared to oral combination ketamine/midazolam as preanaesthetic medication in paediatric patients.

Methods: Sixty-six children aged 2-6 years posted for elective surgical procedures were randomly allocated to one of two groups 'Group D' and 'Group MK'. Group D received oral dexmedetomidine 3 μg/kg and group MK received 0.25 mg/kg oral midazolam (up to a maximum of 15 mg) mixed with 2.5 mg/kg oral ketamine. Drug acceptance was noted. Heart rate, arterial pressure, respiratory rate, sedation score and anxiolysis score were noted before drug administration and every 5 min for up to 30 min after drug administration. Parental separation score at 30 min and mask acceptance score in addition to parental satisfaction were also noted.

Results: premedication with oral MK appeared to be superior to oral dexmedetomidine, in addition to evident haemodynamic stability and higher degree of parental satisfaction (90%), but 97% of children better accepted oral dexmedetomidine. No significant side effects were attributable to either premedication. Emergence from anaesthesia was comparable between groups.

Conclusion: premedication with oral midazolam ketamine appeared to be superior to oral dexmedetomidine, with evident haemodynamic stability and a higher degree of parental satisfaction, although oral dexmedetomidine was more accepted by the children.

KEYWORDS : Dexmedetomidine, Midazolam, Ketamine, Paediatric, Premedication

Introduction

Fear of physicians, injections, operations, the operation theatre and the forced separation from parents make the operative experience more traumatic for young children and can cause nightmares and postoperative behavioural abnormalities. Preanaesthetic medication may decrease the adverse psychological and physiological sequelae of induction of anaesthesia in a distressed child[1]. An important goal of premedication is to have the child arrive in the operating room calm and quiet with intactcardiorespiratoryreflexes. Various drugs have been advocated as premedication to allay anxiety and facilitate the smooth separation of children from parents. The idealpremedicantin children should be readily acceptable and should have a rapid and reliable onset with minimal side effects. Midazolam has sedative and anxiolytic activities, provides anterograde amnesia, and has anticonvulsant properties[2]. Ketamine, on the other hand, provides well-documented anaesthesia and analgesia. It has a wide margin of safety, as the protective reflexes are usually maintainedOral premedication with midazolam and ketamine became widely used inpaediatric anaesthesiato reduce emotional trauma and ensure smooth induction. It provided better premedication than either oral ketamine or midazolam alone[4], but excessive salivation and hallucination were observed[5].

Dexmedetomidine is a highly selective α2-adrenoreceptor agonist drug. Clinical investigations have demonstrated its sedative, analgesic and anxiolytic effects after IV administration to volunteers and postsurgical patients[6]. It has been used to sedate infants and children during mechanical ventilation and also to sedate children undergoing radiological imaging studies[8]In the literature, few articles have used dexmedetomidine orally for the premedication of children. The purpose of this study is to evaluate the efficacy of dexmedetomidine when administered orally as a hypnotic and anxiolytic agent compared to oral combination ketamine/midazolam as preanaesthetic medication in paediatrics.

Methods:

The Hospital Ethics Committee approved the protocol. Written informed consent was obtained from parents prior to inclusion. Sixty six children of ASA physical status I or II, aged between 2 and 6 years and scheduled for elective minor surgery of more than 30 minutes expected duration were enrolled in this prospective, randomized, double-blind study. Exclusion criteria were: a known allergy or hypersensitivity reaction to any of the study drugs, organ dysfunction, cardiac arrhythmia or congenital heart disease, and mental retardation.

Children were randomly allocated to one of the two study groups using computer-generated random numbers. Group D received oral dexmedetomidine 3 μg/kg and group MK received 0.25 mg/kg oral midazolam (up to a maximum of 15 mg) with 2.5 mg/kg oral ketamine. The oral premedication was mixed with 3 ml of apple juice as a carrier to be given thirty minutes before induction of anaesthesia. The oral route was chosen as it is the most acceptable and familiar mode of drug

administration. An independent investigator not involved in the observation or administration of anaesthesia for the children prepared all study drugs. Observers and attending anaesthetists who evaluated the patients for preoperative sedation and emergence from anaesthesia were blinded to the drug administered. Children had premedication in the preoperative holding area in the presence of one parent. All children received EMLA cream unless contraindicated.

After drugs were administrated, the following conditions were observed: 1) response to drug and onset of sedation, 2) response to the family separation circumstance and the entrance to the operating room, 3) response to the venous line (IV) insertion, 4) ease of mask acceptance during induction of anaesthesia. The time to recovery from anaesthesia and to achieve satisfactory Aldrete score were also noted. Onset of sedation was defined as the minimum time interval necessary for the child to become drowsy or asleep.

Sedation statuswas assessed every 5 min for up to 30 min with a five-point scale. A score of three or higher was considered satisfactory. In addition anxiolysis was assessed on a four-point scale. An anxiety score of three or four was considered satisfactory. Cooperation was assessed with a four-point scale. A cooperation score of three or four was considered satisfactory. Taste acceptability was evaluated on a four-point scale. A score of 1–3 was considered satisfactory.

Score	Sedation	Anxiolysis	Cooperation	Taste
1	Alert/active	Poor	Poor	Accepted readily
2	Upset/wary	Fair	Fair	Accepted with grimace
3	Relaxed	Good	Good	Accept with verbalcomplaint
4	Drowsy	Excellent	Excellent	Rejected entirely
5	Asleep			

Heart rate, blood pressure, respiratory rate and arterial oxygen saturation were recorded before premedication, every five minutes for 30 min preoperatively, and then during induction of anaesthesia, every 5 min intra-operatively, every 15 min in recovery room and every 30 min in day-case unit until time of discharge.

The anaesthetic agents administered were standardized.Children were induced with sevoflurane, nitrous oxide in oxygen and fentanyl 1-2 µg/Kg and maintained with the same drugs. The trachea was intubated after administering cisataracurium 0.1 mg/kg.

At the end of the procedure, the neuromuscular blockade was reversed with neostigmine with glycopyrolate and the child was extubated. After that, they were kept in the recovery room (PACU) under observation until discharge. The time to recovery from anaesthesia and to achieve satisfactory Aldrete score were noted. The discharge time was also noted and postprocedure instructions were given. Children were called for checkups the following day, when parents were asked to answer a questionnaire about the surgical experience of the parent and child and side effects experienced, if any.

Statistical analysis was performed using SPSS version 17. All values were reported as mean ± SD and range. Data analysis for numerical data was performed by unpaired Student's t-test to detect the differences between the groups for age, weight, onset of anxiolysis and sedation. Data analysis for categorical data was performed by Fisher's exact test to detect differences for the scores. Other data are reported as mean ± SD or frequency (%). A P value < 0.05 was considered statistically significant. Prior to the study, we chose the null hypothesis (i.e. nosignificantsedation scores between the groups). The number of patients required in each group was determined using power analysis based on previous studies. Assuming that 79% of patients would become drowsy or asleep in the midazolam/ketamine group (15 patients), a sample size of 30 patients per group would have an 80% power of detecting a 20% difference in sedation (from 79% to 99%) at the 0.05 level ofsignificance. We decided to study 66 patients to account for possible dropouts.

Results:

Sixty-six patients were enrolled; four did not receive the study medication and two did not have surgery on the same day, leaving 60 subjects who fulfilled the criteria for the study.Groups were comparable regarding age, sex, weight, ASA physical status, surgical interventions and duration of anaesthesia (Table 1). Operative procedures were evenly distributed and included inguinalherniorrhaphy, hydrocele repair or orchidopexy.

Table 1: Demographic characteristics and duration of anaesthesia:

	Group D	Group MK
No of patients	33	33
No of patients excluded	4	2
Age (years)	4.02±1.98	4.2±1.45
Gender (female/male)	13/16	15/16
ASA (I/II)	25/4	25/6
Weight (Kg)	17.72±4.4	16.56±5.1
Duration of Anaesthesia (min)	35.17±5.9	32.7±8.4

Data are expressed as mean ± SD (range). P > 0.05. No significant difference among groups.
Dex group (D). Midazolam Ketamine group (MK). ASA, American Society of Anesthesiology physical status.

Onset of sedation was significantly faster after premedication with midazolam/ketamine (Fig1), and the level of sedation was significantly better after premedication with

midazolam/ketamine 30 minutes after ingestion of the premedicant.

The anxiolysis score revealed 84 % of children in group MK as being friendly and only 51% of children in group D have similar behaviour (Table 2). The taste of oral dexmedetomidine was judged as significantly better; 13% of children rejected the oral midazolam/ketamine combination (Table 2).

Table 2: Distribution of behaviour and sedation status at time of induction:

	Group D	Group MK	P
Time to onset of sedation (min)	24.52 ± 3.1	18.36 ± 2.6	0.015*
Preoperative sedation score	1.6±0.5	3.1±0.8	0.003*
% asleep at induction	61%	90%	0.024*
Preoperative anxiolysis score	1.4±0.6	2.9±0.7	0.016*
% Face mask acceptance	58%	88%	0.033*
% Venous line insertion acceptance	72%	90%	0.005*
% Satisfactory parental separation	50%	80%	0.04*
% Parental satisfaction	70%	90%	0.036*
% Taste acceptance	97%	87%	0.002*

Data are expressed as mean ± SD (range) or percentage. Dex group (D). Midazolam Ketamine group (MK).
* significant*P <0.05.*

Application of a facemask at induction of anaesthesia was accepted more readily in patients of group MK (Fig 2).Overall, satisfactory cooperation with venous line insertion was found in 90% of children in group MK, while comparatively 72% of children in group D showed satisfactory cooperation with insertion of a venous line (Table 2). Moreover, most of the MK treated children were more calm and sedated than the D-treated group at the time of separation from parents. Parental satisfaction was significantly higher in group MK.

The time interval from end of surgery to spontaneous eye opening in the PACU was significantly less in group D (Fig 1), while the time to discharge from the PACU to ward was similar for groups (Table 3).

Table 3: Time to eye opening and PACU discharge

	Group D	Group MK	P
Time to eye opening (min)	21±4.3	30±6.1	0.032*
Time of PACU discharge (min)	30± 3.9	28.12±5.5	0.316

Data are expressed as median ± SD (range). Dex group (D). Midazolam Ketamine group (MK).
* significant*P < 0.05.*

While no child experienced respiratory complications or arterial oxygendesaturationbefore induction, heart rate and systolic blood pressure were marginally higher after administration of MK. On the other hand, the mean heart rate and systolic blood pressure measurements were 15% lower (than preoperative values) in group D at the same study periods. However, during recovery, haemodynamic responses were similar.

Adverse events were recorded for the three periods. Two children in group MK as well as one in group D experienced nausea but only one patient in group MK vomited before induction. Hallucination was recorded in 10 % of patients in group MK. Excessive salivation occurred in 12% of children receiving the combination of drugs, compared to 7% in D-treated children.

Discussion:

Our study proved that midazolam/ketaminereceiving patients were significantly calmer and more cooperative compared to dexmedetomidine receiving patients during the preoperative period, the insertion of a venous line, during separation from parents and also during the application of a facemask at induction. Several studies have been published demonstrating the advantage of the midazolam/ketamine combination in paediatric premedication[4,9], while others have reported superiority of oral dexmedetomidine premedication to oral midazolam[10,11].

Based on their experience with using oral dexmedetomidineas a preanaesthetic in children, Kamal et al[10] and Zub et al[12] reported that the dose of 3 µg/kg could be safely and effectively applied without haemodynamic side effects.

Midazolam is currently the most commonly usedpaediatric premedication due to easy application, rapid onset, short duration of action and a lack of significant side effects[13]. Meanwhile oral ketamine was used in the 1970s by dentists to facilitate the treatment of mentally handicapped children. In 1982, Cetina found that rectal or oral preanaesthetic ketamine is an excellent analgesic and amnesic agent with no incidence ofdysphoric reactions, possibly related to its high rate of first-pass metabolism[14]. The metabolite norketamine has approximately one-third the potency of ketamine, but reaches higher blood concentration and also causes sedation and analgesia [15]. The use of midazolam and ketamine in combination as a premedicant combines their properties of sedation and analgesia and attenuates drug induced deliriumGhai et al and Funk et al have also reported that a combination of midazolam and ketamine results in better premedication than the individual drugs given alone[4,9].

Like clonidine, dexmedetomidine possesses a high ratio of specificity for the α_2 versus the α_1 receptor (200: 1 for clonidine and 1600: 1 for dexmedetomidine). Through presynaptic activation of the α_2 adrenoceptor, it inhibits the release of norepinephrine and decreases sympathetic tone. There is also an attenuation of the neuroendocrine and haemodynamic responses to anaesthesia and surgery, thereby leading to sedation and analgesia[16]. One of the highest densities of α_2 receptors has

been detected in the locus coeruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance. The hypnotic and sedative effects of α_2-adrenoceptor activation have been attributed to this site in the CNS[16]. This allows psychomotor function to be preserved while letting the patient rest comfortably, so patients are able to return to their baseline level of consciousness when stimulated[17]. Clonidine and dexmedetomidine seems to offer the beneficial properties, but dexmedetomidine has a shorter half-life, which might be more suitable for day surgery. Zuband his colleagues reported that dexmedetomidine may be an effective oral premedicant prior to anaesthesia induction or procedural sedation and it was effective even in patients with neurobehavioural disorders in whom previous attempts at sedation had failedAlso Sakurai et al reported that oral dexmedetomidine could be applied safely and effectively as a preanaesthetic in children[18].

While dexmedetomidine is tasteless and odourless[17] , with 82% bioavailability after extravascular doses in healthy human adults[19], oral midazolam formulations have a bitter taste and were usually prepared by mixing the IV midazolam with a variety of sweet additives. In our study, children judged the taste of oral dexmedetomidine as significantly better than oral midazolam ketamine mixture, although both drugs were given with the same sweet tasting syrup. This observation probably might also reflect the developmental age of these patients and the difficulty of gaining their cooperation in swallowing something that they did not wish to swallow. Recently, new commercially prepared oral midazolam formulations are reported to be more palatable[20], but unfortunately, it is not available yet in our country.

Our data confirmed that onset of sedation and peak sedative effect was significantly slower after oral dexmedetomidine compared to oral midazolam ketamine. These results are consistent with studies by Kamal et al and Schmidt et al who reported slow onset of action of oral dexmedetomidine[21]In addition, Anttila et al reported that, in adults after oral administration, peak plasma concentration is achieved at 2.2 ± 0.5 h after a lag-time of 0.6 ± 0.3 h[19].

In this study, dexmedetomidine premedication with the present study design resulted in slight hypotension and bradycardia, which could be attributed to postsynaptic activation of α_2 adrenoceptors in the central nervous system (CNS) that inhibit sympathetic activity and thus can decrease blood pressure and heart rate[22]. In a finding consistent with our results, Khan et al and Aantaa et al reported that useofdexmedetomidine can beassociatedwithsome cardiovascular side effects including hypotension and bradycardia[24]Conversely, Ray and Tobias did not find significant haemodynamic changes when used dexmedetomidine in providing sedation during electroencephalographic analysis in children with autism and seizure disorders[25].

There were some limitations to this study; the bioavailability of oral dexmedetomidine is based on the adult dataWe need to decide the timing of the oral administration as apremedicantbased on the data in children. Therefore, the bioavailability of oral dexmedetomidine needs to be studied in children. The premedication period was 30 min, however, if a longer premedication period had been allowed, possibly more subjects could have attained satisfactory sedation at separation from parents and at induction of anaesthesia.

Conclusion:

In this study, premedication with oral midazolam/ketamineappeared to be superior to oral dexmedetomidine with evident haemodynamic stability and a higher degree of parental satisfaction demonstrated, although oral dexmedetomidinewas more accepted by the children. No significant side effects were attributable to either premedication. Emergence from anaesthesia was comparable between groups.

Competing Interests
None declared
Author Details
MOHAMED A. DAABISS, Riyadh Armed Forces Hospital, Department of Anaesthesia; Riyadh, Saudi Arabia.
MOHAMED HASHISH, Armed Forces Hospital, King Abdulaziz Airbase Hospital, Dhahran, Department of Anaesthesia; Riyadh, Saudi Arabia.
CORRESSPONDENCE: MOHAMED DAABISS, Department of Anaesthesia, Riyadh Armed Forces Hospital, Mailbox: 7897-D186 Riyadh 11159 Saudi Arabia
Email: madaabiss@yahoo.com

REFERENCES

1. Kain ZN, Caldwell-Andrews AA, Krivutza DM, et al. Trends in the practice of parental presence during induction of anaesthesia and the use of preoperative sedative premedication in the United States, 1995–2002: results of a follow-up national survey. Anesth Analg 2004;98:1252–9.
2. Kupietzky A, Houpt MI. Midazolam: A review of its uses for conscious sedation of children. Pediatr Dent 1993;15:237-41.
3. Sekerci C, D φnmez A, Ate Y, et al. Oral ketamine premedication in children (placebo controlled double-blind study). Eur J Anaesthesiol 1997;13:606-11.
4. Ghai B, Grandhe RP, Kumar A, et al. Comparative evaluation of midazolam and ketamine with midazolam alone as oral premedication. Pediatr Anesth 2005; 15(7): 554-9.
5. Roelofse JA, Joubert JJ, Roelofse PG. A double-blind randomized comparison of midazolam alone and midazolam combined with ketamine for sedation of paediatric dental patients. J oromaxillofacial surg 1996; 54(7): 838-44.
6. Taittonen MT, Kirvela OA, Aantaa R, et al. Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. Br J Anaesth 1997; 78: 400-6.
7. Tobias JD, Berkenbosch JW. Sedation during mechanical ventilation in infants and children: dexmedetomidine versus midazolam. South Med J 2004; 97: 451-5.
8. Mason KP, Zgleszewski SE, Dearden JL, et al. Dexmedetomidine for paediatric sedation for computed tomography imaging studies. Anesth Analg 2006;103:57-62.
9. Funk W, Jakob W, Riedl T, et al. Oral preanesthetic medication for children: double-blind randomized study of a combination of midazolam and ketamine vs. midazolam or ketamine alone. Br J Anaesth 2000; 84(3):335-40.

10. Kamal K, Soliman D, Zakaria D. Oral dexmedetomidine versus oral midazolam as premedication in children. Ain Shams J anaesth 2008;1: 1-18.
11. Üstün Y, Gündüz M, ErdoğanO, et al. Dexmedetomidine versus Midazolam in Outpatient Third Molar Surgery. J oromaxillofacial surg 2006; 64(9): 1353-8.
12. Zub D, Berkenbosch J, Tobias J. Preliminary experience with oral dexmedetomidine for procedural and anesthetic premedication. Pediatr Anesth 2005;15(11): 932-8.
13. McMillan CO, Spahr-Schopfer IA, Sikich N, et al. Premedication of children with oral midazolam. Can J Anaeth 1992;39: 545-50.
14. Cetina J. Schonende Narkoseeinleitung bel kindern durch orale oder rektale Ketamin-Dehydrobenzperidol-Applikation. Anaesthetist 1982;31:277-9.
15. Grant IS, Nimmo WS, Clements JA. Pharmacokinetics and analgesic effects of intramuscular and oral ketamine. Br J Anaesth 1981; 53: 805-10.
16. Hunter JC, Fontana DJ, Hedley LR, et al. Assessment of the role of alpha 2-adrenoceptor subtypes in the antinociceptive, sedative and hypothermic action of dexmedetomidine in transgenic mice. Br J Pharmacol. 1997;122:1339–44.
17. Hall JE, Uhrich TD, Barney JA, et al. Sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions. Anesth Analg. 2000;90:699–705.
18. Sakurai Y, Terui K, Obata T, et al. Buccal administration of dexmedetomidine as a preanesthetic in children. Anaesthesia 2010; 24:49–53.
19. Anttila M, Penttila J, Helminen A, et al. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects. J Clin Pharmacol 2003;56:691–3.
20. Cote ` CJ, Cohen IT, Suresh S, et al. A comparison of three doses of commercially prepared oral midazolam syrup in children. Anesth Analg 2002; 94: 37–43.
21. Schmidt AP, Valinetti EA, Bandeira D, et al. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. Pediatr Anesth 2007;17: 667 -74.
22. Dyck JB, Maze M, Haack C, et al. The pharmacokinetics and haemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. Anesthesiol 1993;78:813–20
23. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. Anaesthesia 1999; 54:146-165.
24. Aantaa R, Jaakola ML, Kallio A, et al. comparison of dexmedetomidine, an alpha2-adrenoceptor agonist, and midazolam as i.m. premedication for minor gynecological surgery. Br J Anaesth 1991; 67(4): 402-9.
25. Ray T ,Tobias J. Dexmedetomidine for sedation during electroencephalographic analysis in children with autism, pervasive developmental disorders, and seizure disorders. J Clin Anesth 2008; 20(5): 364-8.