PREOPERATIVE INDOMETHACIN FOR PAIN RELIEF AFTER THORACOTOMY: COMPARISON WITH POSTOPERATIVE INDOMETHACIN

D. F. MURPHY AND C. MEDLEY

SUMMARY

Indomethacin commenced before operation was compared with postoperative indomethacin administration for pain relief in patients after elective thoracic surgery. In addition to indomethacin, all patients received i.v. opioids titrated to their individual requirements. There was no significant difference between the two groups in quality of pain relief, in cumulative opioid requirement or in the incidence of adverse effects. The quality of pain relief compared well with previous similar studies using this technique. (Br. J. Anaesth. 1993; 70: 298-300)

KEY WORDS

There is convincing evidence from other studies that pre-emptive strategies to prevent pain reduce the quality of pain perceived and the requirement for analgesia after surgery [1-7]. The evidence to date suggests that reduction or prevention of afferent nociceptive impulses reduces central sensitization to pain. In addition to central sensitization, peripheral sensitization of the afferent neuroreceptor also occurs, resulting in primary and secondary hyperalgesia [8, 9].

It is known that several processes contribute to peripheral sensitization, such as release of prostaglandins and other chemicals from the damaged tissues and antidromic nerve impulses from the sensitized neuroreceptors [10]. Although several investigators have tested the effect of pre-emptive treatment on central sensitization, there have been no studies to date on the prevention of peripheral sensitization to painful stimuli in an attempt to reduce postoperative pain.

Non-steroidal anti-inflammatory drugs (NSAID) prevent the synthesis of prostaglandins by inhibiting the cyclo-oxygenase pathway of arachidonic acid metabolism. Previous work at this institution has shown that administration of indomethacin to patients after thoracotomy caused a significant reduction in pain and a significant reduction in cumulative opioid requirements [11]. The aim of the present study was to test the hypothesis that pre-emptive indomethacin administration would further reduce postoperative pain and cumulative opioid requirement.

PATIENTS AND METHODS

In a randomized, controlled, prospective programme, we studied 50 patients undergoing elective thoracotomy, after obtaining approval by the Committee for Human Rights. Patients with a previous history of peptic ulceration were excluded from the study. The patients were allocated randomly to one of two groups. One group received indomethacin suppositories 200 mg commencing on the night before surgery and 100 mg twice daily thereafter. The second group commenced the same indomethacin regimen after completion of surgery. Premedication and anaesthesia were similar in both groups as described previously [11] and included nitrous oxide, enflurane or halothane with supplementary morphine 10-20 mg as required. On completion of surgery, a continuous i.v. infusion of papaveretum was commenced and the rate of infusion adjusted to attain adequate analgesia. The patients were discharged from the recovery room when they were clinically stable and pain was controlled satisfactorily. All patients were given i.v. papaveretum titrated by the attending nurse to maintain adequate postoperative pain relief as determined by the patient. The attending nurses administered bolus doses of i.v. papaveretum as required and altered the rate of infusion, increasing it to attain control of pain and decreasing it in the case of excessive drowsiness in the presence of adequate pain relief. All patients were nursed in the same ward by the same team of senior nurses who were experienced in i.v. opioid administration. Similar recordings were made as in our earlier studies [11]. Measurements undertaken included evaluation of total requirement for papaveretum at 2, 4, 6, 12, 18, 24, 30, 36, 42 and 48 h commencing from return to ward and patient evaluation of pain using a 10-cm visual analogue scale [12] before and after chest physiotherapy, which was undertaken three times daily by the same physiotherapist. Chest physiotherapy involved deep breathing exercises, coughing, percussion, postural drainage and mobil-

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INDOMETHACIN FOR THORACOTOMY PAIN

RESULTS

Of the 50 patients studied, 22 commenced indomethacin before operation and 28 after operation as a result of the random number sequence. Both groups were similar in age, sex and weight (table I).

Pain scores were assessed before and after chest physiotherapy for the first 2 days after operation. Pain scores for the first day after operation are shown in figure 1; pain scores for the second day followed a similar pattern. There was no significant difference between the pain scores in the two groups. Similarly, the cumulative opioid requirement did not differ significantly in the two groups 

There were no adverse effects specifically attributable to indomethacin in these patients and no patient was withdrawn from the study.

DISCUSSION

It is clear from previous studies at this institution that indomethacin administration to patients after thoracotomy significantly reduces pain and opioid requirement after surgery [11]. When compared with patients receiving identical placebo suppositories in a randomized, double-blind controlled trial, patients receiving indomethacin suppositories after such surgery had smaller pain scores (VAS) before and after chest physiotherapy ($P < 0.01$). The cumulative papaveretum requirement in these patients (77.8 (SEM 9.3) mg) was approximately 67 % that of the group receiving placebo (109.1 (10) mg). These results compare favourably with those of most other studies on the opioid sparing effects of NSAID [13].

### TABLE I. Patient characteristics and type of operation (mean (range or SD) or number)

<table>
<thead>
<tr>
<th></th>
<th>Preoperative indomethacin group</th>
<th>Postoperative indomethacin group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.5 (41-77)</td>
<td>62.5 (44-87)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.5 (13.2)</td>
<td>72.9 (17.2)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/8</td>
<td>19/9</td>
</tr>
<tr>
<td>Operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobectomy</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Pneumonectomy</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Surgical pleurodesis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Open lung biopsy</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Oesophagostrectomy</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Repair hiatus hernia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Thoracoplasty</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Excision other neoplasm</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Repair oesophageal tear</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### TABLE II. Cumulative papaveretum requirement (mean (SEM)) in both groups for the first 48 h after operation. $P > 0.05$ for all comparisons

<table>
<thead>
<tr>
<th>Requirement for papaveretum (mg)</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>12 h</th>
<th>18 h</th>
<th>24 h</th>
<th>30 h</th>
<th>36 h</th>
<th>42 h</th>
<th>48 h</th>
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</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>9.05</td>
<td>16.23</td>
<td>22.67</td>
<td>36.98</td>
<td>51.36</td>
<td>63.35</td>
<td>68.98</td>
<td>71.85</td>
<td>73.85</td>
<td>74.53</td>
</tr>
<tr>
<td>indomethacin (n = 22)</td>
<td>1.09</td>
<td>2.05</td>
<td>2.93</td>
<td>3.58</td>
<td>5.86</td>
<td>6.47</td>
<td>6.66</td>
<td>6.88</td>
<td>7.16</td>
<td>7.35</td>
</tr>
<tr>
<td>Postoperative</td>
<td>8.48</td>
<td>16.18</td>
<td>22.75</td>
<td>39.11</td>
<td>50.54</td>
<td>63.47</td>
<td>69.72</td>
<td>73.58</td>
<td>76.29</td>
<td>78.35</td>
</tr>
<tr>
<td>indomethacin (n = 28)</td>
<td>0.68</td>
<td>1.42</td>
<td>1.95</td>
<td>3.72</td>
<td>5.03</td>
<td>6.28</td>
<td>7.29</td>
<td>8.12</td>
<td>8.90</td>
<td>9.53</td>
</tr>
</tbody>
</table>

**FIG. 1.** Mean (SD) pain scores (VAS) on the first day after operation for preoperative (□) and postoperative (■) indomethacin groups.

**FIG. 2.** Papaveretum requirement (mean, SEM) in 6-h periods for preoperative (□) and postoperative (■) indomethacin groups over the first 48 h after operation.
It is surprising that preoperative administration of indomethacin does not significantly enhance its effect. It may be that a loading dose of indomethacin 200 mg and a further 100 mg before operation is insufficient to reduce prostaglandin synthesis significantly in the presence of such extensive surgery. However, this is the maximum recommended daily dosage for indomethacin and the pharmacokinetic profile for its administration in suppository form would suggest that acceptable plasma concentrations should have been achieved by the time of surgery [14]. Perhaps the role of prostaglandin synthesis in the genesis of pain and primary hypersensitivity is small compared with the multitude of other algesic biochemical compounds released from damaged tissues. It may be that the effect of peripheral sensitization of peripheral neuroreceptors is insignificant compared with the magnitude of central sensitization. Nevertheless, these results augment our previous results which showed a reduced requirement for opioid with concomitant use of indomethacin. We have not shown, however, that pre-emptive administration of NSAID produced better analgesia than postoperative administration.

REFERENCES

2. Wall PD, Woolf CJ. The brief and the prolonged facilitatory effects of unmyelinated afferent input on the rat spinal cord are independently influenced by peripheral nerve injury. *Neuroscience* 1986; 17: 1199–1206.