Double-blind comparison of intrapleural saline and 0.25% bupivacaine for ipsilateral shoulder pain after thoracotomy in patients receiving thoracic epidural analgesia

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Background. The aim of this prospective double-blind randomized placebo-controlled study was to investigate the effect of intrapleural bupivacaine on ipsilateral post-thoracotomy shoulder pain in patients receiving thoracic epidural analgesia.

Methods. Of the 68 patients recruited to the study, 41 (60%) developed ipsilateral shoulder pain within 2 h of surgery. These patients were randomly assigned to receive either 40 ml of intrapleural bupivacaine 0.25% with epinephrine 1:200 000 or 40 ml of intrapleural saline. The study solution was injected into the tube of a basal drain that had been clamped distal to the site of administration. Shoulder pain at rest and on coughing was assessed using a visual analogue scale (VAS) and an observer verbal rating score (OVRS) immediately before and 30 min, 1 h, 2 h, 3 h and 4 h after intrapleural bupivacaine/saline. The total volume of epidural solution administered was recorded.

Results. Thirty-nine patients completed the study and were included in the analysis. There were no significant differences in baseline characteristics between the two groups. There were no significant differences between groups for VAS or OVRS pain scores at rest or with cough at any of the six assessment times. The total volumes of epidural solution administered to the bupivacaine and saline groups were 56 ml and 48 ml, respectively. This difference was not significant.

Conclusion. Intrapleural administration of 40 ml of bupivacaine 0.25% does not provide effective pain relief for ipsilateral post-thoracotomy shoulder pain.


Keywords: anaesthetics local, intrapleural bupivacaine; analgesic techniques, subarachnoid; complications, post-thoracotomy; pain, shoulder

Accepted for publication: September 23, 2004

Post-thoracotomy pain can be very severe. Thoracic epidural analgesia provides excellent post-thoracotomy pain relief in the dermatomes incised. However, many patients still experience a constant severe ache in the ipsilateral shoulder.1 Shoulder pain is often difficult to manage as it is relatively resistant to intravenous opioids and increased epidural infusion rates.2 This shoulder pain is referred from the diaphragm to the shoulder via the phrenic nerve and can be abolished by infiltrating the phrenic nerve with lidocaine at thoracotomy.2 However, this technique is not clinically useful as it is of short duration and is not repeatable. Longer-acting local anaesthetics may prolong the analgesia but would also prolong the associated hemidiaphragmatic weakness. A less invasive and repeatable method of controlling this pain would be desirable for routine clinical use.

Intrapleural blocks provide effective pain relief following cholecystectomy,3 but not following thoracotomy,4–7 probably because after thoracotomy the pleural space contains blood and air, promoting the dependent pooling of local anaesthetic and limiting the spread of local anaesthetics. We postulated that in the presence of a functioning thoracic epidural, intrapleural bupivacaine administered via the basal chest drain would pool at the site of this drain, reduce diaphragmatic irritation by the drain and be effective in reducing post-thoracotomy ipsilateral shoulder pain.

Methods

The study was approved by the local research ethics committee and written informed consent was obtained from 68 ASA I–III adult patients scheduled to undergo a thoracotomy for pulmonary resection and receive a thoracic epidural for post-thoracotomy analgesia. Patients with a contraindication to thoracic epidural analgesia, with pre-existing
shoulder pain or who could not understand the visual analogue scale (VAS) pain-scoring system after preoperative coaching were excluded.

Patients were premedicated with oral diazepam (5 or 10 mg) 2 h prior to surgery. When patients arrived in the anaesthetic room, a 20 g radial arterial cannula, a peripheral venous cannula and mid-thoracic epidural were inserted under local anaesthetic. Patients then received an epidural test dose of 3 ml bupivacaine 0.5%. After preoxygenation general anaesthesia was induced with propofol 2–3 mg kg\(^{-1}\) and neuromuscular blockade was maintained with repeated increments of atracurium. Anaesthesia was maintained with isoflurane in oxygen, the tube was confirmed with a fibre-optic bronchoscope.

Prior to the commencement of surgery patients received a 0.1 ml kg\(^{-1}\) bolus of an epidural solution containing fentanyl 5 \(\mu\)g ml\(^{-1}\) in bupivacaine 0.1%. The epidural solution was then infused at 0.1 ml kg\(^{-1}\) h\(^{-1}\). All patients were placed in the lateral position, with care being taken to avoid excessive strain on the shoulder joint by ensuring that there was <90% flexion of the upper arm. A standard surgical technique with respect to rib retraction and chest drain placement was used in all patients. All patients received one apical and one basal chest drain, except for those undergoing pneumonectomy who only received a basal drain.

In the postoperative period the adequacy of epidural dermatomal block was assessed by asking patients if they had pain or tenderness at the incision. The sensory block was mapped out using ice. If patients complained of incisional pain, they received an additional epidural bolus and the infusion rate was increased. The epidural infusion rate was decreased if the sensory block was extensive or if patients with no dermatomal pain became hypotensive. Patients who experienced characteristic isolated shoulder pain within 2 h of the end of surgery were randomly assigned to one of two groups by the hospital’s pharmacy department. One group of patients received 40 ml of intrapleural normal saline. The other group of patients received 40 ml of bupivacaine 0.25% with epinephrine 1:200 000 intrapleurally. The solutions were supplied by the pharmacy department and labelled with the patient’s name and number only to double blind the study.

Immediately prior to administering the study solutions the patient’s position was adjusted, if appropriate, to ensure that he or she was sitting upright in bed. The basal chest drain was clamped. Using an aseptic technique, the drain tube proximal to the clamp was cleaned with alcohol and the study solution injected via a 23 g needle into the basal drain proximal to the clamp. After administration of the solution, the needle was withdrawn but the drain was left clamped for a further 20 min. Throughout this time the apical drain remained open in those patients with residual lung in that hemithorax to prevent the risk of tension pneumothorax due to an air leak from the operated lung.

Shoulder pain, both at rest and with cough, was assessed immediately prior to administering the intrapleural study solution and then 30 min, 1 h, 2 h, 3 h and 4 h after administering the study solution. The severity of the pain was assessed using a 10 cm VAS, where zero represented no pain and 10 the worst pain imaginable, and a five-point observer verbal rating score (OVRS) (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; 4, agonizing pain). The volume of epidural used intraoperatively and until the end of the 4 h study period was recorded.

Tramadol 1 mg kg\(^{-1}\) was administered intravenously if patients complained of severe shoulder pain despite the instillation of the study solution. The time and dose of rescue medication were recorded.

**Statistical analysis**

A power calculation based on previous research\(^2\) showed that to have a 90% chance of showing a one-third reduction in VAS pain scores at a significance level of 0.05, a total sample size of 40 with 20 in each group was required. Data were tested for normality using the Kolmogorov–Smirnov test. Categorical data were analysed using the \(\chi^2\) test. The OVRS scores were analysed with the Wilcoxon rank sum test. VAS scores were tested using the area under the curve as a summary measure. \(P\) values of 0.05 were taken to be significant.

**Results**

Of the 68 patients recruited to this study, 41 developed ipsilateral shoulder pain within 2 h of surgery (an incidence of 60%). Of the 41 patients who developed shoulder pain, 21 were randomized to receive saline and 20 were randomized to receive bupivacaine. Two patients, both from the saline group, were excluded from the analysis, one because of incomplete study data and the other because of epidural failure (the epidural became detached and the patient developed dermatomal pain during the study period). There was no significant difference in age, gender, height, weight, ASA status or type of operation between the two groups for the 39 patients analysed (Table 1). Pain scores

| Table 1 | Patient and surgical details. Age is expressed as mean (range), and height and weight as mean (sd). Gender, ASA and type of operation are expressed as number of patients. There are no significant differences between the two groups |
|-----------------|-----------------|-----------------|
| **Patient and surgical details** | **Saline group** | **Bupivacaine group** |
| Age (yr) | 65 (34–81) | 64 (48–81) |
| Height (cm) | 167 (10) | 167 (9) |
| Weight (kg) | 77 (14) | 71 (15) |
| ASA (I/II/III) | 3/2/7 | 3/1/8 |
| Gender (M/F) | 11/8 | 12/8 |
| Type of operation | 3/14/2 | 2/17/1 |
at rest did not differ significantly between the two groups (Fig. 1 and Table 2). Similarly, pain scores with cough did not differ significantly between the two groups (Fig. 2).

Patients in the saline group received a mean (range) of 48 (34–85) ml of epidural solution, and those in the bupivacaine group received a mean (range) of 56 (15–75) ml of epidural solution. This difference was not statistically significant. Seven patients in the saline group (37%) and six patients in the bupivacaine group (30%) received supplementary analgesia (not statistically significant). The mean time at which breakthrough analgesia was administered was 71 min in the bupivacaine group and 49 min in the saline group (not statistically significant).

## Discussion

Post-thoracotomy pain can be very severe\(^8\) and controlling this pain is a challenge. Thoracic epidural analgesia provides excellent post-thoracotomy analgesia. There is accumulating evidence that thoracic epidural analgesic techniques utilizing local anaesthetics are superior to other techniques in reducing post-thoracotomy morbidity and mortality.\(^9\)–\(^12\) However, the analgesia provided by thoracic epidural analgesia is marred by the development of ipsilateral shoulder pain. The reported incidence of this ipsilateral shoulder pain varies from 75%\(^1\) to 85%.\(^2\) In this study, 60% of the patients developed shoulder pain. Shoulder pain contributes significantly to the total pain experienced by post-thoracotomy patients receiving thoracic epidural analgesia. When shoulder pain is absent or prevented by phrenic nerve block, patients report remarkably little pain.\(^1\) In contrast, patients with shoulder pain frequently described it as severe.\(^1\)

Shoulder pain, usually referred from the diaphragm to the shoulder via the phrenic nerve, is difficult to manage as it is relatively resistant to intravenous opioids and increased epidural infusion rates. Non-steroidal anti-inflammatory analgesics may be at least partially effective but are associated with significant adverse effects in this usually elderly population.\(^13\)–\(^15\) Infiltrating the phrenic nerve with lidocaine at thoracotomy is effective,\(^2\) but is not clinically useful as it is of short duration and not repeatable. Blocking the phrenic nerve with longer-acting local anaesthetics might prolong the analgesia, but this would also prolong the associated hemidiaphragmatic weakness.

Intrapleural blocks, i.e. the deposition of local anaesthetic between the visceral and parietal pleura, have been shown to provide effective analgesia after cholecystectomy.\(^3\) Although some advantage was seen in early post-thoracotomy intrapleural block studies,\(^16\)\(^17\) most post-thoracotomy studies, mainly performed later, showed little or no benefit.\(^4\)–\(^7\) The pleura are normally closely attached to each other and the wide spread of local anaesthetic within this potential space probably accounts for the effectiveness of intrapleural blocks after cholecystectomy. After thoracotomy the pleural space contains blood and air, dependent pooling of local anaesthetics is promoted and the spread of local anaesthetics is limited, probably accounting for the limited efficacy of intrapleural local anaesthesia in this setting. Loss of local anaesthetic into the chest drains\(^7\)\(^18\) may further limit the efficacy of this technique.

We had noted a reduction in shoulder pain after basal chest removal in post-thoracotomy patients and postulated that administering local anaesthetic via the chest drain might

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Table 2 Observer verbal rating pain scores for the saline and bupivacaine groups at rest and with cough. Values are median (range). There was no significant difference between the two groups.

<table>
<thead>
<tr>
<th>Time after intrapleural administration</th>
<th>Saline (n=19)</th>
<th>Bupivacaine (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>With cough</td>
<td>At rest</td>
</tr>
<tr>
<td>Baseline</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>30 min</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>60 min</td>
<td>1 (0–3)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>120 min</td>
<td>1 (0–3)</td>
<td>2 (0–4)</td>
</tr>
<tr>
<td>180 min</td>
<td>1 (0–3)</td>
<td>2 (0–3)</td>
</tr>
<tr>
<td>240 min</td>
<td>0 (0–2)</td>
<td>1 (0–4)</td>
</tr>
</tbody>
</table>
provide an effective method of controlling shoulder pain post-thoracotomy by reducing drain-related diaphragmatic irritation. In this study we found that 40 ml of bupivacaine 0.25% administered intrapleurally via a basal chest drain did not reduce post-thoracotomy shoulder pain in patients receiving a mid thoracic epidural. Table 2 shows that there was no significant difference between the two groups for OVRS pain scores at rest or with cough. Similarly, Figures 1 and 2 show that there was no significant difference between the two groups for VAS scores at rest and with cough.

Several reasons may account for our inability to show a reduction in pain scores with intrapleural bupivacaine. Chest-drain-mediated diaphragmatic irritation is not the only cause of post-thoracotomy shoulder pain. The diaphragm may be irritated by blood or become surgically abraded some distance from the basal drain. An intrapleural block can produce a diaphragmatic (phrenic nerve) block, but large potentially toxic doses may be required to produce this effect post-thoracotomy. A phrenic nerve block at the level of the diaphragm does not abolish shoulder pain in all patients. The phrenic nerve supplies sensory branches to the mediastinal pleura and the pericardium, and a more proximal block may be required to affect these branches. The presence of an accessory phrenic nerve is a further possibility. Distraction of the ipsilateral shoulder joint is a possible cause of post-thoracotomy shoulder pain that is unlikely to have been influenced by intrapleural bupivacaine. We consider this unlikely in this study as care was taken to avoid distraction of the shoulder. Further, it has been shown that supraclavicular nerve block does not reduce this shoulder pain, suggesting that shoulder injury is rarely the cause of this shoulder pain. Loss of local anaesthetic into the chest drains is a further possible explanation for the ineffectiveness of intrapleural bupivacaine in this study. However, we clamped the basal drain before and for 20 min after the administration of bupivacaine to minimize this possibility.

The volume of local anaesthetic used may have been insufficient to reach the part of the diaphragm being irritated and producing shoulder pain. Dilution of the bupivacaine by blood within the pleural cavity may have resulted in a bupivacaine concentration at the level of the diaphragmatic surface that was too low to be effective. A higher dose of bupivacaine might have been more effective. However, post-thoracotomy the presence of a large raw area may expedite the absorption of bupivacaine and cause systemic toxicity. We considered that, to be clinically useful, intrapleural bupivacaine would need to be safe and repeatable and thus effective after modest doses (1.5 mg kg⁻¹). Peak plasma bupivacaine concentrations in patients undergoing thoracotomy who received 1.5 mg kg⁻¹ of intrapleural bupivacaine (40 ml of bupivacaine 0.25% for a 70 kg patient) have been shown to be 1.50 μg ml⁻¹. Increasing toxicity is seen with plasma bupivacaine levels above 2–4 μg ml⁻¹. We considered 1.5 mg kg⁻¹ of bupivacaine to be an appropriate dose if it was to be repeatable in patients receiving an epidural bupivacaine infusion. The outcome measures in this trial were aimed primarily at showing that shoulder pain following thoracotomy could be reduced by administering intrapleural bupivacaine. Since blocking the intercostal nerves by diffusion of the local anaesthetic from the pleural space into the intercostal space would be expected to act synergistically with the epidural, a reduction in epidural requirement might have been expected in the bupivacaine group. The similar requirement in both groups is in keeping with the findings of others who concluded that intrapleural analgesia had little effect on pain control after lateral thoracotomy.

Ipsilateral post-thoracotomy pain remains a significant clinical management problem. Opioids and non-steroidal anti-inflammatory agents are far from ideal agents for use in this population. However, this randomized double blind study demonstrated that, despite being relatively non-invasive, the intrapleural administration of 40 ml of bupivacaine 0.25% with epinephrine 1:200 000 does not have a significant effect on ipsilateral shoulder pain post-thoracotomy.

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