Current Pain and Headache Reports (2023) 27:387–397
https://doi.org/10.1007/s11916-023-01134-1

ACUTE PAIN MEDICINE (R URMAN, SECTION EDITOR)

The Emerging Role of Ketamine in Acute Postoperative Pain Management

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Accepted: 11 May 2023 / Published online: 28 June 2023

Abstract

Purpose of Review Postoperative pain (POP) is among the most unpleasant experiences that patients face after surgery. Interest in and use of N-methyl-D-aspartate (NMDA) receptor antagonists for the management of POP has increased over the years with ketamine being the most popular drug of this class.

Recent Findings Several randomized controlled trials found that the use of ketamine either alone or in combination with other medications leads to decreased postoperative pain and opioid consumption. However, there are other studies that have not found these benefits. The results as of now suggest that the role of intraoperative ketamine in postoperative pain control varies among different operative procedures.

Summary While some studies have shown promise in ketamine's potential use as a postoperative analgesic, there is still a great deal of proposed research and randomized controlled trials needed to deduce the most efficacious and tolerable form and dose of ketamine.

Keywords Ketamine · Opioids · Pain · Acute pain · Postoperative pain

Introduction

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [1]." Postoperative pain (POP) is among patients' most unpleasant experiences after surgery. Appropriate measures should be taken to preemptively manage this pain. In the event of postoperative pain, early and aggressive pain management is crucial, as severe pain can lead to a hyperalgesic condition called persistent postoperative pain [2]. Approximately 75% of patients in the USA who undergo surgery are estimated to receive insufficient pain management [3].

The National Institute for Health and Care Excellence (in the UK) reports that approximately 60% of surgical patients will experience severe pain after the procedure. Properly managing this pain reduces patients' discomfort and distress, aids in their recovery and rehabilitation, and may prevent the transition from acute pain to chronic pain [4]. Although postoperative pain is a common and inevitable outcome of surgery, research indicates that patients often experience

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higher pain levels than necessary [5]. Therefore, acute pain following surgery is a frequent occurrence that often necessitates therapeutic intervention [6].

Ketamine's precursor is a commonly known drug called phencyclidine (PCP), which was synthesized in 1956 and used as a surgical anesthetic. Its use was discontinued due to patients experiencing unmanageable side effects and manic behavior. In 1964, a short-acting analogue of PCP with significantly less severe side effects called ketamine was created. It was approved in 1970 and has since been used as a general anesthetic, analgesic, and antidepressant [7].

Opioid analgesics such as morphine, hydromorphone, meperidine, and fentanyl are the main treatment options for postoperative pain. However, these medications have several adverse effects that can hinder patient recovery, including nausea, vomiting, dizziness, sedation, and reduced gut motility [8]. Additionally, they do not always fully relieve pain, and patients often develop a tolerance [2]. As a result, interest in and use of N-methyl-D-aspartate (NMDA) receptor antagonists for the management of POP has increased over the years, with ketamine being the most popular drug of this class. Ketamine antagonizes NMDA receptors which result in its analgesic effect, and ketamine modulates the central processing of pain sensation. Animal and human studies have demonstrated that ketamine is a potent anti-hyperalgesic drug. Intravenous ketamine has been shown to be advantageous for POP analgesia [9], and it mitigates opioid-induced hyperalgesia and prevents the development of opioid tolerance [2, 7, 9]. While non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly used to manage POP, new ways should be explored to improve the control of POP. This narrative review will focus on the use of ketamine for POP.

Current Treatment of Postoperative Pain

Opioids have been the primary treatment option for moderate to severe acute pain. However, there is a conflict between the advantages of using opioids and the potential negative impact on an individual's postoperative recovery [10]. The main concern regarding opioids is the potential for tolerance, dependence, and addiction, especially for chronic pain. However, most individuals who take opioids for chronic pain do not exhibit addiction-related behaviors, such as experiencing cravings, compulsive use, or losing control over their usage [11]. Another complication of opioid use is opioid-induced hyperalgesia (OIH), a condition where opioid exposure leads to an increased sensitivity to painful stimuli due to nociceptive sensitization. Although the precise mechanism of OIH is not yet fully understood, proposed mechanisms include an enhanced nociceptive response from sensitized spinal neurons and decreased reuptake of neurotransmitters from primary afferent nociceptive fibers. Genetic factors may also play a role. OIH is believed to be responsible for the decreased effectiveness of opioid medications in certain patients, particularly those without a known underlying pathology or disease progression [11, 12].

Non-opioid medications can be used to help control POP. One of which is Acetaminophen; however, care must be used to not give in amounts that are high enough to cause liver damage. Non-steroidal anti-inflammatory drugs, also known as NSAIDs, may also be used but care must be taken to not use these drugs in patients with kidney disease. Anticonvulsants, such as gabapentin and pregabalin, are another class of medication that can be used as a multimodal approach to pain control as they target neuropathic pain.

Ketamine Overview

Ketamine has gained prominence as an increasingly popular option for managing acute pain. In patients under general anesthesia, administering IV or subcutaneous ketamine approximately 15 min before incision can substantially diminish postoperative pain experiences. Compared to subcutaneous administration, IV administration has been shown to provide greater, longer-lasting pain relief after surgery compared to a placebo. Intraoperative and postoperative IV ketamine administration has a particularly pronounced analgesic effect on procedures that elicit more intense pain, such as abdominal, thoracic, orthopedic, or spinal surgeries [13].

Ketamine Clinical Uses

The field of anesthesia has long utilized ketamine (foremost an NMDA receptor antagonist) as a dissociative anesthetic. Currently, the only ketamine formulations approved by the Food and Drug Administration include injectable ketamine hydrochloride for different anesthetic indications and a more recently approved formulation of esketamine that is administered intranasally for treatment-resistant depression and depression with acute suicidal ideation or behavior. Recently, however, ketamine has taken on new uses, such as a potential treatment for status asthmaticus, refractory status epilepticus, substance use treatment, and for the amelioration of pain. Historically, ketamine has been used as a treatment for chronic pain, postoperative pain, phantom limb pain, and other neuropathic conditions [14]. It has also been utilized for procedural sedation and as a treatment for respiratory and neurological conditions [14]. One study showed that while intravenous S-ketamine as an adjunct to general anesthesia could be effective for assisting analgesia and decreasing the intensity of pain and opioid requirements in a short period after surgery, it may increase the psychotomimetic adverse effect event rate [15]. Regarding the drug's

indication as an antidepressant, in 14 publications, the drug provided a rapid antidepressant effect with a maximum efficacy reached at 24 h when used at a subanaesthetic dose. The drug's effect lasted 1–2 weeks after infusion [16]. Given that current first-line treatment for depression includes medications such as selective serotonin reuptake inhibitors, which can take a few weeks to have full effect, ketamine provides an exciting new alternative with rapid onset and apparent efficacy for depressive emergencies [17]. Additionally, ketamine also potentially poses a new method of treatment for anxiety, obsessive–compulsive disorder, bipolar disorder, and post-traumatic stress disorder, with research still ongoing [18–20].

Ketamine, like all drugs, has adverse effects and additionally contains the potential for misuse. It is a scheduled III controlled substance in the USA, which complicates the needed research regarding ketamine's efficacy and safety for various medical purposes. We know that chronic ketamine abuse can produce many adverse effects, including emergence reactions, psychosis, amnesia, significantly elevated blood pressure, elevated pulse, impaired motor function, seizures, and toxicity to the GI system and urinary tract, which may limit the use of this agent in some patient populations [18, 21]. Additionally, there is concern over ketamine not being a suitable long-term solution for psychological indications, given its misuse potential, ability to produce cognitive deficits, and broad side effect profile. It is currently considered an experimental short-acting drug to be used as needed, with the potential to develop drugs with similar efficacy and a lower burden of adverse effects [22].

Ketamine Mechanism of Action

Ketamine is a non-opioid, non-barbiturate dissociative anesthetic [23]. Its primary and most well-known mechanism of action (MOA) is that it is a noncompetitive NMDA receptor antagonist with high affinity, binding at the phencyclidine binding site, where it allosterically modifies the NMDA receptor [2, 7, 23]. However, it also interacts with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), opioid, cholinergic, catecholaminergic, and hyperpolarization-activated cyclic nucleotide-gated (HCN) receptors [7]. It has been called the "nightmare of pharmacology" due to its various multi-stepped MOAs [2]. However, this section will focus on its NMDA effects.

Glutamate is the primary neurotransmitter responsible for excitation in the central nervous system, and it binds to the NMDA receptor to produce its effects. Although the exact mechanism of ketamine is not well known, it is understood that ketamine binds to the NMDA receptors in the brain and blocks the activation of glutamate on these receptors. Ketamine targets NMDA receptors in three locations: post-synaptic neuronal terminals, gamma-aminobutyric acid (GABA) interneurons, and the extra-synaptic space, including glial cells [7, 24, 25]. This action reduces excitatory transmission along pain pathways, resulting in sedation and analgesia. NMDA receptors have many functions related to pain transmission and memory development, making them a target for treating various disease states. Ketamine affects the NMDA receptor independently of the amount of glutamate in the neuron synapse [26].

Ketamine and Pain

Ketamine induces anesthesia by interacting with NMDA receptors in the brain, with higher brain concentrations of ketamine correlating with greater analgesic effects in ischemic pain models. Pain activation in the secondary somatosensory cortex, insula, thalamus, and anterior cingulate cortex is all reduced by ketamine. fMRI studies have shown that ketamine and pain change brain connectivity in areas involved in endogenous pain modulation. Specifically, ketamine is associated with decreased connectivity in brain regions responsible for pain sensing and affective processing [2, 27, 28]. Additionally, the distinctive ability of ketamine to cause dissociation and partially activate mu-opioid receptors allows for the completion of painful procedures while maintaining a consistent level of sedation and patient comfort [23, 26, 29, 30].

Clinical Studies

One study sought to evaluate the effects of intraoperative ketamine on the prevention of rebound pain following the cessation of peripheral nerve block postoperatively. This was a prospective randomized, double-blind, placebo-controlled study [31]. Patients received a single IV ketamine (0.3 mg) or a placebo. Rebound pain was defined as a pain intensity score greater than 7 (on a pain scale of 1–10), and individual postoperative pain was recorded on days 1, 4, and 30 following medical discharge. Results showed that ketamine administration did not reduce rebound pain incidence or intensity. Thus, this study concluded that ketamine showed no benefit to the development of rebound pain when administered at an anti-hyperalgesic dose. A lack of significant difference in rebound pain between ketamine and traditional postoperative analgesia in this study suggests further research should be conducted to investigate the effects of ketamine on patient-specific pain. The different subjective variables used in this study limit the resonance of the conclusions. As previously stated, future studies should seek to find an alternative variable to measure postoperative pain [31].

Considering the limitations of the aforementioned clinical findings, one study investigated the effects of combination

analgesia (methadone and ketamine) perioperatively on postoperative pain control in patients undergoing spinal surgery [32•]. A randomized, double-blind, placebo-controlled trial was conducted, and 130 spinal surgery patients were randomly selected to receive either methadone at 0.2 mg/kg (ideal body weight) intraoperatively and a 5% dextrose in water infusion for 48 h postoperatively (methadone group) or 0.2 mg/kg methadone intraoperatively and a ketamine infusion (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion [no bolus] intraoperatively and then 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ for next 48 h [both medications dosed at ideal body weight]) (methadone/ketamine group). Anesthetic care was standardized among all patients. The primary outcome was quantified with intravenous hydromorphone use on postoperative day 1. Pain scores, IV and oral opioid requirements, and patient satisfaction regarding pain management were assessed on the first 3 days postoperatively. This study revealed median IV hydromorphone requirements were lower in the methadone/ketamine group on postoperative days 1 and 2 compared to the methadone group [32•].

Additionally, fewer oral opioids were needed in the methadone/ketamine group on postoperative days 1 and 3. Pain scores at rest, coughing, and movement were lower in the methadone/ketamine group at 23 of the 24 assessment times [32•]. This study indicated that postoperative analgesia was enhanced by the effects of methadone and ketamine in combination, most likely due to the drugs' effects on N-methyl-d-aspartate and mu-opioid receptors. Considering the results of this study, the therapeutic combination of ketamine and methadone in both the perioperative and 24-h postoperative window should be considered for use in patients undergoing spinal surgery [32•]. Given the statistically significant results of this study, there is potential for future projects to investigate the effects of different combinations of analgesia on postoperative pain.

Another investigation into the efficacy of combination analgesia suggests ketamine as part of a multimodal analgesic regimen is not associated with improved functional outcomes compared to the established analgesic regimen. In this double-blinded, randomized study, 78 patients undergoing total knee arthroplasty (electively) were randomly distributed into either a control group that received spinal anesthesia with intrathecal morphine, IV dexamethasone, periarticular local anesthesia, and a single injection adductor canal nerve block or a study group that receives the same regimen of analgesic treatments in addition to five new interventions [33•]. These five additional interventions included local anesthetic infiltration between the popliteal artery and capsule of the posterior knee, intraoperative IV dexmedetomidine and ketamine, and postoperatively, one additional IV dexamethasone bolus and two additional adductor canal nerve blocks [33•]. The primary outcome of this study was measured with 24-h cumulative opioid consumption following surgery [33•]. Secondary outcomes measured in this study were other analgesics used, patient recovery, functional outcomes, and adverse events [33•]. Results from this study revealed that opioid consumption at 24 h postoperatively did not differ between the control and study groups. Thus, these results concluded that the use of ketamine in combination with analgesia showed no significant difference in postoperative pain compared to the established analgesic regimen. One limitation is the use of a five-part multimodal regimen, suggesting that there may be a restriction in analgesic efficacy when administered with four other drugs [33•].

There is, however, an indication of the role of ketamine in the improvement of postoperative recovery in patients undergoing thoracic procedures such as video-assisted thoracic surgery (VATS). One prospective, randomized, double-blinded, placebo-controlled trial found that the perioperative introduction of S-ketamine enhanced the quality of postoperative recovery and analgesia following VATS procedures [34•]. Patients in this study were enrolled into one of two groups. Group 1 received a bolus of 0.25 mg/kg of S-ketamine followed by an infusion of 0.125 mg/kg/h until 15 min before the end of the surgical procedure [34•]. Group 2 (placebo group) received identical volumes and rates of 0.9% saline [34•]. Results revealed that patients who received S-ketamine treatment perioperatively had statistically significantly lower pain scores at rest and with coughing at 24 and 48 h postoperatively than those who received the placebo. Additionally, the requirement and consumption of oral opioids for breakthrough pain and rescue analgesia were lower in the S-ketamine group. These findings suggest that perioperative S-ketamine can enhance the quality of recovery in patients undergoing VATS and significantly improve postoperative analgesia.

Similar to the study on effects of perioperative ketamine on postoperative recovery in patients undergoing VATS, practices were conducted to determine the effects of intraoperative ketamine on patients undergoing septorhinoplasty. This study was organized using a randomized, prospective, double-blind technique on 48 patients receiving septorhinoplasty. Patients were placed into either a ketamine group or a placebo group. In the ketamine group, an IV ketamine bolus (0.5 mg/kg) was introduced at anesthesia induction, and ketamine infusions at a rate of 0.25 mg/kg/h were continued throughout the surgery [35]. The placebo group received identical volumes of 0.9% saline.

Furthermore, 50 mg of dexketoprogen trometamol was administered 30 min before the end of surgery and then repeated at 12 and 24 h postoperatively [35]. Pain scores, consumptions of intraoperative opioid and sevoflurane, requirements of rescue opioid, patient satisfaction, and reported side effects were recorded. Pain scores were evaluated using the visual analog scale [35]. Results showed that pain scores in the ketamine group were statistically and

significantly lower than the placebo group at all postoperative periods. Additionally, the requirement for rescue opioid analgesia was significantly lower in the ketamine group of patients compared to the patients receiving the placebo. Despite these findings, there was no significant difference in intraoperative sevoflurane and remifentanil consumptions [35]. In summary, the results of this study further support the conclusion that perioperative administration of low-dose ketamine reduces the requirement for rescue opioid analgesia and improves postoperative pain scores.

While the two prior studies investigated the benefits of perioperative ketamine in patients undergoing VATS and septorhinoplasty, a prospective, randomized, single-center trial studied the effects of perioperative ketamine for pain control in patients undergoing breast surgery for breast cancer [36]. This study concluded that the introduction of intraoperative ketamine did not improve the overall quality of recovery in patients undergoing breast surgery on postoperative day 1. Similar to the previous studies discussed, in this trial, 100 patients planned for modified radical mastectomy were randomly assigned to one of two groups: control group (group C) or ketamine group (group K) [36]. Group K received the bolus dose of 0.5 mg/kg ketamine and was followed by 0.25 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ following the induction of surgery, while group C received an equivalent dose and regiment of normal saline was group K. The primary outcome was to assess the effects of low-dose ketamine on postoperative quality of recovery using the 40-Item Quality of Recovery (QoR-40) scale on a postoperative day 1 (POD1) [36]. The secondary outcome was to assess the numeric rating scale (NRS) at hours 4, 24, and 48 following the operation, identity-consequence fatigue scale (ICFS) scores at 3 and 7 days after the operation, hospital anxiety and depression scale (HADS) scores at 2 days and 3 months, and chronic pain at 3 months [36]. Global QoR-40 scores were not significantly different between group C and group K. In a post hoc analysis, pain scores were significantly higher in group K than in group C [36]. However, the secondary outcomes, including NRS, ICFS scores, HADS scores, and chronic pain, had no difference between groups [35]. This study concluded that the introduction of intraoperative ketamine did not improve the overall quality of recovery in patients undergoing breast surgery on postoperative day 1.

The role of intraoperative ketamine in postoperative pain control varies among different operative procedures. Additionally, the effects of ketamine for the use of chronic analgesia postoperatively are variables that are not as widely considered. A randomized controlled trial was conducted to investigate the effectiveness of low-dose IV ketamine in the management of both acute and chronic postoperative analgesia following laparoscopic cholecystectomy [37]. This study separated 50 individuals undergoing laparoscopic cholecystectomy with general anesthesia into two randomized, equal groups (ketamine and control). Patients in ketamine and control groups were given 0.5 mg/kg ketamine and 2 mL of normal saline 15 min before incision [37]. The ketamine group was found to have a greater duration of analgesia and sedation score than the control group [37]. Patients in the ketamine group reported significantly lower numeric pain rating scores immediately following their surgery. However, the numeric pain rating scale score of the ketamine group was considerably greater than the control group 30 min following the completion of the procedure [37]. There was no significant difference among the groups at other time periods postoperatively.

Additionally, the cumulative tramadol demand at 24 h postoperatively and the incidence of chronic pain were not significantly different between the two groups [37]. Results from this study suggest that the substantial analgesic effect of IV intraoperative ketamine had a duration of approximately 30 min postoperatively. Thus, the effectiveness of ketamine for the use of chronic pain prevention following surgery was significantly different than the traditional analgesic regimen, as discerned from these findings. Future clinical trials should consider expanding the number of participants studied and the long-term effects of ketamine on more invasive and complex procedures.

The effect of subanaesthetic ketamine on postoperative pain continues to be equivocal, with some studies showing improved postoperative analgesia, whereas others showing no effect [38]. The clinical studies' findings suggest that the time for administration of ketamine plays a role. Additionally, Nayak et al. studied the preemptive effects (before incision or at the end of surgery) of subanaesthetic ketamine (0.15 mg kg^{-1}) on postoperative pain relief in women undergoing mastectomy. They failed to find a beneficial effect [38]. The authors concluded that although they did not find a reduction in pain with a preemptive dose of ketamine, they felt that this patient population could benefit from perioperative use of ketamine for pain relief.

While preoperative ketamine administration has not been proven efficacious, the clinical findings of the previously mentioned studies have found intraoperative and postoperative ketamine infusions display a statistically significant beneficial effect on pain control and postoperative analgesia. One limitation of the research on subanaesthetic ketamine use is many studies have failed to evaluate the effectiveness of different doses of ketamine. While a temporal association between ketamine administration and pain control could be concluded, there is a gap in understanding the effects of ketamine dosage on postoperative pain control. Table 1 is an overview and summary of the studies discussed in this section.

Table 1 Summaries of studies discussed in this above section regarding ketamine and postoperative pain control

Author	Aims of study	Methods	Results	Conclusion
Touil et al. (2022) [31]	Evaluate the effects of intraoperative ketamine on the prevention of rebound pain following the cessation of peripheral nerve block postoperatively	Prospective randomized, double-blind, placebo-controlled study - Patients received a single dose of IV ketamine (0.3 mg) or a placebo - Rebound pain was defined as a pain intensity score greater than 7 (on a pain scale of 1–10), and individual postoperative pain was recorded on days 1, 4, and 30 following medical discharge	Ketamine administration did not reduce rebound pain incidence or intensity	Ketamine showed no benefit in the development of rebound pain when administered at an anti-hyperalgesic dose A lack of significant difference in this study suggests further research should be conducted to investigate the effects of ketamine on patient-specific pain
Murphy et al. (2021) [32•]	- To investigate the effects of combination analgesia (methadone and ketamine) perioperatively on postoperative pain control in spinal surgery	- Randomized, double-blind, placebo-controlled trial - 130 spinal surgery patients were randomly selected to receive either methadone at 0.2 mg/kg (ideal body weight) intraoperatively and a 5% dextrose in water infusion for 48 h postoperatively (methadone group) or 0.2 mg/kg methadone intraoperatively and a ketamine infusion ($0.3\ mg \cdot kg^{-1} \cdot h^{-1}$ infusion [no bolus] intraoperatively and then $0.1\ mg \cdot kg^{-1} \cdot h^{-1}$ for next 48 h - Primary outcome was quantified with intravenous hydromorphone use on postoperative day 1	- Results from this study revealed that median IV hydromorphone requirements were lower in the methadone/ketamine group on postoperative days 1 and 2 compared to the methadone group - Fewer oral opioids were needed in the methadone/ketamine group on postoperative days 1 and 3	- Postoperative analgesia was enhanced by the effects of methadone and ketamine in combination, most likely due to the drugs' effects on N-methyl-d-aspartate and mu-opioid receptors

Table 1 (continued)

Author	Aims of study	Methods	Results	Conclusion
Muñoz-Leyva2 et al. (2022) [33•]	- To investigate the efficacy of combination analgesia suggests ketamine as part of a multimodal analgesic regimen in functional outcomes compared to the established analgesic regimen	- Double-blinded, randomized study - 78 patients undergoing total knee arthroplasty were randomly distributed into either a control group that received spinal anesthesia with intrathecal morphine, IV dexamethasone, periarticular local anesthesia, and a single injection adductor canal nerve block or a study group that received the same regimen of analgesic treatments in addition to five new interventions - The five additional interventions included local anesthetic infiltration between the popliteal artery and capsule of the posterior knee, intraoperative IV dexmedetomidine and ketamine, and postoperatively, one additional IV dexamethasone bolus and two additional adductor canal nerve blocks - Primary outcome of this study was measured with 24-h cumulative opioid consumption following surgery	- Opioid consumption at 24 h postoperatively did not differ between the control and study groups	- The use of ketamine in combination with analgesia showed no significant difference in postoperative pain compared to the established analgesic regimen - Limitationuse of a five-part multimodal regimen, suggesting that there may be a restriction in analgesic efficacy when administered with four other drugs
Cheng et al. (2022) [34•]	- To investigate the effect of perioperative S-ketamine on postoperative quality of recovery in patients undergoing video-assisted thoracic surgery (VATS)	- Prospective, randomized, double-blinded, placebo-controlled trial - Patients in this study were enrolled into one of two groups where one received a bolus of 0.25 mg/kg of S-ketamine followed by an infusion of 0.125 mg/kg/h until 15 min before the end of the surgical procedure and the other received identical volumes and rates of 0.9% saline	- Patients who received S-ketamine treatment perioperatively had statistically significant lower pain scores at rest and with coughing at 24 and 48 h postoperatively than those who received the placebo	- Perioperative introduction of S-ketamine enhanced the quality of postoperative recovery and analgesia following VATS procedures

Table 1 (continued)

Author	Aims of study	Methods	Results	Conclusion
Ates et al. (2021) [35]	- To determine the effects of intraoperative ketamine on patients undergoing septorhinoplasty	- Randomized, prospective, double-blind technique on 48 patients receiving septorhinoplasty - Ketamine group, an IV ketamine bolus (0.5 mg/kg) was introduced at the induction of anesthesia, and ketamine infusions at a rate of 0.25 mg/kg/h were continued throughout the surgery. The placebo group received identical volumes of 0.9% saline - 50 mg of dexketoprogen trometamol was administered 30 min before the end of surgery and then repeated at 12 and 24 h postoperatively	- Pain scores in the ketamine group were statistically and significantly lower than the placebo group at all postoperative periods - The requirement of rescue opioid analgesia was significantly lower in the ketamine group of patients compared to the patients receiving the placebo	- Perioperative administration of low-dose ketamine reduces the requirement of rescue opioid analgesia and improves postoperative pain scores
Zhao et al. (2021) [36]	- To investigate the effects of perioperative ketamine for pain control in patients undergoing breast surgery for breast cancer	- 100 patients planned for modified radical mastectomy were randomly assigned to one of two groups: control group (group C) or ketamine group (group K) - Group K received the bolus dose of 0.5 mg/kg ketamine and followed by 0.25 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ following the induction of surgery, while group C received an equivalent dose and regiment of normal saline was group K -Primary outcome was to assess the effects of low-dose ketamine on postoperative quality of recovery using the 40-Item Quality of Recovery (QoR-40) scale on a postoperative day 1	- Global QoR-40 scores were not significantly different between groups C and K - In a post hoc analysis, pain scores were significantly higher in group K than in group C	- The introduction of intraoperative ketamine did not improve the overall quality of recovery in patients undergoing breast surgery on postoperative day 1

Table 1 (continued)

Author	Aims of study	Methods	Results	Conclusion
Jan et al. (2022) [37]	- To investigate the effectiveness of low-dose IV ketamine in managing both acute and chronic postoperative analgesia following laparoscopic cholecystectomy	- Randomized controlled trial - 50 individuals undergoing laparoscopic cholecystectomy with general anesthesia into two randomized, equal groups (ketamine and control group) - Patients in ketamine and control groups were given 0.5 mg/kg ketamine and 2 mL of normal saline at 15 min before incision	- Ketamine group was found to have a greater duration of analgesia and sedation score than the control group - Patients in the ketamine group reported significantly lower numeric pain rating scores immediately following their surgery - Numeric pain rating scale score of the ketamine group was considerably greater than the control group 30 min following the completion of the procedure	- The substantial analgesic effect of IV intraoperative ketamine lasted approximately 30 min postoperatively - The effectiveness of ketamine for chronic pain prevention following surgery was significantly different than the traditional analgesic regimen, as discerned from these findings
Nayak et al. (2021) [38]	- To study the preemptive effects (before incision or at the end of surgery) of subanaesthetic ketamine (0.15 mg kg^{-1}) on postoperative pain relief in women undergoing mastectomy	- Randomized controlled trial - Divided into three equal groups received either 5 mL of 0.9% saline or a ketamine dose of either ketamine 0.15 mg/kg or 0.3 mg/kg diluted in 5 ml 0.9% saline before induction	- No effect of preventive dose of subanaesthetic ketamine on postoperative analgesia	- Although no effect was found in the preemptive dose, the authors concluded that there may be value in using ketamine perioperatively

Conclusion

Ketamine remains a promising pharmacologic agent for many indications and has already garnered FDA approval for treatment-resistant depression and anesthetic purposes. While the primary analgesic mechanism of ketamine is through NMDA receptor antagonism, it has also been shown to act on opioid, nicotinic, and muscarinic receptors [39]. Given its combined characteristics as an analgesic, anti-inflammatory, and anti-hyperalgesic, many indications are currently undergoing research, ranging from neuropathic pain to neuropsychiatric diagnoses [18]. From the studies, it seems that when given intraoperative, ketamine exerts a greater effect on pain control that when given preoperative or postoperatively. More research needs to be performed to look at what doses, amounts (single bolus vs. multiple boluses), and what differences exist between different patient populations (opioid naïve vs. opioid dependent and patients with chronic pain). While it poses benefits in the treatment of depression due to its rapid onset of action compared to conventional therapies, given its vast list of side effects, potential toxicities, adverse cognitive effects, and abuse potential, there may be limited utilization of this drug as a long-term maintenance agent for chronic pain, especially given its potential risk of neurotoxicity and impaired long-term memory. Additionally, there are still many unknowns regarding the tolerability and efficacy of this drug, including for the treatment of postoperative pain. There are discrepancies among clinical trial data concerning ketamine's use as a general postoperative analgesic; however, ketamine seems to demonstrate some efficacy in populations undergoing specific surgical procedures (spinal surgery, VATS, etc.).

Interestingly, in the clinical trials that support ketamine as a perioperative analgesic, the data supports the drug's ability to reduce opioid requirement in the acute setting following surgery. The potential role of ketamine in diminishing opioid use postoperatively is supported by data that has revealed lower opioid necessity in patients treated with ketamine as either a single agent or in combination in a multimodal fashion.

As a word of caution, there are populations that may not benefit from the use of ketamine as risks would outweigh the benefits. Those who have experienced a psychotic episode in the pass may or may not have serious adverse psychogenic effects. More research would need to be performed before ketamine could be safely used in this population. Patients with hemodynamic instability should be treated with ketamine using caution. It is reassuring that studies in the past have shown that ketamine has smaller effects on hemodynamic parameters than other anesthetics it is unknown how this could affect hemodynamics in an intraoperative environment. Another patient population in

which ketamine should be used with caution is those with active addiction. A period of sustained sobriety is needed for ketamine treatment of depression at the time of this writing; however, there are emerging studies that show that ketamine could help increase abstinence from certain substances such as alcohol and heroin. More research would need to be performed to be able to highlight the safety of ketamine for POP in these populations.

While some studies have shown promise in ketamine's potential use as a postoperative analgesic, there is still a great deal of proposed research and randomized controlled trials needed to deduce the most efficacious and tolerable form and dose of ketamine to maximize analgesic effect and minimize ketamine's vast adverse effect profile. Additionally, larger studies are required to evaluate ketamine's efficacy for nonanesthetic purposes in the general population.

Author Contribution A.N.E was responsible for the conceptualization of this manuscript. A.N.E., D.A., E.B., K.L.W., E.Z. were responsible for the writing of the original manuscript. A.N.E., E.D.J, D.M.W., E.M.C., A.M.K., and A.D.K. were responsible for all revisions of the manuscript. All authors give consent the publication of this manuscript in this journal.

Compliance with Ethical Standards

Ethics Approval This narrative review did not require consent from subjects or review by an institutional review board.

Conflict of Interest The authors have no conflict of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance

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