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REVIEW

Progress in the Application of Esketamine During the Perioperative Period

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Abstract: Esketamine is the S-enantiomer of ketamine. As a potent NMDA receptor antagonist with high affinity, it exhibits sedative, analgesic, and antidepressant properties, among others. Compared with racemic ketamine, esketamine demonstrates approximately twice the potency, along with several advantages: a rapid onset of action, mild respiratory depression, and fewer adverse psychiatric effects. In recent years, the perioperative application of esketamine has garnered increasing attention. It has demonstrated potential application value in clinical practice, particularly in obstetric anesthesia, pediatric surgical anesthesia, orthopedic surgical anesthesia, painless diagnostic and therapeutic procedures, and special clinical scenarios. The pharmacological mechanism of esketamine has not been fully elucidated to date, and research on its perioperative application remains relatively limited. High quality evidence from large-sample, multicenter studies is scarce, and no unified standard has been established for its administration regimens and dosages. Nonetheless, this paper provides a summary of the pharmacological properties, potential mechanisms of action, and current clinical applications of esketamine across diverse clinical scenarios, with the overarching goal of providing evidence to support its rational use in clinical practice.

Keywords: esketamine, perioperative application, sedation, analgesia, antidepressant

Introduction

Since esketamine was first granted marketing approval for clinical use in Germany in 1997, it has since been approved for clinical application in numerous countries worldwide. Esketamine, administered intranasally, is approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2019. The agent was concurrently granted marketing approval in China that same year. It is indicated in combination with a selective serotonin reuptake inhibitor (SSRI) or a serotonin and norepinephrine reuptake inhibitor (SNRI) for the treatment of treatment-resistant depression (TRD) and major depressive disorder (MDD) accompanied by suicidal ideation in adult patients. According to an EMA assessment report, esketamine is also approved in several European Union countries for the induction and maintenance of anesthesia when administered intravenously or intramuscularly. Beyond its approved indications, it is used off-label for conditions including acute and chronic pain (eg, cancer breakthrough pain), post-operative complications (such as postoperative pain and cognitive impairment), and various psychiatric disorders among them post-traumatic stress disorder (PTSD), anxiety, bipolar disorder (both type I and II), obsessive-compulsive disorder (OCD), and suicidal ideation. Off-label applications of both ketamine and esketamine further extend to the management of epilepsy and migraine.[1–3] Now it has gained widespread use across a broad spectrum of clinical settings, including anesthesia induction and maintenance, perioperative pain management, painless diagnostic and therapeutic interventions, antidepressant therapy, and emergency and critical care during the perioperative period.[4,5] This article presents a review of the current applications of esketamine in the perioperative phase and other clinical scenarios, thereby furnishing valuable guidance for its use in future clinical practice and research endeavors.

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Search Strategy and Eligibility Criteria

This narrative review was conducted based on a systematic literature search across two core databases, namely PubMed and Web of Science. The search timeframe was set from January 1, 2010, to November 1, 2025 (final search date: November 1, 2025), to ensure the inclusion of the most recent research findings. The entire search process adhered to the principles of systematic literature retrieval, so as to contribute to the objectivity and reproducibility of literature screening. The search strategy combined subject headings with free-text terms, and the core keywords included: ketamine, S-ketamine, esketamine, anesthesia, hypnosis and sedation, analgesia, antidepressant effects, obstetrics, pediatrics, orthopedics, gastrointestinal endoscopy, emergency medicine, and critical care medicine. Furthermore, to comprehensively cover research on the pharmacological mechanisms of esketamine, the search scope was expanded to include mechanism studies related to its pharmacological properties, encompassing signal pathway research associated with the NMDA receptor, AMPA receptor, HCN-1, opioid receptors, and the monoaminergic system. The inclusion criteria were explicitly defined as follows: study types included animal experiments, cell model studies, clinical controlled trials (comprising randomized controlled trials (RCTs) and non-randomized controlled trials), and relevant review articles; the language of publications was restricted to English. The exclusion criteria were: editorials, letters to the editor, conference abstracts, studies based on non-mammalian models, literatures with incomplete abstract information, and research for which full texts were unavailable or with significant data deficiencies. The literature selection process adopted a two-independent-reviewer screening model, with specific procedures as follows: first, two researchers independently performed literature searches in accordance with the aforementioned search strategy; after removing duplicate records using EndNote software, initial screening was conducted based on titles and abstracts to exclude studies that clearly did not meet the inclusion criteria. Subsequently, full texts of the literature that passed the initial screening were retrieved for further evaluation, and each article was carefully checked against the inclusion and exclusion criteria to complete the secondary screening. In cases of discrepancies between the two reviewers during the screening process, a third researcher was consulted for joint adjudication to reach a consensus, thereby finalizing the set of literatures included in the analysis and minimizing selection bias to the greatest extent possible.

Pharmacological Properties and Mechanism of Action

Ketamine, a derivative of Phencyclidine (PCP), is a racemic mixture composed of equal amounts of S-and R-enantiomers, whereas esketamine is its pure dextrorotatory S-enantiomer.[6] As a classic noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine shares similar pharmacological effects with esketamine; however, esketamine has a 3- to 4-fold greater affinity for NMDA receptors and a 2-to 3-fold greater analgesic potency than ketamine does.[7,8] Notably, esketamine is characterized by high potency, a lower incidence of adverse psychiatric effects, and prominent analgesic effect.[9,10] Owing to its higher NMDA receptor affinity, favorable lipid and water solubility, and easy penetration of the blood–brain barrier, esketamine has a faster onset of action than ketamine does. Following intravenous administration of 0.5 $mg \cdot kg^{-1}$ esketamine, the time to reach peak plasma concentration (T_{max}) was only 70 seconds. Its pharmacokinetic parameters are as follows: the volume distribution (Vd) is (7390 ± 2704) $mL \cdot kg^{-1}$, the clearance (CL) is (18.1 ± 3.2) $mL \cdot min^{-1} \cdot kg^{-1}$, and the half-life ($t_1/_2$) is (288 ± 110) minutes.[11–13] These parameters indicate that esketamine has distinct pharmacokinetic properties, namely, a large apparent distribution volume, a long half-life, and a slow clearance rate. Clinically, this agent is characterized by a rapid onset of action and a relatively prolonged metabolic duration a profile that coincides well with its key clinical merits: rapid antidepressant efficacy and sustained analgesic effects. Conversely, this prolonged metabolic duration may also extend the duration of adverse reactions.[14,15] The primary metabolic pathway of esketamine involves biotransformation by hepatic cytochrome P450 (CYP450) enzymes (along with other auxiliary pathways) into norketamine and its hydroxylated derivatives. Most of these metabolites are excreted via the renal or biliary route following conjugation with glucuronic acid.[12,16–18] In addition to interacting with NMDA receptors, esketamine interacts with multiple targets including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, opioid receptors, monoaminergic systems, and ion channels to synergistically exert sedative, hypnotic, analgesic, and antidepressant effects (Figure 1).[19]

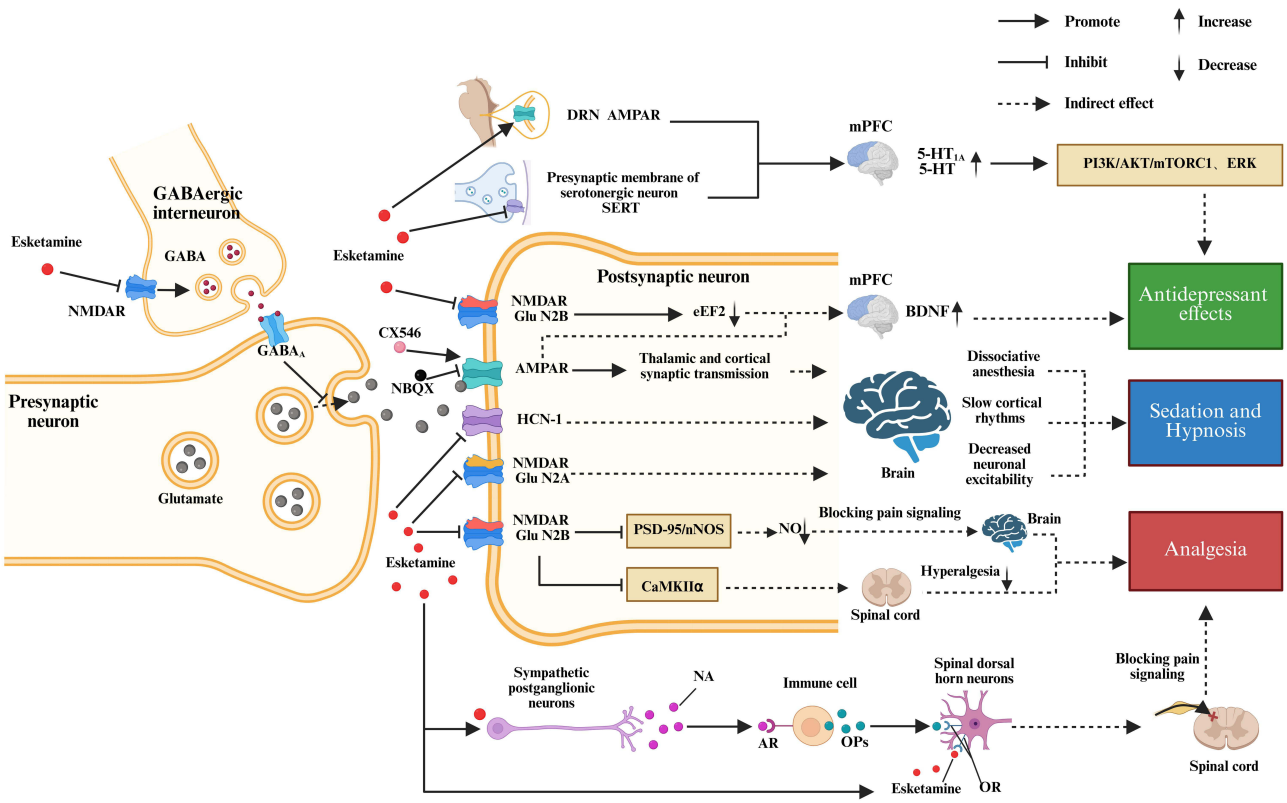

Figure 1 Simple diagram explaining how esketamine produces sedation, analgesia and antidepressant effects. Esketamine acts on NMDA-GluN2A/GluN2B subunits and HCN-1; the blockade of NMDA receptor channels and inhibition of HCN-1 contribute to its effects on loss of consciousness, analgesia, and antidepressant action. It also inhibits presynaptic NMDA receptors to disinhibit glutamatergic neurons, indirectly activating AMPA receptors for dissociative anesthesia and hypnosis. Moreover, following the activation of AMPA receptors in the dorsal raphe nucleus (DRN), the serotonergic (5-HT) system is simultaneously modulated, which in turn exerts antidepressant effects in a coordinated manner. Additionally, stimulation of sympathetic pathways promotes norepinephrine (NA) release, which then drives the secretion of opioids (OPs) from immune cells. Both esketamine and OPs act on opioid receptors in the spinal dorsal horn to exert analgesic effects. This figure is original work by the authors.

Sedative and Hypnotic Effects

Esketamine primarily inhibits glutamate activation and reduces neuronal excitability by acting on specific GluN2A subunits of NMDA receptors within synaptic compartments. In this process, AMPA receptors are indirectly activated, while thalamocortical synaptic transmission is enhanced, thereby inducing the characteristic dissociative state of consciousness (ie, "dissociative anesthesia") and ultimately producing a hypnotic effect.[20–23] Esketamine additionally exhibits voltage-dependent activity that directly inhibits hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 (HCN-1). This inhibition induces membrane hyperpolarization and enhances dendritic synaptic coupling effects that further promote cortical synchronization, support slow cortical rhythms, and contribute to hypnosis induction. Studies have demonstrated that HCN-1 mediates approximately 30–80% of the hypnotic effect of esketamine and plays a key role in mediating cortical synchronization and neuronal activity switching. Notably, the hypnotic effect is attenuated in the absence of HCN-1, indicating that HCN-1 may be the core target underlying the sedative-hypnotic effects of esketamine (Figure 1).[24–26]

Analgesic Effects

Esketamine exerts a primary inhibitory effect on pain signal transduction by selectively targeting and binding to the GluN2B subunit within the extracellular domain of N-methyl-D-aspartate (NMDA) receptors, which in turn suppresses the GluN2B/PSD-95/nNOS signaling axis and attenuates nitric oxide (NO) release.[27] Concomitantly, by suppressing the activation of the GluN2B/CaMKIIα pathway in the spinal cord, esketamine effectively prevents central sensitization and pain hypersensitivity.[28] In addition, the analgesic effects of esketamine are thought to involve modulation of the opioid system. On the one hand, esketamine directly activates μ- and δ-opioid receptors to elicit analgesia.[29] On the other hand,

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through activation of the sympathetic nervous system, it promotes the binding of norepinephrine (NA) to peripheral adrenergic receptors (AR) on sympathetic preganglionic neurons; this stimulates immune cells to release endogenous opioid peptides, which then act on spinal dorsal horn neurons, blocking pain pathways and thereby achieving indirect analgesic effects (Figure 1).[30–32]

Antidepressant Effects

Esketamine primarily exerts its antidepressant effects by blocking the GluN2B subunit of NMDA receptors and inhibiting the kinase activity of eukaryotic elongation factor 2 (eEF2), thereby promoting the synthesis of brain-derived neurotrophic factor (BDNF), which in turn rapidly and sustainably alleviates depressive symptoms.[33,34] Notably, AMPA receptor activation serves as an essential synergistic mediator in this pathway; the administration of the AMPA receptor antagonist NBQX completely abrogates the antidepressant effects of ketamine, whereas the AMPA receptor agonist CX546 elevates BDNF levels in the hippocampus and medial prefrontal cortex (mPFC). These findings confirm that AMPA receptors function as key molecular switches for the therapeutic efficacy of esketamine.[35] Esketamine may also systemically inhibit the serotonin transporter (SERT) and activate AMPA receptors in the dorsal raphe nucleus (DRN) via serotonin (5-HT) modulation, effects that synergistically increase 5-HT levels in the mPFC. Activation of 5-HT_{1A} receptors subsequently triggers downstream signaling cascades, including the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin complex 1 (mTORC1) pathway and the extracellular signal-regulated kinase (ERK) pathway, which ultimately mediate rapid antidepressant effects (Figure 1).[23,36,37] In recent years, emerging evidence has suggested that opioid receptors may mediate, in part, the antidepressant effects of esketamine; studies have demonstrated that the opioid receptor (OR) antagonist naltrexone attenuates the antidepressant and antisuicidal effects of esketamine.[38]

Although the sedative, analgesic, and antidepressant mechanisms of esketamine are complex and have not yet been fully elucidated, it is widely accepted that the direct and indirect antagonism of NMDA receptors, together with the modulation of AMPA receptor-mediated flux, constitute the neurochemical substrate for its antidepressant effects.[39,40] Other potential mechanisms underlying the action of esketamine are also under active investigation. For instance, opioid receptors have been proposed as potential targets, although this view remains a subject of debate in the field.[41]

Clinical Application of Esketamine During the Perioperative Period

Clinical Application of Esketamine in Obstetric Surgery

Postpartum depression (PPD) is among the most prevalent psychiatric disorders following childbirth and has a relatively high incidence. It has profoundly adverse effects on the health of mothers, infants, and families. Currently, the available preventive and therapeutic modalities for PPD are limited, and their efficacy remains inconsistent.[42] As a novel antidepressant, esketamine may hold potential value in the prevention and treatment of PPD. Studies have demonstrated that in most cases, esketamine infusion during pregnancy does not appear to affect uterine perfusion or maternal-fetal hemodynamics, with mild effect on respiration, which supports its potential safety for use in obstetric procedures under careful monitoring.[43] Continuous intravenous infusion of esketamine at 0.2–0.25 $mg \cdot kg^{-1}$ after delivery reduced the Edinburgh Postnatal Depression Scale (EPDS) scores and PPD incidence in parturients at 3 days, 1 week, and 6 weeks post-partum, while improving their postpartum depressive symptoms.[44–46] Although the overall incidence of adverse psychiatric events associated with esketamine is relatively high, most symptoms are transient and typically do not require pharmacologic intervention in clinical practice. To date, no clinical safety risks beyond the scope of routine clinical management have been identified in available studies, though long-term data remain limited. The individualized risks of short-term neuropsychiatric adverse reactions, as well as the long-term safety profile of esketamine, still warrant further clinical monitoring and evaluation.[44] Furthermore, a single intravenous dose of esketamine (0.2 $mg \cdot kg^{-1}$ or 0.25 $mg \cdot kg^{-1}$) administered immediately after fetal delivery, vaginal delivery or cesarean delivery, could reduce the incidence of PPD at 1 week and 6 weeks post-partum without a significant increase in the rate of adverse reactions in the studied population.[47–49] Esketamine for patient-controlled analgesia (PCA) could also lower the risk of PPD: When parturients received esketamine for patient-controlled epidural analgesia (PCEA) at 0.2 $mg \cdot kg^{-1}$, patient-controlled

intravenous analgesia (PCIA) at 0.5 mg·kg^{-1}, or a single dose of 1.5 mg·kg^{-1}, the incidence of PPD at 1 week and 6 weeks post-partum was reduced by more than 50% compared with that of the control group, with no increase in postoperative adverse event rates.[50–52]

On the basis of current research evidence, esketamine application in obstetric settings (including labor analgesia and cesarean delivery) despite variations in administration routes could reduce the incidence of PPD. With its dual effects of antidepressant activity and synergistic analgesia, coupled with favorable safety profiles, esketamine represents a novel agent that can be used to prevent postpartum depression and optimize perioperative pain management. Although high-level studies have supported the efficacy of esketamine in reducing postpartum depression, most such studies are single-center designs with notable limitations, including a relatively high loss to follow-up rate in some trials and over-reliance on the subjective EPDS for outcome assessment (Table 1). The core efficacy conclusions are generally consistent across different routes of administration, while slight heterogeneity exists in the reported incidence of adverse reactions.

Clinical Application of Esketamine in Pediatric Surgery

The incidence of preoperative anxiety in children undergoing elective surgery is as high as 60–70%, which often presents as crying and fear. This not only increases the difficulty of anesthesia induction but also increases the incidence of postanesthesia care unit (PACU) restlessness and postoperative behavioral changes.[53] Therefore, implementing appropriate sedation strategies is crucial for minimizing psychological trauma and optimizing perioperative management. Esketamine, a viable option for pediatric anesthesia, exerts synergistic anxiolytic and analgesic effects that may help reduce the incidence of postoperative complications in children and shorten postoperative recovery time.[82] Because of fear and pain, pediatric patients often fail to cooperate with venipuncture, making intranasal esketamine administration advantageous. Studies have shown that preoperatively (30–40 minutes before surgery), intranasal administration of esketamine 0.5 mg·kg^{-1} combined with dexmedetomidine 1 μg·kg^{-1} as an adjuvant agent improved anesthesia induction compliance and increased the sedation success rate while shortening recovery time. Additionally, this combination reduced the incidence of pediatric emergence delirium (ED) in the PACU, the rate of behavioral changes on postoperative day 7, and the severity of postoperative restlessness.[53,54] Furthermore, either intranasal esketamine (1 mg·kg^{-1}) alone or dexmedetomidine (1 μg·kg^{-1}) alone could provide satisfactory sedation for children aged 1–3 years who underwent transthoracic echocardiography. This approach achieved a sedation success rate of up to 85.4%, with rapid onset of action, prompt awakening, and relatively mild adverse effects in most pediatric patients who received this regimen.[55] It has also been reported that combining intranasal esketamine (2 mg·kg^{-1}) with oral midazolam (0.5 mg·kg^{-1}) results in clinically acceptable moderate sedation with favorable safety and efficacy for dental procedures in children aged 2–6 years.[56] When esketamine (0.4–0.6 mg·kg^{-1}) was administered intravenously in combination with propofol, a dose-dependent increase in anesthetic efficacy was observed. As the esketamine dose increased to 0.6 mg·kg^{-1}, the intraoperative movement rate decreased from 35% to 5%. Concurrently, the propofol requirement was reduced, intraoperative hemodynamics remained relatively stable, with no concomitant increase in the incidence of adverse reactions.[57] Moreover, intravenous esketamine combined with propofol for painless outpatient procedures in children aged 1–12 years resulted in better sedative effects, relatively stable hemodynamics, a low incidence of respiratory depression, and increased satisfaction among examining physicians regarding the procedure.[58–61] However, it should still be noted that esketamine, an NMDA receptor antagonist, may cause neurotoxicity to the developing brain. Studies have demonstrated that the effects of ketamine-based drugs on neurodevelopment are not simply dichotomously harmful or beneficial; instead, they are closely associated with the exposure dose and duration and the specific stage of brain development. During periods of immature neural development, such as the neonatal and early childhood stages, high-dose or long-term exposure to ketamine may induce neuronal apoptosis, which has a persistent adverse effect on the structural and functional integrity of the brain. In contrast, low concentrations of ketamine (eg, 10 μM, 100 μM and 1000 μM in in vitro experiments) can increase the survival rate of hippocampal neurons in fetal rats, inhibit apoptosis, and improve neural plasticity. A single short-term exposure (eg, surgical anesthesia) has only a mild effect on the developing brain with relatively mild detectable neurotoxicity in most cases, whereas repeated and prolonged exposure may result in cumulative toxic effects. Furthermore, there is currently no clinical evidence to confirm that therapeutic doses of ketamine induce long-term neurotoxicity.[83–85]

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Table 1 Proposed Recommended Dosages of Esketamine in Different Clinical Scenarios

Type of Clinical Scenarios	Administration Route and Dosage	Concomitant Medications	Common Adverse Reactions	Study Type & Evidence Quality	N	Limitations	References
Obstetric Surgery	–	–	–	–	–	–	–
Labor Analgesia and Cesarean Section	IV 0.2–0.5 mg·kg^{-1}	–	Dizziness, somnolence, hallucinations	RCT; High & Moderate	364; 308; 282; 117; 115; 298	1.Excluded mothers with prepregnancy mood disorders; 2.The lack of standardized assessment tools; 3.The follow-up time points were set at 1 week and 6 weeks postpartum, other short-term (at 2 and 4 weeks postpartum) and long-term effects of esketamine remain unknown and need further investigation; 4.The strong subjectivity of the PPD evaluation by EPDS	[44–49]
	PCEA 0.2 mg·kg^{-1}	–	Nausea, vomiting, dizziness, nightmares	RCT; Moderate	117	1.The strong subjectivity of the PPD evaluation by EPDS; 2.The severity of PPD was not observed in the study	[50]
	PCIA 0.5–1.5 mg·kg^{-1}	–	Nausea, vomiting, dizziness	RCT; Moderate	375; 246	1.The sample size was small, and the study only included Chinese adults from a single center; 2.Only investigated a single dose of esketamine; 3.The long-term effects of the current intervention remain to be determined	[51,52]
Pediatric Surgery	–	–	–	–	–	–	–
Premedication	Intranasal 0.5–1 mg·kg^{-1}	Intranasal dexmedetomidine 1 μg·kg^{-1}	Nausea, vomiting	RCT; Moderate	88; 191; 121	1.The preoperative anxiety state of parents may affect the preoperative anxiety level of children, but we have not evaluated this aspect; 2.Did not explore the dose-response relationship of the dexmedetomidine-esketamine combination	[53–55]

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Dental Surgery	Intranasal 2 mg·kg^{-1}	Oral midazolam 0.5 mg·kg^{-1}	Nausea, vomiting, tachycardia	PCS; Low	60	1.The heart rate, blood pressure, respiratory rate, and pulse oximetry measured at baseline before dosing may have been inaccurate due to the children's anxiety and crying	[56]
Ambulatory Anesthesia for Diagnostic and Therapeutic Procedures	IV 0.15–0.6 mg·kg^{-1}	IV propofol 2 mg·kg^{-1}, 4–6 mg·kg^{-1}·h^{-1}	Dizziness, headache, nausea, vomiting	RCT; Moderate	60; 111; 72; 124; 119	1.Children outside this age range or with higher American Society of Anesthesiologists (ASA) status scheduled for surgery and sedation for painless diagnosis and treatment were underrepresented in these studies; 2.Did not follow the influence of esketamine on children's postoperative long-term cognitive functioning; 3.We did not observe the sedative effect of higher doses of esketamine in combination with propofol	[57–61]
Orthopedic Surgery	–	–	–	–	–	–	–
Intraoperative Administration	IV 0.2–0.5 mg·kg^{-1}, 0.25–0.5 mg·kg^{-1}·h^{-1}	IV propofol, dexmedetomidine, opioids etc.	Nausea, vomiting, prolonged extubation time, hallucinations, nightmares	RCT, RCS; Moderate & Low	147; 590; 120; 68; 121	1.The follow-up suffers from other well-known weaknesses of written questionnaires: a level of subjectivity, recall bias, interpretation of questions, and researcher imposition; 2.In one retrospective study, some possible confounding variables, including surgical technique and preoperative anxiety level, could not be determined; 3.As the sample size was small, it was not possible to further control potential confounders; 4.The observational indicators in the study were limited to short-term results only, and the lack of long-term outcomes limits its clinical relevance	[62–66]

(*Continued*)

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Table 1 (Continued).

Type of Clinical Scenarios	Administration Route and Dosage	Concomitant Medications	Common Adverse Reactions	Study Type & Evidence Quality	N	Limitations	References
Postoperative Analgesia	PCIA 0.25–0.75 mg·kg^{-1} or 2.5 mg·kg^{-1}	PCIA dexmedetomidine, opioids etc.	Nausea, vomiting, dizziness, logorrhea	RCT; Moderate	199; 100; 132	1.We also noted a wide variation in pain intensity amongst individual patients. Further efforts are required to improve and individualize analgesia in these patients; 2.The optimal dose of esketamine in PCIA application remains to be determined	[67–69]
Anesthesia for Diagnostic and Therapeutic Procedures	–	–	–	–	–	–	–
Gastrointestinal Endoscopy, ERCP	IV 0.15–0.5 mg·kg^{-1}, 0.15 mg·kg^{-1}	IV propofol 2 mg·kg^{-1}, 4–6 mg·kg^{-1}·h^{-1}	Dizziness, headache, nausea, vomiting	RCT, SR/MA; Moderate	32; 100; -; 150; 162	1.The lack of evaluation of cognitive impairment after recovery, such as mood and clustered psychological effects and concentration capacity; 2.The lack of esketamine dose more than 0.5 mg, such as 1 mg·kg^{-1}, the choice of esketamine doses was based on the clinical experience of the investigators and previous studies; 3.Due to the limited number of original studies, many results could not be combined; 4.Only recruited young patients with ASA I–II; 5.It is difficult to determine the equivalent analgesic dose of esketamine and opioids	[12,70–73]
Hysteroscopy	IV 0.12–0.15 mg·kg^{-1}	IV propofol 0.25–0.5 mg·kg^{-1}	Nausea, vomiting, fatigue	RCT; Moderate	150; 31; 130	1.The sample size was small, and the study only included Chinese adults from a single center; 2.The equilibrium point between the optimal clinical effect and minimal adverse effects across varying doses of propofol and esketamine should be further explored	[74–76]

Special Scenarios	–	–	–	–	–	–	–
Prehospital Analgesia in Emergency Settings	IV 0.125 $mg \cdot kg^{-1}$	–	–	CSS; Low	119	1.The main limitation of this study is due to the chosen methodology and lack of linkage between patient feedback and operative documentation; 2.The results are not necessarily generalizable, but represent an insight into the findings of the collective studies	[77]
Procedural Sedation and Analgesia in Emergency Department (ED) and ICU	IV 0.125–0.5 $mg \cdot kg^{-1}$, 0.3–1.5 $mg \cdot kg^{-1} \cdot h^{-1}$	IV propofol, opioids	–	Review, SR; Low	–	1.Due to the scarcity of evidence and study heterogeneity, our results should be viewed cautiously, and more research is needed in this field	[78,79]
Endotracheal Intubation in ED and ICU	IV 0.5–1 $mg \cdot kg^{-1}$	IV propofol, dexmedetomidine, opioids etc.	–	RCT; Moderate	80	1.Did not conduct a comprehensive evaluation of the possible influences of other facets of the medical intervention (eg, anti-infective therapy, fluid management, nutritional support therapy, renal-replacement therapy) on the clinical outcomes after intubation during ICU and hospital stay; 2.Although significant differences in ICU stay duration and ventilator support were observed between the esketamine and midazolam/sufentanil groups, the underlying mechanisms for these differences were not fully explored	[80]

(*Continued*)

Table 1 (Continued).

Type of Clinical Scenarios	Administration Route and Dosage	Concomitant Medications	Common Adverse Reactions	Study Type & Evidence Quality	N	Limitations	References
Analgesia for Severe Burns	IV 0.5 mg·kg^{-1} intraoperatively; 0.5 mg·kg^{-1}·d^{-1} for 72 h postoperatively	–	–	Review, RCT; Moderate & Low	55	1.The sample size was small and lacked sufficient power to detect the effect of esketamine on gastrointestinal function and calculate results for subgroups (extensive and moderate burns); 2.The overall subjective assessment of pain could be influenced by various factors, including patients' satisfaction with nursing care, potentially introducing assessment biases	[78,81]

Notes: Evidence Quality Grading Rubric: The evidence quality in Table 1 was graded using a simple internal rubric to ensure transparency and reproducibility, with four core dimensions as the evaluation basis: study design, sample size, bias control, and study limitations. Specific criteria are as follows: High-quality evidence refers to multicenter randomized controlled trials (RCTs) with a single-study sample size ≥ 300 cases or pooled analysis ≥ 800 cases, equipped with rigorous randomization and double-blind design, extremely low bias risk, and only 1–2 minor limitations (eg, limited follow-up duration). Moderate-quality evidence includes single-center RCTs, prospective cohort studies (PCS), or systematic reviews (SR)/meta-analysis (MA), with a single-study sample size of 50–299 cases or pooled analysis of 100–799 cases, partial bias control measures (eg, randomization only), and 2–3 moderate limitations (eg, single-center design, single assessment tool) that do not compromise the reliability of core conclusions. Low-quality evidence refers to cross-sectional studies (CSS), retrospective cohort studies (RCS), or narrative reviews without original data, with a single-study sample size <50 cases, no randomization or blinding, high bias risk, and ≥3 major limitations (eg, insufficient sample size, unadjusted confounding factors), requiring cautious interpretation of conclusions. This is an internal criterion specific to this review to standardize evidence quality assessment.

Abbreviations: CSS, Cross-sectional Study; IV, Intravenous; N, Number of subjects; PCEA, Patient-controlled Epidural Analgesia; PCIA, Patient-controlled Intravenous Analgesia; PCS, Prospective Cohort Study; RCS, Retrospective Cohort Study; RCT, Randomized Controlled Trial; SR, Systematic Review; SR/MA, Systematic Review and Meta-Analysis.

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Research evidence suggests that the clinical application of esketamine in pediatric patients requires a tailored protocol design on the basis of the route of administration and clinical target. When intranasal esketamine is used as preoperative adjuvant therapy in children aged 1–6 years, monotherapy may increase the risk of ED; thus, intranasal esketamine (0.5–1 $mg \cdot kg^{-1}$) combined with dexmedetomidine (1 $\mu g \cdot kg^{-1}$) is recommended. This regimen synergistically enhances induction compliance and the sedation success rate without increasing adverse reactions. When intravenously administered as an adjunct to propofol, esketamine can improve anesthetic efficacy for outpatient procedures in children aged 1–12 years, reduce adverse propofol-related effects, and enhance safety. However, vigilance is needed for dose-dependent adverse reactions. On the basis of risk benefit analysis and efficacy profiles, the recommended optimal intravenous dose of esketamine is 0.3–0.6 $mg \cdot kg^{-1}$.Clinical evidence for esketamine use in the pediatric population predominantly consists of single-center RCTs, supplemented by several prospective cohort studies (PCS) (Table 1). Despite a moderate level of evidence, the body of evidence carries several potential limitations: a wide age range of included children (1–12 years) without stratified analysis by developmental stage; failure to explore the dose-response relationship in some studies; most neurotoxicity-related data being derived from basic experiments or short-term clinical observations, with a complete lack of evidence regarding long-term cognitive effects. Nevertheless, some studies have shown that for children under 6 years old, using a low dose of esketamine (< 0.3 $mg \cdot kg^{-1}$) could reduce the risk of postoperative dizziness, nausea, vomiting and restlessness.[86,87]

Clinical Application of Esketamine in Orthopedic Surgery

Orthopedic surgery is frequently associated with severe pain. Inadequate postoperative pain management exacerbates patient suffering, increases the risk of complications, and promotes the development of chronic pain. While opioids effectively control postoperative pain, they are associated with numerous adverse effects.[88,89] Thus, the implementation of multimodal analgesia strategies is critically important. Among these strategies, esketamine is regarded as a valuable agent that may optimize postoperative pain management because of its potent analgesic effects, ability to alleviate postoperative anxiety, and ability to reduce hyperalgesia.[90] Existing studies have demonstrated that intraoperative intravenous administration of esketamine (loading dose: 0.2–0.5 $mg \cdot kg^{-1}$; maintenance dose: 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$) alleviated postoperative pain in orthopedic patients, reduced 24-hour postoperative opioid consumption, and tended to lower the incidence of chronic pain at 6 months post-operatively. Notably, this regimen did not result in an increase in the incidence of adverse effects such as post-operative nausea and vomiting (PONV) or hallucinations in the included patients.[62–64] The incorporation of esketamine (0.25–0.75 $mg \cdot mL^{-1}$ or 2.5 $mg \cdot kg^{-1}$) into patient-controlled intravenous analgesia regimens reduced the 24-hour post-operative visual analog scale (VAS) pain score. It may also contribute to improving postoperative sleep quality, mitigating inflammatory responses, and alleviating anxiety and depressive symptoms ultimately facilitating postoperative recovery in patients.[67–69] Furthermore, with the widespread adoption of multimodal analgesia, opioid-free anesthesia (OFA) has emerged as a recommended perioperative analgesic strategy, and esketamine serves as a core agent in this protocol. It has been applied in total hip arthroplasty (THA) for elderly patients, demonstrating certain advantages.[65] Studies have confirmed that when an OFA regimen (esketamine: induction dose 0.3–0.5 $mg \cdot kg^{-1}$; maintenance dose 0.3–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) combined with iliofascial block was implemented in elderly patients undergoing THA, it not only provided adequate intraoperative sedation and analgesia but also maintained relatively stable hemodynamics in elderly patients. Additionally, it did not appear to impair postoperative awakening, further optimized postoperative pain management, improved sleep quality, and was associated with a reduced incidence of anesthesia-related complications in the studied population.[65,66]

In summary, the initial recommended doses of esketamine for various orthopedic surgeries are as follows: the loading dose is typically 0.2–0.5 $mg \cdot kg^{-1}$, and the maintenance dosage is 0.25–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$. In clinical practice, dosages could be titrated on the basis of the age, extent of surgical trauma, and individual tolerance of the patient. For PCIA regimens, when esketamine is combined with opioids or dexmedetomidine, the recommended concentration is 0.25–0.75 $mg \cdot mL^{-1}$; when it is used alone, the recommended dose is 2–2.5 $mg \cdot kg^{-1}$. Notably, the use of esketamine in orthopedic surgery is largely derived from single-center randomized controlled trials (RCTs) and retrospective cohort studies (RCS), with the overall level of evidence predominantly graded as Moderate (Table 1). Major limitations include the high proportion of single-center designs, which compromises external

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validity; uncontrolled confounding factors in retrospective studies (eg, surgical approach, preoperative anxiety); as well as marked variation in sample size across studies, resulting in insufficient statistical power in several investigations.

Clinical Application of Esketamine in Special Clinical Scenarios

Painless Diagnosis and Therapy

Gastrointestinal Endoscopy and ERCP

Gastrointestinal endoscopy is a critical modality for diagnosing gastrointestinal diseases; however, patients frequently experience anxiety and pain because of procedural discomfort. Studies have demonstrated that esketamine (0.15–0.5 $mg \cdot kg^{-1}$) combined with propofol for gastrointestinal endoscopy exhibits satisfactory sedative efficacy. This combination reduces propofol requirements and the incidence of injection pain in a dose-dependent manner, decreases the risk of adverse events such as hypotension and respiratory depression, and decreases patient recovery time.[12,70–72] With respect to endoscopic retrograde cholangiopancreatography (ERCP), the use of low-dose esketamine (0.15 $mg \cdot kg^{-1}$) as an adjuvant to propofol decreased the dosage of propofol, with a safety profile comparable to that of alfentanil.[73] Compared with traditional sedatives, esketamine has relatively mild inhibitory effects on the respiratory and circulatory systems at the recommended doses in studies, which may contribute to a favorable safety profile. During the procedure, under standardized operation and monitoring, patients tend to maintain relatively stable respiratory rates and blood oxygen saturation, which may help reduce the risks associated with respiratory depression. Owing to its rapid onset and short duration of action, esketamine enables patients to awaken quickly postprocedure, with relatively mild impact on daily life and work.[91] However, ketamine and its derivatives are prone to induce adverse reactions, such as transient visual impairment and perceptual disturbances. Diplopia is the main manifestation of visual impairment, whereas hallucinations are the primary symptom of perceptual disturbances. The incidence of such reactions is relatively low in clinical practice. Recent RCTs studies have revealed that the incidence of diplopia is approximately 0.9–1.6% and that of hallucinations is 0.8–1.5%. These symptoms are typically transient and self-limiting, and rarely lead to severe complications with appropriate management.[42,92–94] Although low doses of esketamine exert relatively minor effects on blood pressure and heart rate, a subset of patients may still develop transient hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure > 110 mmHg) and tachycardia (heart rate > 100 beats per minute) even at doses below 1 $mg \cdot kg^{-1}$, which necessitates stringent monitoring of vital signs. This confers a substantial risk upon patients with comorbid hypertension, cardio-cerebrovascular diseases, increased intracranial pressure, or preeclampsia. Therefore, esketamine should generally be avoided or used with extreme caution in these patients, necessitating a careful risk-benefit evaluation.[95,96] Studies have demonstrated that, in contrast to ketamine, esketamine exerts sympathomimetic effects but does not exhibit significant negative inotropic effects on the heart.[97,98] Furthermore, high doses of esketamine may exert neuroprotective effects on the injured brain, though this putative neuroprotective effect is not yet substantiated by high-level clinical evidence.[99,100] These properties constitute a key pharmacological distinction between ketamine and esketamine one that translates to considerable differences in their clinical use, including optimal dosage strategies and administration regimens.[101]

Hysteroscopy

Hysteroscopy is a widely used modality for the diagnosis and treatment of gynecological diseases, and esketamine provides effective sedation and analgesia for this type of procedure. Studies have shown that low-dose esketamine (0.114–0.133 $mg \cdot kg^{-1}$) can help alleviate propofol injection pain in patients who are experiencing painless induced abortion.[74] With respect to hysteroscopy, the combination of esketamine and propofol enhances anesthetic efficacy and prolongs postoperative analgesic duration.[75,76] Compared with other anesthetic agents, esketamine offers certain advantages in hysteroscopic procedures. First, it has a relatively mild effect on uterine smooth muscle and does not induce abnormal uterine contractions, which facilitates the smooth progression of the procedure.[76] Second, it is associated with relatively fewer adverse psychiatric effects in most patients, and the incidence of postoperative adverse reactions (eg, hallucinations and frequent dreams) in patients is relatively low.[71] Additionally, esketamine may cause mild adverse

reactions such as dizziness and nausea; however, these symptoms typically resolve spontaneously within a short timeframe in most cases.[71,76]

Current evidence is primarily derived from single-center randomized controlled trials (RCTs) and systematic reviews/meta-analyses (SR/MA), all of which are graded as moderate quality (Table 1). These studies consistently show that esketamine could reduce propofol consumption, decrease the risk of respiratory depression, and shorten recovery time to a certain extent.However, most studies focus on young patients with American Society of Anesthesiologists (ASA) physical status I–II, with a lack of data in elderly patients or those with comorbidities, as well as an absence of long-term postoperative assessments. Research is also lacking on its applicability in special populations (eg, patients with hypertension, elderly patients) and risk-benefit evaluations of high-dose regimens.

Emergency and Critical Care Medicine Scenarios

Esketamine has demonstrated certain application value in emergency and critical care medicine because of its multiple beneficial properties, including analgesia, sedation, circulatory stabilization, and sympathomimetic activity. Additionally, it may be suitable for patients with conditions such as hemodynamic instability, acute severe trauma, acute respiratory distress, and severe burns.[78] Studies have shown that prehospital intravenous administration of low-dose esketamine (0.125 $mg \cdot kg^{-1}$) effectively relieves moderate-to-severe traumatic pain. This regimen offers satisfactory analgesia for moderate-to-severe traumatic pain and is associated with a lower incidence of adverse effects and higher patient satisfaction in reported cases.[77] In programmed sedation analgesia regimens for emergency settings, a single intravenous dose of esketamine 0.125–0.25 $mg \cdot kg^{-1}$ when combined with opioids or 0.5 $mg \cdot kg^{-1}$ when used alone followed by a maintenance infusion of 0.3–1.5 $mg \cdot kg^{-1} \cdot h^{-1}$, tends to maintain relatively stable hemodynamics and induces only relatively mild respiratory depression in most critically ill patients. This protocol is also applicable to intensive care unit (ICU) patients requiring short-term or prolonged sedation and analgesia.[78,79] In addition, esketamine exerts anti-inflammatory effects while dilating tracheobronchial smooth muscle, making it suitable for patients with acute respiratory distress syndrome (ARDS) who require sedation, analgesia, or anesthesia.[78] The intravenous administration of esketamine (0.5–1 $mg \cdot kg^{-1}$) adequately meets the requirements for emergency tracheal intubation in the ICU, maintains relative hemodynamic stability, and may reduce the need for vasoactive agents in some of these patients.[80] Esketamine also offers potential benefits for patients with severe burns. Intraoperative intravenous injection of 0.5 $mg \cdot kg^{-1}$ esketamine, followed by 0.5 $mg \cdot kg^{-1} \cdot d^{-1}$ for analgesia within 72 hours post-operatively, improved subjective analgesic efficacy and patient comfort and satisfaction. This approach also reduces opioid consumption without increasing the risk of gastrointestinal dysfunction or severe complications in burn patients receiving standardized care, making it potentially applicable to anesthesia during repeated dressing changes and flap transplantation surgeries.[78,81]

In conclusion, the applicability and advantages of esketamine across diverse scenarios primarily stem from its rapid onset, short duration of action, and mild effects on the respiratory and circulatory systems. Despite these advantages, studies included herein comprise cross-sectional studies (CSS), systematic reviews (SR), retrospective analyses, and single-center randomized controlled trials (RCTs). The majority of evidence is rated low quality, with only two single-center RCTs assigned a moderate quality rating (Table 1). Methodological limitations are pervasive, including non-controlled study designs, recall bias, and scant, highly heterogeneous evidence. In addition, the included RCTs have small sample sizes, fail to exclude the confounding effects of concurrent interventions (eg, anti-infective therapy, fluid management) on clinical outcomes, and lack stratification of patients by disease severity. There is also a paucity of data regarding its applicability in critically ill subpopulations (eg, patients with severe ARDS, shock), its associations with long-term prognosis (eg, ICU length of stay, mortality), and the multicenter validation of optimal dosages across different clinical scenarios.

Conclusion

As a novel noncompetitive NMDA receptor antagonist, esketamine shares core pharmacological properties with ketamine. However, as the pure S-(+)-enantiomer of racemic ketamine, it has a higher affinity for NMDA receptors than the L-(-)-enantiomer does, which may be the key factor underlying its more potent anesthetic, analgesic and antidepressant effects. Accumulating evidence indicates the promising utility of esketamine in the perioperative period,

and its clinical value has received initial validation in a variety of clinical scenarios. Furthermore, it is notable that this agent is associated with adverse psychiatric reactions, particularly with prolonged administration at high doses. Perioperative use may also lead to adverse events such as delayed postoperative awakening and emergence agitation. Consequently, vigilant monitoring for esketamine-related adverse reactions is mandatory during clinical administration, and the drug may be unsuitable for specific patient populations. Regarding its current off-label use in many clinical scenarios, the optimal dosing and administration strategies have not yet been sufficiently validated by a substantial number of high-quality RCTs. In the future, more multicenter, large-sample studies are warranted to further explore its appropriate dosing and clinical safety in depth.

Abbreviations

5-HT, 5-Hydroxytryptamine; AKT, Protein Kinase B; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic Acid Receptor; AR, Adrenergic Receptor; BDNF, Brain-Derived Neurotrophic Factor; CaMKIIα, Ca^{2+}/Calmodulin-Dependent Protein Kinase IIα; CX-546, 1-(1,4-benzodioxan-6-ylcarbonyl)piperidine; DRN, Dorsal Raphe Nucleus; ERK, Extracellular Regulated Protein Kinases; GABA, γ-aminobutyric acid; GABAA, γ-Aminobutyric Acid Type A Receptor; HCN-1, Hyperpolarization-Activated Cyclic Nucleotide-Gated Channel 1; mPFC, Medial Prefrontal Cortex; mTORC1, Mechanistic Target of Rapamycin Complex 1; NA, Norepinephrine; NBQX, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f) quinoxaline-2,3-dione; NMDAR, N-methyl-D-aspartate Receptor; NO, Nitric Oxide; nNOS, Neuronal Nitric Oxide Synthase; OPs, Opioid Peptides; OR, Opioid Receptor; PI3K, Phosphatidylinositol 3-Kinase; PSD-95, Postsynaptic Density Protein 95; SERT, Serotonin transporter.

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Disclosure

The authors declare that they have no conflicts of interest in this work.

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