ORIGINAL RESEARCH

The Application Value of Esketamine and Dexmedetomidine in Preventing Postoperative Delirium and Hyperalgesia in Elderly Patients with Thoracic Anesthesia

Yongjian Lu, BD; Guangfen Yin, BD; Congcan Jin, BD; Kaipeng Gu, BD; Danni Bao, BD; Wenzhen Xu, BD; Zhenhua Yang, BD

ABSTRACT

Objective • Our aim was to evaluate the application value of esesketamine and dexmedetomidine in preventing postoperative hyperalgesia in elderly patients who received thoracic anesthesia.

Methods • A total of 94 elderly patients who underwent thoracic anesthesia in Sanmen People's Hospital from January 2021 to October 2022 were selected and divided into a dexmedetomidine group (n = 47) and an esketamine group (n = 47) by the random number table method. All patients were continuously received intravenous (IV) remifentanil. In the dexmedetomidine group, dexmedetomidine 0.7 μg/kg was administered IV, followed by 0.2 to 0.5 μg/kg/h to maintain anesthesia, while in the esketamine group, esketamine 0.5 mg/kg was given IV 20 min after induction of anesthesia was completed.

Results • Visual analogue scale (VAS) scores in the esketamine group were lower than in the dexmedetomidine group at 1, 6, 12 and 24 h postoperatively ($P < .05$), and Ramsay sedation scores were not statistically different from those in the dexmedetomidine group ($P > .05$). At 3 d postoperatively, the Mini-Mental State Examination (MMSE) scores in the dexmedetomidine group were lower than 1 d preoperatively; at 5 d postoperatively, the negative mood and Pittsburgh Sleep Quality Index (PSQI) scores were significantly higher in both groups than 1 d preoperatively; at 14 d postoperatively, the PSQI scores were higher in both groups than 1 d preoperatively, and there was no statistical difference between the negative mood scores at 1 d before surgery ($P > .05$). At 5 d postoperatively in the esketamine group, the negative mood scores were lower than in the dexmedetomidine group at 5 d postoperatively and the PSQI scores at 5 and 14 d postoperatively were lower than in the dexmedetomidine group ($P < .05$).

Conclusion • Both esketamine and dexmedetomidine can be used to prevent postoperative delirium and nociceptive hypersensitivity after anesthesia in elderly patients with thoracic surgery. However, esketamine is superior to dexmedetomidine in analgesic effect, improvement of negative mood and sleep and stabilization of intraoperative hemodynamics, leading to better effect in preventing delirium and hyperalgesia after anesthesia. (*Altern Ther Health Med.* [E-pub ahead of print.])

Yongjian Lu, BD; Congcan Jin, BD; Kaipeng Gu, BD; Zhenhua Yang, BD; Department of Anesthesiology; Sanmen People's Hospital; Taizhou, Zhejiang Province, China. **Guangfen Yin, BD,** Department of Anesthesiology; The First Affiliated Hospital of Dali University; Dali, Yunnan, China. **Danni Bao, BD,** Clinical Laboratory; Sanmen People's Hospital; Taizhou, Zhejiang Province, China. **Wenzhen Xu, BD,** Department of Thoracic Surgery; Sanmen People's Hospital; Taizhou, Zhejiang Province, China.

Corresponding author: Zhenhua Yang, BD
E-mail: yzh12582022@163.com

INTRODUCTION

Many elderly people need to undergo thoracic surgery secondary to conditions such as lung cancer and heart disease, while due to the poor physical quality of elderly patients, they have a lower tolerance for the adverse events that occur after anesthesia.[1-3] And because thoracic analgesia is more cardiopulmonary stimulating in patients, it leads to the vulnerability of elderly patients to accidents during and after thoracic surgery.[4] Whereas delirium and hyperpathia are the most common postoperative complications in elderly patients, some studies have suggested that their occurrence may be related to the application of anesthetic drugs.[5-6] Therefore, clinical consensus is exploring the ideal drugs for anesthesia in thoracic medicine in the elderly, hoping that anesthetic drugs can reduce postoperative delirium and hyperpathia.

Dexmedetomidine is an alpha-2-adrenergic receptor agonist with analgesic and dose-dependent sedative effects that is widely used in various fields such as preoperative medication, general anesthesia adjuncts and postoperative analgesia.[7-9] Esketamine is a new type of dextroketamine with

Table 1. Comparison of General Data in the 2 Groups

Group	n	Gender (n%)		Age (χ±s) yrs	BMI ($\bar{x} \pm s$) kg/m^2	ASA Classification			Type of Surgery (n%)		
		Male	Female			Class I	Class II	Class III	Lung	Esophagus	Other
Dexmedetomidine	47	28(59.57)	19(40.43)	69.25±5.21	24.12±2.15	12(25.53)	21(44.68)	14 (29.79)	25 (53.19)	18 (38.30)	4 (8.51)
Esketamine	47	25(53.19)	22(46.81)	70.05±5.13	24.23±2.28	14(29.79)	19 (40.43)	14 (29.79)	23(48.94)	21 (44.68)	3 (6.38)
χ^2/t		0.389		0.750	0.459	0.254			0.457		
P value		.533		.455	.647	.881			.796		

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index.

a higher affinity for opioid micro-receptors and aspartic acid receptors and a stronger affinity for NMDAR, providing stronger analgesic effects compared with conventional ketamine.[10] Both dexmedetomidine and esketamine have been shown to prevent postoperative delirium and hyperpathia, but the advantages and disadvantages of both have not been reported.[11-19]

Therefore, we conducted this study to observe and compare the value of esketamine and dexmedetomidine in the prevention of postoperative delirium and hyperpathia in elderly patients undergoing anesthesia during thoracic surgery.

DATA AND METHODS

General Information

The study was conducted after approval by the medical ethics committee of Sanmen Country People's Hospital in China. A total of 94 elderly patients who underwent thoracic surgery at our hospital between January 2021 and October 2022, and 94 patients were selected according to the inclusion and exclusion criteria.

Inclusion criteria

Patients (1) were age ≥60 years and ≤85 years, of both genders; (2) had a preoperative core body temperature of 36°C to 38°C; (3) were American Society of Anesthesiologists (ASA) classification I to III; (4) had anesthesia duration of ≥120 min; (5) signed an informed consent form.

Exclusion criteria

Patients who had (1) concomitant endocrine system diseases such as hyperthyroidism and hypothyroidism; (2) a history of infectious fever within 4 weeks; (3) uncontrolled insulin-dependent diabetes mellitus (preoperative glucose >15 mmol/L); (4) concomitant visual or hearing impairment; (5) a history of neurological or psychiatric disorders; (6) concomitant cerebrovascular disease, Raynaud's disease or active liver disease; (7) urinary creatinine >177 umol/L; (8) a preoperative MMSE score ≤17; (9) were taking antidepressants or tranquilizers.

As of October 2022, 94 patients who met the inclusion and exclusion criteria were entered into the study and divided into 2 groups by the random number table method. In the dexmedetomidine group, 47 patients were given dexmedetomidine anesthesia; in the esketamine group, 47 patients received esketamine anesthesia. The general data of the patients in the 2 groups were collected; there was no significant difference by statistical analysis and the data were comparable (see Table 1).

Anesthesia Method

After the patient was admitted to the operating room, they were connected to a device that continuously monitored noninvasive blood pressure (NBP), central venous pressure (CVP), cardiac output (CO), cardiac index (CI) and stroke volume (SV), and intravenous (IV) access was established. Fentanyl 3-4 μg/kg, propofol 2 mg/kg and rocuronium 0.6 mg/kg were injected IV for induction of anesthesia. Intraoperative infusion of disoprofol, remifentanil and atracurium was used to maintain anesthesia and keep the bispectral index (BIS) between 40 and 60. In the dexmedetomidine group, dexmedetomidine 0.7 μg/kg was first administered IV for >10 min after induction of anesthesia was completed, and then anesthesia was maintained at 0.2 to 0.5 μg/(kg-h). In the esketamine group, esketamine 0.5 mg/kg was administered IV for 20 min after the completion of anesthesia induction.

Scoring Criteria

Ramsay Sedation Scale (RSS) score: range 1-5, with 1 indicating restlessness; 2 wakefulness and quiet cooperation; 3 drowsiness but responsiveness; 4 light sleep with rapid arousal; 5 sleepiness and unresponsiveness to calls; and 6 deep sleep with no response to calls.[20]

The **Self-rating Anxiety Scale** (SAS) and **Self-Rating Depression Scale** (SDS) were used to evaluate negative emotions.[21] SAS scores for severe anxiety were ≥75, moderate anxiety 61-74 and mild anxiety 50-60. SDS scores for severe depression were >73, moderate depression 62-73 and mild depression 52-61.

Patients' cough pain and resting pain were assessed by **visual analogue scale** (VAS) score ranging from 0 to 10, with higher scores indicating more pain.[22]

The **Pittsburgh Sleep Quality Index** (PSQI) was used to evaluate the patients' sleep; it is comprised of aspects such as daytime dysfunction, sleep time and time to fall asleep, with a total score of 21. If the patient scores more than 8, it indicates a sleep disorder.[23]

The **MMSE** was used to score the patient's cognitive function, and contains aspects such as language, delayed memory, immediate memory and temporal orientation, with a total score of 30, with <10 representing severe cognitive dysfunction, 10-21 moderate dysfunction, 22-27 mild dysfunction and >28 normal cognitive function.[24]

To compare the incidence of delirium in the 2 groups, patients were assessed with the Confusion Assessment Method (CAM), which comprises 4 symptoms: (1) altered level of consciousness; (2) inattentive state; (3) acute alteration

Table 2. Comparison of Ramsay Sedation and Visual Analogue Scale Scores in the 2 groups [($\bar{x} \pm s$) Minute]

Group	n	Ramsay Sedation Scale Score				Visual Analogue Scale Score			
		1h post- surgery	6h post- surgery	12h post- surgery	24h post- surgery	1h post- surgery	6h post- surgery	12h post- surgery	24h post- surgery
Dexmedetomidine	47	1.87±0.68	2.57±0.71	2.44±0.73	2.02±0.41	2.11±0.35	2.74±0.57	3.25±0.45	3.03±0.37
Esketamine	47	1.96±0.64	2.46±0.69	2.41±0.65	1.93±0.34	1.89±0.34	2.44±0.51	2.87±0.49	2.54±0.41
t		0.661	0.762	0.210	1.158	3.091	2.689	3.916	6.083
P value		.510	.448	.834	.250	.003	.009	.000	.000

Table 3. Comparison of Negative Emotion, PSQI and MMSE Scores in the 2 Groups [($\bar{x} \pm s$), Minute]

Group	n	MMSE Score			SDS Score		
		1 d pre- surgery	3 d post- surgery	5 d post- surgery	1 d pre- surgery	5 d post- surgery	14 d post- surgery
Dexmedetomidine	47	26.98±2.57	25.85±2.66[a]	26.37±2.44	51.74±4.03	54.85±4.74[a]	50.33±3.82
Esketamine	47	27.03±2.44	26.23±2.47	26.96±2.31	50.02±4.79	52.11±4.03[a]	49.14±3.77
t		0.097	0.718	1.204	1.884	3.019	1.520
P value		.923	.475	.232	.063	.003	.132

Group	n	SAS Score			PSQI Score		
		1 d pre- surgery	5 d after surgery	14 d after surgery	1 d pre- surgery	5 d post- surgery	14 d post-surgery
Dexmedetomidine	47	46.89±3.47	52.36±4.15[a]	45.81±3.27	2.23±0.51	7.44±1.78[a]	5.15±1.33[a]
Esketamine	47	47.36±3.22	50.54±3.91[a]	46.09±3.44	2.19±0.65	5.23±1.33[a]	4.28±1.29[a]
t		0.681	2.188	1.848	0.332	6.819	3.219
P value		.498	.031	.068	.741	.000	.002

[a]Compared with the preoperative 1 d; $P < .05$.

Abbreviations: MMSE, Mini-Mental State Examination; PSQI, Pittsburgh Sleep Quality Index; SAS, Self-rating Anxiety Scale; SDS, Self-Rating Depression Scale.

of the state of consciousness, which is seen as repeated abnormal fluctuations; and (4) disorganized thinking. The diagnosis can be confirmed if the patient meets the criteria for the first and second symptoms along with either the third or fourth symptom.[25]

Detection Method

A total of 5 ml of venous blood was collected before induction of anesthesia (T0), 30 min after the beginning of surgery (T1), at the end of surgery (T2), and 2h after surgery (T3), and the levels of angiotensin-II (AT-II) and cortisol (CORT) were measured by radioimmunoassay.

Adverse Events

Adverse events in both groups, such as arrhythmia, hypotension, hypertension, nausea, vomiting, fever, hypoxia, dizziness, sweating, chills, respiratory depression, etc. were recorded.

Statistical Analysis

The data were processed with IBM SPSS 19.0 software, and the Kolmogorov-Smirnov (K-S) method was used to test the normality of the measurement data such as MMSE score and hemodynamics, and ($\bar{x} \pm s$) was applied to describe the measurement data conforming to normal distribution, the *t* test was applied for comparison and the count data such as the type of surgery and adverse events were described by the number of patients (%), and the χ^2 test using the 4-compartment table method or row list was used for comparison; $P < .05$ was considered statistically significant.

RESULTS

Comparison of Ramsay Sedation and VAS Scores in the 2 Groups

Visual analogue scale (VAS) scores in the esketamine group were lower than in the dexmedetomidine group at 1, 6, 12 and 24h postoperatively, and RSS were not statistically different from those in the dexmedetomidine group ($P > .05$) (see Table 2).

Comparison of Negative Emotion, PSQI and MMSE Scores in the 2 Groups

At 1 d preoperatively, there was no statistical difference between the SAS, SDS, PSQI or MMSE scores in the 2 groups ($P > .05$). At 3 d postoperatively, the MMSE score in the dexmedetomidine group was lower than 1 d preoperatively ($P < .05$), but there was no statistical difference compared with the esketamine group ($P > .05$). At 5 d postoperatively, the negative emotion and PSQI scores in the 2 groups were significantly higher than at 1 d preoperatively. At 14 d postoperatively, the PSQI scores were higher than the preoperative 1 d scores in both groups. And for the negative emotion scores, there was no statistical difference between that of 14 d postoperatively and the preoperative 1 d ($P > .05$); the negative emotion scores in the esketamine group were lower than in the dexmedetomidine group at 5 d postoperatively, and the PSQI scores were lower in the dexmedetomidine group at 5 d and 14 d postoperatively ($P < .05$) (see Table 3).

Hemodynamic Comparison Between the 2 Groups

At T0, there was no statistical difference in hemodynamics between the 2 groups ($P > .05$); at T1, mean arterial pressure (MAP), CVP, CO, CI and SV were higher in the 2 groups than at T0 ($P < .05$), and there was no statistical difference in heart rate (HR) compared with at T0 ($P > .05$); at T2, CO, CI, SV and MAP and CVP were higher in the 2 groups than at T0 in the dexmedetomidine group ($P < .05$) and HR compared with at T0 showed no statistical difference ($P > .05$); at T3, there was no statistical difference in hemodynamics between the 2 groups compared with at T0 ($P > .05$); CO, CI and SV in the esketamine group at T1 and T2 were lower than in the dexmedetomidine group, and there was a statistical difference ($P < .05$) (see Table 4).

Table 4. Comparison of Hemodynamics in the 2 Groups

Group	n	MAP (mmHg)				CVP (cmH_2O)				HR (beats/min)			
		T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
Dexmedetomidine	47	78.59±6.77	83.56±7.45[a]	82.14±7.66[a]	77.78±6.91	4.68±0.54	7.85±1.23[a]	5.11±0.87[a]	4.75±0.72	70.58±8.41	72.23±9.05	71.44±10.13	73.65±8.94
Esketamine	47	79.05±7.12	82.14±6.89[a]	81.64±7.13	78.25±7.84	4.71±0.49	7.74±1.33[a]	4.98±0.89	4.59±0.69	72.03±7.97	71.45±8.25	73.01±8.44	72.56±9.47
t		0.321	0.959	0.328	0.308	0.282	0.416	0.716	1.100	0.858	0.437	0.816	0.574
P value		0.749	0.340	0.744	0.759	0.779	0.678	0.476	0.274	0.393	0.663	0.416	0.568
Group	n	CO(L/min)				CI (L/min•m^2)				SV (mL)			
		T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
Dexmedetomidine group	47	4.31±0.57	5.47±0.63[a]	5.67±0.55[a]	4.28±0.63	2.24±0.31	3.21±0.35[a]	3.88±0.37[a]	2.32±0.29	54.21±7.85	63.44±6.97[a]	71.25±6.89[a]	56.11±8.10
Esketamine group	47	4.25±0.63	5.06±0.54[a]	5.21±0.61[a]	4.19±0.57	2.19±0.34	2.92±0.36[a]	3.42±0.32[a]	2.31±0.31	52.98±8.73	57.36±7.36[a]	65.25±7.02[a]	54.78±7.84
t		0.484	3.388	3.840	0.726	0.745	3.960	6.447	0.161	0.718	4.112	4.182	0.809
P value		0.629	0.001	0.000	0.470	0.458	0.000	0.000	0.872	0.474	0.000	0.000	0.421

[a]Compared with T0, $P < .05$

Abbreviations: CI cardiac index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MAP, mean arterial pressure; SV stroke volume; T0, before induction of anesthesia; T1, 30 min after surgery; T2, at the end of surgery; T3, 2 h post-surgery

Table 5. Comparison of Angiotensin-II and Cortisol in the 2 Groups ($\bar{x} \pm s$)

Group	n	AT-II (ng/L)				CORT (n mol/L)			
		T0	T1	T2	T3	T0	T1	T2	T3
Dexmedetomidine	47	70.56±4.15	64.22±5.47[a]	60.89±4.52[a]	53.56±3.23[a]	405.25±81.66	445.36±84.55[a]	459.25±68.66[a]	472.56±88.52[a]
Esketamine	47	71.96±4.28	65.45±4.33[a]	59.16±4.04[a]	52.63±3.77[a]	411.06±76.45	435.96±76.18	448.22±73.62[a]	459.32±71.04[a]
t		1.610	1.209	1.956	1.284	0.356	0.566	0.751	0.800
P value		.111	.230	.053	.202	.723	.573	.454	.426

[a]Compared with T0; $P < .05$

Abbreviations: AT-II, angiotensin II; CORT, cortisol; T0, before induction of anesthesia; T1, 30 min after surgery; T2, at the end of surgery; T3, 2 h post-surgery

Table 6. Comparison of Time to Eye-opening and Incidence of Postoperative Delirium in the 2 Groups

Group	n	Time to eye-opening [(±s), min] $\bar{x}$	Delirium incidence [n (%)]
Dexmedetomidine	47	5.69±0.84	9(19.15)
Esketamine	47	5.12±0.67	2(4.26)
t		3.637	5.045
P value		.000	.025

Table 7. Comparison of Adverse Events in the 2 Groups [n (%)]

Group	n	Low blood pressure	Feeling sick and vomiting	Respiratory depression	Dizziness	Cumulative adverse events
Dexmedetomidine	47	1 (2.13)	3 (6.38)	1 (2.13)	1 (2.13)	6 (12.77)
Esketamine	47	0 (0.00)	2 (4.26)	1 (2.13)	1 (2.13)	4 (8.51)
χ^2						0.448
P value						.503

Comparison of AT and CORT in the 2 Groups

At T0, there was no statistical difference in AT-II or CORT between the 2 groups ($P > .05$); at T1, T2 and T3, AT-II was lower than at T0 in both groups, while CORT was higher than at T0 in both groups ($P < .05$); there was no statistical difference in AT-II or CORT between the 2 groups at T1, T2 and T3 ($P > .05$) (see Table 5).

Comparison of Time to Eye-opening and Incidence of Postoperative Delusion in the 2 Groups

The time to eye-opening in the esketamine group was 5.12±0.67 min, which was shorter than in the dexmedetomidine group (5.69±0.84 min), and the incidence of postoperative delirium was 4.26% (2/47), which is significantly lower than in the dexmedetomidine group (19.15% (9/47), with statistically significant differences ($P < .05$) (see Table 6).

Comparison of Adverse Events in the 2 Groups

The cumulative incidence of adverse events in the esketamine group was 8.51% (4/47 patients) compared with 12.77% (6/47 patients) in the dexmedetomidine group, and there was no statistical difference ($P > .05$) (see Table 7).

DISCUSSION

Delirium is a common complication after general anesthesia, and its occurrence is mainly related to the use of inhaled anesthetics isoflurane, opioids and anticholinergics.[26] Postoperative delirium after general anesthesia occurs mostly in the elderly, and the possible reasons for this are the decreased tolerance of the elderly to surgery, anesthesia and drugs, and the direct or indirect effects of surgical stimulation, anemia, postoperative water-electrolyte disturbances and hypoxia on cerebral blood circulation and metabolism.[27] In addition, the reduced psychological tolerance of elderly patients, preoperative and postoperative concerns about the disease, anxiety, boredom and depression may cause postoperative delirium.[28-29] Hyperpathia is also a common complication after general anesthesia and is mainly associated with prolonged and high-dose use of opioids and rapid changes in blood levels, which can cause hyperpathia by activating the anti-NMDAR, thereby increasing neuronal excitability and sensitizing the pain center.[30]

Dexmedetomidine is an alpha-2-adrenergic receptor agonist that can effectively reduce hyperpathia by decreasing spinal NMDAR activity.[7-9] In contrast, its sedation does not affect respiration or easily lead to cerebral hypoxia and has low affinity for gamma-aminobutyric acid receptors and therefore is less likely to cause postoperative delirium. In addition, it has an inhibitory effect on the stress response and cholinergic effects that contribute to the prevention of postoperative delirium.[12-14] Esketamine is a non-competitive antagonist of NMDAR and attenuates opioid-induced

nociceptive hypersensitivity by inhibiting NMDAR activation. It has also been shown that esketamine has a preventive effect on postoperative delirium after general anesthesia, but its clinical use is still limited.[15-19] Therefore, this study compared the value of esketamine and dexmedetomidine in preventing postoperative delirium and hyperpathia in elderly patients with thoracic anesthesia.

The results showed that the VAS scores in the esketamine group at 1, 6, 12 and 24h postoperatively were lower than in the dexmedetomidine group, and the SAS and SDS scores at 5 d postoperatively and the PSQI scores at 5 d and 14 d postoperatively were lower than in the dexmedetomidine group, while the Ramsay and MMSE scores at each postoperative time point were not statistically different in the 2 groups. The result indicates that esketamine has a stronger postoperative analgesic effect than dexmedetomidine and improves patients' negative mood and sleep more than dexmedetomidine; however, there was no significant difference in the intensity of postoperative sedative effect and the effect on patients' cognitive function.

The comparative results of postoperative hemodynamics in the 2 groups showed that the mean platelet volume (MVP), CVP, HR, CO, CI and SV in both groups increased first and then decreased, and there was no statistical difference between the hemodynamic indices at T3 and T0, suggesting that the hemodynamics in both groups could recover to the preoperative level at 2 h after surgery. However, the CO, CI and SV at T1 and T2 in the esketamine group were lower than in the dexmedetomidine group and were closer to the level at T0, suggesting that the intraoperative hemodynamic fluctuations in the esketamine group were less than those in the dexmedetomidine group. These results indicate that both esketamine- and dexmedetomidine-assisted anesthesia are more hemodynamically stable, and esketamine is slightly better than dexmedetomidine in stabilizing intraoperative hemodynamics.

There was no statistical difference between the 2 groups in terms of AT-II and CORT at each time point. Both AT-II and CORT are indicators of the degree of stress in the body, so the result indicates that the inhibitory effects of esketamine and dexmedetomidine on the stress response were comparable. In the esketamine group, the time to eye-opening was shorter than in the dexmedetomidine group, and the incidence of postoperative delirium was lower than in the dexmedetomidine group, indicating that esketamine is more effective than dexmedetomidine in preventing postoperative delirium after general anesthesia in elderly patients with thoracic anesthesia. The incidence of adverse events in the 2 groups was not statistically different, indicating that the safety of esketamine and dexmedetomidine for adjunctive general anesthesia is similar.

Study Limitations

This study comprehensively compared the anesthesia effects of esketamine and dexmedetomidine used in thoracic surgery from the perspectives of sedative and analgesic effects, hemodynamics, emotions, cognition, sleep, stress reactions, delirium and adverse events, and the results could provide a valuable reference for clinical selection of anesthesia plans. However, the sample size of this study was limited, thus the results need to be confirmed by further studies.

CONCLUSION

In conclusion, both esketamine and dexmedetomidine can be used to prevent postoperative delirium and nociceptive hypersensitivity after anesthesia in elderly patients with thoracic surgery. However, esketamine is superior to dexmedetomidine in analgesic effect, improvement of negative mood and sleep and stabilization of intraoperative hemodynamics, leading to better effect in preventing delirium and hyperalgesia after anesthesia.

CONFLICT OF INTEREST

There is no conflict of interest.

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