Preoperative or postoperative diclofenac for laparoscopic tubal ligation

D. J. Buggy, C. Wall and E. G. Carton

Summary
We have compared the analgesic effects of diclofenac given before operation or immediately after operation in a randomized, double-blind, double-dummy study of 40 healthy female patients undergoing laparoscopic tubal ligation. Group 1 patients received diclofenac 75 mg as a 3-ml i.m. injection 1–2 h before operation and normal saline 3 ml i.m. immediately after surgery. Group 2 patients received normal saline 3 ml i.m. before operation and diclofenac 75 mg i.m. immediately after surgery. Outcome measures were patients’ perception of pain on a visual analogue scale (VAS), verbal response scale (VRS), the number of patients who required postoperative morphine, time to first postoperative morphine injection and total dose of morphine given. VAS at 30 min and at 1, 3 and 6 h after operation were, respectively (median, interquartile range) 4.5 (2.3–6.0) vs 5.3 (2.8–7.8); 3.3 (2.3–5.0) vs 4.4 (3.0–5.8); 1.4 (0–2.3) vs 1.9 (0.8–3.0); 0.5 (0–1) vs 0.7 (0–1.3), (ns). VRS at 1 and 3 h after operation were, respectively, (median, interquartile range) 2.2 (1.5–3.0) vs 2.7 (2.0–4.0) and 0.8 (0–1.3) vs 0.9 (0–1.5) (ns). Sixteen patients in group 1 compared with 17 in group 2 required postoperative morphine. Time to first morphine administration and dose given were, respectively, (median, interquartile range) 50.6 (39–60) min vs 35.7 (20–49) min (P = 0.1) and 9.0 (5–10) mg vs 9.5 (7.5–10) (P = 0.9). We conclude that in patients presenting for laparoscopic tubal ligation, preoperative administration of diclofenac 75 mg i.m. conferred no additional analgesic benefit compared with a similar dose given after operation. (Br. J. Anaesth. 1994; 73: 766–770)

Key words
Surgery, gynaecological. Analgesics non-opioid, diclofenac.

Experimental studies of nociception have shown that peripheral tissue injury may lead to expansion of receptive fields and decrease the threshold of posterior horn neurones for transmission of pain impulses [1–3]. Allodynia (innocuous stimuli generating pain) and hyperalgesia (increased pain to suprathreshold stimulation) may result [1, 4]. The neurophysiological mechanisms may involve wind-up [5], that is amplification of noxious afferent input, lowering of thresholds for transmission of pain and after-discharges of dorsal horn neurones; N-methyl-d-aspartate (NMDA) receptors [6] and alterations of neuronal second messengers may mediate prolonged functional changes [3, 7].

Further studies on nociception suggest that acute pain perception may be attenuated by pre-emptive neural block of afferent stimuli with local anaesthetics [8, 9] and pre-emptive reduction in posterior horn excitability using opioids [10]. These antinociceptive measures were less effective if implemented after the insult [8, 10].

Human cutaneous injury leads to primary hyperalgesia in the area directly affected by the insult and secondary hyperalgesia produced by changes in the surrounding undamaged tissue [4]. The latter may be caused by sensitization of central neurones [11, 12] resulting in amplification and prolongation in postoperative pain [11]. Comparative studies of the analgesic effects of preoperative vs postoperative, local anaesthetic infiltration and extradural analgesia have yielded conflicting results [13–18]. Studies on non-steroidal anti-inflammatory drugs (NSAID) have been negative [19–21].

NSAID inhibit prostaglandin production thereby decreasing peripheral stimulation of nociceptors [22–24]. Moreover, there is recent evidence suggesting a central action for these drugs [25]. Several studies investigating NSAID premedication have shown an analgesic, but not a pre-emptive effect for these agents [26, 27]. Diclofenac sodium is a phenylactic acid derivative which is formulated for oral, i.m. and rectal use [23]. It is an effective analgesic given after operation [24], but no study has yet compared this with its pre-emptive analgesic efficacy.

Therefore, we have compared the preoperative and postoperative analgesic effects of i.m. diclofenac 75 mg in a randomized, double-blind, double-dummy study.

Patients and methods
After obtaining local Ethics Committee approval and informed consent, we studied 40 ASA I patients undergoing elective laparoscopic tubal ligation. Patients were allocated randomly to two groups: group 1 (mean age 34.5 (range 26–42 yr); mean

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weight 60.5 (SEM 2.3) kg received diclofenac 75 mg i.m. 1–2 h before operation and normal saline i.m. immediately after operation; group 2 (age 33.3 (27–42) yr, weight 58.9 (1.9) kg) received the same injections in reverse order. Patients with peptic ulcer disease, renal failure or known allergy to NSAID were excluded.

After oral premedication with diazepam 10 mg, anaesthesia was induced in all patients with propofol 1.5 mg kg$^{-1}$ i.v. and fentanyl 1.5 μg kg$^{-1}$ i.v. and maintained with 1% enflurane and 70% nitrous oxide in oxygen. Atracurium 0.3 mg kg$^{-1}$ was given to facilitate tracheal intubation and maintain neuromuscular block.

During the study, each patient received two identical, coded, 3-ml injections: one containing diclofenac 75 mg, the other containing normal saline. All patients received the first 3 ml i.m. 1–2 h before operation and the second at the conclusion of surgery. After all patients were studied, the sequence of drug-placebo administration was identified for each patient.

Patients were asked to grade the intensity of postoperative pain on a 10-cm visual analogue scale (VAS) and on a four-point verbal response scale (VRS: pain described as “unbearable”, “severe”, “moderate” or “slight”) at 30 min, and at 1, 3 and 6 h after operation. These values were recorded by nursing staff who were unaware of the sequence of the injections. If analgesia was inadequate, as deemed by the same nursing staff, morphine 10 mg i.m. was given as required.

The median time to first morphine injection (interquartile range) was 50.6 (39–60) min vs 35.7 (20–49) min ($P = 0.1$).

**Results**

Group 1 and group 2 patients were similar in duration from first injection to commencement of surgery and duration of anaesthesia (table 1).

<table>
<thead>
<tr>
<th>Group 1 ($n = 20$)</th>
<th>Group 2 ($n = 20$)</th>
<th>$P$</th>
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<tbody>
<tr>
<td>Age (yr) 34.5 (26–42)</td>
<td>33.3 (27–42)</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight (kg) 60.5 (2.3)</td>
<td>58.9 (1.9)</td>
<td>0.7</td>
</tr>
<tr>
<td>Interval* (min) 102.3 (11.5)</td>
<td>101.8 (16.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Duration of anaesthesia (min) 18 (0.6)</td>
<td>19 (0.8)</td>
<td>0.8</td>
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Median (interquartile range) pain scores on VAS (table 2) and VRS (table 3) were similar at all times. The proportion of patients receiving morphine and total dose of morphine given were also similar (table 4).

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>$P$</th>
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<tbody>
<tr>
<td>30 min 4.5 (2.3–6.0)</td>
<td>5.3 (2.8–7.8)</td>
<td>0.19</td>
</tr>
<tr>
<td>60 min 3.3 (2.3–5.0)</td>
<td>4.4 (3.0–5.8)</td>
<td>0.22</td>
</tr>
<tr>
<td>3 h 1.4 (0–2.3)</td>
<td>1.9 (0.8–3.0)</td>
<td>0.13</td>
</tr>
<tr>
<td>6 h 0.55 (0–1)</td>
<td>0.7 (0–1.3)</td>
<td>0.58</td>
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</table>

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>$P$</th>
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<tbody>
<tr>
<td>1 h 2.2 (1.5–3.0)</td>
<td>2.7 (2–4)</td>
<td>0.1</td>
</tr>
<tr>
<td>3 h 0.8 (0–1.3)</td>
<td>0.9 (0–1.5)</td>
<td>0.9</td>
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</table>

The proportion of patients requiring postoperative analgesia received morphine 10 mg i.m. Several patients in each group did not require analgesia ($n = 4$ in group 1; $n = 3$ in group 2) and hence the median dose of morphine given was less than 10 mg in both groups (table 4).

The median time to first morphine injection (interquartile range) was 50.6 (39–60) min vs 35.7 (20–49) min ($P = 0.1$).

**Discussion**

Experimental studies on nociception (the response to a noxious stimulus) have suggested that tissue injury and trauma lead to facilitation of processing of painful stimuli, with amplification and prolongation of pain [1–8]. Human studies on pain also suggest functional alteration of the central nervous system [11, 12]. Nociception has been unequivocally attenuated by pre-emptive analgesia [8, 9], but similar human studies have yielded conflicting results [4, 13–21, 28, 29, 30].

In patients undergoing removal of impacted third molar teeth, naproxen given orally 30 min after surgery provided as effective postoperative analgesia as an equal dose given orally 30 min before surgery [21]. In a similar group of patients, the combination of flurbiprofen administered before and after surgery provided more effective postoperative analgesia than when flurbiprofen was given only after surgery [27]. Patients who received preoperative and postoperative flurbiprofen may have had more effective analgesia because the total dose was greater, therefore the results of this study do not accurately reflect a pre-emptive effect. It has been suggested that giving diclofenac soon after surgery may have a morphine sparing effect [23, 24], but pre-emptive use of indomethacin, another NSAID, was not superior to early postoperative administration [20].

Our double-blind, double-dummy study is the best evidence to date that NSAID do not provide pre-emptive analgesia. However, our outcome measure nearest to significance (time to postoperative morphine injection ($P = 0.1$, table 4) was weakly suggestive of pre-emptive analgesia.
Nevertheless, the power of our study to detect such a difference was 75%, and a power close to 100% may be extremely difficult to obtain in a purely clinical setting. In addition, patients in group 2 had higher initial pain values. Moreover, eight patients in group 1 did not require postoperative morphine injections for more than 1 h, compared with just two subjects in group 2. Perhaps the shorter mean time to morphine requirements in patients in group 2 reflects the time taken for i.m. diclofenac to be absorbed and reach therapeutic plasma concentrations.

In acutely injured tissues, maximal concentrations of prostaglandins occur 3–4 h after injury and this correlates with peak intensity of postoperative pain [21]. NSAID such as diclofenac decrease production of peripheral tissue prostaglandins in response to injury, rather than providing afferent block, although there is some evidence suggesting a central role for NSAID in the reduction of afferent input [25].

No pre-emptive benefit was demonstrated when bupivacaine and morphine were administered extradurally before and after colonic surgery [17] but preoperative rather than postoperative administration of extradural fentanyl was associated with reduced pain scores and morphine requirements at only one of the five assessment times in the 4-h follow-up period of patients undergoing elective thoracic surgery [18]. However, patients in the pre-emptive analgesia group were older and had a greater proportion of females, both of which would tend to decrease pain scores and opioid requirements.

The difference between the results of pre-emptive analgesia studies in experimental models and in clinical studies is intriguing. The specific conditioning stimuli of most experimental models of pain differ radically from clinical surgery which can involve prolonged and extensive cutaneous, visceral and muscular afferent input. Therefore, failure to demonstrate effective pre-emptive analgesia in clinical studies may reflect insufficient afferent block [4, 28, 29].

Kehlet has pointed out that most forms of surgical stimulation outlast the relatively short-lived effect of a single pre-emptive analgesic technique, with the result that central sensitization may occur even after surgery, when preoperative nociceptive block has terminated. Truly effective pre-emptive analgesia may require a multi-modal or “balanced analgesia” approach, including application of local measures at the site of the insult [29].

Acknowledgement

We are indebted to Ann Frankish, hospital pharmacist, for her expertise in coding this study, and to the gynaecology unit staff for their co-operation.

References

20. Murphy DF, Medley C. Preoperative indomethacin for pain

### Table 4 Postoperative morphine requirements (median (interquartile range))

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 20)</th>
<th>Group 2 (n = 20)</th>
<th>P</th>
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<tbody>
<tr>
<td>Received morphine (n)</td>
<td>16</td>
<td>17</td>
<td>0.9</td>
</tr>
<tr>
<td>Total dose (mg)</td>
<td>9.0 (5–10)</td>
<td>9.5 (7.5–10)</td>
<td>0.6</td>
</tr>
<tr>
<td>Interval to first dose (min)</td>
<td>50.6 (39–60)</td>
<td>35.7 (20–49)</td>
<td>0.1</td>
</tr>
</tbody>
</table>


