Intravenous Ketorolac as an Adjunct to Patient-Controlled Analgesia (PCA) for Management of Postgynecologic Surgical Pain

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Study Objective: To determine whether intravenous (IV) doses of ketorolac tromethamine provide safe and effective augmentation of postsurgical analgesia for patients using IV patient-controlled analgesia (PCA) with morphine.

Design: Randomized, double-blind, placebo-controlled, dose-response evaluation.

Setting: Patient care unit at a university medical center.

Patients: 62 ASA physical status I–III females recovering from intra-abdominal gynecologic surgery with general anesthesia who requested postoperative PCA.

Interventions: Following initial pain assessment in the recovery room, patients were randomized to receive either IV saline (placebo) followed by IV saline every 6 hours (Group 1); IV ketorolac 30 mg loading dose followed by IV ketorolac 15 mg every 6 hours (Group 2); or IV ketorolac 60 mg loading dose followed by IV ketorolac 30 mg every 6 hours (Group 3). All patients were provided IV PCA, which was programmed to provide 1.2 mg of morphine with a 6-minute lockout interval.

Measurements and Main Results: Visual analog scale (VAS) resting pain and satisfaction scores were measured every 2 to 12 hours. Cumulative PCA with morphine and the frequency and severity of side effects also were assessed. IV ketorolac showed no clinically significant side effects. Group 2 patients experienced significant reductions in VAS resting pain scores (p < 0.05), and a trend toward decreased morphine self-administration in both active groups was noted. Group 2 and Group 3 patients reported greater satisfaction with postsurgical analgesia than Group 1 patients (p < 0.05).

Conclusions: IV ketorolac used as an analgesic adjunct provided safe and effective augmentation of PCA with morphine in patients recovering from intra-abdominal gynecologic surgery.

Keywords: Analgesia, postoperative; analgesia; intravenous delivery; ketorolac; morphine; patient-controlled analgesia.

Introduction

Ketorolac tromethamine is an injectable nonsteroidal anti-inflammatory drug (NSAID) that has been used as a primary analgesic for control of moderate to severe postsurgical pain. Ketorolac is recommended for use as an analgesic adjunct for intravenous (IV) and epidural patient-controlled analgesia.
Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Intraoperative MSO₂ (mg)</th>
<th>Intraoperative Fentanyl (mg)</th>
<th>PACU MSO₂ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: placebo</td>
<td>30.1</td>
<td>162.8</td>
<td>64.0</td>
<td>3.9</td>
<td>91.3</td>
<td>3.5</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(10.1)</td>
<td>(8.9)</td>
<td>(9.4)</td>
<td>(4.5)</td>
<td>(143.2)</td>
<td>(3.7)</td>
</tr>
<tr>
<td>Group 2: ketorolac 15 mg</td>
<td>42.2</td>
<td>162.6</td>
<td>72.9*</td>
<td>6.5</td>
<td>179.5</td>
<td>3.6</td>
</tr>
<tr>
<td>(n = 20)</td>
<td>(8.4)</td>
<td>(11.2)</td>
<td>(13.3)</td>
<td>(6.8)</td>
<td>(219.4)</td>
<td>(3.5)</td>
</tr>
<tr>
<td>Group 3: ketorolac 30 mg</td>
<td>41.2</td>
<td>163.3</td>
<td>65.6</td>
<td>6.5</td>
<td>165.8</td>
<td>3.7</td>
</tr>
<tr>
<td>(n = 21)</td>
<td>(7.9)</td>
<td>(8.6)</td>
<td>(12.0)</td>
<td>(6.5)</td>
<td>(160.8)</td>
<td>(3.6)</td>
</tr>
</tbody>
</table>

*p < 0.05 between this group and both other groups.

Note: Data are means (SEM).

MSO₂ = morphine; PACU = postanesthesia care unit.

(PCA). In a prior investigation,¹ patients treated with intramuscular (IM) doses of ketorolac self-administered significantly less morphine that did patients treated with a placebo. No improvement in satisfaction was observed, however, as patients were generally dissatisfied with the need for frequent and painful IM injections.

Although ketorolac has yet to receive U.S. Food and Drug Administration approval for IV use, the IM preparation provides safe and effective pain relief when administered as a parenteral analgesic² and is used with increasing frequency in general surgical and pediatric patients.³ Our rationale for IV dosing includes the following: (1) patients are generally fearful of IM injections; (2) pharmacokinetic studies have shown that a 4 minute IV infusion of ketorolac is bioequivalent to that observed with IV dosing;⁴ (3) ketorolac is physically and chemically stable when mixed with a variety of commonly used infusion solutions, and it is not absorbed by IV tubing or polyvinyl chloride syringes;⁵ (4) the IM preparation is nonirritating and is not associated with significant phlebitis when administered as a slow IV infusion.⁶⁻⁷ Furthermore, IV administration of this preparation is not associated with cardiac or hemodynamic changes.⁸

The present double-blind, placebo-controlled evaluation examined the safety and efficacy of IV ketorolac as an analgesic adjunct for PCA with morphine in patients recovering from gynecologic surgery.

Materials and Methods

This study was approved by the Human Investigation Committee of Yale University School of Medicine. Informed written consent was obtained from 62 healthy (ASA physical status I-III) females scheduled for elective intra-abdominal gynecologic surgery with general anesthesia. Excluded were patients over age 65 or under age 18; those with known bleeding diatheses, renal dysfunc-

tion, a history of asthma, or a sensitivity to NSAIDs; and patients weighing less than 50 kg or more than 100 kg. All patients were instructed preoperatively in the use of the PCA device (Abbott PCA Plus II, Abbott Park, Chicago, IL) and oriented to the visual analog scale (VAS) scoring for pain and satisfaction. If indicated, premedication was with IM midazolam 0.05 to 0.05 mg/kg 1 hour prior to surgery.

General anesthesia was provided with nitrous oxide in oxygen plus isoflurane and morphine or fentanyl as required. At the conclusion of surgery, patients were randomized in a double-blind manner to one of three groups: Group 1 patients (n = 21) received IV saline (placebo) 2 ml in the postanesthesia care unit (PACU), followed by four doses of IV placebo 1 ml every 6 hours. Group 2 patients (n = 20) received IV ketorolac 30 mg in the PACU, followed by four doses of IV ketorolac 15 mg every 6 hours. Group 3 patients (n = 21) received IV ketorolac 60 mg in the PACU, followed by four doses of IV ketorolac 30 mg every 6 hours. While in the PACU, patients received IV morphine 1 to 2 mg as needed to achieve acceptable analgesia. Upon transfer to the ward, patients received PCA with IV morphine, with the infusor programmed to provide an incremental dose of 1.2 mg and a 4-hour maximum dose of 30 mg, with a lockout interval of 6 minutes.

The following data were obtained at time 0 (time of first dose of study medication) and at 2, 4, 6, 9, 12, 18, 24, and 36 hours: cumulative interval PCA dose; VAS score for pain (0 = no pain to 10 = worst pain); VAS score for satisfaction (0 = totally dissatisfied to 10 = completely satisfied); 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); blood pressure, heart rate, and respiratory rate; frequency and severity of nausea, vomiting, and pruritus; dose and frequency of antiemetic therapy.

Data were analyzed using the Wilcoxon rank sum test (VAS pain and satisfaction, pain intensity differences), chi-square analysis (adverse effects), and analysis of variance (morphine use). A value of p < 0.05 was considered statistically significant.


Table 2. Number (%) of Patients with Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Nausea &gt; 4 Hours</th>
<th>Treatment for N/V</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: placebo (n = 21)</td>
<td>12 (57%)</td>
<td>8 (38%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Group 2: ketorolac 15 mg (n = 20)</td>
<td>11 (55%)</td>
<td>10 (50%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group 3: ketorolac 30 mg (n = 21)</td>
<td>7 (33%)</td>
<td>7 (33%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

N/V = nausea and vomiting.

Table 3. Percentage Reduction in Patient-Controlled Analgesia with Morphine Compared with Group 1 (Placebo)

<table>
<thead>
<tr>
<th></th>
<th>12 Hours</th>
<th>24 Hours</th>
<th>36 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2: ketorolac 15 mg</td>
<td>25</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Group 3: ketorolac 30 mg</td>
<td>22</td>
<td>30</td>
<td>23</td>
</tr>
</tbody>
</table>

Results

All patients completed the study protocol without complications. There was no difference among groups with respect to patient age, height, dose of premedicant, intraoperative opioid use, or PACU morphine dose; however, patients in Group 2 (ketorolac 15 mg) weighed more than those in the other two groups (p < 0.05; Table 1).

There were no intergroup differences with respect to frequency of opioid-related side effects (Table 2), PCA attempts, or hourly morphine requirements; however, the overall trend was toward reduced self-administration of morphine (Figure 1). Patients in Groups 2 and 3 required an average of 20% less morphine during the study interval than patients treated with saline placebo (Group 1) (Table 3); however, this difference did not reach statistical significance. In the placebo group, baseline pain scores increased to a median value of 5.3 cm at 2 hours and remained essentially unchanged through the first 9 hours. Thereafter, pain scores progressively decreased over the next 24 hours. Patients in Group 2 showed a significant reduction in VAS pain scores at 4, 6, 9, and 12 hours (p < 0.05, ketorolac 15 mg vs. placebo). Pain intensity differences from baseline scores were superior with ketorolac 15 mg versus the placebo at 2, 4, 6, 9, and 12 hours (Figure 2).

Patients in Group 3 (ketorolac 30 mg) began the study with a median VAS pain score of 2.15, which increased over the next 2 hours to 4.3, then gradually diminished to 1.6 during the next 24 hours. VAS pain scores and pain intensity differences in this group were not significantly different from either the placebo or the ketorolac 15 mg group (Figure 2).

VAS scores for patient satisfaction with therapy (Figure 3) indicated that although all patients were satisfied with their therapy (VAS score greater than 5), satisfaction was greatest in those individuals receiving either IV dose of ketorolac (15 mg or 30 mg), with significant improvement (p < 0.05) seen at 4, 6, and 9 hours for ketorolac 15 mg and at 9 and 18 hours for ketorolac 30 mg. No patient receiving ketorolac experienced clinically significant postsurgical bleeding, phlebitis, or gastric upset during the 36-hour study period.
Discussion

IV ketorolac provided safe and effective augmentation of PCA with morphine in patients recovering from gynecologic surgery. To our knowledge, this is the first double-blind, dose-response study of IV ketorolac in which patients self-administered opioids benefited from reduced intensity of postsurgical pain. Although the drug manufacturer (Syntex Corp., Palo Alto, CA) is unable to recommend IV dosing of ketorolac until safety and efficacy trials are completed, we found that this form of administration was well accepted by patients and nursing staff.

Our observations of improved pain scores and a trend toward reduced requirement of PCA with opioids reflect the advantage of balanced or multimodal analgesic therapy in which two or more drugs mediating effects at different sites or via different mechanisms may improve postoperative analgesic efficacy and outcome.12 Katorolac and other NSAIDs reduce pain after surgery by inhibiting synthesis and release of prostaglandins at the site of surgical trauma,13 whereas morphine activates spinal and supraspinal opioid receptors that inhibit the release of nociceptive neurotransmitters.14 Our findings support those of Parker et al.,4 who reported that IV ketorolac reduced PCA with morphine and meperidine requirements in patients recovering from abdominal hysterectomy. The opioid-sparing effect of PCA noted in their single-dose (ketorolac 30 mg) trial was associated with a more rapid return of bowel function and a shortened hospital stay. Although the combination of PCA plus adjunctive analgesic therapy is able to reduce self-administration attempts and total opioid dose,3-5,9 improvements in analgesic efficacy are less commonly observed. Our findings are consistent with those of Grass et al.,6 who reported that the combination of epidural PCA with fentanyl plus ketorolac 30 mg reduced movement-associated pain scores to a greater degree than did fentanyl alone in patients recovering from radical prostatectomy.

When used as an analgesic adjunct, ketorolac appears to have a very shallow dose response.1,5-6* In agreement with previous findings with IM and IV bolus doses or continuous infusions of ketorolac,3,5,6* our study shows that increasing dose size is not associated with greater analgesic effect. In this regard, Kenny et al.7 and Gillies et al.8 reported that a ketorolac 3 μg/hr infusion was no more efficacious than a 1.5 μg/hr infusion. In earlier evaluations of IM ketorolac3 and IV ketorolac,1,7,10 10 to 15 mg administered every 6 hours was as effective as 30 mg in reducing 24-hour requirements of PCA with opioids.

The possible additive (or even synergistic) interactions of morphine and ketorolac will require more extensive dose-response studies. However, based on our finding that 15 mg was just as effective as 30 mg, we again emphasize that overall dose administered should be reduced when ketorolac is coadministered with opioid analgesics. Since ketorolac-related side effects appear to be dose related,15 the improved analgesic effectiveness noted in the low-dose group was gratifying. In this regard, even smaller doses (5 to 7.5 mg) should be examined, especially in patients who are at risk for increased surgical and gastrointestinal bleeding.

Regressions in pain intensity noted in our lower-dose ketorolac group (Group 2) may have been responsible in part for increases in patient satisfaction with analgesic therapy. Overall, patient satisfaction with analgesic therapy reflects a composite of the effectiveness of pain relief balanced by the occurrence of troublesome side effects.16 Despite requiring approximately 20% less PCA with morphine, patients treated with IV ketorolac did not benefit from a reduction in opioid-related side effects. This finding is similar to that reported by Parker et al.,4 who noted that patients receiving IV ketorolac experienced an almost identical rate of pruritus and nausea despite significant reductions in opioid self-administration. Ketorolac-induced side effects are essentially unrelated to, and nonadditive with, those associated with PCA with opioids. Thus, the combination of improved pain relief and a stable (acceptable) level of opioid-induced side effects may have been responsible for the greater level of satisfaction observed. However, the fact that patients receiving the higher dose did not experience statistically significant improvement in pain relief but indicated greater satisfaction with their therapy suggests that other factors may be responsible for patient satisfaction with PCA therapy.

We feel strongly that IM dosing of analgesics is a throw-

back to older, less reliable forms of pain therapy and has no place in the setting of modern acute pain management. The ability to administer both NSAID and opioid analgesia via the IV route avoids absorption variability and pain associated with injection, and it represents an improvement in overall patient care. In this preliminary evaluation, IV ketorolac was withheld during the operative period and administered postsurgically only to patients having minimal intraoperative bleeding. It is conceivable that the effectiveness of ketorolac may be further improved by administering a loading dose prior to the surgical incision rather than waiting for the patient to experience postsurgical discomfort in the recovery room. This may explain why studies using preemptive administration of ketorolac reported significant reductions in requirements of PCA with morphine, especially during the early postsurgical interval.14,5,8

Based on our experience with IV ketorolac, we recommend that a slow loading dose of 30 mg be given following anesthetic induction. Such timing may ensure that ketorolac plasma levels are adequate to attenuate release of prostaglandin and other pain activators associated with incision and intraoperative dissection.14 Maintenance doses of IV ketorolac (15 mg) should be administered as a dilute solution over a 10- to 12-minute period. This slow rate of administration may lower the risk of phlebitis, reduce peak plasma concentrations, and avoid potential toxicity. In this regard, a recent pharmacokinetic investigation16 found that peak plasma levels of ketorolac occurred sooner and were of greater magnitude with IV administration than with IM bolus administration. However, plasma levels declined rapidly in the IV group and after 10 minutes were identical with either mode of administration.16

To summarize, combination analgesic therapy consisting of PCA with opioids and the NSAID ketorolac tromethamine provided improved postsurgical pain scores and greater patient satisfaction than did PCA alone. Further work is required to assess the optimal dose and timing of IV ketorolac administration when combined with PCA with opioids for postoperative analgesia.

Addendum

The average cost of 24 hours of PCA therapy with morphine for each placebo group patient (Group 1) was $10.84; for the group receiving IV ketorolac (Torodol) 30 mg loading dose followed by IV Torodol 15 mg every six hours (Group 2), cost per patient was $23.85; and for the group receiving IV Torodol 60 mg loading dose followed by IV Torodol 30 mg every six hours (Group 3), cost per patient was $24.20.

References