Effect of Combining Naloxone and Morphine for Intravenous Patient-controlled Analgesia


Background: An early study showed that a naloxone infusion decreased the incidence of morphine-related side effects from intravenous patient-controlled analgesia. The authors tested the hypothesis that a more convenient combination of morphine and naloxone via patient-controlled analgesia would decrease the incidence of side effects compared to morphine alone.

Methods: Patients scheduled for hysterectomy under general anaesthesia were enrolled in a double-blind, randomized, placebo-controlled trial. Patients received a standardized general anesthetic and postoperative patient-controlled analgesia. They were randomized to receive 60 mg patient-controlled analgesia morphine in 30 ml saline or 60 mg morphine in 30 ml saline with naloxone 0.8 mg. Parameters for patient-controlled analgesia were a 1-mg bolus of morphine with a 5-min lockout and no background infusion. Patient recall of nausea, vomiting, itching, and pain (at rest and with movement) were assessed at 6 and 24 h postoperatively by verbal rating score. Pain was also assessed by a 0- to 100-mm visual analog score, and sedation was assessed by an observer. The amount of morphine used and the requirements for symptomatic treatment were also recorded.

Results: Ninety-two patients completed the study, with no significant differences in outcomes between groups. At 24 h, the incidence of nausea was 84.8% in each group; the incidence of pruritus was 56.5% in the naloxone group and 58.7% in the placebo group. There were also no differences in symptomatic treatment requirements, pain scores, morphine use, or sedation between groups. The median dose of naloxone received equated to 0.38 µg · kg⁻¹ · h⁻¹ over 24 h.

Conclusions: There was no benefit from administering naloxone combined with morphine via patient-controlled analgesia.

THE use of opioid analgesics is often complicated by troublesome side effects. To avoid these, symptomatic treatments or opioid-sparing techniques can be used, but these strategies may be unsuccessful and expose the patient to other risks.¹ A novel approach to this problem in recent years has been the concurrent use of low-dose opioid antagonists, which has been reported to decrease the incidences of nausea, itching, and constipation.²⁻⁶ It has been suggested that analgesia and opioid side effects have different dose-response curves, permitting the antagonism of side effects while preserving analgesia.² Low doses of opioid antagonists have also been found to improve pain control and decrease opioid requirements, perhaps by inhibition of excitatory opioid receptors involved in the tolerance and hyperalgesia often observed with opioid therapy.²,⁵⁻⁷ Although most studies have involved patients receiving epidural or intrathecal opioids, two reported similar results with intravenous opioid patient-controlled analgesia (PCA).²,³ However, the first of these studies, which used a fixed-rate naloxone infusion, has not been repeated, perhaps because a separate infusion was seen as inconvenient in clinical practice. A recently published study combining naloxone and morphine in a PCA mixture demonstrated an increased requirement for morphine and more analgesic failures in male and female patients undergoing a range of surgical procedures.⁸ No benefit in terms of opioid side effects was seen, but the study was not designed to detect this benefit. The second positive study found a decrease in side effects from a single dose of nalmefene, a longer-acting opioid antagonist, but these benefits have not been confirmed.³ Consequently, we decided to test the hypothesis that a convenient combination of morphine and naloxone via PCA would decrease the incidence of side effects compared to morphine alone in female patients at high risk of postoperative emesis.

Materials and Methods

Patients

The study was approved by the hospital’s institutional review board (Cairns Base Hospital, Cairns, Queensland, Australia), and written informed consent was obtained from all participants. Female patients aged older than 18 yr who were scheduled to undergo abdominal or vaginal hysterectomy for benign disease under general anaesthesia were eligible for inclusion. Patients with known morphine allergy or chronic opioid use were excluded. Patients were instructed before surgery on the use of PCA and the nature of symptom evaluation.

Procedure

A standard general anesthetic was given, comprising 1–3 mg midazolam, 1–2 µg/kg fentanyl, 1–3 mg/kg propofol, 0.1–0.2 mg/kg morphine, nitrous oxide, and sevoflurane or isoflurane. All patients received vecuronium or rocuronium for tracheal intubation and reversal with neostigmine and atropine. No prophylactic antiemetics or nonsteroidal antiinflammatory drugs were permitted.
In the postanesthesia care unit, analgesia was provided with morphine in 1- to 2-mg increments until the patient was comfortable and sufficiently alert to use PCA.

Patients were stratified by operation (abdominal or vaginal hysterectomy) and randomized to naloxone or placebo (saline) groups according to a system of random numbers and a sealed envelope. The study was double blind, with the patient, anesthesiologist, nursing staff, and observers all unaware of the randomization. Two nurses, otherwise uninvolved in the patient’s care, opened the envelope and added the appropriate solution to the PCA syringe. Preservative-free morphine, 60 mg, was added to saline, with or without 0.8 mg naloxone, to a total of 30 ml. The naloxone dose was based on the weight of the patient, and the predicted 24-h morphine use was based on information from our Acute Pain Service database. Parameters for PCA were a 1-mg bolus of morphine with a 5-min lock-out and no background infusion. On the surgical ward, 1 g paracetamol (acetaminophen) every 4 hours was permitted for inadequate analgesia.

In the event of nausea or vomiting, antiemetic treatment was offered and was provided sequentially as 10 mg intravenous metoclopramide, 4 mg ondansetron, and 1 mg droperidol until symptoms were controlled. Troublesome pruritus was treated with 10 mg intravenous promethazine.

At 6 and 24 h postoperatively, patient recall of the severity of pain since the operation, at rest and with movement, was assessed by a 0- to 100-mm visual analog score and a verbal rating score of none, mild, moderate, or severe. Nausea and itch were assessed in the same way by verbal rating score, and the patients were asked if they had vomited. The level of sedation was assessed at these times by the researcher rather than by patient report, using the same categorical scale. Moderate sedation was defined as very sleepy but rousable; severe sedation was defined as difficult to rouse or unrousable. The amount of morphine used and the requirements for supplemental analgesia or symptomatic treatment over 24 h were also recorded.

Statistical Analysis

For determination of sample size, we considered a reduction in the incidence of nausea the most relevant clinical outcome. Gan et al.2 showed a decrease in nausea from 80% of patients with placebo to 35% and 45% with the two treatment arms of their study. We estimated a slightly more conservative decrease, from 75% nausea with placebo to 45% with treatment. Forty-six patients in each group would give an 80% chance of detecting this effect with a P value of 0.05. In the event of patient withdrawal, further patients were to be recruited until 92 patients had completed the study. Data were stored on Access 2000 (Microsoft Corporation, Redmond, WA) and analyzed with SigmaStat 2.0 (SPSS Inc., Chicago, IL). Interval and continuous data were assessed for normality using the Kolmogorov-Smirnov test, with Student t test and Mann–Whitney U test applied for normal and skewed data, respectively. For categorical data, the chi-square (without the Yates correction) or Fisher exact test was used as appropriate.

Results

Ninety-six patients were randomized, and 92 completed the study. One from each group required early reoperation for bleeding, a patient from the naloxone group experienced a suspected antibiotic allergy during surgery, and a patient from the control group underwent a lesser operation. All patients were classified as having American Society of Anesthesiologists physical status I or II. There were no baseline differences between the treatment and control groups (table 1).

There were no differences between the groups in the incidence of nausea, itching, sedation, or the need for symptomatic treatment at either assessment time. No patients were severely sedated (tables 2 and 3). In addition, there were no differences in these outcomes between the two operation groups (abdominal or vaginal hysterectomy). The incidence of nausea in patients receiving more than the median amount of morphine over 24 h was exactly the same as those receiving less.

There were no differences between the groups in terms of pain scores (both visual analog score and verbal rating score), amount of morphine used, or need for supplemental analgesia at either assessment time (table 4).

Among patients receiving naloxone, the median amount received over 24 h was 0.59 mg, which equated to 0.38 μg · kg⁻¹ · h⁻¹ over 24 h. The median amount of naloxone received over the first 6 h equated to 0.56 μg · kg⁻¹ · h⁻¹ and for the last 18 h equated to 0.32 μg · kg⁻¹ · h⁻¹.

Discussion

In three previous studies, the use of opioid antagonists with intravenous PCA morphine resulted in either benefi-
mental effect from adding naloxone to PCA morphine. Sedation

Table 3. Postoperative Pruritus, Promethazine Treatment, and Sedation

<table>
<thead>
<tr>
<th>Pruritus</th>
<th>Control</th>
<th>Naloxone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 h Total</td>
<td>24 (52.2%)</td>
<td>27 (58.7%)</td>
<td>0.529</td>
</tr>
<tr>
<td>Mild</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>24 h Total</td>
<td>39 (84.8%)</td>
<td>39 (84.8%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mild</td>
<td>23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>14</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>10 (21.7%)</td>
<td>10 (21.7%)</td>
<td>1.0</td>
</tr>
<tr>
<td>24 h</td>
<td>24 (52.2%)</td>
<td>27 (58.7%)</td>
<td>0.529</td>
</tr>
<tr>
<td>Antiemetics:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients treated</td>
<td>37 (80.4%)</td>
<td>36 (78.3%)</td>
<td>0.797</td>
</tr>
<tr>
<td>No. of doses per patient</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>0.932</td>
</tr>
</tbody>
</table>

Results for pruritus and patients treated with promethazine are expressed as number of patients (%); number of promethazine doses per patient is expressed as median (interquartile range); sedation results refer to patients moderately sedated.

The reason for the disparity in outcomes between our study and that of Gan et al. is unclear, though the differences in study design raise several possibilities. Conceivably, differences in symptom assessment between our study and that of Gan et al. may have influenced the results. Gan et al. used multiple contemporaneous measures, whereas we used patient recall of symptoms at 6 and 24 h. Although the two modes of assessment are not interchangeable, patient recall of nausea is generally reliable, and the overall incidence of symptoms is similar with the two methods. Indeed, we found an incidence of nausea and pruritus very similar to the placebo group in the study of Gan et al. We also found no difference in the requirement for rescue medications between groups, in contrast to the findings of Gan et al.

The total amount of morphine and the median total dose of naloxone received by our patients are similar to the amounts received by the patients studied by Gan et al. However, because we administered naloxone mixed with PCA morphine, in contrast to the separate infusion technique of Gan et al., factors other than total drug dose may be influential.

We believe there is no pharmaceutical incompatibility when morphine and naloxone are combined in saline, which might have offered an explanation for our negative findings. Although we are unaware of direct information on naloxone stability in this situation, in two published studies, naloxone was shown to have clinical activity when similarly combined with morphine. Using methods similar to ours, Cepeda et al. also combined naloxone with PCA morphine in male and female patients undergoing a range of surgical treatments. They used a lower bolus dose of naloxone of 6 µg for each 1 mg morphine, compared to 13.3 µg per 1 mg morphine in our study, and their total 24-h naloxone dose, equating to 0.10 µg · kg⁻¹ · h⁻¹, was much lower than the 0.38 µg · kg⁻¹ · h⁻¹ in our study. Despite these tiny doses, they found an increase in morphine require-
ments and more analgesic failures in the naloxone group.\textsuperscript{8} They found no difference in opioid-related side effects, though admittedly in patients at lower risk of such complications than those undergoing hysterectomy.\textsuperscript{8}

The lack of benefit from naloxone in our study and that of Cepeda \textit{et al.}\textsuperscript{8} may reflect the intermittent administration of naloxone in these studies, in contrast to the continuous infusion of Gan \textit{et al.}\textsuperscript{2} Naloxone has a half-life of 55 min, so administration by PCA would have resulted in fluctuation of naloxone concentrations.\textsuperscript{11} Perhaps a constant concentration of naloxone is required for it to have a beneficial effect.

Joshi \textit{et al.}\textsuperscript{3,11} studied the longer-acting opioid antagonist nalmefene (half-life, 108 min) in patients receiving intravenous PCA morphine. After a single bolus of 15 or 25 $\mu$g, they found a decrease in patient recall of opioid side effects and pain severity, as well as a decreased requirement for symptomatic treatment.\textsuperscript{3} However, these promising results have not been repeated or confirmed in other situations.\textsuperscript{12}

In summary, we found no benefit from adding naloxone to intravenous PCA morphine in women undergoing hysterectomy. We believe that in view of the limited and contradictory data available, further research is necessary before the routine clinical use of opioid antagonists with intravenous opioids can be recommended. If any benefit exists from this strategy, it would appear to be more likely with naloxone infusions or long-acting opioid antagonists.

\textbf{References}