

The prevention and treatment of postoperative delirium in elderly patients with ketamine

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Abstract. Elderly surgical populations are highly susceptible to Postoperative Delirium (POD), whose core pathological drivers consist of neuroinflammation and impaired Blood-Brain Barrier (BBB) function. Characterized by prominent lipophilicity, esketamine is capable of fast trans-BBB transportation. This agent exerts protective effects on BBB integrity via blocking NMDA receptors, which further suppresses the activation of the TLR4/NF- κ B signaling cascade and limits the secretion of pro-inflammatory mediators. Multiple clinical observations have verified that low-dose esketamine administered either at anesthetic induction or as an isolated intraoperative bolus lowers POD risks among seniors receiving orthopedic or abdominal operations. This pharmacological intervention presents favorable safety profiles: it does not raise the likelihood of mental adverse events, while mitigating perioperative side effects including hypotension, emesis and nausea. Nevertheless, current relevant research still carries prominent limitations such as insufficient sample sizes and inconsistent diagnostic standards for POD. Two critical unresolved questions remain in this field: the establishment of standardized optimal administration protocols, as well as whether esketamine's anti-inflammatory properties function separately from its analgesic potency. Integrating the above pharmacological mechanisms and clinical data can provide the basis for shifting perioperative brain protection strategies toward mechanism-targeted intervention.

Keywords: esketamine, postoperative delirium, elderly patients, anti-inflammatory, anesthesia

1. Introduction

Elderly individuals frequently suffer from Postoperative Delirium (POD), a typical nervous system adverse event triggered by surgical procedures and general anesthesia. This syndrome presents core clinical symptoms such as impaired concentration, fluctuating awareness and disordered cognition. One meta-analysis concentrating on hip-fracture seniors quantified the POD occurrence rate following orthopedic repair as 23% (95% CI: 20%–26%) [1], and another independent study reached an identical 23% morbidity figure within aged cohorts [2]. Beyond extended inpatient duration and elevated medical expenditure, POD also serves as a strong predictive marker for increased post-operative mortality risk. Unfortunately, clinicians still lack reliable pharmaceutical interventions to stop this complication from developing.

As an antagonist targeting N-Methyl-D-Aspartate (NMDA) receptors, esketamine shares identical pharmacological pathways and target locations with its racemic counterpart ketamine. Distinctive advantages

of esketamine include 3–4 times higher binding affinity toward NMDA receptors and 2–2.5-fold superior analgesic efficacy, alongside a lower incidence of psychiatric unwanted effects [3]. An expanding body of literature has explored its perioperative administration, with particular focus on senior surgical populations [3]. Nevertheless, existing relevant research remains fragmented: scholars separately explore its molecular mechanisms or real-world clinical performance without comprehensive synthetic analysis. Up to now, no universal consensus has been reached regarding standardized medication parameters, including optimal dosage, delivery time window and compatible combined therapeutic schemes.

In view of the above problems, this paper systematically integrates the relevant mechanism research, clinical efficacy and safety evidence of esketamine in the prevention of POD in elderly patients, focusing on the differences between its anti-inflammatory and analgesic mechanisms, dose-response relationship, and potential effects independent of pain control.

2. Pathogenesis of POD

Aging is an important risk factor for Blood-Brain Barrier (BBB) dysfunction. With advancing age, degenerative alterations occur in the brain microvasculature, BBB integrity deteriorates, and the risks of neuroinflammation, neurotoxicity and cerebral edema rise correspondingly [2]. At the same time, the perioperative period itself is a state of strong stress. Anesthesia and surgical operation can further damage the BBB and affect brain metabolic function, which is closely related to the occurrence of POD. In the above processes, the activation of Matrix Metalloproteinase 9 (MMP-9) is considered a key mediator. Animal experiments have shown that anesthesia and surgery can activate MMP-9, which in turn can damage the BBB and induce POD-like behavior, which is more obvious in older individuals. Inhibition of MMP-9 can alleviate the above damage and protect the BBB [3]. In addition, neuroinflammation can mediate microglial activation, which in turn affects synaptic remodeling [2]. In general, inhibiting the activation of MMP-9, reducing BBB damage, or lowering the level of neuroinflammation in the early stage is expected to block the pathogenesis of POD at its root.

3. Mechanism of esketamine in preventing and treating POD

3.1. Rapid blood-brain barrier permeation underlies central therapeutic efficacy

Esketamine has the characteristics of high lipid solubility and rapid onset of action. The peak blood concentration can be reached 1-2 minutes after intravenous injection, so it can rapidly enter the central nervous system through the BBB to exert its effect [3]. Compared with ketamine, esketamine has a shorter half-life and allows faster awakening, which means that its central exposure time is more controllable and conducive to perioperative anesthesia management [3]. The above pharmacokinetic characteristics provide the basis for its direct neuroprotective effect at the central level, and are also an important prerequisite for the prevention and treatment of POD.

3.2. Inhibit neuroinflammation and reduce the level of inflammatory factors

Neuroinflammatory response is one of the core pathological mechanisms of POD. Esketamine can inhibit the activation of microglia, thereby reducing the release of inflammatory factors. Some reviews have systematically summarized the anti-inflammatory mechanism: esketamine reduces the transcription and release of pro-inflammatory factors such as IL-1 β , IL-6, TNF- α by blocking NMDA receptors and inhibiting the activation of the downstream TLR4/NF- κ B signaling pathway [4]. A randomized controlled trial of

gastrointestinal surgery in the elderly also supports this mechanism. The trial showed that the level of postoperative inflammatory factors in the esketamine group was significantly lower than that in the control group, and the incidence of POD was significantly decreased [5]. In addition, an RCT on thoracoscopic lung cancer surgery in the elderly also confirmed that esketamine combined with dexmedetomidine regimen can further reduce the level of inflammation (such as IL-6) and reduce the occurrence of POD [6, 7]. From these results, the anti-inflammatory effect should be one of the important mechanisms of esketamine in preventing POD.

3.3. Potential targets for protecting BBB integrity

BBB disruption is a key link in the occurrence of POD, and MMP-9, as a key enzyme that degrades BBB tight junction proteins, may play an important role. A prior study found that elevated serum MMP-9 is associated with postoperative cognitive impairment and proposed a mechanism involving BBB disruption [3]. Inhibition of MMP-9 activity helps protect the BBB. However, direct evidence showing that esketamine inhibits POD via MMP-9 is not yet available. This has not yet been resolved by animal and human studies.

3.4. Mechanism summary

Table 1. Core mechanism and clinical evidence summary of esketamine in the prevention and treatment of POD in elderly patients

Core pathological mechanism	Target/pathway of esketamine	Main effects	Types of evidence	Ref.
BBB disruption	Quickly pass through the BBB and increase the central drug concentration	Ensure effective exposure of the central nervous system and provide pharmacokinetic basis for neuroprotection	Review	[3]
Neuroinflammatory response	Blocking NMDA receptor and inhibiting TLR4/NF- κ B signaling pathway	Reduce the transcription and release of pro-inflammatory factors such as IL-1 β , IL-6, TNF- α	Animal experiments; RCT	[4, 5]
Microglia and synaptic remodeling disorders	Inhibition of microglial activation	Reduce perioperative neuroinflammation and protect synaptic plasticity	RCT	[5, 6]
Clinical manifestations of POD	Single agent (0.2-0.3 mg/kg) or combined with dexmedetomidine	Reduce the incidence of POD in elderly patients undergoing orthopedic, abdominal and thoracic surgery	Meta-analysis; RCT	[6, 8]
Perioperative safety	Low to medium dose regimen	Reduce the risk of postoperative nausea, vomiting and hypotension without increasing mental side effects	Meta-analysis	[9]

The way esketamine is thought to prevent POD has three parts. First, the drug has a good ability to cross the Blood-Brain Barrier (BBB) and reaches high concentrations in the central nervous system. Second, it suppresses the TLR4/NF- κ B pathway and reduces the production of pro-inflammatory factors. Thirdly, it may

help stabilize the BBB by changing the activity of MMP-9. Together, these measures are believed to inhibit the path of POD. Table 1 shows the above mechanisms and related clinical evidence.

4. Clinical efficacy and safety of esketamine in the prevention and treatment of POD

4.1. Dose-effect relationship

The efficacy of esketamine is dose-dependent, but a consensus on its optimal preventive dose in elderly patients has not yet been reached. Low dose may not effectively reduce the incidence of POD, while high dose may increase the risk of hemodynamic fluctuations and mental side effects. Some dose exploratory RCTs suggested that low and medium doses (0.15-0.3 mg/kg) had better hemodynamic stability, while high doses (e.g., 0.5 mg/kg) did not provide additional benefit [5]. It is worth noting that there were also RCTs using low doses (0.20 mg/kg) that did not observe a significant decrease in the incidence of POD [7], suggesting that the optimal preventive dose is still controversial and needs further stratified research. According to existing meta-analyses, low and medium doses are generally considered safe and effective for elderly patients [8, 9].

4.2. Clinical effect of single use and combined use of drugs

Esketamine can be administered alone perioperatively for the prevention of Postoperative Delirium (POD), or given in combination with other sedatives and analgesics including dexmedetomidine. The Dosing schedule will affect the level of prevention by working in cooperation or independently. Based on RCTs and meta-analyses, a single intravenous bolus of esketamine (0.2-0.3 mg/kg) can be given before or during anesthesia induction to reduce the incidence of POD in older adults undergoing orthopedic, abdominal and thoracic surgery [5, 6, 8]. Data from elderly lung cancer patients with pre-existing cerebral damage show that esketamine and dexmedetomidine, when used together, are more protective than either one alone in combination therapy. Collectively, they can reduce the incidence of POD and improve postoperative quality of life [6]. In short, all the above indicate that the two may work better together to exert anti-inflammatory and sedative effects and reduce opioid consumption.

4.3. Safety analysis

Any perioperative medication use should be based on a full risk-benefit assessment. While exerting neuroprotective and analgesic effects, esketamine may also cause adverse reactions such as increased blood pressure, faster heart rate, and psychiatric symptoms, especially in elderly patients. Existing studies have shown that esketamine is generally well tolerated. Compared with the control group, esketamine can reduce the risk of postoperative nausea and vomiting [9]. A meta-analysis of 17 RCTs showed that esketamine could significantly reduce the risk of hypotension ($RR = 0.24$) [9]. However, esketamine is also associated with some side effects, and dizziness and perioperative hypertension are relatively frequent. Data available do not show a statistical difference between esketamine and the control group for psychiatric symptoms such as hallucinations and nightmares [3, 9]. Esketamine is generally considered to have a relatively low risk at a low dose, and its benefits will likely outweigh the risks.

4.4. Limitations of current clinical evidence

Although most of the current research is positive about esketamine for POD prevention, these results should be taken cautiously. Most RCTs have some methodological defects. The sample size is relatively small, and

most of the treatment groups have fewer than 50 patients. The follow-up time is relatively short, generally 3-7 days after surgery, and it may be too early to observe late-onset cognitive decline. In addition, the criteria for POD diagnosis vary among research groups; some use CAM, others use CAM-ICU, and thus there are inconsistent evaluations [8, 10]. Therefore, it is difficult to know whether the present results apply to more people.

Research results from published RCTs are also not uniform. Some trials have shown a protective effect of esketamine for delirium, but others have not found one [7]. There are many reasons for the above differences, such as the kind of operation, the patient's psychological condition before surgery, and specific anesthesia plans. There are no direct comparisons of esketamine with other well-known prophylactic drugs, such as dexmedetomidine and melatonin, in the existing literature either. Based on the above deficiencies, future studies need to conduct large-scale, multi-center prospective studies to verify and extend the preliminary results.

5. Conclusion

Existing studies have basically clarified the core mechanism and clinical value of esketamine in the prevention and treatment of POD in elderly patients. In view of the high incidence of POD in elderly patients, the serious harm of POD, and the lack of specific preventive drugs, esketamine can quickly enter the central nervous system through the BBB by virtue of its high lipid solubility and rapid onset of action, which provides a pharmacokinetic basis for its neuroprotective effect. From the perspective of mechanism, the drug can inhibit the activation of microglia and reduce the levels of inflammatory factors such as TNF- α and IL-6, thereby alleviating the perioperative neuroinflammatory response. At the same time, animal experiments suggested that it might maintain the integrity of BBB by inhibiting MMP-9 activity, and thus block the pathogenic cascade of POD. Clinical studies have further confirmed that a single administration of esketamine before or during anesthesia induction can significantly reduce the incidence of POD in elderly patients undergoing orthopedic, abdominal, or thoracic surgery. Among them, the hemodynamics of low to medium dose regimens are more stable and the benefits are clearer, while the high dose does not show additional advantages. When combined with dexmedetomidine, the prevention effect is better, which can further reduce the incidence of POD and improve sleep quality. In terms of safety, esketamine is generally well tolerated. Although it may increase the risk of dizziness and perioperative hypertension, it has no obvious mental side effects, and it is helpful to reduce the incidence of postoperative nausea, vomiting and hypotension.

Future studies need to further clarify the optimal dose and timing of administration in different types of surgery (such as heart, tumor, orthopedics, etc.), and explore whether the effect of esketamine in preventing POD is independent of pain control, and whether its anti-inflammatory effect and analgesic effect can be distinguished in mechanism. In addition, paying attention to the potential impact of the drug on the immune microenvironment of tumor patients during the perioperative period, and developing a combination drug strategy closer to clinical practice, will help promote the optimization of individualized anesthesia regimens.

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