Efficacy and safety of parecoxib for the treatment of pain following total knee arthroplasty in Korean patients

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INTRODUCTION

- Korea had a growth rate of 407% in total knee arthroplasty (TKA) procedures from 2001 to 2010.¹
- More than half of patients undergoing TKA experience severe postoperative pain.²
- Several factors, including ethnicity, can influence patient perception of pain.^{3,4}
- The current clinical recommendation for postoperative pain is a multimodal analgesic approach intended to efficiently manage pain and to reduce opioid use and opioid-related adverse events (AEs).^{2,5}
- Parecoxib is an injectable cyclooxygenase-2 inhibitor with proven efficacy for postoperative pain, including gynaecological⁶ and oral surgery,⁷ and total hip or knee replacement.⁸⁻¹¹
- The effect of ethnicity on the analgesic efficacy of parecoxib has not been extensively studied.
- The current study assessed the analgesic efficacy and safety of intravenous (IV) parecoxib sodium 40 mg vs. placebo for post-TKA pain in Korean patients.

METHODS

- This parallel-group, double-blind, randomised study was conducted at 4 centres in Korea and in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, the Declaration of Helsinki, and applicable local regulatory requirements and laws.
- Each patient provided written consent to participate in the study prior to enrolment.
- Men and women aged ≥18 years who had undergone unilateral TKA performed under general, regional, or spinal anaesthesia were enrolled in the study.
- Patients were given postoperative analgesia provided by morphine or meperidine, administered by patient-controlled analgesia (PCA).
- Those patients with moderate or severe pain within 6 h after the end of PCA were randomised to receive a single IV dose of parecoxib sodium 40 mg or placebo the day after surgery.
- The primary efficacy variables were:
 - Time-specific pain intensity difference (PID) on a 4-point self-rated scale (0=none to 3=severe).
 - PID was derived by subtracting the pain intensity scores for each time point post-dose from the baseline score.
 - Time-specific pain relief (PR) on a 5-point self-rated scale (0=none to 4=complete).
 - Time-specific sum of PID and PR (PRID).
 - Time to rescue medication, which was provided at the investigator's discretion.
- Efficacy measures were assessed at baseline (time 0) and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 h after dosing, and just prior to taking rescue medication if this was used.
- PID, PR, and PRID were analysed using analysis of covariance (ANCOVA) with treatment and centre as factors and baseline pain intensity as a covariate.
- The median time to rescue medication, with corresponding 95% confidence intervals, was determined using the Kaplan–Meier product limit estimator, with distributions analysed using a log-rank test.
- Safety was assessed by the incidence and nature of AEs and analysed using Fisher's exact test.

RESULTS

- 116 patients were randomised; 58 received parecoxib and 58 received placebo.
- There were no significant differences between treatment groups in patient demographic and baseline characteristics, including duration of surgery, duration of anaesthesia, and baseline pain severity (data not shown).

Efficacy

- Mean PID was significantly greater for parecoxib vs. placebo starting at 1-h postdose and continuing throughout the 24-h treatment period (all $p<0.05$) (**Figure 1**).

Figure 1. Change in mean pain intensity difference, by treatment group

- Mean PR was significantly greater for parecoxib vs. placebo, beginning at 1.5-h postdose and continuing throughout the 24-h treatment period (all $p\leq0.001$) (**Figure 2**).
- Mean PRID was significantly greater for parecoxib vs. placebo starting at 1-h postdose and continuing throughout the 24-h treatment period (all $p<0.05$) (**Figure 3**).
- Over the 24-h treatment period, 28 of 54 (52%) patients in the parecoxib group required rescue medication vs. 51 of 57 (89%) patients in the placebo group ($p<0.001$).
- The median time to rescue medication was significantly longer for parecoxib (21.5 h) vs. placebo (4.1 h; $p<0.001$) (**Figure 4**).

Figure 2. Change in mean pain relief, by treatment group

Figure 3. Change in mean time-specific sum of pain intensity difference and pain relief

Figure 4. Median time to rescue medication

Safety

- 22 (37.9%) patients in the placebo treatment group and 12 (20.7%) patients in the parecoxib treatment group reported treatment-emergent AEs (**Table 1**).
- No serious AEs or deaths were reported.
- AEs were generally mild to moderate in severity.
 - 1 incidence of pruritus in the parecoxib group was judged as severe by the investigator, but resolved within 2 h and was not considered to be treatment-related.
- Of the treatment-emergent AEs, 2 incidences of pruritus in the parecoxib group were deemed treatment-related by the investigator.

Table 1. Treatment-emergent adverse events occurring in ≥3% of patients in either treatment group

Adverse Event, n (%)	Placebo n=58	Parecoxib n=58
All	22 (37.9)	12 (20.7)*
Pruritus	0 (0.0)	4 (6.9)
Headache	4 (6.9)	2 (3.4)
Constipation	0 (0.0)	2 (3.4)
Dyspepsia	2 (3.4)	2 (3.4)
Hypertension	4 (6.9)	1 (1.7)
Nausea	5 (8.6)	1 (1.7)
Vomiting	2 (3.4)	1 (1.7)
Fever	7 (12.1)	0 (0.0)*
Abdominal pain	2 (3.4)	0 (0.0)

* $p<0.05$.

CONCLUSIONS

- In Korean patients with moderate or severe pain after TKA, a single IV dose of parecoxib sodium 40 mg provided significantly greater pain relief for a significantly longer time vs. placebo.
- Few treatment-related AEs were reported in either parecoxib- or placebo-treated patients.
- These results are comparable to those from other studies demonstrating the analgesic efficacy and safety of parecoxib for post-TKA pain in non-Korean patient populations.⁹⁻¹¹
- Korean ethnicity appears to have no impact on the efficacy or safety profile of parecoxib when used for treating post-TKA pain.

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DISCLOSURES

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