INTRAPLEURAL ANALGESIA ON OPEN HEART PATIENTS WITH DEPLETED PULMONARY FUNCTION* RUNNING HEAD: INTRAPLEURAL ANALGESIA IN CABG

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Pain after coronary artery bypass grafting (CABG) operations remains a problem and can cause serious complications due to restricted breathing and can prevent early mobilization. Intapleural analgesia (IPA) for relief of postoperative pain is still a controversial technique for adult patients undergoing CABG. The aim of the study was to investigate the postoperative effectiveness of IPA on pain; related complications; and pulmonary functions depressed due to surgically created discomfort .

125 consecutive patients were randomly selected. Group A (62 patients) received 20 ml bilaterally 0,5 % bupivacaine for every 6 hours and Group B (63 patients) received sterile saline solution until postoperative fourth day. In this double-blind randomized clinical trial, postoperative visual analogue pain scales, analgesic requirements, pulmonary function tests and early postoperative complications, were compared to placebo group following CABG

Group A showed a significantly shorter extubation time than Group B (8,4±0,9 h vs 10,7±4,2 h p<0.001) blood gas analysis showed higher PaO2 and lower PaCO2 levels in Group A. In pulmonary function tests Group A patients had significantly higher FEV1, FVC, VC, MVV, PEF, and FEF 25-75 values postoperatively than Group B. Postoperative analgesic requirement and visual analogue pain scales were significantly lower in Group A than Group B. Intensive care unit stay in Group A was slightly shorter than Group B (1,2±0,7 vs 1,4±0,6 p=0,04) however the hospital stay was not different between the groups.

A clear improvement in lung function parameters correlating with a decreased postoperative pain with IPA was observed. IPA provides a good level of analgesia,

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improving respiratory performance and giving rapid mobilization, essential items in reduction of postoperative pulmonary complications

Key words: Cardiopulmonary bypass, pulmonary function test, intrapleural analgesia, bupivacaine, pulmonary complication

Pain following surgery remains a significant clinical problem. A proper pain management plan is essential because not only the intense pain but also an ineffective pain control may lead to serious pulmonary complications (1). This becomes a more important problem especially in patients with an already compromised pulmonary system because of the additional influence of the cardiopulmonary bypass (CPB) (2-4).

Effective analgesia and blockade of the perioperative stress response may improve outcome and accelerate recovery (5). Intramuscular or intravenous narcotic analgesics are frequently used to control pain usually in inadequate doses due to severe side effects and fear of respiratory depression(6). Recently, interest has emerged in the use of alternative methods of pain control including administration of local analgesics and narcotics epidurally or intrapleurally (7,8).

In this study, intrapleural bupivacaine for postoperative analgesia was compared with placebo following open heart surgery in a double-blind randomized trial.

METHODS

Patients: 125 chronic obstructive pulmonary disease (COPD) patients who underwent isolated coronary artery bypass grafting (CABG) were enrolled in this double blind-randomized, placebo controlled study. This study was approved by the institutional ethics committee and informed consent was obtained from all patients. Exclusion criteria included emergency surgery, significantly impaired ventricular function (ejection fraction less than 0.30), history of cerebrovascular event or inability to cooperate. Patients were randomly assigned to receive intrapleural administration of either 0,5% bupivacaine (n=62) or saline solution (n=63). Patients in Group A received 20 ml of 0,5% intrapleural bupivacaine every 6 hours for 4 days; whereas Group B patients received 20 ml of intrapleural saline solution at the same time intervals. Medications were distributed by the hospital pharmacy by a code unknown to the users. Following bilaterally injection of the study drug chest tubes were clamped for 30 minutes and then unclamped. COPD was defined according to the summit database definition: requirement of therapy for the treatment of chronic pulmonary compromise or has a FEV1 less than 75 % of predicted value.

Anesthesia. All patients received the same anesthetic regimen. Premedication was achieved with diazepam 5 mg peroral and midazolam (0.1 mg/kg) intramuscular. The anesthesia was induced with fentanyl, vecuronium and etomidate. It was maintained with a combination of midazolam, fentanyl and isofluorane.

Surgery. All patients underwent a standard cardiopulmonary bypass with membrane oxygenators and moderate hypothermia (28°C). All operations were performed through a median sternotomy. Left Internal thoracic artery (LITA) was harvested in all patients accompanied by pleurotomy. At the and of the operation and before the chest was closed; intrapleural catheters (Seldiflex 5F 15 cm, Laboratoire Plastimed TM, France) were placed bilaterally and percutanously through the second intercostal space (Figure I). On the left side, the catheter was inserted under direct

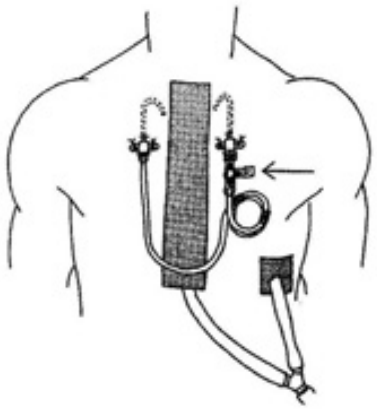

Figure 1. Bilateral intrapleural catheters and drug administration through a stop-cock (arrow).

vision. On the right side, the pleural cavity was opened for 2 cm and then an iatrogenic pneumothorax was created with the aid of surgeon's right hand fingers which passed through the pleural hole, and the second intrapleural catheter was inserted. After the catheter insertion, the anesthesiologist hyperinflated the lungs for deairing the right pleural cavity and then pleural hole was closed with a simple suture. Patients with intrapleural adhesions were not included in the study.

Postoperative management and Pain Control. All patients were managed by the same standardized cardiovascular, respiratory and renal protocols aimed at early extubation. Timing of extubation was managed by the resident in alert, hemodynamically stable patients capable of maintaining self ventilation. Individual pain sensations were assessed with the patient at rest and at forced inspiration during spirometry. Pain sensations were qualified with a visual analogue rating scale (VAS) of 0 to 10, with 0 representing no pain and 10 representing the worst possible pain. Although these VASs for the assessment of pain are not suitable for comparison of pain levels between two groups of patients, a large number of patients were randomly selected for each groups, making negligible the "individual pain threshold".

The first dose of intrapleural agents was given at the time of the awakening from anesthesia in the intensive care unit. The use of additional pain medications were recorded for the first postoperative day. The additional analgesic need was quantified with a numerical scale (Analgesic scale) with 0 representing no additional medication; 1 representing pain relieved with the use of Diclofenac sodium, 2 representing use of Meperidine 1 mg/kg and 3 representing more than 2 doses of Meperidine daily.

Pulmonary Function Tests (PFTs) and Arterial Blood Gases. Preoperatively lung function parameters such as vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), peak expiratory flow rate (PEFR), forced expiratory flow (FEF25-75) and maximal voluntary ventilation (MVV) were evaluated using a transportable spirometer unit (Cosmed Srl -Pony Spirometer Graphic TM Italy). In the case of appropriate flow-volume loop, each test was performed three times and the best trial report were selected for analysis. When the flow-volume loop had an irregular shape and inappropriate curves, the tests were repeated eight times and the best results obtained for FEV1 and FVC were accepted. Postoperatively pulmonary function testing was carried out on 6 hours after extubation, and postoperative day 1, 2, and 4; 30 minutes after the injection through the IPA catheters, by a resident blinded to the medication. Arterial blood gas analyses were determined postoperatively 10 minutes, 1 hour, 2 hours, and 6 hours after extubation with the patient 45o angulated semi- Fowler position and breathing oxygen via a mask.

Statistical Analysis. Data were expressed as mean ± SD. Values were compared using Students t test, Chi-square (c2) and Fisher's exact test when appropriate. Probability (p) values less than 0.05 were considered significant and less than 0,001 considered highly significant. P values greater than 0,05 indicated non significant (ns) difference. Statistical analysis was done using "SPSS 5.0 for Windows TM" statistics package.

RESULTS

For both groups, there were no significant difference in the demographic data and the intraoperative variables (Table 1). Arterial

Table 1: Patients characteristics and operation data.

	Group A	**Group B**	***p***
Age	58,5±9,9	59,2±8,2	0,7
Gender (female)	8 (%12,9)	4 (%6,3)	0,347
Patients requiring therapy for COPD			
No	43 (%69,4)	40 (%63,5)	0,49
Yes	19 (%30,6)	23 (%36,5)	
Bypass number	3,52±1	3,44±1	0,71
Operation time	115,2±38	112±34	0,80
CPB time	68,3±23	65,4±25	0,96
ACC time	42,1±19	41,1±18,4	0,8

Abbreviations: CPB: Cardiopulmonary bypass ACC: Aortic cross clamping.

blood gas analyses showed no significant differences preoperatively and during the mechanical ventilation. Extubation time was significantly shorter in Group A (8,4 ± 0,9 h) than Group B (10.7 ± 4,2 h) p<0,001.

After 10 minutes of extubation, spontanous mean respiratory rates were (in rate Per minute) 23,7±2,3 vs 27,3±4,9 (p<0,001); at the 1st hour 23,8±3,2 vs 25,3±4,2 (p=0,021); at the 2nd hour 22,8±3 vs 25,7±4,6 (p<0,001); at 6th hour 23,3±2,6 vs 25,8±5,1 (p=0,001) in Group A and B respectively.

First arterial blood gas analyses showed that mean PaCO2 (in mmHg) was slightly lower in Group A than Group B (38,4±5,5 vs 40,8±5,9 respectively) p=0,02; but the following analysis showed no difference between the groups. PaO2 in Group A and B were (respectively in mmHg) 107,5±20,3 vs 83,3±20 at the 10th minute after extubation; 119,8±23,2 vs 85,3±25,8 at the 1st hour; 114±23,6 79,3±17,1 at the 2nd hour and 114,7±21,7 vs 79,5±18,6 at the 6th hour (p<0.001 for all intervals).

Table 2 shows the results of PFTs preoperatively, postoperatively at the 6th hour and on postoperative day (POD) 1, 2 and 4. Preoperative pulmonary function parameters were comparable between groups. Postoperatively, in both groups there was a significant impairment in lung function. However, the impairment as shown by pulmonary function parameters was significantly less in Group A than in Group B.

In Group A, patients showed significantly lower pain scores (VAS) on POD1 (1,1 versus 5,5 ; p<0.001), and on PODs 2 and 4 (0.7 versus 3,7 and 0.3 versus 2.6 respectively, p<0.001) than in Group B. Additional analgesic need score on POD 1 was also significantly lower in Group A than in Group B (Table 3).

The mean duration of intensive care was

Table 2. Perioperative changes on pulmonary function tests parameters.

	Group A	Group B	*p*
FEV1 (%)			
Preoperative	72,1±15,7	71,4±1	0,751(ns)
Postop. 6th h	31,3±11,2	24,2±9,4	0,000
Postop. 24th h	32,1±6,5	27,8±5,1	0,000
Postop. 48th h	38,4±10	29,73±5	0,000
Postop. 4th day	41,6±6,3	39,3±6	0,042
FVC (%)			
Preoperative	61,4±11,8	62,2±9	0,664 (ns)
Postop. 6th h	27,7±12,7	24,1±10,9	0,023
Postop. 24th h	35±8,4	25,5±8,9	0,000
Postop. 48th h	35,3±6,7	28±7,1	0,000
Postop. 4th day	37±6,4	31,9±8,3	0,002
VC (%)			
Preoperative	52,5±11,8	52,7±10,4	0,932 (ns)
Postop. 6th h	29,5±8,7	28,6±9,5	0,474 (ns)
Postop. 24th h	40±9,9	33,8±8,2	0,000
Postop. 48th h	52,2±11,3	38±8,1	0,000
Postop. 4th day	52,1±10,2	44,2±8,3	0,000
MVV (%)			
Preoperative	50,9±13,6	50,1±12,1	0,733 (ns)
Postop. 6th h	25,2±3,9	23,6±4	0,012
Postop. 24th h	28,1±5,5	23,4±5,1	0,000
Postop. 48th h	31,5±6,7	25,9±3,8	0,000
Postop. 4th day	33,5±4,8	28,5±3,5	0,000
PEFR (%)			
Preoperative	54,9±9,9	56±14	0,761 (ns)
Postop. 6th h	33,3±11	28,1±8,9	0,005
Postop. 24th h	35,1±7	28,5±8	0,000
Postop. 48th h	40±7,1	28,7±3,9	0,000
Postop. 4th day	42±7,3	34,8±6	0,000
FEF 25-75%			
Preoperative	81,1±12,8	80,6±14,4	0,801 (ns)
Postop. 6th h	52,4±21,7	43,4±14,8	0,010
Postop. 24th h	51,6±9,9	43,7±9,3	0,000
Postop. 48th h	54,6±10,3	41,5±7,3	0,000
Postop. 4th day	62,4±14,3	53,2±12,1	0,000

Table 3. Visual analogue pain scale (VAS), analgesic scale in postoperative first day in intensive care unit (ICU), stay in ICU and hospital and postoperative complications.

	Group A	Group B	*p*
Visual analogue pain scores (VAS)			
24th h	1,1±1,7	5,5±0,2	<0,001
48th h	0,7±1,4	3,8±1,7	<0,001
4th day	0,3±0,9	2,6±1,5	<0,001
Analgesic scores in postoperative first day	0,3±0,6	2,3±0,8	<0,001
Stay in ICU (day)	1,2±0,7	1,4±0,7	0,042
Stay in hospital (day)	6,8±0,6	7,1±2,4	0,451 (ns)
Postoperative complications			
Pneumothorax	2 (%3,2)	4 (%6,3)	0,348 (ns)
Atelektasis	8 (%12,9)	20(%31,7)	0,012
Fiver (>38°C)	(%17,7)	21(%33,3)	0,046
Sternal dehissence	1 (%1,6)	1 (%1,6)	0,748 (ns)
Wound infection	4 (%6,5)	4 (%6,3)	0,632 (ns)

shorter in Group A than Group B (respectively 1,2 vs 1,4); this difference between the groups was moderately significant (p=0,042), however the hospital stays were comparable between the groups (p=0,45). Eight patient in Group A and 20 patients in Group B had apparent atelectasis on the chest X-rays postoperatively. Intrapleural catheters were removed at postoperative day 4 and did not cause any complications.

CONCLUSIONS

Sternotomy, pleurotomy, harvest of internal thoracic artery, and pain may lead to deterioration of pulmonary function (9,10). Furthermore, CPB has been shown to cause pathologic and functional pulmonary changes called the post-perfusion syndrome (11). Like previous studies, the present study demonstrates that there is an evident impairment of pulmonary function in the early postoperative course following CABG surgery.

Postoperative pain for the adult cardiac surgical patients, has many facets and has been pointed out as one of the primary sources of concern. Persistent pain may result in sympathetic hyperreactivity. The influence of the pain leading to inadequate and shallow breathing seems to be higher than expected (9). The pleura is very sensitive to irritation and the friction on drains during breathing, and causes suffering for the patient. Furthermore, intercostal nerve irritation due to chest tube placement will increase pain that will delay pulmonary recovery. This may cause poor pulmonary toilet and atelectasis that might foster pneumonia as a major complication (12).

A proper pain management planning is essential after surgery. Although different approaches can achieve the same goal, a multi modal pain management based on the use of synergistic drugs and alternative routes may provide better analgesia. The potential usefulness of thoracic epidural analgesia (13) in cardiac surgery patients has been addressed in multiple studies, however, the fear of epidural hematoma formation has led to reluctance to place epidural catheters in patients who receive high-level anticoagulation.

An alternate route is the administration of local anesthetic through an intrapleural catheter. In 1984, Kvalheim et al. (14) described a technique of introducing a catheter into the pleural space in 30 patients who underwent renal, breast or gallbladder surgery. None of these patients required narcotics for pain relief and there were no adverse effects of the procedure or the drug. Symreng and colleagues (15) studied patients undergoing thoracic surgery who received unilateral intrapleural bupivacaine for pain relief with excellent pain control and significant improvement in all pulmonary function tests. However, Schneider et al. (16) showed the ineffectiveness of intrapleural bupivacaine following thoracotomy. More recently, Mehta and colleagues (13) compared intrapleural analgesia with thoracic epidural analgesia for postoperative pain relief after minimally invasive direct coronary bypass surgery. They showed pain scores were significantly lower in intrapleural analgesia Group with a low complication rate.

Our insertion technique of intrapleural catheters seems to be easier and safer than the closed percutanous (blind) technique mentioned in the literature(15). Symreng and colleagues studied 21 thoracotomy patients with the IPA catheters inserted preoperatively. After the patients' chest opened there were 3 catheters located extrapleurally and 7 in lung tissue. Our insertion technique provide a protection of the lung and proper placement of the catheter.

We have not observed any systemic manifestations indicating toxic serum levels of bupivacaine. Leaving chest tubes open after 30 minutes of drug administration during first two days and the obese characteristic of the patients (body mass indexes calculated by Roisen formula were 27,1±3,7 and 26,9±4,5 kg/m2 in Group A and B respectively) might have played a role to be free of drug toxicity. Bilaterally administered bupivacaine of 20 ml of 0,5 % may not be a proper dose for each patient. In this double blinded study, we couldn't calculate the doses of bupivacaine

taking into consideration of the patients' weight.. el-Naggar and colleagues declared that bilaterally bupivacaine of 20 ml of 0,75 % is more effective than 0,5 % in adult patients with abdominal or thoracoabdominal procedures (17). This lack of the study may be the explanation of the incomplete pain relief in some patients after bupivacaine administration.

We believe that the sedative effect of meperidine with the summation of the non eliminated anesthetic drugs prolonged the extubation time in Group B. Patients received intrapleural bupivacaine were more cooperated and quite than the patients with placebo and meperidine. None of the patients in Group A needed meperidine in this period, and this comfort resulted more effective breathing mechanics with higher PaO2 levels at any time in the ICU. First blood gas analyses after extubation showed higher PaCO2 levels despite of higher respiratory rate in Group B. We can explain this paradox with an inadequate shallow inspiration due to an incompletely relieved pain, and to prolonged sedation, resulting in ineffective air circulation in the death space of the patients' airways. The discomfort from sternotomy and chest tubes is visceral in nature, and quite responsive to opioids. However, systemic opioids may directly degress the breathing mechanics by means of central nervous system and show a sedative effect (6) that can cause pulmonary complications due to inadequate cough, spittle aspiration and inactivity. Meperidine is a synthetic opioid analgesic with a weak sedative effect, but this sedation can markedly increase by personality and aging (18,19). In this study, we observed that IPA provided a potent analgesic effect on clearly the conscious and wakeful patient, when compared to placebo; intrapleural bupivacaine results in reduced pain and therefore, significantly better pulmonary function in the early postoperative period. The better pain control in Group A, correlated with the faster improvement rate of pulmonary function parameters.

Differences in PFT results reflects the patients' comfort in Group A. Pulmonary restriction due to CPB (20,21) extended up to postextubation 6th hour and concealed the clear superiority of Group A at the first postoperative spirometries. This restriction can be observed in FVC, MVV and markedly in VC at the 6th hour postoperatively. After the resolution of CPB effect, restriction due to the pain began to dominate and significant differences between two groups become evident at the following PFTs .

We have not observed any possible side effects of IPA with bupivacaine such as phrenic palsy or Horner's Syndrome. IPA catheter insertion technique requires deposition of the drug in the posterior-lateral pleural gutters to be effective. Because of the postoperative preferable supine position in sternotomy patients, IPA is a suitable pain control treatment, and position of the patient may play a role to be free of these side effects of intrapleural administration of bupivacaine.

A final issue is whether intrapleural analgesia is needed at all following cardiac surgery through a median sternotomy. Most cardiac surgery patients are easily managed with minimal doses of opioids that cause tolerable sedation, and will not require intrapleural analgesia for postoperative pain relief. However, patients with coexisting chronic pulmonary disease with a limited pulmonary reserve who are prone to the development of serious pulmonary complications will significantly benefit from it.

In conclusion, this study demonstrated a marked decrease in early lung function following CABG surgery. A clear improvement in lung function parameters correlating with a decreased postoperative pain can be seen with intrapleural analgesia. Our results show that, there is still room left for improvement in analgesic administration policy to minimize the intensity of pain especially during the early postoperative period. We believe that intrapleural analgesia is a safe and effective technique for reaching a better pain control with a low complication rate. It warrants a good level of analgesia, improving respiratory performance and giving rapid mobilization in clearly conscious patients; essential items in the reduction of postoperative pulmonary complications.

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