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Effect of pretreatment with low-dose Esketamine on the Propofol requirements and the onset time of cisatracurium during the induction of general anesthesia: a prospective, randomized, double-blinded trial

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Abstract

Background Esketamine has been increasingly used as an adjuvant for propofol-based induction. However, the effective esketamine dose for this indication remains unclear. The authors investigated the effect of different intravenous bolus low doses of esketamine pretreatment on the propofol requirements and the onset time of cisatracurium during anesthesia induction.

Methods 140 patients undergoing elective surgery under general anesthesia were randomly allocated into four groups: pretreatment with saline (Group C), pretreatment with 0.1 mg/kg esketamine (Group K0.1), pretreatment with 0.3 mg/kg esketamine (Group K0.3), and pretreatment with 0.5 mg/kg esketamine (Group K0.5). The propofol dosage was recorded when the eyelash reflex disappeared and the Index of Consciousness (IoC) value reached 60 during the infusion. The onset time for cisatracurium was recorded.

Results The total dose of propofol at the point of eyelash reflex loss was significantly lower in group K0.5 than in groups K0.3 ($P=0.019$), K0.1 ($P<0.001$) and C ($P<0.001$). The dose of propofol at the point of the loss of eyelash reflex was lower in group K0.3 than in groups K0.1 ($P=0.006$) and C ($P<0.001$). The total dose of propofol at an IoC value

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of 60 was significantly higher in group K0.5 than in groups K0.1 ($P < 0.001$) and C ($P < 0.001$). The dose of propofol at an loC value of 60 was higher in group K0.3 than in groups K0.1 ($P = 0.009$) and C ($P < 0.001$). The onset time of cisatracurium during induction was not significantly different among the groups.

Conclusion Esketamine decreases the dose of propofol in a dose-dependent manner at the point of the loss of eyelash reflex, while 0.5 mg/kg esketamine and 0.3 mg/kg esketamine pretreatment before induction significantly increase the dose of propofol at the targeted loC value of 60. Esketamine does not affect the onset time of cisatracurium when it is combined with propofol during loC-guided induction of anesthesia.

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Keywords Esketamine, Anesthesia induction, Propofol, Onset time

Introduction

During general anesthesia, stable induction can prevent a variety of anesthesia-related complications, such as cardiovascular and cerebrovascular events caused by hemodynamic fluctuations. The overall success of rapid sequence induction is mainly dependent on the appropriate selection of induction agents to provide optimal intubation conditions and a stable cardiovascular state during anesthesia induction [1–3]. Propofol is a common anesthetic agent for the anesthesia induction, and it often causes peri-intubation hypotension by rapid infusion [4–6]. Ketamine is the only anesthetic agent with analgesic, hypnotic, and amnesic effects [7], and it can counteract the hemodynamic depression of propofol through its sympathomimetic qualities in general induction [8, 9]. Many studies have demonstrated that ketamine can be a useful adjunct as a supplementary induction agent for potential hemodynamic preservation [10–13]. However, the use of ketamine is limited by its side effects, such as psychomimetic effects, vomiting and agitation during awakening [14–16].

Esketamine is the dextral enantiomer of ketamine, and it is pharmacologically and clinically different from ketamine. Its anesthetic effect is twice as potent as that of a racemic mixture, and its potency is approximately three times higher than that of (R)-ketamine [17]. In addition, compared with traditional ketamine, esketamine enables the use of significantly smaller doses (approximately 1/2 the dosage of ketamine) [18], and it is characterized by a shorter recovery period, less postoperative pain and potentially weaker side effects [19, 20]. Currently, some studies suggest that intraoperative administration of low-dose esketamine can reduce the incidence of adverse events such as induction hypotension and opioid-induced cough through sympathetic stimulation, analgesia and antagonism of the N-methyl-D-aspartic acid (NMDA) receptor [8, 21]. Ketamine, as an induction agent, has been reported to affect intubating conditions and the onset of neuromuscular blockade [22, 23]. However, although esketamine has been increasingly used as an adjuvant for propofol-based induction, few studies have focused on the effect of esketamine on the onset time of neuromuscular blocking agents or intubating conditions. To date, the effective and appropriate dose of esketamine as a supplementary induction agent during general anesthesia remains unclear because the treatment regimens and dosage vary so greatly between trials; thus, it is difficult to draw conclusions by comparing different reports. Additionally, few multiple-dose studies have been performed.

In this study, we investigated the hypothesis that different intravenous boluses of low doses of esketamine administered prior to the induction of anesthesia would affect the propofol requirements for induction as well as the onset time of cisatracurium in patients undergoing general anesthesia.

Patients and methods

This prospective, randomized, double-blind clinical trial was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (Number. B2021-031-01). The trial was registered with the Chinese Clinical Trials Registry (ChiCTR2000041041, Principal Investigator: L.H.C., registration date: December 16, 2020) before patient enrollment. This clinical trial began in May 2021 and ended in December 2021. All patients gave written informed consent before inclusion. Written informed consent was obtained from all subjects, a legal surrogate, the parents or legal guardians for minor subjects, or the requirement for written informed consent was waived by the IRB. The procedures were conducted in accordance with the Helsinki Declaration-2013 in the text.

The inclusion criteria were patients 18 to 75 years of age, classified as American Society of Anesthesiologists (ASA) status I or II, of any sex, and scheduled for elective surgery under general anesthesia. The exclusion criteria were as follows: (1) a history of anesthetic allergy; (2) renal or hepatic insufficiency; (3) neurological disease; (4) pregnancy; (5) difficult airway; (6) esketamine contraindications; (7) opioid drug or alcohol abuse; and (8) medications that interact with neuromuscular blocking agents.

Randomization and preoperative management.

Once eligibility was confirmed, patients were randomly assigned to one of four groups at a 1:1:1:1 ratio using sealed envelopes based on a computer-generated random sequence. Twenty minutes before anesthesia, an anesthesiologist opened the envelope and prepared a syringe of esketamine or saline, all of which were diluted with 20 ml of 0.9% saline (Group C: pretreatment with saline, Group K0.1: pretreatment with 0.1 mg/kg esketamine, Group K0.3: pretreatment with 0.3 mg/kg esketamine, Group K0.5: pretreatment with 0.5 mg/kg esketamine). Anesthesiologists were not involved in data collection and analysis. Other researchers involved in patient assessments or data collection were unaware of group allocation.

Study procedures

Patients fasted for at least 8 h. No premedication was given. Electrocardiogram (ECG), heart rate (HR), noninvasive blood pressure, body temperature, and oxygen saturation were monitored continuously during anesthesia. An IoC-view monitor (Morpheus Medical, Barcelona, Spain) was installed before induction to assess the depth of anesthesia through the index of consciousness (IoC). Neuromuscular monitoring was provided by JS-100 (SLGO, Beijing, China) applied to the adductor pollicis muscle. To assess the degree of neuromuscular blockade, electrodes were placed on the ulnar nerve of the forearm, and all fingers except the thumb were immobilized to assess the contracture of the adductor pollicis muscle of the thumb after administration.

Pretreatment was performed 2 min after preoxygenation. Normal saline (20 mL) or esketamine (in 20 mL saline) was administered in 10 s. Anesthesia induction was performed 1 min after preconditioning. Patients were given fentanyl 3 μg/kg intravenously. Propofol was infused at a rate of 30 mg/kg·h. The patient's left eyelash was stimulated with a cotton swab to determine the disappearance of the eyelash reflex. When the IoC was down to 60, propofol infusion was stopped. Neuromuscular monitoring was calibrated, and cisatracurium 0.2 mg/kg was injected. The injection was finished within 10 s. Then, train-of-four (TOF) stimulation was applied every 10 s until T1 < 5%. Endotracheal intubation was then performed. Each intubation took less than 20 s. Cases in which intubation was not completed at the first attempt were considered failed and excluded from the study. During the operation, sevoflurane, remifentanil, and cisatracurium were used to maintain an anesthesia depth of IoC40-50. Under volume-controlled ventilation, ventilation parameters were Fraction of inspiration O2 (FiO2) 0.6 and tidal volume 8 ml/kg. The respiratory rate was adjusted to maintain normocapnia (end-tidal carbon dioxide 35–45 mmHg). Hypotension (mean blood pressure < 30% from baseline for 60 s) was treated with ephedrine 5 mg iv, or bradycardia (HR < 45 beat/min for 60 s if hypotension occurred) was treated with atropine 0.1 mg iv. Postoperative patients were transported to the postanesthesia care unit (PACU) for recovery.

Outcome measurements

The propofol dosage was recorded when the eyelash reflex disappeared and IoC60. The 'onset time' for cisatracurium, defined as the time from the end of the injection of cisatracurium to T1 < 5%, was recorded by stopwatch. IoC was recorded when the eyelash reflex disappeared. The lowest IoC value was also recorded from propofol infusion to intubation. Body temperature at intubation was recorded. To evaluate changes in hemodynamic variables, mean blood pressure (MBP) and heart rate values were measured from baseline (baseline) to before endotracheal intubation (Inb), immediately after endotracheal intubation (Int), and 1 and 5 min after endotracheal intubation (T1 and T5) (Fig. 1). The definition of ΔP was the change in MBP from one time point to baseline [$\Delta P=(P-P_{Baseline})/ P_{Baseline}$]. The definition of ΔHR was the change in heart rate from one time point to baseline [$\Delta HR=(HR-HR_{Baseline})/ HR_{Baseline}$]. A researcher who was blinded to group allocation was responsible for recording the data.

Anesthesia-related complications, including delirium, postoperative nausea and vomiting (PONV), dizziness,

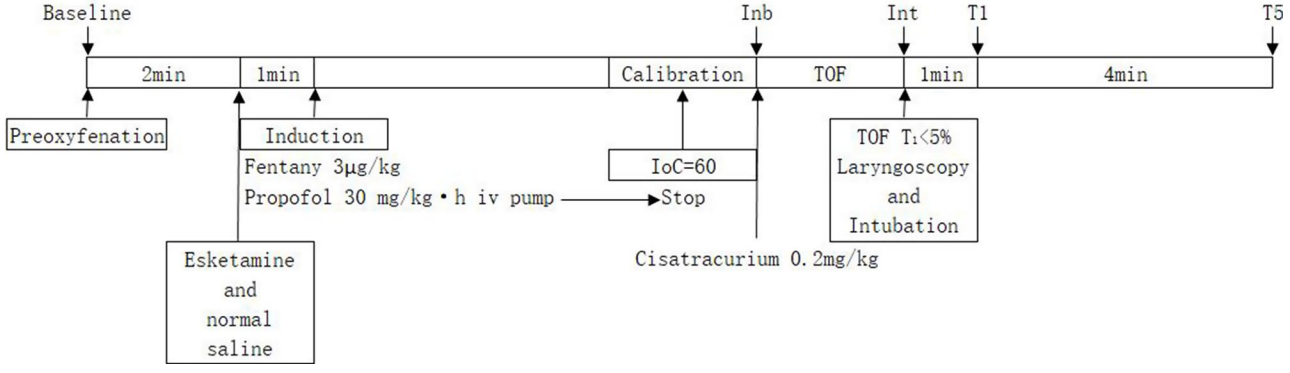

Fig. 1 Schematic diagram of the study protocol

drowsiness and respiratory depression, were recorded up to 48 h postoperatively. The Confusion Assessment Method (CAM) was used to assess delirium. The CAM diagnostic algorithm included four parts: (1). acute onset and fluctuating course; (2). inattention; (3). disorganized thinking; (4). altered level of consciousness. The diagnosis of delirium by CAM requires the presence of features 1 and 2 and either 3 or 4 [24]. Postoperative drowsiness was scored as follows: 0 = fully awake, 1 = sedated but responding to commands, and 2 = hardly responding to commands. A score of 2 was regarded as drowsiness [25]. Respiratory depression was defined as respiratory rate ≤ 5 breaths/min (bpm) for ≥ 3 min, oxygen saturation (SpO2) ≤ 85% for ≥ 3 min, end-tidal carbon dioxide (EtCO2) ≤ 15 or ≥ 60 mm Hg for ≥ 3 min, apnea episode lasting > 30 s, or any respiratory opioid-related adverse event [26].

The primary outcomes include three distinct points: the total dose of propofol at the point of the loss of eyelash reflex, the total dose of propofol at the point of the loss of eyelash reflex, and the onset time of cisatracurium during induction.

The secondary outcomes were the IoC value at the point of eyelash reflex disappearance, the lowest IoC value during induction, hemodynamics during induction and postoperative complications.

Statistical analysis

Data were analyzed using the statistical package SPSS version 25.0 for Windows (SPSS, Inc., Chicago, IL). The normality of the data was assessed with the Shapiro–Wilk test. Homogeneity of variances of the data was tested with Levene's test. Quantitative variables are presented as the mean ± SD or median (IQR). Categorical variables are expressed as numbers (proportions). One-way analysis of variance (ANOVA) for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables were used to compare patient characteristics, surgical characteristics, and anesthesia characteristics among groups. One-way ANOVA with Bonferroni post hoc comparison was used to analyze the onset time of cisatracurium and the lowest IoC after induction. Welch's test was used to analyze the dose of propofol and the IoC at the point of the loss of eyelash reflex with Games-Howell's post hoc comparison. Hemodynamic data were analyzed at each time point with the Kruskal–Wallis test. Pearson's chi-square test or Fisher's exact test was used to compare the rates of postoperative side effects among the groups. All P values < 0.05 were considered statistically significant.

In our pilot trial, the mean ± SD onset time was 185.7 ± 14.7 s in the saline-treated patients, 186.3 ± 13.3 s in Group K0.1, 190.0 ± 14.2 s in Group K0.3 and 198.4 ± 12.7 s in Group K0.5. A sample size of 31 subjects per group was required to detect a significant difference with 90% power (α = 0.05). Assuming a 10% dropout rate, our study aimed to include 35 subjects per group.

Results

The study enrolled 156 patients. After excluding 16 patients who did not meet the inclusion criteria, 140 patients were included in the final analysis (Fig. 2). Thirty-five people were randomly assigned to each group. There were no clinically significant differences in patient characteristics, including age, sex, body mass index (BMI), ASA physical status, body temperature and type of surgery, among the groups (Table 1).

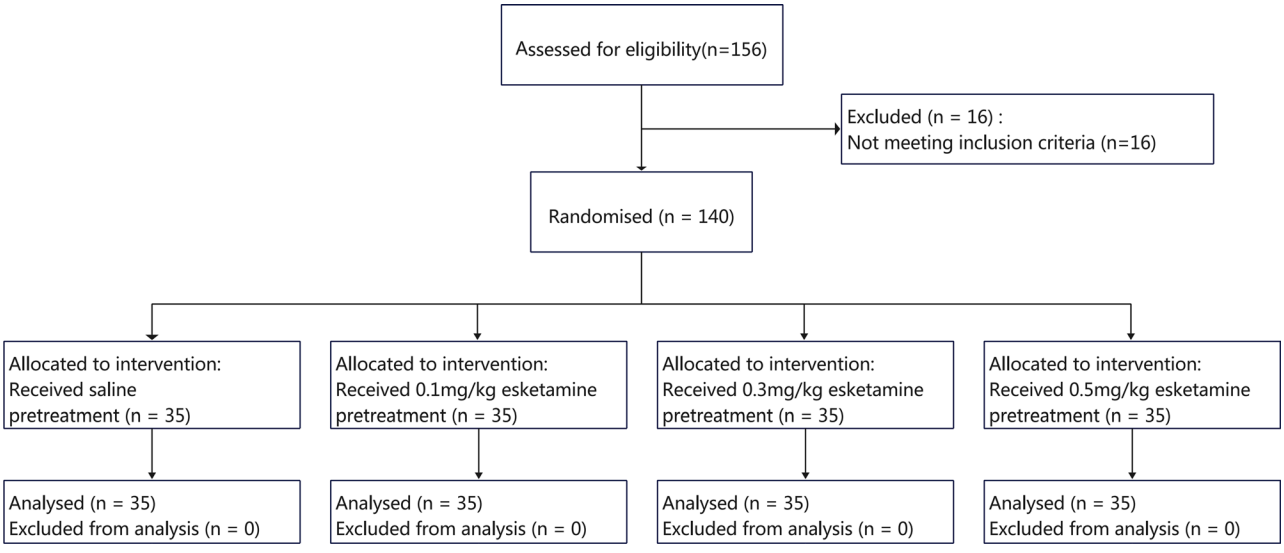

Fig. 2 CONSORT diagram of patient recruitment

Table 1 Characteristics of patients and surgery

	Group C ($n=35$)	Group $K_{0.1}$ ($n=35$)	Group $K_{0.3}$ ($n=35$)	Group $K_{0.5}$ ($n=35$)
Age (yr)	48.2 ± 13.6	49.8 ± 13.7	49.9 ± 12.8	52.0 ± 12.6
Gender (male/female)	18/17	8/27	12/23	10/25
BMI(kg m^{-2})	23.6 ± 3.5	22.1 ± 4.2	21.9 ± 2.8	22.1 ± 3.0
ASA (1/2)	7/28	6/29	3/32	5/30
Body temperature(℃)	36.4(36.2 to 36.5)	36.4(36.2 to 36.5)	36.4(36.2 to 36.5)	36.4(36.2 to 36.5)
Type of surgery				
Head and neck	8	15	13	10
Intra-abdominal	19	17	15	23
Orthopedic	1	0	3	0
Thoracic	1	1	0	0
Other	6	2	4	2

Values are expressed as the mean ± standard deviation, median (interquartile range) or number of patients

Abbreviations: Group C (control): injected with normal saline. Group $K_{0.1}$: injected with 0.1 mg/kg esketamine. Group $K_{0.3}$: injected with 0.3 mg/kg esketamine. Group $K_{0.5}$: injected with 0.5 mg/kg esketamine

Primary outcome

The total dose of propofol at the point of the loss of eyelash reflex was significantly decreased in group K0.5 (0.83 ± 0.13 mg/kg) compared to that in group K0.3 (0.92 ± 0.14 mg/kg, $P=0.019$), group K0.1 (1.05 ± 0.16 mg/kg, $P<0.001$) and group C (1.10 ± 0.19 mg/kg, $P<0.001$) (Fig. 3A). The dose of propofol at the point of the loss of eyelash reflex in group K0.3 was also less than that in group K0.1 ($P=0.006$) and group C ($P<0.001$) (Fig. 3A). However, there was no significant difference between group K0.1 and group C ($P=0.573$).

The total dose of propofol at the targeted IoC value of 60 was significantly increased in group K0.5 (2.22 ± 0.50 mg/kg) compared to that in group K0.1 (1.73 ± 0.41 mg/kg, $P<0.001$) and group C (1.42 ± 0.36 mg/kg, $P<0.001$) (Fig. 3A). The dose of propofol at the targeted IoC value of 60 in group K0.3 was also higher than that in group K0.1 ($P=0.009$) and group C ($P<0.001$) (Fig. 3A); however, there was no significant difference between group K0.5 and group K0.3 ($P=0.919$). The dose of propofol at the targeted IoC value of 60 in group K0.1 was also higher than that in group C ($P=0.006$) (Fig. 3A).

The onset time of cisatracurium during induction was not significantly different among the groups, with times of 181 ± 34 s, 187 ± 31 s, 188 ± 32 s and 200 ± 27 s in the groupsthe K0.1, K0.3 and K0.5, respectively ($P=0.068$) (Fig. 3B).

Secondary outcomes

The IoC value at the point of the loss of eyelash reflex was significantly higher in group K0.5 (81.6 ± 5.0) than in group K0.3 (75.1 ± 4.0 $P<0.001$), group K0.1 (69.3 ± 2.8, $P<0.001$) and group C (69.7 ± 4.1, $P<0.001$). The IoC value at the point of the loss of eyelash reflex in group K0.3 was also higher than that in group K0.1 ($P<0.001$) and group C ($P<0.001$). However, there was no significant difference in the IoC between group K0.1 and group C ($P=0.963$).

The lowest IoC value after induction was not significantly different among the groups, with values of 34.9 ± 4.5, 37.0 ± 6.2, 38.9 ± 5.8 and 36.2 ± 8.4 in the groupsthe K0.1, K0.3 and K0.5, respectively ($P=0.069$).

ΔP represents the degree of change in MBP at each time course from baseline. ΔHR represents the degree of change in HR at each time course from baseline. No significant differences were observed in HR and BP changes between groups at any time point, except for a greater HR change at 5 min after intubation in the K0.5 group compared to the control group ($P=0.018$) (Fig. 4).

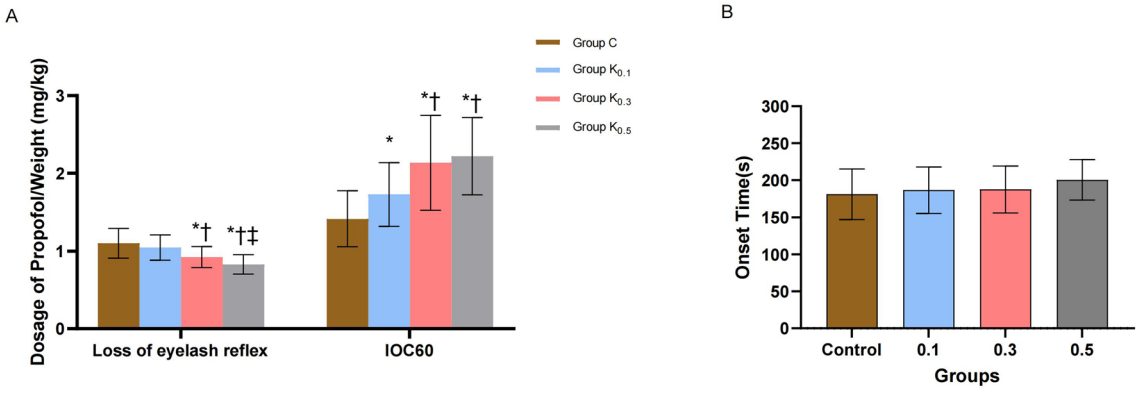

Fig. 3 Ratio of propofol dosage to body weight when loss of eyelash reflex and IOC60 (**A**). Onset time of cisatracurium (**B**). The onset time of cisatracurium was defined as the time from the end of cisatracurium injection to 95% of T1 decay. The ratio of propofol dosage to body weight when loss of eyelash reflex and IOC60 were showed as mean ± SD, and were analyzed with Welch test followed by Games-Howell post hoc comparison. Onset time of cisatracurium were showed as mean ± SD, and were analyzed with One-Way analysis of variance(ANOVA) followed by Bonferroni post hoc comparison. *$P<0.05$ vs. Group C. †$P<0.05$ vs. Group K0.1. ‡$P<0.05$ vs. Group K0.3. Abbreviations: Group C (control): injected with normal saline. Group K0.1: injected with 0.1 mg/kg esketamine. Group K0.3: injected with 0.3 mg/kg esketamine. Group K0.5: injected with 0.5 mg/kg esketamine.

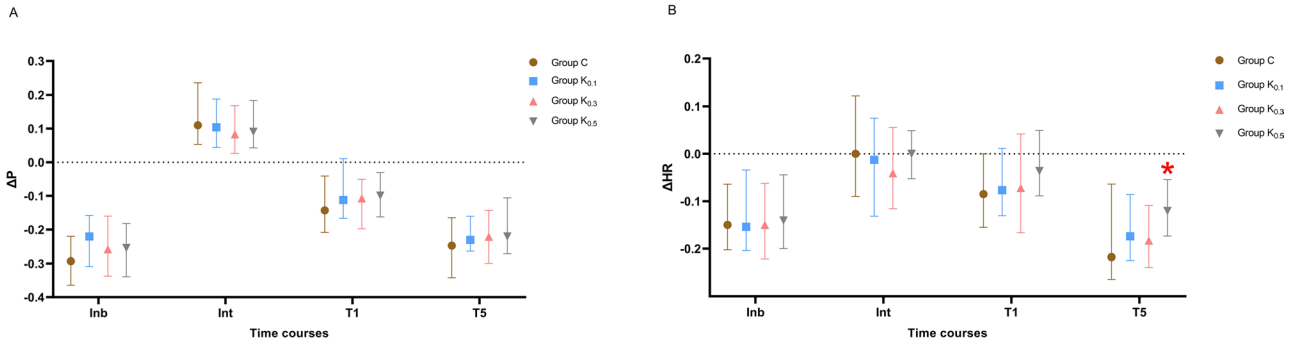

Fig. 4 Changes of ΔP (**A**) and ΔHR (**B**) before and after the induction of general anesthesia and intubation in groups. Values were expressed as median and interquartile range. ΔP and ΔHR were analyzed with Kruskal–Wallis test. *$P < 0.05$ vs. Group C. Abbreviations: ΔP: Degree of change in MBP at each time course from baseline [ΔP=(P-PBaseline)/ PBaseline]. ΔHR: Degree of change in HR at each time course from baseline [ΔHR=(HR-HRBaseline)/ HRBaseline]. Inb = before induction; Int = immediately after intubation; T1 = 1 min after intubation; T5 = 5 min after intubation. Group C (control): injected with normal saline. Group K0.1: injected with 0.1 mg/kg esketamine. Group K0.3: injected with 0.3 mg/kg esketamine. Group K0.5: injected with 0.5 mg/kg esketamine

Table 2 Postoperative side effects

	Group C ($n=35$)	Group $K_{0.1}$ ($n=35$)	Group $K_{0.3}$ ($n=35$)	Group $K_{0.5}$ ($n=35$)	*P* value
Delirium	0(0%)	1(3%)	2(6%)	0(0%)	>0.99[a]
PONV	3(9%)	4(11%)	4(11%)	3(9%)	0.461[a]
Dizziness	2(6%)	2(6%)	3(9%)	2(6%)	0.556[a]
Drowsiness	0(0%)	0(0%)	0(0%)	0(0%)	>0.99[a]
Respiratory depression	0(0%)	0(0%)	0(0%)	0(0%)	>0.99[a]

Values are number (proportion)

Abbreviations: Group C (control): injected with normal saline. Group $K_{0.1}$: injected with 0.1 mg/kg esketamine. Group $K_{0.3}$: injected with 0.3 mg/kg esketamine. Group $K_{0.5}$: injected with 0.5 mg/kg esketamine

[a] Fisher's exact test

There were no significant differences in the incidence rates of postoperative side effects among the groups, including delirium, PONV, dizziness, drowsiness, and respiratory depression (Table 2).

Discussion

This trial reveals that esketamine reduces propofol dose for eyelash reflex loss in a dose-dependent manner, but increases it independently for a targeted IoC of 60. Both 0.5 mg/kg esketamine and 0.3 mg/kg esketamine pretreatment before induction significantly increased the dose of propofol at the targeted IoC value of 60. However, esketamine has no effect on the onset time of cisatracurium when it is used in combination with propofol during IoC-guided induction of anesthesia.

Because of stable hemodynamics and reduced pain of injection, low-dose ketamine has gained increasing popularity as a coinduction agent and in combination with other anesthetics such as propofol during endotracheal intubation [27]. A previous study suggested that low-dose ketamine is defined as a bolus dose of less than 1 mg/kg when administered intravenously [28]. Esketamine has been reported to be able to be administered in smaller doses and cause fewer adverse effects [18, 29]. Therefore, in this study, the low dose of esketamine was determined to be a dose up to 0.5 mg/kg administered intravenously. In this study, esketamine was used one minute prior to induction because it has been established that esketamine reaches NMDA receptors within 1 min of intravenous injection, rapidly crossing the blood–brain barrier [30].

Esketamine is a chiral cyclohexanone derivative with analgesic and anesthetic effects at increasing doses. Eber et al. indicated that the use of esketamine could reduce the dosage of propofol by approximately 20% during surgery [8]. In daily practice, the eyelash reflex is often tested as a parameter of the induction of anesthesia. This study suggests that propofol causes a loss of eyelash reflex at lower concentrations than those causing loss of consciousness [31]. In our study, adjunctive esketamine (group K0.1, group K0.3 and group K0.5) reduced the concomitant doses of propofol required to achieve the loss of eyelash reflex, which suggested that esketamine enhanced propofol-induced hypnosis in a dose-dependent manner. Ketamine reportedly produces dose-dependent unconsciousness and provides an additive anesthetic effect when it is combined with propofol for the induction of anesthesia in dogs [32].

In addition to the commonly employed hypnotic endpoints of the loss of eyelash reflex, we tested IoC to assess the requirements of propofol with or without esketamine i.v. during anesthesia induction. IoC presents a rather strong relation with BIS, a widely validated index. IoC and bispectral index (BIS) also present a similar distribution as a function of the sedation level [33]. A previous study suggested that ketamine increased the BIS significantly despite a deepening level of hypnosis when administered during propofol anesthesia [34]. However, several studies have shown that there was no effect on BIS values when the bolus dose of ketamine was kept low (0.2 mg/kg) under propofol anesthesia [35–37]. The results of our

study show that adjunctive esketamine (group K0.3 and group K0.5) increased the concomitant doses of propofol required to achieve an IoC value of 60, but the lowest IoC value after induction was not significantly different, which suggested that esketamine increased the IoC values during propofol-induced hypnosis. These results may be because ketamine shifted the alpha peak of bicoherence induced by propofol to higher frequencies but did not block their formation [38, 39]. Our findings are clinically important because clinical practitioners should target greater BIS values to achieve the desirable level of sedation when using a BIS-guided sedation regimen with esketamine and propofol. During the induction of esketamine, relying solely on IoC/BIS to adjust the propofol dose may not be appropriate, as it may lead to excessive use of propofol. Relying solely on clinical observations, such as the disappearance of the eyelash reflex, may not achieve sufficient depth of anesthesia. A more reasonable approach is to combine clinical observations, like the disappearance of the eyelash reflex, with IoC monitoring. This can help avoid unnecessary propofol use while ensuring that patients receive adequate sedation.

The onset time of a nondepolarizing neuromuscular blocking drug may be influenced by cardiac output and muscle blood flow, which determine the speed of neuromuscular blocking agents being delivered to the neuromuscular junction. Although its cardiovascular stimulating properties may contribute to the fast distribution of a muscle relaxant, the effect of ketamine on muscle relaxants is controversial [22, 23]. Ahn et al. reported that ketamine pretreatment shortened the onset time of cisatracurium [40]. However, in our study, esketamine pretreatment did not affect the onset time of cisatracurium, which may be due to the large infusion dose of propofol in the esketamine pretreatment groups, which suppressed the cardiovascular stimulating properties of esketamine. Additionally, the sympathomimetic qualities of esketamine can also counteract the hemodynamic depression of propofol and thus reduce the risk of cardiovascular depression during induction.

There were a few limitations in this study. First, it would be better to measure the baseline concentrations and the changes in plasma esketamine and propofol concentrations from blood samples, which could directly reflect the additive interaction between propofol and esketamine. Second, this study reported the usage of esketamine pretreatment during induction without considering the different dosages in the different age populations, especially for elderly individuals or children. In the future, we will address this issue by comparing the dosage of esketamine for different age groups.

In conclusion, esketamine decreases the dose of propofol in a dose-dependent manner at the point of the loss of eyelash reflex, while 0.5 mg/kg esketamine and 0.3 mg/kg esketamine pretreatment before induction significantly increase the dose of propofol at the targeted IoC value of 60. Furthermore, esketamine has no effect on the onset time of cisatracurium when it is combined with propofol during IoC-guided induction of anesthesia. As a coinduction agent in low doses and in combination with other drugs such as propofol during anesthesia induction, more research on esketamine in this area is needed.

Abbreviations

IoC	Index of consciousness
NMDA	N-methyl-D-aspartic acid
ASA	American Society of Anesthesiologists
ECG	Electrocardiogram
TOF	Train-of-four
FiO2	Fraction of inspiration O2
PACU	Postanesthesia care unit
MBP	Mean blood pressure
HR	Heart rate
PONV	Postoperative nausea and vomiting
CAM	Confusion Assessment Method
SpO2	Oxygen saturation
EtCO2	End-tidal carbon dioxide
ANOVA	One-way analysis of variance
BIS	Bispectral index

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Author contributions
Rui An and Longhui Cao wrote the main manuscript text. Chunnan Lin and Zeguang Lu prepared Figs. 1, 2 and 3. Wenqian Lin, Hongying Tan, Tianhua Zhang and Huiting li did data analysis. All authors reviewed the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request VIA email caolh@sysucc.org.cn.

Declarations

Ethics approval and consent to participate
This prospective, randomized, double-blind clinical trial was approved by the Ethics Committee of Sun Yat-sen University Cancer Center (Number. B2021-031-01).

Consent for publication
All patients gave written informed consent before inclusion.

Consent to participate
Informed consent was obtained from all subjects and/or their legal guardian(s).

Competing interests
The authors declare no competing interests.

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