Does the addition of clonidine affect duration of analgesia of bupivacaine wound infiltration in inguinal hernia surgery?

S. ELLIOTT, S. ECKERSALL, L. FLIGELSTONE AND S. JOTHILINGAM

Summary

We conducted a prospective, randomized, double-blind study to compare analgesia obtained by wound infiltration using 29 ml of 0.25% bupivacaine alone, or with the addition of clonidine hydrochloride 150 μg. A third group received bupivacaine wound infiltration with clonidine 150 μg i.m. to control for the systemic effects caused by absorption of clonidine. We studied 46 adults undergoing elective inguinal hernia repair. The general anaesthetic technique, postoperative analgesia and wound infiltration technique were standardized. There was no difference in time to first analgesic request or to total analgesic consumption between the three groups during the 24-h study. Visual analogue scores (VAS) at rest and after coughing were noted over a 24-h period. The only difference was higher VAS scores at rest at 24 h in the control group who received i.m. clonidine. We conclude that for elective inguinal hernia repair, postoperative analgesia obtained by bupivacaine wound infiltration was not improved by the addition of clonidine 150 μg. (Br. J. Anaesth. 1997; 79: 446–449).

Key words


Patients and methods

We studied 46 consecutive adult patients presenting for elective unilateral inguinal hernia repair in a double-blind randomized study. The study was approved by the local Ethics Committee and Medicines Control Agency, and written informed consent was obtained from all patients. Exclusion criteria included: patients receiving alpha adrenergic blocking drugs, those with Raynaud’s disease or thromboangiitis obliterans (caution is recommended as clonidine has been reported to cause a condition resembling Raynaud’s phenomenon), contraindications to the general anaesthetic technique or age less than 16 yr. Operations for recurrent hernia were excluded as the degree of dissection and thus tissue trauma would be expected to be greater than for first repairs.

All patients received the same general anaesthetic. Temazepam 10–20 mg was given orally 1 h before surgery. Anaesthesia was induced with propofol 2–3 mg kg⁻¹ and maintained with isoflurane and nitrous oxide in oxygen. Analgesia was provided with fentanyl 1–2 μg kg⁻¹. The airway was maintained with a laryngeal mask airway. Vecuronium was used to facilitate mechanical ventilation using a Drager Narkomed ventilator. Datex Cardiocap and Capnomac monitors were used to monitor non-invasive arterial pressure, electrocardiogram, pulse oximetry and blood-gas analysis.

Using envelope randomization, patients were allocated to one of three groups before surgery. During surgery, all patients received a 30-ml study mixture infiltrated into the wound and an i.m. injection was given by the anaesthetist into the contralateral deltoid muscle. This injection was either clonidine or saline, to control for any systemic effects of clonidine. Patients in group A underwent wound infiltration with bupivacaine 29 ml and 0.9% saline 1 ml, in addition to an i.m. injection of 0.9% saline 1 ml. Patients in group B underwent wound infiltration with bupivacaine 29 ml and clonidine 150 μg (1 ml), with an i.m. injection of 0.9% saline 1 ml.

Clonidine hydrochloride is an alpha₂ adrenoceptor agonist which has long been used to treat hypertension. In anaesthesia, clonidine given systemically has been found to decrease anaesthetic and analgesic drug requirements. Later it was found that when mixed with local anaesthetic, clonidine extended the duration of both the motor and sensory elements of spinal, extradural, axillary, femoral and intercostal nerve blocks.

As the synergistic effects of clonidine and bupivacaine have been recognized in a progressively peripheral manner, we attempted to continue this progression and show if it extends to the wound itself. Therefore, the purpose of this study was to examine if clonidine mixed with bupivacaine produced significant extension of postoperative analgesia obtained by performing wound infiltration during inguinal hernia repair.

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Patients in group C had wound infiltration with bupivacaine 29 ml and 0.9% saline 1 ml, with an i.m. injection of clonidine 150 μg (1 ml). A three-stage technique of wound infiltration before each stage of dissection was devised and performed by the surgeon. First, along the proposed line of incision, skin, subcutaneous fat and tissue deep to Scarpa’s fascia were infiltrated. After skin incision, further infiltration through the external oblique aponeurosis, and to the deep inguinal ring. The type of hernia repair was at the surgeon’s discretion.

Postoperative analgesia was provided by two co-dydramol tablets 4–6 hourly and morphine 10–15 mg i.m. 3–4 hourly if required for severe pain.

Patient randomization and preparation of the test mixture were performed by an investigator who did not act as observer subsequently. The patient, surgeon and all other medical and nursing staff were blinded to the patient’s treatment. Patient data were recorded by the ward nurses and the acute pain sister, and included: time to first dose of analgesic after operation and total analgesic requirements after operation, and visual analogue pain scores (VAS) at rest and on coughing, recorded in recovery and 6 and 24 h after operation. Patients was asked to indicate the degree of pain on a 10-cm line scale without gradations, the two ends marked “no pain” and “worst imaginable pain”. The type of surgical repair and duration of operation were recorded, together with any complications which required treatment.

Parametric data were expressed as mean (SD) and analysed using analysis of variance with Bonferroni multiple comparison test. Non-parametric data were expressed as median (range) and analysed using the Kruskal–Wallis test followed by Dunn’s multiple comparison test. Proportional data were analysed using the chi-square test. Results were considered significant at the 5% level.

**Results**

Results were obtained for 46 patients; 16 patients in group A, 15 in group B and 15 in group C. The three groups were matched for age, sex, duration and type of surgery (table 1). There was no significant differences in the time to first analgesia or total analgesic consumption (table 2). There was no difference between the rate at which patients in each group first requested analgesia (fig. 1) or the number requiring no analgesia.

Although not statistically significant, the addition of clonidine to bupivacaine appeared to confer an initial advantage in terms of VAS in the initial recovery period, although this was not apparent at 6 or 24 h (table 3). The only significant difference in VAS between groups was at rest 24 h after operation when the score for group C (3.9, range 0–8.4) was significantly higher than those in groups A (2, range 0–6.6) and B (1.2, range 0–6) (P < 0.05 Kruskal–Wallis test).

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.2 (16.6)</td>
<td>66.4 (12.7)</td>
<td>59.8 (17.5)</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>16:0</td>
<td>14:1</td>
<td>15:0</td>
</tr>
<tr>
<td>Repair (mesh:non-mesh)</td>
<td>14:2</td>
<td>11:4</td>
<td>13:2</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>54.8 (15.5)</td>
<td>61.2 (26.5)</td>
<td>56.3 (20.5)</td>
</tr>
</tbody>
</table>

*Table 1 Patient data and operative details (mean (SD or range) or number)*

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total morphine (mg)</td>
<td>0 (0–10)</td>
<td>10 (0–30)</td>
<td>10 (0–20)</td>
</tr>
<tr>
<td>Total co-dydramol (tablets)</td>
<td>4 (0–6)</td>
<td>2 (0–8)</td>
<td>4 (0–6)</td>
</tr>
<tr>
<td>Time to first analgesia (min) (mean (SD))</td>
<td>392 (418.8)</td>
<td>499 (469.9)</td>
<td>418 (466.9)</td>
</tr>
<tr>
<td>No analgesia required</td>
<td>1:15</td>
<td>2:13</td>
<td>1:14</td>
</tr>
</tbody>
</table>

*Table 2 Postoperative analgesic requirements in the first 24 h after inguinal hernia surgery. Data are median (range) except where indicated*

<table>
<thead>
<tr>
<th>Group</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS at rest in recovery</td>
<td>0.85 (0–5.3)</td>
<td>0 (0–4.5)</td>
<td>2.8 (0–7)</td>
</tr>
<tr>
<td>VAS on coughing in recovery</td>
<td>2.1 (0–7.6)</td>
<td>1.3 (0–8.1)</td>
<td>3.55 (0–7.1)</td>
</tr>
<tr>
<td>VAS at rest 6 h postop.</td>
<td>1 (0–8.3)</td>
<td>1.6 (0–4)</td>
<td>1.5 (0–8)</td>
</tr>
<tr>
<td>VAS on coughing 6 h postop.</td>
<td>2.35 (0–8.5)</td>
<td>4.75 (0–6.2)</td>
<td>3.3 (0–9.4)</td>
</tr>
<tr>
<td>VAS on coughing 24 h postop.</td>
<td>2 (0–6.6)</td>
<td>1.2 (0–6)</td>
<td>3.9 (0–8.4)</td>
</tr>
<tr>
<td>VAS on coughing 24 h postop.</td>
<td>3.5 (0–7.5)</td>
<td>4.4 (0.7–10)</td>
<td>5.6 (1.7–10)</td>
</tr>
</tbody>
</table>

*Table 3 Visual analogue scores (VAS) in the first 24 h after inguinal hernia surgery (median (range)). *P < 0.05 (Kruskal–Wallis)*

![Figure 1](image-url) Percentage of patients requiring analgesia in the 24 h after inguinal hernia repair in group A (●), group B (□) and group C (▲).
There was a higher incidence of adverse side effects in group C (three patients had bradycardia, associated with hypotension in two) requiring treatment with atropine and i.v. fluids. One patient in group B had bradycardia. No morbidity was noted in group A.

Discussion

We chose elective hernia surgery for this study as wound infiltration is well established as an effective method of providing postoperative analgesia\textsuperscript{8–10} and indeed as the sole anaesthetic. The benefit of wound infiltration in other operations, for example appendicectomy, is less well demonstrated, perhaps because of the major contribution to postoperative pain of residual localized peritonitis. As there is no clear end-point to injection, we devised a standardized technique of wound infiltration which would provide a reliable distribution of local anaesthetic. This technique used pre-incisional infiltration as this has been shown to be more effective than postoperative infiltration.\textsuperscript{11}

The addition of clonidine to local anaesthetic solutions has been shown to extend the duration of several peripheral nerve blocks. This appears to be a locally mediated effect, as it is not reproduced by systemically administered clonidine.\textsuperscript{5} Gaumann, Brunet and Jirounek,\textsuperscript{12} using the rabbit vagus nerve, demonstrated improved analgesia compared with general or spinal anaesthesia even 10 days after operation. Therefore, a possible reason for our negative findings may have been that any extension in the pharmacological action of local anaesthetic by clonidine was concealed by the prolonged analgesia provided by wound infiltration itself. It should be noted that even in control group A, the mean time to first analgesia exceeded 6 h. Infiltration of the wound produces prolonged analgesia possibly by preemptively blocking hyperalgesia and central nervous system hyperexcitability or “wind-up” caused by surgical trauma. Also, an anti-inflammatory action of amide local anaesthetics has been described.\textsuperscript{13}

The only significant difference between groups was increased pain scores in group C at rest at 24 h. The relevance of this finding is questionable as 24 h is far in excess of the expected duration of action of clonidine. To confirm this finding would require further studies.

Failure to demonstrate significant differences between groups raises the possibility of type II statistical error. We conducted a post hoc power analysis using two assumptions. First, we considered that an important clinical difference between any two techniques would be reflected by a difference of 3.0 cm in the mean linear analogue pain scores between groups. Second, we used pooled data from the study to estimate a population SD. Using a 5% level of significance, we found that 15 patients per group yielded a power of 89%.

We used clonidine 150 μg as the majority of experience in regional anaesthesia is with this dose.\textsuperscript{2,3,5–7} Higher doses may have revealed a peripheral effect, but may also have resulted in an increased incidence of systemic side effects.

In our hospital, hernia repair is a day surgery procedure. As our study was performed on inpatients, our study group consisted of patients with physical or social reasons requiring an overnight stay. This is reflected in the mean age of 62.7 yr in our study group. We decided to study only inpatients as clonidine is known to sometimes cause delayed sedation, hypotension and bradycardia.

In summary, addition of clonidine 150 μg to 0.25% bupivacaine wound infiltration conferred no improvement in either the quality or duration of postoperative analgesia after hernia surgery.

References


