

Anticholinergic premedication-induced fever in paediatric ambulatory ketamine anaesthesia

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Abstract

Objective: A randomized, double-blind, prospective study to evaluate the effect of anticholinergic drugs on thermoregulation in paediatric patients undergoing ambulatory anaesthesia with ketamine.

Methods: Patients were randomized to receive either 0.005 mg/kg glycopyrrolate or the equivalent volume of normal saline (placebo) at 30 min before ketamine anaesthesia. Body temperature was measured tympanically at baseline and at 0, 30, 60 and 90 min postoperatively. The quantity of saliva produced during surgery and incidence of fever were recorded.

Results: Body temperature was significantly higher in the glycopyrrolate group ($n = 42$) than the placebo group ($n = 42$) at 30, 60 and 90 min after surgery, and higher than baseline at 0, 30, 60 and 90 min after surgery. In the placebo group, body temperature was significantly higher than baseline at 0 and 30 min after surgery. Saliva secretion was significantly lower in the glycopyrrolate group than the placebo group.

Conclusion: Routine premedication with adjunctive anticholinergics should not be considered in paediatric patients receiving ketamine sedation due to the increased risk of fever.

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Keywords

Child, outpatient, adverse events, premedication, intravenous agents

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Introduction

Ketamine has been widely used in minor procedures for children for its quick sedative and analgesic effects with minimal impact on airway reflexes and respiratory depression.¹ However, adverse effects such as nausea, vomiting, rash, emergence reactions, increased bronchial secretions and hypersalivation have also been related to ketamine sedations.^{2,3} Increased bronchial and oral secretions hinder oral and bronchial-related procedures, and the suction to remove excessive mucosal secretions can result in laryngospasm.^{2,3} Therefore, adjunctive anticholinergics, such as atropine or glycopyrrolate, have been used prior to ketamine administration. Anticholinergics are used as a premedication in oral or bronchial procedures because they reduce mucosal secretions and the resulting reflexive bronchospasms, thereby preventing vagus-induced bradycardia and improving surgical visibility.⁴⁻⁶ However, anticholinergics inhibit muscarinic acetylcholine receptors, exerting antimuscarinic actions such as dry mouth and fever. Thermoregulation is more dependent on sweating in children than in adults, and children may be more susceptible to higher body temperatures after injection of anticholinergics.⁷⁻⁹

Delayed discharge of paediatric patients due to postsurgical fever is frequently observed in patients anaesthetized with ketamine and adjunctive anticholinergics. Fever accounts for 4.7% of complications in paediatric outpatients after surgery,¹⁰ and may be caused by underlying disease, dehydration after preoperative fasting, or medication. Surgery is usually postponed in paediatric patients with fever or cold symptoms, reducing the likelihood that underlying conditions cause fever in this patient group. Although dehydration after preoperative fasting can cause fever,¹¹ the fact that body temperature was normal before surgery suggests that fasting is unlikely to be the cause of fever in these cases. Of the

medications used routinely in these patients (including Hartmann's solution, normal saline, adjunctive anticholinergics, ketamine and anti-inflammatory analgesic drugs), anticholinergics alone are reported to cause fever as an adverse effects.^{7,8} Ketamine has also been reported to cause fever, but this is not generally regarded as an adverse event.¹² The other listed medications (fluid and anti-inflammatory drugs) are used to treat fever, and are not the cause.¹³

The aim of this study was to evaluate the fever-causing effects of adjunctive anticholinergics in children under ambulatory anaesthesia using ketamine.

Patients and methods

Study population

This randomized, double-blind, placebo-controlled, prospective study recruited sequential paediatric outpatients aged 12 months – 8 years who were scheduled for procedures requiring ketamine sedation (including v-tube insertion, simple incision for cyst removal, and frenuloplasty of the tongue) between May and December 2014 at the Department of Anaesthesia and Pain Medicine, Inje University Ilsan Paik Hospital, Gyeonggi-do, Republic of Korea. Inclusion criteria were: (i) American Society of Anaesthesiologists class I¹⁴; (ii) surgery performed between 08.00 and 09.00 (to minimize variation due to body temperature fluctuations and duration of preoperative fasting). Patients who required endotracheal intubation due to respiratory failure during the procedure and patients who received medications other than ketamine were excluded.

Written informed consent was obtained from the parents or guardians of the patients, and the study protocol was approved by the Institutional Review Board of Inje University Ilsan Paik Hospital, Gyeonggi-do, Republic of Korea.

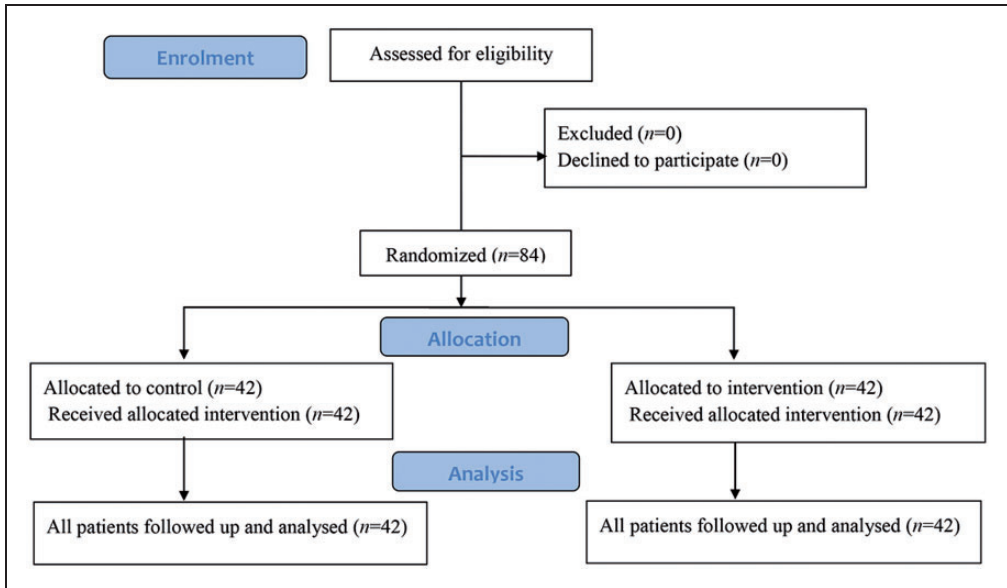


Figure 1. Consort flow diagram for patient enrolment into a randomized controlled clinical trial to evaluate the fever-causing effects of adjunctive anticholinergics in children under ambulatory anaesthesia using ketamine.

Study design

Patients were randomly assigned between two groups (using <http://randomization.com>): glycopyrrolate- group (group G), and saline (control) group (group N; Figure 1). After randomization, a single researcher (K.W.K.) prepared the study drugs (0.005 mg/kg glycopyrrolate [Tabinul injection 0.2 mg/ml; Hana Pharm Co. Ltd., Seoul, Republic of Korea], or the same volume of saline [placebo]) in a blinded manner. Another researcher (M.H.H.) measured the body temperature of the patient prior to surgery using a tympanic thermometer (Braun ThermoScan IRT 4520, Braun GmbH, Germany) three times in each ear, and recorded the highest value as the body temperature for that patient. The second researcher (M.H.H.) then administered the prepared study drugs. Ketamine (1 mg/kg initial dose, 5–10 mg additional dose, intravenous bolus) was used for sedation, and no other drugs were administered until the end

of the study. Oxygen was supplied via nasal cannula, blood pressure and oxygen saturation were monitored, and heart rate was monitored via electrocardiogram. The second researcher (M.H.H.), who was blinded to the experimental grouping of the subjects, measured body temperature at 0, 30, 60 and 90 minutes after surgery. The quantity of oral secretion produced during the procedure was recorded by a third researcher (J.H.K.), using a Visual Analogue Scale (VAS) by indicating a position from 0 mm (no secretion) to 100 mm (maximum secretion); the distance from 0 (in mm) was then measured by the first researcher (K.W.K.). The fluid infusion rate was increased when the body temperature of the patient exceeded 37.8°C, and antipyretics were administered when fever continued after body temperature measurements were completed. Fever was defined as body temperature >37.8°C at more than one time point.

Table 1. Demographic and clinical data of paediatric patients undergoing ambulatory anaesthesia with ketamine sedation and receiving either 0.005 mg/kg glycopyrrolate intravenously or the same volume of saline preoperatively (control group).

Characteristic	Glycopyrrolate group <i>n</i> = 42	Control group <i>n</i> = 42	Statistical significance ^a
Sex, male/female	22/20	23/19	NS
Age, years	3.5 ± 1.6	3.7 ± 2.2	NS
Weight, kg	16.7 ± 3.8	17.7 ± 6.8	NS
Duration of surgery, min	6.7 ± 3.1	7.6 ± 4.0	NS
Ketamine dose, mg/kg	3.1 ± 0.6	2.9 ± 0.9	NS
Baseline temperature, °C	37.0 ± 0.3	37.0 ± 0.2	NS
Postoperative fever ^b	14	4	<i>P</i> = 0.02
Total intravenous fluid, ml	97.4 ± 44.1	76.1 ± 32.6	<i>P</i> = 0.03
Oral secretion volume, VAS	35.3 ± 14.3	44.8 ± 19.5	<i>P</i> = 0.02

Data presented as *n*, or mean ± SD.

NS, not statistically significant (*P* ≥ 0.05); VAS, visual analogue scale (mm).

^aIndependent *t*-test.

^bTemperature ≥ 37.8°C at more than one time point.

Statistical analyses

A preliminary study with ten paediatric patients indicated that around 30% of patients receiving anticholinergics developed postoperative fever, compared with 4.7% of the control group. The incidence of a type I error was 0.05 and a type II error was 0.2. Based on these parameters, 42 patients were required in each group (84 patients in total).

Data were presented as *n* or mean ± SD. Between group comparisons were made using independent *t*-test, with repeated measures analysis of variance used to evaluate between group differences in body temperature. All statistical analyses were performed using Medcalc[®] version 14.8.1 for Windows[®] (MedCalc Software, Ostend, Belgium). *P*-values < 0.05 were considered to be statistically significant.

Results

The study recruited a total of 84 patients, who were randomized between group G (*n* = 42; 22 males/20 females; mean age 3.5 ± 1.6 years; age range 1 – 7 years) and

group N (23 males/19 females; mean age 3.7 ± 2.2; age range 1 – 8 years). Demographic and clinical characteristics of the patients are shown in Table 1. There were no significant between group differences in age, gender, weight, duration of surgery, ketamine dose or preoperative body temperature. The incidence of postoperative fever and total volume of intravenous fluid administered were significantly higher, and the quantity of oral secretions was significantly lower in group G than group N (*P* = 0.02, *P* = 0.03 and *P* = 0.02, respectively; Table 1).

Data regarding mean postoperative body temperature are shown in Figure 2. Overall, mean body temperature was significantly higher in group G than group N (*P* = 0.001). In addition, mean body temperature was significantly higher in group G than group N at 30, 60 and 90 min after surgery (*P* < 0.05 for each comparison, Figure 2). In group G, mean body temperature was significantly higher than baseline at all postoperative time points (0, 30, 60 and 90 min; *P* < 0.05 for each comparison, Figure 2). In group N, mean body temperature was significantly higher than baseline at postoperative 0 and

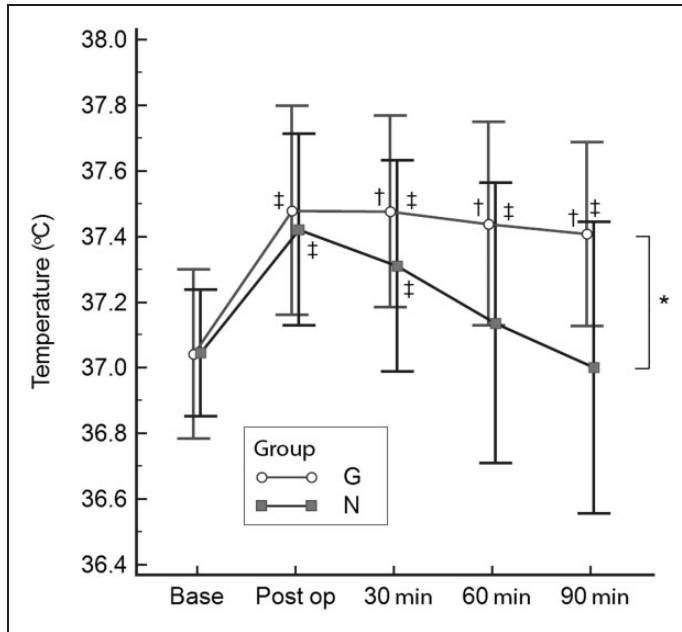


Figure 2. Body temperature in paediatric patients undergoing ambulatory anaesthesia with ketamine sedation and receiving either 0.005 mg/kg glycopyrrolate intravenously (group G, $n = 42$) or the same volume of saline preoperatively (group N, $n = 42$). Body temperature was measured tympanically before surgery (baseline), and at 0, 30, 60 and 90 minutes postsurgery. * $P = 0.001$ between glycopyrrolate and placebo group; † $P < 0.05$ vs control group at same time point; ‡ $P < 0.05$ vs baseline in same group; repeated measures analysis of variance.

30 min ($P < 0.05$ for each comparison, Figure 2), but not significantly different from baseline at 60 and 90 min.

Discussion

Premedication with an anticholinergic drug resulted in increased postoperative body temperature compared with placebo in the present study. This finding could be regarded as clinically negligible because the overall mean body temperature of both groups was $37^{\circ}\text{C} - 37.5^{\circ}\text{C}$, a small difference from the baseline body temperature (37.0°C), and requiring no treatment. Higher body temperatures persisted until 90 min after surgery in patients treated with anticholinergic drugs in the current study, whereas temperatures in the placebo group returned to baseline by 60 min

after surgery. Of clinical importance, however, was the significantly higher incidence of fever in patients treated with anticholinergic drugs than those in the placebo group.

The definition of fever used in the present study was a tympanic temperature of 37.8°C . Fever is generally defined as a rectal temperature of $>38^{\circ}\text{C}$, but the routine use of a rectal thermometer is challenging and tympanic thermometers are preferred. Temperatures measured using tympanic thermometers have been reported to be $0.1-0.2^{\circ}\text{C}$ lower than those measured using a rectal thermometer.^{15,16} We used a declining body temperature $<37.8^{\circ}\text{C}$ as one of our discharge criteria in order to ensure the safety of our patients.

As expected, the quantity of oral secretions was significantly lower in the anticholinergic-treated group than the placebo group,

although there were no secretion-associated complications observed in any patient. The increased amount of suction required to deal with the greater volume of oral secretions in the placebo group did not increase the duration of the procedure. The total volume of administered fluid was higher in the anticholinergic-treated group compared with the placebo group, due to the increase in infusion of fluids when fever was present.

The effectiveness of adjunctive anticholinergics prior to sedation is unclear, and routine administration of anticholinergics in procedures such as bronchoscopy has been viewed skeptically.^{17,18} Some recommend the avoidance of adjunctive anticholinergics in paediatric patients,¹⁹ because of their limited effect on suppressing salivation while increasing the risk of enhancing the adverse effects of ketamine.²⁰ Adjunctive anticholinergics are recommended for the suppression of hypersalivation and for their antiemetic effect in ketamine sedation.²¹ To our knowledge, the only report of the relationship between adjunctive anticholinergics and fever is a study applying atropine to eyes prior to ophthalmic examination.²² Our present findings suggest that routine premedication with adjunctive anticholinergics should not be recommended in paediatric patients receiving ketamine sedation, because the increase in body temperature outweighs any advantages gained from suppression of oral secretions during surgery.

There were several limitations to our study. Various surgical procedures were included and there was no evaluation of the surgical difficulties caused by oral secretions. More informative data could be collected if procedures that are sensitive to the amount of oral secretion are studied, and if any surgical difficulties are evaluated by the surgeon.

In conclusion, routine premedication with adjunctive anticholinergics should not be considered in paediatric patients receiving ketamine sedation due to the increased risk of fever. Use of anticholinergics should

be limited to procedures that require a high level of secretion suppression.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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