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REVIEW

Clinical Benefits and Challenges of Esketamine in Elderly Patients During the Perioperative Period

Shuai Zhang[1], Chen Bai[1], Mingcan Xu[1], Yiqing Li[1], Ying Han[1], Yanwu Jin[1,2], Xin Zhao[1]

[1]Department of Anesthesiology, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China; [2]Department of Anesthesiology, Public Health Clinical Center, Shandong University, Jinan, People's Republic of China

Correspondence: Yanwu Jin; Xin Zhao, Department of Anesthesiology, The Second Hospital, Cheeloo College of Medicine, Shandong University, Jinan, People's Republic of China, Email jinyanwu_aa@163.com; lujnzx@sohu.com

Abstract: Ketamine is a classic intravenous anesthetic. Esketamine is a dextro-isomer of ketamine, with similar mechanism of action, mainly through non-competitive antagonism of N-methyl-D-aspartate receptors, higher potency and fewer adverse effects. The characteristics of esketamine include circulatory stimulation, bronchodilatation, inhibition of inflammation and dissociative anesthetic properties. Esketamine was approved for clinical practice in China in 2019, and has significant advantages for use in pediatric, maternal, elderly or shock patients. The clinical use of esketamine is currently receiving widespread attention. This article reviews the recent progress and limitations of clinical studies on the perioperative use of esketamine in elderly patients, covering its pharmacological properties, hemodynamic effects, analgesic benefits, and impacts on depression, sleep, and neurocognitive function, to provide theoretical reference for its application in anesthesia and offer dosage recommendations for elderly patients.

Keywords: esketamine, elderly patients, clinical application, perioperative period

Introduction

Population aging has resulted in a gradual increase in the demand for geriatric medical care. Elderly patients have reduced physical functions and a variety of underlying diseases (hypertension, coronary heart disease, diabetes, etc). Their tolerance of surgery, anesthesia and medication, as well as their psychological tolerance are reduced.[1] Dramatic perioperative hemodynamic fluctuations increase the risk of cerebral hemorrhage, cerebral infarction, myocardial ischemia and other adverse cardiovascular and cerebrovascular events in elderly patients. Dysregulation of inflammatory mediators and antimicrobial defenses increases the risk of postoperative respiratory-related complications such as lung infection and respiratory failure. Vulnerability of brain function to pathophysiological stressors, especially in the aging brain where there is neuronal loss, decreased cerebral blood flow and damage to the blood–brain barrier, increases the risk of postoperative delirium. High perioperative opioid doses may induce or exacerbate delirium, especially in elderly patients with increased cerebral sensitivity and decreased clearance of opioids. However, inadequate pain relief can also cause delirium, poor sleep quality and other complications. Therefore, the likelihood of postoperative complications and poor prognosis is increased in elderly patients.[2]

In November 2019, esketamine was first marketed in China.[3] Its clinical use and research have received widespread attention. Compared with other intravenous sedatives, esketamine is characterized by good sedative and analgesic effects, small effects on the respiratory and circulatory systems, as well as a stimulating effect on the sympathetic nerves.[4] It can compensate for the inhibitory effect of propofol, sevoflurane and other drugs on the circulation, reduce intraoperative hypotension, and is conducive to maintenance of hemodynamic stability. Previous studies have shown that esketamine is beneficial in improving perioperative negative mood, and promoting postoperative cognitive recovery, sleep quality and perioperative analgesia.[5] In clinical practice, it is particularly beneficial in the anesthetic management of elderly patients.[6]

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This article reviews the perioperative application of esketamine in elderly patients with regard to its pharmacological properties and current research on clinical applications, to provide references and dosage suggestions for rational application.

Subjects and Methods

Clinical studies on esketamine during the perioperative period were identified through searching of the following databases: PubMed, Cochrane Library, EMBASE and Web of Science. The study primarily included clinical trials targeting the elderly population during the perioperative period in the past five years (Table 1). The search strategy was as follows: ((((((esketamine) OR (s-ketamine)) OR (s(+)-ketamine)) OR ((s)-ketamine)) AND (((((((surgery) OR (surgical)) OR (operative)) OR (perioperative)) OR (postoperative)) OR (anesthesia)) OR (anesthetic))) AND (((((elderly) OR (older)) OR (aged)) OR (age≥60)) OR (age≥65))) AND ((((((((randomized controlled trial) OR (controlled clinical trial)) OR (randomized)) OR (randomised)) OR (randomly)) OR (trial)) OR (study)) OR (application)), with manual screening. The inclusion criteria comprised elderly patients receiving general anesthesia; an experimental group receiving esketamine (intravenous injection); a primary outcome of evaluation of the effect of esketamine; a randomized controlled trial study design; and studies with full text availability. A few meta-analyses or studies targeting broader populations/animals were also included to support the pharmacological properties or clinical efficacy of esketamine. The exclusion criteria comprised case reports and non-English literature.

Pharmacological Properties of Esketamine

Ketamine is a phenylcyclohexylamine derivative, a racemic mixture in equal parts of r-ketamine (also called arketamine) and s-ketamine (also called esketamine) (Figure 1). It exerts sedative and analgesic effects, mainly by blocking N-methyl-D-aspartate receptors (NMDARs). It was first synthesized in 1962, but its clinical application was restricted at the end of the 20th century due to a high number of adverse effects (psychiatric symptoms, extravertebral syndromes, increased secretions, etc).[20–22]

Esketamine, the right-handed isomer of ketamine, has an increased affinity for NMDARs. It is about twice as potent as ketamine and has fewer psychomimetic effects. The mechanism of action of esketamine is complex,[23–25] (Figure 2). In addition to non-competitive blockade of NMDARs, it acts on opioid receptors, monoamine system, cholinergic system, γ-aminobutyric acid (GABA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and ion channels to produce a variety of pharmacological effects. For example, by binding to NMDARs, esketamine blocks GABAergic interneurons, leading to a short-term surge of glutamate, which activates AMPA receptors. This initiates a cascade of intracellular signaling reactions that leads to an increase in activation of brain-derived neurotrophic factor (BDNF) and PI3–AKT–mTOR, producing antidepressant effects.[26,27] Esketamine binds to μ and δ opioid receptors, resulting in analgesic and mood-enhancing effects.[24] It stimulates sympathetic nerves and inhibits the reuptake of catecholamines, increasing heart rate and blood pressure. It reduces neuronal death and neuroinflammation, which has anti-inflammatory and neuroprotective properties. It affects the monoaminergic system (including serotonin, norepinephrine and dopamine receptors) and rebalances neurotransmitter levels in the brain. Esketamine acts in a dose-dependent manner and has different advantages in specific populations.[23,28] Its sympathomimetic properties mean that it is safer for the induction of anesthesia in hypotensive, elderly or shocked patients. Its low respiratory depressant effect improves the safety of postoperative analgesia.[29] Its relaxing effect on airway smooth muscle facilitates anesthesia in patients with asthma.[30] It reduces the use of propofol and is conducive to hemodynamic stabilization in combination with propofol.[4,6]

The first pharmacokinetic study exploring esketamine in a Chinese population[31] showed that esketamine and ketamine had similar pharmacokinetic parameters, were not affected by gender and neither caused serious adverse events. This is no different from previous studies in other ethnic populations. Esketamine, like ketamine, has a rapid onset of action, reaching peak concentrations in ~67 s after intravenous administration of 0.5 mg/kg. The half-life (287.50 ± 110.20 min) and recovery time from anesthesia are shorter than those of ketamine.[20,32] Esketamine is metabolized by hepatic microsomal enzymes. The main metabolite is S-norketamine, which is also pharmacologically active, with an affinity for NMDARs about a third of that of esketamine, and an elimination half-life of 519.0 ±

Table 1 The Characteristics of the Included Studies

Study	Age (Type of Surgery)	Group	Observational Indices	Conclusion
Tu et al 2021[6]	≥60y (Surgical patients)	Study group (n=40): esketamine 0.5 mg/kg + propofol; Control group (n=40): sufentanil + propofol.	Hemodynamics (SBP, DBP, MAP, HR); Stress response (AD, NE, ET); Inflammatory response (CRP, PCT, WBC); Cognitive function (MoCA scores); Perioperative indicators (surgical duration, anesthesia time, consciousness recovery time); Adverse responses.	Improve hemodynamics and surgical stress and inflammatory responses, shorten anesthesia time, promote the recovery of postoperative cognitive function, and cause relatively mild adverse responses.
Li et al 2022[7]	65~85y (Unilateral total knee replacement)	Esketamine group (n=40): esketamine 0.2 mg/kg + etomidate; Control group (n=40): normal saline of equal volume + etomidate.	Hemodynamics (SBP, DBP, MAP, HR) and BIS; Cough and myoclonus; Cardiovascular adverse events; RSAS and HADS; Delirium (CAM scale); Adverse events.	Low-dose esketamine can better maintain hemodynamic stability and has no adverse effect.
Liu et al 2024[8]	≥65y (Gastrointest-inal surgery)	Experimental group (n=30): sufentanil 1.5 ug/kg + esketamine 1 mg/kg (PCIA); Control group (n=30): sufentanil 2 ug/kg (PCIA).	Postoperative pain (NRS scores at 4, 24, and 48 h after surgery); Postoperative delirium (CAM); IL-6; Postoperative nausea and vomiting.	Esketamine may enhance postoperative pain management. It has anti-inflammatory effects that reduce the incidence of postoperative delirium.
Min et al 2023[9]	≥60y (Total hip arthroplasty)	Esketamine group (n=75): esketamine 2.5 mg/kg (PCIA); Sufentanil group (n=75): sufentanil 2.5 ug/kg (PCIA).	Postoperative VAS score; The first ambulation time, ambulation distance and PCA compression times; Patient stress index (IL-6, CRP); HAD scores; Harris hip score; Adverse reactions.	Esketamine can relieve pain more effectively, reduce stress responses, improve anxiety and depression symptoms, and promote postoperative recovery.
Ma et al 2023[10]	≥65y (Major abdominal surgery for gastrointesti-nal tumors)	Esketamine group (n=34): esketamine 0.25 mg/kg loading + 0.125 mg/kg/h infusion; Control group (n=34): normal saline.	Incidence of DNR (MMSE score); Intraoperative data (duration of surgery and anesthesia, volume of infusion, blood loss, propofol and remifentanil consumption, use of vasoactive drugs and sufentanil remedial analgesia, SBP, DBP, MAP, HR, cardiovascular adverse events, BIS value); Incidence of POD; NRS pain scores.	Low-dose esketamine reduce the incidence of DNR, improve hemodynamics and BIS value, decrease the incidence of cardiovascular adverse events and the consumption of opioids, and relieve postoperative pain.
Jing et al 2024[11]	≥60y (Resection of gastrointesti-nal tumors)	Esketamine group (n=45): esketamine 0.25 mg/kg loading + 0.1 mg/kg/h infusion; Control group (n=45): normal saline.	VAS pain scores; Remifentanil consumption; PCIA compression times and instances of rescue analgesia; Delirium (CAM), Sleep Quality (AIS); (QoR)-15 score; Inflammation indicators (IL-1β, IL-6); Adverse events.	Esketamine can effectively reduce the intensity of postoperative pain and has no additional adverse reactions.
Lu et al 2024[12]	60~85y (Thoracic surgery)	Esketamine group (n=47): esketamine 0.5 mg/kg for 20min after induction; Dexmedetomid-ine group (n=47): dexmedetomidi-ne 0.7 μg/kg (>10min) loading after induction + 0.2–0.5 μg/kg/h maintenance.	RSS and VAS Scores; Negative Emotion (SAS, SDS); Sleep Quality (PSQI); Cognitive function (MMSE); Delirium (CAM); Adverse events.	Both esketamine and dexmedetomidine can prevent POD and nociceptive hypersensitivity. However, esketamine is superior in analgesia, improvement of negative mood and sleep, and stabilization of hemodynamics.
Cai et al 2024[13]	≥65y (Hip Fracture)	Esketamine group (n=45): esketamine 0.5 mg/kg + sufentanil 2 μg/kg (PCIA); Control group (n=45): saline + sufentanil 2 μg/kg (PCIA).	Depressive symptoms (GDS-15); Serum levels of BDNF and 5-HT; Postoperative pain (VAS); PCIA compression times; Sufentanil consumption; Adverse events.	Esketamine in PCIA could improve depressive symptoms and increase levels of BDNF and 5-HT.
Wei et al 2022[14]	60~90y (Thoracic surgery)	Esketamine group (n=260): esketamine 0.25 mg/kg loading + 0.1 mg/kg/h maintenance; Dexmedetomid-ine group (n=260): dexmedetomid-ine 0.2 μg/kg loading + 0.2 μg/kg/h maintenance; Control group (n=260): normal saline.	Incidence of POD (CAM); Subtype, severity and duration of POD; Pain severity (NRS); Quality of sleep (NRS); Cognitive function (TICS-40); Plasma biomarker (ACh, BDNF, TNF-α); Adverse events.	Not yet reported.

(*Continued*)

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Table 1 (Continued).

Study	Age (Type of Surgery)	Group	Observational Indices	Conclusion
Qiu et al 2022[15]	18~65y (Gynecologic-al laparoscopic surgery)	Esketamine group (n=92): esketamine 0.3 mg/kg/h, intraoperatively; Control group (n=91): an equivalent volume of saline.	Incidence of PSD (NRS, AIS); Postoperative pain (VAS); Postoperative hydromorphone consumption; Anxiety and depression (HADS); Risk factors associated with PSD	Intraoperative infusion of esketamine can improve the incidence of PSD.
Zhang et al 2024[16]	65~85y (Noncardiac surgery)	Esketamine group (n=213): esketamine 0.2 mg/kg, before induction; Control group (n=213): normal saline.	Incidence of POD (3D-CAM); The scores of MMSE and HAD; Profiles of anesthesia management; NRS score; Adverse events.	Low-dose esketamine before anesthesia induction failed to significantly decrease the risk of POD but decrease the risk of intraoperative hypotension and emergence agitation.
Han et al 2023[17]	≥65y (Gastrointest-inal surgery)	Esketamine group (n=42): esketamine (0.15 mg/kg) 5min before the initiation of surgery; Control group (n=42): same volume of saline.	Incidence of dNCR and POCD; Changes in the levels of serum IL-6 and S100β.	Esketamine could improve early postoperative cognitive function, which might be related to the anti-neuroinflammation effects of esketamine.
Huang et al 2024[18]	60~86y (Tumor resection)	Esketamine group (n=108): esketamine (0.5 mg/kg) 10min after induction + 2 mg/kg combination with sufentanil 2 μg/kg (PCIA); Control group (n=101): saline (as a substitutefor esketamine).	Incidence of POD and POCD (CAM, neuropsychologi-cal test, TICSm); Incidence of MCI; Depression (HAMD-17); Pain (NRS); PCIA compression times; Recovery quality (QoR); Adverse reactions.	Intraoperative and postoperative low-dose esketamine has been shown to improve postoperative analgesia and depressive symptoms, and aid in the recovery. However, it did not reduce the incidence of POD or POCD.
Avidan et al 2017[19]	≥60y (Major cardiac and noncardiac surgery)	Lo-K group (n=221): ketamine 0.5mg/kg (after induction); Hi-K group (n=216): ketamine 1mg/kg (after induction); Placebo group (n=217): normal saline.	Delirium (CAM or CAM-ICU); Pain (VAS) Postoperative opioid use; Adverse events	Ketamine may not useful in preventing POD or reducing postoperative pain. Instead, it increases the incidence of postoperative nightmares and hallucinations.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; AD, adrenaline; NE, norepinephrine; ET, endothelin; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell; MoCA, Montreal Cognitive Assessment; RSAS, Ricker Sedation-Agitation Scale; HADS, Hospital Anxiety and Depression Scale; CAM, Confusion Assessment Method; PCIA, patient-controlled intravenous analgesia; NRS, Numerical rating scale; IL-6,interleukin-6; VAS, Visual analogue scale; PCA, Patient-controlled Analgesia; CRP,;HAD, Hospital Anxiety and Depression Scale; DNR, delayed neurocognitive recovery; MMSE, Mini-Mental State Examination; BIS, bispectral index; POD, postoperative delirium; AIS, Athens Insomnia Scale; QoR, Quality of Recovery; IL-1β, interleukin-1β; RSS, Ramsay Sedation Scale; SAS, Self-rating Anxiety Scale; SDS, Self-Rating Depression Scale; PSQI, Pittsburgh Sleep Quality Index; GDS-15, Geriatric Depression Scale-15; BDNF, brain-derived neurotrophic factor; 5-HT, 5-hydroxytryptamine; TICS-40, Telephone Interview for Cognitive Status-40; ACh, acetylcholine; TNF-α, tumour necrosis factor-α; PSD, Postoperative sleep disturbance; AIS, Athens Insomnia Scale; 3D-CAM, 3-Minute Diagnostic Interview for Confusion Assessment Method-defined Delirium; dNCR, delayed neurocognitive recovery; POCD, postoperative cognitive dysfunction; IL-6, interleukin-6; S100β, calcium-binding protein β; HAMD-17, Hamilton Depression Scale 17; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit.

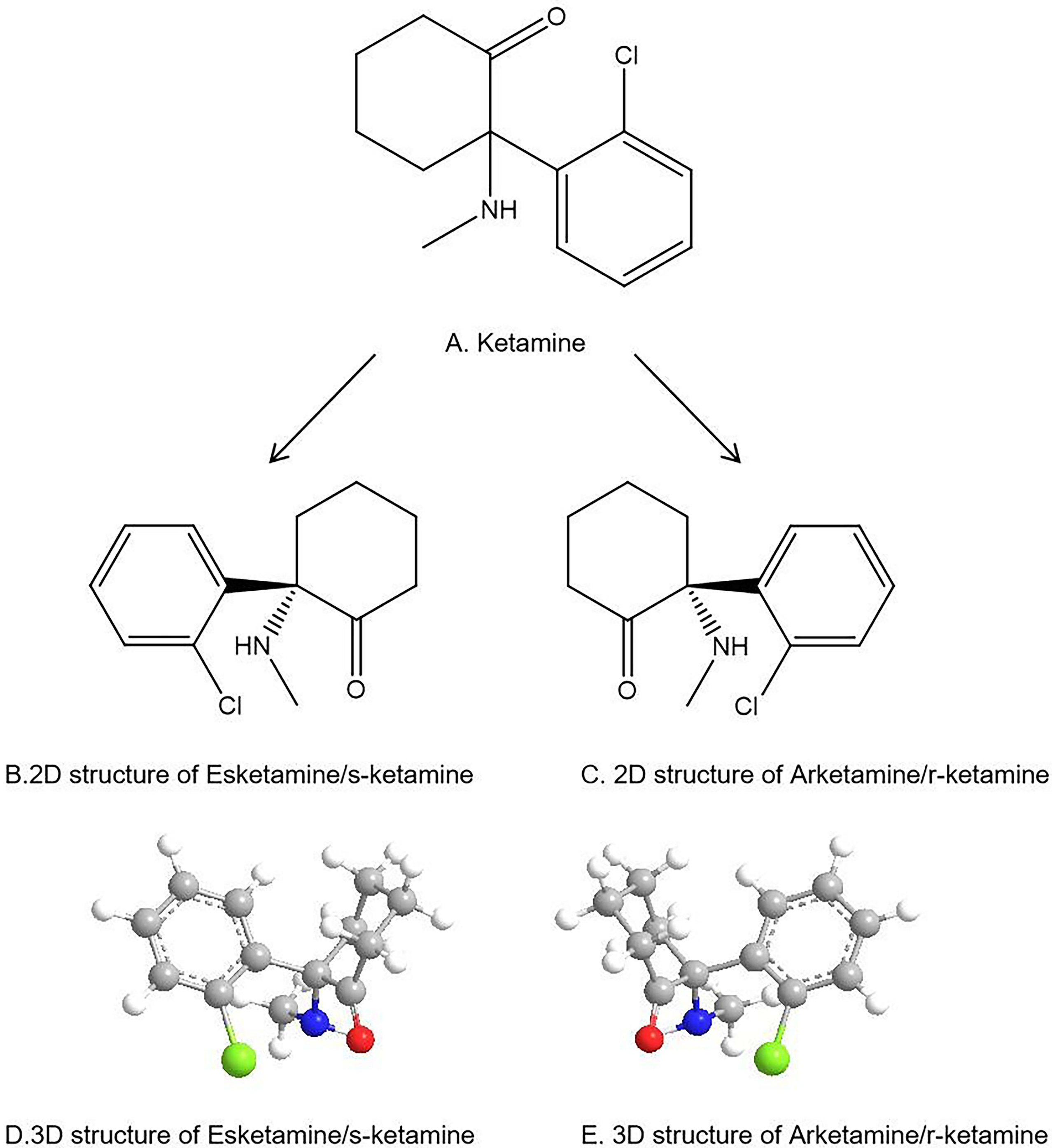

Figure 1 Chemical structure of ketamine (**A**), s-ketamine (**B** and **D**), r-ketamine (**C** and **E**).

117.0 min. Esketamine causes fewer adverse effects than ketamine, with dizziness, nausea, vomiting and drowsiness being common.

A study using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database found gender differences in the adverse effects of ketamine and esketamine.[33] For example, men were more likely to have toxicity to different drugs, bradycardia, cystitis and agitation, while women tended to experience suicidal thoughts, elevated transaminase levels, sclerosing cholangitis and aseptic pyuria. However, there were limitations to that study. First, the data were mostly from the US population; second, there were uncontrollable confounding factors such as age,

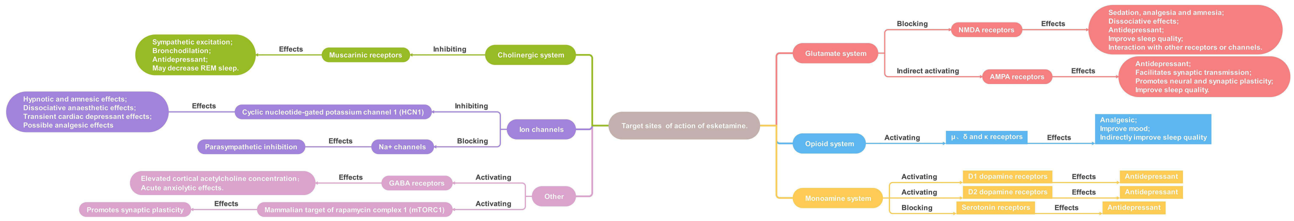

Figure 2 Target sites and effects of esketamine. Data from these studies.[23–25]

underlying medical conditions and drug dose; and third, societal factors also influence the spontaneous reporting of adverse effects. In the future, data sources can be expanded, spontaneous reporting system can be improved, and in-depth studies can be conducted to provide a reference for clinicians to formulate personalized treatment plans and improve drug safety.

Effect of Esketamine on Perioperative Hemodynamics in Elderly Patients

Impaired peripheral perfusion and severe hypotension in patients after anesthesia induction are associated with serious postoperative adverse events. Esketamine (0.2–0.5 mg/kg) as an adjunct to sedation, combined with different drugs, such as midazolam, propofol and etomidate, achieves a satisfactory sedative and analgesic effect, and maintains hemodynamic stability during anesthesia induction.[34] In terms of de-opioidized induction of general anesthesia, the feasibility of esketamine as an analgesic for induction of general anesthesia for tracheal intubation has also been explored.[35]

In a study of 80 elderly patients, Tu et al[6] used propofol combined with esketamine (0.5 mg/kg) instead of sufentanil in the control group for general anesthesia induction. They confirmed that this regimen improved hemodynamics and promoted postoperative recovery of cognitive function, reduced adverse effects, and had good safety and reliability. With regard to the intrinsic sympathomimetic effect of esketamine, tracheal intubation and other procedures often cause catecholamine release and increased peripheral vascular resistance. This results in elevated blood pressure, accelerated heart rate and higher myocardial oxygen consumption, which may increase the risk of perioperative cardiovascular complications.[23,36] In geriatric patients with reduced function of various organs and decreased ability to metabolize drugs, blood concentrations are usually high and the dose administered should be reduced as appropriate. Li et al[7] studied 80 geriatric patients who underwent unilateral total knee arthroplasty under general anesthesia. The experimental group used subanesthetic-dose esketamine (0.2 mg/kg) combined with etomidate (0.2–0.3 mg/kg), sufentanil (0.4–0.5 μg/kg) and rocuronium bromide. The study confirmed that low-dose esketamine for general anesthesia induction better maintained hemodynamic stability and had no adverse effects on early postoperative recovery. The advantages of esketamine in the geriatric population are suggested.

In addition to general anesthesia in the operating theater, an increasing number of surgical options such as painless gastroenteroscopy, bronchoscopy and abortion have been performed under general anesthesia in recent years, as the demand for comfort medicine has increased. This type of non-tracheal intubation general anesthesia requires a fast onset of action, stability, quick recovery and fewer postoperative complications, and a requirement for the safety and efficacy of the anesthetic drug regimen. Currently, the use of propofol as a basic drug for non-tracheal intubation general anesthesia, can cause adverse effects such as respiratory and circulatory inhibition and injection pain. To explore drug combination regimens that can reduce the adverse effects of propofol while maintaining its anesthetic effects, some studies have investigated the effectiveness and safety of esketamine in non-intubation general anesthesia.[4,37–39] A meta-analysis compared the efficacy and safety of propofol in combination with subanesthetic doses of esketamine with traditional anesthetic regimens (eg, propofol alone or in combination with opioids/dezocine/midazolam, etc.) in non-intubation general anesthesia.[40] Propofol combined with a subclinical dose of esketamine under non-intubation general anesthesia provided smoother hemodynamic fluctuations, alleviated injection pain, and significantly reduced the adverse effects of the two drugs, such as respiratory depression, apnea and neuropsychiatric reactions during awakening. This anesthetic regimen has a lower overall incidence of adverse effects than other combinations and may be safer and more effective, especially providing a new option for optimal anesthetic management of elderly patients.[41] The optimal dose of subanesthetic esketamine may need to be validated in additional randomized controlled trials.

Effect of Esketamine on Intraoperative and Postoperative Analgesia in Elderly Patients

Postoperative pain is the most common problem in the perioperative period, enhancing the risk of adverse postoperative events and adversely affecting postoperative recovery. Concerns about opioid adverse effects and risk of addiction have encouraged the use of non-opioid alternatives. Non-opioid analgesics and adjuvants act on different sites within the injury perception system to reduce pain and opioid dependence. Multimodal analgesia has been shown to help reduce the consumption of opioid drugs following various surgical procedures, including orthopedic, gynecological, colorectal and bariatric surgery. Currently, esketamine is receiving particular attention in the field of multimodal analgesia, with more studies identifying additional non-analgesic benefits of its use.

A meta-analysis[42] included 12 studies with 905 adult patients to assess the effect of intravenous esketamine on postoperative pain. Pain scores were observed at 4, 12, 24 and 48 h postoperatively. Intravenous esketamine assisted analgesia in general anesthesia and lowered the pain scores and opioid requirements in the early postoperative period but may have increased the rate of psychotomimetic events. Subgroup analyses showed that this change was more pronounced in the group with intraoperative and postoperative administration compared to the group with intraoperative administration alone.

The same conclusion has been progressively confirmed in the elderly population. Liu et al[8] found that, in elderly patients undergoing gastrointestinal surgery, postoperative analgesia using sufentanil 1.5 μg/kg + esketamine 1 mg/kg reduced opioid use and significantly decreased pain scores at 4, 24 and 48 h post-surgery. The results were confirmed in 150 elderly patients undergoing total hip arthroplasty with postoperative patient-controlled intravenous analgesia (PCIA) using esketamine (2.5 mg/kg).[9] Ma et al[10] studied elderly patients undergoing gastrointestinal surgery. A low dose of esketamine (0.25 mg/kg) was given intraoperatively for anesthetic induction and 0.125 mg/kg/h for maintenance, which significantly reduced pain scores on postoperative day 3. This was consistent with the findings of Jing et al.[11] Evaluating elderly patients receiving thoracic surgery, Lu et al[12] found that a single intraoperative intravenous dose of esketamine 0.5 mg/kg (20 min) significantly reduced pain scores at 1, 6, 12 and 24 h postoperatively compared with dexmedetomidine in elderly patients undergoing thoracic surgery. It also improved postoperative sleep quality. Even in surgery under local anesthesia, the analgesic effect was improved by using 1% lidocaine 200 mg combined with esketamine 25 mg. Although the pain-relieving effect of esketamine was transient in previous studies, it is valuable in the early postoperative period, particularly in the first 24 h, to promote early activity and improve patient comfort.

More randomized controlled trials with larger samples are needed to investigate the safety and efficacy of esketamine-aided analgesia, especially in elderly patients. This is important in enhancing the quality of postoperative recovery and easing the burden on society.

Effect of Esketamine on Postoperative Depression in Elderly Patients

Perioperative depression is a common mood disorder that can increase the risk of complications such as postoperative delirium, pain and infection, significantly affecting postoperative recovery and quality of life.[43–45] However, effective interventions are lacking. In recent years, esketamine, as a fast-acting antidepressant, has been widely studied for the prevention and treatment of perioperative depression due to its unique pharmacological mechanism of action.[27,46–48] In 2019, esketamine nasal sprays were approved by the US Food and Drug Administration for use in refractory depression.

The mechanism of antidepressant effect of esketamine has not been thoroughly clarified.[23–25] Depression is closely related to structural changes in the brain such as the hippocampus and amygdala, glutamine–GABA system, BDNF and its signaling pathways, monoamine neurotransmitters such as 5-hydroxytryptamine (5-HT), activation of microglia, and upregulation of inflammatory factors.[47,49,50] BDNF levels may be negatively correlated with the severity of depressive symptoms. Wang Jie et al showed that S-ketamine increased serum BDNF and 5-HT levels in patients after surgery.[51] Patients with depressive symptoms usually have higher levels of interleukin (IL)-6 and C-reactive protein (CRP).[52,53]

Jiang Ming et al found that the esketamine group had a significant anti-inflammatory function, and expression of pro-inflammatory factors tumor necrosis factor-α, IL-1β, IL-6 and IL-8 decreased.[54] However, Zhang Zhen et al found no significant difference in IL-6 and CRP levels between the esketamine and control groups after bowel resection. This was probably due to the inflammatory reaction caused by the surgery itself masking the anti-inflammatory role of esketamine.[55] Current research on the antidepressant mechanism of esketamine is still limited, and further studies should be carried out to provide a theoretical basis for the development of new antidepressant drugs.

There have been few studies on the perioperative application of esketamine as a rapid antidepressant in the elderly population. Min et al[9] studied 150 patients (age ≥60 years) who underwent elective total hip arthroplasty. Postoperative analgesia was provided by PCIA. Compared with the sufentanil group, patients in the esketamine group (2.5 mg/kg diluted with saline to 100 mL) had significantly lower levels of IL-6 and CRP at 24 and 72 h postoperatively. They also had considerably lower Hospital Anxiety and Depression Scale scores at 3 days and 1 week postoperatively, but there was no difference at 1 month. Esketamine reduced transient depression. One month after surgery, other patient characteristics may have masked the effects of the antidepressant. Cai et al[13] studied 90 patients (age ≥65 years) undergoing elective surgery for hip fractures. Adjunctive esketamine in PCIA (esketamine 0.5 mg/kg, sufentanil 2 μg/kg and tropisetron 5 mg diluted to 100 mL with saline) significantly reduced the Geriatric Depression Scale-15 scores on postoperative day 2. It also increased the levels of BDNF and 5-HT in the blood. Similarly, Liu et al[56] are planning to demonstrate the antidepressant action of esketamine in elderly patients. They intend to recruit 130 perimenopausal women (age 45–60 years) with breast cancer treated with unilateral modified radical mastectomy. Intravenous 0.25 mg/kg esketamine will be given after anesthesia induction and before surgical incision. The incidence of depressive symptoms 30 days after surgery will be explored and evaluated by the Beck Depression Inventory. The study is still in the enrolment phase.

Perioperative depression has an influence on postoperative functional recovery, quality of life and even mortality with increasing age. Moreover, perioperative depression in elderly patients often coexists with neurocognitive disorders. Prevention and treatment of perioperative depression in elderly patients is particularly important. In the future, we will investigate the optimal dosing strategy of esketamine and its effect on postoperative depressive symptoms in elderly patients with or without preoperative depression.

Effect of Esketamine on Postoperative Sleep Disturbance in Elderly Patients

Sleep is an important physiological function in humans, during which the body undergoes several processes, including tissue repair, protein synthesis, immune system strengthening, metabolism, memory enhancement and hormone regulation.[57] Postoperative sleep disorder (PSD) is a common problem, with an incidence of 15–72%, often occurring in elderly patients undergoing major surgery. PSD is related to various factors such as age, gender, pain and anxiety, and may lead to increased sensitivity to pain, postoperative delirium, cognitive deficits and other adverse consequences, which may affect postoperative recovery.[15] Therefore, effective management of PSD is especially important for elderly patients.

In recent years, researchers have begun to focus on the complex interaction between anesthesia and sleep.[57] The use of anesthetics affects sleep architecture: inhalational anesthetics (halothane, desflurane and isoflurane) and intravenous anesthetics (propofol and midazolam) disrupt sleep by inhibiting neurotransmission through their effects on GABA receptors. Opioids, although analgesic, have the adverse effects of inducing arousal, disrupting circadian rhythms and increasing the risk of sleep apnea. Ketamine and esketamine, however, have the potential to ameliorate sleep disorders, but the mechanisms of action are not fully understood[47] (Table 2). Animal studies have shown that esketamine decreased rapid eye movement sleep while increasing slow wave sleep (deep sleep).[58] A previous study of 94 elderly patients undergoing thoracic surgery used the Pittsburgh Sleep Quality Index to evaluate the quality of sleep as a secondary indicator, and found that esketamine was superior to dexmedetomidine in improving postoperative sleep.[12] The study by Wei et al used the Numerical Rating Scale (0 for best quality sleep and 10 for worst) to compare the effect of intraoperative preventive esketamine versus dexmedetomidine on postoperative sleep quality in elderly noncardiac

Table 2 Mechanisms and Reasons for the Improvement of Sleep by Esketamine

Mechanisms of Action	Reasons
Effects on sleep structure	Decrease REM sleep and increase slow-wave sleep (deep sleep).
Anti-inflammatory effects	Reduce activation of the NF-κB pathway (acknowledged regulator of the inflammatory response signaling pathway, closely related to neuroinflammation); Reduce levels of inflammatory factors (IL-6 and TNF-α) in the peripheral blood (improve postoperative complications).
Promotes neurotrophic factor expression	Increase expression of BDNF, which promotes neuroplasticity and repair of neural circuits related to mood and sleep.
NMDA receptor antagonism	Blocking the NMDA receptor reduces the excitatory transmission of glutamate, thereby reducing neuronal hyperexcitability, relieving anxiety and depression, and ultimately improving sleep indirectly.
Neurotrans-mitter modulation	Affects glutamate, GABA, 5-hydroxytryptamine and dopamine. Enhances the inhibitory effect of GABA, reducing hyperexcitability and aiding sleep.
Antidepress-ant and analgesic effects	Indirectly improves sleep problems associated with depression or pain (eg insomnia or hypersomnia).

Notes: Data from these studies[15,47].
Abbreviations: BDNF, brain-derived neurotrophic factor; GABA, γ-aminobutyric acid; IL-6, interleukin-6; NF-κB, nuclear factor-κB; NMDA, N-methyl-D-aspartate; REM, rapid eye movement; TNF-α, tumor necrosis factor-α.

thoracic surgery patients.[14] A single-center, double-blind, placebo-controlled, randomized clinical trial enrolled 183 laparoscopic gynecological surgery patients to investigate the impact of intraoperative injection of esketamine (0.3 mg/kg/h) on the occurrence of PSD.[15] The study suggested that esketamine prevented poor sleep quality and PSD in the postoperative period. Besides, preoperative depression, anxiety scores, anesthesia duration and postoperative pain scores were concluded to be risk factors for PSD. This was the first study to investigate pharmacological prevention of PSD, and no research has focused on the elderly population alone; therefore, large studies are needed to verify the preventive impact of esketamine on PSD.

Effects of Esketamine on Perioperative Neurocognitive Dysfunction in Elderly Patients

Postoperative cognitive dysfunction often occurs in elderly patients and is characterized by declines in memory, attention, information processing and cognitive ability. In 2018, perioperative neurocognitive dysfunction was defined to include acute postoperative delirium (POD), delayed neurocognitive recovery (dNCR; 30 days of recovery), and postoperative neurocognitive dysfunction (POCD; recovery from expected recovery of 30 days to 12 months).[59] Esketamine as a psychoactive drug has hallucinogenic effects and may theoretically lead to perioperative neurocognitive dysfunction. Nevertheless, previous studies have pointed to the potential neuroprotective effects of esketamine.

POD is an acute neuropsychiatric disorder that occurs mainly 2–5 days after surgery. Its pathogenesis and pathophysiology have not been fully elucidated, with multiple theories including: central nervous system injury, neuroinflammation, oxidative stress, worsening circadian rhythms, pain, opioids and sleep deprivation. Inflammation in particular plays a key role. Effective prevention and treatment methods are lacking. Different studies have designed different esketamine dosing regimens to evaluate its effects on postoperative POD.

Zhang et al[16] included 426 patients aged 65–85 years undergoing general anesthesia for non-cardiac surgery, with or without administration of esketamine (0.2 mg/kg, single intravenous injection) prior to anesthesia induction. The esketamine group did not have a significantly lower rate of POD, but had a reduced risk of agitation after awakening. In addition, the timing of the assessment is also worth noting: POD was more common in the morning.[60]

Other studies have obtained different results. A prospective, randomized, controlled clinical trial[8] included 60 patients aged ≥65 years undergoing gastrointestinal surgery. Postoperative analgesia in the experimental group was provided with sufentanil 1.5 μg/kg + esketamine 1 mg/kg. Esketamine reduced the onset of POD compared to sufentanil alone. Lu

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et al[12] evaluated 94 elderly thoracic surgery patients. Dexmedetomidine was administered intravenously at 0.7 μg/kg (>10 min) after anesthesia induction and maintained at 0.2–0.5 μg/kg/h. Esketamine was given intravenously at 0.5 mg/kg (20 min) after anesthesia induction. The incidence of POD was similarly low in the esketamine group. Wei et al[14] conducted a randomized, double-blinded, placebo-controlled and positive-controlled, non-inferiority trial (SKED trial) that only involved elderly patients with thoracic surgery. A loading dose of the study drug was injected 10 min prior to anesthesia induction and a maintenance dose was injected continuously at a constant rate. The dexmedetomidine group was given a loading dose of 0.2 μg/kg and a maintenance dose of 0.2 μg/kg/h. The esketamine group was given a loading dose of 0.25 mg/kg and a maintenance dose of 0.1 mg/kg/h. The aim is to compare the effect of the two drugs on perioperative POD but no results have been published to date. This suggests that the better dose and timing of esketamine in the prevention of POD needs to be further investigated.

Neuroinflammation and neurodegeneration are associated with POCD. Proinflammatory cytokines enter the central nervous system, activating microglia and amplifying neuroinflammation, leading to neuronal apoptosis and POCD. How to effectively control this neuroinflammation and improve postoperative cognitive function through pharmacological interventions remain challenges in current research. It was found that esketamine attenuated POCD by modulating the TLR4/MyD88/MAPK pathway in aged mice.[61] Some studies have identified improvement of postoperative cognitive function by esketamine in elderly patients.

Tu et al[6] studied 80 elderly surgical patients and found that induction of anesthesia with propofol in combination with esketamine (0.5 mg/kg) promoted postoperative cognitive recovery. Ma et al[10] included 68 elderly patients with gastrointestinal cancer surgery. The experimental group was given a low dose of esketamine 0.25 mg/kg for anesthesia induction and 0.125 mg/kg/h for maintenance, which reduced dNCR on postoperative day 3. Han et al[17] studied 84 gastrointestinal surgery patients aged ≥65 years. The esketamine group received an intravenous subanesthetic single dose of 0.15 mg/kg preoperatively. The investigators assessed the patients' cognitive function preoperatively and 7 days and 3 months postoperatively. Esketamine reduced the occurrence of dNCR at 7 days after surgery and improved early postoperative cognitive function but had no effect on long-term neurocognitive prognosis. Lu et al[12] compared the impact of dexmedetomidine and esketamine on postoperative cognitive function. Dexmedetomidine 0.7 μg/kg was given intravenously for >10 min after anesthesia induction and maintained at 0.2–0.5 μg/kg/h. Esketamine 0.5 mg/kg was given intravenously for 20 min after anesthesia induction. Cognitive function was assessed at 1, 3 and 5 days after surgery. Both drugs prevented POCD in elderly thoracic surgery patients, with no significant difference.

However, a recent large clinical study[18] included 209 patients aged 60–86 years who underwent tumor resection. In the experimental group, 0.5 mg/ kg esketamine was given intravenously 10 min after anesthesia induction and PCIA was administered with esketamine (2 mg/kg) and sufentanil. Saline was used in place of esketamine in the control group. There was no significant difference in the occurrence of delirium from 1 to 5 days postoperatively and the rate of cognitive impairment at 90 days postoperatively between the two groups. This is the same as the conclusion of a previous international multicenter randomized controlled trial[19] that a single subanesthetic dose of ketamine did not lower postoperative delirium in adults.

The cognitive enhancement by esketamine changes over time and may occur days or weeks after injection. Thus, the above findings need to be treated with caution and attention paid to the duration of postoperative follow-up. Multicenter trials could be conducted to expand the sample size to validate the above findings; long-term follow-up could be performed to evaluate the effects of esketamine on postoperative cognitive function; and the influence on different types of patient groups and surgery could be explored.

Adverse Events

The common side effects of esketamine include the following: 1) Elevated blood pressure and heart rate, which are typically transient and usually resolve after discontinuation without special intervention. Use of esketamine in combination with medications such as propofol may help stabilize circulation. 2) Neuropsychiatric symptoms, such as agitation, excessive dreaming, hallucinations, nightmares and headaches during the recovery period or postoperatively. These symptoms are largely transient and can generally be managed with psychological counseling. If necessary, sedatives such as dexmedetomidine may be administered to ensure that patients transition smoothly through the recovery period. 3)

Nausea, vomiting, increased respiratory secretions and blurred vision, which can be prevented with antiemetic drugs (ondansetron) and anticholinergic drugs (penehyclidine or atropine). Currently, no studies have clearly indicated the dose at which esketamine causes severe adverse reactions. Previous studies[6,31] have confirmed that a single esketamine dose of 0.5 mg/kg, the recommended dose on the product label, significantly increases heart rate and blood pressure with no serious adverse events. Given that elderly patients often have multiple comorbidities, maintaining hemodynamic stability during induction is important. Therefore, a single low dose of esketamine (0.2 mg/kg) is recommended to achieve clinical benefits while avoiding other adverse events (such as tachycardia).[7] The optimal low-dose range has not yet been clarified by studies for elderly. Some studies[9,40] have also shown that low-dose esketamine might decrease adverse reactions associated with the combination of propofol and other drugs; however, higher-level evidence is needed to validate this finding.

Summary and Prospects

Currently, esketamine is widely applied in clinical practice, and its benefits are gradually being explored and accepted by anesthesiologists. Various uses have been developed, such as intranasal or intramuscular administration. However, while exploring the value of this drug, researchers must be wary of potential abuse liability and adverse events, and carefully monitor its addictive properties.

Esketamine has been consistently recognized by clinical practitioners for its roles in maintaining hemodynamic stability after anesthesia induction and decreasing opioid doses in intraoperative and postoperative analgesia. However, dosage issues must be noted. As an adjunctive drug for general anesthesia induction in elderly patients, a single low dose of esketamine is recommended. Current evidence is insufficient to support the efficacy of esketamine in ameliorating perioperative anxiety, depression, sleep, and neurocognitive dysfunction. Large-scale, multi-center clinical studies are needed to further validate these findings. Relevant clinical models and animal experiments are recommended to clarify the underlying molecular mechanisms. In addition, clinical studies with subanesthetic doses of esketamine are encouraged. It is prudent to extend the current findings to other populations and healthcare institutions prior to validation in multicenter trials with large sample sizes.

Disclosure

The authors report no conflicts of interest in this work.

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