EFFECT OF INTERPLEURAL MEPERIDINE WITH AND WITHOUT BUPIVACAINE ON POSTOPERATIVE PAIN AFTER STERNOTOMY

Omid Aghadavoudi[(1)], Parvin Sajedi[(2)], Hamid Saryazdi[(3)]

Abstract

INTRODUCTION: No unique technique has proved efficient enough in controlling post cardiothoracic surgery pain. A variety of agents and techniques have been used to control pain following cardiothoracic surgery; interpleural regional analgesia is one such technique.

OBJECTIVE: There are many nerve endings in the pleural cavity. The local anesthetic action of meperidine administered interpleurally was evaluated in this study.

METHODS: In a double blind clinical trial, 90 patients undergoing coronary artery bypass graft surgery were randomized into four groups as intravenous meperidine (G1), interpleural meperidine (G2), interpleural meperidine and bupivacaine (G3) and interpleural bupivacaine (G4) groups. At the end of surgery, interpleural catheter was placed in all groups and the medication was prescribed. In the cardiac intensive care unit, narcotic requirements and pain scores were registered. Collected data were analyzed by appropriate tests including t-test and chi-square test. P values below 0.05 were considered as significant.

RESULTS: There were no significant differences in age, weight, sex and ASA (American Society of Anesthesiologists) class between the four groups. At all time periods, the pain levels measured by the visual analogue score (VAS) were significantly lower in the G3 and G4 groups ($P<0.05$). The total narcotic requirements in the first 24 hours of postoperative period were significantly lower in the G3 and G4 groups ($P<0.05$).

CONCLUSION: In spite of analgesic effects of subarachnoid meperidine, intraarticular morphine and interpleural bupivacaine, interpleural meperidine does not change pain scores or narcotic requirements postoperatively.

Keywords: Meperidine, bupivacaine, postoperative, pain, thoracic surgery, cardiac surgical procedure..

***ARYA Atherosclerosis Journal* 2007, 3(3): 147-150**

Date of submission: 21 Sep 2007, ***Date of acceptance:*** 12 Oct 2007

Introduction

Post-thoracotomy pain is one of the most severe forms of pain after surgery and can deteriorate postoperative ventilatory function.[1] The pain associated with thoracotomy incisions can be difficult to target and quantify. Prior studies have evaluated chest tube pain, incisional pain, visceral pain and pain at rest or associated with coughing or movement. Due to the multiplicity of nociceptive inputs from these sites, postoperative pain may be difficult to control with single modalities.[2]

A variety of agents and techniques have been shown to be effective analgesics with varying degrees of functional success. These include systemic opioids, NSAIDs, ketamine, regional analgesia (including epidural, spinal, paravertebral, intercostals and interpleural) and cryoanalgesia.[2,3]

Interpleural regional analgesia has recently been introduced for the treatment of pain due to a number of conditions, including rib fractures, pancreatitis and postoperative pain from mastectomy, cholecystectomy and renal operations. In addition, this technique has been evaluated in patients who have undergone thoracic procedures.[3]

1) MD. Assistant Professor, Anesthesiology and Critical Care Dept. Chamran Heart Hospital, Isfahan University of Medical Sciences and Health Services (IUMS), Isfahan, Iran. Telephone: +983116246813, E-mail: aghadavoudi@med.mui.ac.ir
2) MD. Associate Professor, Anesthesiology and Critical Care Dept, IUMS, Isfahan, Iran.
3) MD. Assistant Professor, Anesthesiology and Critical Care Dept, IUMS, Isfahan, Iran.

Corresponding author: Omid Aghadavoudi

Interpleural analgesia is thought to occur through various mechanisms including diffusion of local anesthetic through the parietal pleura and the innermost intercostals muscles reaching the intercostals nerves where blocking occurs, blockage of the intrathoracic sympathetic chain and direct action of local anesthetic within the pleura.[2,3]

On the other hand, morphine and other opioids have been injected in the vicinity of practically every peripheral nerve and many joints to assess theirs analgesic efficacy.[4] In a meta-analysis intraarticularly administered morphine has a definite and mild analgesic effect.[4] Also in one study, it was demonstrated that bilateral interpleural analgesia using a mixture of bupivacaine 0.5% and morphine may offer satisfactory analgesia for upper abdominal surgery.[5]

The local anesthetic properties of meperidine appear to be superior to those of other opioids. The effects of meperidine appear to be produced by its actions on two independent pathways: the opioid receptor pathways which subserve analgesic action, and the sodium channels which subserve local anesthetic action.[6] Interestingly, the effect of meperidine on the nerve fiber subgroups may vary. The local anesthetic actions of meperidine appear to be equivalent to those of lidocaine after subarachnoid administration.[6-8]

This study was designed in view of the multiplicity of nociceptive inputs in thoracic surgery, the presence of many nerve endings in the pleura, and analgesic effect on nerve endings.[9] The aim of this study was to evaluate the efficacy of interpleural meperidine with and without bupivacaine and also to assess the possible systemic effect of peripherally injected meperidine on post-sternotomy pain relief.

Materials and Methods

In a clinical trial approved by the Research Ethics Committee of Isfahan University of Medical Sciences 96 patients with physical status II and III according to the classification of the American Society of Anesthesiologists (ASA) who were candidates for undergoing coronary artery bypass graft (CABG) surgery were selected using the convenience sampling method. Informed consent was obtained. Patients were not included in the study if they had addiction and/or a history of drug allergy to local anesthetics or narcotics.

Before induction of anesthesia, visual analogue score (VAS) was determined for each patient. All patients underwent the prescribed anesthetic protocol for preparation, induction and maintenance of anesthesia. Following administration of 1.5 mg/kg of lidocaine and 4 μg/kg of fentanyl, induction of general anesthesia was accomplished with 5 mg/kg of thiopental sodium and 0.1 mg/kg of pancuronium. Maintenance anesthesia included isoflurane (1-2%) and oxygen (100%) before cardiopulmonary bypass (CPB) and continuous infusion of midazolam and fentanyl during CPB.

At the end of surgery, interpleural catheter was placed by surgeon through the fifth intercostal space at the left mid-axillary line and the content of one of the coded syringes was injected into the interpleural space. The patients were randomized into four groups according to computer generated tables to receive intravenous meperidine (1.5 mg/kg) in group1 (G1), interpleural meperidine (1.5 mg/kg) in group 2 (G2), interpleural meperidine (1.5 mg/kg) and bupivacaine (2 m/kg) in group 3 (G3), and interpleural bupivacaine (2 mg/kg) in group 4 (G4). For the purpose of study blindness, total volume of injected solutions was increased to 25 ml by adding normal saline. The chest tubes were blocked for the first 15 minutes after injection of the solution.

During the first 24 hours in the cardiac intensive care unit, patients were observed by a blinded investigator in order to record the narcotic requirements, pain scores according to VAS, homodynamic parameters, and arterial CO_2 pressure. Vital signs including heart rate and blood pressure were recorded at 1, 2, 3, 4, 6, 12 and 24 hours after operation. Respiratory rate, arterial blood gas results and VAS scoring were recorded 6, 12, and 24 hours postoperatively after weaning from mechanical ventilation. Postoperative narcotic requirements during the first 24 hours were also registered.

At the end of the study the codes given to four groups were opened and collected data were processed and analyzed by SPSS statistical package and appropriate tests including ANOVA, Duncan, chi-square, Kruskal-Wallis and multiple comparison tests. To assess for statistically significant differences in postoperative pain levels between the four groups, ANOVA and Duncan tests were applied. Results are expressed as means ± standard error of mean (SEM) and statistical significance is considered at a P value less than 0.05.

Results

Ninety-two patients (23 in each of 4 groups) completed the study. Preoperative patients' characteristics are shown in Table 1. Overall, 83.3 % of the patients were male.

The groups were well matched according to demographic and operative details. There were no significant differences in age, weight, sex and ASA class between the four groups (Table 1). In addition, there

were no differences in duration of anesthesia and surgery.

As documented by ANOVA and Duncan tests, at all time periods, the pain levels measured by VAS score were significantly lower in the G3 and G4 groups (receiving the interpleural bupivacaine with or without meperidine) than in the G1 and G2 groups (receiving intravenous or interpleural meperidine) (Table 2).

The time of first analgesic requirement was not significantly different between the four groups. The need for further analgesia was examined by measuring the number of patients receiving morphine and the average dose administered in those who received the drug. Supplemental morphine was administered if the patient had VAS score of more than "2". The total narcotic requirements in the first 24 hours of the postoperative period were significantly lower in the G3 and G4 groups (Table 2). Pain scores and narcotic requirements were not different between the G1 and G2 groups and also between the G3 and G4 groups. There were no significant differences between the nausea scores and the number of patients who had vomiting postoperatively in the four groups. At all time periods, the postoperative hemodynamic parameters including systolic, diastolic and mean arterial blood pressures and heart rate changes were not different between the groups. The differences of respiratory rate and arterial CO_2 pressures between the groups were not significant (Table 3).

TABLE 1. Demographic parameters in the four groups.

Study groups	G1	G2	G3	G4	Test	P value
Sex (female/male)	4/19	4/19	3/20	6/17	$\chi 2$	>0.05
Age (y/o)	54±2	56±1.7	56±2.2	59±1.9	ANOVA	>0.05
ASA (II/III)	5/18	4/19	4/19	5/18	$\chi 2$	>0.05

Note: Data are presented as means± standard error of the mean or percentages.

TABLE 2. Postoperative variables in the four groups.

Study groups	G1	G2	G3	G4	Test	P value
VAS (6h)	4.8± 0.2	4.9±0.2	2.6±0.1	3.2± 0.2	Kruskal-Wallis	<0.001[a]
VAS (12h)	3.9±0.1	3.8±0.1	1.6±0.1	2.1±0.1	Kruskal-Wallis	<0.001[a]
VAS (24h)	2.5±0.1	2.8±0.1	1±0.1	1.2±0.1	Kruskal-Wallis	<0.001[a]
24h-morphine (mg/kg)	0.2±0.07	0.2±0.07	0.1±0.1	0.1±0.03	ANOVA, Duncan	<0.05[a]

Note: Data are presented as means± standard error of the mean or percentages.
[a]The differences were significant between G1 and G2 compared with G3 and G4 according to multiple comparison tests.

TABLE 3. Respiratory rate (RR) and arterial PCO_2 changes during the postoperative period.

Study groups	G1	G2	G3	G4	P value
RR (0h)	17.9± 3	17± 3	18±2	18±3	>0.05
RR (6h)	19± 3	19 ±3	20±2	20±3	>0.05
RR (12h)	20± 3	20±3	20±3	19.5±2	>0.05
RR (24h)	20± 3	20±2	19±3	20±2	>0.05
PCO_2 (0h)	38± 1.6	37±2	37.8±2	38±1.8	>0.05
PCO_2 (6h)	36± 5	34±3	36.8±4	37±8	>0.05
PCO_2 (12h)	37.5± 4.5	36.4±3	37±4	39±4.7	>0.05
PCO_2 (24h)	37.7± 3.4	36.8±5	37±3	37±3.5	>0.05

Note: Data are presented as means± standard deviation.
Arterial PCO_2 numbers are presented as mmHg.

Discussion

This study used a multimodal analgesic approach by using interpleural meperidine or bupivacaine or both. The interpleural administration of meperidine had not been previously studied, but the local anesthetic properties, as well as the opioid analgesic effects of meperidine made it an ideal drug for the present

study. In this study, the administration of interpleural bupivacaine resulted in significantly lower pain scores than interpleural meperidine. Postoperatively, the pain scores were not significantly reduced by equivalent doses of either interpleural or intravenous meperidine.

Schulte-Steinberg et al. examined pain after laparoscopic cholecystectomy in patients receiving intraperitoneal morphine and found no analgesic effects. In their study, neither intraperitoneal nor interpleural morphine produced significant analgesia after laparoscopic cholecystectomy, whereas interpleural bupivacaine was effective but not intraperitoneal bupivacaine.[10]

The opioid chosen for this study was meperidine rather than morphine or fentanyl, because of its dual local anesthetic and analgesic properties. Aside from producing a local anesthetic effect, meperidine has also been shown to potentiate the degree of block produced by other established local anesthetics.[7,11] There is no evidence to prove this additive effect in this study.

The effects of interpleural meperidine in this study may result from systemic activity, because the results are the same in the G1 and G2 groups. It is absorbed from the pleural cavity and has a central analgesic action.

An important aspect of this investigation is that we studied patients undergoing sternotomy who might have lost the drug through the chest drains, but the chest tubes were blocked for the first 15 minutes after injection of the solution.

An additional issue that has to be considered is that meperidine's access to opioid receptors may be restricted in the pleural cavity. Peripheral antinociceptive effects of opioid agonists are brought about by an interaction with opioid receptors located on peripheral sensory nerves.[11,12] Accordingly, we hypothesized that interpleural meperidine may activate opioid receptors on intercostal nerves. However, in the absence of inflammation, such neuronal receptors are not easily accessible because the intact perineurium significantly impedes the penetration of macromolecules.[3,13] Thus, in the non-inflamed pleural cavity, the transperineurial passage may be difficult for hydrophilic meperidine but not for lipophilic bupivacaine.[14,15]

In conclusion, we found that interpleural meperidine did not produce any respiratory depression or rise in arterial CO_2 in patients and also did not change pain scores or narcotic requirements in the cardiac ICU after open-heart surgery; that may be attributable to an insufficient dose and a rapid dilution of the drug within the pleural cavity and rapid absorption into the systemic circulation. Interpleural bupivacaine, but not meperidine produces analgesia after this type of surgery and is recommended for future operations and even for chest trauma patients and pain relief in advanced cancer.[16,17]

For further studies, we recommend the addition of epinephrine to delay the absorption of meperidine and also the use of multiple doses of meperidine for injection into the interpleural space.

Reference

1. Sandel AN. Post thoracotomy analgesia and perioperative outcome. Minerva Anesthesiol. 1999;65(5):267-270.
2. Savage C, McQuitty C, Wang D, Zwischenberger JB. Postthoracotomy pain management. Chest Surg Clin N Am. 2002;12(2):251-63.
3. Detterbeck FC. Efficacy of methods of intercostal nerve blockade for pain relief after thoracotomy. Ann Thorac Surg. 2005;80(4):1550-9.
4. Gupta A, Bodin L, Holmstom B, Beggren L. A systematic review of the peripheral analgesic effects of intraarticular morphine. Anesth Analg.2001;93: 761-70.
5. Demian AD, Wahba AM, Atia EM, Hussein SH. Bilateral interpleural versus lumbar epidural bupivacaine-morphine analgesia for upper abdominal surgery. Middle East J Anesthesiol. 2003;17(3):347-58.
6. Urmey WF. Spinal anaesthesia for outpatient surgery. Best Pract Res Clin Anaesthesiol. 2003;17(3):335-46.
7. Cruz Pardos P, Garutti Martinez I. Usefulness of meperidine in anesthesiology. Rev Esp Anestesiol Reanim. 2000;47(4):168-75.
8. Lewis WR, Perrino AC .Transient neurological symptoms after subarachnoid meperidine. Anesth Analg. 2002;94(1):213-4.
9. Savage C, McQuitty C, Wang D, Zwischenberger JB. Postthoracotomy pain management. Chest Surg Clin N Am. 2002;12(2):251-63.
10. Schulte-Steinberg H, Weninger E, Jokisch D, et al. Intraperitoneal versus interpleural morphine or bupivacaine for pain after laparoscopic cholecystectomy. Anesthesiology. 1995;82: 634–40.
11. Pang WW, Mok MS, Huang S, Chung YT, Hwang MH. The peripheral analgesic effect of meperidine in reducing propofol injection pain is not naloxone-reversible. Reg Anesth Pain Med. 1998;23(2):197-200.
12. Soderlund A, Boreus LO, Westman L, Engstrom B, Valentin A, Ekblom A. A comparison of 50, 100 and 200 mg of intra-articular pethidine during knee joint surgery, a controlled study with evidence for local demethylation to norpethidine. Pain. 1999;80(1-2):229-38.
13. Karakaya D, Baris S, Ozkan F, Demircan S. Analgesic effects of interpleural bupivacaine with fentanyl for post-thoracotomy pain. J Cardiothorac Vasc Anesth. 2004;18(4):461-5.
14. Shrestha BR, Tabadar S, Maharjan S, Amatya SR. Interpleural catheter technique for perioperative pain management. Kathmandu Univ Med J (KUMJ). 2003;1(1):46-7.
15. Higgins PC, Ravalia A. Interpleural anaesthesia for mastectomy. Anaesthesia. 2005;60(11):1150-1.
16. Karmakar MK, Ho AM. Acute pain management of patients with multiple fractured ribs. J Trauma. 2003;54(3):615-25.