A Double-Blinded Evaluation of Propacetamol Versus Ketorolac in Combination with Patient-Controlled Analgesia Morphine: Analgesic Efficacy and Tolerability After Gynecologic Surgery

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We assessed the relative morphine consumption in a combined analgesic regimen (on-demand morphine plus the nonopioids propacetamol or ketorolac) after gynecologic surgery. Two hundred women randomly received two IV doses of propacetamol 2 g or ketorolac 30 mg in a double-blinded, double-dummy trial. Patients were monitored for 12 h, and the following efficacy variables were assessed: total dose of morphine, pain intensity, and global efficacy. Safety and tolerability were evaluated by the occurrence of adverse events, especially the presence and intensity of gastrointestinal symptoms. Hemostatic variables were measured 30 and 60 min after the first infusion; arterial blood pressure, heart and respiratory rates, sedation scores, and renal and hepatic function were also assessed. Total morphine requirements were not significantly different between the propacetamol (10.6 ± 4.8 mg) and ketorolac (10.2 ± 4.4 mg) groups. The evolution of pain intensity and the global efficacy also showed similar patterns in the two groups: 70.2% of patients in the propacetamol group rated the efficacy as “good/excellent” compared with 68.2% in the ketorolac group. There were no clinically significant changes in vital signs or laboratory values and no observed differences between the two groups, although ketorolac slightly, but not significantly, prolonged the bleeding time. Epigastric pain was present in 9% and 15% of patients receiving propacetamol and ketorolac, respectively. There were two adverse events in the propacetamol group and four in the ketorolac group. Propacetamol demonstrates an efficacy similar to that of ketorolac and has an excellent tolerability after gynecologic surgery.

Implications: Propacetamol and ketorolac, combined with patient-controlled analgesia morphine, show similar analgesic efficacy after gynecologic surgery. Morphine consumption and pain scores were comparable in the two studied groups. Propacetamol is as effective as ketorolac and has an excellent tolerability after gynecologic surgery.

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diethylglycine in a 1:1 ratio; thus, the IV administration of 1 g of propacetamol yields 0.5 g of paracetamol. Under these conditions, the pharmacokinetic profile is analogous to that observed after the oral administration of paracetamol 0.5 g, except for a significantly higher maximal plasma concentration as a result of the complete bioavailability of the injectable formulation (7). After the IV injection of propacetamol, paracetamol easily crosses the blood-brain barrier, assuring a central analgesic effect (8,9). The tolerability of propacetamol is almost identical to that of paracetamol, which has a good safety profile. In orthopedic surgery, propacetamol administered in association with morphine provides good pain control with a significant morphine-sparing effect fully comparable to that described for other NSAIDs (10,11).

The aim of the present study was to directly compare the relative on-demand morphine consumption when combined with propacetamol or ketorolac after elective hysterectomy.

Methods

We used a double-blinded, double-dummy, randomized, parallel-group design in this multicenter trial involving seven Italian institutions. The study was conducted in accordance with the ethical principles of the current amended version of the Declaration of Helsinki. Approval from local ethics committees was obtained, and each patient gave signed informed consent before inclusion.

Two hundred women, aged 18–70 yr, undergoing elective hysterectomy by the abdominal route, entered the study. Patients were excluded if they had contraindications to paracetamol, NSAIDs, or morphine; if they were affected by severe hepatic, renal, gastric, or coagulative diseases; or if they were receiving additional analgesic, antipyretic, or antiinflammatory treatment during the study. General anesthesia was induced using a combination of propofol 2 mg/kg, muscle relaxants, and N2O/O2 in combination with isoflurane. The administration of pre- and intraoperative fentanyl was not permitted.

Propacetamol 2 g or ketorolac 30 mg was administered as an IV drip infusion (100 mL saline in 15 min) at tracheal extubation and 6 h postextubation. Allocation of patients to treatment groups proceeded on the basis of a balanced-block (2:2) randomization, each study center receiving four case lots.

Morphine was administered using a patient-controlled analgesia (PCA) device with the following settings: bolus dose 0.02 mg/kg, lockout 5 min, maximal dose of 0.1 mg/kg for the first 4 h. Patients were confined to bed and were monitored during a 12-h period by the medical staff participating in the trial. Surgical procedures were completed by 1:00 pm in 95% of cases.

The primary efficacy variable was the total dose of morphine requested during the 12-h observation period. In addition, several secondary efficacy variables, including the number of self-administered PCA boluses, pain intensity, and patient-assessed global efficacy, were assessed.

Pain assessments were made before the first infusion (T0) and every 1–2 h during the 12-h (T12) observation period. Pain intensity was subjectively measured using both a 100-mm visual analog scale (VAS; 0 = no pain to 100 = unbearable pain) and a 5-point verbal rating scale (VRS; 1 = best to 5 = worst). The overall efficacy of treatment was rated by patients at the end of the 12-h study period on a 5-point VRS (1 = no efficacy to 5 = excellent efficacy). Systolic and diastolic blood pressures, heart and respiratory rates, and sedation scores were recorded at each time point.

Safety and tolerability were assessed by reporting adverse events (AEs) in general, and the presence and intensity of gastrointestinal symptoms (nausea, vomiting, gastralgia) in particular, because gastrointestinal (GI) AEs are the primary AEs associated with ketorolac and other NSAIDs. In addition, hemostatic variables (bleeding time, prothrombin time, partial thromboplastin time) were measured before and 30 and 60 min after the first infusion. Clinical laboratory values, including renal and hepatic function (creatinine, aspartate aminotransferases, alanine aminotransferases), were evaluated at the beginning of the study and within 48 h after the study.

Categorical baseline variables, expressed as proportions, were analyzed by using the Mantel-Haenzel $\chi^2$ test. Quantitative baseline variables and main efficacy criteria (total amount of morphine and number of boluses) are expressed as mean ± sd and were analyzed by using Student’s t-test.

A multivariate analysis taking into account baseline pain intensity and treatment was also performed. The VAS score and the percentage of patients with severe/very severe pain (VRS) were analyzed by using analysis of variance for repeated measures. Only patients with complete data were considered. The global evaluation of treatment efficacy was compared by using the Mantel-Haenzel $\chi^2$ test.

Systolic and diastolic blood pressures, heart and respiratory rates, sedation scores, and hemostatic variables were evaluated by using analysis of variance for repeated measures. Frequency of GI symptoms (considering the highest scores in each case) was analyzed by using the Mantel-Haenzel $\chi^2$ test. Tolerability was evaluated in all patients who received at least one dose of a drug. $P$ values ≤0.05 were considered significant in treatment comparisons (two-sided α). Statistical analyses was performed by using SAS statistical analysis software (version 6.08).
Results

The demographic characteristics of the two treatment groups were similar, and there were no significant differences with respect to duration of surgery or initial pain intensity (Table 1). Of the intent-to-treat cohort of 200 patients, 24 patients were excluded from the main analysis before unblinding, 2 because of equipment failure (doses not registered by the pump) and 22 because of a protocol violation (demand morphine bolus was set at 1/10 of that established by the protocol). Data from these 22 patients (12 in the propacetamol group and 10 in the ketorolac group) were analyzed separately.

Two patients (one from each treatment group) were withdrawn from the study because of AEs that were considered unrelated to treatment (bleeding at surgery site), and two were withdrawn because of lack of efficacy (one in the propacetamol group and one in the ketorolac group). All four of these patients were withdrawn before the second dose of the study drug.

Morphine requirements were not significantly different between the two groups. The total morphine dose and number of self-administered boluses were 10.6 ± 4.8 mg and 7.9 ± 3.6, respectively, in the propacetamol group, and 10.2 ± 4.4 mg and 7.5 ± 2.9, respectively, in the ketorolac group. The cumulative morphine requirements over 12 h are represented in Figure 1. Morphine titration was not performed. However, the maximal 4-h morphine dose was required by 50% of the patients at 2 h and by 75% of the patients after 4 h in both treatment groups. Morphine consumption was significantly associated with baseline VAS scores (P = 0.001), whereas no treatment interaction was found (Fig. 2). The difference between means of PCA morphine in the two treatment groups was 0.95 mg (95% confidence interval 0.44–2.33 mg).

The evolution of pain intensity displayed similar patterns in the two treatment groups; there were significant (P < 0.001) decreases in pain after the first hour (Fig. 3), and there was good correlation between the VAS and VRS scores. A number of patients in both treatment groups had no immediate postoperative pain, which resulted in lower pain scores in these patients at T0 than at T1; approximately 20% of patients had no pain at T0 versus compared with 2% of patients with no pain at T1.

In contrast, a subset of patients with “severe/very severe” baseline pain in each treatment group had significantly greater morphine consumption (12.0 ± 5.0 mg and 10.9 ± 4.5 mg for paracetamol and ketorolac, respectively) than patients with lower baseline pain scores (9.0 ± 4.1 mg and 9.2 ± 4.0 mg) (P < 0.01). However, morphine consumption was not significantly different between the treatment groups for either the subsets with higher baseline pain or for those with lower pain scores. For the 75% of patients who required the maximal morphine dose at 4 h, both the total morphine consumption and the pain scores were higher at all time points, but these values were not significantly different between the treatment groups.

In the 22 patients whose data were analyzed separately, there was no difference in morphine consumption between the treatment groups (5.0 ± 1.2 mg for propacetamol and 5.8 ± 1.6 mg for ketorolac). However, because of the lower instrument setting for the demand bolus, the number of self-administered boluses was considerably greater in both groups (48.6 ± 19.9 and 64.8 ± 34 for propacetamol and ketorolac, respectively), and pain scores measured by VAS and VRS showed poor control of pain in these patients. No significant between-group differences were observed.

Patient-assessed global efficacy at the end of the study was similar in both treatment groups: 70.2% of patients receiving propacetamol/morphine rated the efficacy as “good/excellent,” compared with 68.2% receiving ketorolac/morphine (Fig. 4).

In general, no clinically significant changes in vital signs or laboratory values were observed during the study, and the recorded values were not significantly different between the two study groups. Although no

Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Propacetamol (n = 87)</th>
<th>Ktorolac (n = 89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48.4 ± 6.7 (24–69)</td>
<td>49.8 ± 9.0 (24–70)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.2 ± 5.6 (140–175)</td>
<td>162.7 ± 5.3 (149–174)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>67.0 ± 11.6 (50–103)</td>
<td>67.0 ± 10.6 (48–104)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>97.7 ± 35.6 (30–230)</td>
<td>96.1 ± 34.0 (40–195)</td>
</tr>
<tr>
<td>Pain intensity (T0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visual analog scale</td>
<td>45.0 ± 35.9 (0–100)</td>
<td>47.7 ± 37.3 (0–100)</td>
</tr>
<tr>
<td>Verbal rating scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>17 (20.0)</td>
<td>17 (19.3)</td>
</tr>
<tr>
<td>Mild</td>
<td>11 (12.9)</td>
<td>12 (13.6)</td>
</tr>
<tr>
<td>Moderate</td>
<td>25 (29.4)</td>
<td>21 (23.9)</td>
</tr>
<tr>
<td>Severe</td>
<td>17 (20.0)</td>
<td>18 (20.5)</td>
</tr>
<tr>
<td>Very severe</td>
<td>15 (17.6)</td>
<td>20 (22.7)</td>
</tr>
</tbody>
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Values are expressed as mean ± SD (range) or as n(%).
significant differences were observed in coagulation variables (bleeding time, prothrombin time, and partial thromboplastin time) between the propacetamol and ketorolac groups, there was a tendency toward prolongation of bleeding time in the ketorolac group (Fig. 5).

There were AEs directly or probably related to treatment in four patients: one in the propacetamol group (pain at site of injection) and three in the ketorolac group (atrial fibrillation, hypersedation, and hemo-peritoneum). The incidence of GI symptoms was comparable in the two groups (Table 2).

Discussion

In this study, we demonstrate that the relative morphine requirement of the propacetamol group was similar to that of the ketorolac group. This suggests that propacetamol is effective in the management of postoperative pain when combined with an opioid analgesic.

A morphine-sparing effect, or an additive effect to fixed opioid doses, has been previously reported for both propacetamol and ketorolac in several types of surgery. In gynecologic surgery, the addition of propacetamol with nalbuphine provided better pain relief than doubling the dose of nalbuphine alone (12). In other types of surgery, the use of ketorolac resulted in a morphine-sparing effect that ranged from 16% to 33% during periods up to 24 h (6,13–15). However, the morphine requirements in patients treated with ketorolac/morphine in those studies were almost twice as high as that observed in the present study. In
contrast, morphine requirements after colecystectomy were similar to those found in this study, with ketorolac providing a morphine-sparing effect of 30% (16).

In Italy, both physicians and patients are generally very cautious about the use of morphine. This factor may have affected the total amount of morphine required in the present study, in a manner similar to what has been previously observed in the Italian clinical setting (16). The establishment of a maximal 4-h dose partly limited the use of morphine during the early postoperative period, as indicated by the percentage of patients that requested the maximal allowable dose. The control of pain during the first 4 h in these patients was less than satisfactory, and it may therefore be argued that a less restrictive pump setting would have allowed greater morphine consumption, thus ensuring a greater analgesic effect. Nevertheless, morphine consumption and pain scores were fully comparable between the two treatment groups at all times, even in the subset of patients with higher pain scores, who were more likely to require a greater morphine dose.

The central analgesic effect exerted by paracetamol and, consequently, propacetamol (9), seems to satisfactorily complement the centrally mediated analgesic action of opioids. Such additive or superadditive (synergistic) effects, although likely occurring by different mechanisms, are at least comparable to those attributable to ketorolac (17), as suggested by the same morphine requirements observed in the two treatment groups in the current study. The potential importance of NSAIDs as adjuncts to opioids after major surgery (18) should therefore be extended to propacetamol, which has already proven to be useful as a monotherapy in the management of postoperative pain (19,20).

In this study, we also confirmed a favorable risk-benefit profile for propacetamol. Although the number of adverse events was low in both treatment groups, there was a trend toward a reduction in GI symptoms with paracetamol, as suggested by a reduced incidence of gastralgia (9% of patients compared with 15% in the ketorolac group) that did not reach statistical significance. Ketorolac significantly increases the risk of upper GI complications, such as bleeding and perforation, and its GI toxicity is estimated to be fivefold greater than that of other NSAIDs, regardless of its route of administration (21).

The risk of NSAID-induced GI complications is not limited to chronic use. It has been estimated that the greatest risk occurs during the first 3 mo of NSAID use (22), and consideration has also been given to cases of acute pain relief, particularly in critical clinical conditions, such as the postoperative period (23).

Although the incidence of nausea may depend on several factors, including previous anesthetic treatment,
opioid administration, and pain itself, its occurrence in approximately 50% of patients in this study is within the expected range for the anesthetic regimen used.

Bleeding time tended to be prolonged by ketorolac, although not significantly, compared with propacetamol. This finding is in agreement with previous reports that demonstrate impairment of hemostasis in volunteers (24) and a longer bleeding time without significant prolongation of prothrombin time or partial thromboplastin time in patients treated with ketorolac (16). A significant increase in bleeding time after ketorolac administration also occurs in children (25). However, intraoperative blood losses were similar with and without ketorolac; clinically important bleeding was not noted in these studies (16,25). Nevertheless, a possible relationship between ketorolac and the formation of postoperative hematomas has been hypothesized (26), and other screening tests should be used to more reliably predict possible bleeding risks secondary to NSAID-induced platelet dysfunction (27).

Propacetamol is an effective analgesic that may represent a useful alternative to NSAIDs and a complementary drug to opioids in the management of moderate to severe postoperative pain. Its well known safety profile was confirmed by the present study. Propacetamol may be of particular value, even when considering the recent availability of preferential cyclooxygenase-2 inhibitors (28) or the future introduction of specific cyclooxygenase-2 inhibitors, for which clinical data are only now becoming available (29).

References