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ORIGINAL ARTICLE

Ketamine eliminates propofol pain but does not affect hemodynamics during induction with double-lumen tubes

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Abstract
Background and objective Propofol injection during induction of anesthesia induces pain. Ketamine has been shown to reduce the injection pain. However, ketamine has unfavorable adverse effects, including increased secretion production and hemodynamic responses, which might induce pulmonary or hemodynamic adverse events, especially in patients undergoing lung surgery who require a double-lumen tube (DLT). The aim of this study was to determine whether ketamine can safely reduce propofol injection pain during induction of anesthesia for lung surgery.
Methods Forty-five patients scheduled for elective lung surgery requiring DLT were randomly allocated into three groups. Patients received saline (control), ketamine 0.5 mg kg^{-1} (0.5 ketamine), or ketamine 1.0 mg kg^{-1} (1.0 ketamine), followed by 5 ml propofol 30 s later. An anesthesiologist blinded to the study group assessed pain score during induction, hemodynamics during DLT placement, and secretion production during anesthetic management.
Results Pretreatment of 0.5 mg kg^{-1} ketamine reduced the incidence and intensity of propofol injection pain, whereas 1.0 mg kg^{-1} ketamine completely eliminated the pain. There were no significant differences regarding oxygenation during one-lung ventilation (OLV) and hemodynamics during induction among the three groups, although ketamine increased secretion production.
Conclusions One milligram per kilogram of ketamine completely eliminated pain associated with propofol injection without affecting hemodynamics during induction of anesthesia and oxygenation during OLV.

Keywords Ketamine · Propofol pain · Double-lumen tube

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Introduction

Propofol has been widely used to induce general anesthesia, but injection pain is one of drawbacks to its clinical use [1]. Among 33 low-morbidity clinical outcomes, as assessed by number of anesthesiologists considering clinical importance and frequency, pain during propofol injection was ranked seventh [2]. Pain prevalence on propofol injection has been reported to be up to 90% if a vein on the dorsum of the hand is used [3, 4]. Various methods have been used to reduce this pain [4–13]. Of those, ketamine has been recognized one candidate to effectively reduce the pain [14–16]. However, ketamine has unfavorable adverse effects, including increased secretion production and sympathetic stimulation leading to increased arterial pressure and heart rate [17–22]. For lung surgery, a double-lumen endobronchial tube (DLT) is required to perform surgical procedures, with which intubation and placement of the tube are accompanied by increased heart rate and arterial blood pressure [23–25]. Therefore, ketamine could enhance cardiovascular responses during DLT handling. Patients presenting for lung surgery usually have a high risk for

cardiovascular disease; therefore, marked hemodynamic responses would be undesirable [23, 26]. In addition, increased secretion production might expose the patients to impaired respiratory conditions during one lung ventilation (OLV). Thus, these potential adverse effects should be evaluated for application of ketamine to propofol injection pain for lung surgical patients.

The current study was conducted to investigate whether ketamine can reduce propofol injection pain during induction of anesthesia for lung surgery. Previous reports employed smaller doses of ketamine (0.1–0.5 mg kg^{-1}) could not eliminate the pain completely. Therefore, a larger dose of ketamine (1.0 mg kg^{-1} of ketamine) was chosen in this study [14–16]. In addition, the effects of ketamine on hemodynamics during induction of anesthesia and the impacts of increased secretion production by ketamine pretreatment on respiratory conditions were also evaluated using a secretion-production scale.

Methods

After the study protocol was approved by the institutional ethics committee and written informed consent was obtained from each patient, 45 patients scheduled for elective thoracic procedures in the lateral position were enrolled (lobectomy with thoracoscopic surgery = 37, wedge resection with thoracoscopic surgery = 8). Exclusion criteria were intracranial lesion, documented coagulopathy, or coronary or vascular disease. No patient had a history of myocardial infarction or arrhythmia before the operation. All patients were premedicated with roxatidine (H2 blocker) 75 mg orally 2 h preoperatively. On arrival in the operation room, a 22-gauge IV catheter (Angiocath, Becton, Dickinson and Company) was placed into the dorsal vein of the hand (without local anesthesia). Infusion of acetated Ringer's solution (Veen F, Nikkenkagaku Inc., Tokyo, Japan) was started at 100 ml h^{-1}. Before induction of general anesthesia, an epidural catheter was inserted at the 6–7th, 7–8th, or 8–9th thoracic interspace. Any epidural test drug was not used so as to avoid its influence on the findings. Thereafter, we randomly allocated 45 patients to 1 of 3 groups using computer-generated random numbers: (1) control group (pretreatment of 0.1 ml kg^{-1} normal saline), (2) 0.5 ketamine group (pretreatment of 0.5 mg kg^{-1} ketamine diluted to 0.1 ml kg^{-1} with normal saline), (3) 1.0 ketamine group (pretreatment of 1.0 mg/0.1 ml kg^{-1} ketamine).

Then, patients were given vecuronium 0.02 mg kg^{-1} for precurarization, atropine 0.01 mg kg^{-1}. Subsequently, the test drugs were administered to each group. After 30 s, 5 ml of 1% propofol (at room temperature) was injected at 1 ml/s. After the end of the injection, every 10 s for 30 s, a blinded investigator (MI) assessed pain intensity using a verbal rating scale [5]: 0 = no pain experienced, 1 = mild pain or soreness, 2 = moderate pain, and 3 = severe pain associated with grimacing, withdrawal movement of forearm, or both) and simultaneously recorded pain spread at the site (dorsum of the hand, wrist, or forearm). The interval of 30 s between ketamine pretreatment and propofol injection was employed based on the previous studies [14–16].

Thereafter, the induction of general anesthesia was continued with the remaining dose of propofol, whose total dose was 2 mg kg^{-1}, followed by 0.15 mg kg^{-1} vecuronium and 2 μg kg^{-1} fentanyl. After 3-min mask ventilation under 3% sevoflurane with oxygen, a left-sided DLT, 37 Fr for men and 35 Fr for women (Broncho-Cath, Tyco Healthcare, Argyle, Mansfield, MA, USA) was placed for OLV, and the correct position was confirmed by auscultation and fiber-optic bronchoscopy. After intubation, patient's lungs were mechanically ventilated under 0.5 fraction of inspiratory oxygen (FiO_2) and 1.5% sevoflurane. OLV was started just before opening the pleura. After the endobronchial cuff was inflated, the corresponding limb of the connector of the double-lumen tube was opened to the atmosphere and suctioned through a fiberoptic bronchoscope to facilitate and expedite lung collapse. The inspiratory tidal volume was set at 6–8 ml/kg, the respiratory rate was adjusted to maintain partial pressure of arterial carbon dioxide ($PaCO_2$) at around 40 mmHg, and FiO_2 was changed to maintain pulse oximeter oxygen saturation (SpO_2) >95%. A ratio of 1:2 was applied for the ratio of inspiratory to expiratory time. The tidal volume was decreased if peak airway pressure exceeded 25 cmH_2O. OLV was terminated just after the pleurae were closed. The surgical lung was suctioned and inflated, and the endobronchial cuff was deflated. Routine monitoring included electrocardiogram, radial arterial catheter, noninvasive blood pressure cuff, pulse oximetry, and capnogram.

Heart rate and noninvasive blood pressure were recorded at the following 6 points: time (1) just before induction; time (2) just before injection of the remaining dose of propofol; time (3) just before intubation; time (4) just before determination of the tube position with fiberoptic bronchoscopy; time (5) 1 min after determination of the tube position; time (6) 3 min after determination of the tube position. Production of intrabronchial secretions at intubation (1), starting OLV (2), resuming two-lung ventilation (3), and extubation (4) was also assessed with the following score: none (dry; 0), mild (moist; 1), moderate (more moist but airway patency maintained; 2), severe (necessary to suction to maintain airway patency; 3). In addition, blood-gas analysis was performed 30 min

after starting OLV in the lateral position. PaO_2/FiO_2 ratio (P/F ratio) was calculated to assess oxygenation during OLV. SpO_2 values were recorded every 15 min during OLV. One of the authors (MI) verbally evaluated psychopharmacologic effects that have been reported after ketamine. These effects include dreaming during the operation, altered color perception, reduced visual acuity, changes in hearing, hallucinations, altered body image, feelings of unreality, anxiety, aggression, altered physical strength, dizziness, discomfort, illness, and nausea. Patients were asked whether they had such experience at discharge from the operating room and 24 h later..

Statistical analysis

Study population size was determined using the following procedure: We assumed that propofol injection pain using a vein on the dorsum of the hand would occur in 75% of patients [4–13] and be reduced to 25% with ketamine pretreatment. Based on the formula for normal theory and assuming a type I error protection of 0.05 and a power of 0.95, 15 patients in each group were required for the study. To compare demographic and physiologic value variables of patients among the three groups, analysis of variance (ANOVA) with or ANOVA for repeated measures was used. If the analysis of variance identified significant differences, Scheffe's *F* test was used for post hoc analysis. Comparisons of pain transition and gender among the three groups were performed using the chi-square test or Fisher's exact test. Comparisons of pain spread and secretion production were performed using Kruskal–Wallis tests followed by Mann–Whitney *U* test with Bonferroni's correction. Sample size calculation was performed with G*power (Free software, VIC, Australia), and other analyses were conducted with StatView 5.0 (SAS Institute Inc. Cary, NC, USA). Data from continuous variables are expressed as mean ± standard deviation (SD). Differences were considered significant when P was <0.05.

Results

Demographic variables and PaO_2/FiO_2 ratio during OLV are shown in Table 1. There were no significant differences in these variables among the three groups. Preoperative respiratory function [forced expiratory volume in 1 s (%) and % vital capacity] in each group was almost similar (data not shown). Heart rate and mean blood pressure are shown in Fig. 1. There were no significant differences in the three groups. None of the doses of ketamine used increased hemodynamic responses or prevented depression of hemodynamics that occurs during induction with propofol.

Figure 2 shows pain spread from the dorsum of the hand to the forearm. In the control group, 10 s after, 67% of patients felt the injection pain in the dorsum of the hand, and after 30 s, 93% of patients felt pain in the dorsum of the hand. Amazingly, pain usually expanded and reached the forearm in 53% of patients. Administration of 0.5 mg kg^{-1} ketamine reduced the incidence of pain to some extent. Highly important, no one in the 1.0 ketamine group complained of pain at site or time point. Figure 3 shows transition of pain intensity of the dorsum of the hand. At any time point, 1.0 mg kg^{-1} ketamine successfully eliminated propofol injection pain. In contrast, 0.5 mg kg^{-1} ketamine significantly reduce pain intensity but failed to show complete elimination of pain.

Figure 4 shows production score of secretions. Both ketamine groups significantly produced more secretions. With elapsing time, secretions induced by 1.0 mg/kg ketamine got moister, although secretion production by 0.5 mg kg^{-1} ketamine did not increase significantly. However, as shown above, status of secretions did not affected oxygenation during OLV (Table 1). Continuous SpO_2 monitoring during OLV showed no significant differences among the three groups with 0.5–0.6 FiO_2 (showing 96–97% SpO_2). No patient experienced psychopharmacologic adverse effects of ketamine, such as dreaming or hallucinations upon leaving the operation room and 24 h later (Data not shown).

Table 1 Demographic variables and partial pressure of arterial carbon dioxide ($P/F = PaO_2$)/fraction of inspiratory oxygen (FiO_2) (P/F) ratio

	Control ($n = 15$)	0.5 Ketamine ($n = 15$)	1.0 Ketamine ($n = 15$)
Age (years)	66 ± 10	69 ± 5	68 ± 10
Sex (male/female)	10/5	8/7	8/7
Height (cm)	158 ± 7	159 ± 8	158 ± 10
Weight (kg)	58 ± 11	56 ± 10	56 ± 10
Operation time (min)	162 ± 69	147 ± 64	188 ± 74
Anesthesia time (min)	251 ± 70	234 ± 71	277 ± 73
P/F during OLV (mmHg)	121 ± 32	152 ± 59	163 ± 74

Data are expressed as mean ± standard deviation

OLV one-lung ventilation

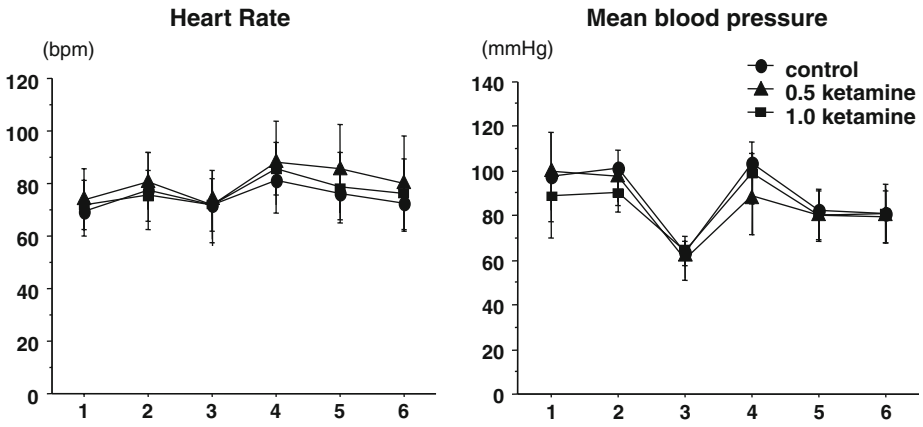

Fig. 1 Changes in heart rate and mean blood pressure during induction: *1* Just before induction, *2* just before propofol injection, *3* just before intubation, *4* just before determination of the tube position with fiber-optic bronchoscopy, *5* 1 min after determining tube position, *6* 3 min after determining tube position. There were no significant differences among the three groups. Data are expressed as mean ± standard deviation

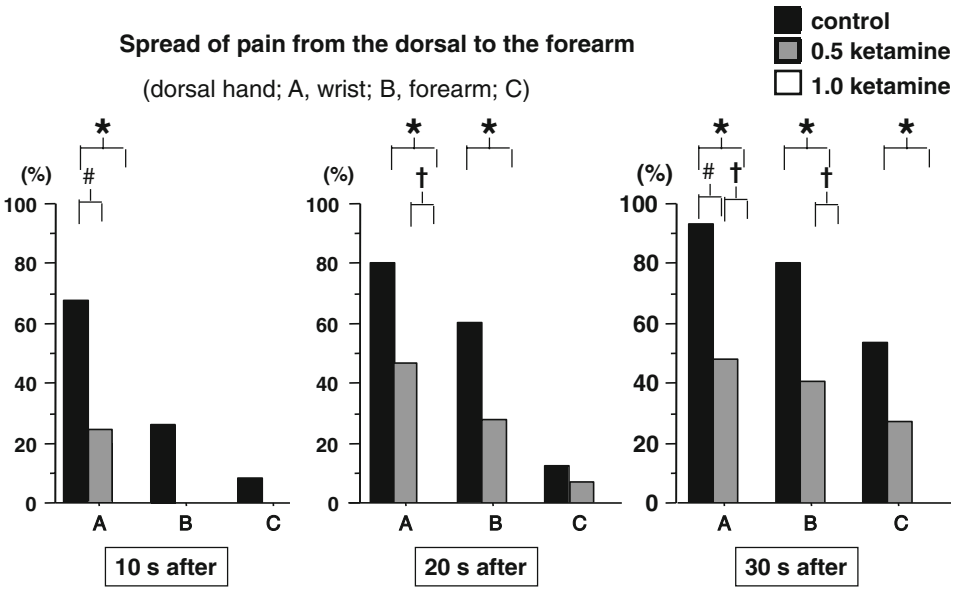

Fig. 2 Spread of pain from the dorsum of the hand to the forearm: $^{*}p < 0.05$ control group versus the 1.0 ketamine group; $^{\#}p < 0.05$ control group versus the 0.5 ketamine group; $^{\dagger}p < 0.05$ the 1.0 ketamine group versus the 0.5 ketamine group. *A*, *B*, and *C* represent incidence of pain in the dorsum of the hand, wrist, and forearm, respectively

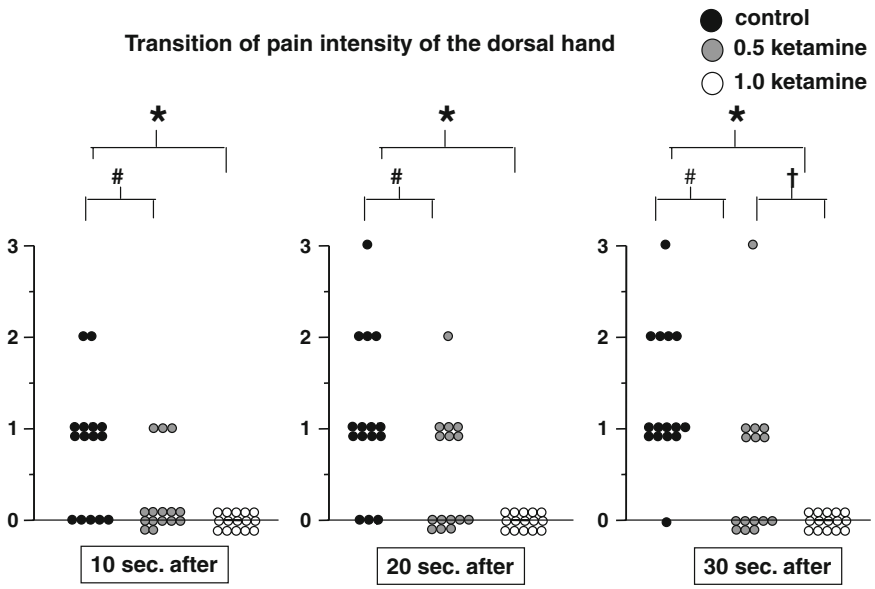

Fig. 3 Transition of pain intensity of the dorsum of the hand. Pain rating scale: *0* no pain experienced, *1* mild pain or soreness, *2* moderate pain, and *3* severe pain associated with grimacing, withdrawal movement of forearm, or both: $^{*}p < 0.05$ control group (*solid circle*) versus the 1.0 ketamine group (*open circle*); $^{\#}p < 0.05$ control group versus the 0.5 ketamine group (*half-tone circle*). $^{\dagger}p < 0.05$ the 0.5 ketamine group versus the 1.0 ketamine group

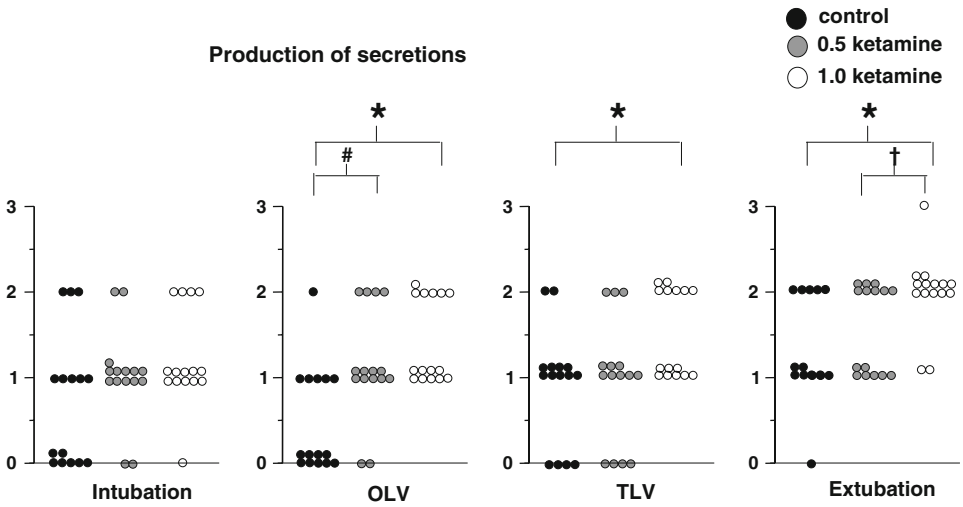

Fig. 4 Secretion production. *1* At intubation, *2* starting one-lung ventilation (OLV); *3* resuming two-lung ventilation; *4* extubation were assessed with the following score: none (dry; 0), mild (moist; 1), moderate (more moist, but airway patency is maintained; 2), severe (suction necessary to maintain airway patency; 3). $^{*}p < 0.05$ control group (*solid circle*) versus the 1.0 ketamine group (*open circle*). $^{\#}p < 0.05$ control group versus the 0.5 ketamine group (*half-tone circle*). $^{\dagger}p < 0.05$ the 0.5 ketamine group versus the 1.0 ketamine group

Discussion

In this study, we observed that 0.5 mg kg^{-1} ketamine significantly reduced the incidence and intensity of propofol injection pain but not completely. We also found that 1.0 mg kg^{-1} ketamine eliminated the pain completely. Regarding potential adverse effects, hemodynamic responses during DLT handling were not affected by ketamine pretreatment. Oxygenation during OLV was not impaired by ketamine, although ketamine increased secretions. Psychopharmacologic adverse effects of ketamine were also negligible.

The prevalence of pain on propofol injection has been reported to be up to 90% if a vein on the dorsum of the hand is used [3, 4]. In our study, almost 90% of patients complained of pain. Various methods have been used to reduce this pain [4–13]. Several positive results have been reported; however, propofol injection pain still occurs at a significant rate. Ketamine has also been used in attempts to reduce the pain [14–16]. Tan et al. [14] reported that 10 mg ketamine pretreatment reduced the propofol injection pain. Ozkoçak et al. [15] demonstrated that 0.5 mg kg^{-1} ketamine reduced the pain intensity. Correspondingly, in this study, 0.5 mg kg^{-1} ketamine reduced propofol injection pain. Moreover, 1.0 mg kg^{-1} ketamine administration eliminated the pain completely.

The short interval of 30 s between ketamine pretreatment and propofol injection might suggest the result of a peripheral local anesthetic action, which attenuated the afferent pain pathway rather than causing a central analgesic effect [14–16]. However, this proposed mechanism is based on previous reports using the same interval employing smaller doses of ketamine (0.1–0.5 mg kg^{-1}), which could not eliminate the pain completely. Considering that the larger dose of ketamine (1.0 mg kg^{-1}) eliminated the pain completely, a central analgesic effect by ketamine might modulate the pain induced by propofol.

Ketamine has side effects, including sympathetic stimulation leading to increased arterial pressure and heart rate and increased secretion production [17–22]. However, neither 0.5 nor 1.0 mg kg^{-1} ketamine administration increased mean arterial pressure or heart rate significantly during DLT handling, which can increase heart rate and arterial blood pressure more severely [23–25]. In contrast, propofol also has side effects that include a large decrease in arterial pressure and occasional severe bradycardia when used to induce anesthesia. Several studies have reported that a combination of propofol and ketamine has the advantage of stabilizing hemodynamics, given that the arterial pressure and heart rate effects of the individual agents tend to cancel one another out [17–22]. We successfully showed prevention of hyperdynamic responses against DLT handling but found no stabilizing hemodynamics during induction of anesthesia, especially before intubation, with a combination of propofol and ketamine compared with propofol alone. Supplemental fentanyl and sevoflurane might have spoiled the combination efficacy of ketamine and propofol. To address this issue, further investigations may be required. In addition, neither doses of ketamine affected oxygenation during OLV, although increased secretion production was observed. Increased intrabronchial secretions might worsen respiratory conditions; however, we believe careful respiratory management, for example, frequent bronchoscopic observation and suctioning, can prevent impaired oxygenation with the observed degree of secretions during OLV.

There are some of limitations in this study. It has been reported that propofol injection pain can be immediate or delayed (latency of between 10 and 20 s) via different mechanisms [27]. We only evaluated pain 10, 20, and 30 s after propofol injection; not immediate pain. However, it might be difficult to distinguish immediate pain and delayed pain at the first assessment (10 s after injection).

The doses of ketamine used in this study could affect emergence from anesthesia after minor surgical procedures. However, the effect on emergence of a single shot of ketamine at these doses can be negligible for lung surgery, which took approximately 2.5 h in this study. As another concern, larger doses of ketamine might have also been effective for stabilizing hemodynamics before intubation. Considering 1.0 mg kg^{-1} ketamine tended to increase secretion production, secretions would have increased with larger doses, which could have disturbed the respiratory management during OLV. In addition, some might question why we gave all patients atropine. The reason was that atropine is listed as an induction drug in the institutional anesthetic protocol. However, the use of atropine may well have masked any possible adverse effect of ketamine. As the final concern, was group allocation truly blinded to the investigator, as patients received ketamine could be anesthetized 30 s after propofol injection. In this study, no patient was anesthetized 30 s after propofol injection, although some were sedated. However, all patients were able to respond to the investigator, who was occasionally aware which group the patients belonged to because the patients' responses were clearly different. However, it was difficult to distinguish the 0.5 ketamine group from the 1.0 ketamine group. In addition, it was sometimes difficult to distinguish the 0.5 ketamine group and the control group. Therefore, it is reasonable to believe that the pain intensity assessment was appropriately performed. A large dose of ketamine (1.0 mg kg^{-1}) might be an induction dose; however, previous reports using the same interval (30 s) and employing smaller doses (0.1–0.5 mg kg^{-1}) could not eliminate propofol injection pain completely. That is why we chose 1.0 mg kg^{-1} ketamine. Consequently, 1.0 mg kg^{-1} ketamine successfully eliminated pain completely without anesthetizing patients during this interval.

In summary, we investigated whether ketamine can reduce propofol injection pain during anesthesia induction for lung surgery using DLT. We observed that 0.5 mg kg^{-1} ketamine reduced the pain to a certain extent, and 1.0 mg kg^{-1} ketamine eliminated the pain completely. Both doses of ketamine only slightly affected hemodynamics during anesthesia induction and oxygenation during OLV.

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