Original Article

Perioperative ketamine to reduce and prevent acute and chronic post-thoracotomy pain: a randomized, double-blind, placebo-controlled clinical trial

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Background: Moderate to severe postoperative pain is common among patients following thoracotomy and serves as a risk factor for developing chronic post-thoracotomy pain (CPTP). This randomized controlled trial evaluated the effects of pre-emptively administered ketamine compared to placebo and standard care on both acute postoperative pain and CPTP.

Methods: Two hundred patients were enrolled in this prospective, randomized trial. The presence and severity of pain were assessed before surgery, first 6 hours after surgery, on postoperative days (PODs) 1–8, 30, and 90. For documentation of neuropathic pain, the Leeds Assessment Score for Neuropathic Symptoms and Signs (LANSS) was used pre- and postoperatively. The incidence and severity of CPTP was assessed by a telephone survey, the self-assessment LANSS (S-LANSS) 30 and 90 days after surgery.

Results: There was significant difference in numeric rating scale (NRS) pain scores when coughing in the first 6 hours after surgery, with less pain in the ketamine group. No difference was seen in NRS pain scores at rest and coughing between the ketamine and placebo group on PODs 1–8. There was no difference in the opioid consumption between the two groups. Thirty-four (18.7%) of the patients had a S-LANSS score ≥12 30 days following surgery, 12 (12.8%) in the ketamine group *vs.* 22 (25%) in the placebo group (P=0.001). Thirty-three (18.2%) of all patients had a S-LANSS score ≥12 90 days following surgery 8 (8.5%) in the ketamine group *vs.* 25 (28.4%) in the placebo group (P<0.001).

Conclusions: In summary, pre-emptive ketamine does not reduce opioid consumption and NRS scores after thoracotomy but more importantly it lowers significantly the incidence of chronic postoperative pain, especially neuropathic pain.

Trial Registration: The study was registered at ClinicalTrials.gov (NCT 03105765).

Keywords: Chronic post-thoracotomy pain (CPTP); ketamine; thoracic surgery; neuropathic pain

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Introduction

Lung cancer ranks as the most prevalent cancer globally and is a leading cause of mortality. Each year, thousands of patients undergo surgical resection of the lung and esophagus (1). Thoracotomies are associated with moderate-to-severe postoperative pain, impairment of respiratory function, and protracted recovery (2).

Inadequate pain control can lead to adverse outcomes, including increased postoperative morbidity, delayed recovery, and the development of chronic post-thoracotomy pain (CPTP) (2,3). The severity of acute postoperative pain has been correlated with the onset of persistent postoperative pain. CPTP is a common consequence of thoracic surgery, with a prevalence ranging from 50% to 80%. While typically mild to moderate, CPTP can be severe and disabling in about 5% of cases (4,5). According to the International Association for the Study of Pain, CPTP is defined as pain that recurs or persists along the thoracotomy incision for at least 2 months following surgery (6). CPTP encompasses various types of pain, most often presenting as dysesthesia with burning and aching sensations characteristic of neuropathic pain (7,8). Neuropathic pain often responds poorly to opioids (9). Managing CPTP poses significant challenges for physicians. Several strategies have been employed to mitigate acute and CPTP, including nonsteroidal anti-inflammatory drugs (NSAIDs), parenteral opioids, epidural and paravertebral infusions of local anesthetics, intercostal and phrenic nerve blocks, and cryotherapy (10). However, the effectiveness of these approaches varies, and no single strategy has proven universally effective.

Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor ion channel. Ketamine produces its analgesic effects on one hand through abolishing peripheral afferent noxious stimulation and on the other hand is believed to prevent central sensitization and opioid-induced hyperalgesia (11). What is the role of ketamine administration for thoracotomy pain? Two systematic reviews (12,13) showed that ketamine has efficacy in reduction of acute pain but the evidence for ketamine as a preventive agent for CPTP is insufficient. But most studies did not address CPTP and did not investigate neuropathic pain. Given that an optimal perioperative analgesic regimen should alleviate acute postoperative pain and reduce the incidence of chronic postoperative pain, particularly neuropathic pain, we investigated the effects of perioperative intravenous (i.v.) ketamine infusion. We present this article in accordance with the CONSORT reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-648/rc) (14).

Highlight box

Key findings

- Pre-emptive ketamine significantly lowers the incidence of chronic postoperative pain after thoracotomy, especially neuropathic pain.

What is known and what is new?

- It is well-established that many patients experience moderate to severe postoperative pain following thoracotomy. Inadequate control of pain after surgery has detrimental effects, such as the occurrence of chronic post-thoracotomy pain (CPTP).
- Perioperative application of ketamine has shown efficacy in reducing acute postoperative pain. However, data of preventing CPTP is insufficient. We could demonstrate a significant reduction in CPTP with the pre-emptive application of ketamine.

What is the implication, and what should change now?

- Perioperative application of ketamine may be established as a prevention option for CPTP. Further large-scale randomized trials are warranted to confirm the efficiency and safety of perioperative ketamine application.

Methods

This prospective randomized, double-blind, placebo-controlled single-center study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local ethics committee of University Hospital Mannheim, University of Heidelberg (No. MC2010-278-MA) and was registered at ClinicalTrials.gov (NCT 03105765).

Patient selection

Two hundred adult (>18 years) patients, scheduled for elective posterolateral thoracotomy between January 2011 and August 2013 in a teaching hospital (Dr. Horst-Schmidt-Kliniken), were included for analysis. At the time of the study, the University Hospital Mannheim was the affiliated university hospital for clinical studies at the Dr. Horst Schmidt Clinics and three of the investigators were employed at the Dr. Horst Schmidt Clinics. Patients were excluded if they had a history of thoracotomy, diagnosed neuropathic pain, hypersensitivity to ketamine, pregnancy, poorly controlled diabetes mellitus, depression or other psychiatric disorders requiring antidepressant medication,

addiction to alcohol or recreational drugs, or an allergy to the study drug. Prior to inclusion in the study, each patient was assessed for their ability to understand the numeric rating scale (NRS), operate a patient-controlled analgesia (PCA) pump, answer a phone call, and comprehend the Leeds Self-Assessment Score for Neuropathic Symptoms and Signs (S-LANSS). For the purpose of the study, a German translation of the Leeds Assessment Score for Neuropathic Symptoms and Signs (LANSS) and S-LANSS was used. Written informed consent was obtained from all patients participating in this trial. consisting one hundred each. Patients, clinical staff and the investigators were blinded to the treatment allocation.

Study groups and intervention

Patients were randomly assigned to one of two groups using computer-generated randomization, which was performed by a team member not involved in patient assessment or surgery. Study drugs were prepared by another team member not involved in patient assessment or surgery, prior to the procedure. Patients and treating physicians as well as nurses where blinded of the allocated group until the end of the study period.

Patients did not receive any oral premedication and were monitored via electrocardiogram, pulse oximetry, and non-invasive blood pressure measurement. TOF-Watch® (Organon Teknika GmbH, Eppelheim, Germany) Neuromuscular Monitor was used to guide muscle relaxant infusion. All patients received total intravenous anesthesia (TIVA) and double-lumen intubation. Anesthesia was induced with propofol 1–2 $mg \cdot kg^{-1}$ (propofol 1% Fresenius, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) remifentanil 1 $\mu g \cdot kg^{-1}$ (Remifentanil-Hameln 2 mg, Hameln Pharma GmbH, Hameln, Germany) and atracurium 0.5 $mg \cdot kg^{-1}$ (atracurium besilate 50 mg/2 mL, Hameln Pharma GmbH). The doses were adjusted based on the ideal body weight (IBW) using the Broca index. The goal was to maintain a bispectral index (BIS) value below 60 during anesthesia induction. If this target was not met with the initial doses of propofol and remifentanil, additional boluses of 0.3 $mg \cdot kg^{-1}$ propofol and/or 0.5 $\mu g \cdot kg^{-1}$ remifentanil were administered as needed. After induction of anesthesia patients received the study drug. The ketamine group received a bolus of ketamine 0.2 $mg \cdot kg^{-1}$ (ketanest 10 mg/mL, Pfizer Pharma GmbH, Berlin, Germany) after induction and prior to surgical incision followed by continuous i.v. infusion of ketamine 0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ for 24 hours. Patients in the placebo group received equal volume of 0.9% saline intraoperatively. Anesthesia was maintained with propofol (4–5 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Anesthetic depth was monitored using the BIS, targeting a value between 40 and 60. Hypotension, defined as a mean arterial pressure (MAP) below 60 mmHg, was documented and managed with catecholamines in accordance with hospital protocols. The selection and dosage of catecholamines were determined at the discretion of the attending anesthesiologist. A posterolateral thoracotomy was performed with the patient positioned in the lateral decubitus position. All surgeries were conducted by the same surgical team. Division of rib was not performed, and the ribs were spread using a self-retaining retractor, taking particular care not to break the ribs. Following lung resection, two 28-French chest tubes were placed in each patient, one anteriorly and one posteriorly. All patients were extubated in the operating room at the end of surgery and subsequently transferred to the post-anesthesia care unit (PACU). Approximately 30 min before the end of the surgery, each patient received piritramide 0.1 $mg \cdot kg^{-1}$ (piritramid 7.5 mg/mL, Hameln Pharma GmbH) and metamizole 1 g (novaminsulfon-ratiopharm 1 g/2 mL, Ratiopharm GmbH, Ulm, Germany).

Postoperative analgesia was administered in accordance with hospital protocols using a systematic opioid-based regimen. Intravenous piritramide was provided through PCA for the first 24 hours. Subsequently, oral opioids (oxycodone), were prescribed based on pain intensity. All patients received additional metamizole (1,000 mg 4 times a daily) and ibuprofen (600 mg 3 times daily) or paracetamol (1,000 mg 3 times daily) if contraindication to either metamizole or ibuprofen were present. Studies have demonstrated that epidural analgesia does not offer superior outcomes compared to a standardized opioid regimen in terms of pain management, bowel function, and hospital length of stay (15,16).

Outcomes

Primary outcome was to evaluate postoperative pain severity with a NRS [0–10], with 0= no pain and 10= worst pain imaginable at rest and when coughing. For the purpose of the study values ≥4 were suggested to indicate severe pain. Pain severity was assessed before surgery, right after surgery, 1 and 6 hours after surgery, and on postoperative days (PODs) 1–8, 30, and 90.

Secondary outcomes included total opioid consumption via PCA pump during the first POD and oral opioid consumption on subsequent days, as well as the incidence of neuropathic pain and chronic pain at 30 and 90 days post-surgery. Neuropathic pain was assessed preoperatively and on PODs 3, 7, 30, and 90 using the methods described below. Neuropathic pain was evaluated using the LANSS scale. The LANSS questionnaire is a validated tool for qualitative pain assessment aimed at identifying neuropathic pain, with reported sensitivity and specificity of 74% and 76%, respectively (17). The questionnaire consists of seven items that are combined into a single score ranging from 0 to 24. A LANSS or S-LANSS score ≥12 is indicative of neuropathic pain (18). For the purpose of this study, a German translation of the LANSS was utilized. The incidence and severity of CPTP were assessed on PODs 3 and 7, and through telephone surveys conducted 30 and 90 days after surgery.

Statistical analysis

In this study, the NRS (for pain) was utilized as the primary endpoint to assess the effectiveness of the intervention, as part of a preliminary investigation. Our focus was on the first three PODs in patients who underwent a lateral thoracotomy. In a preliminary assessment, the average NRS In the control group score at rest and while coughing was 2.39 [standard deviation (SD) ±1.3], compared to 1.9 (SD ±1.0) in the intervention group. To determine the requisite group size, an effect size was initially calculated using Cohen's D, which was approximately 0.42. Based on this effect size, a predetermined alpha level of 0.05, and a target power of 0.8, the statistical power analysis indicated a necessary participant count of about 89 per group. Considering potential drop-outs, the group size was adjusted to 100 participants per group.

All data were analyzed using the Statistical Package for Social Sciences (SPSS), version 15.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as mean ± SD for normally distributed continuous variables, or as medians (interquartile range) with 95% confidence intervals for non-normally distributed continuous variables. The normality of the variables was evaluated using the one-sample Kolmogorov-Smirnov test. Chi-square and Fisher's exact tests were employed to compare dichotomous variables. Statistical significance was defined as a P value of less than 0.05 to achieve 80% power.

Results

Two hundred and fifty-one patients were assessed for eligibility and 199 patients were included and randomized in the two groups, 100 were allocated to the ketamine group and 99 to the placebo group. One hundred and eighty-two patients completed the telephone questionnaire after 30 and 181 patients after 90 PODs (*Figure 1*).

Patient characteristics are summarized in *Table 1*, and no significant differences were observed between the two groups.

In the first 6 hours after surgery the NRS pain scores when coughing was significantly lower in the ketamine group then in the placebo group (P<0.05), at rest only right after surgery (P=0.01), after 1 and 6 hours there was no significant difference (*Table 2*). The pain intensity measured by NRS at rest and during coughing was not significantly different in the 8 days after surgery and at PODs 30 and 90 at rest. At PODs 30 and 90 the NRS scores during coughing were significantly lower in the ketamine group (P<0.001) (*Table 3*).

There was no difference in opioid consumption between the two groups at every measuring point (*Figure 2*). CPTP: after 30 and 90 days significantly, more patients in the ketamine group showed an NRS =0 after coughing compared to patients in the placebo group (P<0.001) (*Figure 3*). On PODs 3 and 7 there was no difference in neuropathic pain (LANSS score ≥12) (on POD 3 in the placebo group 2 *vs.* 3, P=0.14; on POD 7 4 *vs.* 3, P=0.37). Thirty-four (18.7%) of all patients had a S-LANSS score ≥12 30 days following surgery 12 (12.8%) in the ketamine group *vs.* 22 (25%) in the placebo group (P=0.001). Thirty-three (18.2%) of all patients had a LANSS score ≥12 90 days following surgery 8 (8.5%) in the ketamine group *vs.* 25 (28.4%) in the placebo group (P<0.001) (*Figure 4*).

Discussion

Our study provides evidence that perioperative ketamine is effective in preventing CPTP and acute pain in the first 6 hours after surgery when coughing following non-cardiac thoracic surgery with lung resection, but there was no difference between the groups in the severity of postoperative pain or opioid consumption on the first 8 days after surgery.

CPTP is a prevalent and debilitating condition that persists for an extended duration, impacting both patients and

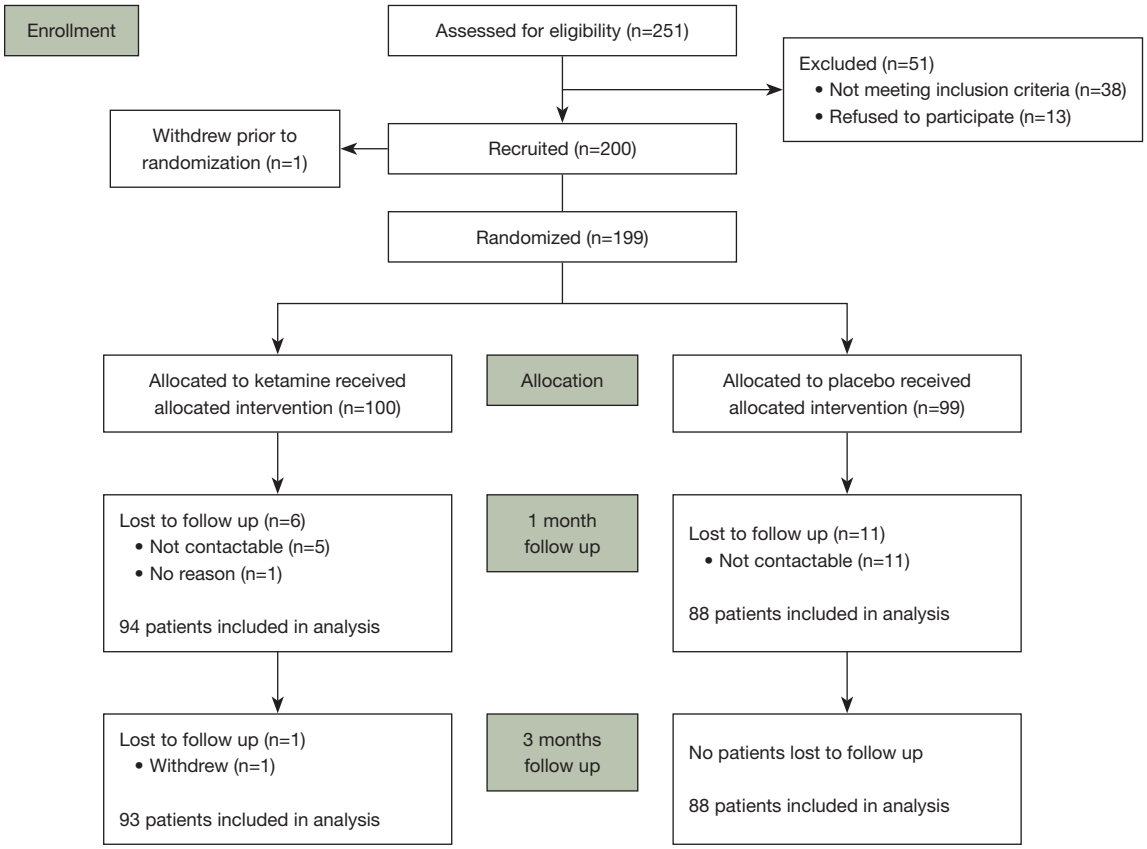

Figure 1 Study flowchart.

society. The overall incidence of CPTP is approximately 10% following general surgical procedures. However, it is notably more frequent after certain surgeries, such as thoracotomy, where the incidence can reach up to 80%. This pain is predominantly neuropathic in origin (19).

Despite advancements in our understanding of the pathophysiology and pharmacology of nociception, both acute and chronic pain remain significant issues and primary concerns for patients (1). Bayman *et al.* (20) reported 57% of thoracotomy patients still having pain at 3 months in their meta-analysis, the more recent study from Chumbley *et al.* (21) reported an 18 % incidence of chronic pain at 3 months. In our study, we can confirm this number of patients with chronic pain (18.2%) at 3 months.

We could show a difference during the early postoperative period (first 6 hours), where additional administered ketamine showed a reduction of pain scores when coughing. But this effect was not present on the following PODs. The median pain score at rest on POD 1 was 1.1 in the ketamine and placebo group and 3.1 *vs.* 3.3 when coughing. At POD 7 the NRS scores where even lower with ketamine group 0.5 *vs.* placebo group 0.6 at rest and 2.0 (ketamine) *vs.* 2.2 (placebo) when coughing. These low pain scores made it impossible to detect a two-point difference on a 11-point NRS scale and made this study underpowered to answer this question. At the time the study was conducted the two-point difference was a reasonable assumption as there was little data available at this time. It is difficult to pinpoint why our study had such low pain scores on POD 1 to 8. The patients in our study did not have an epidural analgesia, even if the use of a thoracic epidural analgesia provides a satisfactory analgesia (22) in a painful surgery, it was no standard operating procedure at our department. An analgesic regime with opioid and non-opioids can also establish satisfying pain relief (15), as our study as well demonstrated.

Although our capacity to manage immediate incisional and inflammatory acute postoperative pain has improved through the combined use of systemic opioids, regional analgesia techniques, and other systemic anti-inflammatory

Table 1 Demographic data

Variables	Placebo (n=99)	Ketamine (n=100)	P value
Age (years)	62.5±10.8	63.3±8.7	0.60
Men/women	52/47	64/36	0.11
BMI (kg/m^2)	25.8±4.9	26.1±4.5	0.74
ASA			0.08
I	0	0	
II	49 (49.5)	34 (34.0)	
III	44 (44.4)	59 (59.0)	
IV	6 (6.1)	7 (7.0)	
Duration of surgery (min)	226.8±79.1	238±81.7	0.36
Operation side: left	40 (40.4)	40 (40.0)	0.56
Extend of surgery			0.39
Lobectomy	68 (68.7)	68 (68.0)	
Wedge resection	11 (11.1)	13 (13.0)	
Pneumonectomy	1 (1.0)	4 (4.0)	
Decortication	2 (2.0)	3 (3.0)	
Sleeve resection	9 (9.1)	8 (8.0)	
Other	8 (8.1)	4 (4.0)	
BISmax	50.1±4.3	51.2±3.4	0.19
BISmin	37±3.8	37.7±3.9	0.37

Data presented as mean ± SD, n, or n (%). BMI, body mass index; ASA, American Society of Anesthesiologist score; BIS, bispectral index; SD, standard deviation.

Table 2 Resting and coughing pain scores according to NRS postoperative, 1, and 6 hours postoperatively

Hours after surgery	NRS (rest)			NRS (coughing)		
	Placebo (n=99)	Ketamine (n=100)	P value	Placebo (n=99)	Ketamine (n=100)	P value
0	4.9±2.9	3.74±3.2	0.01*	6.0±2.7	4.7±3.3	0.002*
1	2.9±2.0	2.4±2.6	0.12	4.4±2.2	3.7±2.7	0.03*
6	1.9±2.0	1.5±1.7	0.07	3.8±1.8	3.2±2.0	0.04*

Data presented as mean ± SD. *, P<0.05. NRS, numeric rating scale; SD, standard deviation.

medications, there has been no corresponding reduction in the incidence and severity of chronic postoperative pain (23). Ketamine, functioning as a non-competitive NMDA receptor antagonist, specifically blocks NMDA receptors, modulates central sensitization, and offers anti-hyperalgesic effects. The concept of pre-emptive analgesia involves administering analgesic medications prior to the onset of nociceptive stimuli to prevent pain before it begins. But data for the pre-emptive use of ketamine are still inconsistent (12,13,24,25). Animal studies showed a pre-emptive administration of ketamine abolishes spinal processing of nociceptive inputs and prevents central sensitization of nociceptors by blocking NMDA receptors (11,26). Clinical studies could not confirm these findings fully and showed mixed results in matters of effectiveness. One reason might be, that if the analgetic regime provides adequate pain

Table 3 Resting and coughing pain scores according to NRS at days 1–8, 30, and 90 following surgery

POD	NRS (rest)			NRS (coughing)		
	Placebo	Ketamine	P value	Placebo	Ketamine	P value
1	1.1±1.4	1.1±1.3	0.96	3.3±1.4	3.1±1.7	0.57
2	1.2±1.5	1.1±1.5	0.70	3.3±1.6	3.2±1.8	0.72
3	1.0±1.4	1.2±3.5	0.75	3.0±1.4	3.0±1.5	0.15
4	1.0±1.3	0.6±1.0	0.054	2.9±1.5	2.5±1.5	0.12
5	0.9±1.2	0.7±1.2	0.35	2.7±1.6	2.4±1.7	0.22
6	0.8±1.2	0.7±1.3	0.73	2.5±1.4	2.4±1.7	0.60
7	0.6±1.0	0.7±1.0	0.78	2.4±1.5	2.7±4.4	0.48
8	0.6±1.0	0.5±1.1	0.78	2.2±1.6	2.0±1.6	0.43
30	0.5±1.1	0.3±0.8	0.60	2.1±0.8	0.9±1.5	<0.001*
90	0.3±0.8	0.2±0.8	0.40	1.8±1.6	0.6±1.3	<0.001*

Data presented as mean ± SD. *, P<0.05. NRS, numeric rating scale; POD, postoperative day; SD, standard deviation.

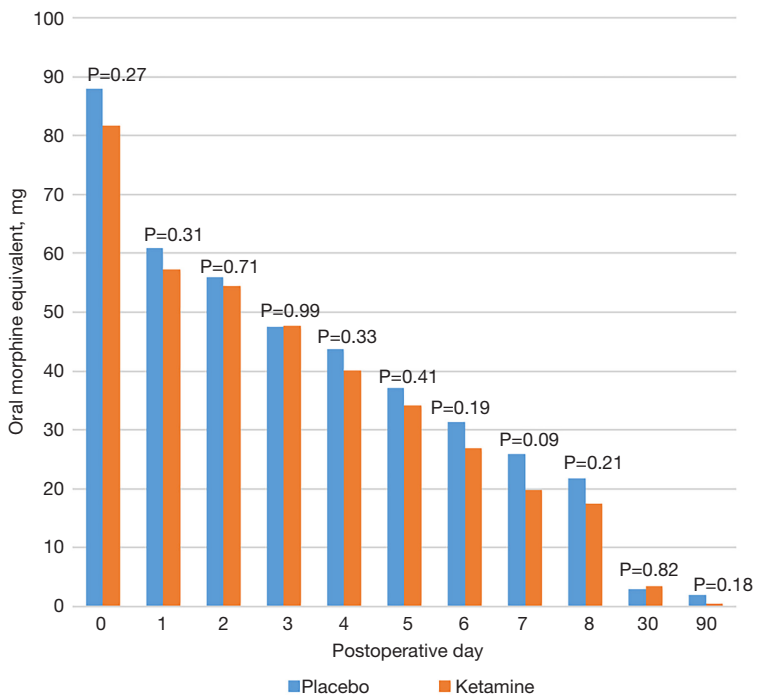

Figure 2 Postoperative opioid consumption.

relief, ketamine shows no additional effect. As the results in our study show the mean pain level (NRS) after surgery where only ≥4 in the early postoperative period (first 6 hours), additional ketamine application made a significant difference in this time period. The NRS scores on PODs 1–8 were below two at rest in the placebo group and three when coughing, so it is not remarkable we could not find an additional effect in the ketamine group on PODs 1–8. Our findings could also not confirm the opioid-sparing effect of ketamine which has been shown in previous studies like Bell

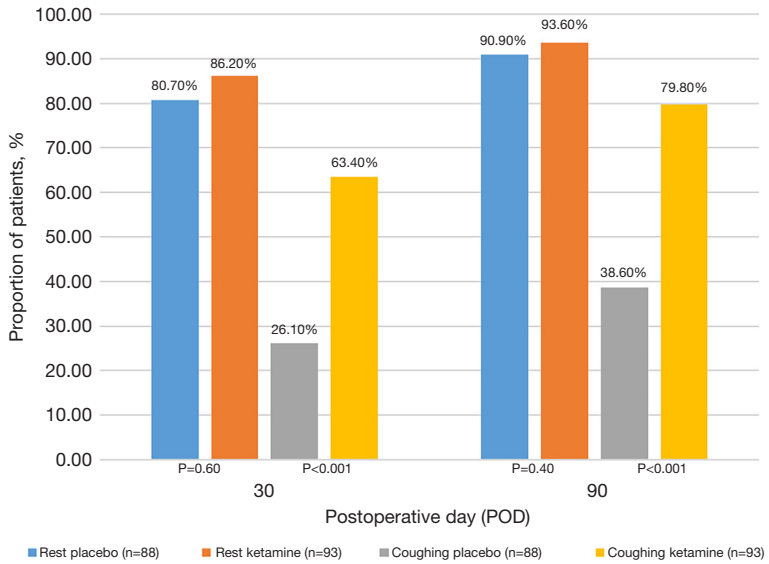

Figure 3 Proportion of patients with NRS =0. NRS, numeric rating scale.

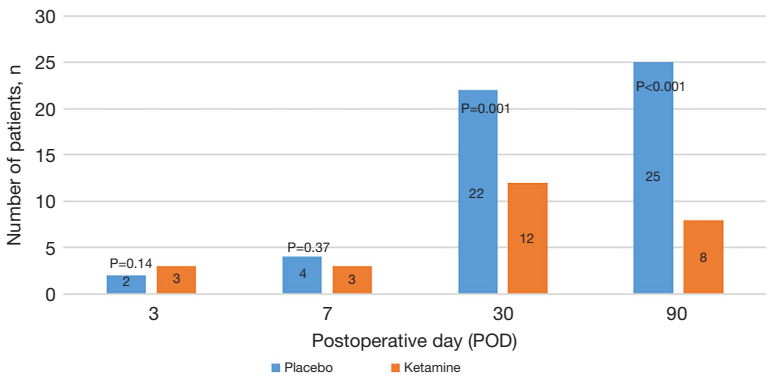

Figure 4 Number of patients with LANSS/S-LANSS ≥12. LANSS, Leeds Assessment Score for Neuropathic Symptoms and Signs; S-LANSS, Self-Assessment Leeds Assessment Score for Neuropathic Symptoms and Signs.

et al. and Subramaniam *et al.* (27,28).

The optimal dose of ketamine, as well as the best type of application, has not yet been established and is still a problem in comparing different studies. Most trials (12,13,29) used perioperative ketamine application in subanaesthetic doses (0.15–0.5 mg·kg^{-1} bolus, 0.06–0.12 mg·k^{-1}·h^{-1}). The duration of the ketamine application varied also from a single-dose approach to bolus and up to 96 hours ketamine infusion (24,25). We chose an intravenous dosing regimen with subanaesthetic ketamine (0.2 mg·kg^{-1} as bolus and 0.2 mg·kg^{-1}·h^{-1} for 24 hours). Given that patient types and surgical techniques can influence outcomes, our study exclusively enrolled patients undergoing posterolateral thoracotomy.

Another aim which should be achieved in the management of postoperative pain is still very challenging, it is preventing chronic pain. The probability of developing chronic pain increases when early postoperative pain is inadequately managed (30). Thirty days after surgery 2.3% of patients in the placebo group *vs.* 0 in the ketamine had a pain score of >4 at rest and 15.9% *vs.* 6.4% when coughing. Especially outstanding is the finding that 1 month after the operation 64% of the patients in the ketamine group had no pain at all (NRS =0) when coughing *vs.* 26% in the placebo group. Three months after surgery we found a similar pattern with 15.9% of the patients in the placebo group

suffered pain when coughing *vs.* 4.2% in the ketamine group. Twice as many patients in the ketamine group (79.8%) had no pain (NRS =0) when coughing than patients in the placebo group (38.6%). The overall incidence of chronic pain in our study was lower than reported in several studies (4,5), but are comparable to the study of Chumbley *et al.* (21). In this study as well as in our study the NRS scores in the first days after surgery where low, which might indicate a successful pain management regime. Intense postoperative pain is an independent risk factor for transition into chronic postoperative pain (25). Additional pre-emptive ketamine application in the perioperative period lowers significantly, especially under exertion, the incidence of chronic pain. A plausible explanation for persistent post-surgical pain involves the activation of NMDA receptors during the perioperative period. The administration of ketamine, an NMDA receptor antagonist, may mitigate this condition (21). This hypothesis aligns with our study findings, where the ketamine group exhibited a significant reduction in CPTP at PODs 30 and 90, despite no observed differences between the groups during the initial 8 PODs. In the literature, only few studies examined the incidence of chronic pain when using ketamine and even less examined neuropathic pain (4,25). As previously described in the literature, CPTP has a neuropathic component (4,7,8). Searle *et al.* (31) performed a study to find the incidence of CPTP and especially the neuropathic component. They searched one hundred patients undergoing video-assisted thoracoscopy or thoracotomy. Eighty-three percent of the patients received a regional anesthesia (paravertebral, epidural, or intercostal) which supposed to reduce the risk of chronic and neuropathic pain. The incidence of chronic pain was >50% and 22% of the patients developed neuropathic pain. We also addressed this issue in our study by adding the LANSS Score to the analysis. The results of our study are encoring half of the patients (12.8%) in the ketamine group suffered from neuropathic pain (S-LANSS score ≥12) 1 month after surgery compared to the 25% of patients in the placebo group. Three months after surgery the difference is even more distinct 8.5% in the ketamine group *vs.* 28.4% in the placebo group. A meta-analysis addressing this issue confirms our findings (32), but with low certainty. Main problem remains the main questions like ideal dosing and treatment duration remain still unanswered. Future research with large randomized controlled trials like the ROCKet trial (Reduction of Chronic Post-surgical Pain with Ketamine; ACTRN12617001619336: 4,884 participants, 12-month observation period) will hopefully provide more definitive evidence on this subject.

There are various limitations to our study, apart from the sample size calculation discussed above. The single-centre design of the study does make it difficult to generalize our findings. The number of patients with chronic pain was lower than in other studies and lower than we expected. We also did not ask explicit about vivid dreams and feeling lightheaded which are frequent adverse effects of ketamine.

Conclusions

Ketamine reduced the acute postoperative pain in the first 6 hours after surgery and also reduced significantly the incidence of post-thoracotomy pain syndrome after one and 3 months, but we were unable to detect any differences in the NRS scores in the first 8 days after surgery and we could not find any reduce in the opioid consumption.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-648/rc

Trial Protocol: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-648/tp

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the local ethics committee of University Hospital Mannheim of University, Heidelberg (No. MC2010-278-MA) and was registered at ClinicalTrials.gov (NCT 03105765). Written informed consent was obtained from all patients participating in this trial.

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