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Efficacy of intravenous perioperative parecoxib administration in the surgical fixation of unstable ankle fracture: a prospective, double-blinded, randomized, placebo-controlled trial

C. ANGTHONG[1], S. MANUWONG[2], V. SINGH[3], P. RAJBHANDARI[4], A. VELJKOVIC[5]

[1]Division of Digital and Innovative Medicine, Faculty of Medicine, King Mongkut's Institute of Technology Ladkrabang, Bangkok, Thailand
[2]Department of Anesthesiology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand
[3]Department of Trauma and Orthopaedics, Homerton University Hospitals NHS Trust, London, UK
[4]Department of Orthopedics Manmohan Memorial Medical College and Teaching Hospital, Kathmandu, Nepal
[5]Department of Orthopedics, University of British Columbia, Vancouver, Canada

Abstract. – OBJECTIVE: Little is known about the efficacy of perioperative intravenous (IV) non-opioid medication administration in patients undergoing orthopedic surgery. The objective of this study was to determine the efficacy of perioperative parecoxib in patients with unstable ankle fractures who were scheduled to undergo surgery.

PATIENTS AND METHODS: In this double-blinded, prospective, randomized controlled trial, 40 patients who underwent open reduction and internal fixation for unstable ankle fractures were randomly allocated to the parecoxib group (parecoxib 40 mg IV 30 min before surgery and then 40 mg IV every 12 h for the initial 48 h postoperatively [n=20]) or the placebo group (saline [n=20]). The efficacy of pain control was assessed according to the total morphine used. Pain intensity (at rest/ambulation) and pain relief (at rest/ambulation) were assessed using the verbal numerical rating score (VNRS) and verbal numerical rating percentage (VNRP), respectively. Subjective rating of medication was performed by each patient. All outcomes were recorded by trained personnel who were blinded to the patient group allocation.

RESULTS: The mean patient age was 49.3±18.0 years. There were no significant differences between the two groups in terms of pain intensity, pain relief, patients' subjective ratings of the medication at both the preoperative and postoperative periods, total quantity of morphine used, side effects, and acute complications of surgery ($p>0.05$). The mean length of hospital stay tended to be shorter in the parecoxib group than in the placebo group (6 *vs.* 9.9 days; $p=0.183$).

CONCLUSIONS: Although the perioperative administration of parecoxib did not provide significantly better postoperative pain control or reduce the opioid requirement relative to placebo, its use led to a shorter hospital stay.

Key Words:
Analgesia, Ankle fractures, Parecoxib, Perioperative, Randomized controlled trial.

Introduction

Perioperative pain control is an essential component of good surgical outcomes. Undeniably, the perioperative period of orthopedic surgical interventions is extremely painful. Open reduction and internal fixation (ORIF) of unstable ankle fractures is no exception. Inadequate analgesia during ankle ORIF has a huge impact on perioperative recovery[1].

There are multiple methods to control postoperative pain, including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), compression therapy, evaporative coolants, ice packs, and re-

Corresponding Author: Chayanin Angthong, MD, Ph.D; e-mail: Chayanin.an@kmitl.ac.th

gional blocks. The most commonly used analgesic is opioids. The drawbacks of this approach are the potential adverse effects of opioid medication, such as opioid overdose and abuse. NSAIDs are one of the options used to reduce postoperative pain and to avoid the adverse effects of opioids. These drugs have potent analgesic effects and have no sedative or opioid side effects. The balance between adequate narcotic prescribing patterns and appropriate postoperative pain management necessitates randomized prospective studies to identify effective non-narcotic perioperative drug protocols[2-6].

Parecoxib sodium is a highly selective cyclooxygenase-2 (COX-2) inhibitor. It can reduce the synthesis of peripheral prostaglandins to induce analgesic effects, relieve inflammation, and prevent central sensitization via the inhibition of peripheral and central COX-2 expression. Parecoxib is indicated for the short-term treatment of postoperative pain in adults[7].

However, little is known about the efficacy of perioperative intravenous (IV) non-opioid medication. A guideline is needed for its use in perioperative pain management in patients undergoing foot and ankle surgery. The aim of the present study was to determine the efficacy of perioperative IV parecoxib for pain management in patients undergoing unstable ankle fracture fixation.

Patients and Methods

Patients and Study Design

This was a prospective, double-blinded, randomized, placebo-controlled trial. A total of 40 patients undergoing ORIF for unstable ankle fractures were randomly allocated to the parecoxib group (parecoxib 40 mg IV 30 min before surgery and then an additional 40 mg every 12 h for the initial 48 h postoperatively [n=20]) or the placebo group (saline [n=20]: saline 10 ml IV was administered as same time point as the parecoxib group) *via* block randomization using a web-based program. Four patients (two patients in each group) were excluded based on the exclusion criteria: contraindication of parecoxib use (one patient), thrombocytopenia on preoperative blood work (one patient), head injury with contraindication for spinal anesthesia (one patient), and re-fracture (one patient). Thus, 36 patients were included in the analysis. However, one patient was included in the placebo group for the initial 24 h postoperatively only. He deviated from the treatment regimen because postoperative intravenous parecoxib was administered for >24 h postoperatively by another physician who was not involved in the research project. His data were analyzed only during the periods before and ≤24 h after the surgery. All other aspects of perioperative care were treated identically and supervised by a fellowship-trained foot and ankle orthopedic surgeon and a senior anesthesiologist.

Data Collection and Assessment

The basic patient characteristics, including age, sex, height, weight, type of implant, operative time, intraoperative blood loss, and amount of postoperative blood loss, were recorded. Efficacy was assessed according to the total morphine use, pain intensity (at rest/ambulation), pain relief (at rest/ambulation), and the patient's subjective rating of medication (PSRM). The PSRM was scored as excellent (3), good (2), fair (1), or poor (0). Patients rated their postoperative pain intensity using the verbal numerical rating score (VNRS) from 0 (no pain) to 10 (worst imaginable pain) and the verbal numerical rating percentage (VNRP) from 0 (no relief) to 100 (complete relief), which were recorded by trained personnel. Time 0 was recorded when the patients were moved to the post-anesthesia care unit (PACU) after surgery. The VNRS, VNRP, and PSRM were recorded at 0, 4, 12, 24, and 48 h after surgery. The amount of intravenous morphine administered was also recorded. Adverse effects of the analgesic procedures, such as dyspepsia, nausea/vomiting, constipation, dizziness, respiratory depression (respiratory rate of <8 breaths per min), and pruritus. Overall adverse effects were recorded in both groups. All outcomes were collected by trained personnel who were blinded to the patient group allocation. All involved surgeons, anesthesiologists, and patients were also blinded to the group allocations. The efficacy, PSRM, clinical score, and overall adverse effects were compared between the two groups.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS software ver. 22.0 (SPSS Inc., Chicago, IL, USA). ANOVA was used to analyze the statistical significance for the quantitative variables between the two groups. Categorical variables were analyzed using the Chi-square or Fisher's exact tests. A p-value <0.05 was considered statistically significant.

Results

The mean age was 49.3±18.0 years. The demographic characteristics of each group are shown in Table I. There were no significant differences between the two groups in terms of age, height, and weight (p>0.05), but there were significantly more men in the placebo group than in the parecoxib group (p=0.018) (Table II).

In the parecoxib group, the mean VNRS was 3.56±1.617 at admission. The mean rest and movement VNRSs were 1.72 and 2.44, 4.11 and 5.28, 2.83 and 4.50, 2.17 and 3.17, and 1.78 and 2.44 at 4, 12, 24, and 48 h postoperatively, respectively. The mean rest and movement VNRPs were 85.56 and 79.44, 64.44 and 57.78, 72.22 and 59.44, 82.78 and 76.67, and 87.78 and 80.56 at 4, 12, 24, and 48 h postoperatively, respectively. The mean PSRM was 2.22±0.43 at admission, and 2.39±0.92, 1.94±0.87, 2.50±0.7, 2.83± 0.383, and 2.83±0.383 at 4, 12, 24, and 48 h postoperatively, respectively.

In the saline group, the mean VNRS was 4±1.2 at admission. The rest and movement VNRSs were 1.94 and 2.44, 4.56 and 5.61, 4.11 and 5.5, 2.44 and 3.78, and 1.47 and 2.78 at 4, 12, 24, and 48 h postoperatively, respectively. The mean rest and movement VNRPs were 89.44 and 82.78, 66.67 and 58.33, 70.0 and 60.0, 79.44 and 76.11, and 90.59 and 84.71 at 4, 12, 24, and 48 h postoperatively, respectively. The mean PSRM was 2.2±0.826 at admission, and 2.44±0.856, 2.06±0.87, 2.28±0.895, 2.61±0.608, and 2.76±0.437 at 4, 12, 24, and 48 h postoperatively, respectively.

The mean morphine consumption was 3±4.3 and 3.24±5.06 mg in the parecoxib and saline groups (p=0.883). The mean length of hospital stay tended to be shorter in the parecoxib group (6±4.34 days) than in the placebo group (9.9±11.28 days) (p=0.183). Hence, the mean morphine consumption and length of hospital stay did not significantly differ between the parecoxib and saline groups.

With regard to the main outcomes, there were no significant differences between the two groups in terms of pain intensity, pain relief, PSRM in the pre- and post-operative periods, total quantity of morphine used, side effects, and acute complications of surgery (p>0.05) (Tables II and III).

Discussion

This study highlighted the determination of the efficacy of perioperative IV parecoxib for pain management in patients undergoing unstable ankle fracture fixation. Parecoxib is a well-known member of NSAIDs. NSAIDs have effective opioid-sparing analgesic effects while reducing morphine consumption by up to 27% in the first 24 h post-operatively[8-10].

Parecoxib has been studied in various perioperative pain models, including cholecystectomy[11]; ear, nose, and throat surgery[12]; thoracic surgery[8]; gastrointestinal surgery[11,13]; gynecologic surgery[14]; and orthopedic surgery[9,15,16]. Huang et al[17] conducted a meta-analysis of studies involving orthopedic patients and concluded that intrave-

Table I. Comparison of age, height, and weight between two groups.

Randomized Group		Age*	Height	Weight
Parecoxib	Mean	48.3889	162.389	64.833
	N	18	18	18
	Std. Deviation	16.73720	7.2853	12.9490
	Minimum	18.00	150.0	38.0
	Maximum	76.00	175.0	95.0
Saline	Mean	50.2222	167.722	70.111
	N	18	18	18
	Std. Deviation	19.54649	8.7636	16.2005
	Minimum	18.00	152.0	53.0
	Maximum	83.00	190.0	115.0
Total	Mean	49.3056	165.056	67.472
	N	36	36	36
	Std. Deviation	17.95840	8.3903	14.6998
	Minimum	16.00	150.0	38.0
	Maximum	83.00	190.0	115.0

Abbreviation: Std. Standard; *Age at patient's permission for the study.

Table II. Statistical Significance comparison between various groups (using p-value).

Variables		*p*-values; Significancet
Age * Random_no.		0.764
Height * Random_no.		0.055
Weight * Random_no.		0.288
VAS_Admit * Random_no.		0.361
PSRM_Admit * Random_no.		0.802
VNRS_RR* Random_no	Rest	0.810
	Movement	1.00
VNRS_4_* Random_no.	Rest	0.677
	Movement	0.752
VNRS_12_* Random_no.	Rest	0.168
	Movement	0.264
VNRS_24_* Random_no.	Rest	0.697
	Movement	0.457
VNRS_48_* Random_no.	Rest	0.593
	Movement	0.596
VNRP_RR_* Random_no.	Rest	0.660
	Movement	0.718
VNRP_4_ * Random_no.	Rest	0.804
	Movement	0.946
VNRP_12_ * Random_no.	Rest	0.796
	Movement	0.946
VNRP_24_ * Random_no.	Rest	0.633
	Movement	0.918
VNRP_48_ * Random_no.	Rest	0.572
	Movement	0.341
PSRM_RR * Random_no.		0.852
PSRM_4 * Random_no.		0.705
PSRM_12 * Random_no.		0.414
PSRM_24 * Random_no.		0.198
PSRM_48 * Random_no.		0.624

Random_no.: compared between randomized groups *Abbreviation:* PSRM, Patients' subjective rating of the medication; VAS, Visual analogue scale; VNRS, verbal numerical rating score; VNRP, verbal numerical rating percentage; Admit, on time of admission; RR, at post-anesthesia care unit (PACU) after surgery.

Table III. Comparison of side effects between two groups.

Side effects					
			Side_effects		
			No.	Yes-Nausea-Vomit	Total*
Randomized Group	Parecoxib	Count	16	2	18
		% within Random_no	88.9%	11.1%	100.0%
		% within Side_effect	50.0%	66.7%	51.4%
	Saline	Count	16	1	17
		% within Random_no	94.1%	5.9%	100.0%
		% within Side_effect	50.0%	33.3%	48.6%
Total		Count	32	3	35
		% within Random_no	91.4%	8.6%	100.0%
		% within Side_effect	100.0%	100.0%	100.0%

p-value = 1.00, % (Percentage), no. (number). *Notes:* *Number of patients with available data; Data of patient number 3 was included as before surgery and until 24 hours after surgery because saline was not given at 24 hours after surgery.

nous parecoxib significantly reduced the interleukin-6 level and improved early postoperative cognitive dysfunction in elderly patients. Further, Lloyd et al[18] reviewed seven randomized,

double-blind, placebo-controlled clinical trials to evaluate the analgesic efficacy of a single dose of IV or intramuscular parecoxib in treating acute postoperative pain. They found that fewer participants in the parecoxib groups than in the placebo groups used rescue medications over 24 hours. Further, the frequency of adverse events did not differ between the parecoxib and placebo groups.

The current study indicated that there were no significant differences between the parecoxib and placebo groups in terms of pain intensity, pain relief, pre- and post-operative PSRM, total quantity of morphine used, side effects, and acute complications of surgery. The length of hospital stay tended to be shorter in the parecoxib group than in the placebo group. This finding was consistent with that of a previous study by McDonald et al[3], who observed that patient-reported pain scores did not significantly improve with the use of ketorolac, an NSAID. Although NSAIDs can be a powerful adjunctive agent in managing postoperative pain[3], pain control may be indirectly diminished by a decrease in inflammation[17]. In the present study, the indirect benefit of the perioperative administration of parecoxib was a trend toward a shorter length of hospital stay relative to the placebo group. This may be due to the potential effect of diminished inflammation and quicker tissue recovery in the parecoxib group than in the placebo group. However, the direct result of pain alleviation could not be demonstrated in the present and previous studies.

The limitations of this study include two main issues. First, the size of this study was not adequate to demonstrate significant differences in the pain intensity level and its related parameters including the length of hospital stay between the two groups. Second, the proportion of men and women differed between the groups. This factor may have influenced the level of pain tolerance and overall results in relation to pain control, as men may have a higher pain threshold and lower perception of pain than women[19,20]. Further studies with a larger number of patients are required to assess the benefit of parecoxib use in the treatment of perioperative pain control in patients undergoing ankle fracture surgery.

Conclusions

The perioperative administration of parecoxib did not significantly improve postoperative pain control as defined by the reduction in opioid requirements, lower pain scores, higher pain relief, and higher PSRM relative to the placebo. The single benefit of the perioperative use of parecoxib seemed to be a shorter length of hospital stay than the placebo group. The present study may serve as a guideline for pain management in patients with unstable ankle fractures with the aim of decreasing overall opioid use. It may lessen the adverse effects of opioid medications and reduce the risk of opioid overdose. Further studies with larger numbers of patients are necessary to clarify the role of perioperative parecoxib in patients undergoing ankle fracture surgery.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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