Comparison of the efficacy of parecoxib versus ketorolac combined with morphine on patient-controlled analgesia for post-cesarean delivery pain management


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1. Introduction

Regarding pain at the site of injury or trauma, cyclooxygenase type-2 (COX-2) plays an important role in both peripheral and central mechanisms of pain. An ideal agent for the treatment of acute inflammatory pain is one that can inhibit COX-2 both peripherally and centrally.

A newer COX-2 inhibitor, parecoxib sodium (parecoxib), has demonstrated powerful analgesic efficacy in well-documented clinical trials. It is the only injectable COX-2 inhibitor with fast onset and long-lasting analgesic effect. Furthermore, it enhances pain relief in multimodal therapy with a significant reduction in opioid consumption, along with overall safety and tolerability profile. Moreover, its analgesic efficacy has been proven in a wide range of surgical procedures, such as total knee and hip...
arthroplasty, gynecologic laparotomy surgery, total abdominal hysterectomy and oral surgery.\(^4\)

However, the post-cesarean delivery pain is caused by surgical incision and uterus contraction with multiple mechanisms, which include both central and peripheral sensitization, and also descending inhibition pathway. Therefore, COX-2 inhibitors and opioids played an important role in the control of such pain. Crews stated that the rational use of combined of analgesic medications can improve pain relief, reduce postoperative adverse effects, and improve functional postoperative recovery.\(^13\) Furthermore, there are few reports mentioning the combination usage of parecoxib with morphine in a patient-controlled analgesia (PCA) manner for routine postoperative pain control for obstetric surgery. In addition, no other study of parecoxib for management of post-cesarean delivery pain is available. For these reasons we ventured to design the study of the combination of a new injectable COX-2 selective inhibitor, parecoxib, and the potent opioid, morphine, for post-cesarean delivery analgesia.

The aim of this study was to compare the clinical efficacy and safety between parecoxib and a common nonsteroidal anti-inflammatory drug (NSAID), ketorolac with nonselective COX inhibition in combination with morphine PCA respectively for post-cesarean delivery pain management.

2. Methods

The study was a randomized, open-label clinical trial of parecoxib and ketorolac, combined with morphine for post-cesarean section pain control. The protocol was approved by the Research and Ethics Committee of our hospital, and patients’ informed consents were obtained after detailed explanation.

The 66 parturients enrolled in this study were between 20 and 40 years of age, of ASA physical status I or II, weighing 60—90 kg, and standing 155—170 cm. The parturients were free of specific cardiovascular, neurological, hematological or gastrointestinal diseases, and were scheduled for elective cesarean section at term, under spinal anesthesia.

No premedication and opioids were given peri-operatively. The parturients were hydrated before anesthesia and monitored on continuous electrocardiogram, pulse oximetry, and noninvasive arterial blood pressure, peri-operatively and post-operatively.

When the parturients were transferred to Post-Anesthesia Recovery Room, abdominal pain usually set in. They were divided into two groups: Group P patients received an intravenous bolus of 40 mg parecoxib (Dynastat\(^6\) - Pfizer Limited, USA) as a loading dose post-operatively; then two subsequent bolus doses of 20 mg parecoxib were separately given at 24-h and 48-h intervals, after the initial dose. Morphine was given in patient-controlled analgesia (PCA) manner during the 3-day study course; and Group K patients received a loading intravenous bolus of 30 mg ketorolac, then 90 mg ketorolac combined with morphine in a PCA fashion throughout the study course. All parturients were informed that they could receive additional pain medication if pain control was unsatisfactory, by pushing the control button of the PCA to deliver a reinforced dose.

Furthermore, PCA machines were programmed to deliver the drugs pursuant to the respective formula, i.e. morphine in continuing dose of 0.2 mg/h, and the bolus dose of 2 mg (each bag of basic PCA solution contained morphine 50 mg in normal saline 250 mL). As to patients of Group K, katabolic 90 mg was only added into each basic analgesic solution.

Breast-feeding was prohibited during the first 3 days post-delivery, and observations and assessments were performed throughout the 3-day study course post-operatively.

2.1. Assessment and evaluation

Efficacy was evaluated by using a verbal ranking scale of five parameters, including 0–10 pain intensity scale (0 = no pain, 10 = excruciating pain) for pain intensity; 1—6 Ramsay sedation score (1 = anxious, agitated, restless, 2 = cooperative, tranquil, oriented, 3 = drowsy, response to verbal command, 4 = asleep, brisk response to light glabellas tap and loud auditory stimulus, 5 = asleep, sluggish response to light glabellas tap and loud

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![Fig. 1. Algorithm for the study design.](image-url)
had lower pain scores than Group K at 24 h (3.1, range 0–5 vs.
4.3, range 0–8, p = 0.005), and 72 h (1.1, range 0–3 vs. 1.9, range
0–4, p = 0.005); and a lower total consumption of morphine, in
72-hour course in of Group P, as compared with Group K
(43.5 ± 19.2 vs. 55.5 ± 21.5, p = 0.02). (Table 2). However, there
were no statistical differences in the adverse effects between two
groups. (Table 3)

4. Discussion

Our results proved that parecoxib was as effective as ketorolac for
post-cesarean delivery analgesia; again, it could reduce the morphine
requirement by 22% in patients with lower pain scores, when
compared with ketorolac. However, it did not significantly reduce the
morphine requirement in the first 24 h, probably by reason of
stronger analgesic effect offered by the loading dose of parecoxib in
the first day, and more significant reduction of the morphine
requirement on the following study days. It was perceivable that the
analgesic effect offered by the loading dose of parecoxib was more
potent than the low dose of ketorolac infusion given in the second and
third days. We are of the opinion if we increase the dose of ketorolac in
the second and third day, the total morphine requirement and the
analgesic efficacy would equate in both groups.

Previous studies revealed that immediate post-operative
treatment with parecoxib for orthopedic, gynecologic and oral
surgeries was proven to have an opioid sparing effect.4–11 It could
also exhibit its analgesic efficacy even administered pre-operatively.12
Although its onset time is considered rapid (10–23 min) with
efficacious analgesia, it takes a significantly longer (two-threelfold)
time to be an analgesia rescuer as compared with ketorolac for post-operative pain, following gynecologic
laparotomy surgery.7 It was well tolerated over several days
and provided improved pain control after gynecologic surgery in a multidose study.10
Moreover, another multiple-dose study by Malan et al. in total hip arthroplasty revealed that
administration of parecoxib with PCA Morphine had improved significantly the postoperative analgesic management, in terms of
reduction in opioid requirement, lowering pain score, reduced time for needing PCA morphine, and higher global
evaluation ratings when compared with placebo; however, parecoxib 20 mg and 40 mg, also reduced the total amount of
morphine required over 36 h by 22.1% (56.5 mg morphine), and
40.5% (43.1 mg morphine), respectively.5

Tang et al. in the report on their study concluded that intravenous parecoxib (20 or 40 mg) was effective in decreasing the PCA
opioid requirement after lower abdominal surgical procedures; but
it failed to reduce opioid-related side effects in the early post-
operative period.14 Furthermore, we could not prove that parecoxib

Table 1
Demographic characteristics, operation/anesthesia times and hospital stay of the
two study groups.

<table>
<thead>
<tr>
<th></th>
<th>Group P</th>
<th>Group K</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>33</td>
<td>33</td>
<td>-</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>30.8 ± 5.6</td>
<td>30.7 ± 4.4</td>
<td>0.903</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.4 ± 5.0</td>
<td>160.9 ± 4.5</td>
<td>0.674</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.7 ± 8.8</td>
<td>71.8 ± 8.4</td>
<td>0.713</td>
</tr>
<tr>
<td>Gravida (n)</td>
<td>1.9 ± 0.9</td>
<td>1.8 ± 0.7</td>
<td>0.758</td>
</tr>
<tr>
<td>Infant birth weight (g)</td>
<td>3095 ± 402</td>
<td>3049 ± 384</td>
<td>0.625</td>
</tr>
</tbody>
</table>

Values are mean ± SD and analyzed with Student’s t-test.
*Study group for parecoxib.
**Study group for ketorolac.

aural stimulus, 6 = coma); 0–3 mood profile scale (0 = no
interference, 1 = mild, 2 = moderate, 3 = severe interference); 0–3
quality of sleep scale (0 = normal sleep, 1 = occasionally awakened
by pain, 2 = always awakened by pain, 3 = insomnia); and 0–4
scale of satisfaction (0 = very unsatisfied, 1 = unsatisfied, 2 = fair,
3 = satisfied, 4 = very satisfied). Adverse effects including gastro-
intestinal upset, nausea/vomiting, dizziness, somnolence, head-
ache, itching, etc. were recorded. The duration of hospital stay and
total dosage of morphine used throughout the study were also
recorded (Fig. 1).

2.2. Statistical analyses

Data were presented as mean ± standard deviation, or as
frequencies, and were analyzed by two-tailed unpaired Student’s t-
test and Chi-squared (χ²) test/Fisher’s exact test; except pain scale
was presented as median with range, and analyzed by a non-
parametric test. A p value less than 0.05 was considered statistically
significant.

3. Results

All parturients completed the study. Both groups had compar-
able demographic data, including age, height, weight, gravida,
infant birth weight and Appgar score. The duration of operation
(operation time), anesthesia (anesthesia time) and hospital stay
were also compared. There were no significant differences con-
cerning the above data between the two groups. (Table 1) There
were no significant differences in the sedation scale, mood state,
quality of sleep and satisfaction between groups, except Group P

Table 2
Efficacy, satisfaction and total morphine dosages of post-operative pain control.

<table>
<thead>
<tr>
<th>Efficacy and satisfaction</th>
<th>24 hr*</th>
<th>72 hr*</th>
<th>p</th>
<th>24 hr*</th>
<th>72 hr*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain scale (0–10)</td>
<td>3.1 (0–5)</td>
<td>4.3 (0–8)</td>
<td>0.005**</td>
<td>1.1 (0–3)</td>
<td>1.9 (0–4)</td>
<td>0.005**</td>
</tr>
<tr>
<td>Ramsay sedation scale (1–6)</td>
<td>1.9 ± 0.6</td>
<td>1.8 ± 0.4</td>
<td>0.606</td>
<td>1.9 ± 0.4</td>
<td>1.9 ± 0.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Mood state (0–3)</td>
<td>0.7 ± 0.8</td>
<td>0.4 ± 0.6</td>
<td>0.151</td>
<td>0.4 ± 0.7</td>
<td>0.2 ± 0.4</td>
<td>0.108</td>
</tr>
<tr>
<td>Quality of sleep (0–3)</td>
<td>1.0 ± 1.0</td>
<td>0.6 ± 0.8</td>
<td>0.102</td>
<td>0.3 ± 0.5</td>
<td>0.2 ± 0.4</td>
<td>0.613</td>
</tr>
<tr>
<td>Satisfaction (0–4)</td>
<td>3.6 ± 0.6</td>
<td>3.3 ± 0.7</td>
<td>0.160</td>
<td>3.9 ± 0.3</td>
<td>3.8 ± 0.4</td>
<td>0.129</td>
</tr>
<tr>
<td>Total dose of morphine (mg)</td>
<td>260.0 ± 13.0</td>
<td>294.4 ± 14.5</td>
<td>0.333</td>
<td>43.5 ± 19.2</td>
<td>55.5 ± 21.5</td>
<td>0.020**</td>
</tr>
</tbody>
</table>

**p < 0.05 is statistically significant.
Bold letters show the significant data.
*Study group for parecoxib.
**Study group for ketorolac.
The data of first or third (final) day of study; Values are mean ± SD and analyzed with Student’s t-test, except pain scale present as median with range and analyzed with non-parametric test.
Parecoxib, Cesarean delivery, Postoperative pain relief, Patient-controlled analgesia, Opioid sparing

Table 3
Adverse effects during post-operative pain control.

<table>
<thead>
<tr>
<th>Adverse effects</th>
<th>24 hr* Group Pa</th>
<th>72 hr* Group Pa</th>
<th>Group Kb</th>
<th>Group Kb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gl disturbance</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Itching</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Palpitation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*The data of first or third (final) day of study;
Values are number of patients; Chi-squared (χ^2^) test/Fisher’s exact test;
No significant differences were noted among the two study groups.

References