http://www.cjmb.org

Open Access Original Article

Crescent Journal of Medical and Biological Sciences
Vol. 8, No. 1, January 2021, 61–66
eISSN 2148-9696

# Comparison of Intrapleural Bupivacaine Versus Bupivacaine Plus Ketamine on Post-Thoracoscopic Pain Control: A Randomized Clinical Trial

**Reza Movassaghi[1], Abbasali Dehghani[1*], Samad Beheshtirouy[2]**

**Abstract**

**Objectives:** Considering the unwanted and undesirable side effects of opioid pain control after thoracoscopic surgery, the present study aimed to compare intrapleural bupivacaine vs. bupivacaine + ketamine on post-thoracoscopic pain control.

**Materials and Methods:** This randomized clinical trial study was performed on 60 candidates for thoracoscopy in Imam Reza hospital (Tabriz-Iran) during 2014-2016. The intervention was started after the random allocation of patients into control and intervention groups each containing 30 people. Before the surgery, patients in the control group received bupivacaine and those in the intervention group received bupivacaine + ketamine through an intrapleural catheter. Then, pain intensity and a need for an opioid after the surgery were measured in two groups based on visual pain criteria. The results of the two groups were compared by paired *t* test, chi-square test, and Mann-Whitney test using SPSS 23.

**Results:** Based on the results, the intensity of pain was significantly lower in the intervention group 6 ($P=0.032$), 12 ($P=0.049$), and 24 ($P=0.048$) hours after the surgery compared with the control group, and the amount of the consumed pethidine in both groups showed that the average pethidine consumption in the intervention group was significantly lower compared to the control group in the first ($P=0.009$), the second ($P=0.014$), the third ($P=0.031$), and the fourth ($P=0.02$) six hours after the surgery.

**Conclusions:** In general, intrapleural low-dose ketamine in combination with bupivacaine is effective in post-thoracoscopy pain control.

**Keywords:** Bupivacaine, Ketamine, Postoperative, Pain, Thoracoscopy

## Introduction

The beneficial effects of postoperative intrapleural analgesia have been confirmed in almost all studies. Therefore, an intrapleural analgesic method can be suggested as an acceptable and recommended method for patients treated with video-assisted thoracoscopic surgery (VATS) (1). The intravenous infusion of ketamine (The MNDS receptor antagonist) is a useful way of reducing acute pain and preventing acute post-operative pain after VATS and thoracotomy (2).

In a study conducted by Forcella et al, the efficacy of continuous intrapleural analgesia was compared with that of intravenous analgesia. Patients undergoing continuous intrapleural analgesia had better pain relief and control and discharged one day earlier from the hospital compared with the control group (3). In another study, patients undergoing intrapleural analgesia had better pain control and lower opioid infusion in comparison with the control group (4). It should be noted that performing VATS is developing and increasing in our centers, and the method of pain control in these patients is the traditional method of intravenous opioids, which is often accompanied by unwanted side effects and inadequate pain control (4,5).

On the other hand, other methods (e.g., the epidural thoracic method) are not risk-free compared to the analgesic needs of these patients (5). Consequently, it seems that the intrapleural method, which is technically easier and less dangerous than the epidural thoracic method, is a practically more appropriate post-surgical pain control technique. There is currently no study available on the effect of prescribing the combination of bupivacaine with ketamine in the intrapleural anesthetics method in acute pain control after thoracoscopy. Accordingly, the present study was designed to assess the beneficial effects of adding ketamine. From another point of view, one of the sub-goals of this study was to clarify the effect of this method for controlling shoulder referral pain, which did not subside in the intrapleural method with local antiesthetic. Given the unwanted and undesirable side effects of opioid pain control after thoracoscopic surgery, the present study sought to compare intrapleural bupivacaine vs. bupivacaine + ketamine on post-thoracoscopic pain control.

**Received** 18 August 2018, **Accepted** 10 September 2019, **Available online** 15 November 2019

[1]Department of Anesthesiology, Medicine Faculty, Tabriz University of Medical Sciences Tabriz, Iran. [2]Department of Thoracic Surgery, Medicine Faculty, Tabriz University of Medical Sciences Tabriz, Iran.
*Corresponding Author: Abbasali Dehghani, Tel: +98914162257, Email: adehghani7@gmail.com

Key Messages

- Thoracoscopy is extremely painful;
- Pain control is highly important after thoracoscopy without opioids;
- Bupivacaine + ketamine can be helpful in controlling pain after thoracoscopic surgery.

## Materials and Methods

### Study Design

This double-blind randomized clinical trial study was conducted on 60 patients undergoing elective thoracoscopy surgery with general anesthesia during 2014-2016 in Tabriz Imam-Reza hospital. The samples were sealed using the parcelled envelope and determined using a computer for identifying the scoring for both groups. The number of the sample size was estimated based on other studies such as Yoshika et al (6) and Ozyalcin et al (7). Finally, thirty patients were considered for each group. The inclusion criteria included male and female patients aged 18-60 years with the ASA classes I and II and of both genders. On the other hand, the exclusion criteria included patients with renal or liver failure, chronic hypertension, pregnancy, amiodarone users, recent thoracic infections, bupivacaine susceptibility, and opioid addiction. A convenience sampling method was used in this study Patients were then randomly divided (using the site http://www.randomizer.org) into two groups of control (bupivacaine = group B) and intervention (bupivacaine +ketamine = group BK).

### Procedure

After the insertion of the intrapleural catheter, group B received 5 cc of the bupivacaine solution (0.25%) with infusion per hour. Group BK received the bupivacaine solution (0.25%) 5 cc/h infusions plus ketamine 5 mg/h after the insertion of the intrapleural catheter. The combination of drugs was used in 2 groups after volume equalization. In the preoperative stage, patients were fully explained how the visual analogue scale (VAS) method was used in measuring pain severity. After induction anesthesia with fentanyl 2 µg/kg, midazolam 0.03 mg/kg, propofol 2 mg, and cisatracurium 0.15 mg/kg, the patients were intubated using a double lumen tube. The maintenance of anesthesia was performed with isoflurane 1-1.5% with liquefied $O_2$+N2O (50/50), and N2O was discontinued if the arterial oxygen saturation represented a decrease. Then, patients underwent one-lung ventilation after changing their positions from the supine to the lateral decubitus position. The necessary changes in this aspect were made in the regulation of the patient's ventilation. Three ports for thoracoscopy were installed for all patients. Standard monitoring was considered for all patients, including end-tidal $CO_2$, haemoglobin oxygen saturation, non-invasive blood pressure, health rate, and body temperature. All patients were given fentanyl 50 µg by venous blood infusion 10 minutes before the surgery. The single-lumen central venous line catheter was entered the intrapleural space with the absence of other portholes before patients went out of one-lung ventilation and were placed under the ventilation of both lungs through one of the ports. The port of the central venous line catheter was inserted through the skin by stitching it to the skin. Thus, bupivacaine or the combination of bupivacaine + ketamine was begun depending on the groups of patients. After the patient left the anesthetics and returned to consciousness, the first assessment of pain intensity began in all patients in the recovery ward, and this assessment and determination of pain intensity based on the VAS method processed every 6 hours and continued up to 24 hours after the operation. The patient's vital signs and postoperative complications were listed on the checklist, along with these symptoms. The severity of the patient's pain by the VAS method was recorded as well. In the event of pain occurrence and the need for treatment, pethidine was given at a 0.5 mg/kg dose intravenously. The required time for opioids and the frequency of opioid use were recorded for all patients. The presence of referral shoulder pain was recorded if present in any of the patients.

### Statistical Analysis

All data were recorded by the researcher in the data collection form. The severity of pain and side effects between the 2 groups of patients were evaluated and the two groups were compared by a paired *t* test, chi-square, and Mann-Whitney tests using SPSS, version 23. The *P*-value of less than 0.05 was considered statistically significant for all variables.

## Results

During the mentioned period, there were 93 patients, of whom 60 cases met the inclusion criteria. Of this number, individuals were placed in the intervention (n = 30) and control (n = 30) groups after random allocation. Then, the intervention was performed for all individuals who continued the procedure until the end of the study, Figure 1 shows the analyzed results related to all individuals.

This study was performed on 60 patients who were candidates for thoracoscopy. Three patients (two females and one male) were excluded from the study due to thoracoscopic transformation into thoracotomy during the surgery. The mean age, mean weight, and mean surgical duration (minutes) in groups BK and K were 35.36 ± 11.91 years and 36.24 ± 12.29 years; 74.71 ± 11.52 kg and 75.66 ± 11.15 kg; 76.43 ± 13.18 minutes and 78.79 ± 12.07 minutes, respectively. The frequency of males and females in groups BK and B was 27 and 1, as well as 27 and 2, respectively. There were no statistically significant differences regarding the age ($P = 0.784$), gender ($P = 0.513$), weight ($P = 0.766$), and the duration of operation ($P = 0.483$) among the two groups. Moreover,

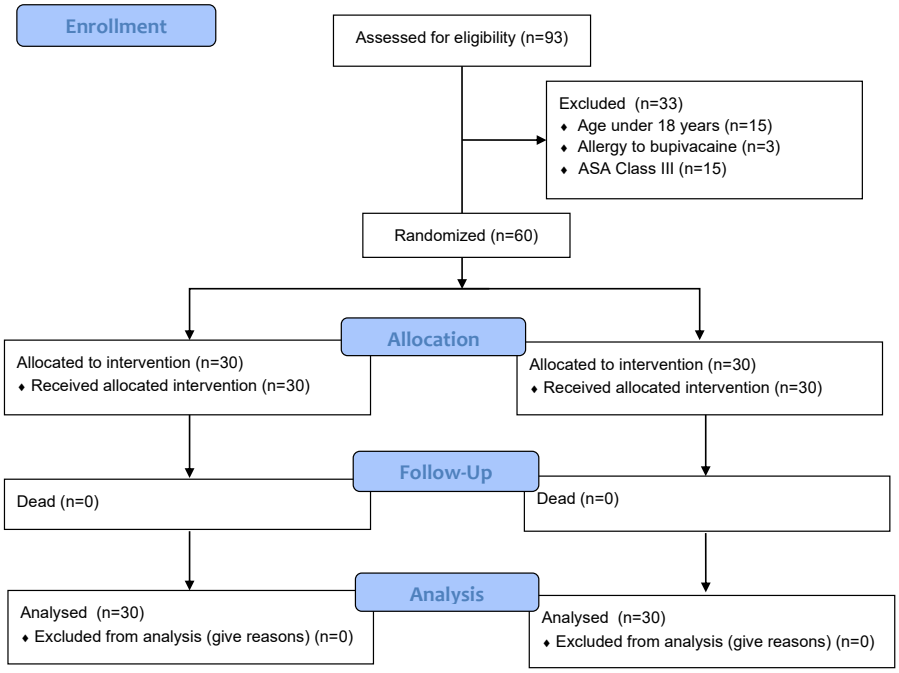


**Figure 1.** The Flow Chart of the Recruitment and Retention of Participants. Note. ASA: American Society of Anesthesiologists.

no significant difference was observed between the two groups in terms of heart rate although the systolic blood pressure in group BK was significantly higher than that of group B. The comparison of the mean blood pressure and heart rate of patients after the surgery in both groups is shown in Table 1.

The evaluation of pain intensity at different times indicated that patients had little pain immediately after the surgery. However, the intensity of pain 6 ($P=0.032$), 12 ($P=0.049$), and 24 ($P=0.048$) hours after the surgery was significantly lower in the intervention group compared to the control group. Conversely, pain intensity 18 ($P=0.112$) hours after the surgery was not statistically significant between the two groups (Figure 2).

The number of patients in group BK requiring analgesic pethidine with the used dose was equal to 8 (1 dose), 15 (2 doses), and 5 (3 doses) patients. In group B, 5 (1 dose), 12 (2 doses), 9 (3 doses), and 3 (4 doses) patients

**Table 1.** Comparison of Hemodynamic Status at Different Times Between the Two Study Groups

| The Studied Variable | Groups (N=60) | | *P* Value |
|---|---|---|---|
| | Control (n=30) | Intervention (n=30) | |
| Heart rate immediately after surgery | 85.23±8.23 | 86.59±7.50 | 0.411 |
| Heart rate in the first 6 hours | 80.41±7.45 | 83.56±6.19 | 0.219 |
| Heart rate in the second 6 hours | 75.15±6.36 | 77.26±6.13 | 0.118 |
| Heart rate in the third 6 hours | 72.30±7.01 | 68.14±6.69 | 0.219 |
| Heart rate in the fourth 6 hours | 70.59±6.14 | 71.59±6.60 | 0.559 |
| Systolic blood pressure immediately after surgery | 139.50±14.10 | 131.15±11.59 | 0.369 |
| Systolic blood pressure in the first 6 hours | 124.55±10.15 | 129.25±10.11 | 0.336 |
| Systolic blood pressure in the second 6 hours | 121.59±10.56 | 124.36±10.19 | 0.285 |
| Systolic blood pressure in the third 6 hours | 125.75±11.39 | 127.23±10.26 | 0.245 |
| Systolic blood pressure in the fourth 6 hours | 123.59±10.59 | 120.48±9.26 | 0.114 |
| Diastolic blood pressure immediately after surgery | 77.24±2.45 | 75.59±2.56 | 0.095 |
| Diastolic blood pressure in the first 6 hours | 73.41±2.26 | 71.15±2.63 | 0.114 |
| Diastolic blood pressure in the second 6 hours | 71.21±2.41 | 72.85±2.15 | 0.225 |
| Diastolic blood pressure in the third 6 hours | 74.45±2.36 | 76.25±2.41 | 0.369 |
| Diastolic blood pressure in the fourth 6 hours | 78.26±2.19 | 75.14±3.19 | 0.326 |
| $SpO_2$ immediately after surgery | 98.72±0.25 | 98.45±0.14 | 0.326 |
| $SpO_2$ in the first 6 hours | 96.25±1.10 | 98.85±0.78 | 0.114 |
| $SpO_2$ in the second 6 hours | 97.21±0.41 | 97.36±0.45 | 0.485 |
| $SpO_2$ in the third 6 hours | 97.41±0.12 | 97.14±0.96 | 0.315 |
| $SpO_2$ in the fourth 6 hours | 97.43±0.25 | 97.11±0.19 | 0.315 |

Note. $SpO_2$: Haemoglobin oxygen saturation.

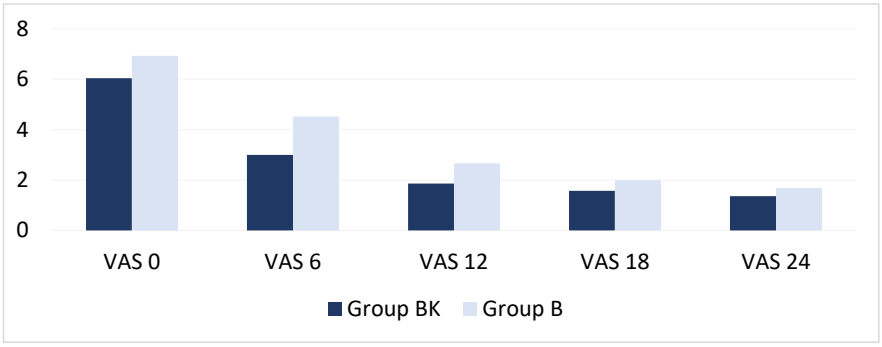


**Figure 2.** Comparison of Pain Intensity at Different Hours Between the 2 Study Groups.

received pethidine. The average time for the first dose of analgesia was 12.07 and 9.38 minutes in groups BK and B, respectively. The difference between the two groups was statistically significant at the time of receiving the first analgesic dose ($P=0.001$). On the other hand, there was no significant difference in the incidence of recurrent shoulder pain in patients between the two groups. Three and two patients in groups BK and B complained of shoulder pain, respectively.

The amount of the consumed pethidine in both groups showed that the average pethidine consumption in the intervention group was significantly lower compared to the control group in the first ($P=0.009$), second ($P=0.014$), third ($P=0.031$), and fourth ($P=0.02$) six hours after the surgery (Table 2).

## Discussion

Pain is a common and noticeable problem in postoperative patients. In the current study, pain intensity was measured by the VAS method every 6 to 24 hours, which was significant at 0, 6, and 12 hours although no significant difference was observed at 18 and 24 hours. Based on the results of a study by Naguib et al on patients with inguinal herniotomy, the number of patients having no or mild pain was higher in the ketamine use group with bupivacaine in the first hour after an operation compared to the group that received bupivacaine alone (8). In another study, Ilkjaer et al evaluated the effect of intravenous ketamine on postoperative pain control in patients undergoing renal surgery and reported no significant difference between ketamine and control groups in terms of postoperative pain during the onset of rest, the period moving from the supine position to the sitting position, and the sync cough (9). Similarly, Nesher et al examined the effect of adding ketamine to intravenous morphine in patients who were thoracotomy candidates. In this study, the mean postoperative pain by the VAS method was 3.7 and 5.6 in the ketamine plus morphine and the morphine-only groups, respectively (10). In their study on patients undergoing elective open-cholecystectomy, Roytblat et al investigated the effect of adding ketamine to the anesthetics regimen. Based on postoperative pain results by the VAS method, the rate of pain in patients undergoing ketamine therapy in the first 5 hours after the surgery was significantly lower in comparison with the control group (11). Likewise, Chia et al evaluated the effect of using epidural ketamine to control postoperative pain and found that pain in the control group by the VAS method was significantly higher compared to the ketamine group on the first and second day after the operation although there was no significant difference in pain between the two groups on the third day (12).

In our study, the time of receiving the first analgesic dose was compared in two groups, which was significantly longer in the ketamine group. In the study by Kararmaz et al regarding the effect of intravenous ketamine on epidural anesthesia, the time of receiving the first analgesic pain after the operation within the ketamine group was significantly longer when compared with the control group (13). However, the time to obtain the first dose of the analgesic in the ketamine group was statistically longer in our study, but it does not seem this small measure of time is a criterion and a strong argument for ketamine usage.

The number of patients receiving analgesic doses was recorded and compared in our study. In the ketamine group with bupivacaine, the number of doses received by patients was significantly lower than that of the bupivacaine-only group. Michelet et al also investigated the effect of adding ketamine to morphine on pain management after thoracic surgery and concluded that the morphine cumulative dose received 36 hours after the surgery was significantly lower in the ketamine group in comparison with the morphine-only group (14). In a study by Cook et al on patients nominated for orchiopexy,

**Table 2.** Comparison of Pethidine Consumption at Different Times After the Surgery Between the Two Study Groups

| Time | Groups (N=60) | | *P* Value |
|---|---|---|---|
| | Control (n=30) | Intervention (n=30) | |
| First 6 hours | 55.10±5.20 | 30.12±2.52 | 0.009 |
| Second 6 hours | 65.25±6.29 | 42.18±3.15 | 0.014 |
| Third 6 hours | 90.35±6.95 | 70.40±5.25 | 0.031 |
| Fourth 6 hours | 70.30±5.51 | 55.18±3.14 | 0.020 |

the number of analgesic doses received in the bupivacaine co-administered ketamine group was significantly lower compared to other groups. There was a bupivacaine group with clonidine and another bupivacaine group with adrenaline admission (15). In the study of Ozyalcin et al, which was based upon the effect of epidural and muscular ketamine on post-thoracotomy pain control after thoracotomy, the obtained morphine and bupivacaine in the epidural ketamine group was significantly lower than those of the muscular ketamine and control groups. Additionally, the amount of the received morphine in the muscular ketamine group was lower compared with the control group (7). According to the report of Kararmaz et al, the average total dose of analgesic in the first and second postoperative days in the ketamine group was significantly lower than that of the control group (13).

Given our study finding demonstrating that ketamine supplementation reduces the use of postoperative opioid analgesics, it seems this conclusion to be a good reason for ketamine usage.

In the present study, heart rate and blood pressure in patients after the surgery were also evaluated, and the results revealed no significant difference in the heart rate between the two groups. However, higher blood pressure after the surgery was recorded in the ketamine group in comparison to the other group.

Ketamine is a sympathomimetic agent which can increase both heart rate and blood pressure in addition to having sedative properties.

Nesher et al performed a study on patients who were candidates for thoracotomy. Accordingly, blood pressure and heart rate were compared in patients who received morphine and morphine plus ketamine although the results represented no significant difference between the two groups in this regard (10). In another study by Murali Krishna et al, postoperative pain relief was performed in patients undergoing lower extremity surgeries. Patients were divided into 3 groups and all groups receiving intrathecal bupivacaine, group 2 received ketamine, and group 3 received ketamine with midazolam. No patient in group 2 required mephentermine for hypotension treatment while 40% and 10% of cases in groups 1 and 3 needed this drug (16). Although the blood pressure between the two groups was statistically different in our study, there was no clinically significant difference.

## Suggestions for Further Research

The intrathecal injection of bupivacaine + ketamine is recommended for controlling pain after thoracoscopy. Further studies are required, including higher sample sizes and focusing on the effects of this intervention in the first three days after the surgery.

## Study Limitations

Low sample size, limited intervention to the first 24 hours after the surgery, uncertainty regarding the type and time of the surgery in different individuals were the limitations of the present study.

## Conclusions

In our study, one of the sub-goals was the evaluation of recurrent shoulder pain, which was not statistically significant in the two groups. It seems that the low dose of intrapleural ketamine is unaffected because of the lack of proper systemic effects in reducing this type of pain. No other studies reported the effect of ketamine on the recurrent pain of the shoulder.

### Conflict of Interests

The authors declared no conflict of interests.

### Ethical Issues

This study was approved by the Ethics Committee of Tabriz University of Medical Sciences (2014: Ethic No: 9323) and registered in the Iranian clinical trial system (identifier: IRCT201411203915N13). Written informed consent was obtained from all patients and no additional fee was charged for any of the patients. Patients participated in this study with full authority and their exclusion from this study was without any penalty.

### Financial Support

This study was financially supported and approved by the Ethics Committee of Tabriz University of Medical Sciences.

### Acknowledgments

The authors would like to thank Tabriz University of Medical Sciences for their kind support. It is noteworthy that the late Dr. Ali Peirovifar also played an important role in this study. The researchers of the present study wish his soul eternal peace.

### References

1. Mottaghi K, Safari F, Sezari P, Salimi A, Nashibi M. Effect of intrapleural meperidine on post-operative pain after open cholecystectomy. Tanaffos. 2019;18(1):79-83.
2. Kwon ST, Zhao L, Reddy RM, et al. Evaluation of acute and chronic pain outcomes after robotic, video-assisted thoracoscopic surgery, or open anatomic pulmonary resection. J Thorac Cardiovasc Surg. 2017;154(2):652-659.e651. doi:10.1016/j.jtcvs.2017.02.008
3. Forcella D, Pompeo E, Coniglione F, Gatti A, Mineo TC. A new technique for continuous intercostal-intrapleural analgesia in videothoracoscopic surgery. J Thorac Cardiovasc Surg. 2009;137(1):e48-49. doi:10.1016/j.jtcvs.2008.03.062
4. Demmy TL, Nwogu C, Solan P, Yendamuri S, Wilding G, DeLeon O. Chest tube-delivered bupivacaine improves pain and decreases opioid use after thoracoscopy. Ann Thorac Surg. 2009;87(4):1040-1046; discussion 1046-1047. doi:10.1016/j.athoracsur.2008.12.099
5. Kaplowitz J, Papadakos PJ. Acute pain management for video-assisted thoracoscopic surgery: an update. J Cardiothorac Vasc Anesth. 2012;26(2):312-321. doi:10.1053/j.jvca.2011.04.010
6. Yoshioka M, Mori T, Kobayashi H, et al. The efficacy of epidural analgesia after video-assisted thoracoscopic surgery: a randomized control study. Ann Thorac Cardiovasc Surg. 2006;12(5):313-318.
7. Ozyalcin NS, Yucel A, Camlica H, Dereli N, Andersen OK, Arendt-Nielsen L. Effect of pre-emptive ketamine on sensory changes and postoperative pain after thoracotomy: comparison of epidural and intramuscular routes. Br J Anaesth.

2004;93(3):356-361. doi:10.1093/bja/aeh220
8. Naguib M, Sharif AM, Seraj M, el Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: comparison with caudal bupivacaine. Br J Anaesth. 1991;67(5):559-564. doi:10.1093/bja/67.5.559
9. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB. Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth. 1998;81(5):707-712. doi:10.1093/bja/81.5.707
10. Nesher N, Ekstein MP, Paz Y, Marouani N, Chazan S, Weinbroum AA. Morphine with adjuvant ketamine vs higher dose of morphine alone for immediate postthoracotomy analgesia. Chest. 2009;136(1):245-252. doi:10.1378/chest.08-0246
11. Roytblat L, Korotkoruchko A, Katz J, Glazer M, Greemberg L, Fisher A. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg. 1993;77(6):1161-1165. doi:10.1213/00000539-199312000-00014
12. Chia YY, Liu K, Liu YC, Chang HC, Wong CS. Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesth Analg. 1998;86(6):1245-1249. doi:10.1097/00000539-199806000-00021
13. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz MA. Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. Anesth Analg. 2003;97(4):1092-1096. doi:10.1213/01.ane.0000080205.24285.36
14. Michelet P, Guervilly C, Hélaine A, et al. Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation. Br J Anaesth. 2007;99(3):396-403. doi:10.1093/bja/aem168
15. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. Br J Anaesth. 1995;75(6):698-701. doi:10.1093/bja/75.6.698
16. Murali Krishna T, Panda NB, Batra YK, Rajeev S. Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. Eur J Anaesthesiol. 2008;25(4):299-306. doi:10.1017/s0265021507002645