Local infusion of bupivacaine combined with intravenous patient-controlled analgesia provides better pain relief than intravenous patient-controlled analgesia alone in patients undergoing minimally invasive cardiac surgery

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Objective: This prospective randomized double-blind study examined the effect of local wound infusion of anesthetics on pain control in the thoracotomy wound of patients undergoing minimally invasive cardiac surgery.

Methods: Patients who underwent coronary artery bypass grafting or cardiac valvular procedures via a minimally invasive thoracotomy were studied. Patients were enrolled and randomly allocated to two groups with different modalities of postoperative analgesia. The thoracotomy wound infusion group received 0.15% bupivacaine infused continuously at 2 mL/h through a catheter embedded in the wound, as well as intravenous patient-controlled analgesia. The control group had patient-controlled analgesia alone with a sham thoracotomy wound infusion of normal saline. Verbal analog pain scores (0–10 points) and recovery profiles were investigated.

Results: There were 19 patients in each group for complete data analysis. On the first day after the operation, infusion of local anesthetics significantly reduced the verbal analog pain scores both at rest and during motion (thoracotomy wound infusion vs control). The improved pain relief with thoracotomy wound infusion persisted at day 3 and even at 3 months after the operation. No difference was noted about time to extubation, length of intensive care unit stay, or hospital stay.

Conclusion: In this controlled double-blind study, thoracotomy wound infusion and patient-controlled analgesia were superior to patient-controlled analgesia alone in reducing pain at 1, 3, and 90 days after minimally invasive cardiac surgery.

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A minimally invasive approach for cardiac surgery (valvular repair/replacement and/or coronary artery bypass) has become a feasible (and sometimes superior) alternative to conventional sternotomy.[1,2] It not only provided better cosmetic outcome, but also improved quality of life, promoted more rapid recovery, reduced blood transfusion, and reduced intensive care unit and hospital recoveries.[3-5] It may also be a safer approach for redo operations.[6,7]

However, the typical thoracotomy causes more severe pain than sternotomy.[8,9] Thus, an effective analgesic regimen is important because it can not only reduce pain and discomfort but also improve postoperative lung function,[10] allow for earlier tracheal extubation, and decrease the incidence of pulmonary complications and cardiac dysrhythmia.[11-14] Among various methods of analgesia, thoracic epidural analgesia is thought to provide better pain control and avoid the potential bleeding complication associated with nonsteroidal anti-inflammatory agents (NSAIDs) or the respiratory depression commonly seen with parenteral opioids.[13] In some modalities, it may also decrease chronic wound pain.[15] These benefits are accompanied by greater technical challenges and, in the setting of cardiac surgery and anticoagulation,

Abbreviations and Acronyms
ICU = intensive care unit
NSAID = nonsteroidal anti-inflammatory agent
PCA = patient-controlled analgesia

the greater risk of epidural hematoma and possible neurologic deficits compared with lumbar epidural.[16] Safe and effective methods to control pain in minimally invasive cardiac surgical procedures are critical to patient well-being.

Delivery of local anesthetics to the wound is a simple and safe method of analgesia. It is effective in iliac crest harvest site,[17,18] sternotomy of cardiac surgery,[19] and hysterectomy.[20] It is not effective in total knee arthroplasty[21] or radical prostatectomy.[22] We hypothesize that the thoracotomy wound infusion of local anesthetic combined with patient-controlled analgesia (PCA) would provide better pain relief than PCA alone after minimally invasive cardiac surgery.

Patients and Methods

After institutional approval and written informed consent, we enrolled patients undergoing minimally invasive cardiac surgery (coronary or valvular surgery) through thoracotomy. Participant were excluded if they underwent emergency surgery, received extracorporal membrane oxygenation support, had preoperative nonsinus cardiac rhythm, or had a history of peptic ulcer disease or preoperative renal insufficiency. Anesthesia was induced with etomidate 0.2 to 0.3 mg/kg, fentanyl 5 to 10 μg/kg, and rocuronium 1mg/kg. Anesthesia was maintained with sevoflurane. Double-lumen endotracheal intubation (Broncho-Cath Left; Mallinckrodt Medical, Athlone, Ireland) was used to achieve one-lung ventilation during surgery. Coronary artery bypass surgery was performed through a left thoracotomy via the fourth or fifth intercostal space without cardiopulmonary bypass. Valvular surgery was through a right lateral thoracotomy with transthoracic clamp technique performed via the fourth intercostal space with cardiopulmonary bypass.

Participants were randomly assigned to thoracotomy wound infusion or sham infusion through a multi-orifice catheter (Portex Epidural Catheter 18-gauge; Smiths Medical ASD Inc, Keene, NH) placed at the subcutaneous layer during wound closure. After 10 mL (0.15% bupivacaine or saline solution) at the end of the operation, the catheter was connected to a continuously infusing container (Two-Day Infusor 2 mL/h Portable Elastomeric Infusion System; Baxter Healthcare Corporation, Deerfield, Ill), which delivered 0.15% bupivacaine or saline solution at a rate of 2 mL/h. The nurse connecting the infusion bag to the catheter, the surgeons, the patient, and the nurse evaluating the pain score were all blinded to the nature of the infusion. PCA was used as the rescuing method of pain control in all patients. Its solution contained morphine 0.5 mg/mL, fentanyl 5 μg/mL, and tenoxicam 0.8 mg/mL with a basal infusion rate of 0.1 mL/h, bolus dose of 1 mL, and a lockout period of 15 minutes, delivered by Aim Plus (Abbott Laboratories, North Chicago, Ill).

Participants were visited by members of the pain service every 8 hours to document PCA dosage, resting and motion verbal analog scores (0–10; 0 = no pain; 10 = worst pain imaginable). At each visit, resting pain score was recorded first; then the patient was asked to take a deep breath and the increasing pain intensity that resulted was recorded as the motion pain score. If the patient was still intubated, we asked whether he or she had a pain score of 10 points. If this was not the case, we repeated the question decreasing the score 1 point at a time until the patient confirmed the answer by nodding. If the patient's conscious state did not allow pain evaluation (Sedation-Agitation Scale ≤ 2 or ≥ 6), his or her data were removed from analysis. The thoracotomy wound infusion catheter was removed 48 hours after the operation. The intravenous PCA was changed to another pain control method (oral or parenteral NSAIDs or opioids) at 72 hours after the operation. We documented PCA requirements in the first 72 hours. The demographic data of patients, comorbidity, extubation time, duration of intensive care unit (ICU) stay and hospital stay, wound complications, and arrhythmia were recorded. At 90 days after the operation, we evaluated each patient's intensity of wound pain by telephone.

Statistics

In a pilot investigation, patients using only PCA had a mean pain score 3 ± 1.0. Assuming a reduction in the mean pain score to 2 after addition of bupivacaine wound infusion to be clinically significant, 16 patients were needed in each group to achieve 80% power and 95% significance. We enrolled 20 patients in each group. The χ^2 and Fisher exact tests were used to examine the categorical data. The Mann–Whitney U test was used to reveal the differences of pain scores and other continuous variables. Noncategorical data were expressed as mean $\pm$ standard deviation. A p value of less than 0.05 was considered significant. All statistic results were calculated by the small STATA 8.2 version (Stata Corporation, College Station, Tex).

Results

Forty patients were enrolled, with 1 patient in each group being excluded as a result of protocol violation (limited consciousness), which left 19 patients in each group for full data analysis. There were no significant differences between the sham and bupivacaine infusion groups in gender, age, height, and weight, or major systemic diseases (Table 1). The distribution of surgical procedure was also similar.

There were no differences in time to extubation, ICU, or hospital stay. Although not statistically significant, there appeared to be a trend in reduction of PCA requirements when bupivacaine was infused into the wound (Table 1). In the first 72 hours there were no differences in arrhythmia, and in the first 3 months there were no differences in wound complications such as infection or dehiscence between the sham and bupivacaine infusion groups.

The sham infusion group had greater and more persistent pain than the bupivacaine infusion group (Figure 1). Not only did the bupivacaine wound infusion reduce pain during the first 48-hour infusion period, but it also provided reduced pain at 24 hours after cessation of the infusion. At 3 months after the operation, the bupivacaine infusion group had significantly less pain than the sham infusion group.

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TABLE 1. Demographic data and perioperative characteristics

	Sham group (n = 19)	TWI (n = 19)	*P* value
Demographic data			
Gender (M/F)	12:7	13:6	NS
Age (y)	57.4 ± 15.2	59.7 ± 13.8	NS
Height (m)	1.59 ± 0.08	1.62 ± 0.10	NS
Weight (kg)	63.6 ± 12.9	63 ± 10.4	NS
Comorbidity			
Diabetes	4	2	NS
Hypertension	9	7	NS
Old stroke	1	0	NS
Obstructive lung disease	0	1	NS
Surgery type			
Coronary artery bypass	5	6	NS
Valve surgery	14	13	NS
Perioperative characteristics			
Operation time (h)	4.3 ± 0.7	4.2 ± 0.8	NS
Extubation time (h)	11.3 ± 8.9	14.4 ± 22.0	NS
ICU stay (h)	56.0 ± 22.6	55.6 ± 30.6	NS
Hospital stay (d)	12.0 ± 8.4	9.0 ± 3.6	NS
IVPCA consumption (mL)			
24 h	36.3 ± 17.3	26.8 ± 11.0	.095
48 h	67.6 ± 30.3	56.4 ± 22.4	.092
72 h	91.4 ± 40.7	70.5 ± 26.4	.117

TWI, Thoracotomy wound infusion; *ICU,* intensive care unit; *IVPCA,* intravenous patient-controlled analgesia; *NS,* not significant.

Discussion

In this study, we documented improved early (72 hours) and late (3 months) pain relief with thoracotomy wound infusion of bupivacaine in minimally invasive cardiac surgery.

Wound perfusion of local anesthetics effectively reduced pain in many different surgical settings.[17,19,20,22-27] To our knowledge, there is little information concerning the pain-reducing effect of local anesthetic wound infusion in thoracotomy wound for minimally invasive cardiac surgery. One retrospective study did demonstrate that a 4-mL/h infusion of 0.25% bupivacaine reduced pain scores and narcotic use compared with epidural analgesia after thoracotomy.[28] Very few studies have compared the efficacy of different pain control modalities in minimally invasive cardiac surgery. This study may be the first prospective trial demonstrating superior efficacy of local anesthetic infusion in the thoracotomy wound, especially for cardiac surgery.

Of substantial importance is that the reduction in pain 24 hours after the bupivacaine infusion was discontinued was not fully anticipated. However, the reduction in wound pain at 3 months was a remarkable and significant clinical finding. Local anesthetic infusion has been shown to improve both acute and chronic pain at the iliac crest bone harvest site.[18] Peripheral and central pain sensitization contributes to persistence of acute pain and induction of chronic pain.[29] The concept of pre-emptive analgesia was first introduced on the belief that by reducing initial pain sensitization, pain-controlling drugs or methods could be more effective in reducing acute pain and even chronic pain if administered before rather than after tissue injury.[30-32] Pre-emptive analgesia has been recently challenged as a result of conflicting results in large trials in some surgical settings.[33-35] Recent evidence shows that perioperative afferent input of sensitized nociceptors is of great importance in pain sensitization and chronic pain formation.[36] This was demonstrated not only by the reduction in acute pain, but also by a reduction in chronic pain 3 months after iliac crest bone harvesting with wound infusion of ropivacaine.[18] In our study, the local anesthetic infusion was initiated at the time of wound closure before emergence from general anesthesia. This provided uninterrupted analgesia contributing to short- and long-term pain relief.

Effective pain control has been associated with reduced time to extubation and pulmonary complication.[12,13] This is thought to be a result of reduced chest splinting caused by pain with deep breathing. In this study, wound infusion of bupivacaine reduced pain both at rest and while taking a deep breath, yet it did not reduce time to extubation. This may be due to a difference in the practice of our ICU. Weaning profile was not evaluated until several hours after surgery. Our effort in reducing pain did not change the practice of our ICU colleagues. There is large variation in the recovery profile (Table 1), and numerous factors affecting time to extubation including preoperative lung function, postoperative

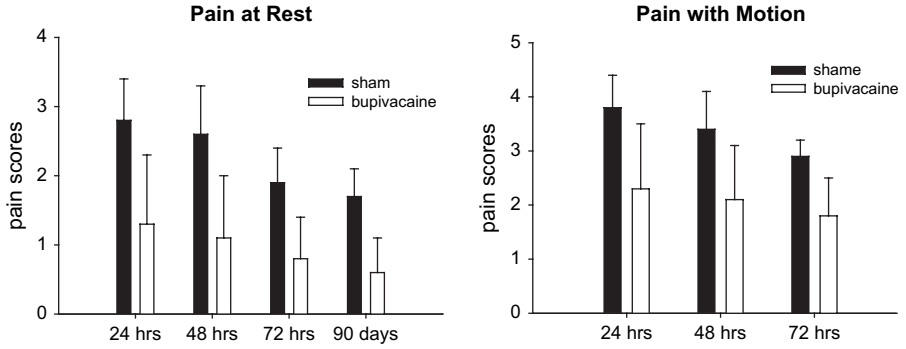

Figure 1. Placement of the epidural catheter in the wound and the fixed catheter circled with 5–0 Prolene polypropylene (Ethicon, Inc, Somerville, NJ).

bleeding, ventricular function, and other comorbidities may make the benefit of reduced pain less significant.

Reduced requirement for analgesics is often used as a parameter to evaluate the effectiveness of specific analgesic procedures. In this study, there was a trend of reducing PCA requirements in the bupivacaine infusion group. Increasing the group size may have revealed a difference in this outcome. However, reduced pain at all intervals in the bupivacaine group supports this analgesic regimen.

Delivered through a catheter embedded in the wound during closure, the infusion of local anesthetics is a simple method that has little effect on the duration of surgery (Table 1). The placement of a thoracic epidural catheter would cause further delay and increase operating room expenditures. The major concern of local anesthetic infusion is neurologic or cardiovascular toxicity of local anesthetics. A 4-mL/h infusion of 0.5% or 0.25% bupivacaine in the sternotomy resulted in safe serum concentrations (<2 μg/mL) in the study by White and associates[19] We did not document serum concentrations, yet there was no observation of arrhythmias in the bupivacaine group.

Local anesthetic infusion is a relatively new technique in minimally invasive cardiac surgery. There is a large amount of literature on analgesic use after thoracotomy for lung surgery; however, data on analgesic methods in minimally invasive cardiac surgery is still inadequate. Additional studies comparing opioid, thoracic epidural analgesia, intercostal block, and wound infusion of local anesthetics are needed to determine the most effective and safest method of pain control. As clinical trials are published and as clinical experience increases, the optimal analgesic modalities or combined modalities will optimize the risk/benefit/expense ratio.

Conclusion

Localized wound infusion of bupivacaine is a simple and highly effective alternative to parenteral opioid analgesia, which substantially reduces acute and chronic pain in patients undergoing minimally invasive cardiac surgery.

References

1. Grossi EA, LaPietra A, Ribakove GH, Delianides J, Esposito R, Culliford AT, et al. Minimally invasive versus sternotomy approaches for mitral reconstruction: comparison of intermediate-term results. *J Thorac Cardiovasc Surg*. 2001;121:708-13.
2. Aybek T, Dogan S, Risteski PS, Zierer A, Wittlinger T, Wimmer-Greinecker G, et al. Two hundred forty minimally invasive mitral operations through right minithoracotomy. *Ann Thorac Surg*. 2006;81: 1618-24.
3. Yamada T, Ochiai R, Takeda J, Shin H, Yozu R. Comparison of early postoperative quality of life in minimally invasive versus conventional valve surgery. *J Anesth*. 2003;17:171-6.
4. Doll N, Borger MA, Hain J, Bucerius J, Walther T, Gummert JF, et al. Minimal access aortic valve replacement: effects on morbidity and resource utilization. *Ann Thorac Surg*. 2002;74:S1318-22.
5. Magovern JA, Benckart DH, Landreneau RJ, Sakert T, Magovern GJ Jr. Morbidity, cost, and six-month outcome of minimally invasive direct coronary artery bypass grafting. *Ann Thorac Surg*. 1998;66:1224-9.
6. Sharony R, Grossi EA, Saunders PC, Schwartz CF, Ursomanno P, Ribakove GH, et al. Minimally invasive reoperative isolated valve surgery: early and mid-term results. *J Card Surg*. 2006;21:240-4.
7. Onnasch JF, Schneider F, Falk V, Walther T, Gummert J, Mohr FW. Minimally invasive approach for redo mitral valve surgery: a true benefit for the patient. *J Card Surg*. 2002;17:14-9.
8. Borges MF, Coulson AS. Minimally invasive coronary bypass surgery: postoperative pain management using intermittent bupivacaine infiltration. *Br J Anaesth*. 1998;80:519-20.
9. Benedetti F, Amanzio M, Casadio C, Cavallo A, Cianci R, Giobbe R, et al. Control of postoperative pain by transcutaneous electrical nerve stimulation after thoracic operations. *Ann Thorac Surg*. 1997;63:773-6.
10. Erdogan M, Erdogan A, Erbil N, Karakaya HK, Demircan A. Prospective, randomized, placebo-controlled study of the effect of TENS on postthoracotomy pain and pulmonary function. *World J Surg*. 2005; 29:1563-70.
11. Chaney MA. How important is postoperative pain after cardiac surgery? *J Cardiothorac Vasc Anesth*. 2005;19:705-7.
12. Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. *Anesthesiology*. 2004;101:153-61.
13. Scott NB, Turfrey DJ, Ray DA, Nzewi O, Sutcliffe NP, Lal AB, et al. A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. *Anesth Analg*. 2001;93:528-35.
14. Deneuville M, Bisserier A, Regnard JF, Chevalier M, Levasseur P, Herve P. Continuous intercostal analgesia with 0.5% bupivacaine after thoracotomy: a randomized study. *Ann Thorac Surg*. 1993;55:381-5.
15. Tiippana E, Nilsson E, Kalso E. Post-thoracotomy pain after thoracic epidural analgesia: a prospective follow-up study. *Acta Anaesthesiol Scand*. 2003;47:433-8.
16. Chaney MA, Labovsky JK. Thoracic epidural anesthesia and cardiac surgery: balancing postoperative risks associated with hematoma formation and thromboembolic phenomenon. *J Cardiothorac Vasc Anesth*. 2005;19:768-71.
17. Singh K, Samartzis D, Strom J, Manning D, Campbell-Hupp M, Wetzel FT, et al. A prospective, randomized, double-blind study evaluating the efficacy of postoperative continuous local anesthetic infusion at the iliac crest bone graft site after spinal arthrodesis. *Spine*. 2005;30: 2477-83.
18. Blumenthal S, Dullenkopf A, Rentsch K, Borgeat A. Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. *Anesthesiology*. 2005;102:392-7.
19. White PF, Rawal S, Latham P, Markowitz S, Issioui T, Chi L, et al. Use of a continuous local anesthetic infusion for pain management after median sternotomy. *Anesthesiology*. 2003;99:918-23.
20. Gupta S, Maheshwari R, Dulara SC. Wound instillation with 0.25% bupivacaine as continuous infusion following hysterectomy. *Middle East J Anesthesiol*. 2005;18:595-610.
21. Nechleba J, Rogers V, Cortina G, Cooney T. Continuous intra-articular infusion of bupivacaine for postoperative pain following total knee arthroplasty. *J Knee Surg*. 2005;18:197-202.
22. Wu CL, Partin AW, Rowlingson AJ, Kalish MA, Walsh PC, Fleisher LA. Efficacy of continuous local anesthetic infusion for postoperative pain after radical retropubic prostatectomy. *Urology*. 2005;66: 366-70.
23. Morgan SJ, Jeray KJ, Saliman LH, Miller HJ, Williams AE, Tanner SL, et al. Continuous infusion of local anesthetic at iliac crest bone-graft sites for postoperative pain relief. A randomized, double-blind study. *J Bone Joint Surg Am*. 2006;88:2606-12.
24. Valkila J, Laranne J, Baer G, Pukander J. How we do it: regular infusion of local anaesthetic in the pedicle of pectoralis major myocutaneous flap to shorten hospitalization of surgically treated head and neck cancer patients. *Clin Otolaryngol*. 2005;30:472-4.
25. Magnano D, Montalbano R, Lamarra M, Ferri F, Lorini L, Clarizia S, et al. Ineffectiveness of local wound anesthesia to reduce postoperative pain after median sternotomy. *J Card Surg*. 2005;20:314-8.
26. Kushner DM, LaGalbo R, Connor JP, Chappell R, Stewart SL, Hartenbach EM. Use of a bupivacaine continuous wound infusion system in gynecologic oncology: a randomized trial. *Obstet Gynecol*. 2005;106:227-33.

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27. Schurr MJ, Gordon DB, Pellino TA, Scanlon TA. Continuous local anesthetic infusion for pain management after outpatient inguinal herniorrhaphy. *Surgery*. 2004;136:761-9.
28. Wheatley GH 3rd, Rosenbaum DH, Paul MC, Dine AP, Wait MA, Meyer DM, et al. Improved pain management outcomes with continuous infusion of a local anesthetic after thoracotomy. *J Thorac Cardiovasc Surg*. 2005;130:464-8.
29. Dirks J, Moiniche S, Hilsted KL, Dahl JB. Mechanisms of postoperative pain: clinical indications for a contribution of central neuronal sensitization. *Anesthesiology*. 2002;97:1591-6.
30. Bourke DL. Preemptive analgesia: an early observation. *Anesth Analg*. 1992;75:637.
31. Woolf CJ, Chong MS. Preemptive analgesia—treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg*. 1993;77:362-79.
32. Katz J, Kavanagh BP, Sandler AN, Nierenberg H, Boylan JF, Friedlander M, et al. Preemptive analgesia. Clinical evidence of neuroplasticity contributing to postoperative pain. *Anesthesiology*. 1992;77:439-46.
33. Hogan QH. No preemptive analgesia: is that so bad? *Anesthesiology*. 2002;96:526-7.
34. Vallejo MC, Phelps AL, Sah N, Romeo RC, Falk JS, Johnson RR, et al. Preemptive analgesia with bupivacaine for segmental mastectomy. *Reg Anesth Pain Med*. 2006;31:227-32.
35. Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg*. 2005;100:757-73, table of contents.
36. Pogatzki-Zahn EM, Zahn PK. From preemptive to preventive analgesia. *Curr Opin Anaesthesiol*. 2006;19:551-5.