A Randomized, Double-blind Comparison of the Effects of Interpleural Bupivacaine and Saline on Morphine Requirements and Pulmonary Function after Cholecystectomy

Timothy R. VadeBoncouver, M.D.,* Francis X. Riegler, M.D.,* Rory S. Gault, M.D.,* Guy L. Weinberg, M.D.†

The effect of interpleural bupivacaine and saline placebo on morphine requirements and pulmonary function after cholecystectomy was investigated. Twenty-six patients were randomly assigned on postoperative day 1 to receive either 20 ml preservative-free saline (group 1) or 20 ml 0.5% bupivacaine with epinephrine, 5 μg/ml (group 2) through an interpleural catheter. Adequacy of pain relief was determined by the amount of morphine used by the patient following interpleural injection. Morphine use via a patient-controlled analgesia (PCA) system was recorded for several hours before and after interpleural injection. All patients had a forced vital capacity (FVC) and FEV\textsubscript{1} measurement immediately before and 1 h after interpleural injection. Mean hourly PCA morphine use ranged from 1.6 to 2.8 mg for the 6 h prior to interpleural treatment for groups 1 and 2. There was no difference in PCA use between the groups during this time. Group 1 patients did not reduce PCA morphine use after interpleural saline. Patients in group 2, however, significantly reduced PCA morphine use after interpleural bupivacaine. Mean PCA morphine use for group 2 was 0.38 ± 0.15 mg/h (mean ± SE) (81% reduction vs. control) for the first 2 h after bupivacaine (P < 0.05). Mean PCA use in group 2 was 0.52 ± 0.2 mg/h (73% reduction vs. control) for the third hour after bupivacaine (P < 0.05).

At the fourth and fifth hours after bupivacaine injection, mean PCA morphine use was not significantly different from that in group 1. FVC and FE\textsubscript{1} did not improve after interpleural saline. In group 2 FVC increased from 1.29 ± 0.1 to 1.76 ± 0.1 l (P < 0.06) after interpleural bupivacaine, whereas FE\textsubscript{1} improved from 0.97 ± 0.1 to 1.53 ± 0.15 l (P < 0.05). In summary, interpleural bupivacaine significantly reduced PCA morphine requirements, and this effect lasted approximately 3 h. Interpleural bupivacaine also had a favorable effect on FVC and FE\textsubscript{1}. (Key words: Analgesics: patient-controlled. Analgesics, opioid: morphine. Anesthetics, local: bupivacaine. Anesthetic techniques: interpleural. Lung function: Pain: postoperative.)

The interpleural injection of local anesthetics is reported to provide effective analgesia following surgery with a subcostal incision.\textsuperscript{1-4} Reiestad and Stromskag\textsuperscript{1} first described the successful use of interpleural bupivacaine following cholecystectomy, and Brismar et al.\textsuperscript{2} designed the first controlled study to compare the analgesic effects of interpleural bupivacaine and saline, as determined by differences in visual analog scale (VAS) pain scores. Other studies\textsuperscript{5,6,7} have also used VAS scores or requests for parenteral narcotics as evidence of analgesia after interpleural injection. We sought to quantify the analgesic efficacy of interpleural bupivacaine following cholecystectomy by comparing opioid requirements before and after interpleural injections of bupivacaine or saline placebo. We used morphine administered via patient-controlled analgesia (PCA) devices to allow patients to continually titrate opioid dosage to their specific analgesic needs. We also measured patients' forced vital capacity (FVC) and FE\textsubscript{1} before and after interpleural injection to determine the effect of interpleural bupivacaine or saline on pulmonary function.

Methods

This study was approved by the Michael Reese Hospital Institutional Review Board. ASA physical status 1 and 2 patients scheduled for elective cholecystectomy were eligible for study. Patients were excluded from participation for any condition precluding interpleural catheter placement (i.e., pleural effusion, recent pneumonia, pleural fibrosis, or other pleural pathology) or PCA (i.e., history of drug abuse, age). The Harvard Bard PCA system was explained to patients before surgery, and postoperatively they were instructed to use the PCA pump, whenever needed, for pain relief.

After obtaining written informed consent, all patients underwent general anesthesia. At the conclusion of surgery and while still anesthetized, the patients were placed in the left lateral decubitus position and an interpleural catheter was inserted at the level of the right seventh rib in the midaxillary line using the technique of Reiestad and Stromskag.\textsuperscript{1} No interpleural injection was made in the operating room. Perioperative analgesia was provided by iv morphine given in the operating room or recovery room. While in the recovery room, a right lateral decubitus chest x-ray film was taken to ensure proper catheter placement and to check for pneumothorax. The interpleural catheters were injected with 2 ml of iohexol (Omnipaque 300, Winthrop-Breon Laboratories) in 18 ml of preservative-free saline prior to x-ray. Catheters were judged to be properly placed if a small radio-opaque "effusion" was present. The test drug was not administered.

* Resident Physician.
† Attending Physician; Assistant Professor.

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Address reprint requests to Dr. VadeBoncouver: Department of Anesthesiology, Michael Reese Hospital and Medical Center, Lake Shore Drive at 31st Street, Chicago, Illinois 60616.
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<th>Saline (group 1)</th>
<th>Bupivacaine (group 2)</th>
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<tr>
<td>N</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>36.6 ± 4.2 (23–71)</td>
<td>31.3 ± 2.4 (24–41)</td>
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<tr>
<td>Weight (kg)</td>
<td>78.3 ± 4.1 (68–95)</td>
<td>70.2 ± 5.3 (59–105)</td>
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<tr>
<td>Height (cm)</td>
<td>164.8 ± 5.0 (160–178)</td>
<td>159 ± 1.5 (150–163)</td>
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<tr>
<td>Pre-PCA morphine (mg)</td>
<td>5.0 ± 0.62 (3–10)</td>
<td>5.6 ± 0.86 (2–10)</td>
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Data are mean ± SE, with ranges in parentheses.

via the interpleural catheter until the morning of the first postoperative day.

When patients were awake and alert in the recovery room, PCA therapy was initiated with the following orders: 1 mg morphine sulfate every 3 min as needed and up to a maximum use of 10 mg of morphine per hour. The patients received no continuous morphine infusion and no opioids or sedatives other than the PCA morphine.

On the morning after surgery each patient’s hourly PCA morphine use was determined. Because PCA use is one variable being studied, we decided to eliminate patients from additional study if they used 2 mg of morphine or less for the 6 h prior to scheduled interpleural injection. A bedside pulmonary function (Eagle One Pulmonary Function Analyzer, Warren E. Collins, Inc.) profile was performed just prior to catheter injection with the patient in the upright sitting position. FVC and FEV₁ were measured, and the highest value of three attempts was recorded. Each patient was then positioned supine, and the interpleural catheter was injected for the first time with 20 ml of either preservative-free saline (group 1) or 20 ml of 0.5% bupivacaine containing 5 µg/ml epinephrine (group 2). The contents of the syringe were determined at random and were unknown to both physician and patient. One hour after interpleural injection, FVC and FEV₁ were reassessed, and hourly PCA use for the 6 h after interpleural injection was recorded.

We compared hourly PCA morphine use for the 6 h before and after interpleural injection. Six hours was chosen as the period of analysis because previous studies have reported analgesia from a single dose of 20 ml of 0.5% bupivacaine to last from 4 to 6 h. We also compared the FVC and FEV₁ immediately before and 1 h after the injection of interpleural bupivacaine or saline.

All results are presented as mean ± SEM. PCA morphine use in groups 1 and 2 was compared using two-way repeated measures ANOVA. Comparisons between groups 1 and 2 were made using Tukey HSD adjusted for six simultaneous comparisons. Paired t tests were used to compare preinterpleural and postinterpleural injection FVC and FEV₁. A P value less than 0.05 was considered significant.

Results

Twenty-six patients consented to be studied. All patients studied were female. Six patients were eliminated from the study prior to injection of their interpleural catheter. Two of these patients had their PCA pumps accidently turned off, making retrieval of their PCA morphine use impossible. Four patients were dropped from the study because they had used less than 2 mg of PCA morphine for the particular 6 h prior to scheduled interpleural injection. Ten patients in the bupivacaine group and ten patients in the saline group completed the study. The two groups were similar with regard to age, height, and weight (table 1). Patients in both groups averaged 5–6 mg of iv morphine prior to starting PCA therapy in the recovery room. There was no difference in this pre-PCA morphine dose between the two groups. All patients had correct interpleural catheter placement verified by chest x-ray after injection of contrast material. Pneumothorax and other anesthesia-related complications were not present in any of the patients studied.

Mean hourly PCA morphine use for groups 1 and 2 ranged from 1.6 mg to 2.8 mg for the 6 h prior to interpleural injection (fig. 1). During this period there were no statistically significant differences found between the two groups with respect to their morphine use. Patients in group 1 did not reduce their PCA use after interpleural injection of saline (fig. 1). These patients averaged 1.2–2.8 mg of PCA morphine per hour for the 6 h after treatment. This was not significantly different from group 1 PCA use before interpleural injection.

Patients in group 2 showed marked reductions in PCA morphine use after interpleural bupivacaine (fig. 1). Hourly morphine use was 0.38 ± 0.15 mg for each of the first 2 h after treatment. This is 81% below the mean values for the first 2 h after interpleural saline. Hourly morphine use was 0.52 ± 0.20 mg and 0.92 ± 0.21 mg, respectively, for the third and fourth hours after treatment. These represent 73% and 67% reductions, respectively, from the mean values for the third and fourth hours after interpleural saline. The values for the first 3 h after interpleural bupivacaine are significantly less (P < 0.05)
than the values for the corresponding times after interpleural saline. By the fourth and fifth hours after interpleural bupivacaine, PCA morphine use in group 2 was not significantly different from that for the same time period in group 1. PCA morphine use in group 2 was significantly greater than that in group 1 during the sixth hour after interpleural injection ($P < 0.05$).

Six patients in each group had FVC and FEV₁ measurements immediately before and 1 h after interpleural injection. FVC in group 1 before and after interpleural saline was $1.10 \pm 0.20$ l and $1.07 \pm 0.21$ l, respectively (table 2). These values are not significantly different. For group 2 the FVC was $1.29 \pm 0.10$ before and $1.76 \pm 0.10$ l after interpleural bupivacaine. This 44% increase in FVC after interpleural bupivacaine reached a significance level of $P = 0.06$, preinterpleural versus postinterpleural bupivacaine FVC.

FEV₁ in group 1 averaged $0.89 \pm 0.15$ l and $0.87 \pm 0.17$ l, respectively, before and after interpleural saline. These values are not significantly different. In group 2 FEV₁ following bupivacaine injection ($1.53 \pm 0.15$ l) was significantly greater ($P < 0.05$, paired $t$ test) than the FEV₁ before bupivacaine ($0.97 \pm 0.1$ l). The average increase in FEV₁ after interpleural injection was $63 \pm 21\%$ in group 2 and $8 \pm 6\%$ in group 1.

**Discussion**

Interpleural injection of 20 ml 0.5% bupivacaine significantly and reproducibly reduced PCA morphine use for several hours in patients following cholecystectomy. Patients receiving interpleural bupivacaine also showed increases in FEV₁ and FVC over preinjection values; however, the change was statistically significant for only FEV₁. Conversely, patients who received interpleural saline did not decrease their PCA use and showed no change in results of pulmonary function tests (PFT). These results indicate that interpleural bupivacaine provides sustained

**Table 2. FVC and FEV₁ before and after Interpleural Administration of Saline or Bupivacaine**

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<td></td>
<td>Before</td>
<td>After</td>
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<tr>
<td>FVC</td>
<td>$1.1 \pm 0.2$</td>
<td>$1.07 \pm 0.21$</td>
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<tr>
<td>FEV₁</td>
<td>$0.89 \pm 0.15$</td>
<td>$0.87 \pm 0.17$</td>
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Values are given in liters and expressed as mean ± SE.
pain relief after cholecystectomy and that such therapy has a salutary effect on pulmonary function.

Previous studies of interpleural analgesia have relied on subjective assessments of pain relief. For example, Brismar et al. compared the effects of interpleural bupivacaine with those of saline and measured pain with the VAS. They considered a VAS reduction of three or more as indicating adequate analgesia and found all patients receiving interpleural bupivacaine met this criteria, whereas none who received saline had such a reduction in VAS. However, the actual pain scores were not reported, and one cannot determine whether the patients with "adequate" analgesia had only minor VAS reductions. Although numerous authors have reported profound pain relief from interpleural bupivacaine after upper abdominal surgery, the aforementioned study is the only previous work to use a control group. Two difficulties faced by such studies are how to quantify pain relief and how to administer interpleural placebo while still maintaining patient analgesia. We solved both problems by allowing patients to use a PCA system. Hourly opioid use via PCA is typically high for the first several hours postoperatively. This initial "loading" period is followed by a period of lower, yet constant, opioid usage lasting from 6 to 30 h after PCA is begun. This trend was also observed in our study. We hypothesize that an analgesic therapy administered during this period will reduce PCA use to a degree proportionate to its analgesic efficacy and for a duration equal to that for which the therapy is effective. It should be noted that in patients who received bupivacaine, PCA use in the sixth hour after interpleural injection was significantly greater than that in the saline group. This may reflect the need for these patients to rebolus with opioid to achieve analgesia after the effects of interpleural bupivacaine have subsided. Plasma morphine levels likely would have been subanalgesic at this time because PCA use was reduced during the period of analgesia produced by interpleural bupivacaine.

We chose arbitrarily to eliminate from study any patient who did not use at least 2 mg of PCA morphine during the 6 h prior to scheduled interpleural injection. A total of four patients were eliminated from additional study for this reason. Two patients reported that they were not having pain and therefore did not need to activate the PCA pump. The other two patients were having pain but did not fully understand how to activate the PCA pump to dose themselves. Although the preinterpleural study period of 6 h coincided with normal sleep time, our patients were awake enough to dose themselves consistently during this period. All patients who were eliminated from the study received interpleural analgesia for the remainder of their postoperative course.

Previous studies have reported a duration of analgesia of 6–10 h following a single interpleural injection of 20 ml of 0.5% bupivacaine. Our results are in agreement with those of Frank et al. and Brismar et al. in that analgesia lasted from 3 to 6 h. These studies and others employed VAS and requests for intramuscular opioids as evidence for analgesia. We equated requests for PCA as evidence of pain and observed a shorter analgesic duration in our study compared with other studies. We are unable to explain the difference. Perhaps requests for PCA are a more sensitive indicator of analgesia, and account partly for the shorter duration of "adequate" analgesia in our study.

Brismar et al. reported improvements in pulmonary function after 10 ml of 0.25% interpleural bupivacaine following cholecystectomy. They showed no increase in FVC after interpleural saline and increases of 69 ± 24% after bupivacaine. Similarly, FEV1 increased by 62 ± 22% after interpleural bupivacaine, compared with increases of 1 ± 10% after saline. Although we demonstrated significant increases only in FEV1 after interpleural bupivacaine, several points should be emphasized. First, we measured PFT in our patients at 16–24 h after surgery, when pulmonary and diaphragmatic function is expected to be most compromised. Second, our patients received several hours of PCA morphine prior to pulmonary testing. Third, as suggested by Covino, a direct effect of interpleural bupivacaine on phrenic nerve and diaphragmatic function could exist. Therefore, any improvement in lung volume produced by painless breathing may be opposed by the respiratory depressant action of morphine, the effects of surgery, and the effects of interpleural bupivacaine on diaphragmatic function.

We believe interpleural bupivacaine provides analgesia of excellent quality that can be sustained if catheters are reinjected every 4–6 h. This creates certain disadvantages when employing the technique for widespread use. Because the injection of large volumes of local anesthetic must be done by an anesthesiologist, significant manpower problems arise when many patients are receiving interpleural analgesia at the same time. Although continuous infusions of interpleural bupivacaine have been used successfully in patients with rib fractures, no such data exist for patients following upper abdominal surgery. Studies are needed to determine whether continuous interpleural infusions can sustain the profound analgesia seen with single injections. A possible limitation of any continuous interpleural technique is the danger of producing toxic blood levels of local anesthetic. Although we did not measure plasma bupivacaine levels in this study, none of our patients experienced symptoms suggestive of local anesthetic toxicity. Previous studies have shown the 20
ml dose of 0.5% bupivacaine to be safe, with peak plasma bupivacaine levels rarely exceeding 2 μg/ml.

The advantages of interpleural analgesia, i.e., lack of respiratory depression or hypotension, simplicity of technique, and the high quality of pain relief, are well described.1,3 We know of no data comparing interpleural bupivacaine with epidural opioids or epidural opioid–local anesthetic solutions for analgesia following upper abdominal surgery. Although epidural analgesia is an effective form of pain relief, it is not without untoward complications and side effects. Studies are needed comparing the effects of epidural and interpleural analgesia on quality of pain relief, incidence of complications, and length of postoperative hospital stay.

In summary, we found that the interpleural injection of bupivacaine provided analgesia sufficient to decrease opioid requirement as measured by patients’ use of PCA. This strategy allows hourly quantification of analgesia and is a useful alternative to VAS scores for determining the intensity, duration, and pattern of recovery from interpleural analgesia. The salutory effect of this treatment on pulmonary function and the decrease in opioid requirement suggest that interpleural bupivacaine may also improve postoperative outcome.

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