

Systematic Review

## Perioperative Ketamine Administration for Thoracotomy Pain

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**Background:** Of all the postsurgical pain conditions, thoracotomy pain poses a particular therapeutic challenge in terms of its prevalence, severity, and ensuing postoperative morbidity. Multiple pain generators contribute to the severity of post-thoracotomy pain, and therefore a multimodal analgesic therapy is considered to be a necessary strategy. Along with opioids, thoracic epidural analgesia, and paravertebral blocks, N-Methyl-D-Aspartate (NMDA) receptor antagonists such as ketamine have been used as adjuvants to improve analgesia.

**Objective:** We reviewed the evidence for the efficacy of intravenous and epidural administration of ketamine in acute post-thoracotomy pain management, and its effectiveness in reducing chronic post-thoracotomy pain.

**Study Design:** Systematic literature review and an analytic study of a data subset were performed.

**Methods:** We searched PubMed, Embase, and Cochrane reviews using the key terms “ketamine,” “neuropathic pain,” “postoperative,” and “post-thoracotomy pain syndrome.” The search was limited to human trials and included all studies published before January 2015. Data from animal studies, abstracts, and letters were excluded. All studies not available in the English language were excluded. The manuscript bibliographies were reviewed for additional related articles. We included randomized controlled trials and retrospective studies, while excluding individual case reports.

**Results:** This systematic literature search yielded 15 randomized control trials evaluating the efficacy of ketamine in the treatment of acute post-thoracotomy pain; fewer studies assessed its effect on attenuating chronic post-thoracotomy pain. The majority of reviewed studies demonstrated that ketamine has efficacy in reduction of acute pain, but the evidence is limited on the long-term benefits of ketamine to prevent post-thoracotomy pain syndrome, regardless of the route of administration. A nested analytical study found there is a statistically significant reduction in acute post-thoracotomy pain with IV or epidural ketamine. However currently, the evidence for a role of ketamine as a preventative agent for chronic post-thoracotomy pain is insufficient due to the heterogeneity of the studies reviewed with regard to the route of administration, dosage, and outcome measures.

**Limitations:** The evidence for a role of ketamine as a preventative agent for chronic post-thoracotomy pain is insufficient due to the heterogeneity of the studies reviewed.

**Conclusion:** The majority of randomized controlled trials reviewed show no role for ketamine in attenuating or preventing post-thoracotomy pain syndrome at variable follow-up lengths. Therefore, additional research is warranted with consideration of risk factors and long-term follow-up for chronic post-thoracotomy pain though the evidence for benefit appears clear for acute post-thoracotomy pain.

**Key words:** Ketamine, postoperative, thoracotomy pain, post thoracotomy pain syndrome, neuropathic pain

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**S**ince the first reported thoracotomy for tuberculosis by Tuffier in 1891 (1), the role of thoracotomy in the surgical management of intrathoracic pathology has expanded from primarily infectious indications to predominately diagnostic and oncologic indications in modern medicine. Despite the trend toward minimally invasive video assisted thoroscopic surgery (VATS), post-thoracotomy surgical pain remains a persistent problem (2-4). Nociception from the incision, intercostal muscles, pleura, and associated structures is transmitted via the intercostal nerves to the spinal cord, and ultimately to the brain, with many complex neural synaptic connections along the way. This nociceptive process is modulated peripherally by inflammatory mediators such as prostaglandins, histamine, and bradykinin that are implicated in the lowering of pain threshold levels by sensitizing the nerve endings peripherally. The processes driving pain transmission and propagation are attenuated with the introduction of thoracic epidural analgesia, paravertebral blocks, and multimodal analgesia. These interventions in the perioperative period have helped with analgesia in the acute postoperative period (5). Despite improvements in aggressive perioperative analgesia, the transformation of acute post-surgical pain into chronic post-thoracotomy pain syndrome is distressingly common, with an incidence of chronic post-thoracotomy pain of 57% and 47% at 3 and 6 months, respectively (6). Most importantly, these outcomes have not improved since the 1990s despite the introduction of processes to better control the acute pain.

### **Post-Thoracotomy Pain**

Post-thoracotomy pain syndrome (PTPS) is defined by the International Association for the Study of Pain (IASP) as "pain that recurs or persists along a thoracotomy incision at least 2 months following the surgical procedure" (7). This pain is often described as burning, with localized, discrete tenderness, and persistent dysesthesias around the incision site. With symptomatology consistent with neuropathic pain and injury, it is likely a complex interplay of peripheral and central insults. The concept of central sensitization is often implicated in the development of chronic pain, as pain long outlasts the peripheral insult and inflammation. Central sensitization is derived from continued nociceptive stimulation that causes hyperexcitability of nerves in multiple regions of the nociceptive pain pathway, from the dorsal horn of the spinal cord, through transmission and processing by the brain (8).

### **Multimodal Analgesia for Thoracotomy Pain and the Role of Ketamine**

Multimodal analgesia for thoracic surgery has emerged as the standard of care, allowing aggressive modulation of pain at multiple different receptors along various points of the pain pathway while helping to reduce systemic usage of opioids and their attendant side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) and local anesthetics help modulate and attenuate peripheral inflammatory mediators and pain transmission. Regional techniques, such as thoracic epidural analgesia and para-vertebral blocks, play a key role in attenuating pain transmission in the dorsal horn and paravertebral space. Intraoperative ketamine combined with thoracic epidural analgesia is well documented to better manage perioperative pain after major digestive surgery (9). Current PROSPECT thoracotomy subgroup (Procedure Specific Postoperative Pain Management, [www.postoppain.org](http://www.postoppain.org)) recommendations support intra-operative thoracic epidural analgesia with local anesthetic plus strong opioid or paravertebral block, given high quality evidence based on randomized controlled trials. The concept of multimodal analgesia has evolved from "pre-emptive analgesia," which postulated that we could prevent the sensory processing of pain before the surgical insult versus treating the acute pain after the surgical insult, and therefore prevent the development of chronic pain. While reducing the progression to chronic pain with pre-emptive analgesia has not been established, in a meta-analysis of Ong et al (10) looking at the efficacy of pre-emptive analgesia for acute pain management, the authors found the strongest benefit for epidural analgesia, NSAIDs, and local anesthetic infiltration, and the least evidence for systemic N-Methyl-D-Aspartate (NMDA) receptor blockade.

### **N-Methyl-D-Aspartate Receptor and Pain**

The physiology of nociceptive transmission and processing is complex. There are many pathways and sites, and several mediators involved in the modulation of pain sensation, from afferent receptors, peripheral transmission, and modulation to central modulation and processing, culminating in a physical, sensory, and emotional response. There is a growing body of evidence that implicates the excitatory neurotransmitter glutamate in nociception and glutamate receptor modulation has a potential therapeutic application in inflammatory and neuropathic pain. Tissue injury can result in temporal summations of post-synaptic depo-

larizations of the NMDA glutamate receptor which in turn results in calcium influx, triggering intracellular signaling pathways that result in phosphorylation of NMDA receptors and prolonged increases in nociceptive transmission (11,12). This process, known as central sensitization or “wind-up,” has been postulated to contribute to hyperalgesia and allodynia seen after surgical insult and the transition from acute to chronic pain (12). This increased excitability is at least partly mediated via NMDA receptors (8,13) which ketamine, as a NMDA receptor antagonist, has been shown to block (12).

### **Ketamine**

Ketamine is a non-competitive antagonist of NMDA in the central nervous system, and exists as an optical isomer in the form of S (+) and R (-) ketamine. S (+) ketamine is known to have a higher affinity for the NMDA receptor, and in addition, ketamine-induced analgesia can also be accounted for by its inhibitory effect on spinal microglia and its peripheral effect via the L-arginine/NO/cyclic GMP pathway (14). In addition to the known analgesic effects mediated by NMDA receptor antagonism, ketamine also has pleotropic effects on the body, which include anti-inflammatory effects and anti-hyperalgesic properties.

### ***Anti-inflammatory Effects of Ketamine***

Postsurgical inflammation is a normal response regulated by complex pro-inflammatory and anti-inflammatory immune mechanisms to maintain homeostasis (15). NMDA antagonists exert myriad anti-inflammatory effects by inhibition of cytokine production (reflected in IL-6 and IL-10 ratio) (16), neutrophil function, and suppression of platelet function (15). In a recent meta-analysis by Dale et al (17), perioperative ketamine administration inhibited early postoperative IL-6 production in a diverse group of surgeries, including cardiac, abdominal, thoracic, and cataract surgeries. Similarly, S-ketamine attenuates cardio-pulmonary bypass induced systemic inflammatory response in patients undergoing coronary artery bypass grafting (CABG) surgery (18). For detailed discussion of the anti-inflammatory effects of ketamine, readers are referred to a review the article by Loix et al (15).

### ***Anti-hyperalgesic Effects of Ketamine***

In rodents treated with subcutaneous morphine for 7 days, ketamine attenuated opioid-induced hyperalgesia as evidenced by blocking spinal long-term potentiation (LTP) (19). In volunteer studies, ketamine

has been shown to significantly change the area of primary and secondary hyperalgesia (20). A study by DeKock et al (21) also demonstrated long-term benefit after subanesthetic doses of intravenous ketamine, where patients receiving ketamine showed less wound hyperalgesia and less residual pain at 6 months assessment. Such promising observations, albeit in a few randomized trials, support the view that ketamine has anti-hyperalgesic properties.

## **METHODS**

### **Literature Search**

Two authors (DM and SP) independently performed the initial search in PubMed, Embase, and Cochrane Database using the key term search “ketamine,” “postoperative pain,” “neuropathic pain,” “post-thoracotomy pain syndrome,” in the English literature. The search was limited to human trials and included all studies published before January 2015, and any disagreements were resolved in consultation with author YQ. Data from animal studies, abstracts, and letters were excluded. All studies not available in the English language were excluded as well. The manuscript bibliographies were reviewed and any additional relevant papers were then reviewed by YQ. We included any randomized controlled trial and retrospective studies.

Each study was scored on 3 items, 1 – 5 quality scoring scale as described by Jadad et al (22). A point was given if randomization was described and an additional point was given if the design of the study included a “double” blind approach.

### **Evidence for Use of Ketamine in Post-thoracotomy Pain**

Surgical insult causes nociceptive pain, and in some patients, this acute pain translates into a chronic postsurgical pain. Although multimodal analgesia, in particular thoracic epidural analgesia, has been demonstrated to result in attenuation of acute postoperative pain and morphine consumption, there is conflicting evidence for the role of adjuncts such as ketamine and gabapentinoids in preventing the development of chronic postsurgical pain. The role of NMDA receptors in the attenuation of chronic PTPS has been the focus of recent studies.

### **Evidence for the Use of Ketamine in Post-Thoracotomy Pain Syndrome**

The systematic literature search yielded 15 ran-

domized controlled trials evaluating the efficacy of ketamine in the treatment of acute and chronic post-thoracotomy pain (Tables 1, 2, and 3). Many of these

studies reviewed show that ketamine has acute efficacy in reduction of pain (Table 1), but there are a few which showed no benefit (Table 2). Evidence is lacking on the

Table 1. Studies showing positive results of perioperative administration of ketamine for acute thoracotomy pain.

Study	Design	Groups and Regimen	Number of (n) Patients and Duration of Study [D]	Pain Assessment	Opioid Consumption vs. Control	Adverse Effects	Comments
Tena B (25), 2014	RCT- double blind, placebo controlled	a. IV KET (preincision bolus 0.5 mg/kg and 0.25 mg/kg/hr for 48 hours) b. Epidural KET (preincision bolus 0.5 mg/kg and 0.25 mg/kg/hr for 48 hrs) c. Normal saline control	n = 104 D = 6 months	a. VAS- 2hr, 4hr, 72 hr, 7 days, 3 mo and 6 mo b. QST- baseline, 72 hr 7 days, 3 mo and 6 mo c. NPSI- Day prior to surgery, 7 d, 3 mo, 6 mo	Not reported	Cognitive changes and diplopia more common in ketamine group	Both ketamine groups had better dynamic pain control up to 72 hours.
Feltracco P (35), 2013	RCT-double-blind	a. Epidural S+ KET at 6 mL/hr of 0.25 mg/kg/hr intraop b. Epidural Ropivacaine 0.25% at 6 mL/hr intraoperatively	n = 140 D = 48 hours	a. VAS at 1, 2, 24, and 48 hours post surgery	Reduction in opioid consumption	None	a. All patients received postoperative epidural ropivacaine and fentanyl. b. Significantly less use of rescue analgesics in KET group
Mendola C (34), 2012	RCT-double-blind, placebo controlled	a. IV KET (preincision 0.1 mg/kg/hr) for 60 hours + thoracic epidural b. Epidural + sufentanil	n = 66 D = 6 months	a. NRS (until discharge) b. Neuropathic Pain Symptom Inventory and NRS at 1, 3, and 6 mo	Neither group required opioids	No difference between groups	a. IV KET is beneficial in the early postoperative period. b. TEA and rescue analgesics may have affected the outcome.
Argiriadou H (23), 2011	RCT-double blind-placebo controlled	a. IV KET (preincision bolus 0.5 mg/kg + 400mcg/kg/h) b. 40 mgs of parecoxib prior to extubation and at 12 h c. Placebo-paravertebral ropivacaine only	n = 80 D = 48 hours	a. VAS at rest and movement b. 4, 12, 24, 48 hours post surgery	Reduction in opioid consumption	None	a. All patients had paravertebral block. b. Lower VAS in KET group both at rest and movement at all study points c. No change in length of stay in all groups.
Chazan S (36), 2010	RCT-double blind	a. Morphine PCA b. Morphine +KET PCA for 3 days	n = 46 D = 7 days	VAS at 1, 2, 3, and 7 days postoperatively	Lower morphine consumption	No difference	KET lowers opioid consumption (40% less) in the first 72 hours.
Duale C (30), 2009	RCT-double blind-placebo controlled	IV KET (1 mg/kg at induction, 1 mg/kg/hr intra-op, 1 mg/kg for first 24 hr post-op)	n = 79 D = 4 months	a. VAS and NPSI b. 2 days, 6 wk, 4 mo	No difference in opioid consumption	No difference in adverse events	a. All patients received interpleural analgesia. b. Ketamine in the first 24 hours improved analgesia.

Perioperative Ketamine Administration for Thoracotomy Pain

Table 1 (cont). Studies showing positive results of perioperative administration of ketamine for acute thoracotomy pain.

Study	Design	Groups and Regimen	Number of (n) Patients and Duration of Study [D]	Pain Assessment	Opioid Consumption vs. Control	Adverse Effects	Comments
Nesher N (24), 2009	RCT-double blind, placebo controlled	a. Postoperative IV PCA Morphine (1.5 mg bolus dose) once patient reached VAS score > 5 b. Postoperative IV PCA Morphine (1.0 mg) + IV KET bolus (5 mg) with 7 minute lock-out once patient reached VAS score > 5	n = 41 D = 4 hours	a. VAS score 1, 2, and 4 hours post-op	KET group used 45% less morphine compared to morphine only group in first 4 hours	No difference between groups	a. KET group showed lower maximal pain score. b. Ketamine group had a better postoperative recovery profile.
Nesher N (24), 2008	RCT-double blind	a. IV PCA Morphine (1.5 mg bolus dose) once patient reached VAS score > 5 b. IV PCA Morphine (1.0 mg) + IV KET bolus (5 mg) once patient reached VAS score > 5	n = 54 D = 72 hours	VAS score hourly for 72 hours	KET group used 50% less morphine compared to control group in first 24 hours.	Less PONV (not statistically significant) in KET group	a. VAS scores lower (in the first 72 hour) for KET group. b. Non statistically significant increase in diclofenac use in morphine group
Suzuki M (33), 2006	RCT-double blind-placebo controlled	a. IV KET (0.05 mg/kg/hr) for 72 hours along with epidural b. Epidural morphine/ropivacaine for 48 hours plus placebo for 72 hours post-op	n = 49 D = 6 months	a. VAS scores at rest and coughing 6, 12, 24, and 48 hours b. NRS for average and worst pain on days 3, 7 and 1, 3, and 6 months	Not reported	No differences between groups	VAS scores significantly less in first 48 hours at rest and with movement in KET group
Ozyalcin NS (31), 2004	RCT-double blind-placebo controlled	a. Intramuscular KET (preincision 1 mg/kg) bolus + epidural normal saline b. Epidural KET (preincision 1 mg/kg) bolus + intramuscular Normal Saline c. Epidural normal saline + intramuscular normal saline All groups received post-op with PCEA morphine/bupivacaine	n = 60 D = 30 days	a. VAS up to 48 hours b. Von Frey hair-allodynia/hyperalgesia/pinprick at 48 hr, days 15 and 30.	Reduction in fentanyl use	No difference between groups	Ketamine decreased opioid consumption and epidural ketamine had greater analgesic effect compared to intramuscular ketamine in acute pain.

Table 2. Studies showing negative results for perioperative administration of ketamine for acute thoracotomy pain.

Study	Design	Groups and Regimen	Number of (n) Patients and Duration of Study [D]	Pain Assessment	Opioid Consumption vs. Control	Adverse Effects	Comments
Hu J (27), 2014	RCT-placebo controlled	a. IV KET (preincision bolus 1 mg/kg) and 2 ug/kg/min for 72 hrs) + Sufentanil PCA b. IV saline as placebo + sufentanil PCA	n = 78 D = 6 months	NRS daily for first 7 days, 2 and 6 mo	Not reported	No difference between groups	Ketamine is not effective for prevention of acute pain.
Joseph C (26), 2012	RCT- double blind, placebo controlled	a. IV KET (preincision 0.5 mg/kg bolus + intraop 3 mcg/kg/min infusion+postop 1.5 mcg/kg/min for 48 h) b. placebo	n = 60 D = 3 months	a. NRS at rest and coughing for 48 hours b. NRS at 1 and 3 mo	No difference between groups	Higher incidence of PONV in KET group	Groups optimized with PCEA may account for lack of KET effect on analgesia.
D'Alonzo RC (28), 2011	RCT-double blind placebo controlled	a. IV KET bolus (preincision 0.5 mg/kg) b. Saline (placebo)	n = 40 D = 24 hours	Verbal scores at 4 h and 24 h post surgery and at discharge	No difference between groups	No psychotropic events reported	a. Only one preincision bolus dose was administered. b. No difference in IL-6/CRP levels and pain scores in both groups regardless of procedure
Yazigi A (32), 2012	RCT – double blind– placebo controlled	a. IV ketamine (preincision 0.1 mg/kg bolus +0.05 mg/kg/hr for 72 hours) b. Placebo normal saline *Continuous intercostal nerve blocks (bupivacaine), paracetamol and ketoprofen in both groups	n = 60 D = 72 hours	VAS every 6 hours post-op for 3 days at rest and coughing	No difference in both groups	Nightmares/hallucinations and blurred vision reported in 2 patients.	Lack of KET effect could be attributed to lower KET infusion doses compared to other studies.

long-term benefit of treatment with ketamine to prevent chronic PTPS (Table 3), regardless of its route of administration.

### Efficacy

Our literature review resulted in 15 randomized controlled trials assessing the perioperative use of ketamine in thoracic surgery, its effect on acute post-operative pain and on the development of chronic PTPS. There was a large heterogeneity in the studies we analyzed with regards to dosage, duration of ketamine administration, and duration of follow-up. Of all the studies reviewed, many did not have definitive data points included in the data analysis, rather overall sta-

tistical analysis was presented by the respective authors. Therefore, a complete meta-analysis of the randomized trials was not attempted.

Although a full meta-analysis of randomized trials was not reasonable, an analytical study was performed within this investigation as a meta-analysis of selected, randomized, placebo-controlled trials of intraoperative ketamine supplementation for post-thoracotomy pain control for which similar raw data was reported in the studies. A total population of 241 patients undergoing thoracotomies with intraoperative ketamine supplementation, administered either intravenously or epidurally, were enrolled and statistically compared to a placebo-controlled group of 119 patients also

Perioperative Ketamine Administration for Thoracotomy Pain

Table 3. Studies showing negative results of perioperative administration of ketamine for chronic thoracotomy pain of more than 3 months duration.

Study	Design	Groups and Regimen	Number of (n) Patients and Duration of Study [D]	Pain Assessment	Long-term Outcome	Comments
Hu J (27), 2014	RCT-placebo controlled	a. IV KET (preincision bolus 1 mg/kg) and 2 ug/kg/min for 72 hrs) + Sufentanil PCA b. IV saline as placebo + sufentanil PCA	n = 78 D = 6 months	a. NRS at 2 and 6 months	No difference in chronic pain at 2 and 6 months between both groups	Chemotherapy, retractor use time, and inadequate pain control were independent risk factors for chronic pain.
Tena B (25), 2014	RCT-double blind, placebo controlled	a. IV KET (preincision bolus 0.5 mg/kg and 0.25 mg/kg/hr for 48 hours) b. Epidural KET (preincision bolus 0.5 mg/kg and 0.25 mg/kg/hr for 48 hrs) c. Normal saline control	n = 104 D = 6 months	a. VAS- 3 mo and 6 mo b. QST-baseline, 72 hr 7 days, 3 mo, and 6 mo c. NPSI- Day prior to surgery, 7 d, 3 mo, 6 mo, d. Catastrophizing Scale- at 3 months.	No difference in chronic pain at 6 months	No difference in post-thoracotomy pain at 6 months
Joseph C (26), 2012	RCT-double blind, placebo controlled	a. IV KET (preincision 0.5 mg/kg bolus + intraop 3 mcg/kg/min infusion + postop 1.5 mcg/kg/min for 48 h) b. placebo	n = 60 D = 3 months	NRS at rest and coughing for 48 hours NRS at 1 and 3 mo	No difference in chronic pain at 1 and 3 months	Ketamine not effective in preventing both acute and chronic pain
Mendola C (34), 2012	RCT-double-blind, placebo controlled	a. IV KET (preincision 0.1 mg/kg/hr) for 60 hours + thoracic epidural (levobupivacaine and sufentanil) b. Epidural + sufentanil	n = 66 D = 6 months	a. NRS (until discharge) b. Neuropathic Pain Symptom Inventory and NRS at 1, 3, and 6 mo	No difference in chronic pain between groups at 6 months	Overall low incidence of moderate-severe chronic pain at 3 and 6 months – may be confounded by multimodal analgesia.
Ryu H (29), 2011	RCT-double blind-placebo controlled	a. Preemptive epidural (bupivacaine+ fentanyl + KET) for 48 h b. Placebo-epidural (bupivacaine + fentanyl)	n = 133 D = 3 months	VAS at 2 wk and 3 months	No difference in chronic pain allodynia, or numbness at 3 months	a. No difference in pain at rest/with movement at 2 weeks or 3 months c. No difference in allodynia, numbness as measured by brush at 3 months
Duale C (30), 2009	RCT-double blind-placebo controlled	IV KET (1 mg/kg at induction, 1 mg/kg/hr intra-op, 1 mg/kg for first 24 hr post-op)	n = 79 D = 4 months	a. VAS and NPSI at 2 days, 6 week and 4 mo	No difference in chronic pain, hyperalgesia at 6 weeks or 4 months	Ketamine is not effective for preventing chronic pain.
Suzuki M (33), 2006	RCT-double blind-placebo controlled	a. IV KET (0.05 mg/kg/hr) for 72 hours along with epidural b. Epidural morphine/ropivacaine for 48 hours plus placebo for 72 hours post-op	n = 49 D = 6 months	a. VAS scores at rest and coughing 6, 12, 24, and 48 hours post-op b. NRS for average/worst pain on days 3, 7; months 1, 3, 6 post-op	No significant difference at 6 months postoperatively as measured by NRS scale at 6 months between 2 groups	a. NRS score for usual pain lower in KET group at 1 and 3 months post-op b. No significant difference for usual pain in NRS score at 6 months, or worst pain at 1, 3, 6 months

undergoing thoracotomies with intravenous opioid supplementation only. Table 3 displays the stratification procedures and demographic characteristics of the 3 study subgroups: (1) the intravenous ketamine group (IV KET), (2) the epidural ketamine (EP KET) group, and (3) the opioid-only control group (CONT).

The outcome measures included postoperative pain control assessed by visual analog scale (VAS) scores rated from 1 (no pain) to 10 (most severe pain) and postoperative adverse events, specifically cognitive and/or visual disturbances and postoperative nausea and vomiting (PONV). VAS scores were assessed by trained postanesthetic care nurses at the following time intervals during respiratory therapy with encouraged coughing (typically by incentive spirometry or respiratory therapy) episodes: 24 hours, 72 hours, one week, 3 months, and 6 months. Since the nested analysis was conducted on pooled raw data presented in prior publications, institutional review board approval was not indicated.

All continuous variables were expressed as means with standard deviations and tested for statistically significant differences among the 3 study groups using analysis of variance (ANOVA) to compute F-statistics and *P*-values. All categorical variables were expressed as exact counts and tested for statistically significant differences using chi-square, 3 x 2-contingency tables to compute chi-square test statistics, and *P*-values. Statistically significant differences were defined by *P*-values less than 0.05. SPSS system software was used to conduct all statistical calculations.

There was an approximately equal number of cases receiving either intravenous or epidural ketamine (*n* = 122) to controls receiving intravenous opioids only (*n* = 119) consistent with balanced case-control study designs (Table 4). In addition, the patients in the EP KET group were significantly older and there were significantly fewer women than in the IV KET and CONT groups (Table 4). When comparing the adverse effects

and VAS scale outcomes among the 3 groups, however, there were significantly more patients in the IV KET group than in the EP KET and CONT groups ( $X^2 = 18.1$ ,  $P < 0.0001$ ).

The IV KET group had statistically significantly less post-thoracotomy pain at 24 hours than the other 2 groups, but both the IV KET and EP KET groups had less post-thoracotomy pain at 72 hours than the CONT group (Table 5). After 72 hours postoperatively, there were no significant differences in the VAS scores among the 3 groups (Table 5). In addition, the EP KET group experienced significantly less PONV than the IV KET and CONT groups (Table 5). There were no statistically significant differences in the prevalence of cognitive and/or visual disturbances among the 3 groups compared (Table 5).

In summary, intraoperative ketamine supplementation, administered either intravenously or epidurally, resulted in reduced, reported post-thoracotomy pain during induced coughing at 24 hours (IV KET) and 72 hours (EP KET) with significantly less PONV than the CONT group and no differences in cognitive and/or visual disturbances when compared to opioid supplementation only for post-thoracotomy pain.

The above subgroup meta-analysis is consistent with the majority of randomized controlled trials which found a statistically significant decrease in pain scores with ketamine administered in the perioperative period. Several studies, including Argiriadou et al (23), showed greater pain relief at rest and at movement in the first 48 hours using ketamine as compared to the control group. In addition to analgesic benefits, Neshar et al (24) demonstrated in their study that ketamine allowed quicker cessation of patient controlled analgesia (PCA) in the postoperative period. In a more recent randomized trial that focused on long-term follow-up, Tena et al (25) showed reduced dynamic pain in groups receiving ketamine in the first 72 hours postoperatively as compared to the control group. The authors claimed

Table 4. Stratification procedures and demographic characteristics of the three study subgroups: intravenous ketamine (IV KET), epidural ketamine (EP KET), and controls (CONT).

N = 241	IV KET	EP KET	CONT	Test Statistic	<i>P</i> -value
Group n	86	36	119	$X^2 = 65.2$	$P < 0.0001^*$
Males	63	26	90	$X^2 = 70.9$	$P < 0.0001^*$
Females	23	10	26	$X^2 = 8.0$	$P = 0.008^*$
Ages (years)	54.3 ± 4.1	63.4 ± 11.9	49.3 ± 11.5	F = 30.2	$P < 0.0001^*$

\*Statistically significant differences,  $P < 0.05$



Table 5. Results of intraoperative thoracotomy ketamine supplementation compared with controls.

N = 135	IV KET	EP KET	CONT	Test Statistic	P-value
Group n	64	36	35	$\chi^2 = 18.07$	$P < 0.0001^*$
PONV	10	2	12	$\chi^2 = 7.44$	$P = 0.0024^*$
Cognitive visual effects	18	15	11	$\chi^2 = 1.89$	$P = 0.389$
VAS 24 hours	$2.15 \pm 1.77$	$2.33 \pm 1.47$	$3.57 \pm 1.70$	$F = 7.62$	$P < 0.001^*$
72 hours	$3.33 \pm 1.76$	$3.31 \pm 1.65$	$4.43 \pm 2.16$	$F = 4.10$	$P = 0.019^*$
1 week	$2.85 \pm 1.44$	$2.78 \pm 1.57$	$3.14 \pm 1.63$	$F = 0.53$	$P = 0.589$
3 months	$0.91 \pm 1.69$	$0.91 \pm 1.88$	$1.38 \pm 1.84$	$F = 0.78$	$P = 0.459$
6 months	$1.30 \pm 1.64$	$1.0 \pm 1.34$	$1.22 \pm 1.22$	$F = 0.43$	$P = 0.654$

\*Statistically significant differences,  $P < 0.05$ .

PONV: postoperative nausea and vomiting; VAS: visual analog scale [scores].

that ketamine administration facilitated respiratory physiotherapy and a better outcome by helping prevent postoperative atelectasis and pneumonia.

However, not all studies showed a decrease in acute pain scores (Table 2). In patients having a thoracotomy, Joseph et al (26) demonstrated that intravenous ketamine (up to 48 hours) in the postoperative period, in addition to patient controlled epidural anesthesia with ropivacaine, did not show any significant difference in pain scores or opioid consumption in the postoperative period in patients undergoing thoracotomy. This study also noted no benefit in pulmonary function with ketamine as compared to control, which contradicts the findings in the study by Tena et al (25).

The ability of perioperative ketamine to prevent or even attenuate the progression of acute pain into chronic PTPS was not established in our analysis. This is primarily because the overall number of patients analyzed in each of the randomized control trials was relatively small, and only 8 of the 14 studies had follow-up to at least one month, with the longest duration of follow-up of 6 months in only 4 studies. As discussed previously, the etiology and progression of post-thoracotomy pain is likely multifactorial. Hu et al (27) noted how chemotherapy, retractor time, and inadequate pain control were risk factors in development of chronic PTPS, while ketamine had no obvious effect in mitigating this process at 6-month follow-up.

Pro-inflammatory cytokines and acute phase biomarkers are thought to influence the development of postsurgical pain, and in this regard, ketamine, which has the potential to reduce pro-inflammatory biomarkers in cardiac surgery did not reduce postoperative IL-6/CRP values after thoracotomy in a randomized study

conducted by D'Alonzo et al (28). Similarly, other studies by Ryu et al (29) and Duale et al (30) showed no difference in chronic post-thoracotomy pain at 3 and 4 months, respectively, following perioperative ketamine administration. On the contrary, Ozyalcin et al (31) reported a lower incidence of hyperalgesia and allodynia along the incision in the epidural ketamine group up to 30 days postoperatively. The authors attributed this difference to possible reduced central sensitization. However, all other randomized trials reviewed showed no difference in perioperative ketamine in preventing or reducing the incidence of PTPS.

#### Route of Administration

Of the studies included in our literature review, ketamine was administered intravenously, intramuscularly, or via the epidural route. In the study by Ozyalcin et al (31), the authors found a greater analgesic effect of ketamine administered via epidural versus intramuscular administration. Epidural ketamine has been hypothesized to have greater concentrations at the level of the spinal cord (25), and therefore more effectively prevents central sensitization. However, in the study by Tena et al (25), they found that systemic levels of ketamine were similar between the intravenous ketamine and epidural ketamine groups. They did note a tendency for lower pain scores and allodynia in the epidural ketamine group, as compared to the intravenous ketamine group, but this was not statistically significant. Our analytic analysis above suggests both routes are efficacious for acute post-thoracotomy pain.

#### Dose and Duration

The dose and duration of ketamine used in the

randomized trials varied, as there is no consensus on the dose and duration of treatment with ketamine. Ketamine was infused intraoperatively in every trial, whether it was via bolus, infusion, or both methods. Infusion length also varied from studies only administering for intraoperative course to studies continuing infusions 3 days postoperatively. Ketamine dosages also varied widely between the different studies, with infusions ranging from 0.05 mg/kg/hr (32,33) to 1 mg/kg/hr (30). The follow-up of the patients ranged from 4 hours postoperatively (24) to the longest being 6 months postoperatively (25,27,33,34).

### Adverse Effects

Ketamine has been well documented in causing adverse effects, including nausea, disorientation, and psychotropic disturbances such as hallucinations. Only the study by Joseph et al (26), reported a higher incidence of nausea and vomiting amongst the ketamine group compared to control. On the contrary, Neshet et al (24) reported a non-statistically significant reduction in postoperative nausea and vomiting in the ketamine group. Tena et al (25) reported a higher incidence of cognitive side effects, postoperative nausea and vomiting, and diplopia. Significantly, these adverse effects did not alter treatment, and patients continued to receive ketamine. In another study, Yazigi et al (32) reported 2 patients having to be withdrawn from ketamine group due to cognitive side effects. Our analytic analysis suggests there may be more PONV with intravenous ketamine as compared with epidural ketamine, (~15% vs ~5%, respectively), though these were both less than the control group (~34%) (Table 5).

### Limitations

Our review of the literature analyzed 15 randomized controlled trials assessing the effect of ketamine on preventing PTPS. While the studies reviewed are all randomized controlled trials, the ability to compare

and perform a meta-analysis of the findings is limited by the relatively small sample sizes, varying dose and regimen of ketamine, and the wide range of follow-up duration. Various studies assessed different routes of administration of ketamine, either via intravenous, intramuscular, or neuraxial administration. Despite the heterogeneity of the studies reviewed in regards to dosage and duration of ketamine administered, route of administration, and length of follow-up, ketamine seems to have a positive acute analgesic effect, with a favorable side-effect profile. However, ketamine has not been demonstrated to be helpful in reducing the incidence of chronic post-thoracotomy pain. A recent meta-analysis reports an incidence of chronic post-thoracotomy pain of 57% and 47% at 3 and 6 months, respectively (6), despite advances in minimally invasive thoracoscopic surgery, the widespread adoption of epidural analgesia, and aggressive perioperative multimodal pain management strategies. Future research is needed; with further randomized control trials with a focus on long-term follow-up to better assess the efficacy of ketamine in the prevention of PTPS, as this remains distressingly persistent. In addition, a study designed to compare intravenous ketamine with epidural ketamine and/or a multimodal analgesic approach is warranted.

### CONCLUSION

Perioperative ketamine administration has beneficial acute analgesic effects in the perioperative period, especially when combined with aggressive multimodal analgesia. Ketamine has been frequently studied, as it offers a powerful adjunct to opioid analgesia, and the potential ability to interrupt peripheral and central processing and transmission of pain. The randomized control trials reviewed show lower pain scores in the immediate perioperative period with a favorable side-effect profile.

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