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Clinical Investigation

CLINICAL INVESTIGATION

Determination of the median effective dose of propofol in combination with different doses of ketamine during gastro-duodenoscopy in children: a randomised controlled trial

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Background: Propofol is used to induce deep sedation or general anaesthesia for procedures in children. Adjuvants, such as ketamine, are routinely added to reduce the dose of propofol required and propofol-related adverse events. We conducted a randomised controlled trial to determine the effective bolus dose of propofol in combination with ketamine that induces adequate depth of anaesthesia in 50% of children (ED_{50}) undergoing gastro-duodenoscopy.
Methods: Children were randomised to one of four doses of ketamine: 0 (control), 0.25, 0.5, and 1 mg kg^{-1}, followed by a dose of propofol according to Dixon's up-and-down methodology. Excessive movement, coughing, gagging, or airway obstruction that prevented endoscope insertion was considered a failure.
Results: The ED_{50} of propofol (median, 95% CI) was greater in the ketamine 0, 0.25, and 0.5 mg kg^{-1} groups compared with the ketamine 1 mg kg^{-1} group (6.1, 4.1–8.1; 4.5, 2.9–6; 4.7, 3.1–6.2 mg kg^{-1} *vs* 1.1, 0.5–1.8 mg kg^{-1}, respectively, $P<0.008$). Total dose of propofol administered during the procedure was reduced with ketamine 1 mg kg^{-1}. The mean arterial pressure was lower in the ketamine 0 mg kg^{-1} group compared with the 1 mg kg^{-1} group during and immediately after the procedure. The ketamine 1 mg kg^{-1} group experienced a higher incidence of nausea and visual disturbances.
Conclusions: Ketamine at 0.5–1 mg kg^{-1} reduces the dose of propofol required to provide general anaesthesia for gastro-duodenoscopy in children and may reduce the incidence of propofol-related changes in haemodynamics.
Clinical trial registration: NCT 02295553.

Keywords: child; duodenoscopy; ketamine; propofol

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Editor's key points

- Ketamine is a commonly used sedative and analgesic adjunct during paediatric sedation and anaesthesia.
- The current study investigated the influence of three different doses of ketamine on propofol requirements for endoscopy.
- Ketamine reduced propofol requirements and was associated with better haemodynamic stability.
- Ketamine doses of 1 mg kg^{-1} were associated with higher incidences of nausea and visual disturbances.

Paediatric patients often require deep sedation, general anaesthesia, or both to tolerate medical procedures, such as lumbar puncture, fracture reduction, and upper gastrointestinal tract endoscopy. Various drugs, such as propofol, opioids, benzodiazepines, and ketamine, either alone or in combination, have been used.[1–5] Despite widespread use and expertise, there is no consensus for a standardised drug regimen in such scenarios. Ketamine offers numerous advantages as an adjuvant, including maintenance of airway tone, reduced apnoea risk compared with opioids, and haemodynamic stability. However, the side effects of ketamine, such as nausea and psychotomimetic effects in children, limit the dose that can be safely administered.

Recent systematic reviews and meta-analyses have shown that the use of propofol combined with an adjuvant, such as ketamine or an opioid (fentanyl), for procedural sedation/anaesthesia is more efficacious and safe compared with either an opioid/benzodiazepine combination or propofol alone.[1,6–13]

A recent meta-analysis of ketamine plus propofol for procedural sedation and analgesia in the emergency department in adults found that the risk of hypotension, bradycardia, and respiratory complications requiring intervention significantly decreased with the combination of ketamine and propofol compared with propofol alone.[13] The authors did not recommend a dose ratio for propofol and ketamine, and noted that the 'optimal ketamine-propofol proportion has not been determined' in adults or children.

To address this gap, we conducted a double-blind randomised controlled trial. Our primary objective was to determine the median effective bolus dose (mg kg^{-1}) of propofol in combination with ketamine in the following doses: 0, 0.25, 0.5, and 1 mg kg^{-1}, which produces an adequate depth of anaesthesia to prevent excessive movement, gagging, or coughing on endoscope insertion in children (ED_{50}). A secondary objective was to explore the type and frequency of adverse events associated with the propofol–ketamine dose combinations.

Methods

Design

We conducted a single-centre, double-blind, randomised four-arm trial to evaluate a range of dose combinations of propofol and ketamine administered to produce deep sedation/anaesthesia to children aged 3–12 yr undergoing elective gastroduodenoscopy. The Research Ethics Board at The Hospital for Sick Children (University of Toronto, ON, Canada) approved the trial. Regulatory approval was obtained from Health Canada for the use of ketamine. The study was registered with www.clinicaltrials.gov (December 2013, NCT 02295553).

Exclusion criteria were weight <10 kg; significant gastroesophageal reflux, vomiting, or both; known gastrointestinal bleeding; obesity (BMI >35 kg m^{-2}); oral sedation (premedication) before i.v. placement; and any contraindication to study medications. We obtained informed written consent from parents, and informed assent from all children aged 7–12 yr.

Randomisation and masking

Eligible children were allocated sequentially using a double-blind, randomisation system in a 1:1:1:1 ratio, using random-number generating computer software and a random number block 4 design to receive one of four doses of ketamine: 0 (control group), 0.25, 0.5, or 1 mg kg^{-1} (Ketamine 50 mg ml^{-1} HCl injection USP; Sandoz, Canada). The allocation sequence was not available to any member of the research team until databases had been completed and locked. Participants and their parents, the anaesthesiologist, the endoscopist, and the procedure room and recovery room nurses were blinded to patient assignment. Group allocation was concealed in opaque, sequentially numbered envelopes. A single study investigator (C.P.) had access to the randomisation code to allow for preparation of the study drugs and in the case of an emergency event during the procedure.

Procedures

A standardised anaesthetic regimen was used in all subjects. Topical local anaesthetic (Ametop, amethocaine/tetracaine hydrochloride 4% gel; Smith and Nephew, Mississauga, ON, Canada) was applied to the dorsum of both hands at least 30 min before the procedure, unless declined by the subject or parent. An i.v. catheter was placed on the dorsum of the hand just before the procedure. The children were offered inhaled nitrous oxide 50–60% in oxygen during i.v. catheter placement, which was turned off immediately afterwards and the children were encouraged to 'washout' the nitrous oxide by taking two or three deep breaths of 100% oxygen before administering the first study drug. Vital signs monitors (electrocardiogram, pulse oximetry, and non-invasive blood pressure cuff) were applied before the induction of anaesthesia, along with nasal prongs to monitor exhaled carbon dioxide and administer oxygen if the pulse oximeter saturation decreased to ≤94%. Heart rate, ventilatory frequency, and oxyhaemoglobin saturation were monitored continuously during the procedure.

An unblinded study investigator (C.P.), who did not participate in patient care during the sedation and endoscopy, prepared the study medications, and the doses were double-checked by a non-investigator anaesthesiologist or anaesthesia assistant (S.J.) not participating in patient care. The ketamine dose was drawn into a 10-ml syringe with normal saline added to produce a final volume of 10 ml of solution. The appropriate dose of propofol (Propofol 1%; Fresenius Kabi Canada Ltd., Toronto, ON, Canada) for that patient, as determined by the study protocol (Table 1), was drawn into either a 10 ml syringe (subjects aged ≤8 yr) or 20 ml syringe (subjects aged >8 yr) with 5% dextrose solution, as per product monograph, added to achieve a final volume of 10 and 20 ml, respectively, with a minimum concentration of 2 mg ml^{-1}. The