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Comparison of nebulised dexmedetomidine, ketamine, or midazolam for premedication in preschool children undergoing bone marrow biopsy

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Abstract

Background: The aim of our study was to compare the efficacy of dexmedetomidine, ketamine, and midazolam for sedative premedication administered by nebuliser 30 min before general anaesthesia in preschool children undergoing bone marrow biopsy and aspiration.
Methods: Ninety children aged 3–7 yr were randomly allocated into three equal groups to be premedicated with either nebulised ketamine 2 mg kg^{-1} (Group K), dexmedetomidine 2 μg kg^{-1} (Group D), or midazolam 0.2 mg kg^{-1} (Group M). The primary endpoint was a five-point sedation score on arrival in the operating room 30 min after end of study drug administration. Secondary outcomes included: parental separation anxiety scale; medication and mask acceptance scales; haemodynamic variables; recovery time; postoperative face, legs, activity, cry, and consolability scale; emergence agitation scale; and adverse effects.
Results: The median (range) sedation score on arrival in the operating room was 3.5 (1–4), 2.0 (2–3) and 2.0 (1–3) in Groups M, D, and K, respectively (P=0.000). Subjects in Group D showed higher medication (P<0.03) and mask acceptance scores (P<0.015) and more satisfactory parental separation anxiety scale (P<0.044). The median (range) recovery time was significantly shorter in Group D [5.5 (4–8) min] compared with Group K [10.0 (5–15) min, P=0.000] and M [8.0 (6–15) min, P=0.000]. The incidence of emergence agitation was lower in Group D (P<0.008).
Conclusions: Preschool children premedicated with nebulised dexmedetomidine had more satisfactory sedation, shorter recovery time, and less postoperative agitation than those who received nebulised ketamine or midazolam.
Clinical trial registration: NCT02935959.

Keywords: children; dexmedetomidine; ketamine; midazolam; preoperative anxiety

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Editor's key points

- Children undergoing procedures commonly need preoperative sedative medication.
- Different routes of administration are available, each with their own advantages and disadvantages.
- The authors compared the clinical efficacy and effects of inhalation of nebulised dexmedetomidine, ketamine, or midazolam.
- Children who received dexmedetomidine had better sedation scores, better recovery scores and less emergence agitation.

For preschool children undergoing surgery, the preoperative period is the most distressing.[1] Parental separation and fear of physicians and needle injections increases their preoperative anxiety.[1] This psychological trauma is much exaggerated in children with cancer who are subjected to frequent needle injections and blood sampling, repeated drug treatment sessions (e.g. chemotherapy), and multiple diagnostic procedures. This preoperative anxiety is an acute stressor that stimulates the sympathetic, parasympathetic, and endocrine systems, leading to an increase in HR, BP, and cardiac excitability.[2] Moreover, it likely predisposes to emergence delirium, sleep disturbances, and behavioural changes.[2,3]

To alleviate preoperative anxiety and enable smooth parental separation, various drugs have been advocated suitable for use as sedative premedication, including midazolam, clonidine, dexmedetomidine, and ketamine.[1,4] Because of its amnestic and anxiolytic properties, midazolam, a $GABA_A$ agonist, is the drug most frequently used for paediatric premedication.[5,6] Dexmedetomidine is a highly selective α-2 adrenergic agonist with both sedative and analgesic effects via actions in the CNS.[5,6] Ketamine is an *N*-methyl-d-aspartate (NMDA) receptor antagonist that produces a state of sedation, anaesthesia, immobility, analgesia, and amnesia.[7,8]

Sedative premedication in children is commonly administered via the oral, rectal, sublingual, and intranasal routes with varying degrees of patient acceptance.[1–8] Inhalation of nebulised drug is an alternative method of administration that is relatively easy to set up, does not require venepuncture, and is associated with high bioavailability of the administered drug.[9,10]

The aim of the current study was to investigate the efficacy of dexmedetomidine, ketamine, and midazolam for sedative premedication when administered by inhalation of a nebulised solution 30 min before general anaesthesia in preschool oncologic children undergoing bone marrow biopsy and aspiration.

Methods

Enrolment and eligibility

This randomised, double-blind comparative study was approved by the local ethics committee of South Egypt Cancer Institute, Assiut University, Egypt. It was performed in the paediatric oncology and anaesthesiology departments, prospectively registered in the Clinical Trials.gov trial registry (identifier: NCT02935959), and strictly followed the regulations and amendments of the Helsinki Declaration. Ninety patients with cancer, ASA physical status 1 and 2, aged 3–7 yr, and undergoing bone marrow aspiration and biopsy were enrolled. Written informed consent was obtained from the parent or authorised guardian representative before participation in the study. Patients with known allergy to the study drugs, significant organ dysfunction, cardiac dysrhythmia, congenital heart disease, use of psychotropic medication, and mental retardation were excluded from the study.

Randomisation and blinding

Ninety patients were randomised to receive as premedication by inhalation, either nebulised ketamine 2 mg kg^{-1} (Group K, 30 patients), nebulised dexmedetomidine 2 μg kg^{-1} (Group D, 30 patients), or nebulised midazolam 0.2 mg kg^{-1} (Group M, 30 patients). Randomisation was based on a computer-generated randomisation table, with group allocation concealed in sealed opaque envelopes. An independent investigator not involved in the study opened the envelopes 1 h before induction of anaesthesia and prepared the study drug solutions in identical syringes with matching random codes. Study drugs were diluted in 3 ml of 0.9% saline and were administrated by standard hospital jet nebuliser via a mouthpiece (Maxineb Nebuliser with 010–631 T piece+tubing; Flexicare Medical Ltd® Mountain Ash, UK), with a continuous flow of 100% oxygen at 6 L min^{-1} for 10–15 min. Treatment was stopped when the nebuliser began to sputter. The attending anaesthesiologist, physician, data collection personnel, and the patient guardians were blinded to the patient group assignment. Each patient had to complete the three phases of the study: preoperative phase (30 min after end of administration of nebulised study drug), intraoperative phase, and the early postoperative phase (1 h after operation).

Study protocol

Before operation, all patients received the inhaled study drug according to the group assignment. At end of nebuliser administration, they were observed for 30 min before general anaesthesia was induced. Standard monitoring included electrocardiography, end-tidal carbon dioxide, arterial oxygen saturation continuously, and non-invasive BP every 5 min (Cardiocap II: Datex-Ohmeda, Helsinki, Finland). The anaesthetic technique was standardised in all patients. Anaesthesia was induced with sevoflurane 8% in oxygen 100% via a Jackson Rees breathing circuit. An i.v. cannula was placed after induction of anaesthesia. Patients then received i.v. propofol 1 mg kg^{-1} and a laryngeal mask airway (LMA) of suitable size was inserted. Anaesthesia was maintained with sevoflurane in a 50% oxygen/air mixture. Spontaneous breathing was maintained during the procedure. No other sedatives or opioids were administered during the procedure. At the end of the procedure, the LMA was removed, and the child was transferred to the PACU once the airway was maintained spontaneously and there was no haemodynamic instability. The face, legs, activity, cry, consolability (FLACC) pain scale and emergence agitation (EA) scale[11,12] were recorded for 1 h. After an Aldrete–Krolik recovery score >9 was reached,[13] the patients were transferred to the ward.

Perioperative adverse events such as hypotension, bradycardia, and vomiting were noted and recorded. Hypotension was defined as systolic arterial pressure <(70 mm Hg+2×age in years), associated with altered peripheral perfusion requiring fluid bolus administration. Bradycardia was defined as HR<60 beats min^{-1} requiring atropine administration.

Assessment parameters

Preoperative assessments

The HR, non-invasive BP, and ventilatory frequency were assessed before (0 min, baseline) and at 5, 10, 20, and 30 min after the end study drug administration. Sedation level was assessed at the same time points mentioned above using a five-point sedation scale score[14] as follows: 1=agitated, 2=alert, 3=calm, 4=drowsy, and 5=asleep. A score ≥3 was considered as acceptable sedation. Patients' acceptance of the medication was assessed using a four-point scale[15] as follows: 1=excellent, accepted medication without complaint; 2=good, complained, was briefly tearful or unhappy, but then accepted medication; 3=fair, complained, initially uncooperative but eventually accepted medication; 4=poor, refused medication.

At the end of the preoperative phase, parental separation was assessed by a four-point parental separation anxiety scale (PSAS)[14] as follows: 1=easy separation, 2=whimpers, but is easily reassured, not clinging, 3=cries and cannot be easily reassured, but not clinging to parents, and 4=crying and clinging to parents. PSAS scores of 1 and 2 signified acceptable separation whereas scores of 3 and 4 were classified as difficult separation (see Table S1).

Intraoperative assessments

When the child arrived in the operating room (OR), his level of sedation was assessed. Patients' acceptance of the anaesthesia mask was assessed using a four-point mask acceptance scale (MAS)[14] as follows: 1=excellent, unafraid, cooperative, accepts mask easily, 2=good, slight fear of mask, easily assured, 3=fair, moderate fear of mask, not calmed with reassurance, and 4=poor, terrified, crying or combative. MAS scores of 1 and 2 denoted 'satisfactory' mask acceptance whereas scores of 3 and 4 were considered 'unsatisfactory' MAS (see Table S1). HR and BP were recorded before (0 min, baseline) and at 5, 10, 15, and 20 min after induction of general anaesthesia. Anaesthesia duration and recovery time (time from discontinuation of sevoflurane until the sedation score returned to baseline) were recorded in minutes.

Early postoperative assessments

HR and BP were recorded upon admission to the PACU (0 min, baseline) and at 15, 30, 45, and 60 min thereafter. Recovery was assessed using the three-point EA scale[12] as follows: 1=calm, 2=restless but calms in response to verbal instructions, and 3=combative and disoriented. A score ≥2 signified sevoflurane EA. Pain intensity was assessed using the FLACC scale,[11] with a maximum score of 10 (see Table S1). If the recorded FLACC scale score was ≥4, i.v. paracetamol 15 mg kg^{-1} was given for rescue analgesia.

Statistical analysis

Power of the study

The primary outcome was the sedation level when the child arrived in the OR 30 min after the end of study drug administration. The secondary outcomes were acceptance of the medication, parental separation, tolerance of mask induction, perioperative HR and BP, postoperative FLACC pain scale, the incidence of EA, and adverse events. Based on a previous study,[9] 22 patients in each group should be sufficient to detect a difference between means of the sedation score of 1, assuming a standard deviation of 0.5 with a power of 80% and a two-sided type I error of 5%. Ninety patients were recruited and were equally distributed between the three treatment groups to account for random errors and for additional comparisons.

Data analysis

Data entry and analysis were done using SPSS version 19 (Statistical Package for Social Science). Data were represented as median (range), number, and percentage. The χ^2 test was used to investigate differences among categorical variables. One sample Kolmogorov–Smirnov normality testing was used to investigate the distribution of continuous variables. It showed that our data were not normally distributed and so non-parametric tests were used for statistical analysis. The Kruskal–Wallis Test was used to compare the quantitative variables among the three groups and if significant differences were seen, then comparisons between pairs of groups were performed with the Mann-Whitney test. A *P*-value of <0.05 was considered statistically significant.

Results

Among the 100 patients who were screened for eligibility, 90 were enrolled into one of the three groups (n=30) (Fig. 1). There were no significant differences between the groups in terms of subject characteristics or clinical data (Table 1).

Preoperative assessments

Subjects in Group K had significantly higher mean HR values from 5 until 30 min after the end of study drug administration compared with Groups D and M (P<0.001). Subjects in Group D had significantly lower systolic BP (SBP) and diastolic BP (DPB) mean values at 5, 10, 20, and 30 min. after the end of study drug administration, compared with Groups K and M (P<0.001). Higher median ventilatory frequencies were recorded in Group D (P<0.015) 5 min after end of study drug administration, with no significant differences between groups at other time points (Table 2). Subjects in Group D had higher acceptance of the medication score (P<0.03), with no difference between Groups K and M (Table 1). Sedation scores varied significantly between groups with the highest scores reported in Group M (P=0.000) (Table 3). PSAS was significantly higher in Groups D and K compared with Group M (P<0.044), with no difference between Groups D and K (Table 1).

Intraoperative assessments

Median (range) sedation scores on arrival in the OR, were 3.5 (1–4), 2 (2–3) and 2 (1–3) in Groups M, D, and K, respectively (P=0.000) (Table 3). Subjects in group D had higher mask acceptance scores compared with Groups K and M (P<0.015), with no difference between Groups K and M (Table 1). Except for a significantly lower mean HR in group D 10 min after anaesthesia induction, compared with Groups M and K (P<0.001), there were no significant differences between groups in the intraoperative HR, SBP, DBP, and ventilatory frequency (Table 4). The median (range) recovery time was significantly shorter in Group D 5.5 (4–8) min compared with Groups K [10 (5–15) min, P=0.000] and M [8 (6–15) min, P=0.000] (Table 1).

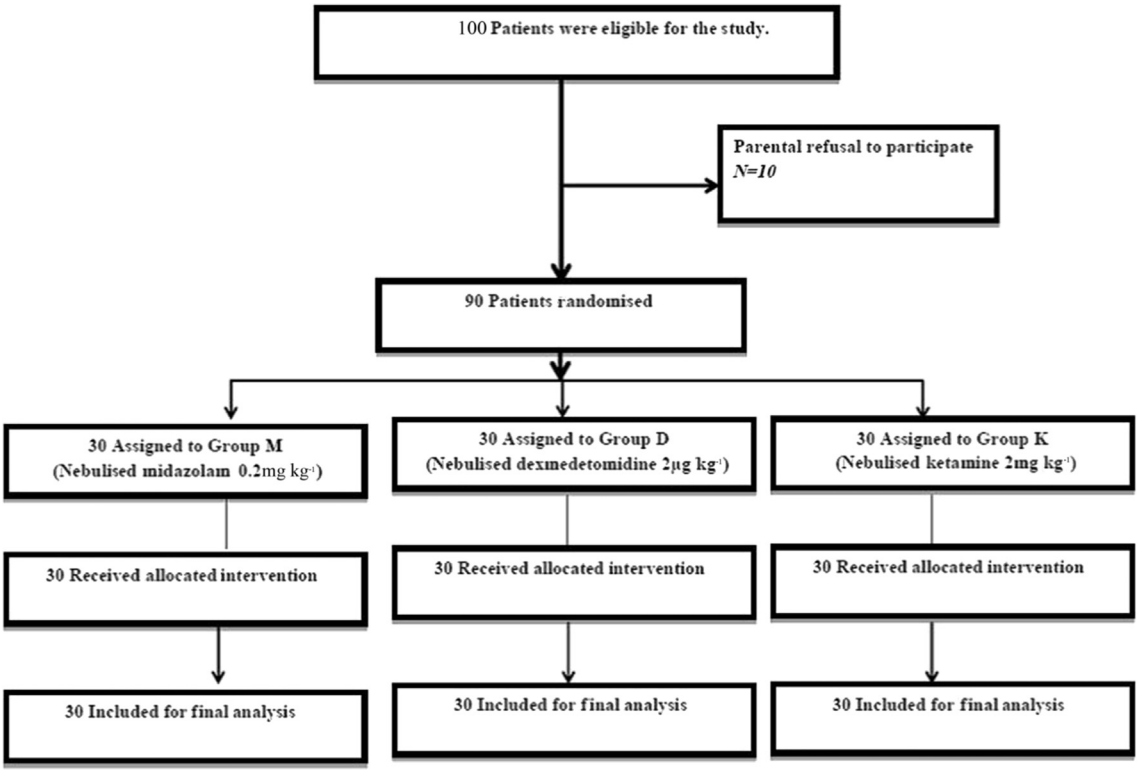

Fig 1. Study flow diagram.

Early postoperative assessments

After operation, 12 subjects (40%) in Group M *vs* two (6.7%) and six (20%) in Groups D and K had EA scores ≥2 ($P<0.008$) (Table 1). The median EAS was significantly lower in Group D at 0-baseline ($P<0.002$) and 15 min ($P<0.021$) after operation with no difference between groups thereafter (Table 5). Except for a significant difference in the DBP at 45 min, there were no significant differences between groups in the early postoperative variables including HR, SBP, DBP, ventilatory frequency, and FLACC score (Table 5).

Regarding postoperative adverse effects, vomiting occurred in one, none, and two patients in Groups M, D, and K, respectively. One child had increased salivation in Group D. No patient in this study exhibited hypotension or bradycardia.

Discussion

We found that children premedicated with inhaled nebulised dexmedetomidine (2 μg kg^{-1}) had more satisfactory sedation scores on arrival in the OR, higher acceptance of the medication, more satisfactory PSAS and MAS scales and shorter recovery times after sevoflurane anaesthesia than those who received nebulised ketamine or midazolam. Moreover, nebulised dexmedetomidine premedication was associated with a lower incidence of postoperative agitation.

Preoperative anxiety in preschool children is distressing.[3] Different pharmacological and behavioural interventions have been suggested[1–6] but no technique or pharmacological agent has been completely satisfactory in this special age group.[1–3]

Selecting the route of sedative drug administration in preschool children is an important task. Different routes of administration have been tried (e.g. i.v., oral, buccal, rectal, and intranasal), with each route having its own advantages and disadvantages.[7] The inhalation route used in this study may offer an alternative mode of administration of sedative premedication that is relatively easy to set up, and does not require an i.v. cannulation or injection, but is still associated with high bioavailability of the administered drug.[9,10,16] McCormick *et al.*[10] compared inhalation of nebulised midazolam with intranasal midazolam administration. They concluded that nebulised midazolam administration causes less discomfort than intranasal administration. Kaabachi *et al.*[16] compared oral *vs* inhalation via nebuliser of midazolam for sedative premedication in children, and also concluded that mask nebulisation with midazolam is an effective, rapid, and safe route for premedication in children. We similarly found that the nebulisation technique was simple and very convenient for our patients.

Use of an atomiser device for intranasal administration generates a spray of drug that maximises surface area coverage with a thin layer of drug that enables rapid drug absorption through the nasal, buccal, and respiratory mucosa, which can help to achieve higher CSF concentrations, better patient acceptability, and improved clinical effectiveness.[10] Data on drug pharmacokinetics for the nebulised route are limited and so in the current study we selected the doses of ketamine,[9] dexmedetomidine,[9] and midazolam[10,15,17] based

Table 1 Subject characteristics and clinical data. Data are expressed as median and range, number, and frequency. ALL, acute lymphocytic leukaemia; BMA, bone marrow aspirate; EAS, emergence agitation scale; MAS, mask acceptance scale; NHL, non-Hodgkin's lymphoma; PSAS, parental separation anxiety scale. $P<0.05$; significance *vs* Group M

Item	Group M (nebulised midazolam) ($n=30$)	Group D (nebulised dexmedetomidine) ($n=30$)	Group K (nebulised ketamine) ($n=30$)	P–value
Age (yr) median (range)	4.5 (3–7)	5.0 (3.5–7)	5.0 (3–7)	P=0.106
Weight (kg) median (range)	17.5 (14–26)	17.0 (12–27)	17.5 (12.6–30)	P=0.403
Sex (male/female)	16/14	13/17	17/13	P=0.062
ASA physical status 1/2	20/10	25/5	23/7	P=0.319
Pathological diagnosis: ALL/NHL/neuroblastoma	22/0/8	17/3/10	18/0/12	P=0.110
Procedure: BMA/BMA and biopsy	23/7	17/13	19/11	P=0.252
Acceptance of medication: excellent/good/fair/poor	17/8/5/0	23/4/3/0	15/7/3/5	P<0.03
PSAS: excellent/good/fair/poor	19/9/2/0	22/6/2/0	12/9/6/3	P<0.044
Sedation score in OR: agitated/alert/calm/drowsy/asleep	4/0/11/15/0	0/16/14/0/0	4/22/4/0/0	P=0.000
median (range)	3.5 (1–4)	2.0 (2–3)	2.0 (1–3)	
MAS:				
Excellent	8	16	6	P<0.015
Good	9	5	14	P<0.042
Fair	5	4	5	P=0.919
Poor	8	5	5	P=0.535
Anaesthesia time (min) median (range)	10.5 (8–20)	11.0 (10–15)	10.0 (8–22)	P=0.620
Recovery time (min) median (range)	8.0 (6–15)	5.5 (4–8)	10.0 (5–15)	P=0.000
EAS: –calm/restless/combative –incidence of agitation	24/6/0 (20%)	28/2/0 (6.7%)	18/12/0 (40%)	P<0.008

on previous clinical studies that proved the clinical effectiveness of these doses.

Previous studies have compared the efficacy of midazolam, dexmedetomidine, ketamine, or all three as sedative premedication when administered through different routes of administration and different doses with varying results.[9,18–20] Zanaty and Metainy[9] compared inhaled nebulised dexmedetomidine (D) and ketamine (K), and a low dose combination (DK) in paediatric outpatient dental surgeries. The sedation level at 30 min was significantly greater in Group DK than in Group K or Group D with no difference between D and K groups. There were no significant differences between groups in the ease of parental separation, ease of venepuncture, or face mask acceptance. They concluded that a nebulised combination of low dose ketamine and dexmedetomidine produced more satisfactory sedation and provided a smoother induction of general anaesthesia than nebulised ketamine or dexmedetomidine alone.[9]

Surendar and colleagues[19] compared the efficacy and safety of intranasal dexmedetomidine (1.0 and 1.5 μg kg^{-1}), midazolam (0.2 mg kg^{-1}), and ketamine (5 mg kg^{-1}) for sedation in paediatric dental patients. They found that the onset of sedation was significantly more rapid in the midazolam and ketamine groups than in the dexmedetomidine groups. The overall sedation success rate was highest with 1.5 μg kg^{-1} dexmedetomidine, followed by 1.0 μg kg^{-1} dexmedetomidine, ketamine, and midazolam, although these differences were not statistically significant.[19]

In to the above studies, we recorded significant differences between the three groups in the sedation score. Moreover, subjects in Group D showed higher medication and mask acceptance scores, more satisfactory PSAS, and shorter recovery times from anaesthesia.

The significant differences we recorded between groups in the sedation score represent the different quality of sedation produced; mild dissociation (ketamine group), as opposed to mild to moderate (dexmedetomidine group) and moderate (midazolam group) sedation. The sedative effect of dexmedetomidine is described as an arousable sedation state[21] which is different to that of other clinically available sedatives. Unlike midazolam (which acts as an agonist at the $GABA_A$ receptor) and ketamine (NMDA receptor antagonist), dexmedetomidine is an α-2 agonist acting primarily at the locus coeruleus where it induces EEG activity similar to that seen during natural sleep.[22] Whilst sedated with dexmedetomidine, patients are also less likely to become disorientated and uncooperative than with other drugs,[23] which might explain our results.

The incidence of postoperative sevoflurane EA in preschool children varies from 10% to 66%.[24] Sedative premedication with propofol,[25] midazolam,[26] α-2 adrenergic agonists,[27] and opioids[28] has been administered to reduce the incidence of this problem. In the current study, the incidence of EA was reduced with all three drugs studied. However, nebulised dexmedetomidine premedication was associated with the highest decrease. These results are in accordance with many

Table 2 Preoperative HR, systolic (SBP) and diastolic (DBP) non-invasive BP, and ventilatory frequency (VF). Data are expressed as median and range. Group M (nebulised midazolam 0.2 mg kg^{-1}), Group D (nebulised dexmedetomidine 2 μg kg^{-1}), Group K (nebulised ketamine 2 mg kg^{-1}). $P<0.05$: significance *vs* Group M

	Baseline	5 min	10 min	20 min	30 min
HR:					
Group M	100 (85–120)	96 (80–119)‡	94 (81–120)‡	91 (82–122)‡	90 (80–120)*
Group D	100 (85–120)	95.5 (84–119)	93.5 (80–118)	94 (82–118)	94.5 (84–118)
Group K	100.5 (80–118)	112 (85–122)	110 (87–125)	110 (89–120)	100 (84–123)
SBP:					
Group M	95 (85–110)	95 (86–106)†	93.5 (83–103)‡	92.5 (82–100)‡	90 (82–100)‡
Group D	92.5 (85–100)	91 (86–99)	90 (85–97)	89.5 (80–95)	87 (80–96)
Group K	97 (86–120)	97 (87–115)	95.5 (86–115)	95 (87–116)	95 (87–120)
DBP:					
Group M	58 (50–65)	57 (52–63)*	56 (50–61)†	55.5 (50–62)‡	54.5 (50–63)‡
Group D	55.5 (48–63)	54.5 (47–62)	53 (48–62)	53 (45–62)	50.5 (46–60)
Group K	60 (54–70)	58 (54–65)	58 (53–65)	59 (52–67)	59 (53–68)
VF:					
Group M	22 (16–26)	22 (16–26)*	22 (16–28)	21 (18–30)	21 (16–26)
Group D	23.5 (18–30)	24.5 (18–30)	23 (16–30)	22 (18–30)	20 (16–30)
Group K	22.5 (12–28)	22 (15–27)	22.5 (15–28)	22 (14–27)	21.5 (16–28)

*P<0.05, †P<0.01, and ‡P<0.001.

Table 3 Sedation score. Data are expressed as median and range. Group M (nebulised midazolam 0.2 mg kg^{-1}), Group D (nebulised dexmedetomidine 2 μg kg^{-1}), Group K (nebulised ketamine 2 mg kg^{-1}). $P<0.05$: significance *vs* Group M

	Immediately	5 min	10 min	20 min	30 min
Group M	2.0 (1–2)	2.0 (1–2) ‡	3.0 (1–3) ‡	3.0 (1–4) ‡	3.5 (1–4) ‡
Group D	1.0 (1–2)	2.0 (1–2)	2.0 (2–3)	2.0 (2–3)	2.0 (2–3)
Group K	1.0 (1–2)	1.0 (1–2)	2.0 (1–2)	2.0 (1–3)	2.0 (1–3)

*P<0.05, †P<0.01, and ‡P<0.001.

Table 4 Intra-operative HR, systolic (SBP) and diastolic (DBP) non-invasive BP, and ventilatory frequency (VF). Data are expressed as median and range. Group M (nebulised midazolam 0.2 mg kg^{-1}), Group D (nebulised dexmedetomidine 2 μg kg^{-1}), Group K (nebulised ketamine 2mg kg^{-1}). $P<0.05$: significance *vs* Group M

	Baseline	5 min	10 min	15 min	20 min
HR:					
Group M	120 (110–130)	118.5 (105–130)	112 (100–130) ‡	110 (100–120)	115.5 (115–122)
Group D	130 (105–155)	110 (90–147)	100 (70–140)	90 (90–140)	–
Group K	123 (100–168)	111 (62–155)	110 (66–155)	100 (70–141)	109 (75–145)
SBP:					
Group M	90 (85–100)	90 (80–98)	91 (80–97)	90 (82–97)	90 (85–99)
Group D	90 (85–100)	90 (80–95)	88.5 (58–95)	90 (83–90)	–
Group K	90 (85–100)	90 (82–110)	89 (80–115)	89 (86–107)	89 (85–110)
DBP:					
Group M	57.5 (50–65)	55 (50–65)	55 (50–67)	62.5 (51–67)	62.5 (52–66)
Group D	55 (50–60)	54.5 (50–62)	55 (50–63)	65 (52–65)	–
Group K	56 (50–70)	56 (50–70)	56.5 (50–67)	55 (52–66)	52 (50–70)
VF:					
Group M	20.5 (17–26)	20 (16–26)	20 (16–28)	20 (14–21)	18 (16–21)
Group D	20 (16–28)	20 (17–26)	21 (16–26)	22 (21–22)	–
Group K	22 (18–26)	21 (18–24)	20 (16–24)	20 (16–22)	20 (16–22)

*P<0.05, †P<0.01, and ‡P<0.001.

Table 5 Early postoperative heart rate (HR), systolic (SBP) and diastolic (DBP) non-invasive blood pressure, ventilatory frequency (VF), faces legs activity cry consolability (FLACC), and emergence agitation scale (EAS) scores. Data are expressed as median and range. Group M (nebulised midazolam 0.2 mg kg^{-1}), Group D (nebulised dexmedetomidine 2 μg kg^{-1}), Group K (nebulised ketamine 2 mg kg^{-1}). $P<0.05$:significance *vs* Group M

	Baseline	15 min	30 min	45 min	60 min
HR:					
Group M	97.5 (88–125)	100 (87–120)	100 (89–116)	99.5 (88–122)	98 (87–129)
Group D	99.5 (90–120)	95 (90–115)	98.5 (90–120)	100 (94–119)	101 (90–120)
Group K	97 (89–120)	96 (80–125)	97.5 (72–125)	97 (73–125)	98 (71–122)
SBP:					
Group M	97 (85–100)	95.5 (86–100)	95 (85–99)	95 (88–100)	94.5 (85–101)
Group D	93 (88–99)	92 (88–100)	93 (89–100)	94.5 (87–99)	95 (58–100)
Group K	90 (85–110)	92 (85–105)	91.5 (85–107)	91 (84–110)	91 (85–110)
DBP:					
Group M	54.5 (46–86)	55 (48–87)	57 (45–84)	56 (47–85)‡	57 (48–84)
Group D	55 (50–62)	56 (51–64)	55 (51–66)	56 (50–67)	57 (50–65)
Group K	53.5 (48–86)	54 (40–84)	53.5 (46–87)	52 (40–88)	53.5 (47–85)
VF:					
Group M	22 (16–26)	20 (16–26)	20 (17–26)	20 (16–28)	20 (16–28)
Group D	20 (18–26)	20 (16–24)	21 (16–26)	20 (17–25)	20 (17–25)
Group K	21 (17–26)	22 (16–26)	21.5 (18–24)	20 (16–27)	20 (16–27)
FLACC:					
Group M	0.0 (0–1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Group D	0.0 (0–1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Group K	0.0 (0–1)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
EAS:					
Group M	1.0 (1–2)‡	1.0 (1–2)*	1.0 (1–1)	1.0 (1–1)	1.0 (1–1)
Group D	1.0 (1–2)	1.0 (1–1)	1.0 (1–1)	1.0 (1–1)	1.0 (1–1)
Group K	1.0 (1–2)	1.0 (1–2)	1.0 (1–2)	1.0 (1–1)	1.0 (1–1)

*$P<0.05$, **$P<0.01$, and ‡$P<0.001$.

studies that investigated the preventive role of dexmedetomidine in EA.[7–9,27]

Plambech and Afshari[29] showed that hypotension and bradycardia are the most common adverse events associated with dexmedetomidine and that respiration is only slightly affected. In accordance, patients in our study who received nebulised dexmedetomidine showed lower HR and BP mean values in the preoperative phase of the study and lower mean HR at 10 min intraoperatively, with no effect on respiration at any time-point. However, these haemodynamic changes were not clinically significant and did not require any intervention. Zanaty and Metainy,[9] investigated the combination of reduced doses of dexmedetomidine and ketamine nebulised premedication and concluded that by this combination, we can attenuate the cardio-depressant effects of dexmedetomidine by the cardio-stimulatory effects of ketamine.

A potential weakness of the study is the choice of scoring system to assess the patients' co-operation. Although this system has been used in several published studies,[5–11] it has not been formally validated, and the intra- and inter-rater variability have not been established.

In conclusion, preschool oncologic children premedicated with nebulised dexmedetomidine (2 μg kg^{-1}) showed more satisfactory sedation 30 min later on arrival at the OR, higher acceptance of the medication, more satisfactory PSAS and MAS scale scores, shorter recovery times from anaesthesia, and less postoperative agitation than those who received nebulised ketamine (2 mg kg^{-1}) or midazolam (0.2 mg kg^{-1}). The nebulised route for premedication in children is underutilised and further drug combinations and dose finding studies are needed.

Authors' contributions

Study design, writing, and editing of the manuscript: H.S.A.-G.
Conduct of study: S.M.K.
Data collection: S.M.K., S.A.-B.M.
Excel sheet revision and statistical analysis: F.A.E.S.
Preparation and excel sheets preparation: S.A.-B.M.

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Declaration of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.03.039.

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