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Tailoring perioperative analgesia: Selecting ketamine or dexmedetomidine based on patient-specific factors

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Highlights

- Ketamine and dexmedetomidine offer effective non-opioid perioperative analgesia, each with distinct cardiovascular, hepatic, and neurological profiles.
- Dexmedetomidine provides stable sedation and potential neuroprotection, making it particularly suitable for patients with hepatic dysfunction and those undergoing neurosurgery.
- Ketamine helps maintain hemodynamic stability and possesses anti-inflammatory and anti-depressant properties, making it beneficial for high-risk or unstable patients.
- Agent selection should be tailored to individual comorbidities, with combination therapy offering potential synergistic advantages.

Abstract

Ketamine and dexmedetomidine are widely used non-opioid agents for perioperative analgesia and sedation, each with distinct mechanisms and side effect profiles. Dexmedetomidine, an α2-adrenergic agonist, is preferred in patients with hepatic dysfunction due to its stable sedation and lower risk of delirium, though it may cause side effects such as bradycardia and hypotension. Ketamine, a non-competitive N-methyl-D-aspartate receptor antagonist, increases heart rate and blood pressure via catecholamine release and provides additional benefits such as anti-inflammatory, neuroprotective, and antidepressant properties. Although both agents have overlapping clinical roles, selection should be guided by patient comorbidities, including cardiac, hepatic, and neurological conditions. This review summarizes current evidence to support individualized decision-making in postoperative pain management.

Keywords: Ketamine, dexmedetomidine, pain management

Introduction

Dexmedetomidine is a selective, non-opioid α2-adrenergic receptor agonist widely used for short-term sedation and pain management [1]. In the central nervous system, it binds to α2-adrenergic receptors in the locus coeruleus, inhibiting pain transmission. Peripherally, it hyperpolarizes presynaptic membranes in the posterior horn and postsynaptic membranes of interneurons, thereby impeding nociceptive signaling to the brain [2]. Although primarily recognized as a sedative–anxiolytic due to its high α2-adrenergic receptor affinity, dexmedetomidine is also employed for analgesia and has been used in the treatment of hypertension [3]. It is typically administered via intravenous titration due to its short half-life, requiring careful monitoring for dose-dependent adverse effects, despite its favorable sympatholytic and sedative profile [3].

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Ketamine, introduced as an anesthetic in 1964, is another non-opioid analgesic that primarily acts by antagonizing the N-methyl-D-aspartate (NMDA) receptor [4, 5]. In addition to NMDA antagonism, ketamine may exert partial agonist effects at μ and κ opioid receptors, although this remains under debate [6]. It also interacts with other targets, such as muscarinic acetylcholine receptors, and may inhibit gamma-aminobutyric acid activity, contributing to its distinct psychoactive side effect profile [7]. Ketamine exists as two enantiomers, (S)-ketamine and (R)-ketamine, with the S-enantiomer demonstrating greater potency at the NMDA receptor [5]. Beyond its anesthetic use, ketamine has been applied in treating depression and in experimental models of psychosis [5].

Despite differing mechanisms and chemical structures, dexmedetomidine and ketamine share overlapping roles in clinical practice. Both agents are widely used by anesthesiologists and critical care providers. However, a comprehensive comparison of their use in patients with comorbidities such as hepatic, cardiac, or neurological diseases is still lacking. This review aims to address this gap by highlighting how organ-specific conditions influence pharmacodynamics and clinical outcomes. Additionally, we propose a practical decision-making framework and explore the potential of combination therapy to maximize benefits while minimizing side effects.

Mechanistic insights supporting clinical applications

Analgesia and sedation of dexmedetomidine

Dexmedetomidine offers several advantages that make it an ideal anesthetic and analgesic agent in both the operating room and intensive care unit. As a non-opioid medication, it avoids many of the common side effects associated with opioid use, such as nausea, constipation, dependency, and respiratory depression [8, 9].

Dexmedetomidine exerts its sedative and analgesic effects through selective activation of α2-adrenergic receptors, particularly the α2A subtype, G protein–coupled receptors, located in the locus coeruleus of the brainstem [10-12]. Activation of G proteins inhibits adenylyl cyclase, leading to reduced cyclic adenosine monophosphate production [13]. Lower cyclic adenosine monophosphate enhances potassium channel conductance, causing potassium efflux and hyperpolarization of noradrenergic neurons. Simultaneously, calcium channel suppression reduces calcium influx, further inhibiting neurotransmitter release [13, 14]. The synergistic effect of hyperpolarization and calcium-channel inhibition results in decreased neuronal firing and reduced norepinephrine release, thereby jointly suppressing nociceptive signal propagation in the ascending pain pathway (**Figure 1a**).

Anti-inflammatory effect of dexmedetomidine

Both clinical and preclinical studies have demonstrated the anti-inflammatory properties of dexmedetomidine [15]. This effect is believed to be mediated, at least in part, through modulation of intracellular signaling pathways such as Jun N-terminal kinases and p38 mitogen-activated protein kinases [16]. In rat primary astrocyte cultures, high concentrations of dexmedetomidine (0.1, 1, and 10 μM) modulated JNK and mitogen-activated protein kinase activity and significantly attenuated inflammation [17]. However, at lower concentrations (0.01 μM), no significant changes were observed in tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) expression [17]. Given the evolutionary conservation of the mitogen-activated protein kinase family, it is reasonable to hypothesize that similar effects may occur in mammalian, including human, astrocytes at higher concentrations (**Figure 1b**).

Further supporting its anti-inflammatory potential Xiang et al. demonstrated that dexmedetomidine modulates the cholinergic anti-inflammatory pathway to downregulate systemic cytokine levels [18]. In a lipopolysaccharide (LPS)-induced inflammation model, dexmedetomidine significantly reduced TNF-α, interleukin-1β, and IL-6 levels compared to saline controls [18] These preclinical findings were mirrored in a clinical trial involving 86 patients undergoing intestinal surgery, in which dexmedetomidine not only suppressed inflammatory cytokines but also improved anesthesia recovery time and Mini-Mental State Examination scores [19].

Neuroprotection and immunomodulatory effects of dexmedetomidine

In a study, Oriby et al. reported that dexmedetomidine attenuated neurocognitive impairments [20]. This neuroprotective effect is believed to stem from the drug's ability to counteract necrosis, apoptosis, oxidative stress, and immune responses. One proposed mechanism involves the reduction of catecholamine release during neurosurgical procedures, limiting oxidative stress and enhancing neuronal protection in vulnerable brain regions [19]. Supporting this,

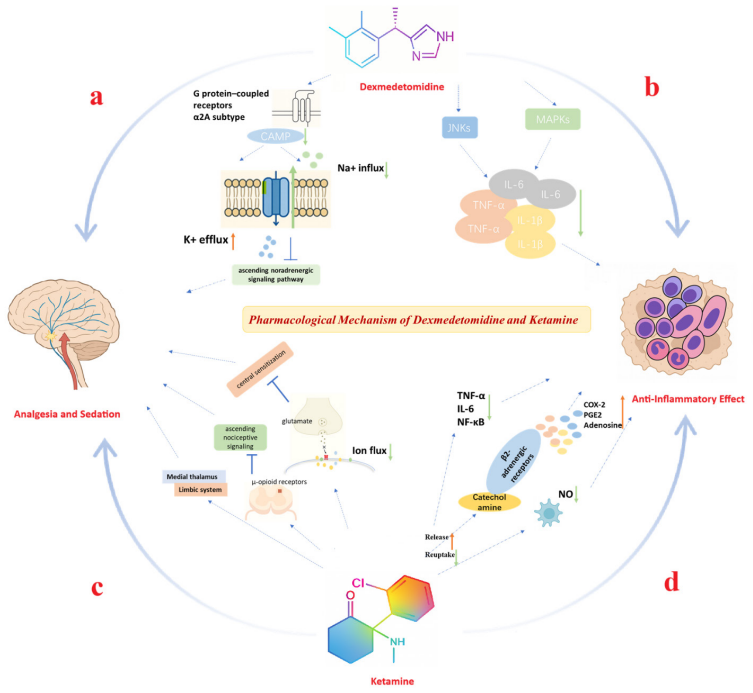

Figure 1. Pharmacological Mechanism of Dexmedetomidine and Ketamine. (a) Analgesia and Sedation of Dexmedetomidine; (b) Anti-Inflammatory Effect of Dexmedetomidine; (c) Analgesia and Sedation of Ketamine; (d) Anti-Inflammatory Effect of Ketamine. CAMP, cyclic adenosine monophosphate; Na+, sodium ion; K+, potassium ion; JNKs, c-Jun N-terminal kinases; MAPKs, mitogen-activated protein kinases; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6; IL-1β, interleukin-1 beta; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NF-κB, nuclear factor kappa-B; COX-2, cyclooxygenase-2; PGE_2, prostaglandin E_2.

Schoeler et al. demonstrated in organotypic hippocampal slice cultures that dexmedetomidine promoted neuroprotection in traumatic brain injury models through activation of extracellular signal-regulated kinases [21]. Oxidative stress, a key contributor to postoperative cognitive dysfunction, is also directly mitigated by dexmedetomidine. The drug has been shown to lower malondialdehyde levels and promote the nuclear translocation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, enhancing mitochondrial function and cellular resilience against oxidative damage [22].

Beyond its neuroprotective actions, dexmedetomidine also modulates immune responses implicated in postoperative cognitive dysfunction. Excessive cytokine release and lymphocyte activation are known contributors to neuroinflammation in the perioperative period. Research shows that dexmedetomidine downregulates both innate and adaptive immune activity by modulating cytokine levels and immunological signaling pathways, further supporting its potential to reduce neuroinflammation and cognitive impairment after surgery [23, 24].

Clinical data, though limited, suggest potential neuroprotective effects of dexmedetomidine in humans. For example, retrospective studies in aneurysmal subarachnoid hemorrhage patients showed better neurological outcomes in those receiving dexmedetomidine, potentially due to reduced oxidative stress and inflammation. While no randomized clinical trials have directly measured proliferator-activated receptor gamma coactivator 1-α expression, these findings are consistent with preclinical data indicating mitochondrial preservation via the AMPK/proliferator-activated receptor gamma coactivator 1-α pathway [25].

Analgesia and sedation of ketamine

Ketamine is a non-competitive NMDA receptor antagonist used for analgesia and anesthesia in perioperative settings [26]. It blocks the NMDA receptor channel in a non-competitive manner. When glutamate dissociates and the ion channel closes, ketamine remains trapped inside, preventing normal ion flux, impairing receptor function, and attenuating central sensitization [27]. Ketamine also interacts with μ-opioid receptors and neurons in the presynaptic spinal dorsal horn. It reduces the release of excitatory neurotransmitters from presynaptic neurons in the spinal dorsal horn and inhibits ascending nociceptive signaling (**Figure 1c**) [28]. For its sedative effects, ketamine acts on multiple brain regions, including the thalamocortical and limbic systems. It suppresses excitatory activity in the medial thalamus while enhancing activity in the limbic system, such as the hippocampus and amygdala, leading to a dissociative state characterized by profound sedation with preserved airway reflexes and spontaneous breathing [29].

Due to its engagement with multiple receptors in both the central and peripheral nervous systems, and its slow dissociation (slow “off-rate”) from these targets, ketamine is an effective option for both acute and chronic pain management [27, 28]. Ketamine is often combined safely with sedatives like midazolam and propofol for enhanced analgesic and sedative

effects [30]. Additionally, ketamine is favored in emergency and intensive care unit settings for acute non-cancer pain because it does not cause respiratory depression and has minimal hemodynamic disruption [31, 32].

It is worth noting that the analgesic and anesthetic effects of ketamine are dose-dependent. At concentrations around 200 ng/mL, ketamine can produce anesthesia by blocking voltage-gated sodium (Na^+) channels in neurons and lipid bilayers [33]. Additionally, ketamine interacts with muscarinic receptors and voltage-sensitive calcium channels, which may further enhance its analgesic and anesthetic properties [33]. At higher plasma concentrations (-2000 ng/mL), ketamine induces hypnosis, likely through combined blockade of NMDA receptors and hyperpolarization-activated cyclic nucleotide-gated potassium channel 1 [27]. Its dose-dependent pharmacological profile allows clinicians to tailor administration for different outcomes, making it a versatile agent [34].

Anti-inflammatory effect of ketamine

Ketamine also exhibits anti-inflammatory properties [35]. In a study by Lankveld et al. using an equine macrophage cell line, ketamine inhibited LPS-induced production of IL-6 and TNF-α in a dose-dependent manner [36]. Similarly, Yang et al., using a rat model, found that high doses (50 mg/kg) of ketamine reduced LPS-induced lung injury [37]. TNF-α, IL-6, nuclear factor kappa-light-chain-enhancer of activated B cells, and neutrophil infiltration were all significantly decreased in the ketamine group, indicating reductions in oxidative stress and inflammatory damage [37].

Ketamine also modulates the catecholaminergic system by stimulating catecholamine release and inhibiting its reuptake [35]. This accumulation overstimulates β2-adrenergic receptors, resulting in adenosine release [38]. Adenosine then triggers a cascade that includes cyclooxygenase-2 and prostaglandin E2 synthesis, ultimately enhancing anti-inflammatory cytokine production by mononuclear cells [35]. Ketamine further reduces nitric oxide production in immune-stimulated macrophages, contributing to its dose-dependent immunomodulatory effects [39]. Importantly, ketamine is capable of reducing exaggerated inflammation without inhibiting essential immune responses, which is better characterized as an anti-proinflammatory rather than a traditional anti-inflammatory agent (**Figure 1d**) [35].

Although most evidence for ketamine's neuroprotective effects comes from preclinical models of ischemic stroke and traumatic brain injury, emerging clinical data support these mechanisms in humans. An electrocorticography study in acute stroke patients demonstrated that ketamine suppressed cortical spreading depolarizations, a phenomenon strongly associated with secondary neuronal damage and infarct expansion. This suggests that ketamine's NMDA receptor antagonism may attenuate excitotoxic cascades in acute neurological injury [40].

Anti-cancer and antidepressant of ketamine

Studies have also explored ketamine's anti-cancer effects. Saito et al. compared ketamine and MK-801 in neuroglioma and lung cancer cells, finding that ketamine significantly inhibited cell proliferation, migration, and induced apoptosis in a dose-dependent manner [41]. However, this was associated with increased reactive oxygen species, leading to cellular apoptosis [41]. Malsy et al. tested ketamine, S-ketamine, and MK-801 on pancreatic cancer cells and found reduced proliferation and migration, though apoptosis did not significantly differ from controls [42]. In contrast, ketamine induced apoptosis in gastric cancer models [43]. These findings suggest that ketamine's anti-cancer effects may vary by cancer type and dose.

Beyond its anesthetic applications, ketamine has gained attention as a rapid-acting antidepressant. Several proposed hypotheses involve mechanisms independent of NMDA receptor antagonism, including modulation of glutamatergic transmission, enhancement of synaptic plasticity, and regulation of intracellular signaling pathways [44].

Adverse effects and clinical evidence

Dexmedetomidine

While dexmedetomidine can enhance hemodynamic stability, it often induces hypotension and bradycardia due to its potent α2-adrenergic receptor selectivity [45]. These cardiovascular effects are dose-dependent: a loading dose of 1 μg/kg given over less than 10 minutes, or a continuous infusion rate exceeding 0.7–1.0 μg/kg/h, is associated with a higher incidence of hypotension and bradycardia. In contrast, a maintenance dose of 0.2–0.4 μg/kg/h provides effective sedation and analgesia while minimizing the risk of severe hemodynamic instability [46]. These cardiovascular effects may be poorly tolerated in patients with structural heart disease or other cardiovascular comorbidities [47].

The drug's suppression of sympathetic nervous system activity can complicate intraoperative blood pressure and heart rate management. Respiratory depression is another potential concern with dexmedetomidine. In a clinical trial of 40 patients, Abdollahpour et al. observed a lower respiratory rate in those receiving dexmedetomidine compared to the placebo group [34]. Additionally, the PaO_2/FiO_2 ratio was significantly higher in the treatment group, possibly indicating improved oxygenation [34]. Other common side effects include nausea, vomiting, and chills, which can prolong recovery and increase hospitalization time [47].

Ketamine

Neurotoxicity, addiction, nausea, delirium, and myocardial depression are common side effects of ketamine, particularly with chronic administration [28, 48]. Its adverse effects may vary based on patient characteristics and are generally categorized as cardiovascular, central nervous system-related, or hepatic [28]. In a study by Coull et al., 13 healthy young volunteers exhibited reduced performance in color discrimination and timing perception tasks after receiving ketamine at 100 ng/mL plasma levels [49]. Another study found that ketamine at doses of 0.4 and 0.8 mg/kg caused dose-dependent impairments in memory, attention, and executive function, indicating cognitive side effects even in healthy individuals [50]. These neurocognitive side effects are closely linked to plasma concentration and dosage: mild perceptual disturbances are typically observed at plasma levels around 200 ng/mL, corresponding to subanesthetic doses of approximately 0.3–0.5 mg/kg IV, whereas higher doses (1–2 mg/kg IV) can elevate plasma levels to 2,000 ng/mL or more, resulting in profound dissociation, hallucinations, and severe short-term cognitive impairment [48]. Additionally, co-administration with alcohol or other central nervous system depressants may result in severe respiratory depression or even death.

Cardiovascular side effects are also a concern. A study by Christ et al. involving 25 ventilated patients with catecholamine-dependent heart failure found that ketamine significantly reduced heart rate, cardiac index, and stroke volume index compared to sufentanil [51]. These effects may stem from negative inotropic or myocardial depressant properties, though the exact mechanism remains unclear. In contrast, a placebo-controlled study by Liebe et al. found ketamine increased heart rate and blood pressure (without inducing hypertension) [52]. This apparent discrepancy can be explained by the patients' catecholamine reserves and sympathetic tone. Ketamine generally exerts indirect sympathomimetic effects by promoting catecholamine release and inhibiting reuptake, resulting in increased blood pressure and heart rate in patients with adequate sympathetic reserve. However, in patients with advanced heart failure or catecholamine depletion, this indirect mechanism is impaired, and ketamine's direct negative inotropic effect on myocardial contractility predominates, resulting in decreased cardiac output and hypotension. Interestingly, women experienced greater and earlier increases in diastolic blood pressure than men. Other studies have shown that S-norketamine, the primary metabolite of S-ketamine, appears to attenuate its stimulatory effects on cardiac function [53].

Hepatotoxicity is another consideration. In a clinical case series by Jakobsen et al., three out of six patients with complex regional pain syndrome developed elevated liver enzymes after three weeks of continuous S-ketamine infusion, with cumulative doses ranging between 500–700 mg [54]. Enzyme levels, including alanine transaminase, alkaline phosphatase, aspartate transaminase, and γ-glutamyl transferase, returned to normal after treatment cessation, indicating that liver injury may be reversible. The underlying mechanism is not fully understood, but possible explanations include reduced hepatic oxygen delivery, increased lipid peroxidation with free radical formation, and immune-mediated hepatitis [28].

Patient-specific considerations

Building upon the previously discussed mechanisms of action, clinical advantages, and potential adverse effects, the following section examines dexmedetomidine and ketamine in the context of common patient situations, aiming to provide practical insights for clinical decision-making.

Cardiovascular considerations

Dexmedetomidine and ketamine have distinct cardiovascular profiles that significantly influence anesthetic decision-making, particularly in patients with underlying cardiac disease. Dexmedetomidine acts via central sympatholysis, suppressing catecholamine release and reducing sympathetic tone. This leads to decreased heart rate, myocardial contractility, and blood pressure, which may manifest clinically as bradycardia, sinus arrest, or hypotension [19, 53]. As such, it may be less suitable for patients with pre-existing bradycardia or hypotension.

In contrast, ketamine stimulates sympathetic activity by enhancing catecholamine release, producing positive inotropic and chronotropic effects that increase heart rate, blood pressure, and cardiac output [53]. These properties make ketamine advantageous in hemodynamically unstable patients. However, in those with depleted catecholamine or norepinephrine stores, such as in prolonged heart failure or septic shock, this effect may paradoxically result in myocardial depression, tachycardia, and hypotension [53].

In patients with coronary artery disease, ketamine's increased myocardial oxygen demand and shortened diastolic perfusion time raise concerns about ischemic complications [54]. A large trial by Turan et al. in 3,357 cardiac surgery patients showed that Dexmedetomidine did not significantly reduce atrial fibrillation or delirium [55]. Conversely, a review by Mazzeffi et al. highlighted ketamine's usefulness in maintaining hemodynamic stability in patients with ventricular dysfunction [56].

Neurological considerations

Dexmedetomidine is widely used in neurosurgical procedures, such as awake craniotomy, due to its sedative, anxiolytic, and mild analgesic effects, all while preserving respiratory function [57, 58]. Kulikov and Lubnin demonstrated its ability to maintain spontaneous ventilation and patient cooperation during intracranial surgery. In contrast, ketamine has shown superior postoperative analgesia in certain settings[58]. For example, in a randomized trial of laparoscopic cholecystectomy, ketamine outperformed dexmedetomidine in pain control, while both agents, when combined with total intravenous anesthesia, effectively reduced opioid use and improved recovery profiles [59].

Beyond surgical sedation, ketamine also exhibits unique psychiatric and neuroprotective properties. It has been effective in managing agitation, cognitive impairment, and treatment-resistant depression, where dexmedetomidine shows limited benefit. Ketamine has also been applied in the treatment of anti-NMDA receptor encephalitis, particularly in patients with movement disorders or status epilepticus [60, 61]. While paradoxical, these benefits are likely attributable to ketamine's complex receptor interactions, meriting further investigation.

In patients with stroke or subarachnoid hemorrhage, both agents have been explored for their neuroprotective potential. Von der Brelie et al. reported a lower incidence of delayed cerebral ischemia in ketamine-treated patients with SAH [62]. Studies suggest that dexmedetomidine can reduce brain edema, vasospasm, and neurological deficits, although clinical data remain inconclusive [63].

Hepatic considerations

Both dexmedetomidine and ketamine undergo hepatic metabolism, and their pharmacokinetics are notably affected by liver function [64, 65]. Dexmedetomidine is generally well tolerated in patients with hepatic dysfunction, even when administered continuously for over 48 hours. It may provide hepatoprotective benefits during procedures involving hepatic vascular occlusion and has been used safely in liver transplantation to maintain hemodynamic stability and reduce ischemic injury [66, 67].
However, Dexmedetomidine's clearance is dependent on hepatic perfusion. In patients with obstructive jaundice or severe liver impairment, metabolism is delayed, and dose reduction is advised to prevent prolonged sedation and delayed estuation [68, 69].

Ketamine is generally considered safe for short-term use in hepatic impairment, but chronic or repeated exposure, particularly in recreational settings, has been linked to hepatobiliary complications, including cholestasis and sclerosing cholangitis [70]. Therefore, careful consideration of dosing and duration is essential in patients with compromised liver function.

Combination therapy: Dexmedetomidine and ketamine

The combination of dexmedetomidine and ketamine has emerged as a promising strategy to optimize analgesia and sedation while minimizing adverse effects. Their complementary pharmacodynamics can potentially balance hemodynamic responses. A meta-analysis by Li et al. concluded that their co-administration in pediatric patients led to more stable heart rate and oxygen saturation than either agent alone and was associated with improved safety [71].

In clinical practice, this combination has been successfully applied in pediatric sedation, TIVA protocols, and enhanced recovery pathways. A study has shown that the dexmedetomidine–ketamine combination improves intraoperative behavior in uncooperative pediatric dental patients compared to dexmedetomidine alone, despite lower drug acceptance [72]. The addition of ketamine to dexmedetomidine provids

more stable hemodynamics and deeper sedation during awake fiberoptic intubation [73]. This pharmacological synergy may allows for reduced dosages, better control of postoperative pain, and lower opioid requirements, without significantly increasing the risk of cardiovascular or respiratory complications. Nonetheless, further high-quality studies are needed to establish standardized dosing regimens and define patient populations most likely to benefit.

Medication considerations in special populations

Elderly individuals often exhibit increased pharmacodynamic sensitivity and reduced hepatic and renal clearance, which necessitates cautious dosing of both dexmedetomidine and ketamine [74]. Dexmedetomidine's sympatholytic effects may exacerbate age-related autonomic dysfunction, leading to clinically significant bradycardia or hypotension, particularly at loading doses ≥1 μg/kg or maintenance infusions above 0.7 μg/kg/h. Additionally, ketamine's dissociative and cognitive side effects may heighten the risk of postoperative delirium in older adults, especially at doses >1 mg/kg [46]. Therefore, lower initial doses and slower titration are recommended in geriatric patients, alongside vigilant hemodynamic and cognitive monitoring.

Beyond its co-administration with ketamine, dexmedetomidine alone is increasingly used in pediatric sedation for diagnostic imaging, procedural anesthesia, and ICU management [75]. It provides effective anxiolysis without significant respiratory depression [76]; however, its prolonged half-life may delay recovery in short-duration procedures. Ketamine remains a widely accepted pediatric sedative due to its cardiovascular stability, but it can induce hypersalivation, emergence agitation, or hallucinations [77]. Co-administration with anticholinergic agents (e.g., glycopyrrolate) or benzodiazepines is often employed to mitigate these effects. Both agents require individualized dosing based on age, weight, and comorbidities, with attention to developmental pharmacokinetics.

Limited data are available regarding the safety of dexmedetomidine or ketamine in pregnancy. Dexmedetomidine readily crosses the placenta and has been associated with reduced fetal heart rate variability, likely due to central sympatholysis [78]. Its use is generally avoided unless maternal benefit clearly outweighs fetal risk.

Economic considerations

From a cost-effectiveness perspective, dexmedetomidine is generally more expensive than ketamine due to its higher acquisition cost and the need for continuous infusion. However, studies have shown that its opioid-sparing effects, reduced incidence of delirium, and shortened intensive care unit stay may partially offset these costs by reducing the total cost of perioperative care [79]. Although ketamine is inexpensive and easily accessible, it may increase the cost of postoperative monitoring due to its psychoactive effects and potential for cognitive impairment [80]. Therefore, individualized drug selection based on patient comorbidities and expected postoperative course may achieve the best balance between clinical efficacy and medical expenditures.

Conclusion

The perioperative and critical care use of dexmedetomidine and ketamine should be tailored to individual patient characteristics, particularly in the context of cardiac, neurological, and hepatic comorbidities. While both agents offer minimal respiratory depression and valuable non-opioid analgesic effects, their contrasting pharmacodynamic profiles necessitate context-specific selection. Co-administration may provide synergistic benefits in select populations, but further research is warranted to establish optimal dosing strategies and define patient subgroups most likely to benefit.

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