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Original Article

Influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients

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Abstract: Objective: To analyze the influence of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition in elderly surgical patients. Methods: A total of 80 elderly surgical patients were randomly divided into a control group (n=40) and a study group (n=40). The control group received anesthetic induction with propofol combined with sufentanil, while the study group received anesthetic induction with propofol combined with esketamine. Hemodynamics, stress and inflammatory responses and changes in cognitive function, perioperative related indexes and adverse responses were compared between the two groups. Results: At T_1, the levels of adrenaline, norepinephrine, endothelin, C-reactive protein, white blood cell and procalcitonin in the two groups were not markedly changed compared with those at T_0. The levels of the indices at T_2 and T_3 were elevated compared with those at T_1. However, the levels of the indices at T_4 were almost close to those at T_0, and the levels in the study group were higher than those in the control group. There were statistically significant differences in the comparison of the interaction of the levels of the aforementioned indices between groups, between time points, and between groups and time points ($P < 0.05$). At 24 h after surgery, the Montreal Cognitive Assessment (MoCA) scores were decreased in both groups, and the MoCA scores in the study group were higher than those in the control group ($P < 0.05$). The anesthesia time and consciousness recovery time in the study group were shorter than those in the control group ($P < 0.05$). Conclusion: The anesthetic induction of propofol combined with esketamine, exhibits a good safety profile and reliability, it can improve hemodynamics and surgical stress and inflammatory responses, shorten anesthesia time, promote the recovery of postoperative cognitive function, and cause relatively mild adverse responses.

Keywords: Elderly surgical patients, stress response, inflammatory response, cognitive function, propofol, esketamine

Introduction

With the continuous aging of the elderly population, patients can experience gradually deteriorated functions of their bodies, a low surgery tolerance, and multiple underlying health conditions. Additionally, spinal surgery causes trauma and severe stress response during the surgery, thereby easily leading to severe fluctuations in hemodynamics [1, 2]. During the surgery, the trauma can cause the release of massive inflammatory mediators, involving the central nervous system and inducing a series of postoperative complications (e.g., cognitive dysfunction, delirium) [3]. Therefore, on the premise of ensuring the quality and safety profile of anesthesia, the alleviation of the anesthesia-induced injuries has been widely explored clinically. Propofol is a short-acting intravenous anesthetic indicated for induction and maintenance of general anesthesia, which is often used in combination with spinal or epidural anesthesia. It takes effect in 40 seconds and patients wake up faster. However, propofol has a weak analgesic property, and it is often used clinically combined with analgesics [4]. Ketamine hydrochloride was first developed by Parke-Davis in 1962. After acquiring Parke-Davis, Pfizer developed dextroketamine, namely, esketamine [5]. Com-

pared with other intravenous sedatives, esketamine has the greatest advantage, that is, it has a strong analgesic effect and little effect on the respiratory and circulatory system of patients. Currently, it is the only sedative drug that can be injected intramuscularly in clinical anesthesia practice [6]. Compared with the traditional ketamine, esketamine has a stronger analgesic effect and a higher clearance rate *in vivo*, but the dosage is only 1/2 of ketamine [7]. To date, there is no study pertaining to the specific use experience of esketamine in China. On this basis, this study further investigated the influences of anesthetic induction of propofol combined with esketamine on perioperative stress and inflammatory responses and postoperative cognition of elderly surgical patients.

Materials and methods

Clinical data

From April 2020 to August 2020, a total of 80 elderly surgical patients in our hospital were randomly divided into a control group (n=40) and a study group (n=40). Inclusion criteria: patients aged ≥ 60 years old; American Society of Anesthesiologists (ASA) [8] anesthesia grades: Grade I-III; those with surgical indications; those with normal hepatic and renal functions; those with normal coagulation function. All the families of patients voluntarily signed the informed consent. Exclusion criteria: those with infectious diseases and blood system diseases; those with increased blood lactic acid or metabolic disorders; those with end-stage chronic diseases, active bleeding, severe pulmonary hypertension, heart failure and acute myocardial infarction; those with history of surgical contraindications; those with history of contraindication of anesthetics; those who were accompanied by severe infections and functional abnormality of important organs (heart, brain, lung, *etc*.); those who were unable to cooperate with investigators due to mental disorders or psychological illness. This study was reported to Yichun People's Hospital and approved by the Medical Ethics Committee.

Methods

The control group received an anesthetic induction of propofol combined with sufentanil: the patients were instructed to abstain from water 6 h before surgery, and were injected intramuscularly with atropine (0.01-0.02 mg/kg), etomidate (0.2-0.3 mg/kg), sodium hydroxybutyrate (60 mg/kg) and vecuronium (0.1 mg/kg) for induction 30 min before surgery. The vital signs and oxygen saturation were continuously monitored using ECG. The patients were intubated after being unconscious, and 0.4 ng/mL sufentanil (Yichang Renfu Pharmaceutical Co., Ltd., SFDA approval number H20030200) and 4 μg/mL propofol (Guangdong Jiabo Pharmaceutical Co., Ltd., SFDA approval number H20143369) were given via target controlled infusion (TCI). TDX-FLX fully automatic plasma concentration detector (Abbott Laboratories, IL, USA) was used to monitor the plasma concentration of patients in real time. The maintenance of anesthesia was performed based on the plasma concentration, and propofol (4 mg/kg) was used for maintenance of anesthesia. If the anesthetic effects were not satisfactory, 3 ml of 2% lidocaine could be additionally injected, and anesthesia infusion was stopped upon the completion of surgery. The study group received an anesthetic induction of propofol combined with esketamine (Jiangsu Hengrui Pharmaceutical Co., Ltd., SFDA approval number H20193336). The sufentanil used in the control group was replaced with esketamine (0.5 mg/kg) in the study group.

Observational indices

(1) Hemodynamics: The changes of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR) were recorded before anesthesia (T_0), when anesthesia started (T_1), 30 min after anesthesia (T_2), at the end of surgery (T_3), and 12 h after surgery (T_4).

(2) Stress response: Three ml of peripheral venous blood was collected at different time points, and centrifuged at 3000 r/min for 10 min. The supernatant was collected, and adrenaline (AD) and norepinephrine (NE) were detected by fluorescence method, and endothelin (ET) was detected by radioimmunoassay (RIA). The detection kits were purchased from Wuhan Purity Biotechnology Co., Ltd.

(3) Inflammatory response: An OTA-400 fully automatic biochemical analyzer (Shenyang

Wantai Medical Equipment Co., Ltd.) was adopted, and the serum C-reactive protein (CRP) level was detected by the immune scattering turbidimetry. The procalcitonin (PCT) level was detected using the double-antibody sandwich immunofluorescence assay and fully automatic fluorescent enzyme labeling system (BioMérieux, Inc., French). The white blood cell (WBC) count level in blood *was detected* by the double-fluorescence method and Mindray BC300 fully automatic blood cell analyzer (Shenzhen Mindray Biomedical Electronics Co., Ltd.).

(4) Cognitive function: The Montreal Cognitive Assessment (MoCA) [9] was adopted to assess the cognitive function of the patients before surgery and at 24 h after surgery. The scale comprises 8 items, namely, delayed recall, memory, abstract generalization, visual space and executive function, attention, orientation, language, naming, and calculation. The total score is 30 points, among which < 10 points indicates severe cognitive disorders, 10-17 points indicates moderate cognitive disorders, 18-26 points indicates mild cognitive disorders, and > 26 points indicates no cognitive disorder.

(5) Perioperative related indicators: The surgical duration, anesthesia time and consciousness recovery time of the patients were recorded.

(6) Adverse responses: The adverse responses (nausea and vomiting, respiratory depression, delayed awakening) were recorded during and after surgery.

Statistical analysis

SPSS 23.0 was adopted for statistical analysis. The measurement data conforming to anormal distribution were expressed as $\bar{x} \pm s$. The comparison between groups was detected using the independent sample *t* test, and the comparison within groups was detected using the paired *t* test. The enumeration data were expressed as n (%), and detected using χ^2 test. The comparison of single indices at multiple time points between the two groups was detected by the general linear repeated-measure analysis of variance. $P < 0.05$ indicated a statistical significance.

Results

General data

There was no statistical significance in the general data between the two groups ($P > 0.05$), which were comparable (**Table 1**).

Hemodynamics

At T_1, the levels of SBP, DBP, MAP and HR in the two groups were not markedly changed compared with those at T_0 ($P > 0.05$). The levels of the aforementioned indices at T_2 and T_3 were elevated compared with those at T_1, but the levels were decreased at T_4 and were close to those at T_0. The levels in the study group were higher than those in the control group. There were statistically significant differences in the comparison of the interaction of the levels of the aforementioned indices between groups, between time points, and between groups and time points ($P < 0.05$). This suggested that the anesthetic induction of propofol combined with esketamine was more conducive to stabilizing the hemodynamics of elderly surgical patients (**Figure 1**).

Stress response

At T_1, the levels of AD, NE and ET in the two groups were not remarkably changed compared with those at T_0 ($P > 0.05$). The levels of the aforementioned indices at T_2 and T_3 were elevated compared with those at T_1, but the levels were decreased at T_4 and were almost close to those at T_0. The levels in the study group were higher than those in the control group. There were statistically significant differences in the comparison of the interaction of the levels of the aforementioned indices between groups, between time points, and between groups and time points ($P < 0.05$). This revealed that the anesthetic induction of propofol combined with esketamine was more conducive to reducing the stress response of elderly surgical patients (**Figure 2**).

Inflammatory response

At T_1, the levels of CRP, WBC and PCT in the two groups were not remarkably changed compared with those at T_0 ($P > 0.05$). The levels of the aforementioned indices at T_2 and T_3 were

Table 1. Comparison of general data between the two groups [($\bar{x}$ ± sd)/n (%)]

Group	Number of cases	Gender (M/F)	Age (years)	BMI (kg/m^2)	Site				Type of surgery		
					Cervical vertebra	Lumbar vertebrae	Thoracic vertebrae	Anterior cervical decompression and fusion with internal plate fixation	Percutaneous pedicle screw fixation	Fenestration discectomy	Artificial disc replacement and others
Control group	40	22/18	65.27±5.16	22.16±1.71	10	25	5	8	10	8	14
Study group	40	20/20	66.01±5.35	22.39±1.75	12	24	4	7	12	6	15

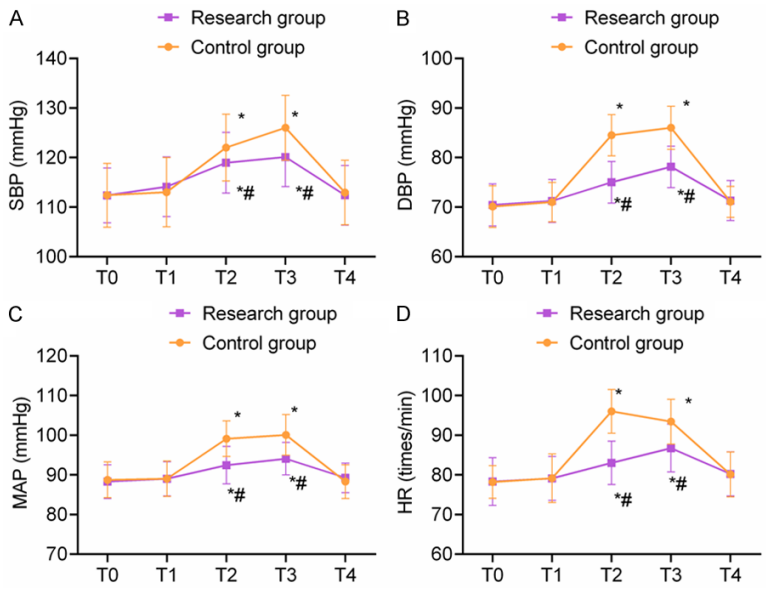

Figure 1. Comparison of hemodynamic indices between the two groups. Note: A. BP; B. DBP; C. MAP; D. HR. Compared with other time points, $^{*}P < 0.05$; compared with the control group at the same time point, $^{\#}P < 0.05$.

elevated compared with those at T_1, but the levels were decreased at T_4. The levels in the study group were higher than those in the control group. There were statistically significant differences in the comparison of the interaction of the levels of the aforementioned indices between groups, between time points, and between groups and time points ($P < 0.05$). This exhibited that the anesthetic induction of propofol combined with esketamine was more conducive to alleviating the inflammatory response of elderly surgical patients (**Figure 3**).

Cognitive function

Before surgery, there was no statistically significant difference in MoCA scores between the two groups (P > 0.05). At 24 h after surgery, MoCA scores were decreased in the two groups, but MoCA scores in the study group were higher than those in the control group ($P < 0.05$). This demonstrated that the anesthetic induction of propofol combined with esketamine was more conducive to promoting the recovery of cognitive function of elderly surgical patients (**Figure 4**).

Postoperative related indices

There was no statistically significant difference in the surgical duration between the two groups ($P > 0.05$), but the anesthesia time and consciousness recovery time in the study group were shorter than those in the control group ($P < 0.05$). This exhibited that the anesthetic induction of propofol combined with esketamine was more conducive to shortening anesthesia time and promoting consciousness recovery of elderly surgical patients (**Figure 5**).

Adverse response

There was no statistically significant difference in the incidence of adverse responses between the two groups ($P > 0.05$). This revealed that the anesthetic induction of propofol combined with esketamine exhibited a good safety profile and could be easily tolerated by elderly surgical patients (**Table 2**).

Discussion

Based on the theories of pharmacokinetics and pharmacodynamics and the regulation of plasma or effector drug concentration, TCI is a technique of infusing IV drugs through an infusion pump controlled by a computer to simulate the specific process in human body, which is of great significance for maintaining the depth of anesthesia and inhibiting the stress response of the body [10, 11]. Remifentanil takes effect fast and has obvious analgesic effects and mild respiratory depression effects. It is hydrolyzed by non-specific esterases in the body without affecting hepatic and renal functions. However, it has a short half-life, and the ester bonds in remifentanil molecular structure are easily decomposed in the hydrolysis process of the non-specific esterase, disrupting the pharmacokinetics [12, 13]. Propofol can effectively inhibit sympathetic nervous activity and reduce hormone levels (e.g., catecholamine and cortisol). Combined with remifentanil, it can reduce the distribution and clearance of propofol, increase plasma concentration, inhibit the sensitivity of baroreceptors, exert sedative and analgesic effects, alleviate stress and inflammatory responses, and stabi-

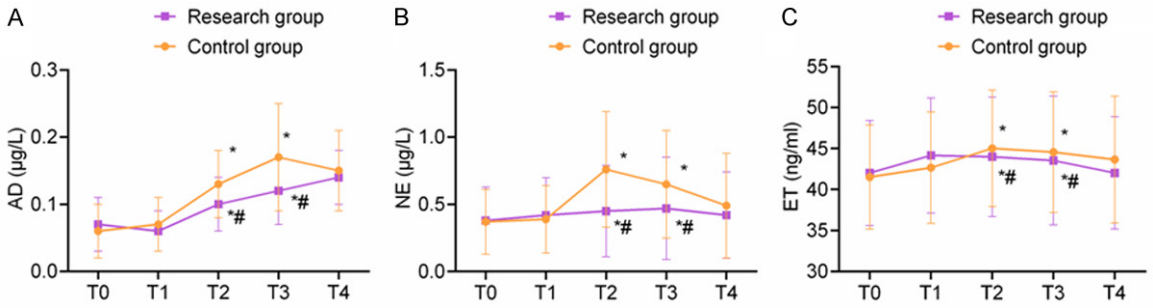

Figure 2. Comparison of stress response indices between the two groups. Note: A. AD; B. NE; C. ET. Compared with other time points, $^{*}P < 0.05$; compared with the control group at the same time point, $^{\#}P < 0.05$.

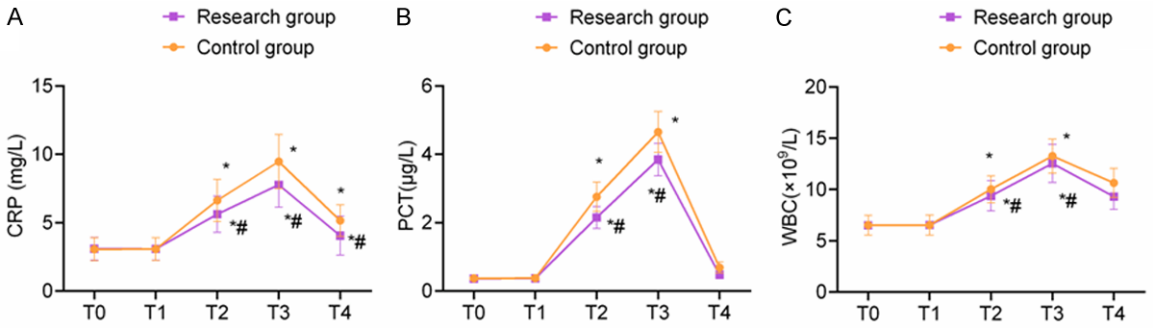

Figure 3. Comparison of inflammatory responses between the two groups. Note: A. CRP; B. PCT; C. WBC. Compared with other time points, $^{*}P < 0.05$; compared with the control group at the same time point, $^{\#}P < 0.05$.

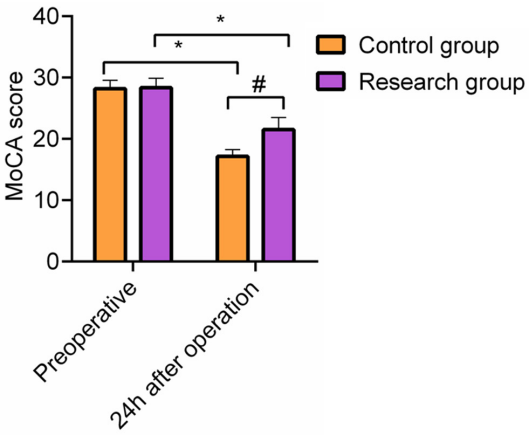

Figure 4. Comparison of MoCA scores between the two groups (points). Note: Compared with this group before surgery, $^{*}P < 0.05$; Compared with the control group at the same time point, $^{\#}P < 0.05$.

lize hemodynamics. Additionally, combined with TCI, it can more effectively control the accuracy of anesthesia amount and ensure the safety profile of surgery [14, 15].

Esketamine is a chiral cyclohexanone derivative with analgesic and anesthetic effects at increasing doses. Combined with hypnotics, it is applicable to the induction and general anesthesia or serves as a supplement to local anesthesia [16]. Wang et al. [17] indicated that there was no difference in the onset time between esketamine and ketamine, yet the half-life of esketamine (287.5±110.2 min) was obviously shorter than that of ketamine, and the awakening time (9 min) using esketamine was shorter than that (13 min) using ketamine. This study results suggested that the study group had more stable hemodynamics, relatively mild stress and inflammatory responses and adverse responses, faster recovery of awakening time and cognitive function after surgery compared with the control group. It indicated that propofol combined with esketamine, exhibited a good safety profile and high reliability, was more conducive to stabilizing the hemodynamics, alleviating surgical stress and inflammatory responses, promoting postoperative recovery of elderly surgical patients, and causing relatively mild adverse responses. Eber et al. [18] indicated that the use of esketamine could reduce the dosage of propofol by approximately 20% during the surgery, and

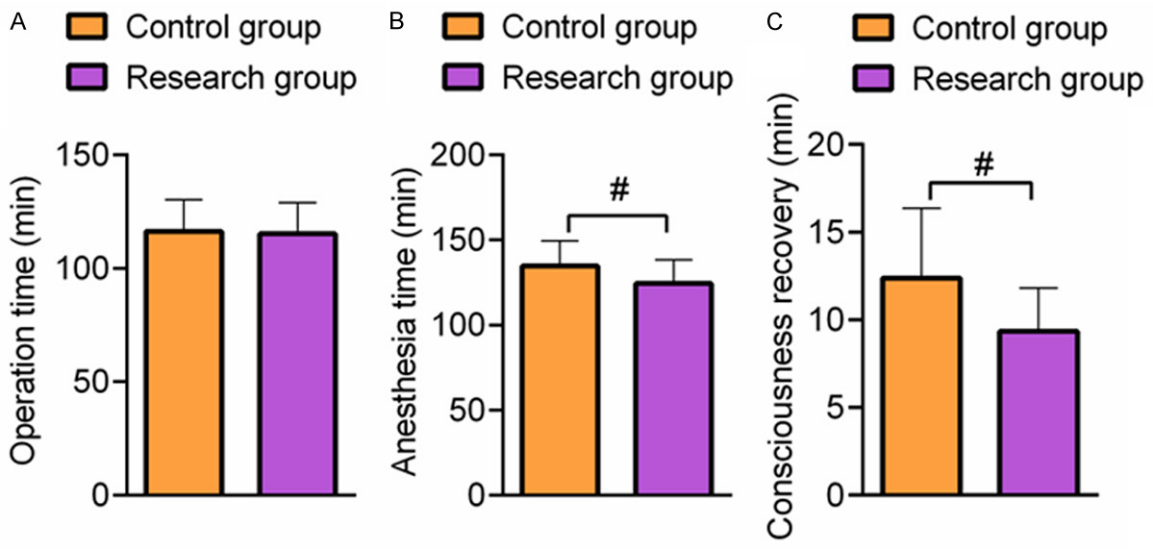

Figure 5. Comparison of perioperative related indices between the two groups. Note: A. Surgical duration; B. Anesthesia time; C. Consciousness recovery time. Compared with the control group, $^{\#}P < 0.05$.

Table 2. Comparison of adverse responses between the two groups [n (%)]

Group	Number of cases	Nausea and vomiting	Respiratory depression	Delayed awakening	Slow heart rate, hypotension and others	Total incidence rate
Control group	49	3 (6.12)	1 (2.40)	0 (0.00)	2 (4.08)	6 (12.24)
Study group	49	2 (4.08)	0 (0.00)	1 (2.04)	1 (2.04)	4 (8.16)

there was no significant difference in adverse drug reactions between the two groups, but the incidence of esketamine-induced hypotension was relatively low, which is consistent with the study results. There was no marked difference in postoperative awakening time between the two groups, which was different from the study results. This may be related to the small sample size in this study.

Esketamine has a high fat solubility. The plasma concentration can peak after the intramuscular injection of esketamine within 5 min. It easily passes through the blood-cerebrospinal fluid barrier, and then rapidly redistributes from the brain to other tissues with abundant blood supply. The fast awakening of patients is mainly related to the results of redistribution and degradation *in vivo* [19, 20]. Esketamine is mainly converted into norketamine by hepatic microsomal enzyme *in vivo*. Norketamine has a pharmacological activity, and its anesthetic potency is equivalent to 1/5-1/3 of that of esketamine, but its elimination half-life is longer. This can be explained by the fact that esketamine still has certain analgesic effects after patients awake from anesthesia [21, 22]. Esketamine has little effect on respiration, and can directly inhibit the myocardium and indirectly excite the cardiovascular system by exciting the sympathetic nervous center. The comprehensive manifestations are increased HR and blood pressure. However, patients with decreased sympathetic nervous activity may experience a decreased blood pressure and myocardial contractility [23]. Blocking N-methyl-D-aspartate (NMDA) receptors mainly inhibits the nociceptive information transmission in spinal dorsal horn, and may also affect the participation of peripheral NMDA receptors in information transmission, thus producing central analgesic effects and exerting analgesic effects [24]. Surgical trauma, stress and other factors lead to the release of massive inflammatory cytokines, the imbalance between anti-inflammatory cells and pro-inflammatory cytokines, and systemic inflammatory responses accompanied by corresponding damage and the generation of oxygen free radicals. Propofol can react with oxygen free radi-

cals to form stable phenoxyl groups, scavenge oxygen free radicals and protect tissues and organs from being damaged by oxygen free radicals [25]. Esketamine has anti-inflammatory and pro-inflammatory effects, and can inhibit the release of inflammatory cells stimulated by oxygen free radicals, reduce the secretion of interleukin, tumor necrosis factor and other cytokines by leucocytes, thus alleviating the inflammatory response. Moreover, propofol combined with esketamine exhibits a high safety profile and leads to relatively low adverse drug reactions. Therefore, it is applicable to elderly patients.

In summary, the anesthetic induction of propofol combined with esketamine can improve hemodynamics and surgical stress and inflammatory responses, shorten anesthesia time, promote the recovery of postoperative cognitive function, and cause relatively mild adverse responses, exhibiting a safety profile and reliability. However, it is worth noting that esketamine has not been extensively adopted in China due to the high-tech and high-risk characteristics of pharmaceutical products. The study has the limitation of a small sample size. Therefore, the scope of application of esketamine awaits further investigation.

Disclosure of conflict of interest

None.

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