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Clinical Investigation

CLINICAL INVESTIGATION

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.