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Effects of Interpleural Morphine on Severity of Post-Thoracotomy Pain

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Background: Thoracotomy is one of the most painful surgical procedures because of the extent of surgical insult.
Objectives: The aim of this study was to evaluate the effect of interpleural morphine on pain after thoracotomy.
Patients and Methods: An experimental and a randomized double-blind study were designed to assign 31 patients in Masih Daneshvari Hospital, Tehran, Iran. In 16 patients, 0.2 mg/Kg morphine sulfate in 40 mL of 0.9% normal saline (N/S) was injected via interpleural (IP) catheter, after surgery. Meanwhile, 10 mL of 0.9% normal saline was administered intravenously (IV) [interpleural morphine (Ipm) group]. In 15 patients, 40 mL of 0.9% N/S IP and concurrently morphine sulfate 0.05 mg/kg in 10 mL of N/S IV were injected [interpleural sulfate (Ips) group]. After the first injection in the operating room, infusion of the aforementioned solutions was repeated every four hours, for 24 hours in ICU. The severity of pain was measured according to the facial pain scale (FPS), before drug injection and 30 minutes after it was evaluated.
Results: The results of the proportional odds marginal regression model showed significant difference between the opium and Ips groups ($P = 0.024$), adjusting for baseline pain scores, sex, age and time of the measurements. The reported odds ratio of the group variables was 4.18, showing that the odds of having no pain in the Ipm group were 4.18 times of the same odds in the Ips group. The negative estimation for the variable of time showed that the severity of pain decreased over time in these patients.
Conclusions: In general, our findings revealed that administration of interpleural morphine can cause effective and favorable analgesia after thoracotomy.

Keywords: Thoracotomy; Interpleural Analgesia; Pain Management

1. Background

Thoracotomy is one of the most painful surgical procedures because of the extent of surgical insult. It has been shown that 5%–80% of patients still have thoracic pain two to three months after surgery, lasting even up to seven years (1-4). These problems can be more severe in obese or elderly people, smokers, and those with existing pulmonary diseases (5, 6). Postoperative pain control after thoracotomy can decrease postoperative pulmonary complications, such as mucous plugging, hypoxia, ventilation-perfusion mismatch, and pulmonary infections. Inadequate pain control after thoracic procedures can result in increased morbidity, length of stay, and delay in overall recovery (7-9).

To provide solutions for alleviating the pain improving the quality of life, many studies have been carried out in various fields (10-12). Systemic opioids, regional techniques, and adjuvant therapies are all used to manage pain. Intrapleural administration of bupivacaine has been recommended for post-thoracotomy analgesia, because it may produce unilateral conduction blockade of multiple intercostal nerves without applied-like side effects (13-15). Interpleural analgesia is induced by introducing drug into the interpleural space, which lies between the parietal and visceral pleura. The mechanism of action appears to be diffusion of the drug through parietal pleura and intercostal muscle to reach the intercostal space, where blockade of multiple intercostal nerves occurs. Interpleural administration of opioids, particularly morphine, has been studied for management of post-thoracotomy pain (16-18).

Recent studies have shown that opium has peripheral analgesic effects, by activating the opioid receptors located on peripheral nerves, without producing significant systemic side effects. Therefore, interpleural morphine injection may also induce analgesia directly via activation of opioid receptors on intercostal nerves. Different results have been obtained in different studies considering the analgesic effect of interpleural morphine and its side effects. Some researchers doubt the efficacy of this method (19).

2. Objectives

Our aim in this study was to compare the effects of two

injection of interpleural morphine on patients' pain, after thoracotomy.

3. Patients and Methods

3.1. Study Participants

In this double-blind randomized trial, 36 patients were recruited to verify the effect of interpleural morphine on post-thoracotomy pain management. The patients were selected by simple random sampling in Masih Daneshvari Hospital, Tehran, Iran. They were candidates for thoracotomy of various selective intrathoracic surgical procedures with the American Society of Anesthesiologists (ASA) class I-II. The inclusion criteria were as follows: age > 12 years, weight > 30 kg, lack of mental retardation, using no alcohol and drugs, no depression and psycho disorder, absence of pleural diseases (inflammation, fibrosis, destructive lesions, bronchopleural fistula, bullous emphysema, empyema, and pleural adhesion), and lack of coagulopathies. The exclusion criteria were tachypnea and dyspnea and increasing air leakage from alveoli at the end of surgery. There were no limitations in gender, height, duration and type of surgery, lung pathology, and location and type of thoracotomy incision (17, 20-22).

This study was attested by the ethical committee of the hospital, and informed consent was obtained from each participant. The procedure of post-thoracotomy analgesic induction and its possible complications were explained to each patient. After their approval, a written consent was obtained from each patient.

3.2. Interventions

After closure of the thoracotomy incision, prior to full recovery and endotracheal extubation, the patients were placed in supine positions. Afterwards, chest tubes were clumped for 15 minutes. In the interpleural morphine (Ipm) group, 0.2 mg/kg morphine sulfate in 40 mL normal saline (N/S) interpleurally (IP) and 10 mL of 0.9% N/S concomitantly were administered. In the interpleural sulfate (Ips) group, 40 mL of 0.9% N/S IP and 0.05 mg/kg morphine sulfate in 10 mL N/S IV were similarly administered. The dose of administered morphine was calculated based on earlier studies (23). The patients remained in supine position for 15 minutes, and then clumps of the chest tubes were removed. After reversing the muscle relaxant action using atropine 0.03 mg/kg and neostigmine 0.07 mg/kg, all the patients recovered from anesthesia, were extubated and transferred first to the recovery room and then to the ICU.

After the first IP injection (time zero), the following injections were carried out every four hours: for 24 hours in the Ipm and Ips groups through the aforementioned method, without considering the pain severity (at postoperative hours 4, 8, 12, 16, 20, and 24). The interpleural catheter was pulled out after 24 hours and the location was dressed, then the evaluation was stopped.

3.3. Randomization and Blinding

Using NCSS PASS 11 software procedure menu, DOE submenu, and with simple randomization, numbers 1 to 36 were randomly divided into two groups, Ipm and Ips. Drug syringes were prepared by a technician who was not participated in this study and they were injected by personnel who were not aware of the types of drugs. Throughout the study, only one fixed nurse who did not have any information about drug interactions participated in the evaluation of pain severity and side effects of drugs in patients and completed the questionnaires. The patients and attending nurses were not aware of the types of drugs used in ICU. Therefore, this was a double blind study to ensure that the obtained results were dependable and free of any subjective bias.

3.4. Main Outcome and Other Variables of the Study

The patients' age, BMI and gender were registered. The faces pain scale (FPS) was used to assess the efficacy of treatments (24, 25). FPS was designed in the anesthesia department of this center for evaluation of pain in illiterate patients, including the ones with low socioeconomic status, which comprised a significant percentage of patients in this center, some of which were immigrants and refugees of the neighboring countries like Afghanistan. FPS was prepared as published pages and shown to the patient by the researcher in resting position before and 30 minutes after interpleural injection. After that, the patient was evaluated for pain severity by pointing to one of the face features, and the pain score was recorded on the basis of linear scale. This pain scale was defined as: no pain (score 0), mild (scores 1-3), moderate (scores 4-6) and severe (scores 7-10) (26). The pain was postoperatively evaluated in resting position as follows: first 30 minutes after the first IP injection (time zero) in the recovery room, then every four hours in the resting position before interpleural injection and 30 minutes after that (in hours 4, 8, 12, 16, 20, and 24, postoperatively) in the ICU, using FPS.

3.5. Statistical Analysis

For descriptive purposes, we used a frequency table for the qualitative variable (sex). In addition, the quantitative variables (age, BMI) were summarized using statistical indices such as mean and standard deviation. For analytical purposes, independent samples t-test, chi square test, and Mann-Whitney test were applied. K-S and Shapiro-Wilk tests were used for assaying the normality of quantitative variables. Moreover, the proportional odds marginal regression modeling (POMRM) approach and generalized estimating equation (GEE) methodology with autoregressive(1) (AR(1)) correlation structure were used to assess the concurrent effect of explanatory variables on repeated ordinal outcome variables (27-30). Data were analyzed using SAS 9.2 for Windows software (SAS® Cary, NC) and $P < 0.05$ were considered statistically significant.

Table 1. Comparing Different Characteristics of Patients in Ipm and Ips Groups [a]

Characteristic	Ipm Group	Ips Group	P Value
Sex			0.27 [b]
Male	9 (56.2)	11 (73.3)	
Female	7 (43.8)	4 (26.7)	
Age, y	41.5 ± 15.24	41.06 ± 15.43	0.93 [c]
BMI, kg/m^2	25.68 ± 3.99	23.23 ± 3.46	0.051 [c]

[a] Data are presented as mean ± SD or No. (%).
[b] Chi-square test result
[c] Independent sample t-test result

Table 2. Comparison of the Pain Severity at Six Time Points in Ipm and Ips Groups [a]

Pain Severity	Ipm	Ips	P Value [b]
4 hours			0.007
None	1 (6.2)	0 (0.0)	
Mild	12 (75.0)	3 (20.0)	
Moderate	3 (18.8)	10 (66.7)	
Severe	0 (0.0)	2 (13.3)	
8 hours			0.002
None	3 (18.8)	0 (0.0)	
Mild	11 (68.8)	4 (23.5)	
Moderate	2 (12.5)	11 (64.7)	
Severe	0 (0.0)	2 (11.8)	
12 hours			0.002
None	2 (12.5)	0 (0.0)	
Mild	11 (68.8)	5 (33.3)	
Moderate	3 (18.8)	7 (46.7)	
Severe	0 (0.0)	3 (20.0)	
16 hours			0.037
None	2 (12.5)	0 (0.0)	
Mild	12 (75.0)	8 (53.3)	
Moderate	2 (12.5)	5 (33.3)	
Severe	0 (0.0)	2 (13.3)	
20 hours			0.004
None	4 (25.0)	0 (0.0)	
Mild	11 (68.8)	8 (53.3)	
Moderate	1 (6.2)	6 (40.0)	
Severe	0 (0.0)	1 (6.7)	
24 hours			0.003
None	5 (31.2)	0 (0.0)	
Mild	10 (62.5)	10 (66.7)	
Moderate	1 (6.2)	4 (26.7)	
Severe	0 (0.0)	1 (6.7)	

[a] Data are presented as No. (%).
[b] Mann-Whitney test result

Table 3. Results of Proportional Odds Marginal Regression Modeling Approach and Generalized Estimating Equation Methodology Methodology With Autoregressive (1) Correlation Structure

Variables	Estimate	SE	OR	P Value
Group				0.024
Ipm	reference category	reference category	reference category	
Ips	1.43	0.64	4.18	
Baseline				< 0.05
None	Reference Category	reference category	reference category	
Mild	0.876	0.89	2.40	
Moderate	1.23	0.92	3.42	
Severe	1.56	1.03	4.76	
Sex				0.339
Female	Reference Category	reference category	reference category	
Male	0.56	0.59	1.75	
Time	-0.54	0.19	-	0.004
Age	-0.003	0.14	-	0.853

4. Results

In this trial, of 36 patients, two from the Ipm group and three from the Ips group were excluded according to the criteria. The remaining patients with mean age of 41.28 ± 15.12 were studied. No significant differences were found between the two groups regarding age, BMI, and gender (Table 1). Table 2 displays the descriptive statistics for the reported severity of post-thoracotomy, by patients at different times. At each time point, Mann-Whitney test showed that the pain severity in the Ipm group was significantly lower than that of the Ips group. The results of POMRM with AR (1) correlation structure showed a significant difference between the opium and Ips groups (P = 0. 024), adjusting for baseline pain scores, sex, age, and time of measurements (Table 3). The reported odds, 4.18, for the group variable showed that the odds of having no pain in the Ipm group was 4.18 times more than the same odds in the Ips group. The negative estimate for the variable of time showed that the severity of pain decreased over time in these patients.

5. Discussion

Research examining analgesia efficacy following thoracotomy is essential to ensure that optimum postoperative care is provided to patients. Perineural opiate injection can induce analgesia via occupying the opioid receptors located on peripheral nerves without prevalent side effects. Morphine is diffused from the pleural space into the intercostal space in interpleural morphine injection, causing intercostal space, leading to intercostal nerves blockage and analgesia by activating the opioid

receptors located on intercostal nerves (19, 31-33). Our study showed that subjects who received interpleural morphine every four hours could maintain analgesia at a favorable level. Several studies have reported that interpleural morphine is effective for pain relief after thoracotomy. Scheinin and colleagues reported a significant decrease in opiate consumption during the first postoperative day in patients receiving interpleural analgesia plus oxycodone supplementation, compared with the control group who received systemic oxycodone alone (34). Another study demonstrated that interpleural morphine and bupivacaine 30 minutes after each injection decreased the pain scores significantly. However, in the interpleural morphine group, the pain scores and supplementary analgesic requirements were significantly lower. Pain management with interpleural morphine was better than interpleural bupivacaine after a posterolateral thoracotomy (35). Our findings supported other positive results of interpleural administration of opioids in patients undergoing thoracotomy (36, 37).

As a final recommendation, although we can guess that administration of interpleural morphine for 24 hours can be effective for pain relief after thoracotomy; further investigations should be performed on analgesia duration of interpleural morphine. In general, our findings demonstrated that administration of interpleural morphine can cause effective and favorable analgesia after thoracotomy.

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Authors' Contributions

Study concept and design: Neda Gilani, Shide Dabir. Acquisition of data: Mehdi kazempour Dizaji, Shide Dabir. Analysis and interpretation of data: Neda gilani, Farid Zayeri, Anoshirvan Kazemnejad. Drafting of the manuscript: Neda Gilani, Farid Zayeri, Anoshirvan Kazemnejad. Critical revision of the manuscript for important intellectual content: Shide Dabir, Anoshirvan Kazemnejad. Statistical analysis: Neda Gilani, Farid Zayeri. Administrative, and technical and material support: Shide Dabir, Anoshirvan Kazemnejad.

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