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REVIEW ARTICLE

Perioperative ketamine for acute analgesia and beyond

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Abstract

There has been substantial interest in the use of ketamine for perioperative analgesia. Recently published articles on 'low dose' ketamine mark the resurgence in interest in the use of the drug for acute pain. Continued interest in ketamine as an anti-depressant also has opened the door to applications beyond the operating room. In this article, we will review: the history of ketamine's clinical use; basic ketamine pharmacology; evidence for the use of perioperative ketamine for analgesia; comments on patient selection for ketamine research; a discussion of the safety and side effect profile of ketamine infusions beyond the operating room; and, lastly, ketamine as a treatment option for psychiatric diseases.

Key words: ketamine, perioperative analgesia, subanesthetic ketamine, acute pain, acute postoperative pain

Historical background

In 1965, Domino, Chodoff, and Corssen published their results from the use of "CI-581", later named ketamine, in 20 prisoner 'volunteers' [1]. Subsequent studies resulted in the clinical use of ketamine as an induction agent as well as a sole anesthetic for procedures or minor surgeries. Eventually ketamine came to take its place as an intravenous anesthetic agent along with thiopental, propofol, and others in anesthesia textbooks and dogma. Ketamine's well known side effect profile limited its use as a common, sole anesthetic agent for most surgical populations. These side effects were evident from the first paper by Domino et al.:

"During the recovery period the subjects showed considerable variability in psychic reaction. Some were completely oriented in time and place and showed no significant changes. Others showed marked alteration in mood and affect, some becoming apprehensive and aggressive and others markedly withdrawn. Almost all the subjects felt entirely numb, and in extreme instances stated that they had no arms or legs, or that they were dead. If they were touched, however, or moved, such stimuli were perceived. Neurologically all subjects showed rotatory nystagmus and ataxia. Diminution of visual acuity was marked. Other reactions noted included feelings of estrangement or isolation, negativism, hostility, apathy, drowsiness, inebriation, hypnogenic states, and repetitive motor behavior.

At times some of the subjects had vivid dreamlike experiences or frank hallucinations. Some of these involved the recall of television programs or motion pictures seen a few days before, or they were at home with their relatives, or were in outer space, and so on. Some of these phenomena were so real that the subjects could not be certain that they had not actually occurred." [1]

Thus, for clinical use, anesthesiologists have always been vigilant and wary of side effects such as emergence delirium, hallucinations and nightmares, hypersalivation, nystagmus, hypertension and tachycardia, as well as dysphoria. Ketamine's general anesthetic effects are mediated by N-methyl-D-aspartate (NMDA) receptor antagonism [2]. Other potential mechanisms of action include mu, kappa, and delta opioid receptors [2]. Ketamine is frequently referenced as an antagonizer of 'frequency dependent potentiation

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of pain responses' or 'wind-up phenomena' [2-3]. The classification of ketamine as an anesthetic versus as an analgesic is based on dosing. An induction dose of ketamine is approximately 2 mg/kg with analgesic doses varying between 0.1-0.5 mg/kg. Infusion doses of ketamine for analgesia also vary with doses ranging from 2-10 mcg/kg/min, approximately 10-40 mg/h. No set infusion rate is classified as without the risk of side effects, as there is no hard and fast distinction in any one given patient between an analgesic dose and the dose at which a patient experiences altered consciousness.

Basic ketamine pharmacology for the clinician

Ketamine is a chiral phencyclidine derivative. It is most commonly used in the United States in its racemic form (R, S) ketamine but it is available in the more potent S-ketamine form as well. Ketamine is metabolized by multiple p450 enzymes and has a number of metabolites including norketamine and hydroxynorketamine which all cross the blood-brain barrier [4-5]. Early ketamine research established ketamine and norketamine as the relevant compounds for the production of general anesthesia via mechanisms associated with the NMDA receptor. Hydroxynorketamine received less attention from early research. More recent science led by Irving Wainer, PhD while at the National Institutes of Health has suggested a more important role for downstream ketamine metabolites including hydroxynorketamine in the treatment of psychiatric disorders as well as chronic pain conditions [6-8]. These treatment effects appear to be NMDA-pathway independent [9]. Proposed mechanisms include intracellular changes via the mTOR pathway [10]. For example, in mouse models of depression, subjects who received isolated hydroxynorketamine performed as well as those who received racemic ketamine in forced swim tests and escape failure models [9].

Evidence to support ketamine as a perioperative analgesic

Ketamine has been used in a wide variety of surgical populations, with varying results. To focus our discussion, we will discuss its clinical use as an analgesic in spine and orthopedic surgery.

One of the most important clinical trials for perioperative ketamine was performed by Loftus et al in American patients undergoing major spine surgery [11]. This prospective, randomized, controlled trial (PRCT) included approximately 100 patients assigned to a ketamine or placebo infusion intraoperatively.

These patients all had to have chronic back pain for at least 3 months and had to have been using oral opiates for at least 6 weeks. Their dosing strategy was a 0.5 mg/kg bolus (hereafter referred to as a standard bolus) of study drug after induction of anesthesia but prior to incision, followed by an infusion of 10 mcg/kg/min (approximately 40 mg/h in a 70 kg patient) for the duration of surgery. The average duration of surgery was 3.5 hours. Their primary outcome of interest was morphine equivalents (ME) consumption at 48 hours postoperatively. There was a statistically significant decrease of approximately 120 mg of ME between the two groups favoring ketamine. Further, there was a statistically significant decrease in pain scores and opioid consumption at 6 weeks follow-up in the ketamine group. Importantly, side effects of hallucinations, nausea, vomiting, and urinary retention, did not differ between the two study groups. However, on subgroup analysis, the in-hospital ME reduction appeared only in those patients who were consuming at least 40 mg of ME daily pre-operatively. In those patients taking at least 40 mg ME daily prior to surgery, there was a reduction of 230 mg of ME compared to placebo over 48 hours. However, there was no difference in ME consumed in the ketamine versus placebo arms for patients consuming < 40 mg of ME prior to surgery. The authors write in their conclusion that "not all opiate-dependent patients with chronic pain require adjunctive medication such as ketamine, but there is a patient subset that does very poorly without adjunctive therapy that needs to be identified preoperatively" [11]. Thus the effect of perioperative ketamine was dramatic, but only in those patients taking significant amounts of pre-operative opiates. Further, although reducing ME very significantly, the high pre-operative opiate patients in the ketamine arm still consumed significant amounts of opioids postoperatively. Ketamine appeared to allow these patients 'less worse' pain control. The Loftus study had relatively real world exclusion criteria such as patients with a history of psychosis. Other studies, see below, tend to exclude patients on chronic opioids, perhaps missing a treatment effect that would have been evident had these patients been included, or, even, targeted.

Other PRCTs in spine surgery suggest benefits of ketamine as well (Table 1). In two smaller studies, opioid consumption was reduced. It is important to note some of the differences in dosing strategies. Pacreu et al studied 20 Spanish patients for multilevel lumbar arthrodesis and randomized them to ketamine versus placebo [12]. Patients were ineligible for this study if they had a history of psychiatric illness or took any number of psychiatric or anticonvulsant medications. Their dosing strategy was a standard bolus after induction and prior to incision, and an infusion of 2.5

Table 1. Summary of PRCTs: ketamine in spine surgery

Author (Year)	No of pts (country) Type of surgery	Dose	Time period	Other analgesics and adjuncts	Ketamine beneficial?
Loftus (2010)	102 (USA) lumbar spine surgery	0.5 mg/kg bolus, 10 mcg/kg/min infusion	Induction through end of surgery	I.v. PCA postop, 8 mg dexamethasone	↓OME for 48 h, ↓opioids and pain at 6 wks postop, significant ↓for pts on > 40 mg/day p.o. OME only
Aveline (2006)	69 (France) lumbar discectomy	0.15 mg/kg bolus only	Pre-incision bolus	Morphine i.v. PCA	↓OME and ↓VAS in M+K group compared to M, K only for 24-48 h
Pacreu (2012)	20 (Spain) multilevel spine fusion	0.5 mg/kg bolus, 2.5 mcg/kg/min	Induction through end of surgery	Methadone, dexketo-prophen, paracetamol	↓OME at 24 and 48 h

PRCT: placebo controlled randomized clinical trial; PCA: patient controlled analgesia; OME: oral morphine equivalents; VAS: visual analogue scale; M: morphine; K: ketamine

mcg/kg/min (approximately 10 mg/h in a 70 kg patient). This is 1/4th the dose of the infusion used in the Loftus study. Methadone consumption (the primary analgesic utilized in this study) was significantly reduced at 24 and 48 hours (15 vs 3.4 mg at 24 h, and 9.5 vs 2 mg at 48 h, respectively) and patients requested significantly less boluses of their patient-controlled i.v. analgesia (PCA) in the ketamine group. No differences in side effects were noted and no study patients experienced psychotomimetic effects. It should be noted that methadone itself is known to have NMDA-receptor antagonistic properties and this may muddy the picture if the analgesic effect of ketamine is thought to be NMDA pathway mediated. Aveline et al. studied 69 French patients for lumbar disc surgery [13]. This PRCT investigated a single bolus dose of 0.15 mg/kg (approximately 10 mg in a 70 kg patient) prior to incision with or without concomitant morphine bolus. There were three study arms: ketamine, morphine, or ketamine + morphine pre-incision. Patients were ineligible for this study if they had a history of psychiatric illness or chronic opioid treatment. Intravenous morphine use was significantly reduced only in the combination ketamine + morphine group at 24 h (15 mg vs 29-35 mg). Visual analog pain scores were also reduced at 24 and 48 hours (2.9 vs 3.8-3.9, and 2.8 vs 3.5-3.8, respectively) in the combination group, and there was a reduction in postoperative nausea and vomiting (PONV). In terms of side effects, one patient in the ketamine-only group experienced unpleasant dreams, but there were no instances of hallucinations, blurred vision, or mental disturbances in this study. It should be noted that the dose of ketamine in this study was quite small and may not have been expected, a priori, to have a significant clinical effect.

Total joint replacements (TJR) are common, elective surgeries associated with moderate to severe postoperative pain. Much like spine surgery, many TJR patients have surgery primarily due to pain and may already be taking pre-operative opioids. For this reason, clinically relevant successful pain interventions should be detectable in research. Although there are significant differences in surgical techniques, both TJR and spine surgery involve cutting and drilling through bone. The positive effects of ketamine for perioperative analgesia for spine surgery have not necessarily been reproduced in TJR patients (Table 2).

For example, Remerand and colleagues investigated the effects of perioperative ketamine in 154 French patients undergoing total hip arthroplasty (THA), in a PRCT [14]. They infused ketamine at 10 mg/h after a standard bolus for 24 hours in patients undergoing general anesthesia without regional anesthesia. There was no clinically relevant decrease in opioid consumption or pain scores. On secondary analysis, there was a trend towards less pain in the operative hip at 6 months. There was no difference in side effects between the two groups. Exclusion criteria included chronic opioid consumption and posterior surgical approach. In general, a posterior approach to THA is associated with more surgical dissection, a larger incision, and more postoperative pain and could represent another potential study population. On the other hand, in a smaller PRCT of 140 French patients broken down into four groups that investigated ketamine as well as pregabalin for pain after THA, ketamine (as well as pregabalin) was shown to decrease opioid consumption after intraoperative use (a standard bolus followed by 3 mcg/kg/min or approximately 12 mg/h) [15]. This study also utilized general anesthesia without regional anesthesia. Those authors did not conclude that the opioid-sparing effect of either drug was clinically relevant, as the incidence of opioid-induced side effects did not differ significantly with the control group. It is of note that the study was not designed or powered to investigate opioid-related side effects.

Lastly, in a small PRCT of 40 French patients undergoing total knee arthroplasty (TKA), Adam et al

Table 2. Summary of PRCTs: ketamine in TJR surgery

Author (Year) No of pts (country) Type of surgery	Dose	Time period	Other analgesics and adjuncts	Ketamine beneficial?
Remerand (2009) 154 (France) total hip arthroplasty	0.5 mg/kg bolus, 2 mcg/kg/min infusion	Induction through 24 hours postop	i.v. morphine/droperidol PCA, i.v. acetaminophen, ketoprofen	↓OME at 24 h, ↓persistent pain at rest from 1-6 months postop, ? ↓crutches at 30 days
Adam (2005) 40 (France) total knee arthroplasty	0.5 mg/kg bolus, 3→1.5 mcg/kg/min	Pre-incision bolus, intraop infusion through 48 h	Femoral nerve catheter, i.v. morphine PCA	↓OME, ↔VAS at 48 h, earlier time to 90° flexion
Martinez (2014) 142 (France) anterior hip arthroplasty	0.5 mg/kg bolus, 3 mcg/kg/min	Induction through end of surgery	Pregabalin, i.v. morphine PCA	↓OME at 48 h, synergy with pregabalin, ↓2° hyperalgesia

PRCT: placebo controlled randomized clinical trials; TJR: total joint replacement; PCA: patient controlled analgesia; OME: oral morphine equivalents; VAS: visual analogue scale

utilized a 48 hour infusion of 2-3 mcg/kg/min (8-12 mg/h) after a standard bolus of ketamine but did not have clinically significant effects on pain scores or opioid consumption [16]. Exclusion criteria included psychiatric disorders, chronic pain, or chronic opioid use. All surgeries were performed under general anesthesia but patients also received a femoral nerve catheter, which was their standard of care at the time of the study. It is therefore possible that in the absence of the nerve block, a clinically detectable effect of ketamine may have been unmasked but that is purely speculative. The published clinical trials on the use of TJR are presented in Table 2.

A systematic review of over 4700 patients receiving intravenous ketamine for perioperative analgesia versus placebo found that ketamine was most effective in thoracic, upper abdominal, and major orthopedic surgery [17] (Table 3).

When efficacious in those studies, there was a concurrent decrease in PONV. In studies with positive findings, patients were found to have both decreased pain scores and decreased opioid consumption, suggesting a qualitative effect on the pain response. In that review, hallucinations and nightmares were found to be more common in ketamine study groups versus placebo. Differences in sedation levels between the patients and controls, however, were not evident. The Cochrane review's plain language summary on this topic, which included over 2200 patients, describes the side effects of subanesthetic ketamine as "minimal to absent" [18].

Study design and excluded patients

As described above, many studies of subanesthetic ketamine were designed with the potential for side effects in mind. Patients with a history of psychiatric illness (not specifically, for example, schizophrenia or psychosis) were excluded in three of the six studies discussed above [12-13, 16]. Although none of these studies found an increased rate of psychomimetic side effects, it remains certainly a risk. However, interestingly, small infusions of ketamine (0.5 mg/kg over 40 minutes) have been found to be effective in patients with recalcitrant major depressive disorder (MDD), bipolar disorder (BPD), and post-traumatic stress disorder (PTSD) (see below). Loftus and colleagues discovered anecdotally that there was a statistically significant decrease in patients still using antidepressant medications at 6 weeks follow-up [11]. Other patients commonly excluded from acute pain studies are patients with chronic pain and/or chronic opioid use, as in four of the six studies discussed above [13-16]. If the evidence from Loftus is reproducible, these excluded patients may in fact be the target population for effective perioperative ketamine use.

Table 3. Summary of systematic reviews and meta-analyses of perioperative ketamine

Author (Year)	No of studies (No of pts)	Mode of delivery	Ketamine beneficial?
Bell (2006)	37 (2240)	Epidural or i.v.	27/37 trials showed ↓OME or ↓VAS or ↓both, ↓PONV, ↔side effects
Laskowski (2011)	70 (4701)	i.v. only	↓OME with ↓pain scores, ↓PONV, ↑hallucinations

OME: oral morphine equivalents; VAS: visual analogue scale; PONV: post-operative nausea and vomiting

Ketamine beyond the operating room

The evidence is not clear if continuing ketamine beyond the operating room is significantly more effective than 'only' intraoperative use. According to data from systematic reviews and meta-analysis, no specific dosing regime has been found to be definitively more effective than another [17-18]. Much of this is due to the large heterogeneity of clinical trials of ketamine, as well as different patient populations. For example, in the studies discussed above, bolus dosing ranged from 0.15 to 0.5 mg/kg followed by infusions ranging from 2 to 10 mcg/kg/min for between 2-48 hours. It is very difficult to make conclusive statements about dose-dependent effects of ketamine with ranges of data such as these.

Many of the clinical trials with ketamine report no increase in side effects over placebo. One recent report from Schwenk et al reviewed 321 consecutive patients receiving continuous infusions of ketamine postoperatively following a variety of surgeries [19]. They found that approximately 1/3 of these patients had at least one adverse drug effect. These were categorized as CNS excitation, sedation, visual disturbances, hemodynamic instability, nausea, or other. Of those approximately 100 patients with at least 1 adverse drug effect, another 1/3 had their infusion discontinued due to these side effects. Of the patients who had the infusions stopped due to side effects, 95% had resolution of the side effects after it was discontinued. It is impossible to know with certainty if the catalogued side effects were, in fact, caused by the ketamine infusion. Further details of the side effects are not contained in the paper. While appropriate to characterize and group the side effects, there is a difference in the clinical relevance of, for example, vivid dreams and delirium, both of which were placed under the umbrella term of CNS excitation. Although it has been suggested that ketamine-related side effects at doses of 10 mg/h or less are minimal to absent [20], Schwenk and colleagues found no association with infusions of 20 mg/h and the need to discontinue the infusion due to side effects, when compared to lower doses [19].

Unfortunately, it is difficult to point to definitive evidence that continuing ketamine beyond the operating room provides significantly improved perioperative analgesia compared to dosing ketamine solely in the operating room. For example, two studies discussed above continued ketamine or placebo for 24-48 hours and did not demonstrate clinically significant reductions in opioid consumption, pain scores, or other recovery variables in patients undergoing TJR [14, 16]. Other studies of ketamine infusions of 3-5 days duration for chronic pain syndromes such as complex regional pain syndrome are not discussed here [21].

If an acute pain service is managing patients on ketamine in the hospital setting, as previously reported, certain standard order sets can help to streamline patient care [22]. Routine nursing assessments, the consideration of continuous pulse oximetry, 24 hour a day availability to reach someone with questions or concerns, using modified intravenous tubing without ports or placing the medication in a key-locked device are all methods we employ in the management of over 1000 patients treated with perioperative ketamine infusions beyond the operating room over the last 5 years [22].

Ketamine for the treatment of psychiatric disorders

Some of the most common concerns with the use of ketamine among clinicians are the potential risks of dysphoric psychiatric side effects. Nightmares, hallucinations, and unpleasant disorientation are not helpful symptoms for the patient recovering from surgery. Avoiding ketamine in patients with pre-existing psychiatric disorders may preclude specific benefits to patients. PRCTs of ketamine for the treatment of MDD, BPD, and PTSD have been published with positive findings. Much of this work comes from a psychiatry research group led by Dennis Charney, with participation from colleagues in anesthesiology as well [23]. Patients are generally brought to the hospital or clinic setting for monitoring and an intravenous dose of 0.5 mg/kg of ketamine or placebo (commonly, midazolam) is infused over 40 minutes. Patients are monitored for side effects and the appropriate psychiatric index scale is quantified pre- and post-treatment. Ketamine has been found to have rapid acting (within 2 hours) and long-lasting (up to 7 days) clinically significant reductions in symptomatology in recalcitrant cases [23]. No increase in deleterious neurocognitive effects has been found on short-term follow-up [24]. Ketamine has been established as a safe and well tolerated treatment option for treatment-resistant depression [25]. In chronic PTSD patients, ketamine has been shown to be efficacious without clinically significant dissociative symptoms [26]. Ketamine has even been used as an intervention for reduction of suicidal ideation [27]. As this review is not focused on the treatment of psychiatric disorders, this data is presented so as to assuage fears that the anesthesiologist may have about using ketamine in patients with MDD, BPD, or PTSD. Perhaps, then, future studies would consider unique inclusion/exclusion criteria to confirm or refute the potential benefits of perioperative ketamine for patients with chronic pain, on chronic opioids, and concomitant psychiatric illness.

Summary

Ketamine has a history of clinical use for over 50 years in the practice of anesthesiology. Side effects associated with induction doses of ketamine tempered enthusiasm for the drug as a sole anesthetic. At subanesthetic doses, ketamine has been proven to decrease pain and opioid consumption in certain patient populations such as spine surgery. Variability in both study design and surgical subpopulations makes it difficult to find a dose-dependent effect of ketamine. Some clinicians have recommended a dosing strategy of 0.25-0.5 mg/kg followed by an infusion of approximately the same dose per hour in patients undergoing surgery associated with moderate-to-severe postoperative pain. Continuing infusions beyond the operating room depends on local practice policies and future research will help to determine the added benefit of infusions on the order of days compared to hours for postoperative recovery. Safety data on patients receiving infusions has been helpful in establishing the tolerability of the drug in the hospital setting. The role of ketamine is unclear in opioid naïve patients undergoing surgeries with less postoperative pain. Ketamine has gained attention as a treatment option for patients with recalcitrant psychiatric disorders. It should be considered for perioperative use in patients with these disorders based on PRCT data. Future research should include patient populations that combine elements of chronic pain and psychiatric illness to further elucidate the ideal targets for benefits of perioperative ketamine therapy.

Conflict of interest

Nothing to declare

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