The analgesic efficacy of continuous presternal bupivacaine infusion through a single catheter after cardiac surgery

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ABSTRACT

Background: Median sternotomy, sternal spreading, and sternal wiring are the main causes of pain during the early recovery phase following cardiac surgery. Aim: This study was designed to evaluate the analgesic efficacy of continuous presternal bupivacaine infusion through a single catheter after parasternal block following cardiac surgery. Materials and Methods: The total of 40 patients (American Society of Anesthesiologist status II, III), 45–60 years old, undergoing coronary – artery bypass grafting were enrolled in this prospective, randomized, double-blind study. A presternal catheter was inserted with continuous infusion of 5 mL/h bupivacaine 0.25% (Group B) or normal saline (Group C) during the first 48 postoperative hrs. Primary outcomes were postoperative morphine requirements and pain scores, secondary outcomes were extubation time, postoperative respiratory parameters, incidence of wound infection, Intensive Care Unit (ICU) and hospital stay duration, and bupivacaine level in blood. Statistical Methods: Student’s t-test was used to analyze the parametric data and Chi-square test for categorical variables. Results: During the postoperative 48 h, there was marked reduction in morphine requirements in Group B compared to Group C, (8.6 ± 0.94 mg vs. 18.83 ± 3.4 mg respectively, P = 0.2), lower postoperative pain scores, shorter extubation time (117 ± 10 min vs. 195 ± 19 min, respectively, P = 0.03), better respiratory parameters (PaO₂/FiO₂, PaCO₂ and pH), with no incidence of wound infection, no differences in ICU or hospital stay duration. The plasma concentration of bupivacaine remained below the toxic threshold (at T24, 1.2 ug/ml ± 0.3 and T48 h 1.7 ± 0.3 ug/ml). Conclusion: Continuous presternal bupivacaine infusion has resulted in better postoperative analgesia, reduction in morphine requirements, shorter time to extubation, and better postoperative respiratory parameters than the control group.

Key words: Postoperative pain, presternal bupivacaine infusion, sternotomy

INTRODUCTION

Effective pain relief after cardiac surgery has assumed importance with the introduction of fast track discharge protocols that requires early weaning from ventilation. Inadequate pain control reduces the capacity to cough, mobility, increases the frequency of atelectasis, and prolongs recovery.¹⁻⁴ A major cause of pain after cardiac surgery is the median sternotomy particularly on the first two postoperative days.⁶ The most often used analgesics in these patients are parental opioids which can lead to undesirable side-effects as sedation, respiratory depression, nausea, and vomiting.⁵,⁷ Infiltration of local anesthetics near the surgical wound has shown to improve early postoperative pain in various surgical procedures.⁸⁻¹¹ This study was designed to examine the efficacy of presternal infusion of bupivacaine 0.25% through a single catheter after parasternal block in controlling postoperative pain after cardiac surgery.
Our primary outcome was postoperative morphine requirements and pain scores, the secondary outcomes were extubation time, postoperative respiratory parameters, incidence of wound infection, Intensive Care Unit (ICU) and hospital stay duration, and bupivacaine level in blood.

**MATERIALS AND METHODS**

After approval of the institutional ethics committee and written informed patients’ consent, 40 patients, 45–60 years old, American Society of Anesthesiologist (ASA) status II and III, scheduled for open heart surgery with sternotomy (for coronary – artery bypass grafting with cardiopulmonary bypass [CPB]), were enrolled in this prospective, randomized, controlled, double-blind study.

The patients exclusion criteria included; emergency surgery, previous sternotomy, patients with preoperative poor left ventricular function (ejection fraction <40%), preexisting pulmonary or neurological dysfunction, clinically significant kidney or liver disease, patients allergic to local anesthetics, preexisting coagulopathy, patients with prolonged CPB time (>120 min), intraoperative inotropic support (dobutamine >5 µg/kg/min or epinephrine infusion >1 µg/min), patients required intra-aortic balloon pump, postoperative hemodynamic instability (including the occurrence of serious arrhythmia) or bleeding that required surgical re-exploration.

Patients were trained to report pain on a visual analog scale (VAS) during the preanesthetic examination; the routine preoperative cardiac medications were continued till the morning of surgery.

All patients were premedicated with intramuscular morphine 0.1 mg/kg about 30 min before the operation. On arrival at the operating room, a 16-G intravenous (l.v) cannula and a 20-G radial arterial cannula were inserted; general anesthesia was induced with fentanyl 10 µg/kg, midazolam 0.1 mg/kg and propofol 3–4 mg/kg. Pancuronium 0.15 mg/kg was administered to facilitate endotracheal intubation and was repeated during surgery as required to ensure proper muscle relaxation. Anesthesia was maintained using 0.5–1.5% sevoflurane in an oxygen-air mixture (1:1 ratio). Mechanical ventilation was provided by a Narkomed anesthesia machine (North American Dräger, Telford, PA, USA) using a tidal volume of 10 mL/kg according to weight. A 3-port central jugular venous line was inserted (Certofix Duo, B. Braun Melsungun A.G.) for central venous pressure monitoring. Standard monitoring included an electrocardiogram, invasive blood pressure, pulse oximetry, capnography, temperature (central-distal), urine output, airway volume and pressure.

All operations were performed by the same surgical team in a standard method through a median sternotomy incision with saphenous veins and internal thoracic arteries harvesting for coronary artery bypass graft.

At the end of the operation and just before sternal wire placement, patients were randomly divided into two equal groups using computer-generated random numbers with closed-sealed envelopes to receive either 0.25% bupivacaine solution (Group B) or 0.9% saline solution, control group (Group C). A series of intercostal blocks was performed by the surgeon just lateral to the sternum border, 2 ml of either bupivacaine or saline for each of the 5 interspaces bilaterally (total 20 ml). The patients were observed for 10 min for any bleeding caused by an inadvertent vascular injury before the closure of the sternum. After sternal wiring, a small diameter multihole soft catheter generally used for epidural analgesia (Portex Epidural Catheter 18-gauge; Smith Medical ASD Inc., Keene, NH) was positioned anteriorly to the sternum above the fascia in the subcutaneous tissue during wound closure. Steri-strips (3M Neuss, Germany) and wound dressing were used to secure the catheters. Before connection of the catheter to the pump, the syringes used for intercostal block and the infusion pump were filled with either bupivacaine or saline solutions prepared by the anesthesiologist in charge of the patient who opened the allocation envelope and who was not part of the study, both solutions looked identical.

A bolus of 5 mL of the study solution was injected in the catheter after aspiration test before connection to an elastometric infusion pump (Accufuser plus® P 4003, Korea), this infusion pump consists of a disposable 275 ml elastomeric reservoir that delivers continuous infusion of either solution at a fixed rate of 5 ml/h. Because the filling volume of the pumps for the solution was supposed to provide an infusion for >48 h (expected duration 55 h), pumps were not refilled to avoid the risk of manipulation. To reduce the number of painful interventions, the catheter was concomitantly removed with the chest drain tube removal.

At the end of surgery, neuromuscular block was not antagonized, patients were transferred intubated to
the ICU where they were mechanically ventilated (Servo 900 D, Siemens, Uppsala, Sweden). The criteria for extubation were hemodynamic stability, absence of arrhythmias, adequate airway reflexes, normothermia, mediastinal drainage (<100 ml/h for 2 h), and acceptable blood gas analysis (pH >7.30, arterial oxygen tension >60 mmHg and arterial carbon dioxide tension <50 mmHg) at an inspired oxygen fraction of 0.4.

An anesthesiologist blinded to group assignment recorded pain score postoperatively on patient’s arrival at the ICU (T₀), every 4 h for 12 h then every 6 h for 48 h using a VAS (0 = no pain, 10—the worst pain imaginable). The patients were asked to take a deep breath and intensity of pain was recorded. If the patients were still intubated, the observer asked whether he or she had a pain score of 10 points, if this was not the case, the observer repeated the question decreasing the score 1 point each time until the patients confirmed the answer by nodding. Intravenous (i.v) morphine 2 mg i.v. bolus was administered if VAS pain score was ≥3 and the total amount of morphine given during the first postoperative 48 h was recorded.

Quality of oxygenation was assessed by arterial blood gas (ABG) analysis (baseline [after insertion of arterial cannula and before induction of general anesthetic], at extubation, 6, 12, and 24 h), this consisted of PaCO₂, pH, PaO₂ with calculation of PaO₂/FiO₂ ratio. The FiO₂ is estimated either from the raw data measures during mechanical ventilation or the estimated FiO₂ during spontaneous breathing (if face mask was used at O₂ rates 8, 9, and 10 (L/min) then the estimated FiO₂ was 0.35, 0.45, and 0.55, respectively, if nasal cannula was used at O₂ rates 1, 2, 3, 4, 5 (L/min) then the estimated FiO₂ was 0.24, 0.28, 0.32, 0.36, and 0.4, respectively. When no oxygen was administered, FiO₂ was 0.21.

Extubation time (from arrival at the ICU till tracheal extubation) was recorded, time to discharge from the ICU and hospital were recorded (according to the institution’s standardized protocol for all patients undergoing cardiac surgery).

Medical administration and data collected were performed in a double–blinded manner such that the patient, the surgeon administering the block, the anesthesiologist providing anesthesia, the ICU staff in the postoperative care unit, were not aware of the group assignment. Randomization and allocation were only revealed for data analysis after the study was completed.

The safety outcome of the study was the bupivacaine blood level. Blood samples were drawn 24 h and 48 h after surgery for analysis of the bupivacaine concentrations. Samples were centrifuged at 50,000 revolutions/min for 10 min. Then the bupivacaine concentration in samples was determined by a high–performance liquid chromatography. Only the samples taken from patients who received bupivacaine were analyzed. Plasma concentration of >4 µg/ml was taken as toxic threshold.

The occurrence of any postoperative sternal wound infection or delayed wound healing during hospitalization was also recorded.

Statistical analysis
The primary outcome of the study was postoperative morphine requirement compared with the Control group. A sample size of 15 patients was needed in each groups to achieve 80% power to detect 50% difference in postoperative morphine consumption between the two groups, 20 patients/group were included to replace any drops and to increase power on secondary outcomes. Statistical analysis was done on a personal computer using the Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago Illinois , USA). Data were expressed as mean values ± standard deviation or numbers (%), Student’s t-test was used to analyze the parametric data and discrete (categorical) variables were analyzed using the Chi-square test, with P < 0.05 was considered statistically significant.

RESULTS
The total of 40 patients were enrolled in this study; three patients had accidental catheter removal (two patients in the control group and one patient in the bupivacaine group) and were excluded.

There were no significant differences between bupivacaine group (Group B) and control group (Group C) with respect to age, sex, body surface area, ASA status, preoperative ejection fraction, duration of surgery, cross-clamping, and CPB times (Table 1).

The overall morphine requirements over the first 48 h in the ICU were significantly less in Group B than Group C (8.6 ± 0.94 mg vs. 18.83 ± 3.4 mg, respectively, P = 0.02) [Table 2]. The mean VAS score of pain was significantly less in Group B than Group C at most time points [Figure 1].
The time to extubation was obviously shorter in Group B compared to Group C (117 ± 10 min vs. 195 ± 19 min, respectively, P = 0.03). However, there were no statistically difference between the two groups in the ICU and the hospital stay duration [Table 2].

The respiratory parameters (PaO₂/FiO₂, PaCO₂ and pH) were better in Group B compared to Group C at extubation (although they were acceptable for extubation in Group C). PaO₂/FiO₂ was better at 6 h, 12 h and 24 h in Group B compared to Group C, with no significant differences in PaCO₂ and pH value at the same times between the two groups [Table 3].

There was no incidence of sternal infection or delayed wound healing recorded in either group.

The plasma concentration of bupivacaine remained below the toxic threshold (at T24, 1.2 ug/ml ± 0.3 and at T48 h 1.7 ± 0.3 ug/ml), with no signs or symptoms of bupivacaine toxicity observed.

**DISCUSSION**

The present study demonstrated that parasternal bupivacaine infiltration followed by continuous subcutaneous presternal infusion of bupivacaine 0.25% at 5 ml/h for 48 h in patients undergoing cardiac surgery with median sternotomy, had resulted in better postoperative analgesia, reduction in morphine requirements, shorter time to extubation, better postoperative respiratory parameters, with no incidence of wound infection, no difference in ICU and hospital duration with no signs or symptoms of bupivacaine toxicity compared to control group.

Wound infiltration of local anesthetics has been studied for postoperative analgesia in different surgical settings and has proved to reduce postoperative pain effectively.⁶⁻¹¹ Although the same method applied directly to the sternotomy incision in cardiac surgery has been studied, results were controversial.¹²⁻¹⁶

In the present study, bupivacaine 0.25% was infiltrated to block the anterior cutaneous branches of the intercostal nerves (close to the sternal border) followed by continuous infusion of bupivacaine in the subcutaneous fascia above the sternum through a multihole catheter, which resulted in better postoperative analgesia and reduction in postoperative morphine requirements.

Similar to our results, Chiu, et al. in their study found that bupivacaine 0.15% infused continuously at 2 ml/h initiated at time of wound closure provided uninterrupted analgesia and contributed to short- and long-term pain relief for thoracotomy patients.¹³ Four other trials studied different local anesthetic solutions applied directly to the sternal wound through two catheters from an elastomeric pump, the 1st study used bupivacaine 0.5% at 4 ml/h (3), the 2nd and 3rd used ropivacaine 0.2% at 4 ml/h,¹⁵,¹⁷ the 4th one used ropivacaine 2 ml/h.¹⁸ The results of the previous
Nasr, et al.: Presternal bupivacaine infusion in sternotomy

Table 3: Postoperative respiratory outcomes

|                      | Group C (n=18) | Group B (n=19) | P     |
|----------------------|----------------|----------------|-------|
| **Baseline (Before induction of anesthesia)** |                 |                |       |
| PaO2/FiO2 mmHg       | 339.9±16.3     | 337.6±23.1     | 0.74  |
| PaCO2 mmHg           | 39.4±3         | 38.6±2.9       | 0.3   |
| pH                   | 7.36±0.04      | 7.38±0.04      | 0.6   |
| **At extubation**    |                 |                |       |
| PaO2/FiO2 mmHg       | 337.2±12.1     | 351.7±15.5*    | 0.004 |
| PaCO2 mmHg           | 39.4±3         | 36.6±2.9*      | 0.03  |
| pH                   | 7.31±0.08      | 7.36±0.06*     | 0.04  |
| **At 6 h**           |                 |                |       |
| PaO2/FiO2 mmHg       | 330.8±16.8     | 347.7±22*      | 0.018 |
| PaCO2 mmHg           | 39.3±5.4       | 37.0±4.3       | 0.67  |
| pH                   | 7.33±0.03      | 7.32±0.06      | 0.09  |
| **At 12 h**          |                 |                |       |
| PaO2/FiO2 mmHg       | 332.9±20.3     | 347.1±12.3*    | 0.013 |
| PaCO2 mmHg           | 38.4±1.8       | 37.5±5.3       | 0.95  |
| pH                   | 7.36±0.02      | 7.36±0.05      | 0.09  |
| **At 24 h**          |                 |                |       |
| PaO2/FiO2 mmHg       | 335±9.3        | 350±9.5*       | 0.001 |
| PaCO2 mmHg           | 39±2.4         | 39±2.3         | 0.54  |
| pH                   | 7.36±0.3       | 7.4±0.3        | 0.88  |

Data are presented as mean±SD. *P<0.05; statistical significant difference between the two groups. SD: Standard deviation

Studies showed a reduction in postoperative pain and opioid consumption with a significant decrease in hospital stay duration.

On the contrary, Magnano et al. used bupivacaine 0.5%; 10 ml for wound infiltration followed by continuous infusion of 10 mg/24 h[14] and Agarwal et al. used ropivacaine 0.3% for wound infiltration followed by continuous infusion of 4 ml/h for 64 h.[16] Both studies showed that local anesthetic infusion after median sternotomy did not reduce postoperative pain, VAS and time to extubation. Magnano et al. attributed their results that they used a catheter with few holes only at the tip which was ineffective in long surgical incisions as in median sternotomy and that the lower portion of the wound was probably “uncovered” by the anesthetic drug. They recommended to prolong the duration of bupivacaine infusion to be more effective in controlling delayed postoperative pain.[14] Agarwal attributed the failure of their analgesic technique that their study was stopped earlier than planned due to wound infection.[16] In our study, it was possible that placing catheters for sternal wound infusion closer to the anterior branches of the intercostal nerves has improved analgesic efficacy.[15]

Patients in the bupivacaine group were extubated earlier with better respiratory parameters (indicated by the ABGs analyses) at time of extubation and at the subsequent readings compared to the control group. Eljezi et al., demonstrated no improvement in the postoperative respiratory functions with improvement of analgesia in their study group.[15] The main explanation for such difference is that they depend on pulmonary function tests to assess oxygenation which needs deep inspiratory maneuvers of the spirometric volumes tests and that sternotomy pain was a minor factor in the respiratory dysfunction observed while we just assessed the ABGs.

As regarding ICU and hospital stay duration, White et al. demonstrated no improvement in length of ICU stay probably because there were no attempt by the ICU staff in his study to fast – track cardiac patients.[13] In our study, reducing pain, earlier tracheal extubation, and good pulmonary function in the bupivacaine group did not change the policy of the ICU team as regard ICU and also hospital stay durations (as they follow routine discharge protocols), and hence differences between groups if found are not easy to identify.

There were no serious adverse events reported in all the previous studies except in one of them where sternal wound infection with increased incidence of catheter-related problems was noticed which lead to discontinuation of the trial.[16] An increased wound infection could be consistent with a theoretical concern that local anesthetics exert multiple antiinflammatory effects on granulocytes and on release of some inflammatory modulators and may enhance some aspects of immuno-suppression that is more likely to occur with levorotatory stereoisomer, ropivacaine, and its closely related chiral congener, levobupivacaine than racemic anesthetics, like bupivacaine.[19,20]

In the present study, the plasma levels of bupivacaine remained beneath the mean level observed for occurrence of neurologic symptoms in human (unbound drug 0.6 µg/ml, i.e. 4 µg/ml of total drug), there were no signs or symptoms of local anesthetic toxicity (neurological or cardiovascular) observed in any of our patients, White et al. found that 0.25% or 0.5% bupivacaine infusion at 4 ml/h in the sternotomy wound resulted in safe serum concentration (<2 µg/ml).[3] We chose the lower concentration of bupivacaine (0.25%), which has resulted in effective pain management in the above study and at the same time to avoid any adverse effects of the high concentration. Furthermore, we used a more simple method to infuse bupivacaine 0.25% in the...
Nasr, et al.: Presternal bupivacaine infusion in sternotomy

presternal tissue via a single catheter. The bupivacaine infusion was started before sternal wire closure to provide an afferent block as earlier as possible, with no need of refilling which decreased the incidence of manipulation and therefore infection. There were no pump malfunction, disconnection, or breakage of the catheter noted in the study period.

There were several limitations in our study; first, our study was performed on relatively cardiac stable patients. We are aiming to assess the efficacy of this block on more complicated cases. Second, although the patients in Group B were extubated earlier than in Group C, the time of assessing the respiratory parameters was at fixed intervals (at extubation, 6, 12, and 24 h) to maintain blind collection of data.

CONCLUSION

Delivering bupivacaine 0.25% through a single catheter embedded anteriorly to the sternum during the wound closure is a simple technique, it provided adequate postoperative analgesia with less morphine requirements.

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