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ACUTE PAIN MEDICINE (R URMAN, SECTION EDITOR)

Ketamine Use in the Surgical Patient: a Literature Review

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Abstract

Purpose of Review While ketamine is an established anesthetic, its role in the management of acute surgical pain is less certain. Therefore, a literature review is warranted to examine the role of ketamine in acute pain management.

Recent Findings The use of ketamine appears to be most efficacious in larger procedures that lead to increased systemic inflammation or extensive tissue damage. In addition, ketamine seems to be most successful when administered consistently throughout a procedure, such as by an infusion instead of a single bolus, in order to have adequate dosing for an analgesic effect.

Summary Therefore, the focus of research should be on procedures that lead to moderate to severe pain using frequent dosing to determine the most effective role of ketamine. Most importantly, the current literature shows that ketamine can be used as a successful part of multimodal anesthesia with few side effects in patients undergoing major procedures associated with moderate to severe pain.

Keywords Ketamine · Acute pain · Analgesia · Pain management · Surgery · Multimodal anesthesia

Introduction and Background

Ketamine is a well-established anesthetic despite limited understanding of all its effects. With increased interest in the use of ketamine for management of acute surgical pain, an examination of the recent literature is necessary to reassess the efficacy and suitability of its use. Ketamine was developed in 1962, following the discovery of the anesthetic phencyclidine (PCP), in an attempt to find a similar anesthetic with fewer side effects [1–3]. Shortly after this, in 1964, ketamine was used as a human anesthetic for the first time, and the first FDA-approved preparation, Ketalar, became available in 1970 [1, 4]. Many favored its use due to its cardiorespiratory stability, and research examining its utilization in acute and chronic pain grew in the 1990s [3]. In addition, ketamine gained popularity as a drug of abuse going by names like "Kit Kat," "Vitamin K," and "Monkey Business" [4]. However, as newer drugs were developed, ketamine fell out of popularity. Due to a greater understanding of ketamine's interactions with various receptors in the body, however, it has resurged as an area of interest in pain management.

Ketamine's mechanism of action was unknown until the early 1980s when Lodge and colleagues discovered that ketamine inhibited neuronal activation of N-methyl-D-aspartic acid (NMDA) receptors. Specifically, ketamine acts as a noncompetitive NMDA receptor antagonist, requiring NMDA ion channel activation to block the receptor [5, 6]. Additional studies have demonstrated that ketamine also interacts with other receptors including opioid, cholinergic, and monoamine receptors [5, 7]. Interestingly, some studies propose that ketamine's interaction with these additional receptors greatly contribute to its short- and long-term analgesic effects [3]. The chemical structure of ketamine as well influences its effects and has been an area of recent research interest. Ketamine contains a chiral center leading to the presence of two optical stereoisomers: S (+) and S (−) [6]. Typically, ketamine is marketed as a racemic mixture, composed of equal parts of its two stereoisomers. However, the stereoisomer S (+) has a two times greater receptor affinity compared to the racemic mixture but is not currently available for clinical use in the USA [1, 6]. Ketamine is certainly effective as an analgesic, but what is uncertain is its role in multimodal analgesia, especially in conjunction with opioids.

Ketamine has several important effects including analgesia and anesthesia. NMDA excitatory glutamate receptors are widely expressed in the central nervous system (CNS) but, under normal physiological conditions, are not the major

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receptors involved in nociception. They do still play a vital role in nociception, because with repeated stimulation, the sustained change of membrane potential allows for alleviation of negative inhibition by magnesium, therefore increasing the response of the receptors [5, 6]. Nevertheless, with its short half-life of 10–15 min, this does not explain why ketamine has been shown to reduce pain for longer durations. Longer term analgesic actions are likely due to alterations of cell signaling cascades, including modification of NMDA expression [3]. It also has been shown to have significant early postoperative anti-inflammatory effects, which may also contribute to its ability to provide analgesia [3, 8]. In addition, ketamine at sub-analgesic levels has also been shown to attenuate the development of rebound hyperalgesia and acute tolerance to opioids [9].

The multiple potential indications for the use of ketamine are of growing significance. Clinicians recognize that adequate treatment of postoperative pain improves rehabilitation and reduces potential complications. Conversely, overtreatment of pain can negatively impact recovery [10, 11]. In addition, pain is challenging to treat as it is an individualized experience [10]. In the last decade, the abuse of opioids has been a major concern for clinicians and the public, and up to 80% of those addicted to prescription opioids report being initially exposed to opioids through treatment of pain, most commonly acute postoperative pain [12]. In addition, side effects of opioids are well-recognized by the medical community including sedation, respiratory depression, emesis, gastrointestinal paralysis, urinary retention, and hyperalgesia, all of which can delay recovery [13, 14]. Therefore, methods of reducing opioid usage while maintaining adequate analgesia is of utmost importance. A reduction of morphine consumption by only 3 mg was related to prevention of one clinically meaningful adverse event [15]. Given these results, there is great interest in using multiple pharmacological agents in combination to provide adequate analgesia. This approach targets the multiple mechanisms of pain while reducing the negative side effects of any one agent [10, 16, 17]. Such approaches have been shown to reduce length of hospital stay without reducing the quality of patient care [10]. The question that remains is where ketamine fits in as part of this approach.

Methods

A literature review was conducted utilizing the OVID Medline database using the terms "ketamine" and "general surgery" with the addition of "acute pain," "pain measurement," or "postoperative pain" as shown in Fig. 1. Publications were initially searched from years 1946–2020 and limited to humans and for articles written in English. Results were further narrowed from 2017 to 2020 for further analysis of the recent literature. In addition, the Cochrane database of systematic reviews was searched using the terms "ketamine," "surgery," and "acute pain." In total, 437 articles were found and narrowed down to 108 articles for final review based on relevance. Upon further review, 34 articles were chosen to be included based on their relevance, applicability, and recency of publication.

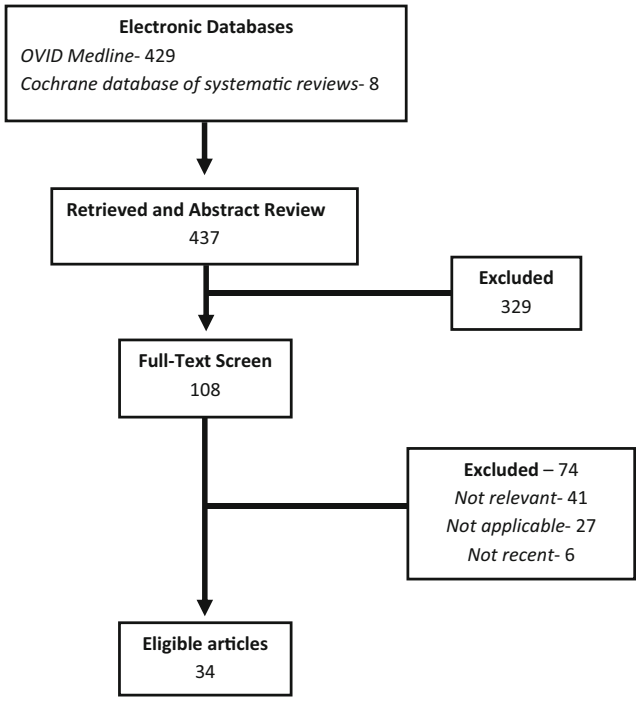

Fig. 1 A summary of literature search methodology. The electronic databases OVID MEDLINE and Cochrane database of systematic reviews were searched using the terms "ketamine" and "general surgery" with the addition of "acute pain," "pain measurement," or "postoperative pain" and "ketamine," "surgery," and "acute pain," respectively. Results were limited to humans, articles written in English, and published between 2017 and 2020. In total, 437 articles were found, and their abstracts were reviewed for relevance. Of these, 108 articles underwent final review through full-text screening. Upon further review, 34 articles were chosen to be included based on their relevance, applicability, and recency of publication

Discussion

The role of ketamine in acute pain management is an important area of study due to the contradictory results seen in research over the past two decades. Many studies have found favorable results, especially in the ability of ketamine to reduce opioid requirements. Studies found that IV ketamine, albeit at high doses, can reduce cumulative analgesic requirements and the amount of hyperalgesia patients experience, especially in orthopedic procedures [7, 18••]. In one meta-analysis, they found that 78% of placebo groups reported significantly higher pain compared to ketamine groups, despite receiving more opioids as shown in Fig. 2. This result suggests that ketamine may provide additional benefits beyond

reduction of opioids [2]. Yet some clinicians have struggled to find similar success in their specific surgical fields.

Many studies use various dosages of ketamine, making it difficult to compare studies and interpret results due to the concern of inadequate dosing. In clinical practice, the dosage of ketamine should be guided by the expected magnitude of pain and timing of desired pain control effects. However, some guidelines exist. For example, in the acute trauma setting, ketamine is typically dosed at 0.1–0.3 mg/kg IV boluses or if given by continuous infusion at 0.1–0.4 mg/kg/h IV. Non-weight-based doses are typically 50 mg IM every 30–60 min or 20 mg IV push over 1 min every 20 min [17]. Many studies, though, have been interested in the effects of ketamine at "low doses" (less than 1 mg/kg for a single bolus or infusion of less than 20 μg/kg/min) and have had various success [7]. This has further made comparisons between studies more difficult. Emphasis also has been placed on developing an adequate dosing schedule given that inflammation and nociceptive signals are created throughout a procedure and remain active after surgery. In theory, a single dose prior to surgery may be inadequate analgesia given its short half-life, yet many studies have used such a dosing schedule. Frequent use of ketamine throughout a procedure and postoperatively may provide better results [6, 17]. In a recent Cochrane review, a significant reduction in morphine equivalents at 48 h was found between patients receiving ketamine postoperatively (average reduction of 21 mg morphine equivalents) compared to those who only received ketamine prior to incision (average reduction of 3.6 morphine equivalents) as shown in Fig. 3 [18••]. Therefore, this may have led to insufficient dosing, inappropriately influencing practitioners to avoid the use of ketamine where it may be beneficial.

In examining the literature, the efficacy of ketamine may further depend on the specific procedure. The most successful uses of ketamine involve procedures with high levels of expected postoperative pain. Yet, one systematic review found that ketamine had the least opioid sparing effect for head and neck, dental, and tonsillectomy procedures while having a greater impact on abdominal, thoracic, and orthopedic procedures [2]. Although the authors did not propose an explanation for these results, other studies have noted that ketamine appears most effective when inflammation and tissue injury extend beyond the surgery site itself [2, 19]. A summary of the use of ketamine in various procedures is shown in Table 1.

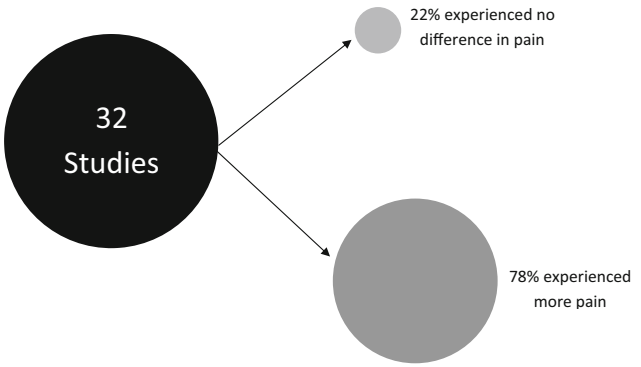

Fig. 2 Reported pain scores of placebo group compared to ketamine group. In the meta-analysis by Laskowski et al., 78% of placebo groups (25 out of 32 studies) reported higher pain scores compared to ketamine treatment groups despite having higher opioid requirements when examining studies when ketamine was effective

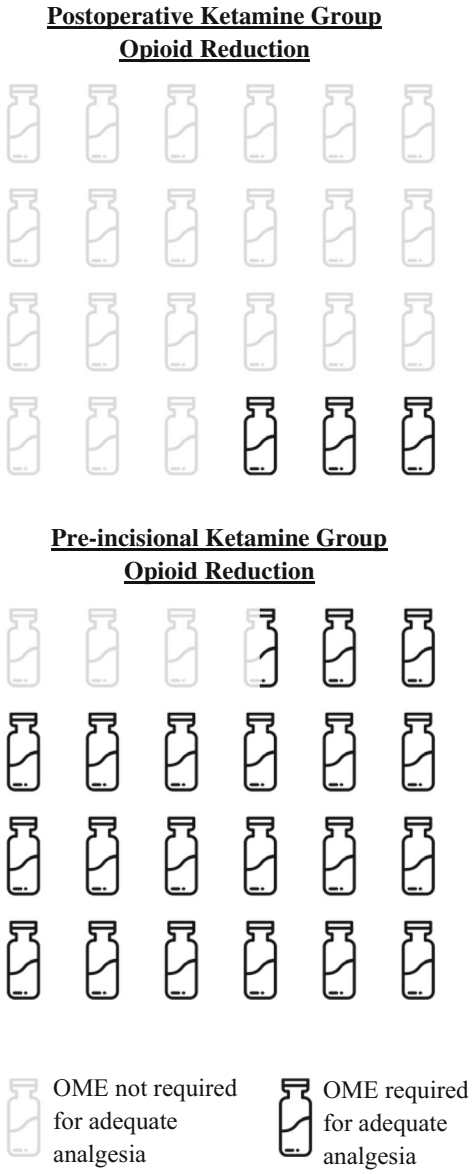

Fig. 3 Reduction in oral morphine requirement in ketamine group compared to placebo group. Each vial represents one oral morphine equivalent (OME). A light gray vial represents one OME that was not required for achievement of adequate analgesia. A black vial represents one OME that was required for achievement of adequate analgesia. The total number of vials (24) was chosen for illustrative purposes only and does not represent total OME requirements. In a Cochrane review by Brinck et al., they found that patients treated with ketamine postoperatively (typically by continuous infusion) required significantly fewer OME at 48 h postoperatively (average reduction of 21 mg morphine equivalents) compared to those who only received ketamine prior to incision (average reduction of 3.6 morphine equivalents)

Therefore, review of the literature per specific procedure is warranted to examine the appropriateness of using ketamine for analgesia.

Orthopedic Procedures

The most encouraging positive results have been seen with orthopedic procedures. This may be because patients undergoing orthopedic procedures typically experience more severe pain than those undergoing laparotomy [20]. One meta-analysis examined studies that included patients undergoing orthopedic procedures who received IV ketamine, either through a bolus (0.1–0.5 mg/kg) prior or during procedures or a continuous infusion (1–10 μg/kg/min). They found that these patients required fewer total opioids, especially those undergoing total joint replacements. In addition, patients undergoing spinal procedures reported less pain at 24 h, while those undergoing total joint procedures reported significantly lower pain scores at 48 h. Due to these results, the authors suggested the use of 0.5 mg/kg ketamine boluses for such procedures. In addition, the majority of studies with ketamine infusions used sub-anesthetic doses, leading the authors to conclude that a ketamine infusion should be considered for longer procedures (> 90 min) at a surprisingly low dose of 2–5 μg/kg/min [21••].

Specifically, the use of ketamine in total knee replacements has shown very promising results. One randomized controlled trial found that patients who underwent total knee arthroplasty and received a ketamine infusion had lower pain scores and a 45% reduction in morphine requirements at 24 h postoperatively [22]. Similarly, a meta-analysis examining knee arthroscopy found that the use of ketamine intraoperatively was associated with decreased pain scores, a reduction in analgesic consumption, and an increased time to first analgesic requirement [11]. However, not all studies have shown such positive results. One such study found no lasting difference in pain scores between patients receiving a ketamine infusion during total knee replacement while under spinal anesthesia. They also failed to find any significant reduction in opioid consumption [23]. This may be due to the sole use of spinal anesthesia compared to other studies where most patients underwent general anesthesia. In addition, conflicting results among many of these studies may be due to the finding that patients who receive ketamine analgesia tend to be younger, have higher ASA status, and undergo longer procedures, all of which could confound results. A summary of these results is shown in Table 2.

Table 1 Summary of favorability of the use of ketamine for acute pain management in specific procedures

Head and neck procedures	
Head and neck (in general)	Likely unfavorable
Robotic thyroidectomies	Likely favorable
Dental	Likely unfavorable
Tonsillectomy	Likely unfavorable
Abdominal procedures	
Abdominal (in general)	Likely favorable
Laparoscopic cholecystectomy	Likely favorable
Open nephrectomies	Likely favorable
Laparoscopic bariatric surgery	Unfavorable
Thoracic procedures	
Thoracic (in general)	Likely favorable
Cardiac surgery	Inconclusive
Orthopedic procedures	
Orthopedic (in general)	Likely favorable
Total joint replacements	Favorable
Spinal orthopedic procedures	Likely favorable
Additional procedures	
Gynecological procedures	Unfavorable
Breast surgery	Inconclusive

The use of ketamine during spinal procedures has become a growing area of interest, especially given the higher pain levels these patients experience [24]. A meta-analysis of patients undergoing spinal procedures found that patients who received ketamine required fewer morphine equivalents in the first 24 h postoperatively. However, no significant difference was noted at 36 h, suggesting that ketamine may provide the most benefit during the initial day after surgery. Interestingly, in the same study, they found that patients had similar levels of pain until 6 h postoperatively at which time the patients receiving ketamine had significantly reduced pain scores. Similar to the reduction in opioid consumption, this effect lasted up to the 48-h time point but was no longer significant at 36 h [25]. This suggests that the greatest benefit may not be immediately after surgery, but that the pain reduction lasts for several days postoperatively. In contrast, a randomized controlled trial of patients undergoing elective spinal instrumentation found that patients receiving a ketamine bolus followed by infusion had no significant difference in analgesic consumption in the first day postoperatively, although the placebo group did report higher pain scores. Of note, this study may have been confounded by the increased use of sevoflurane in the ketamine group, thereby making the two groups in the study fundamentally different [26].

Some of the most striking results have been noted in opioid-tolerant patients. A study found that opioid-tolerant patients who received a ketamine infusion postoperatively required significantly less opioids, yet this same effect was not observed in opioid-naïve patient cohorts [27]. This suggests that the use of ketamine should be considered in patients with opioid tolerance. In addition, like previous studies, the analgesic effects of ketamine may not be appreciated directly postoperatively. One study found that despite patients receiving a

Table 2 Summary of recent literature examining the use of ketamine in total knee replacement or arthroscopic procedures

Article	Procedure	Modality of ketamine administration	Summary of significant findings	Summary of favorability of ketamine use
Riddell et al. (2019) [21••]	Total knee replacement	Low-dose single bolus and/or continuous infusion	Decreased opioid requirements[a,b] Decreased pain scores[b,c]	Favorable
Cengiz et al. (2014) [22]	Total knee replacement	Low-dose infusion	Decreased opioid requirements[a] Delayed time to first analgesic request Decreased pain scores[a,c]	Favorable
Pan et al. (2019) [11]	Knee arthroscopy	Single bolus, infusion, or intra-articular injection	Decreased pain scores[d,c] Decreased analgesic consumption[d,e] Delayed time to first analgesic requirement[d,e]	Favorable
Tan et al. (2019) [23]	Total knee replacement	Low dose infusion[f]	No difference in pain scores[c,g] No difference in opioid requirements[e,h]	Unfavorable

[a] Result measured at 24 h postoperatively

[b] Result measured at 48 h postoperatively

[c] Pain score assessed by visual analogue scale or numerical rating scale

[d] Result measured at 2 h postoperatively

[e] Secondary outcome

[f] Only included patients receiving spinal anesthesia

[g] Averaged maximum pain scores across postoperative day 0 to postoperative day 4

[h] Result measured on postoperative day 0 to postoperative day 2

ketamine bolus followed by an infusion, they used the same amount of rescue analgesics directly after surgery as the placebo group. However, the ketamine group required less morphine over the initial 24-h postoperative period [28].

Thoracic Surgery

Analgesia for thoracic procedures can be difficult due to the severity of pain experienced by patients. The pain following thoracotomy tends to peak at 24 h, indicating these patients have a more intense but shorter lasting pain [29]. However, there is a high rate of heterogeneity among the studies in the literature, leading to difficulty in determining the applicability of ketamine use in thoracic surgeries. One systematic review of thoracic surgery patients found that patients receiving IV ketamine had significantly less pain at 24 h postoperatively compared to the opioid only group. However, there was a high rate of heterogeneity among the studies examined with many individual studies having contradictory results and a variety of doses used, therefore limiting the ability to draw strong conclusions [30]. In contrast, another study found that patients receiving ketamine infusions intra- and postoperatively had lower pain scores only at rest at 48 h after surgery. Yet, the ketamine group used significantly less opioids in the first 24 h (median of 77 vs. 138 mg morphine equivalents) suggesting that both groups were adequately able to control their pain, despite the ketamine group consuming fewer opioids [31]. Similarly, another study found that patients receiving low-dose IV ketamine through a PCA in conjunction with fentanyl did not have significantly different pain scores compared to the group receiving a bupivacaine PCA epidural [29].

Cardiac Surgery

Recent literature on the use of ketamine for analgesic purposes in cardiac surgery is very limited. A study found no difference in pain scores or analgesic consumption between patients undergoing coronary artery bypass grafting who received a ketamine bolus followed by infusion compared to the placebo group 48 h after surgery despite adequate dosing based on previous literature [32]. Yet, in a recent systematic review, the use of S (+) ketamine vs. placebo reduced opioid consumption following cardiac surgery. However, patients in the ketamine group had lower pulmonary function and decreased scores on mobilization tests and walking exercises. The authors emphasized ketamine use in post-cardiac surgery pain control should be done so with caution considering the need for more dose-related studies and concerns about psychomimetic side effects [33]. In addition, these results have limited applicability given S (+) ketamine is not yet approved for use in the USA.

Abdominal Surgery

A significant amount of research has been done concerning the use of ketamine in various abdominal surgeries with

varying outcomes. In particular, the use of ketamine in laparoscopic cholecystectomies is an area of active research given the high prevalence of the procedure. Several meta-analyses found that patients receiving ketamine had lower pain scores and reduced opioid usage at 12, 24, and 48 h postoperatively. Also, those receiving ketamine also had a lower incidence of postoperative nausea and vomiting (PONV) in addition to a decreased risk of pruritus and ileus. However, the evidence quality for each of these outcomes were low, indicating that further high-quality research is needed [34, 35] In contrast, one study found that patients who received remifentanil analgesia and a ketamine bolus prior to incision did not have a significantly different quality of recovery compared to placebo using the quality of recovery questionnaire. They proposed that laparoscopic procedures, due to their less invasive nature, may have limited postoperative pain. However, this study used a single ketamine bolus preoperatively instead of an infusion or repeated bolus dosing, which may have led to inadequate dosing [19]. Further research is needed in this area to draw more conclusive answers.

Beyond cholecystectomies, other abdominal procedures also may benefit from the use of ketamine. One study found that patients undergoing open nephrectomies who received ketamine infusions had significantly lower morphine consumption and lower pain scores at 24 h after surgery compared to placebo. Other benefits included shorter time to first defecation, first flatus, and first meal in addition to shorter length of hospital stay compared to placebo. However, lidocaine analgesia outperformed ketamine in these parameters, raising the question if lidocaine may be a better option in such a procedure [36]. Additional studies are needed to further investigate these findings.

One area of keen interest is bariatric surgery, especially given the prevalence of obesity, and some have attempted to use ketamine as part of a multimodal analgesic regimen for such procedures. One study found that patients undergoing laparoscopic gastric bypass and gastrectomy who received a single bolus of ketamine (0.4 mg/kg) in the PACU had similar amounts of pain and opioid usage as the patients who received placebo. However, the authors recognized that the use of a single dose is probably ineffective given its short half-life and that a continuous infusion could have different results. In addition, patients in both groups reported very low pain scores following surgery, limiting the ability to detect any significant differences [37]. Further research into such procedures would likely be unfruitful.

Gynecological Surgery

The use of ketamine has also been investigated for use during gynecological procedures given the moderate to severe pain commonly experienced by patients following many of these procedures. Previous studies have found limited efficacy of ketamine in pain control for these patients [38]. More recent studies have continued to support these conclusions. One current study found that in women undergoing total abdominal hysterectomy, the use of pre- and post-incisional ketamine S(-) boluses led to no significant difference in consumption of opioids 24 h after surgery [39]. Of note, the use of the S (-) isomer may have contributed to these results. Interestingly, a study examining patients undergoing oocyte retrieval found that patients receiving IV ketamine for conscious sedation and remifentanil for analgesia had reduced intraoperative remifentanil requirements and lower reported pain scores. However, the authors were concerned that ketamine may have helped to improve patients' moods, thereby decreasing pain scores without having direct anti-nociceptive effects [40].

Pediatric Surgery

The use of ketamine for analgesia in pediatric surgery is an area of great debate. Many previous studies have contradictory results leading to a lack of definitive conclusions, particularly concerning tonsillectomies [41]. More recent studies have attempted to clarify these results with little success. A study examining pediatric patients undergoing procedures to correct their scoliosis was unable to find any significant benefits to the use of ketamine. The authors concluded that there was insufficient data to support the routine use of ketamine and further research is necessary [42]. Similarly, another systematic review found that half of the studies examined had positive conclusive evidence of efficacy with adequate safety with the strongest evidence for the use of IV and caudal ketamine [43]. Additional focused research is needed to determine for what procedures and in which pediatric patients ketamine may be most beneficial.

Additional Surgical Procedures

The use of ketamine has also been investigated in breast surgery. A recent meta-analysis found that the use of pre-emptive ketamine yielded mixed results with limited clinical effect. However, these were very limited studies, and the authors commented that the use of ketamine in breast surgery warrants further investigation [44]. In contrast, ketamine has been studied for use during robotic thyroidectomies with more successful results. One study found that patients undergoing robotic thyroidectomy receiving a ketamine bolus followed by an infusion had lower reported pain scores at rest and with coughing until 24 h postoperatively. In addition, the number of patients who needed rescue analgesics was higher in the control group (56% vs. 28%). These positive results may be due to the fact that this type of surgery often causes moderate to severe pain due to wide hydro-dissection of the skin flaps from the axilla to the anterior neck and forceful lifting of tissues [45].

While many studies have focused on trying to determine the clinical benefit of ketamine, examination of its side effect profile is equally as important. One of the major concerns about the use of ketamine as an analgesic are the side effects which include hallucinations, dysphoria, and stimulatory cardiac effects (e.g., tachycardia, hypertension). However, these tend to be transient and self-limited [17]. The risk is minimal when ketamine is used at low doses [3]. Interestingly, females and adults appear to be at higher risk of negative side effects [46]. In a small observational study, the authors observed that 31.8% of patients receiving ketamine during a spinal procedure had an adverse drug event, most commonly CNS excitation, sedation, or visual disturbances. One-third of these patients chose to discontinue ketamine due to these events. However, these effects rapidly resolved following the cessation of ketamine which is reassuring [24]. A recent Cochrane review failed to find significant differences in negative CNS side effects in those receiving ketamine [18••]. Therefore, side effects of ketamine, especially those significant enough to warrant cessation of the drug, are uncommon and reversible, making ketamine a relatively safe analgesic option.

Conclusions

The limitations of this review include the likelihood that not all recent publications were included due to constraints of the literature search. In addition, the literature was limited to those published in the English language which may have excluded significant publications and biased the findings towards English-speaking countries.

While the use of ketamine as part of multimodal analgesia certainly remains an active area of research, its use appears to be most efficacious in larger procedures that lead to increased systemic inflammation or extensive tissue destruction. With smaller procedures, the addition of ketamine appears to be of little benefit likely due to the small amount of additional analgesia needed. Additional research into such cases is likely to be unproductive. Therefore, the use of ketamine in larger procedures should continue to be investigated to further evaluate its role in modern analgesia. From the literature, ketamine appears to be most beneficial in procedures such as total joint replacements as well as thoracic, abdominal, and thyroid surgeries. In addition, ketamine appears to be most successful when administered consistently throughout a procedure, such as by an infusion instead of a single bolus, in order to have adequate dosing for an analgesic effect. This effect appears to be most prominent 6–24 h postoperatively, suggesting that ketamine may have a unique role to provide specific timing of analgesia.

Much remains to be investigated about the use of ketamine in the operating room and beyond. Additional procedures need further investigation, such as major cardiac procedures. In addition, the use of ketamine in chronic pain remains an area of interest. Further insight into the appropriate dosing, particularly in children, the role of individual differences in pain sensitivity, and ketamine's use in outpatient procedures is warranted. The literature shows that the use of ketamine in procedures that lead to mild to moderate pain does not produce effective analgesic effects. Therefore, the focus of research should be on procedures that lead to moderate to severe pain to determine the most effective role of ketamine. Most importantly, the current literature shows that ketamine can be used as a successful part of multimodal anesthesia with few side effects in patients undergoing major procedures associated with moderate to severe pain where additional analgesics can be particularly useful.

Code Availability Not applicable.

Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest Tiffany Moon, MD, receives grant funding and honoraria from Merck and MDoloris. The remaining authors declare no competing interests.

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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- •• Of major importance

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