Effects of Chlorpheniramine on Emergence Agitation After General Anesthesia for Ureteroscopic Stone Surgery: a Retrospective Cohort Study

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Abstract

Background: The presence of a urinary catheter, postoperative pain, and postoperative nausea and vomiting are risk factors for emergence agitation (EA). Antimuscarinic agents have been the primary agents used for urinary catheter-related bladder discomfort prevention and treatment. Chlorpheniramine has antimuscarinic, antinociceptive, and antiemetic effects. This retrospective study investigated the effect of chlorpheniramine on EA prevention in patients following ureteroscopic stone surgery.

Methods: Of 110 adult patients who underwent ureteroscopic stone surgery under general anesthesia between January and December 2019, the medical records of 93 patients were analyzed retrospectively. The patients were divided into control (n = 52) and chlorpheniramine (n = 41) groups according to they receipt of intravenous chlorpheniramine before the induction of anesthesia. The incidence and severity of EA were compared between the groups as primary and secondary endpoints, respectively. The effects of chlorpheniramine on the requirement for inhalation anesthetic (desflurane) during surgery, changes in mean blood pressure and heart rate during emergence, and adverse events were also compared.

Results: The incidence (21.2% in the control group, 24.4% in the chlorpheniramine group) and severity of EA did not differ between groups. The intraoperative requirement for desflurane, changes in mean blood pressure and heart rate during emergence, and adverse events were also similar between groups.

Conclusion: Chlorpheniramine did not affect EA in patients after ureteroscopic stone surgery.

Trial registration: CRiS Registration number KCT0004879. Initial registration date was 3 April 2020 (Retrospectively registered).

Background

Emergence agitation (EA) is characterized by restless, excited, disoriented, and non-purposeful movement that can have clinical consequences, such as accidental removal of intravenous or drainage catheters, unintended extubation, bleeding at surgical sites, or injury of patients' selves or medical staff, resulting in increased patient care burden and medical care costs [1, 2]. The incidence of EA varies according to the type of surgery, but is known to be 9.8–13.6% in patients undergoing urological surgery [3, 4]. However, the incidence of EA increases to 63.5% in patients with urinary catheters [3]. The presence of a urinary catheter is an identified risk factor for EA [1–4]. Antimuscarinic agents, such as butylscopolamine, tolterodine, oxybutynin, glycopyrrolate, and solifenacin, have been used to prevent or treat catheter-related bladder discomfort (CRBD) [5].

Chlorpheniramine is an alkylamine first-generation potent H_1 antihistamine that is generally used to prevent and treat hypersensitivity and allergic disorders [6, 7]. It not only competitively inhibits central and peripheral H_1 receptors to provide sedative and local anesthetic effects, but also inhibits muscarinic receptors, resulting in antimuscarinic effects [6–8]. In addition, chlorpheniramine has an antiemetic effect and can be used to prevent and treat postoperative nausea and vomiting (PONV) [9]. The antiemetic, local

anesthetic and antimuscarinic effects of chlorpheniramine are expected to attenuate EA by reducing PONV, postoperative pain and CRBD. However, the use of anticholinergics is a risk factor for EA [10]; thus, the impact of chlorpheniramine on EA is difficult to predict. No study has evaluated the effect of chlorpheniramine on EA in patients undergoing urological surgery requiring urinary catheterization. Thus, we assessed the effect of a single bolus dose (8 mg) of chlorpheniramine administered before the induction of anesthesia on EA in patients undergoing ureteroscopic stone surgery.

Methods

This retrospective cohort study was approved by the Institutional Review Board of Konyang University Hospital, Daejeon, Korea (permit number KYUH 2020-01-005), and was registered with the Korea Clinical Research Information Service (http://cris.nih.go.kr; permit number, KCT 0004879). This study adhered to STROBE checklist. Written informed consent was not obtained from patients due to the retrospective nature of the study. The medical records of patients who underwent elective ureteroscopic stone surgery under general anesthesia in our hospital between January 2019 and December 2019 were reviewed retrospectively. Two anesthesiologists were in charge of anesthesia for the urological surgeries; they used the same anesthetic agents and patient monitoring and extubation criteria, according to our institutional protocols. However, only one anesthesiologist intravenously administered 8 mg chlorpheniramine (Peniramine inj®; Yuhan Co., Seoul, Korea) 5–10 min before the induction of anesthesia, in the absence of contraindication, to provide a sedative effect before anesthesia induction, to reduce PONV, and to help prevent perioperative hypersensitivity reactions [11, 12]. According to this procedural difference, the patients were divided into chlorpheniramine and control groups. The inclusion criteria for this study were age 19–65 years and American Society of Anesthesiologists physical status classification I–III. All patients underwent elective ureteroscopic stone surgery under general anesthesia. The exclusion criteria were: the presence of a urinary catheter before anesthesia induction, induction of general anesthesia using a supraglottic airway device, cognitive or neuropsychological disorder, combined operation, contraindication to chlorpheniramine (e.g., prostatic hyperplasia, irritable bladder symptoms, bladder outlet obstruction, or glaucoma), and concomitant administration of steroids (e.g., dexamethasone or hydrocortisone) to prevent or treat an allergic reaction or anaphylaxis.

All patients were fasted for at least 8 hours and arrived in the operating room without premedication. Patients in the chlorpheniramine group received 8 mg chlorpheniramine intravenously, whereas patients in the control group did not. All subsequent anesthesia care and surgical procedures were the same in the two groups. Routine monitoring included electrocardiography, noninvasive blood pressure measurement, pulse oximetry, end-tidal carbon dioxide ($EtCO_2$) measurement, Patient State Index (Psi; SedLine®; Masimo Corp., Irvine, CA, USA) determination, and neuromuscular train-of-four (TOF) stimulation by acceleromyography (TOF-Watch SX®; Organon Ltd., Dublin, Ireland) on the adductor pollicis muscle. Anesthesia was induced with intravenous propofol (1.5–2 mg/kg) and fentanyl (1–2 μg/kg). Then, endotracheal intubation was facilitated with rocuronium (0.6 mg/kg). Volume-controlled mechanical ventilation was initiated at a tidal volume of 8 mL/kg and a respiratory rate of 12 breaths/min. During the

maintenance of anesthesia, the $EtCO_2$ was maintained at 30–40 mmHg by adjusting the respiratory rate. Anesthesia was maintained with an oxygen/nitrous oxide mixture (50:50) and 3–8 vol% of the end-tidal concentration of desflurane to maintain the PSi at 25–50. All operations were performed in a lithotomy position. After surgery, each patient was catheterized with a Foley catheter, and the balloon was inflated with 5 mL normal saline by the urologist. After urinary catheterization, the patient was moved to the supine position. Desflurane and nitrous oxide were stopped, and manual ventilation was performed with 100% oxygen at 6 L/min. The neuromuscular block was reversed with 50 μg/kg neostigmine and 10 μg/kg glycopyrrolate. The extubation criteria were: PSi > 75, tidal volume ≥ 5 mL/kg, spontaneous respiratory breathing rate 10–25/min, TOF ratio ≥ 0.9, and response to verbal commands. All patients were transferred to the post-anesthesia care unit (PACU) 5 min after extubation.

Measurements

Emergence was defined as the time interval between the discontinuation of all anesthetics (desflurane and nitrous oxide) and 5 min after extubation. The attending anesthetist (nurse), who has assessed agitation during emergence in all patients in our hospital since 2017, recorded the results on the patients' electronic medical charts [13]. EA was assessed using the Ricker Sedation-Agitation Scale (RSAS, 7 points; 1 = unarousable, 2 = very sedated, 3 = sedated, 4 = calm and cooperative, 5 = agitated but responding calmly to verbal instructions, 6 = very agitated requiring restraint, 7 = pulling at the tracheal tube, trying to remove catheter or striking the staff) [14], and the highest RSAS score during emergence was recorded. RSAS scores > 5 were considered to reflect EA. The incidence of EA was analyzed as the primary endpoint, and the severity of EA was analyzed as the secondary endpoint. The time to extubation during emergence was also analyzed.

Data on hemodynamic parameters (mean blood pressure and heart rate) before the induction of anesthesia, at the end of surgery, at extubation, and 5 min after extubation were collected and analyzed. In addition, the highest and lowest concentrations of desflurane administered during the maintenance of anesthesia were determined and compared to exclude the effect of a difference in the concentration of inhalation anesthetic on EA.

Among the PACU data, the severity of postoperative pain (evaluated using an 11-point numerical rating scale [NRS; 0 = no pain, 10 = worst pain imaginable]), requirements for analgesics and antiemetics, and all adverse events were analyzed.

Statistical analyses

The primary endpoint of this study was the incidence of EA. In a previous study [3], the incidence of EA was 63.5% in patients who received urinary catheters. Assuming that a 50% reduction in the incidence of EA after administration of chlorpheniramine would be clinically relevant, a sample of 38 patients per group was required, with a power of 0.8 and a two-sided α value of 0.05.

The statistical analysis was performed using SPSS software (ver. 18.0 for Windows; SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using Student's *t*-test or the Mann–Whitney *U*-test, depending on the Kolmogorov–Smirnov normality test result. Categorical variables were analyzed with the χ^2 test, the χ^2 test for trends (linear-by-linear association), or Fisher's exact test, as appropriate. Changes in mean blood pressure and heart rate were analyzed using repeated-measures analysis of variance, followed by the *t*-test with Bonferroni correction. *P* values < 0.05 were considered to be significant.

Results

A total of 110 patients among those who received elective ureteroscopic stone surgery under general anesthesia in our hospital between January and December 2019 satisfied the inclusion criteria. Of these, 17 patients were excluded; thus, 93 patients were included in the final analysis (control group, *n* = 52; chlorpheniramine group, *n* = 41; Fig. 1).

The patient characteristics and operative data were comparable between the groups (Table 1).

Table 1
Patient characteristics and operative data

	Control (n = 52)	Chlorpheniramine (n = 41)	P value
Age (years)	49.7 ± 10.3	48.0 ± 12.0	0.485
Sex (male/female)	34/18	23/18	0.361
Height (cm)	162.3 ± 9.4	165.1 ± 8.7	0.147
Weight (kg)	70.6 ± 15.1	70.8 ± 14.9	0.961
Body mass index (kg/m^2)	26.7 ± 4.5	25.8 ± 4.4	0.378
ASA classification			
I/II/III	11/36/5	9/31/1	0.454
Position of stone			
Kidney/ureter/both	17/25/10	13/15/3	0.427
Duration of surgery (min)	69.7 ± 50.9	53.2 ± 32.2	0.059
Duration of anesthesia (min)	97.5 ± 52.0	81.1 ± 32.6	0.093
Fluids (ml)	200 [150–300]	200 [150–300]	0.715
Urinary catheter size (Fr)			
14/16/18	10/40/2	11/30/0	0.229

Values are means ± standard deviations, numbers, or medians [interquartile ranges]. ASA: American Society of Anesthesiologists.

The intraoperative and recovery data are presented in Table 2. The incidence of EA was similar in the two groups (21.2% [11/52] in the control group and 24.4% [10/41] in the chlorpheniramine group; odds ratio, 0.832; 95% confidence interval, 0.3–2.2; P = 0.711). EA severity did not differ between groups (P = 0.688). Changes in mean blood pressure and heart rate during emergence were comparable between the two groups (Fig. 2). In addition, the highest and lowest intraoperative concentrations of desflurane, times to extubation, NRS scores for postoperative pain, and numbers of patients requiring analgesics or antiemetics in the PACU were similar in the two groups (Table 2).

Table 2
Intraoperative and recovery data

	Control (n = 52)	Chlorpheniramine (n = 41)	P value
In operating room			
Desflurane concentration, vol%			
Highest concentration	5.75 [5.0–6.0]	5.0 [5.0–6.0]	0.361
Lowest concentration	6.0 [5.0–6.0]	6.0 [5.0–6.0]	0.149
Time to extubation (min)	8.0 [6.3–9.0]	7.3 [5.5–8.6]	0.210
Emergence agitation, *n* (%)	11 (21.2%)	10 (24.4%)	0.711
RSAS (3/4/5/6/7), *n*	2/39/8/2/1	4/27/5/3/2	0.688
In PACU			
NRS for pain	2.0 [1.0–3.0]	1.0 [0–2.5]	0.055
Analgesics, *n* (%)	3 (5.8%)	1 (2.4%)	0.628
Antiemetics, *n* (%)	2 (3.8%)	0 (0%)	0.502

Values are medians [interquartile ranges], numbers, or numbers (%). RSAS: Ricker Sedation-Agitation Scale; NRS: numerical rating scale (0 = no pain, 10 = worst imaginable pain).

All adverse events are presented in Table 3; no difference was detected between groups.

Table 3
Adverse events

	Control (n = 52)	Chlorpheniramine (n = 41)	P value
Sore throat	8 (15.4%)	11 (26.8%)	0.174
Hoarseness	1 (1.9%)	0 (0%)	> 0.999
Dry mouth	2 (3.8%)	1 (2.4%)	> 0.999
Nausea	3 (5.8%)	0 (0%)	0.252
Vomiting	2 (3.8%)	0 (0%)	0.502
Headache	0 (0%)	2 (4.9%)	0.192
Dizziness	0 (0%)	1 (2.4%)	0.441
Dyspnea	1 (1.9%)	0 (0%)	> 0.999
Diarrhea	1 (1.9%)	0 (0%)	> 0.999
Values are numbers (%).			

Discussion

In this retrospective cohort study, a single dose of chlorpheniramine administered before the induction of anesthesia did not attenuate EA in adult patients undergoing ureteroscopic stone surgery with desflurane anesthesia. In addition, 8 mg chlorpheniramine administered before the induction of anesthesia did not affect the requirement for desflurane during surgery or the changes in mean blood pressure and heart rate during emergence.

The etiology of EA is not known. EA has been reported more often in the context of the use of newer, short-acting halogenated compounds, such as desflurane and sevoflurane, than with the use of other inhaled anesthetics [15]. Proposed hypotheses for EA seen with desflurane use include rapid emergence with insufficient time to adjust to the strange environment, late recovery of cognitive function compared with other brain functions resulting in altered cognitive perception, increased pain sensation, and activation of the sympathetic nervous system [16].

Although the etiology of EA remains unknown, extended duration of surgery, CRBD, PONV, anticholinergics, type of surgery (e.g., otolaryngological and oral cavity surgeries), pain, and the presence of invasive devices (e.g., urinary catheter, tracheal tube, or chest tube) contributed to EA in adult patients undergoing general anesthesia [2]. Drugs that prevent EA include propofol, N-methyl-D-aspartate receptor antagonists (e.g., magnesium sulfate, ketamine, and tramadol), α2-adrenoreceptor agonists (clonidine and dexmedetomidine), and μ-opioid agonists (e.g., fentanyl and remifentanil); these drugs have sedative and/or analgesic effects in common [13].

Antihistamines are among the drugs used most commonly during the perioperative period [17], and some researchers have recommended routine prophylaxis with an antihistamine to prevent life-threatening histamine-related consequences after the induction of anesthesia [18]. Depending on their impacts on the central nervous system (CNS), H_1 antihistamines are classified into first-generation sedating antihistamines and second-generation antihistamines that provide less or no sedation [6]. First-generation antihistamines act on central and peripheral H_1 receptors, and second-generation antihistamines have high affinity and selectivity for peripheral H_1 receptors [6]. Thus, second-generation antihistamines are less anticholinergic, with fewer adverse CNS effects, than are first-generation antihistamines, but no injectable formulation is available due to their low aqueous solubility [7]. Chlorpheniramine can be administered intravenously and can be used in patients who are scheduled to receive general anesthesia that requires fasting.

Chlorpheniramine is a first-generation H_1 receptor antagonist (H_1 antihistamine) and one of the most potent antiallergic agents in the alkylamine group; thus, it is commonly used to prevent or treat hypersensitivity and allergic reactions [8]. In addition, chlorpheniramine has sedating, antinociceptive, antiemetic, anti-inflammatory, and antimuscarinic effects [9, 19]. These effects are expected to have a positive influence on EA, but chlorpheniramine did not reduce EA in this study. Possible explanations are as follows. First, although chlorpheniramine provides a sedative effect by penetrating the blood–brain barrier and acting on central H_1 receptors, it can impair cognitive and psychomotor performance, cause problems with coordination, and, paradoxically, cause excitability and restlessness, even at therapeutic doses [6]. These effects contribute to EA by further delaying the recovery of cognitive function after desflurane anesthesia. Second, previous studies have shown that anti-inflammatory and antimuscarinic agents (e.g., paracetamol, oxybutynin, tolterodine, glycopyrrolate, and butylscopolamine) reduce CRBD [20, 21], but the effects of chlorpheniramine on CRBD have not been verified. The antimuscarinic effects of chlorpheniramine are weak [7]; thus, this drug may not reduce CRBD. In addition, chlorpheniramine acts on serotoninergic and cholinergic receptors, which can cause adverse effects, such as dizziness, tinnitus, anxiety, blurred vision, problems with concentration, dry mouth, and difficulty urinating [22]. These adverse effects would act negatively on EA. Third, in this study, postoperative NRS scores for pain were low (medians = 1 and 2) in both groups, and only a few patients in the control group complained of PONV. These findings suggest that postoperative pain and PONV are not important risk factors for EA in patients undergoing ureteroscopic stone surgery. Consequently, the antinociceptive and antiemetic effects of chlorpheniramine do not appear to contribute to the attenuation of EA.

The incidence of EA in this study was lower than the 63.5% reported in patients with urinary catheters [3]. This difference may reflect the evaluation of EA only in patients undergoing ureteroscopic stone surgery, which causes less postoperative pain, in this study, whereas previous studies included patients undergoing various types of surgery known to be associated with high risks of EA, such as oral cavity, otolaryngological, and orthopedic and abdominal surgeries [2, 3]. In contrast, the incidence of EA in our study was more than double that of 9.8% reported in patients undergoing urological surgery [4]. However, not all patients in that study had urinary catheters, and some patients had surgery under general

anesthesia comprising total intravenous anesthesia (TIVA) and/or induced with a supraglottic airway device [4]; TIVA is a protective factor against EA [23], and the use of a supraglottic airway device may have induced less EA than would the use of an endotracheal tube [24].

In a previous study, intravenous chlorpheniramine (8 mg) caused no significant hemodynamic change during anesthesia [17]. However, EA itself can cause hemodynamic changes (e.g., hypertension and tachycardia) by increasing the sympathetic tone during emergence [13]. In this study, the mean blood pressure and heart rate during emergence did not differ between groups, supporting the lack of a significant difference in EA between groups.

The effect of the difference in anesthesia depth according to differences in inhalation anesthetic concentrations on EA is controversial [25, 26]. In a randomized controlled trial, the difference in depth of sevoflurane anesthesia did not affect EA in pediatric patients [25], but the effect of desflurane dose on EA in adult patients was unclear. In this study, desflurane concentrations were adjusted under PSi monitoring in both groups, and the highest and lowest desflurane doses during anesthesia were comparable between groups. Thus, the effect of the difference in anesthesia depth on EA could be excluded.

This study has some limitations. First, all patients received 1–2 μg/kg fentanyl during the induction of anesthesia. In a meta-analysis of data from 3,172 children, fentanyl showed a prophylactic effect against desflurane-related EA [27]. Thus, fentanyl may have contributed to the reduction of EA in both groups in this study. Second, in this retrospective study, chlorpheniramine was not administered for preventing EA. The effect of the drugs on EA may vary depending on the dose and timing of administration [2]. Therefore, prospective studies are needed in which the dose and timing of chlorpheniramine were set to prevent EA.

Conclusion

The administration of a single dose (8 mg) of chlorpheniramine before the induction of anesthesia did not reduce the incidence and severity of EA in patients after ureteroscopic stone surgery.

Abbreviations

ASA: American Society of Anesthesiologists; CNS: central nervous system; CRBD: catheter-related bladder discomfort; EA: emergence agitation; PACU: post-anesthesia care unit; PONV: postoperative nausea and vomiting; PSi: Patient State index; RSAS: Ricker Sedation-Agitation Scale; TOF: train-of-four

Declarations

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Not applicable.

Authors' contributions

Conceptualization: MC, TYS

Data curation: CKC, MC, TYS

Formal analysis: MC, TYS

Investigation: SJL, TYS, YSJ

Writing-original draft: CKC, SJL, TYS, YSJ

Writing-review and editing: CKC, TYS

All authors have read and approved the manuscript

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This retrospective cohort study was approved by the Institutional Review Board of Konyang University Hospital, Daejeon, Korea (permit number KYUH 2020-01-005). Written informed consent was not obtained from patients due to the retrospective nature of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

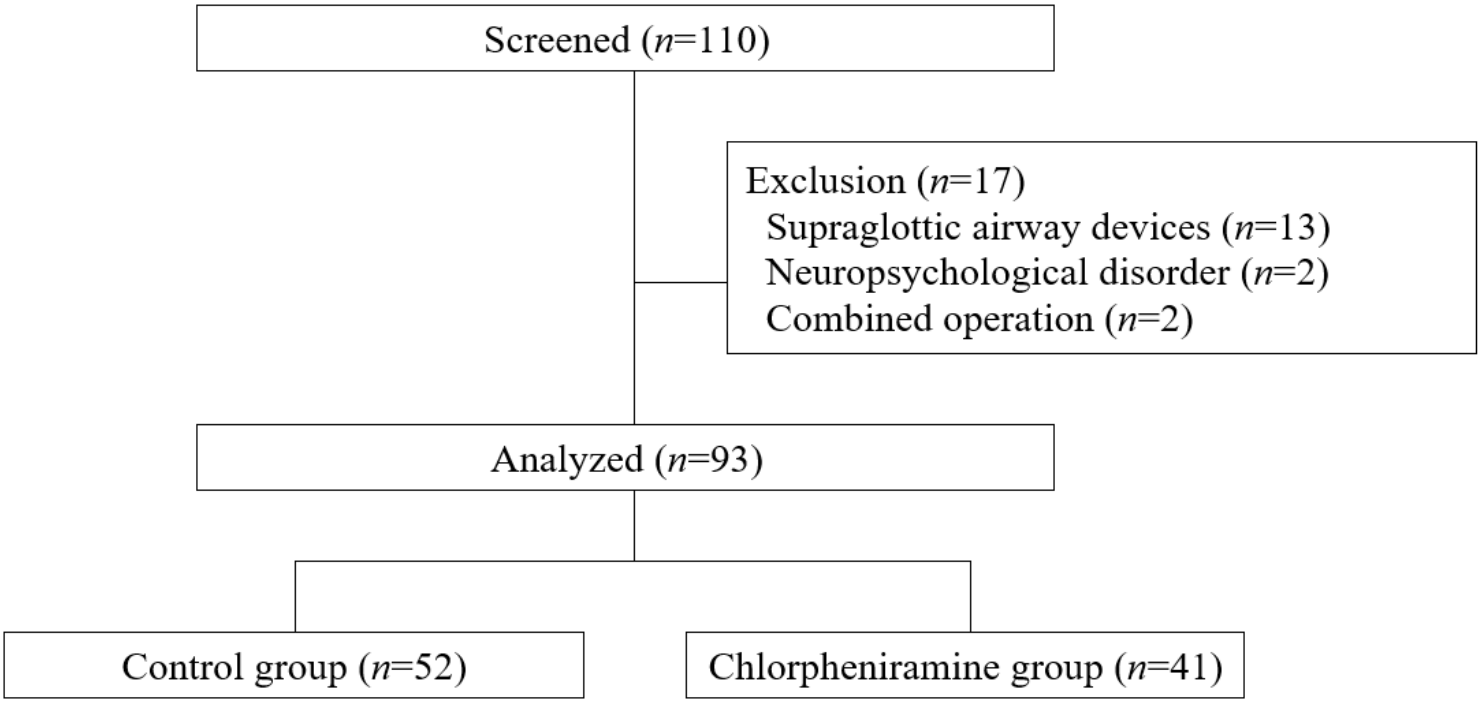

Figure 1

Flow diagram.

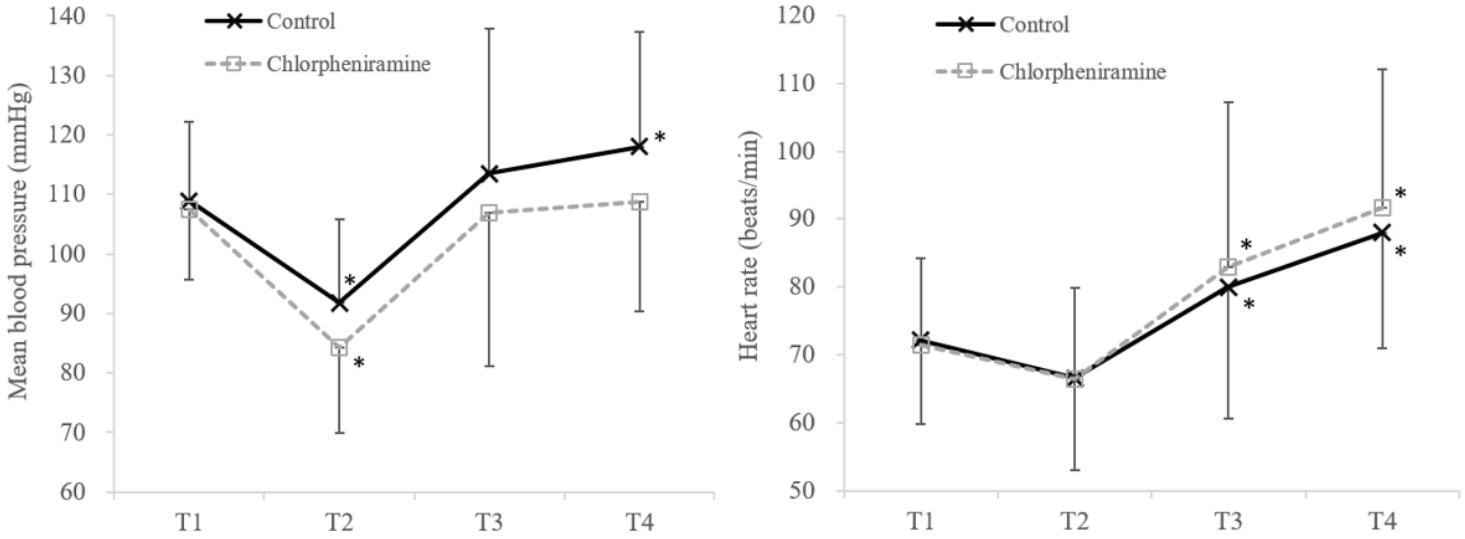

Figure 2

Changes in mean blood pressure and heart rate. Data are means ± standard deviations. *P < 0.05 vs. baseline in each group (Bonferroni corrected). T1 = before induction of anesthesia, T2 = at the end of surgery, T3 = at extubation, T4 = 5 min after extubation.