Influence of dose and timing of administration of morphine on postoperative pain and analgesic requirements

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Summary
In a randomized, double-blind study, we have investigated the effect of dose and timing of administration of morphine on postoperative pain and analgesic requirements in 60 patients undergoing hysterectomy and analgesia significantly reduced postoperative pain. Patients were allocated randomly to one of three groups: during standardized general anaesthesia, group post received morphine 0.15 mg kg\(^{-1}\) i.v. at peritoneal closure after hysterectomy; group pre-low received morphine 0.15 mg kg\(^{-1}\) on induction of anaesthesia; and group pre-high received morphine 0.3 mg kg\(^{-1}\) on induction of anaesthesia. Median postoperative morphine consumption (first 24 h) from a PCA system was 68 mg (group post), 56 mg (group pre-low) and 43 mg (group pre-high), and total perioperative morphine consumption (induction of anaesthesia to end of 24 h after surgery) was 77 mg (group post), 65 mg (group pre-low) and 63 mg (group pre-high). Pain scores (at rest and on movement) were similar in the three groups. A large dose of morphine 0.3 mg kg\(^{-1}\) i.v. on induction of anaesthesia significantly reduced postoperative PCA morphine requirements compared with the smaller dose (0.15 mg kg\(^{-1}\)) administered at induction or peritoneal closure, in patients undergoing hysterectomy, with or without salpingo-oophorectomy. The use of a patient-controlled analgesia system (PCAS) (Graseby Medical, Watford, UK), visual analogue scales and verbal rating scores was explained on the evening before surgery. All patients provided written informed consent, and recruitment continued until 60 evaluable patients had been included. We included only patients whose surgery was performed through a Pfannenstiel incision. Exclusion criteria were: patient request; any significant organ dysfunction; history of chronic pain; regular medication with any opioid or non-steroidal anti-inflammatory preparation; drug or alcohol abuse; or psychiatric disorder.

Management of pain after surgery is often inadequate but optimal pain relief is important as it may reduce postoperative complications and speed recovery and discharge of patients from hospital [1]. Increasing attention is now being focused on strategies to reduce, or even abolish, postoperative pain.

The objective of pre-emptive analgesia is to prevent reflex central neuronal hyperexcitability which occurs in the spinal cord in response to the afferent barrage from peripheral nociceptors after a noxious stimulus [2, 3]. When established, this central sensitization is difficult to suppress, and may make effective pain relief difficult or impossible to achieve [3]. Laboratory work in animals has shown that it is possible to reduce, or even block completely, spinal cord hyperactivity in response to a painful stimulus, using either local anaesthetics [4, 5] or opioids [6].

Various pre-emptive strategies have been used with opioid analgesics [7–11], local anaesthetics [7, 12–14] and N-methyl-D-aspartate receptor antagonists [15]. While some studies have supported a pre-emptive analgesic effect, others have been unable to demonstrate an effect clinically. We have attempted to confirm the findings of a study on patients undergoing hysterectomy [9] which showed a pre-emptive effect with morphine 10 mg administered on induction of anaesthesia, compared with giving the same dose at peritoneal closure. In addition, we investigated the difference between two doses of morphine, administered pre-emptively, on postoperative pain and analgesic requirements. An abstract of this work has been published previously [16].

Patients and methods
After obtaining local hospital Ethics Committee approval, we studied in a double-blind, randomized study, female patients, ASA I or II, aged 18–70 yr, weighing 45–100 kg, undergoing total abdominal hysterectomy, with or without salpingo-oophorectomy. The use of a patient-controlled analgesia system (PCAS) (Graseby Medical, Watford, UK), visual analogue scales and verbal rating scores was explained on the evening before surgery. All patients provided written informed consent, and recruitment continued until 60 evaluable patients had been included. We included only patients whose surgery was performed through a Pfannenstiel incision. Exclusion criteria were: patient request; any significant organ dysfunction; history of chronic pain; regular medication with any opioid or non-steroidal anti-inflammatory preparation; drug or alcohol abuse; or psychiatric disorder.

Before starting the study our hospital pharmacy prepared 75 pairs of ampoules, each ampoule
containing 10 ml of colourless solution. Each pair of ampoules was boxed and numbered consecutively, 1 to 75, and comprised one ampoule labelled “induction” and one labelled “closure”. Pairs of ampoules contained one of three possible combinations: Group post: placebo in the induction ampoule, morphine 1.5 mg ml\(^{-1}\) in the closure ampoule; Group pre-low: morphine 1.5 mg ml\(^{-1}\) in the induction ampoule, placebo in the closure ampoule; and Group pre-high: morphine 3 mg ml\(^{-1}\) in the induction ampoule, placebo in the closure ampoule. All investigators were blinded as to the contents of the pairs of ampoules; the only codes to randomization were held in the pharmacy. Each patient was allocated randomly by being allocated the next pair of consecutively numbered ampoules.

All patients received premedication with temazepam 20 mg orally, approximately 90 min before operation. Routine monitoring comprised electrocardiography, non-invasive arterial pressure and pulse oximetry. Patients received a standardized general anaesthetic with induction of anaesthesia with propofol 2 ml kg\(^{-1}\). Immediately after induction, patients received 0.1 mg kg\(^{-1}\) i.v. from the ampoule labelled “induction”. Neuromuscular block was achieved with vecuronium 0.1 mg kg\(^{-1}\) and anaesthesia maintained with isoflurane and 66% nitrous oxide in oxygen. After tracheal intubation, patients were transferred to the operating theatre and surgery commenced. After completion of the hysterectomy, as the surgeon started to close the peritoneum, all patients received 0.1 ml kg\(^{-1}\) i.v. from the ampoule labelled “closure”. Surgery was completed and patients transferred to the recovery area.

During operation, patients received one of three analgesic regimens: group post: placebo on induction, morphine 0.15 mg kg\(^{-1}\) on closure; group pre-low: morphine 0.15 mg kg\(^{-1}\) on induction, placebo on closure; and group pre-high: morphine 0.3 mg kg\(^{-1}\) on induction, placebo on closure.

After operation patients were made comfortable in the recovery area with incremental i.v. morphine boluses, administered by one of the investigators, and then returned to the ward with a PCAS containing morphine (1-mg bolus with a 5-min lockout time and no background infusion). Twenty-four hours after surgery the PCAS was removed, as is routine practice in our institution, and patients then received diclofenac suppositories, 100 mg every 12 h. Co-proxamol was available for breakthrough pain in the second 24 h if required.

Pain was assessed at 1, 2, 4, 24 and 48 h after operation using visual analogue scales (VAS) for pain at rest and on movement (0 mm = no pain, 100 mm = worst pain ever had), and an eight-point verbal rating score for pain at rest (no pain = 0, just noticeable = 1, mild = 2, weak = 3, moderate = 4, strong = 5, severe = 6, excruciating = 7, same random word displayed shown to each patient). For pain on movement patients were asked to take a deep breath followed by a cough.

I.v. morphine administered by the investigator in the recovery room and total 24-h PCAS morphine consumption were recorded, together with analgesic consumption in the second 24 h after operation. Side effects, including nausea and vomiting, and requirements for antiemetic drugs were noted.

The Kruskal–Wallis test followed by the Mann–Whitney U test were used to compare total 24-h postoperative morphine consumption in the three groups. The area under the curve over time was calculated for visual analogue scores for pain intensity at rest and on coughing in individual patients. These summary data were then subjected to Kruskal-Wallis and Mann-Whitney U tests as appropriate [17]. The incidence of side effects was compared by chi-square test. Statistical analyses were performed in Minitab release 9.2. In all cases P < 0.05 was considered to indicate significance.

**Results**

Sixty-six patients were recruited in total and six were withdrawn because of: midline incision (two patients in group post), possible allergic reaction to morphine (one patient in group pre-high), severe anxiety altering the anaesthetic technique (one patient in group post) and further surgery within first 6 h after operation (two patients in group pre-high). The possible morphine allergy was evidenced by marked erythema of the face and neck with mild facial oedema, and was noted 4 h after operation. Patient-controlled analgesia was discontinued immediately and substituted with pethidine by intermittent i.m. bolus injection. The patient was not distressed, and the signs dissipated gradually over approximately 4 h.

Patient characteristics and type and duration of operation performed were similar in the three groups (table 1). The apparent difference in total postoperative morphine consumption (table 1) between the post and pre-low groups was not statistically significant. Patients in group pre-high used significantly less morphine in the first 24 h after surgery compared with patients in group post (P = 0.0002) and group pre-low (P = 0.0016). Total perioperative morphine consumption (i.e. allowing for additional i.v. morphine given during operation in group pre-high) was still significantly less in group pre-high compared with group post (P = 0.018) but not with group pre-low (P = 0.27). There were no differences between the groups in analgesic requirements in the second 24 h after operation.

<table>
<thead>
<tr>
<th>Group</th>
<th>Post (n = 18)</th>
<th>Pre-low (n = 22)</th>
<th>Pre-high (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45 (41–48)</td>
<td>43 (39–49)</td>
<td>42 (36–46)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61 (55–65)</td>
<td>61 (55–68)</td>
<td>64 (60–70)</td>
</tr>
<tr>
<td>Duration of op. (min)</td>
<td>66 (46–83)</td>
<td>60 (49–67)</td>
<td>55 (51–78)</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Hysterectomy + BSO</td>
<td>14</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>24-hour postoperative morphine use (mg)</td>
<td>68 (56–92)</td>
<td>56 (50–75)</td>
<td>43 (30–53)</td>
</tr>
<tr>
<td>Total perioperative morphine use (mg)</td>
<td>77 (65–102)</td>
<td>65 (60–84)</td>
<td>63 (51–73)</td>
</tr>
</tbody>
</table>
Figure 1  Visual analogue scores (VAS) for pain at rest (median, interquartile range) for group post (●), group pre-low (■) and group pre-high (▲).

Figure 2  Visual analogue scores (VAS) for pain on coughing (median, interquartile range) for group post (●), group pre-low (■) and group pre-high (▲).

Visual analogue scores for pain at rest and on movement are shown in figures 1 and 2. There were no significant differences between VAS at rest or on coughing, or verbal rating scores for pain at rest, in the three groups.

The incidences of nausea and vomiting were unacceptably high with 67% (group post), 59% (group pre-low) and 85% (group pre-high) of patients experiencing some degree of nausea or vomiting in the first 24 h after operation. Antiemetic therapy was required at least once by 44% (group post), 41% (group pre-low) and 60% (group pre-high) of patients. There were no significant differences in the incidence of nausea or emesis in the three groups.

Discussion

Only one study to date [9] has shown a clear pre-emptive analgesic effect using a simple opioid regimen. In that study it was found that morphine 10 mg i.v. significantly reduced postoperative PCA morphine consumption when administered on induction of anaesthesia compared with the same dose at the time of peritoneal closure. We have been unable to confirm this finding. In another study the same group [10] reached the conclusion that there was no clinical benefit in increasing the dose of pre-emptive analgesia. They also found that more sedation and an increased incidence of nausea and vomiting were sequelae of a larger dose of morphine.

Pre-emptive analgesia depends on reduction or prevention of central neuronal hyperexcitability (wind-up) which occurs in the spinal cord in response to peripheral nociceptive inputs. In the case of morphine analgesia, this is mediated by μ receptor stimulation. It has been shown that spinal cord wind-up begins almost immediately after a no-ciceptive stimulus [6], and thus any pre-emptive analgesic administered must be stimulating μ receptors at the commencement of such a stimulus. It is possible that a large dose of i.v. morphine may flood spinal opioid receptors more rapidly and to a greater extent than a smaller dose, and that this might result in a greater pre-emptive analgesic effect.

This possible explanation concurs with the findings in our study where group pre-high used 37% less morphine than group post, and 23% less than group pre-low in the first 24 h after operation. Obviously, group pre-high received twice as much intraoperative morphine as the two other groups but, even allowing for this, they still used 18% less morphine than group post in the perioperative period and this was statistically significant.

There was an unacceptably high incidence of nausea, vomiting, or both, in our study. Prochlorperazine was available to all patients after operation but we did not administer any intraoperative antiemetic. It should be stressed that even mild nausea was recorded, but 60% of patients in group pre-high required prochlorperazine at least once.

If the main purpose of intraoperative analgesia is to make patients more comfortable in the postoperative period (or permit an equal degree of comfort requiring less analgesic medication) then we conclude that a large dose of morphine administered on induction of anaesthesia significantly reduces postoperative morphine requirements from a PCA machine compared with a smaller dose given on induction of anaesthesia or at the time of abdominal closure.

References

Dose and timing of administration of morphine on postoperative pain