Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration?

R. Collis, B. Brandner, L. M. Bromley and C. J. Woolf

Summary
Pre-emptive treatment with an i.v. infusion of morphine 10 mg at induction reduces postoperative analgesic requirement and wound hypersensitivity compared with the same dose administered at the end of operation. Increasing the dose of pre-emptive morphine may potentially reduce postoperative pain further, while administering morphine at the end of operation, in addition to the beginning, may reduce pain generated by the sensory activity elicited from the wound in the immediate postoperative period. To examine this we have conducted a randomized, double-blind study in patients undergoing abdominal hysterectomy to compare the effect of morphine 20 mg administered before operation with 10 mg at induction and 10 mg on closure of the peritoneum. Postoperative pain was assessed by visual analogue score (VAS) at rest and on movement and by total morphine consumption administered by patient-controlled analgesia (PCA). Wound sensitivity was assessed by von Frey pain thresholds. Both groups had similar morphine consumption, VAS scores and touch and pain thresholds, and in both, secondary hyperalgesia was prevented. Nausea and vomiting scores were higher in the 20-mg group. There was no significant difference between the two groups and neither regimen appeared to offer obvious clinical advantages compared with a lower dose (10 mg) morphine analgesic strategy. Therefore, there may be a ceiling effect to the production of pre-emptive analgesia by morphine. (Br. J. Anaesth. 1995; 74: 396–399)

Key words

The optimal regimen for postoperative pain relief has not yet been defined and postoperative pain is generally managed inadequately [1]. Pre-emptive analgesia is based on the realization that nociceptive signals generate a prolonged period of increased excitability in central neurones so that the responses to normal inputs are amplified [2–4]. Two general approaches have been adopted; block of sensory conduction using local anaesthetics before incision [5–10] or prevention of central excitability using opioids [10–13] or an NMDA receptor antagonist [12]. Although both approaches have been shown to produce some clinical benefit in several randomized, double-blind trials [5, 8, 10–13], a few have failed to demonstrate significant effects [7, 14–16] for a variety of reasons that may include: administration of intraoperative opioids to all groups, studying relatively painless procedures so that postoperative pain scores are low in the comparison groups, untested nerve blocks, insufficient time between pre- and post-treatments and inadequate outcome measurements.

Administration of morphine 10 mg before operation has been shown to reduce postoperative morphine consumption and wound hypersensitivity compared with the same dose administered at the end of operation [11] but this treatment did not eliminate the need for postoperative analgesics or pain on movement, and the effect was limited in duration. This could reflect incomplete prevention of the central excitability increases established during surgery and to test this we have now used an increased pre-emptive dose of morphine 20 mg i.v. Pain after surgery only partly reflects the changes produced during surgery and activity in the postoperative period from the injured tissue contributes. Several possible approaches to overcome this have been suggested. One is to use a combination of analgesic interventions: local anaesthetic, opioids and anti-inflammatory drugs [11, 17]; the other is to use a pre-emptive approach but not restrict it to a single intervention before incision, but maintain or continue treatment in advance of the pain generated after operation by the inflammatory response to tissue injury [2, 10]. To investigate the latter further we have combined an adequate pre-emptive dose of morphine before incision (10 mg) with another dose at the end of operation (10 mg) to see if a greater clinical benefit can be produced.

Patients and methods
We studied healthy women, ASA I–II, admitted for elective total abdominal hysterectomy after written informed consent was obtained. The study was approved by the local Ethics Committee.

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Pain and touch sensitivity was assessed before, 24 and 48 h after operation with von Frey hairs (a set of 20 nylon monofilaments of variable diameter, calibrated to exert a specific punctate mechanical force of between 0.0174 and 263 g on the skin). Touch and pain thresholds were assessed 10 cm above the wound and forearm. Touch thresholds were the lowest force von Frey hair that could be detected, pain threshold was the lowest force von Frey hair that was perceived as unpleasant, uncomfortable or painful. Patients acted as their own control. Results were expressed as relative thresholds: forearm minus abdomen. Pain scores were recorded using a visual analogue score (VAS) (0 mm = no pain, 100 mm = worst pain imaginable) at rest and on movement at 4, 24 and 48 h after operation.

Sedation and nausea were rated by the patients using a VAS for sedation (0 = wide awake, 100 mm = extremely sleepy) and nausea (0 = no nausea, 100 mm = terrible vomiting).

Table 1 Relative touch detection and pain thresholds (forearm — abdomen) (mean (SEM)) before and 24 and 48 h after operation in the group given morphine 10 mg before (pre.) and after (post.) operation compared with the group given morphine 20 mg before operation.

<table>
<thead>
<tr>
<th></th>
<th>Touch detection threshold</th>
<th>Pain threshold</th>
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<tbody>
<tr>
<td></td>
<td>Morphine</td>
<td>Morphine</td>
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<tr>
<td>10 mg pre./</td>
<td>10 mg post. 20 mg pre.</td>
<td>10 mg pre./</td>
</tr>
<tr>
<td>16</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Preop.</td>
<td>—1.5 (0.5)</td>
<td>—0.9 (0.3)</td>
</tr>
<tr>
<td>24 h</td>
<td>—1.2 (0.5)</td>
<td>—1.2 (0.4)</td>
</tr>
<tr>
<td>48 h</td>
<td>—1.4 (0.5)</td>
<td>—1.3 (0.4)</td>
</tr>
</tbody>
</table>

Table 2 Sedation and nausea and vomiting visual analogue scores (mm) (mean (SEM)) at 4, 24, and 48 h after operation in the group given morphine 10 mg before (pre.) and after (post.) operation compared with the group given morphine 20 mg before operation. * P < 0.05

<table>
<thead>
<tr>
<th></th>
<th>Sedation</th>
<th>Nausea and vomiting</th>
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<tbody>
<tr>
<td></td>
<td>Morphine</td>
<td>Morphine</td>
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<tr>
<td>10 mg pre./</td>
<td>10 mg post. 20 mg pre.</td>
<td>10 mg pre./</td>
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<tr>
<td>16</td>
<td>21</td>
<td>16</td>
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<tr>
<td>4 h</td>
<td>77.0 (4.6)</td>
<td>76.7 (4.4)</td>
</tr>
<tr>
<td>24 h</td>
<td>28.1 (7.2)</td>
<td>39.7 (8.8)</td>
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<tr>
<td>48 h</td>
<td>13.4 (5.5)</td>
<td>17.1 (5.6)</td>
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Results

Of the 49 patients included in the study, nine were excluded from analysis for multiple reasons: one patient did not receive any premedication, two required naloxone in recovery, two had severe nausea and vomiting, for one the anaesthetist was unable to find trial syringes, for one the surgeon had to change to a midline incision and two patients were unable to use the PCA. The study was terminated when 40 patients had been included but on breaking the code, one patient could not be assigned to either group and therefore the data from 39 subjects have been used. After breaking the code 16 patients were found to be in group A (10 mg before and 10 mg after) and 23 in group B (20 mg before). The unequal sample numbers was because of patients dropping out of the study. The groups did not differ in age (group A: 46.3 (range 32–67) yr, 95% CI 41.7–50.86 yr; group B: 44.3 (31–67) yr, 95% CI 39.6–48.9 yr (P = 0.5)) or weight (group A: 74.1 (SEM 4.3) (range 54–106) kg, 95% CI 65–83 kg; group B: 66.7 (3.2) (49–104) kg, 95% CI 60–73 kg (P = 0.2)).

There was no significant difference in total postoperative (24 h) morphine consumption between the two groups, with values in group A of 43.4 (SEM 6.5) (range 12–105) mg, 95% CI 29.6–57 mg and in group B of 33.1 (3.1) (8–69) mg, 95% CI 26.7–39.5 mg (P = 0.17). The thresholds for touch detection (before operation and 24 and 48 h after operation) were slightly higher on the abdomen than on the forearm for all three assessments, generating
negative relative thresholds, and a significant difference could not be demonstrated either between groups or before vs after operation (table 1). A similar finding was found for the relative pain thresholds for the two study groups. The relative von Frey assessments were similar for all three study times for both groups (table 2). The expected decrease in threshold on the abdomen in the vicinity of the wound was not observed, which suggests that both regimens prevented secondary hyperalgesia ($P < 0.05$, Mann–Whitney $U$ test).

VAS pain scores at rest, at 4 and 24 h were not significantly different between the two groups (fig. 1). The scores were lower for pain on rest compared with moving in both groups. Only at 48 h did the group that received morphine 20 mg before operation show significantly less pain on movement than the 10 mg before and 10 mg after group ($P < 0.05$) (fig. 2).

Sedation scores were similar for both groups. Both groups were very sleepy 4 h after operation. Nausea and vomiting were significantly higher for the morphine 20 mg group 24 h after operation.

Discussion

As a result of an increase in the excitability of neurones in the spinal cord produced by the nociceptive afferent input, tissue injury leads to a state of central sensitization [2,18]. This is manifest as allodynia, the production of pain by low threshold sensory fibres [19], and secondary hyperalgesia, an area of increased pain sensitivity in the normal tissue surrounding an injured site [20]. Pre-emptive analgesia is an attempt to reduce postoperative pain by preventing the establishment of central sensitization [2]. Several approaches can be used: blocking access of sensory inputs by reducing action potential condition in peripheral axons using regional local anaesthetics before incision [6,9,10,15,21–23] or preventing the central effect of the nociceptive sensory inputs either with opioids [10–13,21,22] or N-methyl-D-aspartic acid (NMDA) receptor antagonists [12]. There is clinical evidence that all three approaches work [5,10–13].

We found previously that morphine 10 mg i.v. at the time of induction significantly reduced postoperative total cumulative morphine consumption over 24 h and abolished the postoperative sensitivity in the vicinity of the wound in patients undergoing total abdominal hysterectomy [11]. In the present study in a similar group of patients, we have confirmed our earlier finding that patients given double the dose of morphine, either as a single 20-mg bolus at induction or as 10 mg at induction and 10 mg on closure of the peritoneum, also fail to develop wound hypersensitivity or secondary hyperalgesia. In neither group did the pain threshold on the abdomen decrease below that of the arm or that of the preoperative level, whereas patients given morphine only after cessation of surgery did display such sensitivity [11].

Central sensitization may be produced by activity generated at the time of actual tissue damage and as a result of the activity produced later in sensory fibres from inflammatory responses at the wound site. The rationale for doubling the pre-emptive dose of morphine to 20 mg and for comparing this with a regimen where patients received both an effective pre-emptive dose (10 mg) and adequate postoperative dose, was to see if a higher initial dose of morphine produced a greater pre-emptive analgesic effect and also to see if an additional postoperative dose might pre-empt the effect of signals generated by the wound. However, the results of the study failed to show a clinically obvious advantage of each approach compared with the previously demonstrated effects of morphine 10 mg administered i.v.
before operation. Both protocols eliminated wound hypersensitivity, but neither reduced pain on movement to a greater extent than morphine 10 mg before operation.

The reduction in total morphine consumption in the first 24 h after operation in patients given morphine 10 mg i.v. before operation compared with the same dose after operation was 27% (from 48 (SEM 4 mg) to 38 (SEM 3.2 mg) [11]). Morphine consumption in this study in patients given 20 mg i.v. before operation was 33.1 (SEM 3.1) mg, which was 45% less than that found for 10 mg i.v. after operation in our earlier study. Nevertheless, high-dose pre-emptive morphine did not eliminate postoperative morphine requirements nor did combining pre- with postoperative morphine. Moreover, there was a higher incidence of sedation, nausea and vomiting in this study than in that where only 10 mg was administered, and overall our assessment is that increasing the pre-emptive dose of morphine does not increase the clinical benefit.

Our measurements were obtained in the immediate postoperative period only and it is possible that the benefits of pre-emptive treatment might be restricted to within the first day after surgery or may have effects some considerable time after operation, but this has to be investigated further. The importance of the decrease in pain on movement in the morphine 20 mg group at 48 h is difficult to evaluate as an analgesic administration after discontinuing PCA was not standardized.

Acknowledgements

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References