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Effects of Esketamine Combined with Dexmedetomidine on Early Postoperative Cognitive Function in Elderly Patients Undergoing Lumbar Spinal Surgery: A Double-Blind Randomized Controlled Clinical Trial

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Background: Postoperative cognitive dysfunction (POCD) is a common complication after surgery in elderly patients, and its prevalence can be up to 25.6% at one week after noncardiac surgery. This study mainly evaluates the combined effects of esketamine and dexmedetomidine on the incidence of POCD in elderly patients undergoing lumbar spine surgery and explores the underlying mechanisms.

Methods: A total of 162 elderly patients undergoing lumbar spine surgery were randomized into three groups: esketamine combined with dexmedetomidine group (ED group), esketamine group (E group), and dexmedetomidine group (D group). Primary outcome measures included the incidence of POCD on the first postoperative day. Secondary outcomes included the incidence of POCD on the third postoperative day, first postoperative day serum levels of neuron-specific enolase (NSE) and calcium-binding protein β (S100β), patient visual analog scale (VAS) scores at 2, 24, and 48 hours postoperatively, and the incidence of adverse events.

Results: The incidence of POCD on the first postoperative day was significantly lower in the ED group compared to the E group (P = 0.017), with no significant differences when compared to the D group (P = 0.064). The levels of serum NSE in patients in the ED group on the first postoperative day were significantly lower than those in E group and D group (ED group vs E group, P = 0.028; ED group vs D group, P = 0.048). The results for the S100β were similar to those for the NSE (ED group vs E group, P = 0.005; ED group vs D group, P = 0.011).

Conclusion: The combination of esketamine and dexmedetomidine effectively reduces the incidence of POCD on the first postoperative day in elderly patients undergoing lumbar spine surgery.

Keywords: esketamine, dexmedetomidine, postoperative cognitive dysfunction, neuroinflammatory

Introduction

POCD is a common perioperative neurological complication that occurs after surgery in elderly patients and is characterized by a decline in cognitive function compared to preoperative cognitive function.[1] Unlike postoperative delirium (POD), which is characterized by disturbance in attention and awareness, emotion, cognition, and fluctuating

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severity of consciousness, POCD is primarily characterized by cognitive deficits, including impaired memory, perceptual functions, language, and task-assembly abilities.[2] Studies have shown that in elderly patients undergoing noncardiac surgery, the incidence of POCD was 25.6% at one week postoperatively and 9.9% at three months postoperatively.[3] More critically, POCD not only affects the recovery of patients, increases the economic burden of patients, but also may lead to the increase of patient mortality.[4,5] Consequently, developing effective strategies to mitigate POCD is an urgent and significant challenge. Numerous studies have identified older age and general anesthesia as major risk factors for POCD.[6,7]

Current research about esketamine primarily focuses on its nasal spray use in treatment-resistant depression,[8,9] it is frequently utilized in specific anesthesia scenarios due to its higher bioavailability, rapid metabolism, potent analgesic properties, and fewer adverse effects compared to ketamine.[10] In the context of general anesthesia, esketamine has been shown to reduce opioid consumption, maintain hemodynamic stability, and decrease patient stress and postoperative pain.[11–13] A previous clinical study highlighted the neuroprotective effects of subanesthetic doses of esketamine in elderly patients.[14] Moreover, basic research indicates that esketamine may exert an anti-inflammatory effect within the central nervous system, thereby improving postoperative cognitive function in rodents.[15,16] Additionally, unlike other anesthetic sedatives, esketamine increases blood pressure and heart rate.[17]

Dexmedetomidine possesses sedative, analgesic, anti-inflammatory, and anxiolytic properties.[18,19] Its perioperative use has been associated with a reduction in the inflammatory response and potential alleviation of POCD in patients.[20,21] A meta-analysis by Zeng et al identified dexmedetomidine as the anesthetic most likely to reduce the incidence of POCD.[22] However, its administration may lead to significant occurrences of bradycardia and hypotension, as indicated by previous studies.[23,24]

Lumbar spine surgery, commonly performed on older adults, addresses conditions such as lumbar disc herniation and lumbar spine slippage. Studies have shown that the incidence of POCD following spinal surgery can be as high as 43%.[25] We therefore selected elderly patients undergoing lumbar surgery hypothesized that the combination of esketamine with dexmedetomidine could reduce the incidence of POCD in these patients attribute to its anti-inflammatory effect.

Methods

Ethical Considerations

This study was approved by the Institutional Research Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (Approval No. 2022-92, dated June 08, 2022) and was registered with the Chinese Clinical Trial Registry (ChiCTR2200062599). All participants enrolled in the study provided written informed consent before inclusion and conducted in accordance with the Declaration of Helsinki.

Participants

As shown in Figure 1, 162 patients (at least 60 years old) having American Society of Anesthesiologists (ASA) class I to III undergoing elective lumbar spine surgery under general anesthesia at the Third Affiliated Hospital of Anhui Medical University were enrolled from August 17, 2022, to August 8, 2023. Exclusion criteria were 1) a body mass index (BMI) $\geq$ 30 kg/m^2; 2) resting heart rate < 50 bpm; 3) Mini-Mental State Examination (MMSE) scores below 17 for illiterate patients, below 20 for those with elementary education, and below 22 for those with secondary education or higher; 4) presence of severe cardiovascular, pulmonary, renal, or hepatic diseases; 5) history of neuropsychiatric illness or severe brain trauma; 6) known intolerance or allergy to esketamine or dexmedetomidine; 7) transfer to intensive care unit after surgery; 8) or refusal to sign informed consent.

Randomization and Blinding

Before the study began, a researcher not involved in other parts of the study used a random number table generated by Microsoft Excel to assign patients to esketamine group (E group), dexmedetomidine group (D group), or the combination of esketamine and dexmedetomidine group (ED group) on a 1:1:1 ratio. Randomization results are sealed in sequentially numbered opaque envelopes. After confirming that the participants were qualified, the anesthesiologist assistant opened

the envelopes in turn, formulated the intervention medication according to the instructions in the envelope and delivered the medication to an experienced anesthesiologist. This experienced anesthesiologist is not aware of patient grouping and is responsible for the completion of patient anesthesia and intraoperative data collection. The patient's cognitive function was assessed by another anesthesiologist who was not involved in the anesthesia process and did not know the grouping. In addition, patients and researchers who performed statistical analysis of the data were blinded.

Anesthesia Protocol

Anesthesia induction and monitoring were performed by the same senior anesthesiologist for all patients. Upon admission to the operating room, routine measurements were recorded. Patients were administered sodium lactate Ringer's solution intravenously and received oxygen via a mask. For induction of anesthesia, patients in the D and ED groups received 0.4 μg/kg dexmedetomidine intravenously, while the E group received an equivalent volume of saline. The induction of anesthesia was processed with etomidate, sufentanil, and cis-atracurium. Following 3 minutes of assisted ventilation, 5 mL of a surface anesthetic mixture was applied to the tracheal mucosa using a disposable laryngopharyngeal mucosal atomizer. The mixture for the ED and D groups contained 0.6 μg/kg dexmedetomidine and 40 mg of 1% ropivacaine diluted to 5 mL, whereas the E group received only the ropivacaine solution. Patients were intubated after ventilation maintained for 2 minutes. Anesthesia was sustained with propofol and remifentanil, supplemented with 1% sevoflurane and intermittent cis-atracurium. Patients in ED group and E group were injected intravenously with 0.5 mg/kg of esketamine after completion of tracheal intubation, and the D group were injected with equal amounts of saline. The depth of anesthesia was regulated to maintain BIS values (40–60). Vasoactive agents were used to keep intraoperative blood pressure fluctuations within 20% of baseline levels. If heart rates dropped below 50 bpm, 0.25 mg of atropine was administered intravenously and noted as an adverse event. Sevoflurane was discontinued 20 minutes before surgery ended, and propofol and remifentanil ceased after skin suturing completion. Ondansetron (4 mg) was administered intravenously to prevent postoperative nausea and vomiting (PONV). Extubation was performed upon confirmation of recovery of consciousness (ROC), defined by responsiveness to verbal commands and adequate spontaneous breathing in Post-Anesthesia Care Unit (PACU).[26] Patients with a Steward Awakening Score above 4 were then transferred to the ward. A patient-controlled intravenous analgesia (PCIA) composed of flurbiprofen axetil (150 mg), sufentanil (2 $\mu g \cdot kg^{-1}$), and dexamethasone (10 mg) in 100 mL of 0.9% saline was used for postoperative pain management.

Primary and Secondary Outcomes

The primary outcome of this study was the incidence of POCD on the first day after surgery. Cognitive function was assessed on the preoperative day (D0), the first postoperative day (D1), and the third postoperative day (D3), using Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). These assessments were conducted by the same trained anesthesiologist. POCD was diagnosed if the postoperative scores decreased by ≥1 standard deviation from the patient's preoperative scores for each test.[27]

Secondary outcomes included the serum levels of neuron-specific enolase (NSE) and S100β. After cognitive assessment at D0 and D1, 5 mL of venous blood was withdrawn from each patient, left at room temperature for 20 minutes, and then centrifuged at 1000 rpm for 20 minutes before the separated serum was stored at −80°C and serum levels were assayed using an enzyme-linked immunosorbent assay (ELISA). The hemodynamic of mean arterial pressure (MAP) and heart rate (HR) were recorded at six time points: preoperatively (T0), at tracheal intubation (T1), 10 minutes post-intubation (T2), at skin incision (T3), one hour into the surgery (T4), and the endotracheal tube removed (T5). Pain levels were assessed using the Visual Analog Scale (VAS) at 2, 24, and 48 hours postoperatively. Awakening time, defined as the duration from cessation of propofol and remifentanil until the patient's eyes opened, was also recorded. Additionally, perioperative anesthesia-related adverse events such as bradycardia, annoyance, PONV and nightmares were documented.

Statistical Analysis

Sample size was calculated based on the incidence of POCD on the first postoperative day observed in preliminary trials, assuming incidences of 5%, 15%, and 30% for groups ED, E, and D, respectively. Using PASS 15.0 software, we calculated that 144 patients would provide 85% power at a 0.05 two-sided significance level. To accommodate a potential 10% loss to follow-up, the sample was increased to 160 patients, distributed equally across the three groups. Finally, 54 patients were included in each group in the study.

Data were analyzed using SPSS 25.0 (IBM). Shapiro–Wilk test was used to assess for the normal distribution. Normally distributed continuous data and non-normally distributed data were presented as mean ± standard deviation and median (interquartile range), respectively. Categorical data were expressed as frequencies and percentages. One-way ANOVA was utilized for normally distributed continuous data, such as age and body mass index, followed by pairwise comparisons with Bonferroni correction. The Kruskal–Wallis rank sum test was employed for non-normally distributed data including the duration of surgery and anesthesia, estimated blood loss, estimated urine volume. The VAS pain scores and awakening time. Categorical data comparisons were performed using the χ^2 test. The repeated-measures data, including the MMSE and MoCA scores, serum marker concentrations, MAP and HR between the three groups, were evaluated by mixed-effects models followed by a post hoc analysis with Bonferroni correction. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

A total of 185 patients were recruited but 23 were excluded among them. Of the remaining 162 patients (3 patients were lost to follow-up), 159 completed the study. Postoperatively, 1 patient each from the D and ED groups was transferred to the ICU, and 1 patient in the E group withdrew consent (Figure 1). The general demographic characteristics or surgical details among the three groups were similar (Table 1).

The incidence of POCD on the first postoperative day was significantly lower in the ED group compared to the E group, but not differ statistically from the D group (11.3% vs 32.1% vs 24.5%, $P < 0.05$, Figure 2). On the third postoperative day, the differences in POCD incidence among the groups were not significant (9.4% vs 18.9% vs 15.1%,

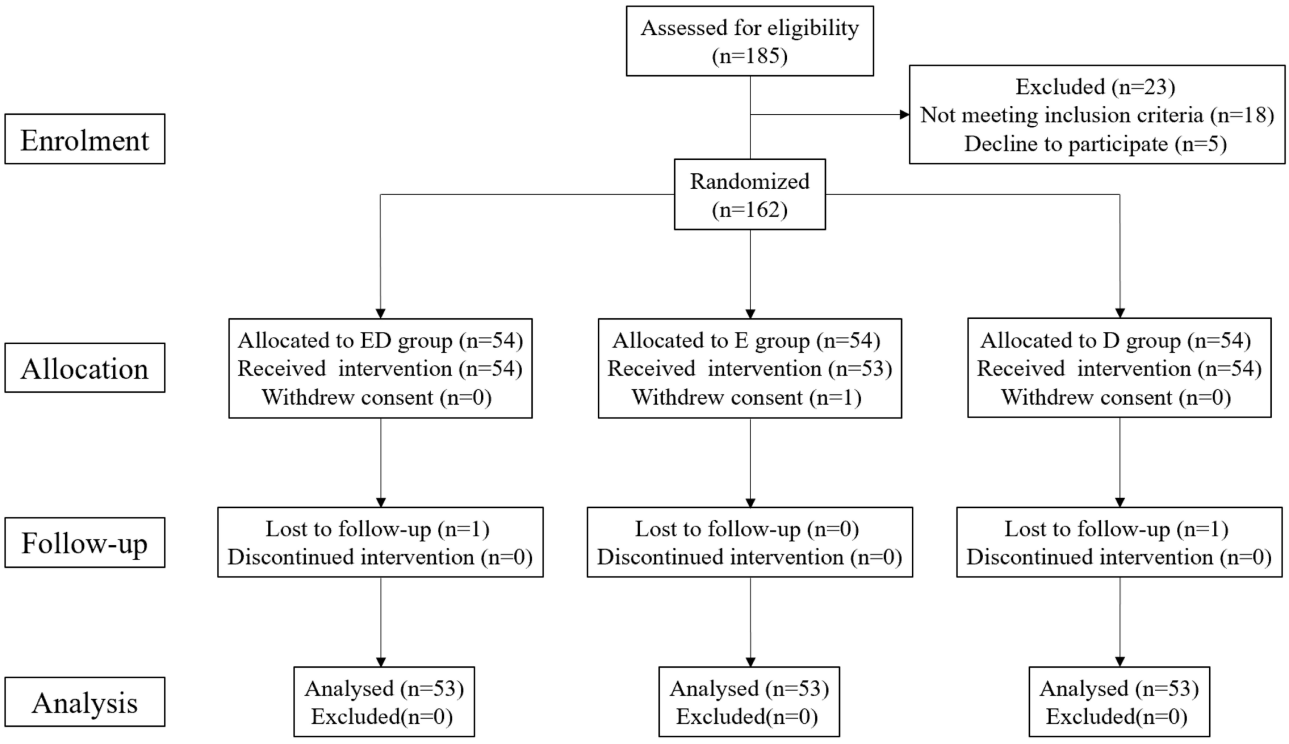

Figure 1 CONSORT diagram of study.

Table 1 Basic Characteristics

Characteristic	ED Group (n=53)	E Group (n=53)	D Group (n=53)	*P* value
Age (years)	71.9 (7.7)	71.6 (7.2)	72.2 (6.2)	0.907
Sex (male/female)	20/33	21/32	20/33	0.974
Body mass index (kg/m^2)	23.8 (3.3)	23.8 (3.2)	23.6 (3.2)	0.970
Degree of education, n (%)				
Illiteracy	16 (30.2)	16 (30.2)	14 (26.4)	0.821
Primary school education	21 (39.6)	23 (43.4)	27 (50.9)	0.821
Secondary school education or above	16 (30.2)	14 (26.4)	12(22.6)	0.821
ASA class II/III	48/5	47/6	43/10	0.316
Duration of surgery (min)	145.0 (120.5–190.5)	140.0 (108.5–174.5)	132.0 (110.5–172.5)	0.505
Duration of anesthesia (min)	180.0 (150.0–224.0)	174.0 (143.5–210.0)	167.0 (148.5–212.5)	0.662
Estimated blood loss (mL)	200.0 (100.0–200.0)	150.0 (100.0–285.0)	150.0 (100.0–200.0)	0.597
Estimated urine volume (mL)	400.0 (200.0–500.0)	300.0 (200.0–700.0)	300.0 (100.0–500.0)	0.866
Surgical method, n (%)				
TLIF	48 (90.6)	44 (83.0)	49 (92.5)	0.563
Mis-TLIF	4 (7.5)	8 (15.1)	3 (5.7)	0.563
Spinal Endoscopic surgery	1 (1.9)	1 (1.9)	1 (1.9)	0.563
Preoperative comorbidities, n (%)				
Hypertension	19 (35.8)	20 (37.7)	19 (35.8)	0.973
Diabetes	12 (22.6)	11 (20.8)	14 (26.4)	0.781
Coronary artery disease	6 (11.3)	5 (9.4)	4 (7.5)	0.802
Previous stoke	5 (9.4)	5 (9.4)	7 (13.2)	0.768
COPD	4 (7.5)	3 (5.7)	5 (9.4)	0.761

Notes: Data are expressed as mean (SD), median (25th to 75th percentiles), or number of patients (%).
Abbreviations: ASA, American Society of Anesthesiologists; TLIF, Transforaminal lumbar interbody fusion; Mis-TLIF, Minimally invasive transforaminal lumbar interbody fusion; COPD, chronic obstructive pulmonary disease.

$P > 0.05$, Figure 2). Preoperative (D0) MMSE and MoCA scores showed no statistical differences across these groups ($P > 0.05$, Table 2). And no significant differences were observed in MMSE scores among the groups on the first (D1) and third (D3) postoperative days ($P > 0.05$, Table 2). However, MoCA scores were significantly lower in the E group compared to the ED group on the first and third postoperative day (D1 and D3), ($P < 0.05$, Table 2), whereas scores for the D group did not significantly differ from those in the ED group ($P > 0.05$, Table 2). The analysis of MMSE

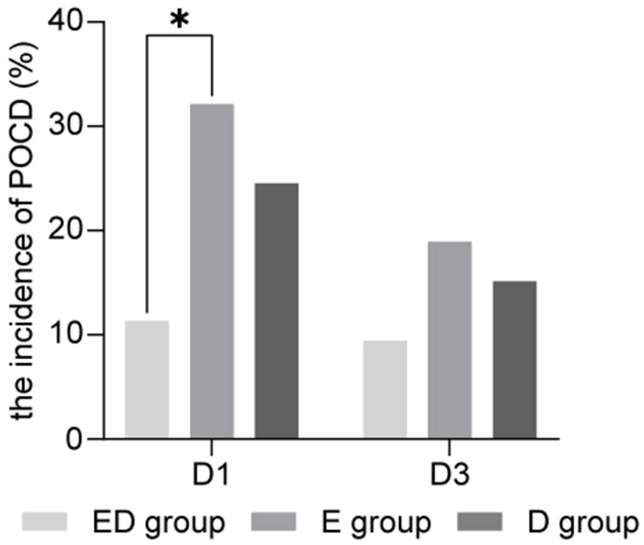

Figure 2 Changes in the incidence of POCD during perioperative. D1 the first postoperative day. D3 the third postoperative day. *$P < 0.05$ compared to the ED group.

Table 2 The MMSE and MoCA Scores at Different Time Points

	Time	ED Group (n=53)	E Group (n=53)	D Group (n=53)	*P* value		
					ED vs E	ED vs D	E vs D
MMSE	D0	24.23 (1.93)	24.19 (1.82)	24.19 (2.02)	> 0.999	> 0.999	> 0.999
	D1	23.42 (2.02)	22.72 (2.06)	23.09 (2.39)	0.243	> 0.999	> 0.999
	D3	23.09 (2.19)	22.62 (2.05)	22.91 (2.21)	0.713	> 0.999	> 0.999
MoCA	D0	23.58 (1.78)	23.36 (2.14)	23.49 (2.12)	> 0.999	> 0.999	> 0.999
	D1	22.23 (1.97)	20.87 (2.13)[a]	21.49 (2.33)	0.002	0.198	0.359
	D3	22.15 (1.89)	21.02 (2.14)[a]	21.55 (2.15)	0.015	0.393	0.558

Notes: [a]*P* versus ED group, $P < 0.05$. Data are expressed as mean (SD).
Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

subdomain showed that the scores of ED group and D group were significantly higher than those of E group in memory subdomain on the first day after surgery ($P < 0.05$). In the subdomain of delayed recall, the score of ED group was significantly higher than that of D and E group on the first day after surgery, and ED group was higher than that of D group on the third day after surgery ($P < 0.05$) (Supplementary Table 1). Similarly, the analysis of various subdomains of MoCA showed that the attention and delayed recall scores of patients in ED group and D group were significantly higher than those in E group on the first and third day after surgery ($P < 0.05$, Supplementary Table 2).

Initially, blood samples were intended for collection from all enrolled patients at D0 and D1. However, due to hemolysis in some samples and some patients' refusing, viable samples were ultimately obtained from 30, 29 and 31 patients in ED, E and D group. ELISA results indicated no significant differences between groups in serum levels of NSE or S100β at D0 ($P > 0.05$). On D1, serum NSE levels in the ED group were significantly lower than those in the E and D groups ($P < 0.05$). The S100β results on D1 were consistent with those of NSE ($P < 0.05$) (Figure 3).

Postoperatively, VAS scores at 2 and 24 hours were significantly lower in the ED group compared to the E and D groups ($P < 0.05$). No significant differences were observed in VAS scores at 48 hours postoperatively among these groups ($P > 0.05$) (Table 3).

MAP in the E group was significantly higher than those in ED and D groups at tracheal intubation, but it in the D group was significantly lower than those in ED and E groups at 10 minutes post-intubation ($P < 0.05$). In addition, HR in the E group was significantly higher than those in ED and D groups from tracheal intubation completed to the endotracheal tube removed ($P < 0.05$) (Figure 4).

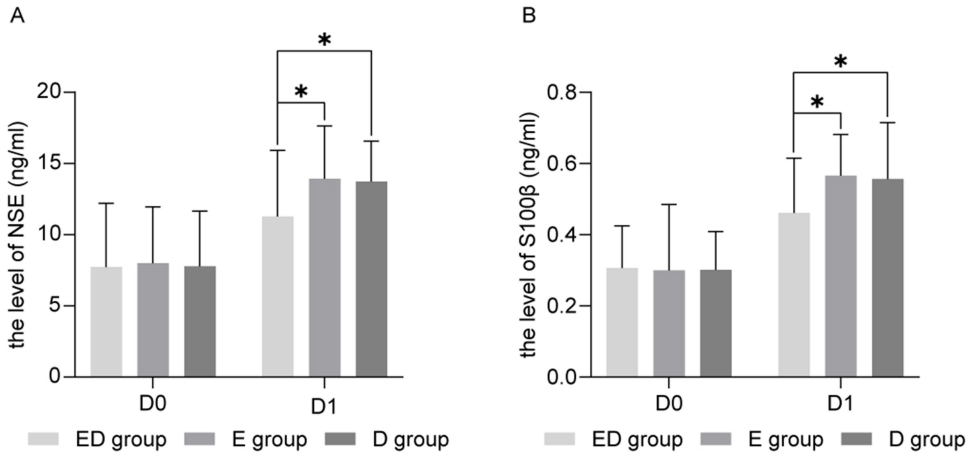

Figure 3 The levels of serum markers at different time points ((**A**) NSE, and (**B**) S100β). Data are expressed as mean (SD). D0 the preoperative day. D1 the first postoperative day. *$P < 0.05$ compared to the ED group.

Table 3 The VAS Pain Scores at Different Time Points

	ED Group (n=53)	E Group (n=53)	D Group (n=53)	*P* value		
				ED vs E	ED vs D	D vs E
VAS at postoperative 2 h	2.0 (1.0–2.0)	3.0 (1.0–4.0)[a]	3.0 (1.0–4.0)[a]	0.003	0.002	> 0.999
VAS at postoperative 24 h	1.0 (1.0–1.5)	2.0 (1.0–3.0)[a]	2.0 (1.0–3.0)[a]	0.002	< 0.001	> 0.999
VAS at postoperative 48 h	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–2.0)	0.955	> 0.999	> 0.999

Notes: [a]*P* versus ED group, $P < 0.05$. Data are expressed as median (25th to 75th percentiles).

The awakening times for patients in the ED and D groups were longer compared to the E group ($P < 0.05$). The incidence of bradycardia was significantly lower in the ED and E groups compared to the D group and the incidence of annoyance was significantly higher in the E group compared to the ED and D groups ($P < 0.05$). There were no significant differences between the groups in the incidence of PONV and nightmares. ($P > 0.05$) (Table 4).

Discussion

Our findings demonstrated that the combination of esketamine and dexmedetomidine significantly reduced the incidence of POCD on the first postoperative day in elderly patients undergoing lumbar spine surgery compared to esketamine alone. However, no significant difference was observed when comparing the effects of dexmedetomidine alone to the combination therapy on this primary outcome. Furthermore, the serum levels of NSE and S100β, measured before surgery and on the first postoperative day, support our observations. The combination therapy significantly lowered these serologic markers compared to the individual drugs, aligning with our expectation that the combination of esketamine and dexmedetomidine would more effectively reduce the biomarkers associated with neuroinflammation and neuronal damage.

Esketamine is the S-enantiomer of ketamine. As an N-methyl-D-aspartate (NMDA) receptor antagonist, esketamine can reduce the opening time and frequency of calcium ion channels and inhibit the transmission of excitatory neurotransmitter glutamate.[28] In addition, it also binds to γ-aminobutyric acid (GABA) receptors to enhance the inhibitory effect of the inhibitory neurotransmitter GABA, and binds to opioid receptors to mediate the anti-nociception of the central nervous system.[29] Esketamine binds to various receptors in the central nervous system to produce anesthetic, sedative and analgesic effects. In addition, a number of basic studies have found that esketamine may play a neuroprotective role by anti-inflammatory, reducing oxidative stress, enhancing autophagy and protecting synaptic plasticity.[15,16,30,31] Unlike esketamine, dexmedetomidine is a highly selective α2 adrenergic receptor agonist with sedative, analgesic and anti-inflammatory effects. The sedative effect of dexmedetomidine is accomplished by stimulating α2 receptors in the locus coeruleus nucleus. This sedation is similar to the unconscious state of natural sleep and is characterized by the patient's ease of waking up and cooperation.[32] In addition, dexmedetomidine has shown potential neuroprotective effects in some recent studies, such as improving postoperative cognitive function and reducing the

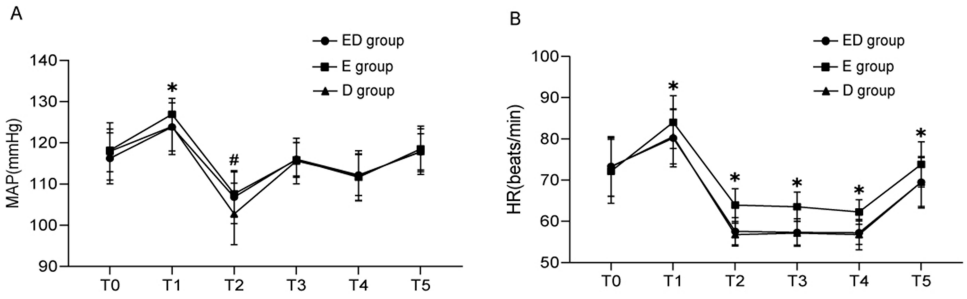

Figure 4 Hemodynamics during the perioperative period ((**A**) mean arterial pressure, and (**B**) heart rate). Data are expressed as mean (SD). T0, preoperatively; T1, at tracheal intubation; T2, 10 minutes post-intubation; T3, at skin incision; T4, one hour into the surgery; T5, the endotracheal tube removed. *$P < 0.05$, E group vs ED group and D group; #$P < 0.05$, ED group and E group vs D group.

Table 4 Comparison of Awakening Time and Adverse Events

	ED Group (n=53)	E Group (n=53)	D Group (n=53)	*P* value
Awakening time (min)	16.0 (12.0–20.0)	12.0 (9.0–16.0)[a]	17.0 (11.0–22.0)	0.003
Adverse events				
Bradycardia, n (%)	16 (30.2)	9 (17.0)	30 (56.6)[b]	< 0.001
Annoyance, n (%)	7 (13.2)	18 (34.0)[a]	4 (7.5)	0.001
PONV, n (%)	5 (9.4)	8 (15.1)	7 (13.2)	0.670
Nightmares, n (%)	6 (11.3)	10 (18.9)	6 (11.3)	0.430

Notes: [a]*P* versus ED group and D group, $P < 0.05$; [b]*P* versus ED group and E group, $P < 0.05$. Data are expressed as median (25th to 75th percentiles) or number of patients (%).
Abbreviation: POVN, postoperative nausea and vomiting.

incidence of postoperative delirium.[21,33] Therefore, we originally suspected that esketamine combined with dexmedetomidine was effective in reducing the incidence of POCD on the first day after surgery compared with esketamine or dexmedetomidine alone. However, there was no statistical difference in the incidence of POCD betweenpatients in ED and D goups on the first day after surgery. The discrepancy might be attributed to the potential inadequacies of the scales employed. The subjects, undergoing lumbar spine surgery under general anesthesia, likely experienced only mild cognitive dysfunction postoperatively due to advances in surgical techniques that minimize trauma. The MMSE and the MoCA are widely used, easy-to-administer cognitive scales suitable for bedside application, and have been utilized in various POCD studies.[27,34] However, neither scale is specifically designed for POCD, and they may not sensitively detect mild cognitive impairments, particularly with MMSE, known for its lower sensitivity.[35] MMSE and MoCA were chosen based on their brevity, patient compliance, and suitability under the study conditions. Serological results support our conjecture on the other hand.

NSE is an acidic protease found in neurons and neuroendocrine cells, playing a crucial role in glycolysis and energy metabolism within the central nervous system.[36] Its release from neurons following nerve injury also establishes NSE as a non-specific marker of neuronal damage.[37] Various neurological disorders, such as stroke, traumatic brain injury, and epilepsy, are associated with elevated levels of NSE,[38–40] and thus are considered potential biomarkers for POCD. A meta-analysis by Wang et al highlighted that high postoperative NSE levels could predict POCD, corroborated by several randomized controlled trials linking NSE levels with POCD incidence.[41–43] Our study aligns with these findings, showing that esketamine and dexmedetomidine effectively reduced NSE levels on the first postoperative day, similar to outcomes observed in previous research on dexmedetomidine. For instance, a study by Fu et al demonstrated that dexmedetomidine administration in elderly patients lowered plasma NSE concentrations and improved cognitive function postoperatively. Conversely, S100β, an acidic calcium-binding protein produced by astrocytes and oligodendrocytes, serves as a neurotrophic factor at physiological levels but may become neurotoxic when overexpressed, contributing to neuroinflammation and subsequent nerve damage.[44] The clinical relevance of S100β extends to its utility as a marker of nerve injury,[45] with recent research underscoring its strong association with the occurrence and prognosis of POCD.[46] In this context, the observed reduction in serum S100β levels in our study could be indicative of the inhibitory effects of esketamine and dexmedetomidine on astrocyte activation. Supporting this, studies have shown that dexmedetomidine may protect neurons by inhibiting inflammatory vesicle activation and apoptosis in astrocytes.[47,48] Furthermore, research by Zhao et al suggested that esketamine may exert similar neuroprotective actions by inhibiting astrocyte activation and inflammation.[49] Our findings suggested that the protective effects of esketamine and dexmedetomidine on postoperative cognitive function might be mediated by these compounds' ability to modulate astroglial activity and reduce inflammatory responses, an inference that is indirectly supported by the modulation of inflammatory biomarkers observed in this study.

Regarding the administration routes for dexmedetomidine, both intratracheal and intravenous applications at 0.6 μg/kg have been reported to alleviate postoperative delirium within three days, with intravenous administration being more beneficial for improving sleep quality.[23] This advantage likely stems from the higher bioavailability of the intravenous route compared to intratracheal delivery, as oral or nasal routes also exhibit lower bioavailability.[50] In this study, an additional 0.4 μg/kg of dexmedetomidine was administered intravenously to ensure effective serum drug concentrations.

Hemodynamic outcomes indicated that the combination of esketamine and dexmedetomidine helped stabilize patient hemodynamics before skin incision. Specifically, suggesting that dexmedetomidine, especially when administered endotracheally, effectively mitigates the stress response to tracheal intubation, but significantly reduces HR.

In addition, we noted significant differences in the VAS scores among the three groups at 2 and 24 hours post-operatively, with the ED group exhibiting lower VAS scores than both the E and D groups at these time points. This suggests that the combination of esketamine and dexmedetomidine was more effective in alleviating postoperative pain. This observation aligns with findings from Huang et al,[51] although there were discrepancies at 2 hours postoperatively. The continuous infusion in Huang et al's study likely contributed to lower VAS scores at 2 hours postoperatively. Further supporting this, several randomized controlled trials have demonstrated that esketamine or dexmedetomidine could relieves postoperative pain.[52–54] Additionally, basic research indicates that these drugs suppress inflammation and astrocyte activity, contributing to their analgesic effects, as seen in models of spinal cord injury in rats.[49] Wang et al also noted that esketamine might mitigate remifentanil-induced nociceptive hypersensitivity via the NMDA receptor-CaMKII pathway, providing a mechanistic insight into its analgesic properties.[55]

In terms of awakening time, our results revealed that esketamine shortened the time to awakening, corroborating with Duan et al's findings regarding esketamine's role in promoting faster recovery from anesthesia.[56] Duan et al suggested that esketamine facilitates arousal by activating glutamatergic neurons in the paraventricular nucleus of the thalamus, a mechanism that our clinical observations support, reinforcing the potential of esketamine to enhance arousal in patients under general anesthesia.

The limitations of this study include the following points. Firstly, cognitive function was assessed only on the first and third postoperative days without longer-term follow-up, primarily because most patients are discharged within one-week post-surgery at our institution. Furthermore, patients' cognitive function on the seventh postoperative day recovered in our pilot study. Studies have also demonstrated a relatively low incidence of POCD after one week postoperatively,[14,20] so we only followed up to the third postoperative day in this study. Secondly, we did not make a differential diagnosis of early POCD and POD, although the relationship between the two is not completely clear and they have different characteristics. We should have evaluated patients for the occurrence of POD before assessing their cognitive function in this study. Thirdly, we used the MMSE and MoCA, two screening scales for cognitive functioning, instead of the more comprehensive neuropsychological test batteries, in consideration of convenience and patient cooperation. Lastly, the repetition of three cognitive tests in a short period of time may back lead to a learning effect that interferes with the results of the study, and perhaps the use of a z-score approach to diagnosing POCD could mitigate the effect of the learning effect.

While esketamine combined with dexmedetomidine appears to benefit postoperative cognitive function in elderly patients, these limitations underscore the need for future multicenter studies with larger sample sizes. Such studies should employ comprehensive neuropsychological testing, differentiate between POCD and POD, explore longer follow-up periods, and determine the optimal dosage of this drug combination across different surgical contexts.

Conclusion

In conclusion, the combination of esketamine and dexmedetomidine can reduce the incidence of early postoperative POCD in elderly patients undergoing lumbar spine surgery, potentially through the mitigation of postoperative central neuroinflammation.

Acknowledgments

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com). The data sets that were generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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