# COMPARISON OF THE EFFECTS OF INTRAPLEURAL BUPIVACAINE AND MORPHINE ON POST-THORACOTOMY PAIN

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**Background:** Post-thoracotomy pain is the most severe types of postoperative pain. This study compares the effects of intrapleural bupivacaine and morphine on post-thoracotomy pain.

**Methods:** In a double blind clinical trial study, 30 patients candidate for unilateral thoracotomy were randomly divided into bupivacaine and morphine groups. Patients in the morphine group received 0.2 mg/kg morphine and those in the bupivacaine group received 1 mg/kg bupivacaine by an intrapleural catheter placed at the end of surgery by direct vision. Intrarpleural morphine and bupivacaine continued every 4 hours for the next 24 hours. If required, systemic analgesia with morphine (patient-controlled analgesia, PCA) also used as a postoperative analgesic. The amount of morphine consumption and level of postoperative pain at 2, 6, 12 and 24 hours after surgery were recorded.

**Results:** Patients did not differ significantly in terms of age, gender and duration of surgery. There were no significant differences between the two groups with regard to their mean score of pain at 2 and 6 hours of the surgery; however, the level of pain was significantly lower in the bupivacaine group compared to the morphine group at 12 and 24 hours of the surgery. In the bupivacaine group, the mean level of intravenous opioid used over the 24 hours following surgery was significantly lower than in the morphine group.

**Discussion:** Intrapleural injection of bupivacaine can be more effective in reducing post-thoracotomy pain compared to intrapleural morphine.

## Introduction

Post-thoracotomy pain is the most severe types of post-operative pain and occurs in more than 70% of patients. Pain control and restoration of proper lung function is a primary objective in the post-thoracic surgery period[1]. By creating a vicious cycle of hypoventilation, discharge accumulation and atelectasis the pain causes hypoxia, hypercapnia and, consequently, progressive intrapulmonary shunt, and ultimately exacerbates the patient's problems[2]. In addition, the failure to properly improve pain leads to stressful postoperative responses and endocrine and metabolic

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disorders[3]. Given that most patients undergoing thoracotomy have underlying cardiopulmonary problems and are usually ASA (American Society of Anesthesiologists) III and IV, pain control becomes even more important[3]. Accordingly, some surgeons tend to use less harmful techniques such as muscle-sparing posterolateral thoracotomy or video-assisted thoracoscopy[4,5], while others focus on improving pain management techniques, such as the use of regional anesthesia, epidural anesthesia, and intravenous patient-controlled analgesia. Another pain management technique used is the intrapleural anesthesia - an effective simple technique with few side-effects[6,7]. In this technique a catheter is placed between the visceral and parietal pleura, which then exits through the skin and thus a permanent or intermittent anesthetic infusion is performed. Numerous studies have confirmed the effects of intrapleural bupivacaine and morphine on post-thoracotomy pain as well as their minimal side-effects[7,8,9]. Considering the different mechanisms of these two drugs and the potential side-effects of each, this study aims to compare the effects of intrapleural bupivacaine and morphine on post-thoracotomy pain.

## Methods

In a double-blind and random manner, 30 patients of ASA of class I-III aged between 18 and 80 years admitted to Shahid Beheshti hospital of Kashan for elective unilateral thoracotomy were selected. Patients with allergic reactions to local anesthetics, obesity (Body Mass Index greater than 40), significant central nervous system disease, who have pneumonia, empyema, or known pleuritic, with a history of alcohol, drugs, anticonvulsants, antidepressants, benzodiazepines, antihistamines consumption, as well as patients with liver and kidney failure were excluded.

Following the approval of the university's Ethics Committee and after obtaining the patients' informed consent, they were admitted to the operating theater and received 10 mg/kg Ringer's lactate solution intravenously. Premedication was performed with 0.05 mg/kg midazolam in addition to 2 µg/kg fentanyl. General anesthesia was induced using 5 mg/kg thiopental while 0.5 mg/kg atracurium was used for facilitating intubation. Anesthesia was maintained with 0.5%-1% isoflurane and 100% oxygen. Atracurium was repeated according to neuromuscular monitoring of the patient while fentanyl dosage was repeated every hour with the last does given 30 minutes before the end of surgery. Surgery was performed with a posterolateral incision on the 5$^{th}$ and 6$^{th}$ intercostal space. At the end of the surgery, an 18G epidural needle was inserted through the 1$^{st}$ intercostal space right above the incision line and a 20 G catheter was inserted into the pleural space at approximately 15 cm insertion level, the catheter was fixed to the parietal pleural while sutured to the skin. Two posterior or anterior chest tubes were then inserted. At this stage, the patients were divided into either morphine or bupivacaine group using the random number table. Prior to extubating the patient, the chest tube was blocked for about 15 minutes and the initial dose of both drugs were administered interpleurally. Patients in the morphine group received 0.2 mg/kg morphine sulfate while patients in the bupivacaine group received 1 mg/kg bupivacaine. After reversal of the muscle relaxant with 0.04 mg/kg atropine and 0.07 mg/kg neostigmine and ensuring proper ventilation, the patients were extubated and then transferred to the recovery room followed by admission to the ICU. Patients who required tracheal intubation after surgery were excluded from the study.

After 4 hours from first intrapleural injection, patients in the morphine group received 0.1 mg/kg morphine sulfate, while patients in the bupivacaine group received 1 mg/kg bupivacaine and continued to receive the drugs every 4 hours for 24 hours. In both groups, the chest tube was closed for 30 minutes prior to the administration of the drugs. Syringes containing equal volumes (40 ml) of drugs were prepared by trained nurse not involved in the study and administered by surgeon blinded to the contents and then the questionnaires were completed.

Patients in both groups received intravenous patient-controlled analgesia (PCA) with morphine (0.2mg/ml, 4 ml /hour background infusion, 1ml / 15 min bolus dose, lockout 15 minutes) with a PCA device for 24 hours postoperatively. Pain scores were calculated at 2, 6, 12 and 24 hours of the surgery (from hour zero of recovery) during the rest and deep breathing, using the Visual Analogue Score (VAS)[9].

Fifteen five patients per group was calculated

with a power of 80% for detecting a 50% difference in pain scores between the 2 study groups at a significance level of 0.05.

Demographic characteristics of patients, duration of surgery, the amount of morphine consumption, pain at 2, 6, 12 and 24 hours after surgery during the rest and the deep breathing were recorded and analyzed by SPSS software. Statistical tests of the T-test, and chi-square test was used. Data are presented as mean± standard deviation(Mean±SD). A p-value 0.05 was considered significant.

## Results

Patients demographics for both group were not statistically different (Table1).

There was no significant difference between the bupivacaine and the morphine group with respect to the mean scores of pain at rest and deep breathing at 2 and 6 hours after the surgery; however, the level of pain at rest and deep breathing was significantly lower in the bupivacaine group at 12 and 24 hours after surgery compared to the morphine group (Table 2) (Table 3).

## Discussion

Effective postoperative pain management is an integral part of the treatment procedure of patients undergoing thoracic surgery[10]. Several methods are used to relief pain after thoracotomy[11-14]. In this study we used intrapleural bupivacaine and morphine on post-thoracotomy pain The mean scores of pain at rest and deep breathing at 2 and 6 hours after the surgery in two groups were equal; however, the level of pain

*Table 1*

*Mean age, duration of surgery and sex in the two groups*

| group<br>Variable | Bupivacaine | Morphine | P-value |
|---|---|---|---|
| Age(Mean±SD) | 44.46±15.08 | 48.02±18.34 | 0.54 |
| Sex(Male/Female) | 18/12 | 16/14 | 0.1 |
| Duration of surgery (Mean±SD) | 108.4±10.41 | 105.73±5.71 | 0.08 |

*Table 2*

*Visual Analog Scores in the two groups after surgery at rest*

| group<br>Postoperative pain | Bupivacaine | Morphine | P-value |
|---|---|---|---|
| VAS at 2 hrs | 3.66±0.89 | 4.06±1.27 | 0.331 |
| VAS at 6 hrs | 3.73±0.79 | 3.80±0.77 | 0.81 |
| VAS at 12 hrs | 2.53±0.51 | 3.33±0.81 | 0.003 |
| VAS at 24 hrs | 1.73±0.59 | 2.53±0.74 | 0.003 |

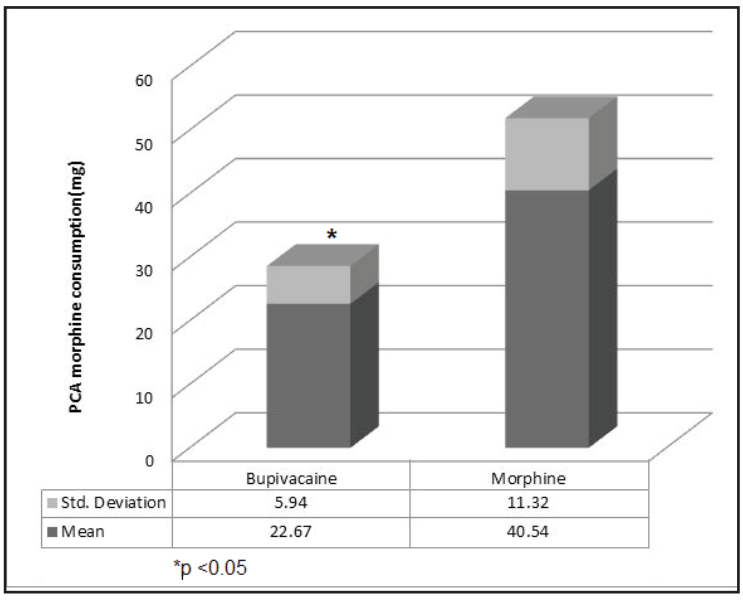
*Table 3*

*Visual Analog Scores in the two groups after surgery with deep breath*

| group<br>Postoperative pain | Bupivacaine | Morphine | P-value |
|---|---|---|---|
| VAS at 2 hrs | 4.20±0.77 | 4.66±1.06 | 0.43 |
| VAS at 6 hrs | 4.4±0.73 | 4.46±0.91 | 0.82 |
| VAS at 12 hrs | 3.13±0.63 | 4.20±0.56 | <0.001 |
| VAS at 24 hrs | 2.26±0.45 | 3.66±0.48 | <0.001 |

Morphine consumption with the PCA device (Mean±SD) was significantly lower in the bupivacaine group compared to the morphine group during the 24 hours period after surgery (Figure 1).

*Fig. 1*
*Morphine consumption with the PCA (Mean±SD) in the two groups during 24 hours after surgery*




at rest and deep breathing was significantly lower in the bupivacaine group at 12 and 24 hours after surgery compared to the morphine group. Morphine consumption was significantly lower in the bupivacaine group compared to the morphine group during 24 hours after surgery. In a study, Mann et al[16] used a 50 mg/kg of intrapleural bupivacaine every 4 hours for post-thoracotomy pain and succeeded in significantly reducing postoperative pain compared to the negative control group. In another study conducted by Mansuri et al[17] in order to control post coronary artery bypass pain, 20 ml 2.5%intrapleural bupivacaine (50 mg) was used prior to the surgery, which led to a lower postoperative pain in the bupivacaine group compared to the control group. In Kadkhodaie et al[18] study, patients received 2 mg/kg bupivacaine through the thoracic catheter post-thoracotomy and were compared the group that received intravenous pethidine. Results showed the same level of pain in both groups but greater complications in the pethidine group. On the other hand, other studies have investigated the effects of intrapleural opioids. Dabir et al[19] compared 0.2 mg/kg intrapleural morphine against intravenous morphine and showed that intrapleural morphine is more effective. Few studies have compared the effects of intrapleural opioids and bupivacaine. Esem et al[20] evaluated the effects of intermittent paravertebral intrapleural bupivacaine and morphine on pain management in patients undergoing thoracotomy and compared with intermittent systemic analgesia over a period of 72 hours. Pain score was lower in the morphine and bupivacaine groups compared with control group at all postoperative time points. After 6 and 24 hours, the level of pain was lower in the morphine group compared to the bupivacaine group. In a study by Dabir et al[21] intrapleural morphine resulted in greater pain reduction compared to the bupivacaine group. In the present study, however, no significant difference was observed in the analgesic effects of morphine and bupivacaine in the first 6 hours after surgery, but after 12 and 24 hours of the surgery, the level of pain was significantly lower in the bupivacaine group compared to the morphine group. For understanding the differences between the results of the present study compared to results of other studies, two major. First, a lower dose of morphine was used in the present study compared to other studies. The initial dose of intrapleural morphine used was 0.2 mg/kg, which was repeated at a dose of 0.1 mg/kg every 4 hours; however, in the studies by Dabir et al[19] and Esem et al[20], a 0.2 mg/kg dose of intrapleural morphine was used and repeated every 4 hours so that their maintenance dose of morphine was twice as in the current study. In the aforementioned studies, the higher dose of opioids used can justify the lower degree of pain in the morphine group compared to the bupivacaine group. Second, difference can also be attributed to the direct effects of opioids on pain terminals in the

pleural space. Many human and animal studies have shown that in addition to their central effects, opioids can also develop analgesia in surgery-damaged tissues by affecting the peripheral pain receptors at nerve endings. Another point that has been proved in human and animal studies is that the topical and systemic use of d, k and m receptor agonists and the endogenous opioids affect the damaged tissues more than the healthy tissues[22,23]. These opioid receptors are placed on the sensory neurons of small, medium and large diameters. Inflammation of peripheral tissues broadly acts as a regulator of opioid receptors in the sensory neurons, which increases the analgesic effects of opioids on the inflamed tissues. Therefore, in the first hours of neuron damaging, both the peripheral and central opioid receptors play a role in the management of postoperative pain[24].

As such, it seems that in the present study, during the first hours within surgery, morphine reduced the level of pain in the patients through both peripheral and central mechanisms. In the later hours, by reducing inflammation and eliminating the peripheral effects of intrapleural morphine, only its central effects remained involved in pain control. As a result, within 6 hours, the analgesic effect of intrapleural bupivacaine was greater than morphine's. This also supported is borne true by the lower amount of PCA opioid used by patients in the bupivacaine group.

## Conclusion

Results of the present study thus showed that the injection of intrapleural bupivacaine can be more effective in reducing post-thoracotomy pain compared to intrapleural morphine. Given that intrapleural bupivacaine does not increase the respiratory depression risk that is often associated with opioids, it can be a suitable pain management option for thoracic surgeries.

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