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Original Article

Analgesic Efficacy of Interpleurally Administered Morphine and Fentanyl After Posterolateral Thoracotomy

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Abstract

Pain control is a major concern in post-thoracotomy patients. The current prospective randomized double-blind study was designed to evaluate the analgesic effects of morphine and fentanyl given interpleurally after posterolateral thoracotomy. Thirty patients undergoing elective posterolateral thoracotomy in a teaching hospital in Tehran were divided into 3 groups with equal number of patients. Patients in group IPM, IPF_1 and IPF_2 received 0.1 mg/kg morphine sulfate, 5 μg/kg fentanyl and 2.5 μg/kg fentanyl in a total volume of 40 ml injected via an intrapleural catheter placed in the pleural space before the closure of chest. Subsequent doses of interpleural injections were administered at 4 and 8 h after operation. The intensity of pain was evaluated at rest and with coughing just before each interpleural injection and 30 min afterwards using a 10 point visual analogue scale (VAS). If patients needed additional analgesia, indomethacin suppository and intravenous morphine were given during the 20-h postoperative study period. In all of the 3 study groups VAS scores were significantly reduced 30 min after interpleural administration of the study solutions ($p<0.05$). However, inter-group comparisons revealed no significant differences for VSA scores, supplemental analgesic usage and systemic side effects. Briefly, interpleural morphine and fentanyl following thoracotomy produce equal analgesia without major side effects.

Keywords: Thoracotomy; Pain; Interpleural analgesia; Morphine; Fentanyl.

Introduction

Post-thoracotomy pain is one of the most distressing surgical experiences that is intensified by ventilation. Inadequate control of post-thoracotomy pain may cause shallow respiration and decreased cough leading to atelectasis and pulmonary complications. Thoracotomy can cause immediate severe pain in postoperative patients that may last for months or even years (1, 2, 3). Therefore, effective analgesia improves lung function and allows effective physiotherapy as well as early mobility after surgery. It could also reduce patients' morbidity.

Interpleural analgesia is induced by introducing drug into the interpleural space that lies between the parietal and visceral pleura. The mechanism of action appears to be diffusion of drug through the parietal pleura and the intercostal

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muscle to reach the intercostal space where blockade of multiple intercostal nerves occurs (4-6). Interpleural administration of opioids, in particular morphine, has been studied for the management of post-thoracotomy pain. The analgesic action of interpleurally administered morphine is probably attributed to a peripheral mechanism. It may act on opioid receptors in intercostal nerves producing analgesia with the least systemic adverse effects (7, 8). However, in the current literature there are publications providing evidence for and against of the effectiveness of this method (7-12).

In the present study, in patients undergoing elective posterolateral thoracotomy surgery we determined pain scores and additional systemic analgesic consumption to assess the analgesic efficacy of interpleural morphine and 2 different doses of fentanyl for their pain management. Drug doses were chosen based on the previous studies (8-10).

Experimental

This study was preformed in Masih Daneshvari teaching hospital affiliated to the Shaheed Beheshti Medical University, Tehran, Iran. This prospective randomized and double-blind study was approved by the hospital ethics committee. Patient informed consent was obtained before entering the study. 30 ASA (American Society of Anesthesiology) class I and II patients undergoing elective posterolateral thoracotomy were enrolled in the study. In the operation room, they were randomly categorized into three groups with equal sample size ($n_1=n_2=n_3=10$). Exclusion criteria were pleural adhesions and fibrosis, empyema, bullous emphysema, postoperative air leak through the chest tubes, contraindications to use non-steroidal anti inflammatory drugs (NSAIDs) and psychiatric diseases. Subjects less than 14 years of age, unable to cooperate, drug abused and opium addicts were also excluded from the study.

Oral diazepam (10 mg) was administered to all patients at the night before surgery. General anesthesia was induced with midazolam 1-2 mg, fentanyl 100-150 µg, sodium thiopental 5 mg/kg and atracurium 0.6 mg/kg. Patients were intubated with a double-lumen endobronchial tube. Anesthesia was maintained with halothane in oxygen, and atracurium. Bolus doses of fentanyl were given when needed.

At the end of surgery and before the chest closure, the surgeon inserted a 20-gauge epidural catheter (Portex Ltd., Hythe, UK-Epidural minipack system 2) percutaneously via a Tuohy needle from one intercostal space above the incision site. The catheter tip was placed in the pleural space on the paravertebral groove under direct surgeon vision. It was loosely sutured to the parietal pleura and skin. After closure of the chest and prior to tracheal extubation while patients were in supine position, the chest tubes were clamped. Identical syringes of trial solutions were injected into the pleural cavity through the interpleural catheter. The patients in the interpleural morphine group (IPM group) received 0.1 mg/kg morphine sulfate. Those in the number one interpleural fentanyl group (IPF_1 group) and in number two interpleural fentanyl group (IPF_2 group) received 5 µg/kg and 2.5 µg/kg fentanyl, respectively. Normal saline solution was used to prepare 40 ml of diluted solutions of each study drug. The chest tubes were kept clamped for 15 min after each interpleural administration while patients remained in the supine position. All patients were extubated in the operating room and admitted to the intensive care unit (ICU).

Subsequent bolus doses of the interpleural study solutions were administered 4 and 8 h after operation through the same technique. Upon patients demand for additional analgesic, indomethacin 100 mg was given rectally every 6 h. If analgesia was still inadequate, patients received intravenous morphine in increments of 2 mg.

Patients were monitored for 20 h after operation and their pain assessment was performed by the ICU nursing staffs that were unaware of patients' randomization. All drugs injected interpleurally were unknown to patients, surgeons, head nurses and those nurses monitored the patients.

The analgesic effect of the first interpleural injection was evaluated by patient's demand for supplemental analgesia during the first 4 h after operation. Furthermore, to evaluate the analgesic

efficacy of the second and third interpleural injections at 4 and 8 postoperative hours, patients were asked to evaluate the severity of thoracotomy pain by using a 10 point visual analog scale (VAS: 0-10; 0=no pain and 10= worst possible pain) (13). The pain scores were assessed at rest and with coughing just before and at 30 min after interpleural administrations. However, supplemental analgesic drugs were not given to the patients during the first 30 minutes following interpleural administrations.

Once again, after 8th postoperative hour (from 9th through 20th postoperative hours), patient's demand for additional analgesics was used to estimate the degree of analgesia. Total dose of supplemental analgesic usage was also documented for each patient during the 20-h postoperative study period.

Side effects (i.e., somnolence, nausea, vomiting, respiratory depression, pruritus and rash) were recorded hourly through the study period. Somnolence was assessed using a six point Ramsay sedation scale with scores of 1: anxious, agitated, restless; 2: cooperative, oriented, tranquil; 3: responds to commands only; 4: asleep, brisk response to stimulus; 5: asleep, sluggish response to stimulus and 6: unarousable (14).

A sample size of 10 patients per group would have 80% power to detect a difference between two points of pain scores amongst three study groups at the 5% significance level. Data analyses were performed using computer softwares of statistical package for social sciences (SPSS) version 11.5 and Microsoft Excel 2002. Differences between ratio data (e.g., age, body weight, and height), intraoperative fentanyl usage and surgery duration were analyzed using the analysis of variance (ANOVA) test. Differences between study groups regarding gender distribution, preoperative pain scores, pulmonary diagnosis, type of surgery, and postoperative complications (e.g., respiratory depression, pruritus, rash, nausea, and vomiting) were tested using the chi-square test. Comparison of the study groups for sedation scores was preformed using the Kruskal -Wallis test. Differences between the mean VAS scores within the groups before and after the administration of interpleural opioid solutions were evaluated using the Wilcoxon's signed rank test. Similarly the mean VAS scores of the study groups and the dose of supplemental analgesics consumption (intravenous morphine or indomethacine suppository) were compared using the Kruskal -Wallis test. The postoperative pain intensity (mean VAS scores $\geq$ and ≤ 3) and supplemental analgesic consumption were compared between male and female patients using the chi-square and *t*-tests, respectively. The $p < 0.05$ was considered as the significance level.

Results

From 30 enrolled patients, 13 were men and 17 women. Mean±SD age of patients was 42 ±16.5 years (range: 16 to 72 years). Despite randomization, the interpleural morphine group had significantly more female patients than the other study groups (Table 1). There were no significant differences regarding age, weight, height, duration of surgery and intraoperative fentanyl usage between the 3 groups (Table 1). Surgical procedures included wedge resection (n=1), mediastinal procedures (n=6), lobectomies (n=9), cyst excisions and enucleations (n=12), metastatectomy (n=1), and myotomy (n=1). Preoperative pain scores were the same for all groups.

After operation, mean VAS scores were significantly reduced 30 min after interpleural injections of morphine and fentanyl 2.5 and 5 µg/kg ($p < 0.05$). With regards to the analgesic effect of the first interpleural injection (assessed by supplemental analgesic use at initial 4 h postoperatively), there was no significant difference between the groups.

Inter-group comparisons revealed that there were not significant differences between mean VAS scores at rest and when coughing either before or after the interpleural administration of the study drugs at 4 and 8 hours after operation between the groups (Figure 1). Also, patients did not differ in terms of need for supplemental analgesics during the 9th through the 20th h after surgery and for total additional analgesic consumption (Table 2). Likewise, no significant difference was found in the number of patients who received intravenous morphine (9:9:9 in each group) and indomethacine suppository (9:10:10

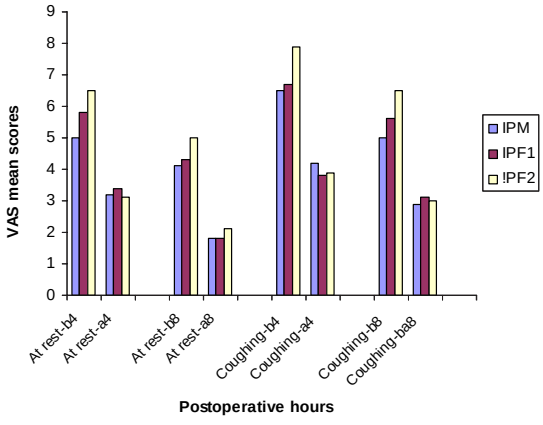

Figure 1. Visual analogue scale (VAS) mean scores before and 30 min after interpleural administration of morphine 0.1 mg/kg (IPM group), fentanyl 5 µg/kg (IPF_1 group), or fentanyl 2.5 µg/kg (IPF_2 group). Treatment significantly reduced mean pain scores in three groups, however no significant differences in pain scores were observed between groups. (b4, b8; before interpleural injection of study solutions at 4 and 8 postoperative hours. a4, a8; 30 min after interpleural injection of study solutions at 4 and 8 postoperative hours).

in IPM, IPF_1, IPF_2 groups, respectively).

The chi–square and t-test showed no significant difference between post operative pain scores of male (n=13) and female (n=17) patients at rest and with coughing as well as supplemental analgesic usage.

With regards to the incidence of side effects evaluated, i.e. nausea, vomiting and pruritus, there were no significant differences amongst the study groups (Table 1). No intervention was needed for symptomatic relieve of the side effects. No development of somnolence, respiratory depression and skin rash were also seen amongst any of the patients. Sedation scores did not vary significantly between groups (2.06 ± 0.16 in IPM group, 2.14 ± 0.24 in IPF_1 group, and 2.32 ± 0.7 in IPF_2 group). No catheter related complications (e.g. infection, rupture, displacement) were noted and all catheters were removed without difficulty.

Discussion

Pain is a serious complication in post–thoracotomy patients and its severity is exacerbated by respiration and coughing. Effective pain relief allows patients to take deep breaths and cough effectively. This may result in a reduction in atelectasis and pulmonary infection risk. Many attempts have been made to combine systemic drug administration with different kinds of regional anesthesia to improve post-thoracotomy pain control. A variety of techniques and agents have been shown to be effective for this purpose (2). However, most analgesic techniques carry the risk of concomitant complications associated with systemic drug administration or invasive procedures (e.g. epidural catheterization). Epidural analgesia is the most common route for post thoracotomy pain management. Moreover, the combination of opioids and local anesthetics through a thoracic epidural catheter is the most effective method for the treatment of pain after thoracotomy, however, one limitation to the use of epidural anesthesia is considerable skills and experience required for the placement of catheters and the management of patients. Furthermore, thoracic epidural catheter placement is more difficult than placement of a lumbar catheter. It is not also suitable in patients with spinal deformities or neurological disorders (2).

Opioids used by various routes of administration continue to be the mainstay of analgesia for post-thoracotomy pain, however their most effective and suitable administration route is controversial. After thoracotomy, pain therapy with systemic opioids has the potential for a good pain relief at rest but lacks effective pain reduction when coughing or breathing deeply. It is, however, well recognized that these drugs may cause adverse effects such as major respiratory depression, somnolence, prolonged nausea/vomiting as well as pruritus when administered via systemic or epidural route (15). Patients receiving epidural narcotics may also need to receive care in a setting that monitors their respiration (2).

Interpleural analgesia is reported to be an effective technique for post thoracotomy pain management (4, 6). This technique is analogous to the blockade of multiple intercostal nerves unilaterally. If the interpleural catheter is placed intraoperatively under direct supervision of surgeon, this technique will be safe and easy without the intrinsic risk of thoracic epidural blockade.

The current randomized double blind study was designed to evaluate analgesic effect of

Table 1. Patient characteristics, operation data, and postoperative complications in patients receiving interpleural morphine 0.1mg/kg (IPM group), fentanyl 5 µg/kg (IPF_1group), or fentanyl 2. 5 µg/kg (IPF_2 group).*

	IPM group *n=10*	***IPF_1 group*** *n=10*	***IPF_2 group*** *n=10*
****Sex (M/F)**	1/9	6/4	6/4
Age (yr)	40.9±19	40.4±16	43.8±15.7
Weight (kg)	64.4±8	70.4±14	70.4±10
Height (cm)	159±8.6	168±7.44	165.7±10.6
Surgery			
Lobectomy	1	4	4
Wedge resection	1	0	0
Cyst excision/enucleation	4	4	4
Mediastinal procedures	3	1	2
Metastatectomy	0	1	0
Myotomy	1	0	0
Diagnosis			
Malignancy	1	3	1
Benign pathology	9	7	9
Intraoperative fentanyl (µg)	230±85	220±105	220±50
Surgery duration (min.)	180±42.4	261.5±135	198±62
Postoperative complications			
Nausea	6	3	1
Vomiting	2	1	1
Pruritus	1	1	0

** Data are given as mean ± SD, or number. With the exception of sex, there were no statistically significant differences between the groups. The numbers of female patients were significantly higher in IPM group (p = 0.03).*
*** $p<0.05$ in IPM group versus IPF_1 and IPF_2.*
Abbreviations: F, femal; M, male.

interpleural administration of either 40 ml of 0.1 mg/kg of morphine or 5 µg/kg and 2.5 µg/kg of fentanyl after thoracotomy. Based on the obtained results, all of the interpleurally administered solutions could significantly reduce pain scores at rest and during coughing. Nonetheless, we could not find any difference in pain scores and supplementary analgesic requirements after operation for any of them.

The results of our study confirmed those reports that found analgesia significantly improved after interpleural administration of opioids in patients undergone a posterolateral thoracotomy (8-10, 12). Karakaya et al.

Table 2. Supplemental analgesic usage through 20-h postoperative study period in patients receiving interpleural morphine 0.1 mg/kg (IPM group), fentanyl 5 µg/kg (IPF_1group), or fentanyl 2. 5 µg/kg (IPF_2 group).

	IPM group	***IPF_1 Group***	***IPF_2 group***
Intravenous morphine (mg)			
0-4 postoperative hr	5.2±5.6	3±3.4	2.3±3
9-20 postoperative hr	2.4±3	4.4±5	3.4±2.5
Total consumption	8.8±7	8.4±8	6.3±3
Indomethacine suppository (mg)			
0-4 postoperative hr	190±99.44	150±108	160±84
9-20 postoperative hr	100±94	170±82	140±171
Total consumption	330±156.7	340±150.5	360±222

Data are given as mean±SD. There were no statistically significant differences between groups (p>0.05).

showed that after posterolateral thoracotomy, an interpleural bupivacaine, fentanyl and epinephrine combination improves pain relief better than interpleural bupivacaine alone (12). Aykac et al. found interpleural morphine (20 mg) more effective than the same dose given intravenously (8). Similarly, another study showed that 0.2 mg/kg of interpleural morphine could provide an effective analgesia after posterolateral thoracotomies without major adverse complications (9). In contrast, Welte et al. showed that 2.5 mg of interpleural morphine did not reduce post thoracotomy pain intensity (7). However, in their study, the dose of morphine was too low to relieve pain sufficiently. This could be led to an evident reduction in the concentration of morphine at the receptor sites because of its dilution in the pleural space and the drainage of drug from the chest tubes (16, 17).

Moreover, our study showed a low and clinically insignificant incidence of opioid related side effects. This finding may suggest a peripheral action for interpleural opioids. However, to support this hypothesis, opioid blood levels should be measured in future studies. Aykac et al. found differences in the analgesic and safety profile characteristics of interpleural and intravenous administration of morphine so that, patients receiving intravenous morphine had higher morphine plasma levels as well as higher serious systemic adverse effects than those receiving interpleural morphine (8).

In addition, in the current study, since there was an unequal distribution of the sex within the groups, we also analyzed the relationship between gender and postoperative pain intensity. Our results showed that pain either at rest or during coughing and also additional analgesic usage were not related to gender. Our findings are in some measures in accordance and in some in contrast with findings of Silomone et al. (18). They showed that supplemental opioid demand was similar in both sex. As well, pain intensity was not significantly different in both sexes during coughing. On the other hand, they also found that pain scores at rest were significantly higher in women undergone posterolateral thoracotomy. Furtheremore, there is evidence indicating greater pain severity in women than men. The possible mechanism for this difference remains unclear (19).

In conclusion, it seems that interpleural morphine and fentanyl administration is an effective route to obtain analgesia that can also provide equal pain relief without major systemic side effects.

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