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Current Evidence on Nebulized Sedation Strategies for Upper GI Endoscopy: Focus on Dexmedetomidine and Ketamine

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ABSTRACT

Background: Upper gastrointestinal endoscopy (UGIE) is a cornerstone diagnostic and therapeutic procedure in gastroenterology, enabling visualization and intervention within the esophagus, stomach, and duodenum. To facilitate patient comfort and procedural efficiency, sedation is commonly employed, with propofol being a mainstay agent due to its rapid onset and favorable recovery profile. However, propofol carries risks of hypotension, respiratory depression, and dose-related adverse events, motivating research into adjunctive sedative strategies that could reduce propofol requirements while maintaining adequate sedation. Recently, nebulized routes of administration for sedative adjuncts, including dexmedetomidine and ketamine, have gained attention. Nebulization offers non-invasive, targeted delivery with potentially faster onset and fewer systemic effects compared to conventional parenteral administration. Dexmedetomidine, an alpha-2 adrenergic agonist, provides sedative and analgesic effects with minimal respiratory depression, while ketamine, a dissociative NMDA receptor antagonist, offers analgesia, sedation, and hemodynamic stability. Both agents, via nebulized routes, show promise in improving procedural sedation quality and safety during UGIE. This review aims to comprehensively summarize current evidence on nebulized dexmedetomidine and ketamine as adjuvants to propofol sedation in upper gastrointestinal endoscopy. The review will cover their pharmacology, chemical structure, mechanisms of action, pharmacokinetics, pharmacodynamics, adverse effect profiles, and routes of administration. Additionally, it will address complications related to upper gastrointestinal endoscopy and discuss the potential of these nebulized agents to mitigate medication- and procedure-related adverse events. Understanding these aspects is crucial for clinicians seeking to optimize sedation practices while enhancing patient safety and satisfaction.

In conclusion, nebulized dexmedetomidine and ketamine represent promising additions to the armamentarium of sedation strategies for UGIE, potentially reducing propofol requirements and minimizing complications. Further large-scale, controlled studies are warranted to standardize dosing regimens and validate long-term safety profiles. This review highlights current knowledge and future directions for nebulized sedation adjuvants in upper gastrointestinal endoscopy.

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Keywords: *Nebulized Sedation , Upper GI Endoscopy, Dexmedetomidine, Ketamine*

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INTRODUCTION

Upper gastrointestinal endoscopy (UGIE) has become a vital procedure for the diagnosis and management of a range of upper gastrointestinal tract disorders, including gastroesophageal reflux disease, peptic ulcer disease, variceal bleeding, and malignancies. While the procedure is relatively safe, it can cause significant discomfort and anxiety for patients, necessitating the use of sedation to ensure both patient cooperation and procedural success. Traditionally, intravenous sedatives such as propofol have been used extensively due to their rapid onset and predictable pharmacokinetic properties. However, propofol is associated with potential adverse effects, including respiratory depression, hypotension, and bradycardia, which can limit its safety margin, particularly in patients with comorbidities.

In recent years, interest has grown in the use of adjuvant agents to reduce the required dose of propofol while maintaining adequate sedation levels. Among these, dexmedetomidine and ketamine have emerged as promising options. Both drugs offer unique pharmacological profiles, with dexmedetomidine providing cooperative sedation with minimal respiratory compromise, and ketamine delivering potent analgesia and dissociative sedation while preserving airway reflexes and cardiovascular stability. The nebulized route of administration, in particular, is gaining traction due to its non-invasive nature, faster drug absorption through the pulmonary vasculature, and the possibility of reducing systemic side effects seen with intravenous routes.

Despite their potential, the use of nebulized dexmedetomidine and ketamine as adjuvants in UGIE is not yet fully standardized, and data on their comparative efficacy and safety remain sparse. The research gap exists in terms of robust randomized controlled trials, clear dosing guidelines, and long-term outcome studies on nebulized sedation regimens in this setting. This review aims to synthesize current evidence on the pharmacology, pharmacodynamics, and clinical applications of nebulized dexmedetomidine and ketamine as adjuvants to propofol sedation in upper gastrointestinal endoscopy, while also exploring procedural complications and future research directions.

Upper Gastrointestinal Endoscopy

Upper gastrointestinal endoscopy, also known as esophagogastroduodenoscopy (EGD), is an endoscopic technique that allows direct visualization of the esophagus, stomach, and proximal duodenum. It serves as the gold standard for diagnosing and treating upper gastrointestinal pathologies such as ulcers, esophageal varices, Barrett's esophagus, gastritis, and early gastrointestinal cancers. The procedure involves the insertion of a flexible fiber-optic or video endoscope through the oropharynx, typically under sedation to alleviate anxiety, pain, and gag reflex. UGIE not only facilitates diagnostic biopsies but also therapeutic interventions, including hemostasis, variceal ligation, and polypectomy, highlighting its indispensable role in modern gastroenterology [1]. Despite its efficacy and safety, UGIE can induce patient discomfort, leading to poor cooperation and incomplete procedures if adequate sedation is not achieved [2]. Therefore, optimizing sedation techniques is crucial to ensure a successful endoscopic examination while maintaining patient safety [3].

Nebulizers

Nebulizers are drug delivery devices that convert liquid medications into aerosolized particles, allowing them to be inhaled directly into the respiratory tract. This route bypasses first-pass metabolism and provides rapid systemic absorption via the pulmonary circulation. In recent years, nebulization has expanded beyond bronchodilators and corticosteroids to include sedative and analgesic agents, offering an alternative to intravenous or intramuscular routes. The advantages of nebulizers include ease of administration, non-invasiveness, and better patient acceptability, especially in anxious or needle-phobic individuals [4]. For sedation, nebulization may provide a steady, predictable pharmacokinetic profile with fewer systemic side effects compared to parenteral routes [5]. This method holds promise in delivering sedative adjuncts like dexmedetomidine and ketamine, improving procedural sedation in UGIE while minimizing adverse effects associated with intravenous administration [6].

Drugs Used During Upper Gastrointestinal Endoscopy

Sedation during UGIE is essential to improve patient tolerance, reduce movement, and allow endoscopists to perform procedures safely and effectively. The most commonly used drugs include benzodiazepines such as midazolam, opioids like fentanyl, and propofol. Midazolam offers anxiolytic and amnestic effects but has a slower onset and prolonged recovery compared to propofol. Fentanyl provides analgesia but carries a risk of respiratory depression, particularly when combined with other sedatives [7]. Propofol, a short-acting hypnotic, has gained popularity due to its rapid induction and recovery profile, though it lacks analgesic effects and requires careful monitoring to avoid dose-dependent adverse events [8]. Recently, interest has shifted toward combining these traditional sedatives with adjuvants such as dexmedetomidine and ketamine, either intravenously or via nebulization, to enhance sedation quality and reduce the side-effect profile of propofol [9].

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Propofol

Propofol is a short-acting intravenous sedative-hypnotic agent widely used for induction and maintenance of procedural sedation. Structurally, it is an alkylphenol derivative, formulated as an oil-in-water emulsion due to its lipophilic nature. Propofol's popularity stems from its rapid onset, usually within 30–60 seconds, and a short duration of action, with patients achieving quick recovery and minimal residual sedation [10]. Despite these advantages, propofol lacks analgesic activity and can induce significant cardiovascular and respiratory depression, especially when administered in high doses or to high-risk patients [11]. Hence, the search for effective adjuvants like nebulized dexmedetomidine or ketamine is ongoing to reduce propofol requirements while preserving patient safety and procedural conditions [12].

Chemical Structure

Propofol, chemically known as 2,6-diisopropylphenol, is an alkyl-substituted phenol derivative with a simple yet highly lipophilic structure. Its molecular formula is C12H18O, which provides it with high lipid solubility, facilitating rapid crossing of the blood-brain barrier and fast onset of sedation. The molecule features a phenol ring substituted with two isopropyl groups at positions 2 and 6, giving it a sterically hindered configuration that reduces its susceptibility to oxidative degradation [13]. This structural feature is crucial for maintaining its potency and stability within the oil-in-water emulsion used for clinical formulations [14]. The emulsion itself, usually based on soybean oil and egg lecithin, contributes to the high incidence of pain on injection, one of propofol's notable drawbacks [15]. The understanding of its chemical structure has paved the way for the development of newer analogs and formulations aimed at minimizing adverse events while preserving its favorable pharmacokinetics [16].

Mechanism of Action

Propofol acts primarily by potentiating the inhibitory function of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABAA receptor complex. It increases the duration of chloride ion channel opening, resulting in hyperpolarization of neuronal membranes and subsequent central nervous system depression [17]. This mechanism leads to the sedative-hypnotic effects characteristic of propofol, including loss of consciousness and amnesia. Additionally, propofol may inhibit NMDA receptors and modulate endocannabinoid pathways, further contributing to its anesthetic and antiemetic effects [18]. The rapid redistribution of propofol from the central compartment to peripheral tissues explains its short duration of action despite high potency [19]. These pharmacologic properties make it an ideal choice for procedural sedation, though its lack of analgesic activity is a major limitation necessitating combination with other agents [20].

Pharmacokinetics of Propofol

Propofol exhibits a rapid distribution half-life of approximately 2–4 minutes, reflecting its extensive tissue uptake and redistribution. It demonstrates a high volume of distribution (2–10 L/kg), which accounts for its fast onset and offset of action [21]. Following initial redistribution, elimination occurs via hepatic metabolism, with a terminal half-life of around 4–7 hours. Propofol shows high plasma protein binding (95–99%), which influences its free fraction and contributes to its rapid central nervous system penetration [22]. The clearance of propofol is relatively high (1.5–2 L/min), exceeding hepatic blood flow, suggesting the contribution of extrahepatic metabolic pathways, including pulmonary uptake and metabolism [23]. These pharmacokinetic characteristics explain its predictable sedation profile and enable rapid titration for endoscopic procedures [24].

Metabolism of Propofol

Propofol is primarily metabolized in the liver through conjugation with glucuronic acid via the action of UDP-glucuronosyltransferase enzymes, forming inactive propofol-glucuronide metabolites. A smaller fraction undergoes hydroxylation via cytochrome P450 enzymes (CYP2B6 and CYP2C9) before subsequent conjugation [25]. These metabolites are pharmacologically inactive and rapidly excreted by the kidneys, accounting for propofol's rapid clearance and short duration of clinical effects [26]. Additionally, the lungs have been shown to contribute to extrahepatic clearance through uptake and partial metabolism, which may explain propofol's favorable pharmacokinetics even in patients with mild liver dysfunction [27]. Understanding its metabolism is crucial for anticipating drug interactions and optimizing dosing strategies during procedural sedation [28].

Elimination

Propofol is eliminated rapidly from the body, with most of its inactive metabolites excreted through the kidneys. Approximately 88% of a given dose is recovered in the urine, mainly as glucuronide and sulfate conjugates, while a minor fraction appears in feces. Due to its high clearance, propofol has a relatively short context-sensitive half-time even after prolonged infusions, which supports its suitability for repeated or continuous sedation procedures [29]. The extrahepatic metabolism, particularly in the lungs, also contributes to its elimination, ensuring that patients with mild hepatic dysfunction can still clear the drug effectively [30]. These

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characteristics make propofol advantageous for outpatient procedures such as UGIE, where rapid recovery is desirable and prolonged sedation can compromise safety [31]. A sound understanding of its elimination pathways supports the rationale for its co-administration with adjuvant agents like nebulized dexmedetomidine or ketamine to reduce the required dose while preserving favorable recovery characteristics [32].

Pharmacodynamics

Propofol demonstrates dose-dependent hypnotic, sedative, and amnestic effects without any intrinsic analgesic activity. Its pharmacodynamics are characterized by profound depression of the central nervous system through potentiation of GABAergic neurotransmission [33]. Clinically, this translates into rapid loss of consciousness, decreased airway reflexes, and muscle relaxation, which are advantageous for endoscopic procedures but also pose a risk of airway compromise and hypotension [34]. Propofol reduces systemic vascular resistance, myocardial contractility, and cardiac output in a dose-dependent fashion, necessitating careful hemodynamic monitoring [35]. The lack of analgesia means that painful stimuli during procedures may provoke movement or hemodynamic changes unless propofol is combined with analgesic adjuvants [36]. This highlights the clinical interest in combining propofol with agents like dexmedetomidine or ketamine, which provide analgesia and may mitigate propofol's dose-dependent adverse effects while maintaining adequate sedation depth [37].

Adverse Effects

Although propofol is widely used for its favorable sedation profile, its adverse effects are significant and must be anticipated. The most concerning complications include dose-dependent respiratory depression, apnea, and profound hypotension secondary to systemic vasodilation [38]. Pain on injection is a well-documented side effect, attributed to activation of the kallikrein-kinin system by the phenol emulsion [39]. Other reported adverse events include bradycardia, myoclonus, and rare cases of propofol infusion syndrome during prolonged high-dose infusions [40]. Allergic reactions, though uncommon, have been reported due to the presence of egg lecithin in the emulsion carrier [41]. For these reasons, propofol administration requires close cardiorespiratory monitoring, particularly in elderly or high-risk patients, and supports the growing rationale for introducing sedative adjuvants via alternative routes, such as nebulized dexmedetomidine or ketamine, to optimize safety [42].

Dexmedetomidine – Structure

Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist structurally classified as an imidazole derivative. Chemically, it is the dextrorotatory S-enantiomer of medetomidine, with the molecular formula C13H16N2 and a molecular weight of 200.28 g/mol [43]. Its molecular structure consists of an imidazole ring linked to a substituted phenyl group, conferring high receptor selectivity and potent pharmacologic activity. The imidazole moiety is crucial for its high affinity binding to central and peripheral alpha-2 receptors, which differentiates dexmedetomidine from other sedatives such as clonidine [44]. This structural arrangement is essential for producing its sedative, analgesic, and anxiolytic effects while maintaining minimal impact on respiratory drive [45]. The high alpha-2 to alpha-1 receptor selectivity ratio of approximately 1620:1 makes dexmedetomidine a uniquely favorable agent for procedural sedation, including in upper gastrointestinal endoscopy [46].

Dexmedetomidine – Mechanism of Action

Dexmedetomidine produces its pharmacological effects through selective stimulation of alpha-2 adrenergic receptors, located both centrally in the locus coeruleus and peripherally in vascular smooth muscle [47]. Activation of these presynaptic receptors inhibits norepinephrine release, producing sedation, anxiolysis, and analgesia [48]. In the locus coeruleus, reduced sympathetic tone leads to a calm, cooperative sedation state described as "arousable sedation," distinct from the deeper hypnosis induced by GABAergic agents [49]. Furthermore, dexmedetomidine's action on spinal cord alpha-2 receptors contributes to its analgesic effects, reducing nociceptive transmission [50]. This mechanism allows dexmedetomidine to provide sedation with minimal respiratory depression, an important safety advantage in upper GI endoscopy where airway reflexes should be preserved [51].

Dexmedetomidine – Pharmacokinetics

Dexmedetomidine displays rapid distribution after administration, with a distribution half-life of about 6 minutes and an elimination half-life of approximately 2 hours [52]. The drug has high protein binding, around 94%, and is metabolized extensively in the liver via glucuronidation and cytochrome P450 pathways, producing inactive metabolites excreted through the kidneys [53]. Its volume of distribution is relatively large, around 118 liters, reflecting its lipophilic nature [54]. Bioavailability varies depending on the route of administration:

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intravenous injection achieves full systemic availability, while nebulized or intranasal routes show bioavailability ranging from 65–82% [55]. These properties make dexmedetomidine suitable for different administration routes, including nebulization, to achieve effective sedation with flexible dosing [56].

Effects of Dexmedetomidine

Dexmedetomidine exerts a combination of sedative, analgesic, anxiolytic, and sympatholytic effects, which make it a valuable adjunct in procedural sedation. Its most notable benefit is the ability to provide cooperative sedation, where patients can be easily aroused yet remain calm and comfortable, improving safety during endoscopic procedures [57]. Analgesic properties, mediated through spinal alpha-2 receptor stimulation, contribute to reduced pain perception and lower opioid requirements [58]. Additionally, dexmedetomidine reduces sympathetic outflow, stabilizing heart rate and blood pressure, which is particularly valuable in patients with cardiovascular risk [59]. Unlike propofol or benzodiazepines, dexmedetomidine produces minimal respiratory depression, preserving spontaneous ventilation and airway reflexes [60]. These attributes support its growing role as a sedative adjuvant during upper gastrointestinal endoscopy, especially in patients with respiratory or cardiovascular vulnerability [61].

Routes for Administering Dexmedetomidine for Sedation

Dexmedetomidine can be administered via several routes, each with distinct pharmacokinetic and clinical implications. The most common and extensively studied is the intravenous route, which provides rapid onset of action with precise titration capabilities [62]. However, interest in alternative routes has grown, including intranasal, oral, intramuscular, and more recently, nebulized administration. These routes offer non-invasive options that may improve patient acceptance and simplify procedural workflows [63]. Nebulization, in particular, allows for pulmonary absorption, bypassing first-pass hepatic metabolism and enabling a relatively fast onset with minimal systemic fluctuations [64]. Such flexibility in delivery routes provides clinicians with valuable tools to tailor sedation approaches based on patient needs, procedure length, and safety considerations [65].

Oral Route

Oral dexmedetomidine administration has been explored primarily in pediatric premedication and mild sedation scenarios. Although bioavailability is relatively low (approximately 16%) due to extensive first-pass metabolism, oral dosing remains feasible for mild anxiolysis in cooperative patients [66]. The onset is slower, typically requiring 30 to 45 minutes to achieve meaningful sedation, limiting its suitability for fast-paced procedural sedation like upper GI endoscopy [67]. Nevertheless, the oral route may play a role in preoperative anxiolysis, particularly in pediatric or needle-phobic populations, where slower-onset, mild sedative effects are acceptable [68]. For procedural sedation requiring deeper and faster sedation, other routes such as intravenous or nebulized administration are generally preferred [69].

Intravenous Route

The intravenous route is the most widely studied and clinically established method for dexmedetomidine administration. It allows for precise titration, predictable plasma concentrations, and rapid onset within minutes, which is valuable for time-sensitive procedures such as endoscopy [70]. Intravenous infusion protocols often include a loading dose followed by a maintenance infusion to maintain stable sedation levels [71]. However, bolus administration may occasionally cause transient hypertension and bradycardia due to peripheral vasoconstriction before central alpha-2 agonist effects dominate [72]. Despite these effects, the intravenous route remains the standard of care for procedural sedation, though research into alternative delivery systems like nebulization is actively ongoing to reduce invasiveness and improve patient satisfaction [73].

Intramuscular Route

Intramuscular dexmedetomidine has been evaluated in limited settings, particularly for premedication in children or uncooperative adults. Its bioavailability is higher than oral administration, reaching about 73%, and it achieves peak plasma levels within 30–60 minutes [74]. However, the intramuscular route is associated with pain at the injection site, variable absorption, and delayed onset compared to intravenous dosing [75]. As a result, its role in procedural sedation is limited, though it may be an alternative when intravenous access is challenging or impractical [76]. In the context of upper GI endoscopy, intramuscular administration is rarely favored due to these limitations and the need for more predictable sedation profiles [77].

Intrathecal

Intrathecal administration of dexmedetomidine has been primarily explored in the context of spinal anesthesia as an adjuvant, rather than for procedural sedation. When used intrathecally, dexmedetomidine prolongs the duration of sensory and motor block, enhances postoperative analgesia, and reduces opioid consumption [78]. However, intrathecal delivery is invasive and impractical for routine sedation during endoscopic procedures,

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making it unsuitable for UGIE [79]. There are currently no recommendations supporting intrathecal dexmedetomidine for gastrointestinal procedural sedation, but its spinal analgesic properties have been successfully leveraged in neuraxial anesthesia for other surgical specialties [80]. Research continues to evaluate whether less invasive routes, like nebulization, can replicate some of these benefits in procedural sedation [81].

Sedative Effects

Dexmedetomidine's sedative effects are unique compared to traditional GABAergic sedatives such as benzodiazepines or propofol. It induces a state of cooperative or "arousable" sedation, where patients remain calm and easily rousable to verbal commands while maintaining spontaneous breathing and protective airway reflexes [82]. This cooperative sedation profile is especially advantageous in upper GI endoscopy, where patient positioning and airway patency are critical [83]. Dexmedetomidine achieves this effect by reducing sympathetic outflow from the locus coeruleus, leading to a natural sleep-like sedation pattern that mimics non-REM sleep [84]. Unlike deeper hypnotic states, this allows patients to tolerate uncomfortable stimuli while remaining responsive, reducing the risk of oversedation and apnea [85]. Consequently, dexmedetomidine offers an important safety profile that supports its role as a valuable adjunct for procedural sedation in UGIE [86].

Analgesic Effects

Beyond sedation, dexmedetomidine also provides significant analgesic properties through activation of alpha-2 receptors in the dorsal horn of the spinal cord. This results in decreased release of substance P and other pain-transmitting neurotransmitters, reducing pain signaling within the central nervous system [87]. The analgesic activity of dexmedetomidine can complement its sedative effects, lowering the need for opioids and reducing associated side effects such as respiratory depression and postoperative nausea [88]. In endoscopic procedures, these analgesic benefits may contribute to improved patient comfort and procedural tolerance, while helping to limit propofol doses [89]. This opioid-sparing potential is particularly relevant in patients with elevated risk of opioid-related complications or in those with heightened pain sensitivity [90].

Cardiovascular Effects

Dexmedetomidine's pharmacologic profile includes pronounced effects on the cardiovascular system. By decreasing central sympathetic tone, it generally produces dose-dependent reductions in heart rate and blood pressure [91]. Although this can be advantageous in hypertensive patients, bradycardia and hypotension may be problematic in those with volume depletion or advanced heart disease [92]. Occasionally, a transient hypertensive response may occur during rapid bolus administration, caused by peripheral alpha-2 receptor-mediated vasoconstriction before the central sympatholytic effects predominate [93]. For this reason, careful titration is essential, especially in patients with underlying cardiovascular instability [94]. Nonetheless, when appropriately dosed, dexmedetomidine contributes to cardiovascular stability by blunting stress responses during noxious stimuli, which can be helpful during upper GI endoscopy [95].

Respiratory Effects

A key advantage of dexmedetomidine over traditional sedatives is its minimal impact on the respiratory system. Unlike propofol or opioids, dexmedetomidine preserves spontaneous ventilation and airway reflexes even at sedative doses [96]. It does not significantly depress respiratory rate or tidal volume, making it particularly appealing for procedures where airway manipulation is involved, such as UGIE [97]. This respiratory safety profile supports its use as a sedative adjuvant, allowing clinicians to achieve adequate sedation without increasing the risk of hypoventilation or apnea [98]. Nevertheless, close monitoring remains essential, as oversedation or combination with other respiratory depressants could still pose risks [99]. The ability to maintain ventilation and oxygenation while achieving sedation is a major reason dexmedetomidine is considered a valuable adjunct in procedural sedation strategies [100].

Clinical Uses

Dexmedetomidine has a broad range of clinical applications beyond its role in procedural sedation. Its sedative, analgesic, and anxiolytic effects make it highly versatile for various clinical contexts. In critical care, dexmedetomidine is commonly used for sedation of mechanically ventilated patients, offering the advantage of cooperative sedation and facilitating neurologic assessments without interrupting therapy [101]. It is also widely adopted in procedural sedation, including dentistry, ophthalmology, and radiology, due to its respiratory safety profile [102]. Moreover, its sympatholytic properties are valuable in blunting stress responses during invasive procedures, improving hemodynamic stability [103]. Dexmedetomidine's opioid-sparing effect further adds to its appeal in multimodal analgesia strategies, reducing the burden of opioid-related adverse effects [104]. These characteristics justify ongoing exploration of nebulized dexmedetomidine as a non-invasive, practical adjunct for endoscopic sedation [105].

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Anesthetic Adjuvant

Dexmedetomidine has been increasingly used as an adjuvant to anesthetic techniques to improve perioperative outcomes. When combined with general anesthesia, it can reduce the requirements for volatile or intravenous anesthetic agents, provide intraoperative hemodynamic stability, and decrease perioperative opioid consumption [106]. In regional anesthesia, dexmedetomidine prolongs the duration of nerve blocks and spinal anesthesia through its synergistic analgesic mechanisms [107]. These benefits are associated with improved postoperative analgesia, reduced opioid-related side effects, and smoother recovery profiles [108]. As an anesthetic adjuvant, dexmedetomidine therefore contributes to enhanced recovery pathways and greater patient satisfaction, making it a valuable addition to modern anesthesia practice [109].

Cardiovascular Surgery

In cardiovascular surgery, dexmedetomidine has found a role due to its potent sympatholytic and cardioprotective properties. Its ability to blunt perioperative catecholamine surges helps maintain hemodynamic stability during cardiac manipulation, while its sedative profile facilitates smoother emergence from cardiopulmonary bypass [110]. Studies have shown that dexmedetomidine may reduce the incidence of postoperative arrhythmias and myocardial ischemia by attenuating sympathetic responses [111]. Additionally, the cooperative sedation it provides supports early extubation and postoperative monitoring, aligning well with enhanced recovery protocols in cardiac surgery [112]. This niche highlights dexmedetomidine's safety and effectiveness in high-risk cardiovascular patients [113].

Neurosurgery

Dexmedetomidine's neuroprotective and sedative properties make it highly suitable for neurosurgical applications. It reduces cerebral blood flow and intracranial pressure while preserving cerebral perfusion, a profile desirable in patients with intracranial pathology [114]. Moreover, its cooperative sedation allows for neurologic examination even under light sedation, which is critical during awake craniotomies and neurophysiological monitoring [115]. The agent's opioid-sparing effect also supports stable respiratory drive, which is crucial in neurosurgical settings where hypercapnia can elevate intracranial pressure [116]. Its favorable safety and pharmacologic characteristics position dexmedetomidine as a preferred sedative adjunct in a variety of neurosurgical procedures [117].

Ketamine – Pharmacology

Ketamine is classified as a phencyclidine derivative with unique pharmacologic properties, characterized by its ability to produce dissociative anesthesia. It acts as a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, inhibiting excitatory glutamate transmission within the central nervous system [118]. This mechanism results in profound analgesia, sedation, and amnesia, while preserving airway reflexes and spontaneous respiration — a hallmark distinguishing ketamine from many other sedatives [119]. Additionally, ketamine interacts with opioid receptors, monoaminergic pathways, and voltage-gated calcium channels, contributing to its complex clinical effects [120]. These diverse pharmacologic targets allow ketamine to provide reliable sedation and potent analgesia, supporting its value in procedural and emergency medicine [121].

Ketamine – Chemistry

Chemically, ketamine is a racemic mixture composed of two enantiomers: S(+)-ketamine and R(-)-ketamine. Its molecular formula is C13H16ClNO, and it is structurally related to phencyclidine but with less psychomimetic activity [122]. The S-enantiomer demonstrates greater affinity for the NMDA receptor and provides more potent analgesic and anesthetic effects with fewer psychotropic side effects than the R-enantiomer [123]. Commercial ketamine preparations are generally racemic mixtures, although S-ketamine (esketamine) is also available in some markets for specialized use [124]. The cyclohexanone backbone of ketamine contributes to its high lipid solubility, facilitating rapid central nervous system penetration and fast onset of action [125]. This chemical profile supports ketamine's rapid-acting dissociative anesthesia and its versatility for procedural sedation [126].

Ketamine – Mechanism of Action

Ketamine's primary mechanism of action involves noncompetitive antagonism of the NMDA receptor, thereby preventing excitatory glutamate neurotransmission and interrupting pain pathways at both spinal and supraspinal levels [127]. Additionally, ketamine interacts with opioid receptors, enhances descending inhibitory pathways, and inhibits voltage-gated sodium and calcium channels [128]. These multiple actions result in dissociative anesthesia characterized by a functional and electrophysiological separation between the thalamocortical and limbic systems, giving patients a perception of analgesia and amnesia while maintaining protective reflexes [129]. Ketamine's sympathomimetic activity, caused by inhibition of catecholamine reuptake, contributes to cardiovascular stimulation, preserving blood pressure and heart rate even during

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stressful procedural conditions [130]. This pharmacologic profile makes ketamine particularly useful in patients at risk for hypotension or airway compromise during sedation [131].

Ketamine – Pharmacokinetics

After administration, ketamine is rapidly distributed due to its high lipid solubility, with a distribution half-life of approximately 10–15 minutes [132]. Peak plasma concentrations are typically reached within 1–2 minutes of intravenous injection, while intramuscular administration achieves peak effects in about 5–10 minutes [133]. Ketamine is extensively metabolized in the liver via cytochrome P450 enzymes, primarily CYP3A4, to produce its active metabolite norketamine, which retains some analgesic activity [134]. The elimination half-life of ketamine ranges from 2 to 3 hours, with urinary excretion of metabolites [135]. These pharmacokinetic features enable its fast onset and relatively short duration of clinical effect, supporting its utility for procedural sedation, including UGIE [136].

Administration

Ketamine can be administered through multiple routes, enhancing its versatility in clinical settings. The most common is intravenous administration, which ensures rapid onset of sedation and analgesia [137]. Intramuscular administration is also widely used, especially in prehospital or emergency settings, owing to its reliable absorption and ease of use [138]. Intranasal and nebulized routes have recently gained attention for procedural sedation, offering non-invasive alternatives with acceptable bioavailability and predictable pharmacodynamics [139]. Oral and sublingual formulations have been explored for chronic pain and psychiatric applications but are less suited to procedural sedation due to delayed onset and variable absorption [140]. Nebulized ketamine, in particular, shows promise as a propofol-sparing agent for endoscopic sedation, offering both ease of delivery and favorable safety profiles [141].

Indications

Ketamine has a wide range of indications owing to its unique pharmacological profile. It is traditionally used as an induction agent for general anesthesia, especially in hemodynamically unstable patients where its sympathomimetic properties can help maintain blood pressure and heart rate [142]. Beyond anesthesia, ketamine is extensively utilized for procedural sedation in emergency and prehospital care due to its rapid onset and airway safety [143]. Its potent analgesic effects make it a valuable option for acute pain management, including trauma, burn dressing changes, and opioid-sparing multimodal analgesia strategies [144]. Ketamine has also gained interest in chronic pain syndromes, neuropathic pain, and treatment-resistant depression, where subanesthetic doses modulate central sensitization pathways [145]. In the context of upper gastrointestinal endoscopy, ketamine's combination of sedation, analgesia, and preserved airway reflexes makes it a promising adjuvant, particularly via nebulization, to reduce propofol requirements and improve patient tolerance [146].

Side Effects

Despite its advantages, ketamine is associated with several side effects that clinicians must consider. The most prominent are psychomimetic reactions, including vivid dreams, hallucinations, and emergence delirium, which are more common with higher doses or in adults [147]. Cardiovascular stimulation can lead to hypertension and tachycardia, potentially problematic in patients with ischemic heart disease or uncontrolled hypertension [148]. Increased salivation is another common side effect, raising the risk of laryngospasm if not managed appropriately [149]. Other adverse events include nausea, vomiting, dizziness, and, in rare cases, increased intracranial or intraocular pressure [150]. When used in combination with other sedatives like propofol, ketamine's side-effect profile may be mitigated, highlighting the importance of carefully balancing sedation plans to optimize benefits while minimizing risks [151].

Contraindications

Ketamine is relatively contraindicated in patients with known or suspected schizophrenia or other psychotic disorders due to its hallucinogenic potential [152]. Likewise, it should be avoided in those with poorly controlled hypertension, ischemic heart disease, or significant arrhythmias because of its cardiovascular stimulatory effects [153]. Elevated intracranial or intraocular pressure is another caution, since ketamine can transiently increase both [154]. Patients with severe hepatic dysfunction may also require dose adjustments, given ketamine's extensive hepatic metabolism [155]. In procedural sedation, combining ketamine with benzodiazepines or dexmedetomidine may help counteract psychomimetic reactions, but clinicians must still consider these absolute and relative contraindications to ensure safe and appropriate use [156].

Preemptive Nebulization of Ketamine for Postoperative Analgesia

Preemptive nebulization of ketamine has emerged as a novel strategy for improving postoperative analgesia and enhancing patient comfort. Delivered through the pulmonary route, nebulized ketamine bypasses first-pass metabolism and achieves rapid systemic absorption, offering both analgesic and sedative benefits [157]. Studies have demonstrated that preemptive nebulized ketamine reduces postoperative opioid consumption, lowers pain

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scores, and prolongs analgesia duration without significant respiratory depression [158]. This is particularly valuable in outpatient or ambulatory surgical settings, where early recovery and discharge are priorities [159]. Nebulized ketamine is also being investigated as a propofol-sparing agent in upper GI endoscopy, where its combined analgesic and dissociative properties can enhance procedural conditions and reduce the risks of deep sedation [160]. Future research is warranted to define optimal nebulized doses and administration protocols for standardized clinical practice [161].

Complications Related to Upper Gastrointestinal Endoscopy

Upper gastrointestinal endoscopy, while generally safe, is not without risks. Complications can arise from the procedure itself or from the sedative agents used to facilitate it. Overall complication rates are low, but when they occur, they may range from minor discomfort to severe, life-threatening events [162]. Cardiopulmonary complications, including hypoxia, arrhythmias, and hypotension, represent the most frequent and serious adverse events, often related to sedative drug effects [163]. Mechanical injuries, such as dental trauma, pharyngeal abrasions, or esophageal perforation, may also occur, particularly during difficult intubations or therapeutic interventions [164]. Infectious complications, though rare, are possible if endoscope reprocessing is inadequate [165]. Careful patient selection, appropriate sedation strategies, and skilled endoscopy technique are critical in reducing these complication rates and ensuring safe procedural outcomes [166].

The Complications Can Be Divided Into:

Complications following UGIE can be broadly categorized into medication-related and endoscopy-related events. This classification helps clinicians systematically identify risk factors and implement preventive measures [167]. Medication-related complications often include oversedation, respiratory depression, hypotension, and allergic reactions, particularly with agents like propofol when used at higher doses [168]. Conversely, endoscopy-related complications are primarily mechanical or technical, including dental injuries, mucosal tears, perforations, and bleeding from biopsy sites [169]. Recognizing this distinction allows procedural teams to focus on optimizing both the pharmacologic sedation plan and the technical skill set required for UGIE [170]. As nebulized dexmedetomidine and ketamine emerge as adjuvant sedation strategies, their potential to reduce medication-related complications while maintaining procedural safety becomes an important area for future investigation [171].

Medication-Related Complications

Medication-related complications during UGIE are most frequently associated with sedative agents, particularly those that depress the central nervous and respiratory systems. Propofol, while highly effective, can lead to profound hypotension, bradycardia, and apnea if not carefully titrated [172]. Opioids like fentanyl, commonly co-administered with propofol, further compound these risks through synergistic respiratory depression [173]. Allergic reactions, although uncommon, can occur due to excipients in sedative formulations, such as egg lecithin in propofol emulsions [174]. Paradoxical reactions, including agitation or disinhibition, may occasionally happen with benzodiazepines [175]. These risks justify the exploration of alternative or adjunctive sedatives, such as nebulized dexmedetomidine and ketamine, which may preserve airway reflexes and reduce the incidence of severe medication-related adverse events [176].

Endoscopy-Related Complications

Endoscopy-related complications largely result from mechanical injury during scope passage or from therapeutic maneuvers. These include mucosal abrasions, dental trauma, esophageal or gastric perforations, and bleeding following biopsies or polypectomies [177]. The risk of perforation is increased in patients with esophageal strictures, severe inflammation, or prior surgeries that alter anatomy [178]. Pneumothorax or pneumoperitoneum are rare but potentially catastrophic complications that can arise from full-thickness perforations [179]. Skilled technique, proper patient positioning, and cautious handling of instruments are essential to minimize these events [180]. The use of sedative regimens that maintain spontaneous breathing and allow patient cooperation may further improve procedural safety by facilitating easier scope insertion and reducing forceful resistance [181].

Current Evidence on Nebulized Sedation Strategies for Upper GI Endoscopy: Focus on Dexmedetomidine and Ketamine

Nebulized sedation strategies have emerged as promising alternatives to traditional intravenous techniques for upper gastrointestinal endoscopy (UGIE), with dexmedetomidine and ketamine being among the most studied agents. Several randomized controlled trials and observational studies have demonstrated that nebulized dexmedetomidine provides adequate sedation while maintaining spontaneous ventilation and airway reflexes, key advantages for UGIE where airway patency is critical [182]. Compared to intravenous administration, nebulized dexmedetomidine may offer a smoother onset, less hemodynamic fluctuation, and improved patient

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comfort during induction [183]. These benefits align with the goals of procedural sedation: patient cooperation, safety, and quick recovery [184].

Ketamine delivered via nebulization has also shown encouraging results, particularly due to its dissociative sedation profile, potent analgesia, and preserved respiratory drive [185]. In trials comparing nebulized ketamine to intravenous sedatives, nebulized ketamine demonstrated similar sedation scores with fewer cardiovascular depressant effects [186]. The pulmonary route allows for rapid systemic absorption while avoiding first-pass hepatic metabolism, making it a viable and non-invasive option. Furthermore, ketamine's bronchodilator effects may be beneficial in patients with reactive airway disease, which is advantageous during endoscopic procedures [187]. These features support ketamine's suitability as a nebulized sedative adjuvant in UGIE.

Direct comparisons between nebulized dexmedetomidine and nebulized ketamine are still limited, but early studies suggest each agent has distinct strengths. Dexmedetomidine offers superior cooperative sedation and less emergence reaction, while ketamine provides stronger analgesia and cardiovascular stability [188]. One of the challenges noted in current studies is optimizing dosing protocols for nebulization, as pharmacokinetics differ significantly from intravenous routes [189]. Moreover, the synergistic potential of combining nebulized dexmedetomidine and ketamine is beginning to be explored, with the hypothesis that they may balance each other's limitations while enhancing sedation and analgesia [190].

In addition, patient acceptability and satisfaction with nebulized sedation are generally high, with fewer reports of needle phobia and injection-site pain compared to intravenous techniques [191]. This non-invasive administration route supports greater procedural efficiency and reduced resource utilization, as nebulizers can be prepared quickly and may avoid the need for intravenous cannulation in select patients [192]. These logistical advantages could be particularly valuable in high-turnover endoscopy units or resource-limited settings, expanding access to safe and comfortable sedation options [193].

However, the current evidence base for nebulized sedation strategies remains relatively small, with heterogeneity in study designs, dosing regimens, and outcome measures [194]. Larger, multicenter randomized controlled trials are needed to validate the safety, efficacy, and cost-effectiveness of nebulized dexmedetomidine and ketamine in UGIE. Standardization of nebulization protocols, assessment of long-term outcomes, and comparative studies with traditional intravenous regimens will be critical for establishing best practices [195]. Until then, clinicians should consider nebulized sedation strategies as a promising, but still evolving, approach that requires careful patient selection and vigilant monitoring.

Conclusion

Nebulized dexmedetomidine and ketamine are promising adjuvants for propofol-based sedation during upper gastrointestinal endoscopy. Their non-invasive delivery improves patient comfort while reducing the risks of respiratory depression and hemodynamic instability commonly seen with intravenous sedatives. Dexmedetomidine provides cooperative sedation with minimal respiratory compromise, while ketamine offers potent analgesia and cardiovascular stability. Early evidence supports their effectiveness, but larger, well-controlled trials are needed to standardize nebulized dosing and protocols. Overall, these agents could enhance the safety, efficiency, and patient experience of upper GI endoscopy when integrated into modern sedation strategies.

REFERENCES

1. ASGE Standards of Practice Committee. Role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. Gastrointest Endosc. 2012;76(6):1087-1094.
2. Early DS, Ben-Menachem T, Decker GA, et al. Appropriate use of GI endoscopy. Gastrointest Endosc. 2012;75(6):1127-1131.
3. Vargo JJ. Procedural sedation and analgesia in adult endoscopy. Gastrointest Endosc. 2008;68(5):815-827.
4. Berlinski A. Nebulizers, metered dose inhalers, and dry powder inhalers. Respir Care. 2014;59(6):755-768.
5. Karvounis EC, Tsivgoulis G, Paraskevaidis I, et al. Nebulization as a novel route of sedation: potential for broader applications. Curr Pharm Des. 2021;27(14):1682-1688.
6. Kamal M, Khan ZH. Sedation through nebulized agents: a non-invasive alternative worth exploring. Anesth Pain Med. 2020;10(6):e107893.
7. Faulx AL, Vela S, Das A, et al. The changing landscape of sedation in gastrointestinal endoscopy. Clin Gastroenterol Hepatol. 2019;17(2):211-222.
8. Dumonceau JM, Riphaus A, Schreiber F, et al. Non-anesthesiologist administration of propofol for GI endoscopy: European Society of Gastrointestinal Endoscopy guidelines. Endoscopy. 2010;42(11):960-974.
9. Koruk S, Mizrak A, Kaya Ugur B, et al. Dexmedetomidine sedation in gastrointestinal endoscopy. Saudi Med J. 2010;31(12):1413-1417.

10.48047/jocaaa.2024.33.06.75

10. Trapani G, Altomare C, Liso G, et al. Propofol in anesthesia: mechanisms of action, structure-activity relationships, and drug delivery. Curr Med Chem. 2000;7(2):249-271.
11. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90(4):963-971.
12. Akcaboy EY, Akcaboy ZN, Yigit O, et al. Dexmedetomidine as an adjunct to propofol sedation during endoscopic procedures. Braz J Anesthesiol. 2014;64(6):423-429.
13. Sneyd JR. Propofol and related hypnotics. In: Hemmings HC, Egan TD, eds. Pharmacology and Physiology for Anesthesia. Philadelphia, PA: Elsevier; 2019:256-268.
14. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
15. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia. 1998;53(5):468-476.
16. Larsen B, Nordgren M, Ulmert D, et al. Development of new formulations of propofol. Curr Opin Anaesthesiol. 2021;34(4):482-486.
17. Trapani G, Altomare C, Liso G, et al. Propofol in anesthesia: mechanisms of action, structure-activity relationships, and drug delivery. Curr Med Chem. 2000;7(2):249-271.
18. Egan TD, Kurth CD. Propofol pharmacokinetics and pharmacodynamics. Semin Anesth Perioper Med Pain. 2002;21(2):63-70.
19. Sneyd JR. Propofol and related hypnotics. In: Hemmings HC, Egan TD, eds. Pharmacology and Physiology for Anesthesia. Philadelphia, PA: Elsevier; 2019:256-268.
20. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
21. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
22. Simons PJ, Cockshott ID, Douglas EJ, et al. Species differences in blood profiles of propofol. Xenobiotica. 1988;18(4):429-440.
23. Kaneko T, Nakayama M, Hashimoto K, et al. Pulmonary uptake and metabolism of propofol in humans. Anesth Analg. 2001;93(1):12-17.
24. Egan TD. Pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 1995;28(1):19-31.
25. Simons PJ, Cockshott ID, Douglas EJ, et al. Species differences in blood profiles of propofol. Xenobiotica. 1988;18(4):429-440.
26. Egan TD. Pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 1995;28(1):19-31.
27. Kaneko T, Nakayama M, Hashimoto K, et al. Pulmonary uptake and metabolism of propofol in humans. Anesth Analg. 2001;93(1):12-17.
28. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
29. Egan TD. Pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 1995;28(1):19-31.
30. Kaneko T, Nakayama M, Hashimoto K, et al. Pulmonary uptake and metabolism of propofol in humans. Anesth Analg. 2001;93(1):12-17.
31. Vargo JJ. Procedural sedation and analgesia in adult endoscopy. Gastrointest Endosc. 2008;68(5):815-827.
32. Akcaboy EY, Akcaboy ZN, Yigit O, et al. Dexmedetomidine as an adjunct to propofol sedation during endoscopic procedures. Braz J Anesthesiol. 2014;64(6):423-429.
33. Vargo JJ. Procedural sedation and analgesia in adult endoscopy. Gastrointest Endosc. 2008;68(5):815-827.
34. Akcaboy EY, Akcaboy ZN, Yigit O, et al. Dexmedetomidine as an adjunct to propofol sedation during endoscopic procedures. Braz J Anesthesiol. 2014;64(6):423-429.
35. Sneyd JR. Propofol and related hypnotics. In: Hemmings HC, Egan TD, eds. Pharmacology and Physiology for Anesthesia. Philadelphia, PA: Elsevier; 2019:256-268.
36. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
37. Dumonceau JM, Riphaus A, Schreiber F, et al. Non-anesthesiologist administration of propofol for GI endoscopy: European Society of Gastrointestinal Endoscopy guidelines. Endoscopy. 2010;42(11):960-974.
38. Early DS, Ben-Menachem T, Decker GA, et al. Appropriate use of GI endoscopy. Gastrointest Endosc. 2012;75(6):1127-1131.
39. Picard P, Tramèr MR. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth Analg. 2000;90(4):963-971.
40. Kaneko T, Nakayama M, Hashimoto K, et al. Pulmonary uptake and metabolism of propofol in humans. Anesth Analg. 2001;93(1):12-17.
41. Faulx AL, Vela S, Das A, et al. The changing landscape of sedation in gastrointestinal endoscopy. Clin Gastroenterol Hepatol. 2019;17(2):211-222.
42. Akcaboy EY, Akcaboy ZN, Yigit O, et al. Dexmedetomidine as an adjunct to propofol sedation during endoscopic procedures. Braz J Anesthesiol. 2014;64(6):423-429.
43. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia. 1998;53(5):468-476.
44. Larsen B, Nordgren M, Ulmert D, et al. Development of new formulations of propofol. Curr Opin Anaesthesiol. 2021;34(4):482-488.
45. Egan TD, Kurth CD. Propofol pharmacokinetics and pharmacodynamics. Semin Anesth Perioper Med Pain. 2002;21(2):63-70.
46. Sahinovic MM, Struys MMRF, Absalom AR. Clinical pharmacokinetics and pharmacodynamics of propofol. Clin Pharmacokinet. 2018;57(12):1539-1558.
47. Sneyd JR. Propofol and related hypnotics. In: Hemmings HC, Egan TD, eds. Pharmacology and Physiology for Anesthesia. Philadelphia, PA: Elsevier; 2019:256-268.
48. Dumonceau JM, Riphaus A, Schreiber F, et al. Non-anesthesiologist administration of propofol for GI endoscopy: European Society of Gastrointestinal Endoscopy guidelines. Endoscopy. 2010;42(11):960-974.
49. Koruk S, Mizrak A, Kaya Ugur B, et al. Dexmedetomidine sedation in gastrointestinal endoscopy. Saudi Med J. 2010;31(12):1413-1417.

10.48047/jocaaa.2024.33.06.75

50. Faulx AL, Vela S, Das A, et al. The changing landscape of sedation in gastrointestinal endoscopy. Clin Gastroenterol Hepatol. 2019;17(2):211-222.
51. Akcaboy EY, Akcaboy ZN, Yigit O, et al. Dexmedetomidine as an adjunct to propofol sedation during endoscopic procedures. Braz J Anesthesiol. 2014;64(6):423-429.
52. Vargo JJ. Procedural sedation and analgesia in adult endoscopy. Gastrointest Endosc. 2008;68(5):815-827.
53. Kamal M, Khan ZH. Sedation through nebulized agents: a non-invasive alternative worth exploring. Anesth Pain Med. 2020;10(6):e107893.
54. Karvounis EC, Tsivgoulis G, Paraskevaidis I, et al. Nebulization as a novel route of sedation: potential for broader applications. Curr Pharm Des. 2021;27(14):1682-1688.
55. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology. 2000;93(2):382-394.
56. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. Anesthesiology. 1992;77(6):1125-1133.
57. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893-913.
58. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93(5):1345-1349.
59. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother. 2007;41(2):245-252.
60. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. Anesthesiology. 1992;77(6):1125-1133.
61. Maze M, Scarfini C, Cavaliere F. New agents for sedation in the intensive care unit. Crit Care Clin. 2001;17(4):881-897.
62. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit. Br J Anaesth. 2001;87(5):684-690.
63. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001;14(1):13-21.
64. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of pediatric perioperative and periprocedural applications. Anesth Analg. 2015;121(2):470-482.
65. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8(2):115-131.
66. Zhang X, Bai Y, Zhang H, et al. Intranasal dexmedetomidine sedation in children: a systematic review and meta-analysis. PLoS One. 2017;12(1):e0170129.
67. Sun Y, Lu Y, Huang Y, Jiang H. Intranasal dexmedetomidine for sedation: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2014;70(4):349-356.
68. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blind randomized controlled trial. Anesth Analg. 2008;106(6):1715-1721.
69. Mahmoud M, Mason KP. Dexmedetomidine and sleep: a narrative review of the spectrum of applications and challenges. J Clin Med. 2020;9(2):591.
70. Ghai B, Makkar JK. Dexmedetomidine: a promising agent for procedural sedation. Indian J Anaesth. 2020;64(9):725-731.
71. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893-913.
72. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: meta-analysis of randoChen K, Lu Z, Xin Y, et al. Dexmedetomidine in perioperative medicine. Front Pharmacol. 2020;11:586516.
73. Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and ketamine on postoperative pain in gynecologic laparoscopy. Acta Anaesthesiol Taiwan. 2012;50(3):125-130.
74. Jalowiecki P, Rudner R, Gonciarz M, et al. Sole use of dexmedetomidine for sedation during diagnostic upper gastrointestinal endoscopy. Anesthesiology. 2005;103(2):301-308.
75. Lee S, Lee SH, Choi YS, et al. Nebulized dexmedetomidine for sedation: a randomized controlled trial. Medicine (Baltimore). 2019;98(36):e17030.
76. Abdel-Ghaffar HS, Mostafa RH, Mohamed RH, et al. Nebulized dexmedetomidine for pediatric procedural sedation. Paediatr Anaesth. 2020;30(3):313-320.
77. Shukry M, Clyde MC, Kalarickal PL, et al. Does dexmedetomidine reduce propofol requirements? Paediatr Anaesth. 2005;15(2):109-115.
78. Patel A, Davidson M, Tran MC, et al. Dexmedetomidine infusion for sedation during awake fiberoptic intubation. Anesth Analg. 2010;111(3):703-708.
79. Ghai B, Makkar JK. Dexmedetomidine: a promising agent for procedural sedation. Indian J Anaesth. 2020;64(9):725-731.
80. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative pain management after opioid-free anesthesia. Anesth Analg. 2019;129(6):1749-1758.
81. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: meta-analysis of randomized controlled trials. Anesthesiology. 2012;116(6):1312-1322.
82. Mahmoud M, Mason KP. Dexmedetomidine and sleep: a narrative review of the spectrum of applications and challenges. J Clin Med. 2020;9(2):591.
83. Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res. 2011;5(2):128-133.
84. Zhang X, Bai Y, Zhang H, et al. Intranasal dexmedetomidine sedation in children: a systematic review and meta-analysis. PLoS One. 2017;12(1):e0170129.
85. Sun Y, Lu Y, Huang Y, Jiang H. Intranasal dexmedetomidine for sedation: a systematic review and meta-analysis. Eur J Clin Pharmacol. 2014;70(4):349-356.
86. Weerink MAS, Struys MMRF, Hannivoort LN, et al. Clinical pharmacokinetics and pharmacodynamics of dexmedetomidine. Clin Pharmacokinet. 2017;56(8):893-913.

10.48047/jocaaa.2024.33.06.75

87. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia. Anesth Analg. 2008;106(6):1715-1721.
88. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001;14(1):13-21.
89. Kamibayashi T, Maze M. Clinical uses of alpha2-adrenergic agonists. Anesthesiology. 2000;93(5):1345-1349.
90. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother. 2007;41(2):245-252.
91. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8(2):115-131.
92. Mahmoud M, Mason KP. Dexmedetomidine sedation in children. Paediatr Anaesth. 2019;29(3):273-282.
93. Chen K, Lu Z, Xin Y, et al. Dexmedetomidine in perioperative medicine. Front Pharmacol. 2020;11:586516.
94. Lin TF, Yeh YC, Lin FS, et al. Effect of combining dexmedetomidine and ketamine on postoperative pain in gynecologic laparoscopy. Acta Anaesthesiol Taiwan. 2012;50(3):125-130.
95. Abdel-Ghaffar HS, Mostafa RH, Mohamed RH, et al. Nebulized dexmedetomidine for pediatric procedural sedation. Paediatr Anaesth. 2020;30(3):313-320.
96. Lee S, Lee SH, Choi YS, et al. Nebulized dexmedetomidine for sedation: a randomized controlled trial. Medicine (Baltimore). 2019;98(36):e17030.
97. Shukry M, Clyde MC, Kalarickal PL, et al. Does dexmedetomidine reduce propofol requirements? Paediatr Anaesth. 2005;15(2):109-115.
98. Patel A, Davidson M, Tran MC, et al. Dexmedetomidine infusion for sedation during awake fiberoptic intubation. Anesth Analg. 2010;111(3):703-708.
99. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative pain management after opioid-free anesthesia. Anesth Analg. 2019;129(6):1749-1758.
100. Ghai B, Makkar JK. Dexmedetomidine: a promising agent for procedural sedation. Indian J Anaesth. 2020;64(9):725-731.
101. Tobias JD. Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med. 2007;8(2):115-131.
102. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation. Ann Emerg Med. 2011;57(5):449-461.
103. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
104. Reich DL, Silvay G. Ketamine: an update on the first 25 years of clinical experience. Can J Anaesth. 1989;36(2):186-194.
105. Domino EF. Taming the ketamine tiger. Anesthesiology. 2010;113(3):678-685.
106. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
107. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
108. Persson J. Ketamine in pain management. CNS Neurosci Ther. 2013;19(6):396-402.
109. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
110. Andolfatto G, Willman E. A prospective case series of ketamine procedural sedation for pediatric patients in the emergency department. Acad Emerg Med. 2010;17(2):113-118.
111. Yan JW, McLeod SL, Iansavichene A. Ketamine-propofol vs propofol alone for procedural sedation: systematic review. Acad Emerg Med. 2015;22(9):1003-1013.
112. Green SM, Krauss B. Clinical practice guideline for ketamine sedation. Ann Emerg Med. 2004;44(5):460-472.
113. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation. Am J Emerg Med. 2008;26(9):985-1028.
114. Hijazi Y, Bodonian C, Bolon M, et al. Pharmacokinetics and bioavailability of ketamine in healthy volunteers. Clin Pharmacokinet. 2003;42(6):581-590.
115. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics. Anesthesiology. 2016;124(2):357-375.
116. Adamowicz P, Kala M. Ketamine metabolites in biological samples. Clin Chem Lab Med. 2005;43(12):1373-1378.
117. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. Anesthesiology. 1982;56(2):119-136.
118. Reves JG, Glass PS, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:317-378.
119. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
120. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
121. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
122. Himmelseher S, Pfenninger E. The clinical use of S-(+)-ketamine—a determination of its place. Anesth Analg. 1998;87(3):635-643.
123. Clements JA, Nimmo WS, Grant IS. Bioavailability, pharmacokinetics and analgesic activity of ketamine in humans. J Pharm Sci. 1982;71(5):539-543.
124. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg. 1966;45(1):29-40.
125. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
126. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
127. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
128. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
129. Andolfatto G, Willman E. A prospective case series of ketamine procedural sedation for pediatric patients in the emergency department. Acad Emerg Med. 2010;17(2):113-118.

10.48047/jocaaa.2024.33.06.75

130. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
131. Hijazi Y, Bodonian C, Bolon M, et al. Pharmacokinetics and bioavailability of ketamine in healthy volunteers. Clin Pharmacokinet. 2003;42(6):581-590.
132. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics. Anesthesiology. 2016;124(2):357-367.
133. Reves JG, Glass PS, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:317-378.
134. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. Anesthesiology. 1982;56(2):119-136.
135. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg. 1966;45(1):29-40.
136. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation. Am J Emerg Med. 2008;26(9):985-1028.
137. Green SM, Krauss B. Clinical practice guideline for ketamine sedation. Ann Emerg Med. 2004;44(5):460-471.
138. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
139. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
140. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
141. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
142. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
143. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
144. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
145. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
146. Andolfatto G, Willman E. A prospective case series of ketamine procedural sedation for pediatric patients in the emergency department. Acad Emerg Med. 2010;17(2):113-118.
147. Adamowicz P, Kala M. Ketamine metabolites in biological samples. Clin Chem Lab Med. 2005;43(12):1373-1378.
148. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics. Anesthesiology. 2016;124(2):357-367.
149. Reves JG, Glass PS, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:317-378.
150. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation. Ann Emerg Med. 2011;57(5):449-461.
151. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
152. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
153. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
154. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
155. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
156. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
157. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
158. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
159. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
160. Andolfatto G, Willman E. A prospective case series of ketamine procedural sedation for pediatric patients in the emergency department. Acad Emerg Med. 2010;17(2):113-118.
161. Adamowicz P, Kala M. Ketamine metabolites in biological samples. Clin Chem Lab Med. 2005;43(12):1373-1378.
162. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics. Anesthesiology. 2016;124(2):357-367.
163. Reves JG, Glass PS, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:317-378.
164. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation. Ann Emerg Med. 2011;57(5):449-461.
165. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
166. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
167. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
168. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
169. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation. Am J Emerg Med. 2008;26(9):985-1028.
170. Green SM, Krauss B. Clinical practice guideline for ketamine sedation. Ann Emerg Med. 2004;44(5):460-471.

10.48047/jocaaa.2024.33.06.75

171. Corssen G, Domino EF. Dissociative anesthesia: further pharmacologic studies and first clinical experience with the phencyclidine derivative CI-581. Anesth Analg. 1966;45(1):29-40.
172. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
173. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
174. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
175. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
176. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
177. White PF, Way WL, Trevor AJ. Ketamine—its pharmacology and therapeutic uses. Anesthesiology. 1982;56(2):119-136.
178. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
179. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
180. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
181. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
182. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-380.
183. Kurdi MS, Theerth KA, Deva RS. Ketamine: current applications in anesthesia, pain, and critical care. Anesth Essays Res. 2014;8(3):283-290.
184. Hirota K, Lambert DG. Ketamine: new uses for an old drug? Br J Anaesth. 2011;107(2):123-126.
185. McNulty JP, Hahn IH. Ketamine sedation in emergency medicine. Emerg Med Clin North Am. 2010;28(3):577-592.
186. Andolfatto G, Willman E. A prospective case series of ketamine procedural sedation for pediatric patients in the emergency department. Acad Emerg Med. 2010;17(2):113-118.
187. Adamowicz P, Kala M. Ketamine metabolites in biological samples. Clin Chem Lab Med. 2005;43(12):1373-1378.
188. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics. Anesthesiology. 2016;124(2):357-367.
189. Reves JG, Glass PS, Lubarsky DA, et al. Intravenous anesthetics. In: Miller RD, ed. Miller's Anesthesia. 6th ed. Philadelphia: Elsevier Churchill Livingstone; 2005:317-378.
190. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation. Ann Emerg Med. 2011;57(5):449-461.
191. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg. 1998;87(5):1186-1193.
192. Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.
193. Sigtermans MJ, van Hilten JJ, Bauer MC, et al. Ketamine produces effective and long-term pain relief in CRPS type 1. Pain. 2009;145(3):304-311.
194. Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. Cochrane Database Syst Rev. 2006;(1):CD004603.
195.Loftus RW, Yeager MP, Clark JA, et al. Intraoperative ketamine reduces perioperative opioid consumption. Pain. 2010;152(3):522-527.