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ORIGINAL ARTICLE

A randomized, double blind, placebo controlled clinical trial of the preoperative use of ketamine for reducing inflammation and pain after thoracic surgery

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Abstract
Purpose We hypothesized that patients who received ketamine during thoracic surgery would benefit from suppression of the inflammatory cascade, represented by lower interleukin (IL)-6 and C-reactive protein (CRP) plasma levels.
Methods This study was a randomized, double blind, placebo controlled clinical trial of ketamine in patients undergoing thoracic surgery. The setting was a single university teaching hospital. Forty patients who presented to the preoperative clinic prior to thoracic surgery (20 control, 20 treatment) were randomized to receive either a 0.5 mg/kg ketamine bolus or an equivalent volume of normal saline intravenously prior to chest wall incision. Plasma samples taken prior to induction of anesthesia and at 24 h following surgery were assayed for IL-6 and CRP levels. Verbal pain scores were reported at 4 and 24 h following surgery and at discharge.
Results IL-6 plasma levels did not differ significantly at 24 h for patients receiving ketamine (245 ± 287 pg/ml, mean ± SD) compared to patients who received placebo (269 ± 210 pg/ml), $p = 0.39$. Additionally, CRP levels at 24 h were not significantly different (8.8 ± 4.5 mg/dl for ketamine, 9.3 ± 5.6 mg/dl for placebo patients), $p = 0.37$. Finally, verbal pain scores were not significantly different between patient groups at 4 or 24 h, or at discharge.
Conclusions These findings suggest that the routine use of a single dose of ketamine prior to chest wall incision is not effective at reducing pain or inflammation in thoracic surgery patients at 24 h postoperatively.

Keywords Ketamine · Thoracic surgery · Acute pain · IL-6 · CRP

Introduction

Complications after thoracic surgery are common and may arise as a result of an excessive inflammatory response to a surgical insult [1, 2]. For example, inflammation may play a significant role in the initiation and maintenance of atrial fibrillation, which occurs in 10–20% of patients following lung resection [3, 4]. The inflammatory response to surgery is characterized by a sequential release of different cytokines [5]. The later stage is characterized by a second wave of cytokine expression that includes interleukin-6 (IL-6). C-reactive protein (CRP) is an acute phase reactant that is synthesized by the liver in response to IL-6 stimulation and is considered to be a marker of total-body inflammation [6, 7]. The systemic inflammatory response to surgery has been studied in many surgical settings, and particularly in post-cardiopulmonary bypass patients [8–10]. In these studies, high levels of both IL-6 and CRP were found to be predictors of postoperative complications. In addition to cardiopulmonary bypass patients, serum levels of IL-6 and CRP in thoracic surgery patients also show marked increases postoperatively [11–13].

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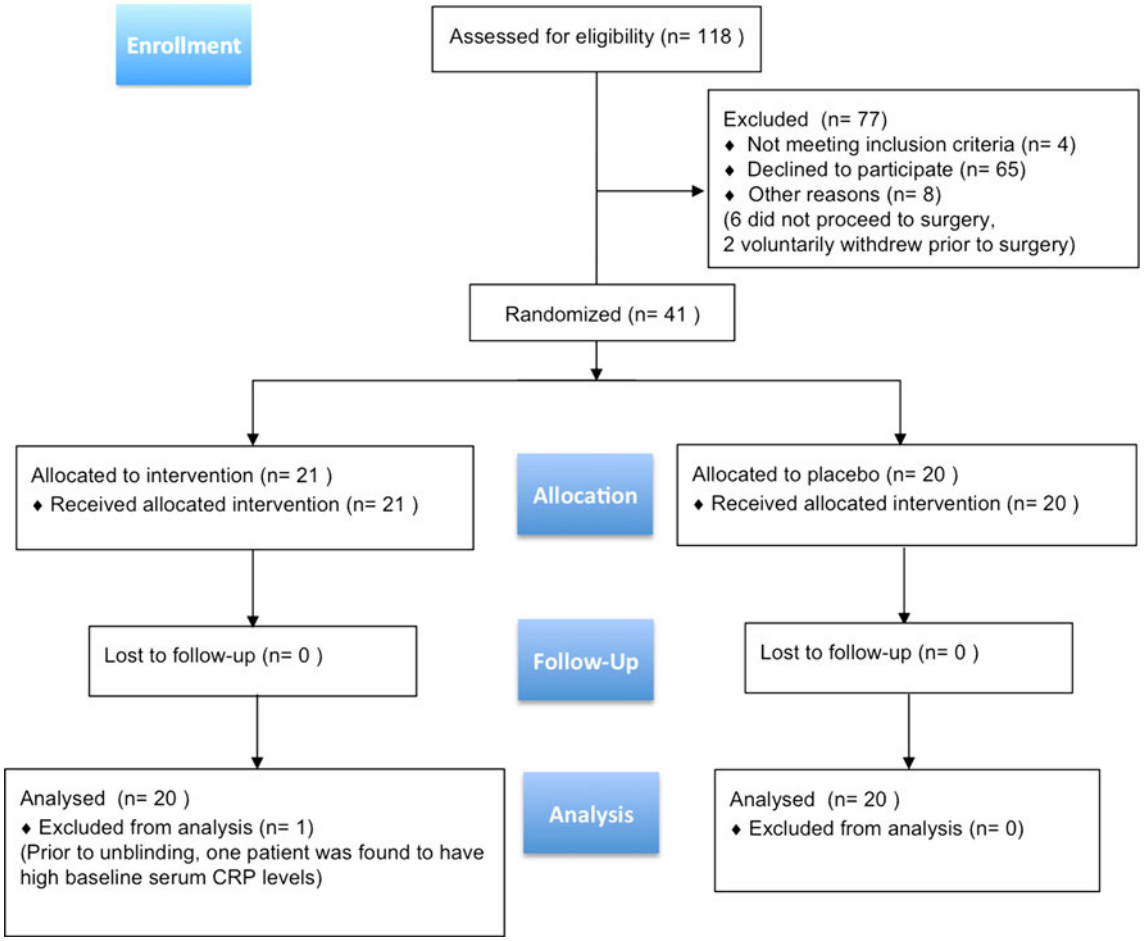

Fig. 1 Participant flow diagram. *CRP* C-reactive protein

In low doses, ketamine has been shown to exert anti-inflammatory effects, possibly by acting via inhibition of the nuclear factor kappa B pathway, to reduce cytokine expression [14, 15]. In previous studies of cardiac surgery patients, a singe dose of ketamine, administered following induction of anesthesia, significantly reduced postoperative serum levels of IL-6 [6, 16] and CRP [6]. Although ketamine reduced IL-6 and CRP plasma levels following cardiac surgery, no study has evaluated the effects of ketamine in general thoracic surgery. We hypothesized that ketamine would reduce IL-6 and CRP plasma levels postoperatively in thoracic surgery patients.

Patients, materials, and methods

This study was designed as a randomized, double blind, placebo controlled clinical trial of ketamine in patients undergoing lobectomy by video assisted thoracoscopic surgery (VATS) [17] or open thoracotomy at Duke University Medical Center, Durham, NC, USA. The trial is registered at ClinicalTrials.gov with number NCT00504725. Following Institutional Review Board (IRB) approval, patients scheduled for lobectomy at Duke University Medical Center were approached in the preoperative clinic. The assessment of eligibility occurred over 6 months. The participant flow diagram is shown in Fig. 1. Patients were excluded from the study for the following criteria: age less than 18 years, recent myocardial infarction (within 6 months), a history of psychotic disorder, uncontrolled hypertension, allergy to ketamine, an acute intracranial process, or evidence of uncontrolled intracranial or intraocular hypertension. Written informed consent was obtained from a total of 49 patients. Of these 49 patients, six patients did not proceed to surgery and two voluntarily withdrew from the study prior to surgery. Thus, a total of 41 patients were randomized to one of two parallel groups. In the first group, 21 patients received intravenous ketamine, 0.5 mg/kg, while the other 20 patients received an equivalent intravenous volume of normal saline.

Equal randomization was used with an allocation ratio of 1:1. Independent pharmacists dispensed the ketamine or the normal saline to the attending anesthesiologist for each

surgery according to a computer-generated randomization list. The anesthesia team was blinded to the medication, as the ketamine and normal saline were dispensed as clear liquids in syringes that were identical in appearance with no distinguishing markings. The study was not unblinded until all of the blood samples were retrieved and assayed. The anesthetic procedure was left to the discretion of the anesthesiologist, but was supplemented by an epidural catheter placement as needed to control pain. The surgical procedures were performed by one of three surgeons using similar techniques. The primary endpoint was the measurement of IL-6 serum levels. The study was designed to provide 90% power to detect a change in IL-6 of 20 pg/ml from a mean of 100 pg/ml, with two-tailed alpha = 0.05. Secondary endpoints included CRP serum levels, pain scores, and a cytokine panel.

Pain scores, rated by the patient on a scale of 0–10, were recorded preoperatively, postoperatively at 4 and 24 h, and prior to discharge. Blood samples were taken prior to surgical incision and at 24 h postoperatively. Serum samples were isolated from whole blood by centrifugation and then assayed for IL-6 and CRP levels. CRP levels were measured by the institutional laboratory using rate nephelometry. Cytokine serum levels were measured using a commercially available multi-cytokine detection system that utilizes dyed microparticles coated with analyte specific antibodies (Beadlyte; Upstate, Temecula, CA, USA) and a dual laser, flow-based sorting system (Luminex, Austin, TX, USA). The specific analytes assayed by the multi-cytokine detection system included: IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)-α, granulocyte macrophage colony stimulating factor (GM-CSF), and interferon-γ (IFN-γ). The cytokine detection range of the system was 6.9–5000 pg/ml. Individual differences in cytokine levels were analyzed by Student's *t*-test. Student's *t*-test and Fisher's exact test were used to analyze pain scores, and demographic, intraoperative, and postoperative data. Separate 2-way analysis of variance (ANOVA) tests were done on the ranks of the values of each cytokine, to test the effect of ketamine treatment. All the cytokines were tested as dependent variables. A p value of <0.05 was taken as significant.

Results

Twenty-one patients were ultimately randomized to receive 0.5 mg/kg of intravenous ketamine, while another twenty patients received normal saline as placebo. Only one protocol deviation occurred, in one female patient, during the study. Prior to unblinding of the study, she was removed when she was found to have CRP levels that were significantly higher at baseline compared to the other patients. It was later determined that the patient had active sarcoidosis. The demographics, comorbidities, and perioperative details of the remaining forty patients are presented in Table 1. Most placebo (95%) and ketamine-treated patients (80%) received epidurals, while the majority (55% ketamine, 70% placebo patients) received an intravenous anesthetic. Intravenous anesthetics consisted of a combination of propofol, dexmedetomidine, and remifentanil as determined by the anesthesiologist. The minority of patients received anesthesia by volatile anesthetics (isoflurane or sevoflurane). Ketorolac was given, either intraoperatively or within the first 24 h postoperatively, to 50% of placebo patients, and 60% of ketamine-treated patients. Intraoperative narcotic use was similar in the two groups.

As demonstrated in Table 1, although all of the patients were posted to receive lung lobectomy surgery preoperatively, several of the patients received only wedge resections (30% of the control patients, 20% of ketamine-treated patients). Additionally, two patients in the placebo group did not receive a lung resection; one patient received a resection of a diaphragmatic nodule, while another received a decortication and incurred a vascular injury that required a repair to the innominate vein. Overall, more patients in the ketamine-treated group received open thoracotomies (35%) compared to the control group (10%). No patients complained of hallucinations postoperatively. Adverse events recorded postoperatively included: chest tube reinsertion, atrial fibrillation/atrial flutter, return to operating room for bleeding, respiratory insufficiency, new oxygen requirement at discharge, small bowel obstruction, and small bowel ischemia. The adverse event rate was 40% for the placebo group and 45% for the ketamine-treated group. Both groups had three patients that were diagnosed with atrial fibrillation or atrial flutter postoperatively.

Figure 2 illustrates the results of the IL-6 and CRP plasma assays. IL-6 plasma levels were significantly elevated postoperatively, but levels in patients receiving ketamine (245 ± 287 pg/ml, mean $\pm$ SD) compared to levels in patients who received placebo (269 ± 210 pg/ml) did not differ significantly, $p = 0.39$. Likewise, serum CRP levels at 24 h were increased compared to preoperative levels, but they were not significantly affected by ketamine administration (8.8 ± 4.5 mg/dl for ketamine, 9.3 ± 5.6 mg/dl for placebo patients, $p = 0.37$). Minimal to no expression of IL-4, IL-12, TNF-α, and IFN-γ were found at both time points regardless of patient treatment. IL-1β, IL-2, and GM-CSF levels were detectable (averages of 40 pg/ml or less), but were not significantly changed 24 h after surgery and were not significantly influenced by ketamine administration. Small increases in IL-8 were detected at 24 h postoperatively, but these increases were not significantly affected by ketamine administration (11.3 ± 12.6 pg/ml for ketamine, 14.8 ± 10.8 pg/ml, $p = 0.18$).

Table 1 Patient characteristics and operative data

	Ketamine ($n = 20$)	Placebo ($n = 20$)	p
Age (years)	61 ± 12	66 ± 10	0.08
Gender (female/male)	9/11	8/12	0.75
Weight (kg)	81 ± 19	82 ± 18	0.41
Height (cm)	170 ± 8	171 ± 9	0.43
Hypertension (%)	30% (6)	50% (10)	0.33
Diabetes (%)	5% (1)	10% (2)	1.0
History of MI	0%	20% (4)	0.11
History of CVA	5% (1)	5% (1)	1.0
Creatinine—baseline (mg/dl)	0.9 ± 0.3	1.1 ± 0.5	0.1
Duration of surgery (min)	160 ± 52	150 ± 88	0.34
Anesthetic			
Intravenous	55% (11)	70% (14)	0.51
Volatile gas	45% (9)	30% (6)	
Surgical approach			
Open thoracotomy	35% (7)	10% (2)	0.13
VATS	65% (13)	90% (18)	
Surgical procedure			
Lobectomy	90% (18)	60% (12)	0.06
Wedge resection	10% (2)	30% (6)	0.24
Diaphragm nodule	0	5% (1)	1
Vascular repair	0	5% (1)	1
Diagnosis			
Malignant	95% (19)	85% (17)	0.6
Non-malignant	5% (1)	15% (3)	
Bronchoscopy	65% (13)	60% (12)	1
Mediastinoscopy	50% (10)	45% (9)	1
Ketorolac given	60% (12)	50% (10)	0.75
Epidural analgesia	80% (16)	95% (19)	0.34
Intraoperative			
Fentanyl (μg)	206 ± 103	177 ± 68	0.15
Hydromorphone (mg)	0.67 ± 0.53	0.55 ± 0.26	0.2
Remifentanil (μg)	0.88 ± 0.79	0.83 ± 0.46	0.45

Data are provided as means ± standard deviation or numbers (%). p value represents two-tailed unpaired value or Fisher's exact test with two-tailed p value

MI myocardial infarction, *CVA* cerebrovascular accident, *VATS* video assisted thoracic surgery

Similarly, small in increases in IL-10 were detected at 24 h, but again, these increases were not significantly changed by ketamine administration (3.0 ± 4.7 pg/ml for ketamine, 4.9 ± 5.8 pg/ml, $p = 0.14$). Overall, no significant difference was found in any cytokine in any of the tests between patients treated with ketamine compared to placebo. Cytokine levels were similar at baseline and at 24 h, and in amount of change. The multivariate ANOVA test for joint change likewise found no significant effect of ketamine treatment for all 10 cytokines together ($p = 0.18$). Finally, verbal pain scores were not significantly different between patient groups at baseline (0.30 ± 0.73 for ketamine, mean ± SD, 0.35 ± 1.35 for placebo patients, $p = 0.44$), 4 h (3.8 ± 2.1 for ketamine, 3.1 ± 2.8 for placebo patients, $p = 0.20$), 24 h (2.6 ± 2.2 for ketamine, 2.8 ± 2.1 for placebo patients, $p = 0.37$), or at discharge (1.8 ± 2.5 for ketamine, 1.1 ± 1.8 for placebo patients, $p = 0.15$). Pain scores were rated by patients on a scale from 0 to 10.

Discussion

This study was designed to determine whether ketamine could significantly decrease IL-6 levels in thoracic surgery patients. Pain scores, CRP levels, and a cytokine panel were also assessed as secondary endpoints. Similar to the earlier studies in thoracic surgery patients [11–13], significant rises in postoperative IL-6 and CRP serum levels were noted. However, this study failed to demonstrate any significant difference in IL-6, CRP, or pain scores in patients who were treated with ketamine prior to surgical

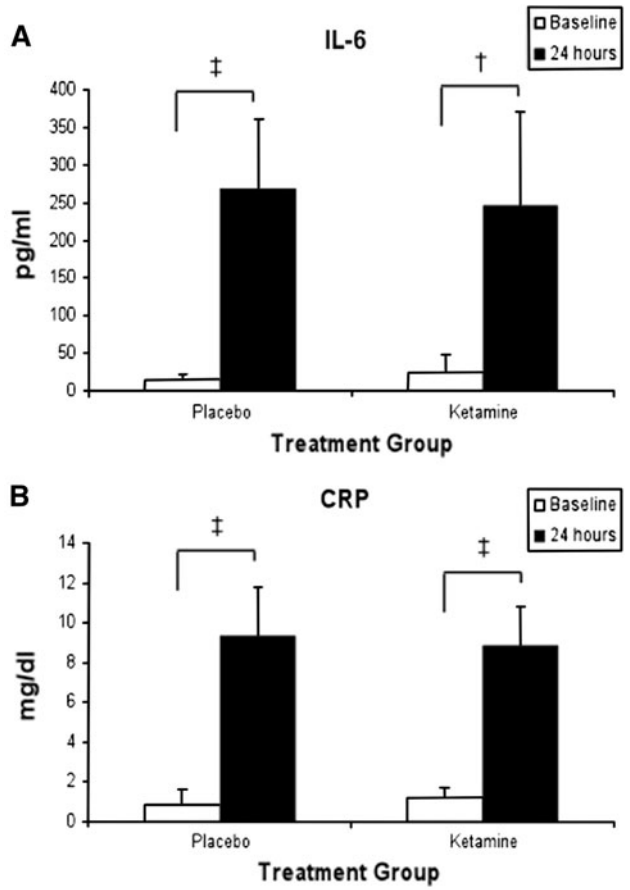

Fig. 2 Results of the interleukin-6 (*IL-6*) and C-reactive protein (*CRP*) plasma assays

incision. Conversely, two previous prospective studies in cardiac surgery patients reported attenuation of IL-6 levels with preoperative administration of ketamine [6, 16]. For example, Bartoc et al. [6] showed, in a randomized study of 50 cardiac surgery patients, that either a 0.25 or 0.5 mg/kg dose was sufficient to decrease IL-6 levels by 50% postoperatively.

One reason for the lack of ketamine effect in the present study compared to previous cardiac studies may be due to the inflammatory process initiated by cardiopulmonary bypass. Cardiopulmonary bypass is a well-known initiator of inflammation, and Bartoc et al. [6] showed that on postoperative day one the serum levels of CRP increased to over 80 mg/dl in bypass patients. These levels are almost tenfold higher than those found in our study. Cruickshank et al. [18] reported that IL-6 levels increased with increasing surgical trauma. However, the IL-6 levels detected in the present study were similar in magnitude to those found in cardiac surgery patients.

Although powered to detect changes in IL-6 based on studies in cardiac surgery patients, it is possible that our study was not powered to sufficiently detect a change in IL-6 in thoracic surgery patients. There does appear to be a trend towards a decrease in the medians of the IL-6 levels, but this trend is not statistically significant. The lack of change in IL-6 and CRP levels, combined with the lack of change in pain scores and complication rates argues that there is minimal, if any, effect of administration of 0.5 mg/kg ketamine prior to thoracic surgery. Furthermore, ketorolac administration resulted in a significant reduction in IL-6 and CRP levels.

We chose to measure serum levels of IL-6 and CRP at 24 h following surgery because in previous thoracic and cardiac studies, at 24 h, both IL-6 and CRP were expressed at high levels [6, 11–13, 16]. IL-6 levels peak between four and 24 h postoperatively in thoracic surgery patients, while CRP levels do not reach high levels until 24 h postoperatively, with a peak at 50 h [11–13]. Furthermore, previous studies of cardiac surgery patients demonstrated that ketamine significantly inhibited IL-6 and CRP serum levels at the 24-h time point [6, 16]. Additionally, a recent study in abdominal surgery patients reported inhibition of IL-6 levels by ketamine at 4 h, but not 24 h postoperatively [19]. However, the significance of lower IL-6 levels for only 4 h after surgery is not known. By comparison, in cardiac surgery patients, ketamine administration significantly decreased IL-6 levels for 7 days [16].

One additional factor that could have influenced IL-6 and CRP levels in our study was the higher number of open thoracotomies rather than VATS operations in the ketamine group. Several papers have reported decreased levels of IL-6 in patients who underwent VATS compared to those with open thoracotomies [11–13]. Craig et al. [11] also found lower CRP levels in VATS versus open thoracotomy. It is possible that the greater number of open thoracotomies in our ketamine-treated group might have raised the absolute levels of CRP and IL-6, potentially leading to higher values even after treatment with ketamine. However, although a greater number of open thoracotomies was performed in the ketamine-treated group, open thoracotomies were still performed in a minority of patients in both groups (35 vs. 10%).

In addition to measuring IL-6, we used a cytokine multiplex panel to measure a battery of other analytes including IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12, TNF-α, GM-CSF, and IFN-γ. It was expected that raised serum levels of transient early activated cytokines, such as TNF-α and IL-1β, might be dissipated at 24 h. Yim et al. [13] detected only minimal expression of TNF-α and IL-1β at all time points in their study of thoracic surgery patients. Similarly low levels were found in our study. TNF-α and IL-1β, unlike IL-6 and CRP, have not been shown to be related to a patient's clinical course [5]. Yim et al. [13] reported peak serum IL-8 and IL-10 levels at 4 h following surgery and then a decrease to almost baseline levels at

24 h. Data from the present study also show low IL-10 and IL-8 expression at 24 h. GM-CSF levels showed a declining trend at 24 h postoperatively, but this trend was not significant.

There were no significant between-group differences in acute pain scores following surgery in the present study. However, pain scores were a secondary aim of this study and the study may not have been powered efficiently to detect a change in pain scores. Overall, most of the patients had thoracic epidural catheters in place that adequately managed their pain postoperatively. We chose to administer a single dose of ketamine prior to surgery, as this was the dosing regime chosen in previous studies of cardiac surgery patients to maximize the anti-inflammatory effects of ketamine while avoiding the untoward side effects [6, 16]. Other studies, particularly studies studying pain as an outcome, often use a regime that includes a continuous ketamine infusion during the surgery [20]. Using an infusion of ketamine may be more effective at modulating postoperative pain, but other pain studies using a single dose of ketamine have been shown to be effective in helping to regulate postoperative pain [21].

As mentioned earlier, inflammation following thoracic surgery may have a significant influence on complications such as atrial fibrillation, which occurs after 10–20% of lung resection surgeries. The occurrence of atrial fibrillation following cardiopulmonary bypass has been well studied, and high levels of both IL-6 and CRP have been linked with the development of atrial fibrillation [4, 22–25]. The present study was not powered to measure complication rates postoperatively, but it was noted that the incidence of atrial fibrillation/atrial flutter was equal in both the placebo and ketamine-treated groups.

When administered at lower doses, ketamine provides analgesia but avoids much of the cardiovascular stimulation and psychotomimetic disturbance that is seen with higher doses [26, 27]. Conversely, opioids and local anesthetics appear to have little effect on stress-induced inflammation and IL-6 levels [16]. However, the results of the present study show that no significant effect was noted at 24 h with ketamine administration. Furthermore, no significant differences were noted in CRP levels, postoperative pain scores, or complications. These findings suggest that the routine use of a single dose of ketamine prior to chest wall incision is not effective at reducing pain or inflammation in thoracic surgery patients in the immediate postoperative period.

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