Ibuprofen Provides Longer Lasting Analgesia Than Fentanyl After Laparoscopic Surgery

Martin Rosenblum, PhD, MD, Robert S. Weller, MD, Pattilyn L. Conard, CRNA, Ellen A. Falvey, RN, and Jeffrey B. Gross, MD
Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, Connecticut

The authors compared the analgesic efficacy of one dose of oral ibuprofen with that of intravenously administered fentanyl for relief of pain after outpatient laparoscopic surgery. Thirty healthy female patients received either 800 mg of oral ibuprofen preoperatively or 75 μg of intravenous fentanyl intraoperatively plus respective intravenous or oral placebos in a randomized, double-blind manner. Patients recorded their degree of pain and nausea in the recovery room, in the same-day surgery stepdown unit, during the ride home, and upon arrival at home. The postanesthesia care nurse recorded the amount of fentanyl and droperidol needed to treat pain and nausea in the recovery room. Patients who received ibuprofen were more comfortable in the stepdown unit (P < 0.05) and after arrival home (P < 0.05) than those in the fentanyl group. Additionally, patients who received ibuprofen had lower nausea scores in the step-down unit (P < 0.05); this may have been related to the lower total fentanyl dose in these patients. The authors conclude that ibuprofen may be a useful alternative to fentanyl for providing postoperative analgesia for outpatient surgery.


After laparoscopy for gynecologic surgery, patients often complain of abdominal discomfort, shoulder pain, and uterine cramps; these are commonly treated with opioid analgesics. Opioids, however, may increase the incidence of nausea and vomiting after laparoscopy, thus possibly prolonging recovery room stays (1). Although it is primarily an antiinflammatory agent, ibuprofen can provide effective analgesia for patients with mild-to-moderate postoperative pain (2-7). In addition, because ibuprofen decreases prostaglandin concentrations in menstrual fluid, it is the drug of choice for treating dysmenorrhea (8). Such prostaglandins may contribute to postlaparoscopy pain; therefore, ibuprofen may be especially suited to provide analgesia after gynecologic surgery. We designed the present randomized, double-blind study to compare the efficacy of ibuprofen with that of fentanyl for relieving pain after laparoscopic surgery.

Methods

Thirty consenting nonpregnant, ASA physical status I or II female patients scheduled for outpatient laparoscopic surgery for infertility (lysis of adhesions and excision of endometriosis with a CO₂ laser) participated in this study approved by our institutional review board. We excluded patients with histories of allergy or adverse reactions to nonsteroidal antiinflammatory agents, peptic ulcer disease, and coagulation disorders, as well as those whose operation was scheduled to last longer than 2.5 h. We assigned patients to receive either 75 μg of fentanyl or 800 mg of ibuprofen for postoperative analgesia based on a randomization table. Patients in the ibuprofen group received 800 mg of ibuprofen orally 1 h before the operation and 1.5 mL of a saline placebo intravenously 30 min before the anticipated end of the operation, whereas patients in the fentanyl group received an oral placebo 1 h before the operation and 75 μg of fentanyl intravenously 30 min before the estimated time of completion of the operation. All study drugs and placebos were prepared by the hospital pharmacy; the patient, the anesthesia care team, and the investigators evaluating the patient were unaware of the study group assignment.

After induction of anesthesia and paralysis with 4 mg/kg of thiopental and 0.1 mg/kg of vecuronium, respectively, tracheal intubation was performed. We controlled ventilation and maintained anesthesia with isoflurane and 50% N₂O in O₂. The anesthesiologist, who was unaware of the study group assign-
Table 1. Discomfort Scores Used to Determine Need for Additional Fentanyl in the Postanesthesia Care Unit

<table>
<thead>
<tr>
<th>Score</th>
<th>Condition</th>
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<tbody>
<tr>
<td>0</td>
<td>Quiet and comfortable</td>
</tr>
<tr>
<td>1</td>
<td>Sedate but uncomfortable</td>
</tr>
<tr>
<td>2</td>
<td>Restless and agitated</td>
</tr>
<tr>
<td>3</td>
<td>Uncontrollably agitated</td>
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</table>

ment, adjusted the isoflurane concentration based on routine clinical criteria. At the end of surgery, we aspirated each patient’s gastric contents via an orogastric tube and reversed residual neuromuscular blockade with intravenous administration of 3 mg of neostigmine and 0.6 mg of glycopyrrolate. Patients breathed spontaneously until they awakened, at which time we removed the endotracheal tube and transferred them to the recovery room.

At 5, 15, 30, 60, and 90 min after the patients arrived in the recovery room, one of the investigators used the 4-point scale shown in Table 1 to determine whether additional analgesia was necessary. At the same times, we recorded the presence and severity of nausea and vomiting on a scale ranging from 0 (no nausea) to 3 (severe nausea with recurrent vomiting). At 15, 30, 60, and 90 min after arrival in the postanesthesia care area, patients evaluated their own pain on a 10-cm visual analogue pain scale.

Patients whose discomfort score in the postanesthesia care area was 2 or 3 (Table 1) received incremental doses of 25 μg of fentanyl intravenously until they were comfortable (discomfort score < 2). Note that if fentanyl was necessary during the first half-hour postoperatively, we asked patients to score their pain on the visual analogue pain scale before receiving the first dose of fentanyl. In addition to the pain and nausea scores, we also recorded the duration of the postanesthesia recovery period and the total dose of fentanyl administered. We asked all patients to complete a postoperative questionnaire regarding their level of pain (10-point scale) and degree of nausea (4-point scale) at several times after discharge from the recovery room: in the same-day surgery stepdown unit, during the ride home, and after arrival at home. Patients were instructed to call us if pain, nausea, or vomiting were intractable.

We analyzed pain data using two-way analysis of variance (9), with Tukey t-tests for individual times if overall significance was present. We analyzed nausea data using Bonferroni-corrected Wilcoxon rank-sum tests. For demographic data, we used one-way analysis of variance. To determine if postoperative nausea was related to the total dose of fentanyl, we used Spearman rank correlation. Values are shown as mean ± se, with P < 0.05 indicating significance throughout the analysis.

Table 2. Comparison of the Ibuprofen and Fentanyl Groups

<table>
<thead>
<tr>
<th></th>
<th>Ibuprofen (n = 15)</th>
<th>Fentanyl (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29 ± 1.2</td>
<td>30 ± 1.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165 ± 1.5</td>
<td>165 ± 2.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.9 ± 2.6</td>
<td>59.1 ± 2.5</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td>85 ± 7.1</td>
<td>99.4 ± 9.8</td>
</tr>
<tr>
<td>Time in the PACU (min)</td>
<td>99 ± 4.0</td>
<td>104 ± 4.0</td>
</tr>
<tr>
<td>Number of patients requiring fentanyl in the PACU</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Fentanyl dose in the PACU (μg)</td>
<td>36.7 ± 9.1</td>
<td>26.7 ± 6.7</td>
</tr>
<tr>
<td>Total fentanyl dose (μg)</td>
<td>36.7 ± 9.1*</td>
<td>101.7 ± 6.7</td>
</tr>
<tr>
<td>Number of patients requiring droperidol in the PACU</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Postoperative droperidol (mg)</td>
<td>0.29 ± 0.08</td>
<td>0.21 ± 0.08</td>
</tr>
</tbody>
</table>

PACU, postanesthesia care unit.
Values are mean ± se.
*P < 0.05 vs fentanyl.

Results

Age, height, weight, duration of surgery, time in the recovery room, and postoperative droperidol dose did not differ significantly between patients in the ibuprofen and fentanyl groups (Table 2). The investigator’s assessment of discomfort in the recovery room did not differ between groups; this was confirmed by the fact that patients in each group received similar doses of fentanyl in the recovery room. However, as might be expected, patients in the fentanyl group received a larger total (intraoperative plus postoperative) dose of fentanyl than those in the ibuprofen group. Neither epigastric pain nor heartburn developed in any of the patients as a result of the ibuprofen therapy.

Analysis of variance revealed that patients who received ibuprofen had significantly less pain in the postoperative period than those in the fentanyl group (Figure 1, P < 0.001). Post hoc testing revealed that this overall difference could be attributed to differences observed in the stepdown unit and after patients arrived at home. Patients who received ibuprofen also reported significantly less nausea in the same-day surgery unit than those in the fentanyl group (Figure 2, P < 0.05). There was a significant correlation between severity of nausea in the same-day surgery unit and the total fentanyl dose (Figure 3, r = 0.59, P < 0.01).

Discussion

With the proliferation of same-day surgery, anesthesiologists must reevaluate strategies for postoperative pain management. In the outpatient setting, it is especially important to avoid side effects such as
excessive sedation, nausea, and vomiting, while providing effective analgesia. In fact, Gold et al. (10) found that pain, vomiting, and postoperative somnolence are the most common reasons for unanticipated hospital admission after same-day surgery.

In the present study, 800 mg of oral ibuprofen provided longer lasting analgesia than did 75 μg of intravenous fentanyl after laparoscopic surgery. The validity of this conclusion is based on the premise that the patients received equal analgesic doses of the two therapies (i.e., ibuprofen and fentanyl). Unfortunately, there are no studies directly comparing the analgesic potency of ibuprofen with that of parenterally administered narcotics. However, the maximum analgesic effect that can be obtained from nonsteroidal antiinflammatory drugs appears to be equivalent to that of 8–10 mg of morphine administered inra-

muscally (11–13). An 800-mg oral dose provides the maximum analgesia obtainable with ibuprofen (14); this dose should be approximately equianalgesic to 75 μg of fentanyl assuming a 100:1 potency ratio of fentanyl to morphine (15). Furthermore, our finding that the patients required equal fentanyl doses in the postanesthesia care unit suggests that 75 μg of fentanyl and 800 mg of ibuprofen were approximately equianalgesic under the conditions of this study.

Nonsteroidal antiinflammatory drugs act peripherally as well as centrally. Peripherally, their mechanism of action is to inhibit the cyclooxygenase enzyme system that metabolizes arachidonic acid to its endoperoxide intermediates (14). This results in decreased production of thromboxanes, prostacyclins, and prostaglandins. Thus, fewer intermediates and end products of the arachidonic acid cascade are available to interact with local mediators of inflammation such as bradykinin, histamine, and 5-hydroxytryptamine to promote erythema, edema, and pain, or to promote uterine contractions. Nonsteroidal antiinflammatory drugs may also act centrally to decrease pain by inhibiting cyclooxygenase within the central nervous system (14).

Ibuprofen may be particularly effective in treating perioperative pain after gynecologic procedures because of its peripheral effect on prostaglandin synthesis. By decreasing elevated prostaglandin levels, ibuprofen effectively relieves uterine pain associated with both primary dysmenorrhea (8,16–18) and secondary dysmenorrhea induced by intrauterine devices (8,18). A similar mechanism may help to relieve the pain that follows surgical manipulation of the uterus.

Our results confirm previous reports suggesting...
that ibuprofen compares favorably with moderate doses of opioids for postoperative analgesia. For example, after dental surgery, 400 mg of ibuprofen is more effective than 30 mg of codeine (2), 30 mg of dihydrocodeine (3), 65 mg of propoxyphene (4), aspirin-codeine (650 mg/60 mg) (5), acetaminophen-codeine (600 mg/60 mg) (5), and aspirin-codeine-caffeine (375 mg/30 mg/30 mg) (6). After herniorrhaphy, the analgesic efficacy of 400 mg of oral ibuprofen is intermediate between that of aspirin-codeine-caffeine (375 mg/30 mg/30 mg) and that of aspirin-codeine-caffeine (750 mg/16 mg/60 mg) (7).

Our observation that the difference in pain control between ibuprofen and fentanyl first became apparent in the same-day surgery unit may be related to differences in the pharmacokinetics of the two analgesics. Although fentanyl has a long terminal elimination half-life (2.5–7 h), its duration of action after a small (<7 µg/kg) dose is primarily determined by redistribution (analogous to other lipid-soluble drugs such as thiopental) (19). After a single 1-µg/kg intravenous dose, such as patients received in the present study, plasma fentanyl levels can be expected to exceed the analgesic threshold for no longer than 2 h (20–22). In contrast, although the plasma elimination half-life of ibuprofen is 2 h (23), it is not fully absorbed from the gastrointestinal tract until 3 h after an 800-mg oral dose (23,24). Because of the complex interaction between absorption and elimination kinetics, the therapeutic effects of a single dose of ibuprofen may last more than 4 h (3–6,14). Because the mean duration of surgery in the present study was approximately 1.5 h, one would expect that by the time patients arrived in the same-day surgery unit, the analgesic effect of fentanyl was probably wearing much more rapidly than that of ibuprofen.

Patients in the fentanyl group had a significantly more severe nausea and vomiting in the same-day surgery unit than those who received ibuprofen. In fact, the significant correlation between total fentanyl dose and nausea scores in the same-day surgery unit suggests that fentanyl was a causative factor. Opioids are well known to produce nausea and vomiting by direct stimulation of the chemoreceptor trigger zone (25). Nausea and vomiting are relatively uncommon in recumbent patients given opioids but increase significantly when patients move, suggesting that vestibular stimulation may potentiate the emetic effect (25). This is consistent with our observation that nausea was most severe when patients were transferred to the same-day surgery unit, where they first got out of bed.

Chronic ibuprofen therapy may cause gastrointestinal side effects (epigastric pain, nausea, heartburn, abdominal discomfort, and sensations of abdominal “fullness”) in 5%–15% of patients (26). However, a single perioperative dose of ibuprofen is almost always well tolerated (2–4,6). In the present study, we excluded patients who had prior histories of intolerance to nonsteroidal antiinflammatory drugs; therefore, our findings regarding postoperative nausea and vomiting do not apply to patients with such histories.

Of course, the present study compared fixed doses of ibuprofen and fentanyl. It is conceivable that had we chosen different doses of ibuprofen and/or fentanyl, or constructed dose-response curves for the two drugs, our results might have been different.

In summary, we observed that 800 mg of oral ibuprofen, given preoperatively to patients undergoing laparoscopic surgery of less than 2.5-h duration, provided longer lasting analgesia than 75 µg of intravenous fentanyl given intraoperatively. Furthermore, probably by decreasing the total perioperative dose of fentanyl, ibuprofen reduced postoperative nausea in the same-day surgery unit, where patients first ambulated and took oral fluids.

References