The Efficacy of Intramuscular Ketorolac in Combination with Intravenous PCA Morphine for Postoperative Pain Relief

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Study Objective: To examine the efficacy of intramuscular (IM) ketorolac used in combination with intravenous (IV) patient-controlled analgesia (PCA) morphine for postoperative pain relief following intra-abdominal gynecologic surgery.

Design: Randomized, double-blind, placebo-controlled study.

Setting: Patient care unit at a university medical center.

Patients: Thirty-five healthy women undergoing intra-abdominal gynecologic surgery who requested postoperative PCA.

Interventions: Postoperatively, all patients received IV PCA morphine, with the PCA device programmed to deliver a maximum of 1 mg every 6 minutes (maximum of 30 mg over 4 hours). In addition, patients received one of three regimens: (1) IM saline every 6 hours; (2) IM ketorolac 30 mg while in the postanesthesia care unit (PACU), followed by 15 mg every 6 hours; or (3) IM ketorolac 60 mg while in the PACU, followed by 30 mg every 6 hours.

Measurements and Main Results: Patients were assessed at regular intervals. Visual analog scale (VAS) scores were used to assess analgesia and patient satisfaction with therapy. Data on morphine usage were obtained from the PCA device, and the frequency and severity of adverse effects were assessed for the presence or absence of side effects. Cumulative morphine dosages were lower (p < 0.05) in both ketorolac groups at 12, 18, and 24 hours. VAS scores and the frequency of side effects did not differ significantly among groups.

Conclusions: IM ketorolac significantly decreased PCA morphine requirements. The analgesic effects of the two drugs appear to be additive.

Keywords: Nonsteroidal anti-inflammatory drugs, ketorolac; opioids, morphine; analgesia, postoperative; methods, patient-controlled analgesia.
Introduction

Intravenous (IV) patient-controlled analgesia (PCA) offers a number of clinical advantages in the postsurgical setting, including a rapid onset of pain relief, accommodation for individual variability in requisite plasma opioid concentration, and increased patient control. Such therapy is, however, not without limitations: effective plasma concentrations may not be maintained during periods of sleep; dosing generally is limited to a single analgesic drug; and dose-dependent, opioid-related side effects may lead to morbidity, limited self-administration of the analgesic drug, and decreased overall satisfaction.

The aforementioned limitations of PCA may be overcome by supplementing opioid PCA with a nonopioid analgesic. The use of a nonsteroidal anti-inflammatory drug (NSAID) has been facilitated by the recent introduction of ketorolac tromethamine (Toradol, Synex Labs, Palo Alto, CA) in a preparation suitable for intramuscular (IM) administration. In an initial evaluation, Gillies et al. noted that a continuous IM infusion of this drug reduced opioid requirements. The continuous IM route is, however, not practical clinically. We, therefore, undertook the present double-blind, placebo-controlled, prospective evaluation of intermittent IM administration of ketorolac as a supplement to IV PCA opioid analgesia.

Materials and Methods

The study was approved by the Human Investigations Committee of the Yale University School of Medicine. Informed written consent was obtained from 35 patients scheduled for elective intra-abdominal gynecologic surgery. All patients were instructed preoperatively in the use of the PCA device (Abbott Lifecare II, Abbott Medical Products, Chicago, IL) and oriented to visual analog scale (VAS) scoring for pain and satisfaction. Premedication was with midazolam 0.05 to 0.05 mg/kg IM. Patients underwent general anesthesia with nitrous oxide in oxygen plus isofluurane and morphine as required. At the conclusion of surgery, patients were randomized in a double-blind fashion to one of three groups: Group 1 (n = 12) received 3 ml of saline (placebo) while in the postsurgery care unit (PACU), followed by four doses of 3 ml IM every 6 hours on the ward; Group 2 (n = 12) received ketorolac 30 mg IM while in the PACU, followed by four doses of 15 mg IM every 6 hours; Group 3 (n = 11) received ketorolac 60 mg IM in the PACU, followed by four doses of 30 mg IM every 6 hours. While in the PACU, patients also were given 1 to 2 mg of morphine as needed to achieve an acceptable level of analgesia. On the ward, all patients received standard IV PCA morphine, with a 1 mg incremental dose, a 6-minute lockout, and a 4-hour maximum of 30 mg.

The following data were obtained at time 0 (time of first dose of study drug) and at 2, 6, 9, 12, 18, 24, and 36 hours thereafter: (1) cumulative PCA morphine dose; (2) VAS score for pain (0 = no pain; 10 = worst pain); (3) VAS score for satisfaction (0 = totally dissatisfied; 10 = completely satisfied); (4) level of alertness as scored by the blinded observer (1 = alert, oriented, initiates conversation; 2 = drowsy, oriented, initiates conversation; 3 = drowsy, oriented, does not initiate conversation; 4 = very drowsy, disoriented; 5 = stuporous); (5) blood pressure, heart rate, respiratory rate; (6) frequency and severity of nausea, vomiting, and pruritus; (7) dose and frequency of antiemetic therapy.

Data were analyzed using Wilcoxon rank sum, chi-square, and least squares mean tests. A value of p < 0.05 was considered statistically significant.

Results

All patients completed the study protocol satisfactorily and without complications. There were no differences among the groups with respect to patient age, height, weight, the intraoperative morphine dose, the dose of morphine received in the PACU, or baseline VAS pain scores (Table 1).

Patients receiving ketorolac required less PCA morphine at each interval evaluated (Figure 1). Reductions in cumulative dose reached statistical significance at 12, 18, and 24 hours. There were no significant differences among groups with respect to VAS pain scores. There was, however, a nonsignificant trend toward lower pain scores in those individuals receiving 30 mg of ketorolac when compared with patients receiving the placebo (Figure 2).

All individuals enrolled in this study were satisfied with their analgesic therapy, and there were no significant differences among groups with respect to patient satisfaction at any time interval. Although the frequency of nausea and pruritus tended to be lower in ketorolatreated patients, there were no statistically significant dif-

Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Intraoperative Morphine</th>
<th>PACU Morphine</th>
<th>Time to Ambulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: placebo</td>
<td>12</td>
<td>39.8 ± 7</td>
<td>164.8 ± 5</td>
<td>66.1 ± 9</td>
<td>3.0 ± 2.5</td>
<td>2.5 ± 2.5</td>
<td>8.4 ± 1.6</td>
</tr>
<tr>
<td>2: ketorolac 15 mg</td>
<td>12</td>
<td>40.6 ± 8</td>
<td>164.5 ± 5</td>
<td>72.6 ± 15</td>
<td>3.9 ± 6.1</td>
<td>3.1 ± 3.3</td>
<td>8.2 ± 4.8</td>
</tr>
<tr>
<td>3: ketorolac 30 mg</td>
<td>11</td>
<td>38.7 ± 11</td>
<td>162.6 ± 8</td>
<td>63.9 ± 8</td>
<td>3.3 ± 4.7</td>
<td>3.8 ± 3.9</td>
<td>9.6 ± 4.8</td>
</tr>
</tbody>
</table>

Note: No significant differences among groups were found.

PACU = postanesthesia care unit.

The beneficial effect of ketorolac in the present series is not surprising. Previous studies suggested that indomethacin may reduce opioid requirements and improve analgesia. NSAIDs and opioids act at different sites in the pain pathway. NSAIDs provide analgesia primarily by inhibiting prostaglandin synthesis at the site of peripheral injury, while opioids act primarily at specific receptor sites in the spinal cord and supraspinal nuclei.

Ketorolac has more potent analgesic activity than other NSAIDs; 30 mg of ketorolac has been shown to be equivalent to 10 mg of morphine in patients undergoing less extensive surgical procedures. In the present study, the reduction in morphine usage was most evident 24 hours postoperatively, where a 48% reduction in total PCA requirement was achieved. This corresponded to a 27.2 mg decrease in morphine use for 75–100 mg of ketorolac. Although VAS scores did not differ significantly, they tended to be higher for placebo-treated patients. Perhaps this was a consequence of these patients accepting a greater degree of discomfort rather than a greater degree of opioid-related side effects.

The side effects of NSAIDs and opioids are essentially unrelated. Ketorolac does not elicit the respiratory depression, sedation, psychomotor effects, nausea, ileus, constipation, biliary colic, and urinary retention that may be associated with opioids. Therefore, the ability of ketorolac to decrease opioid usage while maintaining and/or improving analgesia offers a potential for fewer dose-dependent, opioid-induced side effects. Such benefits may be appreciated with larger sample sizes.

Although no adverse effects associated with ketorolac were noted in the present study, NSAIDs have the potential to elicit unwanted side effects. While NSAIDs may be safe even when administered chronically, there is evidence to suggest that relatively short term use may cause dose-related gastric mucosal damage and mildly increase the bleeding time. Significant problems are more likely to occur with long-term therapy, especially in the context of underlying pathology or during concomitant use of other gastric irritants or antiplatelet drugs.
Ketorolac is contraindicated in patients who have demonstrated previous hypersensitivity (angioedema or bronchospasm) to aspirin or other NSAIDs. Another theoretical concern is that NSAID therapy may "mask" hyperpyrexia. Of note, the present data indicate that ketorolac 15 mg administered every 6 hours was almost as effective as 30 mg every 6 hours in reducing the PCA morphine requirement. This is consistent with the finding by Gillies et al. that the morphine-sparing effects of infusions of 1.5 and 3.0 mg/hr were equivalent. Thus, a relatively low dose of ketorolac may be used, reducing the likelihood of dose-related side effects.

In conclusion, the present data indicate that IM administration of ketorolac decreases morphine requirements. While the analgesic effects of morphine and ketorolac are additive, the adverse effects appear to be independent. Hence, this combination may improve the risk-benefit relationship of analgesic therapy.

References