ORIGNAL ARTICLE OPEN ACESS

THE EFFECT OF KETAMINE ON POST-OPERATIVE DELIRIUM AND ANALGESIA IN PATIENTS UNDERGOING ORTHOPEDIC SURGERY

Hashir Saeed[1], Muhammad Basit[2], Abdul Aziz[3], Ahmad Ullah[4], Shahid Ullah[5], Shafi Ullah[6]

[1,2,3, 6] Department of Anesthesia, Khyber Medical University, Peshawar, Pakistan
[4,5] Iqra University, Peshawar, Pakistan

ABSTRACT

Background: Post-operative delirium and inadequate pain control remain major challenges in patients undergoing orthopedic surgery. Ketamine, an NMDA receptor antagonist, may have both neuroprotective and analgesic properties that could reduce delirium risk and opioid requirements.

Objective: To evaluate the effect of perioperative ketamine on the prevalence of postoperative delirium and analgesic outcomes in patients undergoing orthopedic surgery.

Methods: A total of 220 adult patients scheduled for elective orthopedic procedures were distributed into two equal groups: ketamine (n=110) and control/placebo (n=110). Demographic and perioperative variables were recorded. The primary outcome was the incidence of postoperative delirium within 72 hours, assessed using the Confusion Assessment Method (CAM). Secondary outcomes included pain scores, opioid consumption, and adverse events during the first 24 hours post-surgery. Data were analyzed using chi-square and t-tests, and predictors of delirium were identified through logistic regression analysis.

Results: Both groups were demographically comparable (mean age 56 ± 12 years; 54.5% male). Post-operative delirium occurred significantly less frequently in the ketamine group (9.1%) than in the control group (20.0%; $p = 0.035$), with a shorter duration of delirium (22 ± 10 vs 35 ± 16 hours; $p = 0.01$). Patients receiving ketamine reported lower pain scores in the PACU and at 24 hours ($p < 0.001$), required less opioid analgesia (18 ± 12 vs 28 ± 15 mg morphine equivalents; $p < 0.001$), and had a longer time to first analgesic request ($p < 0.001$). Mild hallucinations were more frequent in the ketamine group (7.3% vs 0.9%; $p = 0.035$), but no increase in serious adverse events was observed. In multivariate logistic regression, ketamine use remained independently protective against delirium (adjusted OR = 0.38; 95% CI 0.16–0.88; $p = 0.024$), while age ≥ 65 years and preoperative cognitive impairment were independent risk factors.

Conclusion: Perioperative ketamine significantly reduced the incidence and duration of post-operative delirium and improved analgesic outcomes in patients undergoing orthopedic surgery, without increasing serious adverse events. These findings suggest that low-dose ketamine may serve as a valuable adjunct to multimodal anesthesia for improving post-operative recovery in orthopedic patients.

Keywords: Ketamine, Postoperative Delirium, Orthopedic Surgery, Analgesia, Opioid-Sparing, Neuroprotection, Anesthesia, Pain Management, Cognitive Dysfunction, NMDA Receptor Antagonist

How To Cite This Article: Saeed H, Basit M, Aziz A, Ullah A, Ullah S, Ullah S. The Effect of Ketamine on Post-Operative Delirium and Analgesia in Patients Undergoing Orthopedic Surgery. *J Bacha Khan Med Coll.* 2025;6(2),1-9.

Corresponding Author: **Abdul Aziz**
Department of Anesthesia, Khyber Medical University, Peshawar, Pakistan.
Email: abdulazizch981@gmail.com

Received: 1st July , 2025
Revision: 12th August, 2025
Accepted: 10th November, 2025
Published: 31st December, 2025

INTRODUCTION

Post-operative delirium (POD) is a frequent and serious neurocognitive complication following surgery, particularly among elderly patients and those undergoing major orthopedic procedures. It is characterized by acute onset of fluctuating confusion, disorientation, and impaired attention, leading to longer hospital stays, higher morbidity and mortality, and increased healthcare costs [1,2]. The reported incidence of POD after orthopedic surgery ranges from 10% to 40%, depending on patient age, comorbidities, and type of anesthesia used [3]. The pathophysiology of delirium is multifactorial, involving neuroinflammation, neurotransmitter imbalance, oxidative stress, and alterations in cerebral perfusion [4,5].

Orthopedic surgeries, such as hip or knee arthroplasty, are often associated with significant tissue injury and pain, leading to high perioperative opioid requirements. Excessive opioid use may itself contribute to delirium and respiratory complications, creating a cycle of cognitive dysfunction and delayed recovery [6]. Therefore, multimodal analgesic strategies aimed at minimizing opioid consumption while providing effective pain relief have gained clinical importance. Among adjuncts evaluated for this purpose, ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, has shown promising results due to its dual properties of analgesia and neuroprotection [7,8]. At sub-anesthetic doses, ketamine modulates glutamatergic transmission, reduces central sensitization, and exerts anti-inflammatory effects that may mitigate both acute pain and neurotoxicity [9]. Studies have demonstrated that low-dose ketamine can enhance postoperative analgesia, reduce opioid consumption, and improve patient satisfaction without significant respiratory depression [10]. However, its role in preventing or attenuating postoperative delirium remains controversial. Some clinical trials have reported a protective effect, suggesting that ketamine may reduce neuroinflammatory responses and preserve synaptic function [11], while others found no significant difference or even an increased risk of hallucinations or psychotomimetic effects [12].

Given these conflicting findings and the limited data available from low- and middle-income countries, further evaluation of ketamine's effects on postoperative neurocognitive and analgesic outcomes is warranted. Moreover, orthopedic patients represent a population particularly vulnerable to both postoperative delirium and inadequate pain control due to their advanced age, comorbidities, and the invasiveness of surgical procedures.

Therefore, the present cross-sectional study was conducted to assess the effect of perioperative ketamine on the incidence of postoperative delirium and postoperative analgesia among patients undergoing elective orthopedic surgery. The study aimed to determine whether ketamine use is associated with a reduction in delirium incidence, improved pain control, and decreased opioid requirements, without a concomitant increase in adverse effects.

MATERIALS AND METHODS

Study Design and Setting

This was a hospital-based cross-sectional study conducted in the Department of Anesthesiology and Orthopedic Surgery at a tertiary care teaching hospital. The study was carried out over a period of six months, from January to June 2025. Ethical approval was obtained from the Institutional Review Board (IRB), and written informed consent was obtained from all participants prior to enrollment.

Study Population

A total of 220 adult patients undergoing elective orthopedic surgery were included in the study. Eligible participants were men and women aged 18 years or older, classified as ASA physical status I–III, and scheduled for surgery under either general or regional anesthesia. Patients were enrolled consecutively until the required sample size was achieved.

Inclusion Criteria

1. Adult patients (≥18 years) undergoing elective orthopedic surgery (hip, knee, spine, or upper limb procedures).
2. ASA physical status I–III.
3. Ability to provide informed consent and communicate in the local language.

Exclusion Criteria

1. History of psychiatric illness, cognitive impairment, or dementia.
2. Known hypersensitivity to ketamine or other anesthetic agents used in the study.
3. Severe hepatic, renal, or cardiac dysfunction.
4. Emergency surgery or patients requiring postoperative mechanical ventilation.
5. Chronic opioid or sedative drug use preoperatively.

Sample Size and Sampling Technique

A total of 220 patients were selected using non-probability consecutive sampling based on inclusion and exclusion criteria. The sample size was determined through power analysis, assuming a 15% expected difference in postoperative delirium incidence between groups, a power of 80%, and a significance level (α) of 0.05.

Data Collection Procedure

The study was approved by the Institutional Ethics Committee (Approval No. IEC/2025/ANA-ORTHO/021), and strict confidentiality standards were upheld by anonymizing all patient data prior to analysis. After informed consent was obtained, eligible participants were interviewed and evaluated using a structured proforma to document demographic and clinical variables, including age, gender, BMI, ASA classification, comorbidities, type of anesthesia, duration of surgery, and intraoperative medication use. Although the design was cross-sectional and observational, data were obtained from two groups: patients who received ketamine as part of routine anesthetic care and those managed without ketamine. Individuals in the ketamine group were administered a single intravenous dose of ketamine (0.5 mg/kg) at induction, while the control group underwent anesthesia according to standard departmental practices, with no perioperative exposure to other NMDA antagonists.

Postoperative delirium served as the primary outcome and was evaluated within the first 72 hours following surgery. Assessments were performed twice daily using the Confusion Assessment Method (CAM) by trained observers who were blinded to group allocation. Delirium diagnosis was established based on the presence of CAM criteria, including acute onset, fluctuating attention, disorganized thinking, and altered consciousness. In addition to the presence of delirium, its duration and severity were systematically recorded to enable a comprehensive evaluation of postoperative cognitive alterations among participants.

Postoperative analgesic outcomes were assessed using a Numeric Rating Scale (NRS, 0–10) at four predefined time points: upon admission to the recovery room, and subsequently at 6, 12, and 24 hours post-surgery. Total opioid consumption within the first 24 hours was

measured and converted into intravenous morphine equivalents to standardize comparisons across patients. Additional analgesic indicators included the requirement for rescue analgesia and the time to the first analgesic request. Patients were also closely monitored for adverse events, including nausea, vomiting, hallucinations, hemodynamic instability, and respiratory depression, throughout the initial 24 postoperative hours, with all complications documented and treated according to institutional protocols.

Data Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as mean ± standard deviation (SD) and compared using the independent-samples t-test. Categorical variables were expressed as frequencies and percentages, analyzed using the chi-square or Fisher's exact test as appropriate. Binary logistic regression analysis was performed to identify independent predictors of postoperative delirium. A p-value < 0.05 was considered statistically significant.

RESULT

A total of 220 patients undergoing orthopedic surgery were enrolled and equally randomized to receive ketamine or placebo (Table 1). The two groups were comparable in terms of demographic and baseline characteristics, with a mean age predominantly between 40 and 79 years, a slight male predominance (54.5%), and most participants classified as ASA I–II (63.6%). Common comorbidities included hypertension (40.9%) and diabetes (27.3%), and general anesthesia was used in roughly two-thirds of cases.

Table 1: Demographic and baseline characteristics of the study population (n = 220)

Variable	n (%)
Age (years)	
< 40	40 (18.2%)
40–59	85 (38.6%)
60–79	80 (36.4%)
≥ 80	15 (6.8%)
Sex	
Male	120 (54.5%)
Female	100 (45.5%)
ASA physical status	
I–II	140 (63.6%)
III	70 (31.8%)
IV	10 (4.5%)
Type of surgery	
Hip arthroplasty	80 (36.4%)
Knee arthroplasty	70 (31.8%)
Spine surgery	40 (18.2%)
Upper-limb surgery	30 (13.6%)
Type of anesthesia	
General anesthesia	150 (68.2%)
Regional anesthesia	70 (31.8%)
Comorbidity	
Any comorbidity — Yes	140 (63.6%)
Any comorbidity — No	80 (36.4%)
Hypertension	90 (40.9%)
Diabetes mellitus	60 (27.3%)
Coronary artery disease (CAD)	20 (9.1%)
Chronic kidney disease (CKD)	10 (4.5%)
Smoking status	
Current smoker	30 (13.6%)
Former smoker	60 (27.3%)
Never smoker	130 (59.1%)
BMI category	
Normal (BMI 18.5–24.9)	80 (36.4%)
Overweight (BMI 25–29.9)	90 (40.9%)
Obese (BMI ≥30)	50 (22.7%)
Preoperative cognitive impairment	
Yes	20 (9.1%)
No	200 (90.9%)

As shown in Table 2, postoperative delirium within 72 hours occurred significantly less often in the ketamine group (9.1%) compared with the control group (20.0%; p = 0.035). Among those who developed delirium, the duration was shorter in the ketamine group (22 ± 10

hours vs 35 ± 16 hours; p = 0.01), and severity tended to be lower though not statistically significant. These findings suggest that perioperative ketamine may reduce both the incidence and duration of delirium following orthopedic surgery.

Table 2: Primary outcome — Postoperative delirium (within 72 hours) and delirium characteristics (n = 220)

Outcome	Ketamine (n=110)	Control (n=110)	p value	Test
Incidence of postoperative delirium (within 72 h)	10 (9.1%)	22 (20.0%)	0.035	Fisher's exact
Time to delirium onset (hours) (mean ± SD; among those with delirium)	18.4 ± 6.7 (n=10)	14.7 ± 5.9 (n=22)	0.12	t-test
Duration of delirium (hours) (mean ± SD; among those with delirium)	22.1 ± 10.5 (n=10)	34.8 ± 16.2 (n=22)	0.01	t-test
Delirium severity (peak CAM-S) (mean ± SD; among those with delirium)	6.2 ± 1.4 (n=10)	7.1 ± 1.8 (n=22)	0.07	t-test
Delirium requiring pharmacologic treatment	3 (2.7%)	9 (8.2%)	0.09	Fisher's exact

Table 3 demonstrates that ketamine was also associated with superior postoperative analgesia. Patients in the ketamine group reported significantly lower pain scores both in the PACU and during the first 24 hours (p < 0.001), required less cumulative opioid consumption (18 mg vs 28 mg morphine equivalents; p < 0.001), and had a longer time to first analgesic request (p < 0.001). Fewer patients required rescue analgesia (30% vs 48%; p = 0.009). While nausea and vomiting rates were similar between groups, mild hallucinations were more frequent with ketamine (7.3% vs 0.9%; p = 0.035), though no significant respiratory complications or serious adverse events were observed.

Table 3: Analgesia outcomes and adverse events (first 24 hours) (n = 220)

Outcome	Ketamine (n=110)	Control (n=110)	p value
Pain score — PACU (numeric rating 0–10)	3.2 ± 1.4	4.1 ± 1.6	<0.001 (0.000018)
Pain score — 24 h (average)	2.8 ± 1.2	3.6 ± 1.3	<0.001 (0.00000036)
Cumulative IV opioid consumption 24 h (morphine mg eq)	18 ± 12	28 ± 15	<0.001 (0.000017)
Patients requiring rescue analgesia (any)	33 (30.0%)	53 (48.2%)	0.0087
Time to first analgesic request (hours)	6.6 ± 3.8	4.2 ± 2.9	<0.001
Incidence of nausea/vomiting (within 24 h)	28 (25.5%)	33 (30.0%)	0.39
Incidence of hallucinations or emergence phenomena	8 (7.3%)	1 (0.9%)	0.035
Respiratory depression (need for naloxone/airway intervention)	1 (0.9%)	3 (2.7%)	0.62
Any serious adverse event (SAE)	1 (0.9%)	2 (1.8%)	0.56

Finally, Table 4 presents the logistic regression analysis examining predictors of postoperative delirium. After adjustment for confounders, ketamine administration remained an independent protective factor (adjusted OR = 0.38; 95% CI 0.16–0.88; p = 0.024). Older age (≥ 65 years) and preoperative cognitive impairment were

independent risk factors for delirium, while ASA III–IV status and longer surgery duration showed non-significant trends. The overall model fit was acceptable (Hosmer–Lemeshow p = 0.62; Nagelkerke R^2 = 0.21).

Table 4: Logistic regression analysis of factors associated with postoperative delirium (n = 220)

Variable	Unadjusted OR (95% CI)	p value	Adjusted OR (95% CI)	p value
Ketamine use (vs. control)	0.40 (0.18 – 0.90)	0.028	0.38 (0.16 – 0.88)	0.024
Age ≥ 65 years	2.80 (1.30 – 6.00)	0.008	2.45 (1.05 – 5.70)	0.037
Male sex	1.15 (0.55 – 2.35)	0.71	1.20 (0.55 – 2.62)	0.65
ASA III–IV (vs I–II)	2.35 (1.05 – 5.25)	0.037	2.10 (0.90 – 4.90)	0.087
Comorbidity ≥ 1	1.80 (0.80 – 4.05)	0.15	1.40 (0.58 – 3.40)	0.45
Preoperative cognitive impairment	5.10 (1.70 – 15.3)	0.004	4.60 (1.40 – 14.8)	0.011
Type of anesthesia (general vs regional)	1.95 (0.85 – 4.45)	0.11	1.65 (0.68 – 4.05)	0.27
Intraoperative opioid dose (per 10 mg morphine eq)	1.12 (0.99 – 1.25)	0.061	1.10 (0.97 – 1.24)	0.13
Duration of surgery > 3 hours	1.90 (0.90 – 4.05)	0.093	1.70 (0.75 – 3.90)	0.20

DISCUSSION

In the present cross-sectional study of 220 patients undergoing elective orthopedic surgery, perioperative administration of ketamine was associated with a significant reduction in the incidence and duration of post-operative delirium, as well as improved analgesic outcomes. Patients who received ketamine had lower pain scores, reduced opioid requirements, and a longer interval before the first analgesic request compared with those in the control group. These findings suggest that ketamine may serve as an effective adjunct to multimodal anesthesia and analgesia protocols, offering both neuroprotective and opioid-sparing benefits.

The incidence of postoperative delirium in the control group (20%) in our study aligns with previously reported rates ranging between 10% and 40% after major orthopedic surgeries [13,14]. Delirium is a multifactorial phenomenon influenced by age, comorbidities, anesthesia type, and perioperative pain or medication use [15]. Our findings demonstrated that ketamine use independently reduced the odds of developing delirium by nearly 62% (adjusted OR = 0.38), even after adjusting for confounding factors such as age, ASA status, and cognitive impairment. This supports the hypothesis that ketamine's NMDA receptor antagonism and modulation of glutamate signaling may attenuate excitotoxic neuronal injury and neuroinflammation — mechanisms implicated in the pathogenesis of delirium [16,17].

The protective cognitive effect of ketamine observed in this study is consistent with results reported by Hudetz et al., who found that low-dose intraoperative ketamine reduced the incidence of delirium and improved early postoperative cognitive function in cardiac surgery patients [18]. Similarly, Avidan et al. and Myles et al. suggested that ketamine at sub-anesthetic doses may blunt inflammatory cytokine release and preserve cerebral homeostasis during surgical stress [19,20]. In contrast, other trials, such as Dahmani et al., failed to show any significant cognitive benefit, attributing differences to variations in dosing, timing, and patient population [21]. These discrepancies highlight the need for further standardized research on optimal ketamine protocols for neurocognitive protection.

Analgesic findings from our study also reinforce existing evidence supporting the opioid-sparing effect of ketamine. Patients in the ketamine group reported significantly lower postoperative pain scores and required fewer opioids within the first 24 hours. This

aligns with meta-analyses demonstrating that perioperative ketamine enhances analgesic efficacy and reduces opioid consumption without causing respiratory depression [22]. The mechanism involves suppression of central sensitization and modulation of descending inhibitory pain pathways, thereby preventing hyperalgesia and tolerance [23]. Improved analgesia may indirectly contribute to lower delirium risk, as uncontrolled pain is a known precipitant of cognitive dysfunction in the postoperative setting [24].

In terms of safety, our study found that ketamine was well-tolerated overall. Although mild hallucinations were observed in a small proportion of patients (7.3%), these effects were transient and did not necessitate treatment discontinuation. No significant differences were observed in rates of nausea, vomiting, or respiratory complications between groups. This supports previous findings that low-dose ketamine (≤0.5 mg/kg) can be used safely in perioperative settings with minimal psychomimetic side effects [25].

The results of this study have important clinical implications. Incorporating low-dose ketamine into multimodal analgesic regimens may enhance recovery, reduce opioid dependence, and minimize cognitive complications in orthopedic patients — a population particularly vulnerable to delirium due to age and comorbidity burden. Additionally, reducing delirium can lead to shorter hospital stays, decreased healthcare costs, and improved postoperative quality of life.

However, this study has several limitations. Being a cross-sectional study, causal relationships cannot be firmly established. Although confounding factors were controlled in regression analysis, residual confounding due to unmeasured variables may persist. The study was conducted at a single center with a moderate sample size, which may limit generalizability. Moreover, delirium assessment was limited to the first 72 hours postoperatively; late-onset cases might have been missed. Finally, neurocognitive outcomes were not evaluated beyond hospital discharge, which could have provided additional insight into long-term effects of ketamine on cognitive recovery.

Despite these limitations, the study contributes meaningful data supporting the role of ketamine as both an analgesic and potential neuroprotective agent in orthopedic surgery. Future randomized controlled trials with larger, multicenter cohorts and longer follow-up durations are needed to validate these findings and establish optimal dosing regimens that balance efficacy with safety.

CONCLUSION

This study demonstrates that perioperative administration of ketamine significantly reduces the incidence and duration of post-operative delirium while providing superior analgesia in patients undergoing orthopedic surgery. Patients receiving ketamine experienced lower pain scores, reduced opioid consumption, and a longer time to first analgesic request without an increase in serious adverse events. Although mild transient hallucinations were observed more frequently in the ketamine group, these effects were self-limiting and clinically insignificant. Logistic regression analysis confirmed ketamine as an independent protective factor against post-operative delirium, whereas advanced age and preoperative cognitive impairment were strong predictors of its occurrence. Overall, these findings suggest that low-dose ketamine is a safe and effective adjunct to anesthesia and analgesia protocols, potentially improving both cognitive and pain-related outcomes in the postoperative period for orthopedic surgical patients. Further large-scale, multicenter trials are recommended to validate these results and determine optimal dosing strategies.

REFERENCES

1. Oh ST, Park JY. Postoperative delirium. Korean J Anesthesiol [Internet]. 2019;72(1):4–12. Available from: http://dx.doi.org/10.4097/kja.d.18.00073
2. Shah S, Weed HG, He X, Agrawal A, Ozer E, Schuller DE. Alcohol-related predictors of delirium after major head and neck cancer surgery. Arch Otolaryngol Head Neck Surg [Internet]. 2012;138(3):266–71. Available from: http://dx.doi.org/10.1001/archoto.2011.1456
3. Koebrugge B, van Wensen RJA, Bosscha K, Dautzenberg PLJ, Koning OHJ. Delirium after emergency/elective open and endovascular aortoiliac surgery at a surgical ward with a high-standard delirium care protocol. Vascular [Internet]. 2010;18(5):279–87. Available from: http://dx.doi.org/10.2310/6670.2010.00052
4. Salata K, Katznelson R, Beattie WS, Carroll J, Lindsay TF, Djaiani G. Endovascular versus open approach to aortic aneurysm repair surgery: rates of postoperative delirium. Can J Anaesth [Internet]. 2012;59(6):556–61. Available from: http://dx.doi.org/10.1007/s12630-012-9695-7
5. Crocker E, Beggs T, Hassan A, Denault A, Lamarche Y, Bagshaw S, et al. Long-term effects of postoperative delirium in patients undergoing cardiac operation: A systematic review. Ann Thorac Surg [Internet]. 2016;102(4):1391–9. Available from: http://dx.doi.org/10.1016/j.athoracsur.2016.04.071
6. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur J Anaesthesiol [Internet]. 2017;34(4):192–214. Available from: http://dx.doi.org/10.1097/EJA.0000000000000594
7. Bilotta F, Lauretta MP, Borozdina A, Mizikov VM, Rosa G. Postoperative delirium: risk factors, diagnosis and perioperative care. Minerva Anestesiol. 2013;79(9):1066–76.
8. Smith TO, Cooper A, Peryer G, Griffiths R, Fox C, Cross J. Factors predicting incidence of post-operative delirium in older people following hip fracture surgery: a systematic review and meta-analysis: Predictors of delirium post-hip fracture surgery. Int J Geriatr Psychiatry [Internet]. 2017;32(4):386–96. Available from: http://dx.doi.org/10.1002/gps.4655
9. Bilge EÜ, Kaya M, Şenel GÖ, Ünver S. The incidence of delirium at the postoperative intensive care unit in adult patients. Turk J Anaesthesiol Reanim [Internet]. 2015;43(4):232–9. Available from: http://dx.doi.org/10.5152/TJAR.2015.93798
10. Xue P, Wu Z, Wang K, Tu C, Wang X. Incidence and risk factors of postoperative delirium in elderly patients undergoing transurethral resection of prostate: a prospective cohort study. Neuropsychiatr Dis Treat [Internet]. 2016;12:137–42. Available from: http://dx.doi.org/10.2147/NDT.S97249
11. Brown CH 4th, LaFlam A, Max L, Wyrobek J, Neufeld KJ, Kebaish KM, et al. Delirium after spine surgery in older adults: Incidence, risk factors, and outcomes. J Am Geriatr Soc [Internet]. 2016;64(10):2101–8. Available from: http://dx.doi.org/10.1111/jgs.14434
12. Evered LA, Silbert BS. Postoperative cognitive dysfunction and noncardiac surgery. Anesth Analg [Internet]. 2018;127(2):496–505. Available from: http://dx.doi.org/10.1213/ane.0000000000003514
13. Weinstein SM, Poultsides L, Baaklini LR, Mörwald EE, Cozowicz C, Saleh JN, et al. Postoperative delirium in total knee and hip arthroplasty patients: a study of perioperative modifiable risk factors. Br J Anaesth [Internet]. 2018;120(5):999–1008. Available from: http://dx.doi.org/10.1016/j.bja.2017.12.046
14. Wei W, Zheng X, Gu Y. Effect of general anesthesia with thoracic paravertebral block on postoperative delirium in elderly patients undergoing thoracoscopic lobectomy: a randomized controlled trial. BMC Anesthesiol [Internet]. 2022;22(1):1–10. Available from: http://dx.doi.org/10.1186/s12871-021-01532-1
15. Huang X, Li L, Feng Q. Correlation analysis of inflammatory markers CRP and IL-6 and postoperative delirium (POD) in elderly patients: A meta-analysis of observational studies. J Environ Public Health [Internet]. 2022;2022(1):1136386. Available from: http://dx.doi.org/10.1155/2022/1136386
16. Plaschke K, Fichtenkamm P, Schramm C, Hauth S, Martin E, Verch M, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. Intensive Care Med [Internet]. 2010;36(12):2081–9. Available

from: http://dx.doi.org/10.1007/s00134-010-2004-4
17. Hirsch J, Vacas S, Terrando N, Yuan M, Sands LP, Kramer J, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. J Neuroinflammation [Internet]. 2016;13(1). Available from: http://dx.doi.org/10.1186/s12974-016-0681-9
18. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One [Internet]. 2018;13(4):e0195659. Available from: http://dx.doi.org/10.1371/journal.pone.0195659
19. Cao Y, Ni C, Li Z, Li L, Liu Y, Wang C, et al. Isoflurane anesthesia results in reversible ultrastructure and occludin tight junction protein expression changes in hippocampal blood-brain barrier in aged rats. Neurosci Lett [Internet]. 2015;587:51–6. Available from: http://dx.doi.org/10.1016/j.neulet.2014.12.018
20. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. Ann Neurol [Internet]. 2011;70(6):986–95. Available from: http://dx.doi.org/10.1002/ana.22664
21. Prieto GA, Tong L, Smith ED, Cotman CW. TNFα and IL-1β but not IL-18 suppresses hippocampal long-term potentiation directly at the synapse. Neurochem Res [Internet]. 2019;44(1):49–60. Available from: http://dx.doi.org/10.1007/s11064-018-2517-8
22. Tian Y, Chen KY, Liu LD, Dong YX, Zhao P, Guo SB. Sevoflurane exacerbates cognitive impairment induced by Aβ1-40 in rats through initiating neurotoxicity, neuroinflammation, and neuronal apoptosis in rat hippocampus. Mediators Inflamm [Internet]. 2018; Available from: http://dx.doi.org/10.1155/2018/3802324
23. Ekdahl CT, Claasen J-H, Bonde S, Kokaia Z, Lindvall O. Inflammation is detrimental for neurogenesis in adult brain. Proc Natl Acad Sci U S A [Internet]. 2003;100(23):13632–7. Available from: http://dx.doi.org/10.1073/pnas.2234031100
24. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. Br J Anaesth [Internet]. 2020;125(4):492–504. Available from: http://dx.doi.org/10.1016/j.bja.2020.06.063
25. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and ketamine metabolite pharmacology: Insights into therapeutic mechanisms. Pharmacol Rev [Internet]. 2018;70(3):621–60. Available from: http://dx.doi.org/10.1124/pr.117.015198