Low Dose Ketamine Infusion Versus Thoracic Epidural Infusion for Post Thoracotomy Analgesia

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Ketamine, a phencyclidine derivative has got a unique set of actions among anaesthetic drugs causing dissociative anaesthesia. It has been mainly used for induction of anaesthesia and intraoperative analgesia. Recently, there has been a resurge in ketamine owing to its efficacy as an infusion for perioperative and postoperative analgesia. The aim of this study was to compare intravenous infusion of ketamine with thoracic epidural bupivacaine-fentanyl infusion in managing postoperative analgesia in patients undergoing thoracotomy. METHODS: 62 patients posted for elective thoracotomy for decortication were randomised into two groups. Patients in group K (n=32) received 0.5 mg/kg bolus followed by an infusion of 2 mcg/kg/min infusion of ketamine and patients in group E (n=30) received thoracic epidural bupivacaine fentanyl infusion for 48 hrs post-surgery. Numerical rating scale (NRS) pain scores were noted at rest and on cough every 4 hrs till 48 hrs post-surgery. Ramsay sedation scores, incidence of side effects, and dose of rescue analgesics were also noted. RESULTS: NRS scores were significantly lower in Group K compared to group E, both at rest and on cough (p=0.002 and p=0.001). There was no difference in the levels of sedations or the need for rescue analgesic of paracetamol (p=0.356) though there was a difference between need for second rescue analgesic of tramadol (p=0.034) in group E. CONCLUSION: Low dose ketamine infusion provides better postoperative analgesia post thoracotomy compared to thoracic epidural infusion.

Key words: Postoperative analgesia, Low dose ketamine infusion, Thoracic epidural infusion, Thoracotomy

Introduction

Ketamine, a phencyclidine derivative drug has a unique set of anaesthetic actions causing dissociative anaesthesia. It is used mainly during induction and for intraoperative analgesia. In subanaesthetic doses, ketamine provides good analgesia. Recently, there have been various studies regarding its efficacy as an infusion for perioperative and postoperative analgesia.

Skin incision, rib resection, intraoperative tissue dissection and retraction, presence of drainages all contribute to intense pain after thoracic surgery.[1]Postoperative pain is the primary reason for prolonged convalescence after major surgeries hampering physiotherapy and incentive spirometry leading to ineffective chest wall expansion and predisposing to atelectasis, ventilation/perfusion mismatching, hypoxemia, and infections.[2,3] Post-operative analgesia plays a vital role in recovery post-surgery. Ketamine reduces the need for postoperative opioids for acute pain management and also has a role in long term effect on residual pain.[4]

We designed this study to compare the effects of ketamine infusion with a thoracic epidural infusion of bupivacaine-fentanyl combination on postoperative pain at rest and on coughing, and the need for rescue analgesics.

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Materials and methods

This is a prospective randomised controlled study. Institutional ethical committee approval was taken. From December 2018 to May 2020, 75 patients between 18 to 65 yrs of age with no cardiac co-morbidities, no history of allergy to ketamine, bupivacaine or fentanyl posted for thoracotomy and decortication were found eligible. 13 patients were excluded from the study either due to presence of renal or hepatic

dysfunction, a history of psychiatric illness or those not consenting for the study. Numerical rating scale (NRS) pain score chart (0-10), the risk of postoperative hallucinations, vivid dreams, dizziness were explained to the patients during pre-anaesthesia evaluation. Informed consent was taken.

Patients were premedicated with oral pantoprazole and alprazolam. 2 peripheral venous lines and an arterial line were secured before induction. Induction was done with propofol, analgesia maintained with 2 mcg/kg fentanyl during induction and vecuronium was used for muscle relaxation. Additional fentanyl of 1 mcg/kg/hr was given every hour beyond 2 hours duration of surgery. Appropriately sized double lumen tube was inserted based on the patient's height. Intraoperative anaesthesia was maintained with 60% oxygen in air and 1% isoflurane. Patients were randomised into 2 groups based on computer generated randomisation schedule. 32 patients were included in group K and 30 patients in group E.

Patients in group K received ketamine 0.5 mg/kg bolus at the start of surgery and were maintained on 2 mcg/kg/min infusion throughout the surgery till 48hrs post-surgery. Patients developing hallucinations, dizziness or vivid dreams post extubation would have their infusions stopped for 2 hours and then continued at a lower dose of 1 mcg/kg/min. Patients in group E received thoracic epidural after induction of anaesthesia with 18 g Tuohy needle, catheter inserted in the T7-8 space and were maintained with combined 0.125% bupivacaine with 2mcg/ml fentanyl infusion at 5ml per hour for 48 hrs post-surgery. Intraoperative monitoring included electrocardiogram, pulse oximetry, arterial blood pressure monitoring and blood gas monitoring. The primary endpoint was level of analgesia and use of rescue analgesics with an intention to treat the pain.

The surgical team consisted of a team of 2 surgeons. Posterolateral incision was used for all the patients. Both our surgeons operate with a mini-thoracotomy incision of around 8-10cm and incision extended if needed. Patients were shifted to the post-operative ICU post-surgery with intercostal drain in situ and extubated within an hour of shifting after getting chest roentgenogram and adequate reversal. NRS was used for postoperative pain assessment every 4 hours starting post-extubation till 48 hrs both at rest and on coughing. Level of sedation was monitored using the modified Ramsay sedation scores (Score 1 awake; 2-Lightly sedated; 3-Moderately sedated but follows simple commands; 4-Deeply sedated, responds to non-painful stimuli; 5- Deeply sedated but responds to painful stimuli; 6-Deeply sedated and no response to painful stimuli).Presence of other side effects were noted. Patients complaining of pain or who had NRS scores of more than 4 received 15mg/kg of paracetamol intravenously as first rescue analgesic. Patients continuing having pain received intravenous tramadol 0.5 mg/kg as second rescue analgesic. The amount of rescue analgesics given were noted.

Statistical analysis was achieved with SPSS for Windows software. The primary endpoint of the study was VAS pain scores. Data were reported as mean values±standard deviation. NRS scores at rest, on cough and Ramsay sedation scores were compared by Repeated measures analysis of variance (ANOVA) between the two groups. Patients′ demographics, duration of surgery, dose of rescue analgesics were compared by independent samples test. The Chi-square test was used to compare sex distribution and the frequency of side effects. $P \leq .05$was considered statistically significant.

Results

There was no significant difference between group K and group E in age, sex distribution, height and weight as shown in Table I. Even though patients in group K had longer duration of surgery (Group K 118+/-40 min vs Group E 90+/-28 min), the total amount of fentanyl used for intraoperative analgesia was similar between the groups (Table 1).

NRS pain scores at rest were significantly lower in group K throughout the period of study (p=0.002) (Figure 1). The average pain scores at rest were in the range of 2-4 in our study in the early postoperative period. Pain scores after the initial 24 hours were almost the same between the groups. Intensity of pain on coughing was also significantly less in the group K patients (p=0.001) (Figure 2).Patients in group K were less sedated than those in group E. (p=0.112) (Figure 3).

Table 1.*Patients' demographics*

	Group K	Group E	p value
Age (years)	41+/- 15	45+/-12	0.246
Sex M: F %	69:31	80:20	0.104
Height (cms)	166+/- 7	166+/-5	0.686
Weight (kgs)	63+/-14	64+/-8	0.728
Duration of surgery (min)	118+/-40	90+/-28	0.003
Intraoperative Fentanyl Dose (mcg)	132+/- 35	129+/-16	0.656

Figure 1. *NRS scores at rest*

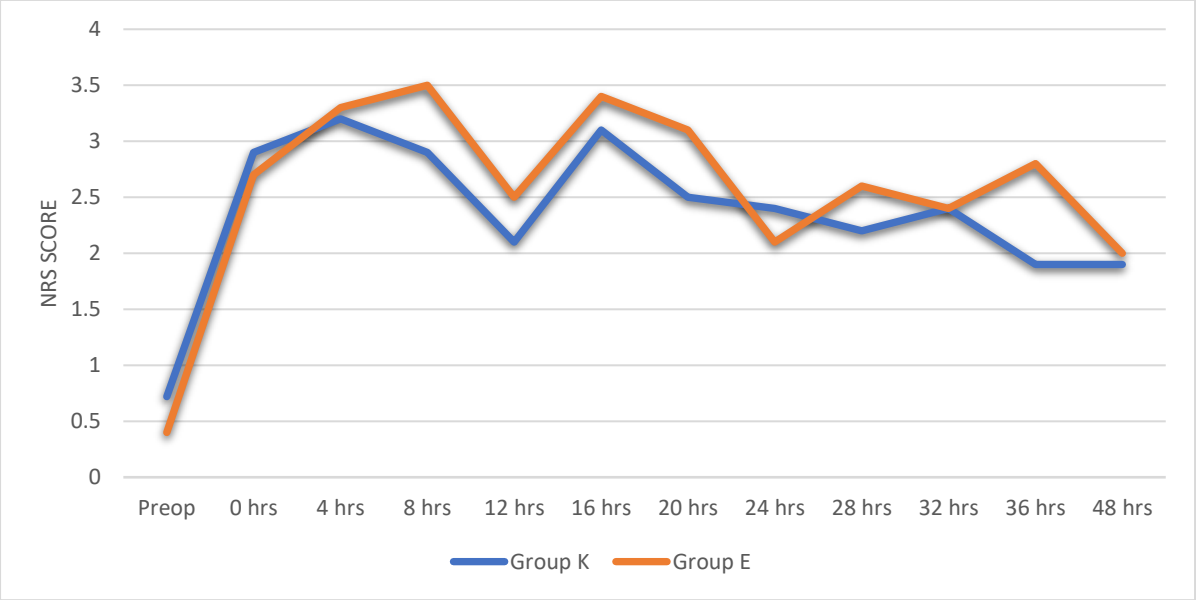


Figure 2*. NRS scores on coughing.*

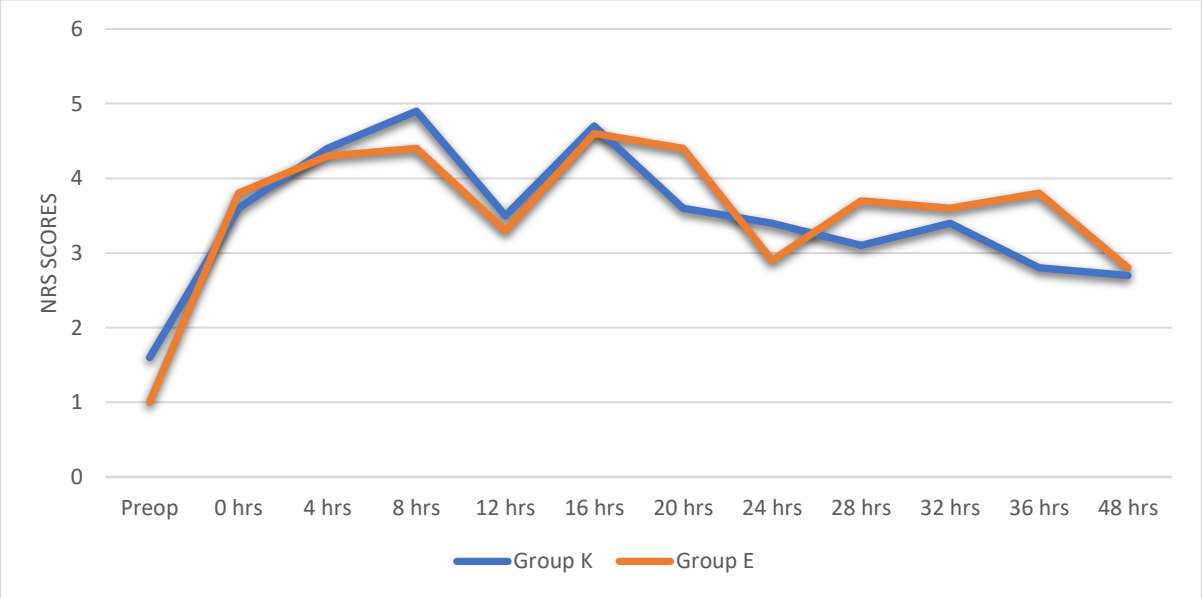
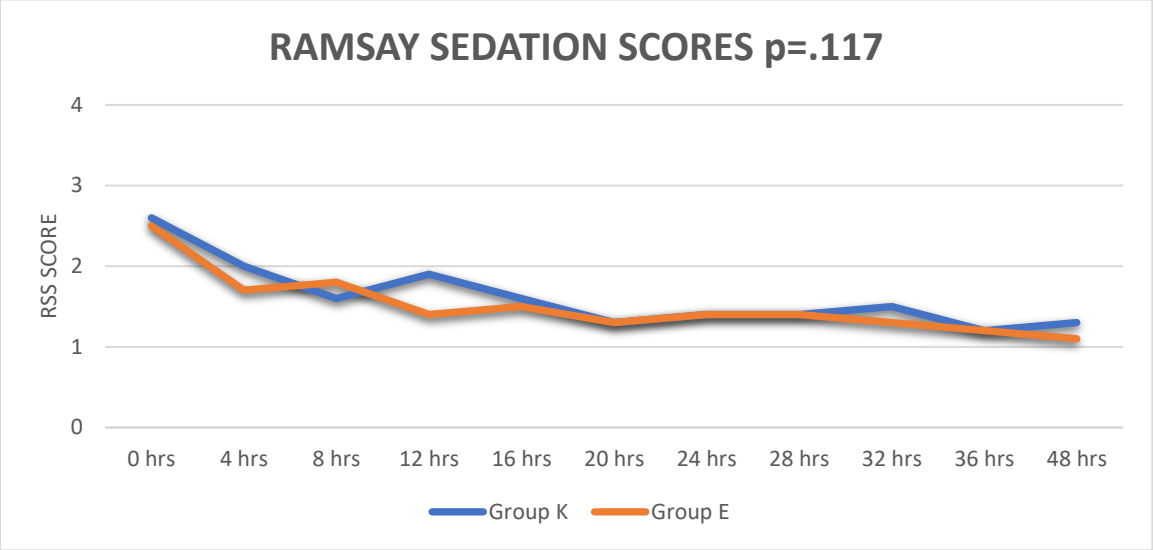


Figure 3. *Ramsay sedation scores*



There was no significant difference in the requirement for first rescue analgesic of paracetamol (p=.356) (Table 2). There was a significant difference for additional tramadol in group E (p<.05) which could correlate with the higher NRS pain scores in group E.

Table 2. *Rescue analgesic doses andincidence of side effects*

	Group K	Group E	p value
Paracetamol (Gms)	2.3+/-1.17	2.6+/-0.9	0.356
Tramadol (mgs)	9.6+/-18	24+/-34	0.034
Vasopressor Support	18.8%	6.7%	0.156
Dizziness	3.1%	0	
Gastritis	3.1%	0	
Postoperative hypertension	3.1%	0	0.399
No side effects	29	30	

There was no significant difference between the two groups in the incidence of postoperative complications (p=0.399). Some of the patients needed postoperative vasopressor infusion support though there was no significant difference between the groups (p=0.156) (Table 3). Since some of our patients were operated early in their disease course with empyema, release of septic foci into the circulation could be a reason for the need for vasopressor support. None of our patients required any other analgesic and were overall satisfied with the level of analgesia.

Discussion:

Postoperative pain management with ketamine infusion has seen a resurgence. Its analgesic action is mediated through NMDA receptor antagonism causing anaesthetic, amnesic, dissociative and hallucinogenic effects. It also prevents central sensitization in dorsal horn neurons by interfering with pain transmission in the spinal cord. Production of nitric oxide, a pain transmitter is lowered by nitric oxide synthase inhibition, further contributing to analgesia. Ketamine has antidepressant effect, the mechanism of which is yet to be elucidated. Ketamine produces analgesia at plasma concentrations of 100 to 200 ng/mL, which represents a small fraction of plasma concentrations attained after general anaesthesia doses (9000–25,000 ng/mL).[5]

There have been no studies comparing ketamine with an epidural infusion for postoperative

analgesia following thoracotomy. Hence, our study was aimed to compare intravenous infusion of ketamine with thoracic epidural bupivacaine-fentanyl infusion in managing postoperative analgesia in patients undergoing thoracotomy.

Ketamine is used alone or with adjuvants for managing the post-surgical pain. Suzuki et al studied the effects of ketamine infusion on potentiation of epidural in thoracotomy patients who received continuous epidural infusion of ropivacaine and morphine, along with either intravenous ketamine infusion (50 mcg/kg/h, n=24) or placebo (saline, n=25). With epidural analgesia continued for 2 days, and infusion of ketamine or placebo for 3 days' post-surgery, the pain scores at rest and on coughing after thoracotomy were lower in the ketamine group than in the control group ($p<0.001$ and $p=0.02$). Ketamine also reduced the analgesic requirement at 1and 3months post-surgery indicating a long-term effect.[6]

Dong Ho Kim et al reported lower pain scores post-bilateral axillo-breast approach robotic thyroidectomy in patients receiving ketamine infusion with no significant difference in the need for rescue analgesics as in our study. We used a smaller bolus of 0.5 mg/kg bolus followed by 2 mcg/kg/min infusion compared to 1mg/kg bolus and 1 mcg/kg/min infusion used in this study.[7]Jiwon Lee et al found lower requirement for rescue analgesics and lower pain scores in the initial 24hrs post-surgery on using 0.15 mg/kg bolus with 2 mcg/kg/min infusion intraoperatively on patients undergoing robotic thyroidectomy.[8]

Ketamine is effective in reducing opiate requirements in opioid dependant patients undergoing back surgery. A bolus of 0.5 mg/kg along with 10 mcg/kg/min infusion throughout the surgery versus a placebo infusion were used. Reduced pain scores, decreased total morphine consumption at 24 hrs, 48 hrs and 6 weeks' post-surgery were noted. Interestingly in this study, ketamine infusion was stopped at the end of surgery whereas its effects lasted a much longer duration withno postoperative complications.[9]

Postoperative pain scores were significantly lower and the first rescue analgesic requirement were significantly prolonged in caesarean section patients receiving ketamine compared to those receiving placebo.[10]

Ketamine significantly reduces pain scores ($p=0.01$), C reactive protein levels ($p=0.001$) and also morphine consumption ($p=0.001$) on pre-emptive administration in patients undergoing thoracotomy.[11] Ketamine has also been used epidurally. A systematic review by Daniel Moyse et al concluded that both intravenous ketamine and epidural ketamine reduced post-thoracotomy pain during coughing with significantly less complications when compared to only opioid use for pain management.[12]

Ketamine infusion reduced pain intensity significantly from 4 to 48 hrs postoperatively in patients undergoing head and neck surgery. Ketamine produced analgesia equivalent to remifentanil analgesia and also helped in earlier extubation of patients.[13]

However, not all studies have shown a beneficial effect of ketamine. Alexandre Yazigi et al studying the effect of low dose ketamine with continuous intercostal nerve block in thoracotomy noted no difference in pain scores either at rest or on coughing compared to a placebo. Sedation scores, number of morphine deliveries and cumulative morphine infused were equal.[14]

Epidural ropivacaine consumption, postoperative pain scores and spirometry parameters was similar, with an increased incidence of postoperative nausea in patients receiving ketamine undergoing thoracotomy as compared to those receiving placebo.[15]

A review article noted multiple intravenous dosing strategies including intra- and postoperative bolus with or without an infusion have all demonstrated efficacy, improving pain scores and reducing perioperative opioid consumption in multiple surgical scenarios with minimal risk of side effects. They further noted that ketamine can be used as a bolus of 0.1-0.3 mg/kg followed by an infusion of 100-300 mcg/kg/hr infusion for optimal analgesia.[16] We used a bolus of 0.5 mg/kg with 2 mcg/kg/min infusion for similar results. This study could not be blinded as we could not load the infusions without knowing the drug being used and the epidural infusion. The postoperative NRS pain scores were less in both the study arms. Our study shows that subanaesthetic doses of

ketamine may be used as a sole agent for post-operative analgesia in patients undergoing thoracotomy.

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