

## Original Article

# The application of pre-emptive parecoxib alleviated postoperative pain after percutaneous endoscopic lumbar discectomy

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**Abstract:** Purpose: The purpose of this study was to determine the clinical efficacy of pre-emptive parecoxib in the percutaneous endoscopic lumbar discectomy. Methods: Eighty patients were randomly allocated to receive either parecoxib or sodium chloride brine as placebo 30 minutes prior to the percutaneous endoscopic lumbar discectomy. Clinical data was obtained and recorded at 1, 6, 12, 24 hours after operation, including surgery time, intraoperative blood loss and hospitalization duration. The functional outcomes were evaluated by postoperative complications, visual analogue scale (VAS) of leg pain, oswestry disability index (ODI) and modified Macnab criteria. Time to achieved straight leg raises, time to 1st rescue analgesia, Sum of analgesics consumed during the first 5 days was noted. Incidences of adverse events were recorded. Results: The patients' characteristics and operative data were similar between the groups. The VAS score of leg pain and ODI score were lower in the parecoxib group than in the placebo group; the differences were confirmed as significant at 1, 6 and 12 hours after operation while not significant at 24 hours. The patients in the parecoxib group achieved straight leg raises earlier than those in the placebo group. Patients in the parecoxib group reported a longer pain free interval and consumed less sum of rescue analgesics during the first 5 days than those in the placebo group, the difference was statistically significant. With respect to modified Macnab's criteria, more patients exerted excellent and good clinical outcomes in parecoxib group than those of placebo group. Conclusions: The application of pre-emptive parecoxib significantly alleviated early postoperative pain decreased the sum of rescue analgesics and improved patient satisfaction after percutaneous endoscopic lumbar discectomy. Therefore, pre-emptive parecoxib may be useful in pain relief of the percutaneous endoscopic lumbar discectomy.

**Keywords:** Pre-emptive parecoxib, postoperative pain, disc herniation

## Introduction

Percutaneous endoscopic lumbar discectomy (PELD) has been proved to be a safe, efficient surgery option for the treatment of intractable ischialgia from lumbar intervertebral disc herniation or accompanying foraminal stenosis [1, 2]. This novel procedure owns many advantages over open lumbar discectomy, such as less damage to normal paravertebral muscles and ligaments, lower risk of segmental instability, shorter hospitalization time and earlier restoration of function [3, 4]. However, the procedure usually needs to be processed under local anesthesia so that the patient can perceive the occurrence of pain and cooperate with the sur-

gery [5]. Moreover, osseous resection from facet joints is often required for the sake of intervertebral foraminotomy, and it is inevitable for annulus fibrosus and nucleus pulposus resection or intraoperative nerve root irritation harassment, which may inflict pain and discomfort on patients [6]. Clinical studies have suggested that a number of patients are still subjected to moderate or severe postoperative pain despite the progress in speculative knowledge of pain control [7, 8]. Hence, optimal perioperative pain management in PELD remains to be a challenge.

Postoperative pain usually results from intraoperative tissue damage or postoperative inflam-

matory reaction and may further influence the effectiveness of a surgical procedure [9]. Acute pain without proper disposal is associated with higher risk of developing into chronic pain or even central sensitization [10]. Thus, timely, aggressive intervention prior to the entrenched pain stimulus symptoms is of particular significance. It is well established that pre-emptive analgesia, which is carried out before surgery or incision, contributes to the alleviation of hyperalgesia and central sensitization [11, 12]. Parecoxib is broadly applied in daily anesthesia process and its monoaminergic effect makes it appropriate for pre-emptive analgesic regimen, particularly for short course surgery [13, 14]. To the best of our knowledge, no study has so far tested the preemptive analgesic effect of parecoxib in the PELD operation. We therefore conducted a prospective, randomized controlled study to determine the clinical efficacy pre-emptive parecoxib that were administered intravenously in the PELD.

### Materials and methods

#### *Ethics*

This prospective, randomized controlled study was conducted in accordance with the Declaration of Helsinki. All the patients consented by writing for their inclusion in the study. The proposal was registered and warranted by Ethics Committee of Dongfeng General Hospital, Hu Bei University of Medicine, China.

#### *Patients*

The inclusion criteria were as follows: (1) 20 to 65 year old patients with American Society of Anesthesiologists Physical Status Classification (ASA) I-II; (2) simple lumbar disc herniation, associated with ipsilateral sciatica or other neurological damages such as hypaesthesia and decreased myodynamia; (3) radiological diagnosis were consistent with symptoms and signs of nerve localization; (4) no symptomatic improvement with regular conservative treatment for 3 months or recurrence of other minimally invasive surgery. The exclusion criteria were: (1) lumbar spinal stenosis; (2) two or more segmental disc herniation; (3) obvious disc calcification; (4) vertebral posterior osteophyte formation; (5) segmental instability; (6) complicated with other pathological conditions that cannot fit or tolerate surgery. There were 80

consecutive patients enrolled in this study from March 2012 to May 2014, among which 33 were male and 41 were female with an average age of 48.6 years (range from 31 to 65). All participants received the examination of X-ray and CT/MRI scan prior to surgery, 54 herniated disk were in L4-5 and 26 were in L5-S1.

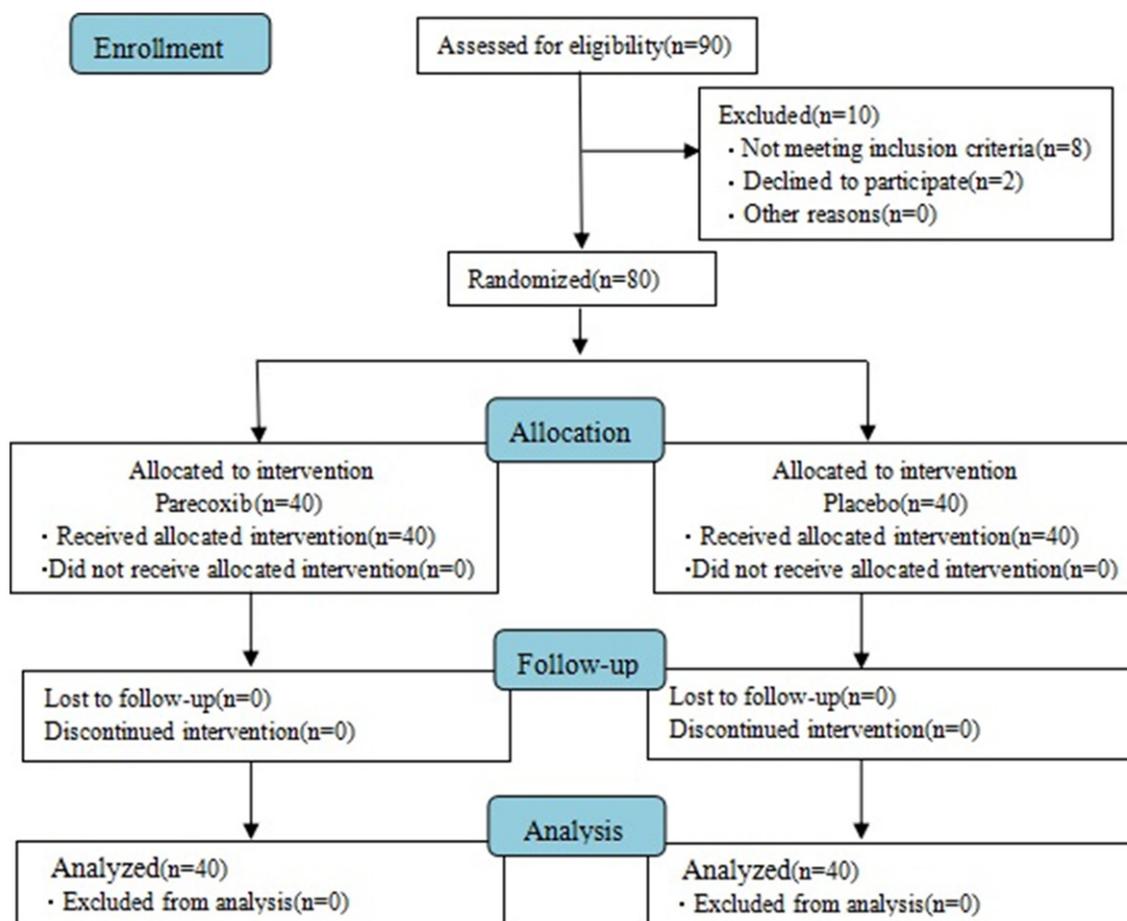
#### *Randomization and pre-emptive intervention*

The study was processed in a randomized, double blinded method. The computer automatically generated block randomization schedule was provided by a statistician who was not involved with patient care to create a tabulation of randomized numbers. For each patient, group assignments were kept in sequentially numbered opaque, sealed envelopes that were opened by an investigator who was not involved with patient care. Patients were thus randomly allocated into either parecoxib group (n=40) or placebo group (n=40). In the parecoxib group, 40 mg parecoxib in 500 ml 0.9% NaCl was intravenously infused 30 minutes prior to the operation. In the placebo group, 500 ml 0.9% NaCl was intravenously infused 30 minutes prior to the operation. The anesthesia was conducted by two anesthetists who were blinded to the patients grouping and observation process.

#### *Surgical procedures*

The surgical procedure was processed using posterolateral approach, which was consistent with the description of previous literature [15]. Patient was couched on the radiolucent operating table in prone position. By virtue of C-arm fluoroscopy, the entry point was determined at approximately 8-12 cm from the spinous process and 20 degrees to the horizontal direction, pointing to the protrusion. After the operation area being disinfected and sterile drapes being whisked, local infiltration anesthesia was performed with morphine (10 mg) and lidocaine (30 mg, 1%). Under fluoroscopic guidance, a 20 G puncture needles was advanced along the calibration line direction to the former edge of lower vertebral articular process. The needle core was pulled out and a conducting wire was inserted; then a 7 mm skin incision was performed. The soft tissue was expanded through graded dilator and intervertebral foramen was enlarged with graded trephine, a working channel was subsequently installed over the dilator.

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**Figure 1.** Flow chart describing recruitment, allocation, follow-up and analysis.

**Table 1.** Summary of patients' characteristics and operative data in each group

Parameters	Parecoxib group (n=40)	Placebo group (n=40)	P value
Age (years)	49.22±9.35	47.60±11.81	0.4245
Surgery time (minutes)	68.84±25.39	70.44±30.06	0.6348
Blood loss (ml)	20.55±25.39	21.38±18.65	0.2324
Height (cm)	164.85±10.11	164.62±10.56	0.4420
Weight (kg)	62.27±12.59	62.44±12.56	0.9658
ASA (I/II)	16/24	18/22	0.2384
Hypertension (n)	13 (32.5%)	14 (35%)	0.8715

Values are number of patients (percentage), mean ± standard deviation. ASA, American Society of Anesthesiologists Physical Status Classification.

Fluoroscopy confirmed the presence of the working channel to the edge of protrusions. Whereafter, the herniated disc tissues were taken out through a nucleus pulposus clamp under spinal endoscopy. The hyperplasia tissues around the nerve root were cleaned to

reset the nerve root. Plasm radiofrequency at low temperature was applied to stop bleeding, followed by irrigation of disc cavity with normal saline. The working channel and spinal endoscopy were then extracted, the incision was closed and a sterile dressing was covered on wounds. The straight leg rising test was conducted to check the range of motion and function improvement of lower limbs. Tramadol infusion (100 mg) in 500 ml 0.9% NaCl was administered intravenously on demand for postoperative analgesia.

### Data collection and outcomes evaluation

Clinical data was obtained and recorded at 1, 6, 12, 24 hours after operation, including surgery time, intraoperative blood loss and hospitalization duration. The functional outcomes

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**Table 2.** The VAS score of leg pain and ODI score in two groups

Parameters	VAS score				ODI score			
	1 hour	6 hours	12 hours	24 hours	1 hour	6 hours	12 hours	24 hours
Parecoxib group	0.44±0.35	1.43±0.52	2.31±0.65	2.01±0.48	20.12±2.43	23.64±2.88	19.61±2.10	18.27±1.72
Placebo group	2.19±0.37	3.04±0.78	3.26±0.53	2.31±0.46	29.64±2.56	32.56±3.02	26.34±2.33	21.18±1.89
<i>p</i> value	0.0016	0.0125	0.0410	0.1374	0.0128	0.0135	0.0220	0.2434

**Table 3.** Comparison between the two groups in terms of time of straight leg raising test, time to 1st rescue analgesia, sum of analgesics consumed during the first 5 days

Parameters	Parecoxib group (n=40)	Placebo group (n=40)	<i>P</i> value
Time to straight leg raising (hours)	1.14±0.38	2.62±0.56	0.0170
Time to 1st rescue analgesia (hours)	9.21±9.35	2.34±0.77	0.0001
Sum of analgesics consumed during the first 5 days	7.32±1.95	11.68±1.81	0.0012

**Table 4.** Summary of primary clinical outcomes in each group

Parameters	Parecoxib group (n=40)	Placebo group (n=40)	<i>P</i> value
Hospitalization duration (days)	3.04±0.68	3.12±0.55	0.2380
Complications	2 (5.0%)	3 (7.5%)	0.4625
Macnab criteria			
Excellent	19 (47.5%)	16 (40.0%)	
Good	16 (40.0%)	15 (37.5%)	
Fair	3 (7.5%)	6 (15.0%)	
Poor	2 (5.0%)	3 (7.5%)	

were evaluated by postoperative complications, visual analogue scale (VAS) for leg pain, Oswestry disability index (ODI) and modified Macnab criteria. Time to achieved straight leg raises, time to 1st rescue analgesia, sum of analgesics consumed during the first 5 days were noted. Incidences of adverse events like pain on injection of the study drug, local reactions, nausea and vomiting were recorded.

### Statistical analysis

Statistical analysis of the present study was conducted using SPSS 20.0 software. Continuous baseline and demographic variables were analyzed using Analysis of variance (ANOVA) with normal distributions. We used nonparametric methods instead where the distributions were skewed and could not be normalized. Statistical significance was defined as  $P < 0.05$ .

### Results

Among the 90 patients assessed for eligibility, 80 patients who met the inclusion criteria and

agreed to participate in this study were enrolled from March 2012 to May 2014 (**Figure 1**). Of the 80 patients, study could be completed in all patients and thus, no patient was excluded from statistical analysis.

The patients' characteristics and operative data are exhibited in **Table 1**. No statistically significant difference was detected in mean age, surgery time and intraoperative blood loss. The patients' height, weight, ASA status and prevalence of hypertension were similar between the groups.

The VAS score of leg pain and ODI score were lower in the parecoxib group than in the placebo group, the differences were confirmed as significant at 1, 6 and 12 hours after operation while not significant at 24 hours (**Table 2**).

The patients in the parecoxib group achieved straight leg raises earlier than those in the placebo group; the difference was statistically significant (**Table 3**). When the mean time of first rescue analgesic was assessed, patients in the parecoxib group reported a longer pain free interval than the placebo group, the difference was statistically significant. Patients in the parecoxib group consumed less sum of rescue analgesics during the first 5 days compared with those in the placebo group, a statistically significant value was noted between the groups.

The difference with regard to hospitalization duration was confirmed as not significant

between groups (**Table 4**). Complications appeared in 2 patients (5.0%) in the parecoxib group and three patients (7.5%) in the placebo group up to the final follow-up, the difference was not statistically significant ( $P=0.4625$ ). Two patients in the parecoxib group complained of continuing ache of lower limbs after operation owing to disc fragment remnants, which were eliminated after revision of the PELD thereafter. Two patients in the placebo group developed dysesthesias of lower extremity in a dermatomal distribution, which were alleviated by increased dosage of medication yet persistent to the last follow-up. One patient in the placebo group suffered from recurrent disc herniations and was treated successfully with second PELD. With respect to modified Macnab's criteria at the final follow-up, a total of 35 patients (87.5%) exerted excellent and good clinical outcomes in parecoxib group, which was higher than that of placebo group (31 patients, 77.5%).

### Discussion

Postoperative pain may induce severe negative impact on functional recovery, prolong the time of hospitalization and return to work, and lower patient satisfaction [16, 17]. As to PELD, the postoperative pain is largely due to tissue damage caused by the operation, such as intervertebral foramen enlargement, osseous resection of superior facet joints, and removal of nucleus pulposus, which will probably induce muscle and nerve roots irritation [18]. These processes will increase the secretion of algogenic substances in local as well as in plasma, which thereby stimulate peripheral receptors and trigger the occurrence of peripheral pain. Long-term oppression and intraoperative blood stimulation may give rise to nerve root edema that directly stimulate the central nervous system and create radicular pain [19]. The peripheral inflammatory stimulation can also arouse secondary hyperalgesia by increasing the excitability of spinal neurons [20]. On the other hand, the secretion of inflammatory cytokines such as PGE-2, IL-6 is associated with up-regulation of the cyclooxygenase-2 (COX-2) level, thus decrease central pain threshold and induce hyperalgesia, leading to prolonged time course of pain, increased analgesic consumption and dissatisfied functional rehabilitation [21-23]. Moreover, the PELD is conducted under local anesthesia; the patients can feel pain throughout the operation [24]. Therefore,

it is essential to offer prompt, reasonable analgesia medication and eliminate or alleviate discomfort from postoperative pain.

The concept of pre-emptive analgesia is derived from a large body of evidence-based clinical researches and progress in the basic science of pain [11, 25, 26]. The majority of the studies authenticated the beneficial effects of pre-emptive analgesia through both animal and human research. It was first proposed by Wall et al [27] and defined as an antinociceptive treatment given before incision or surgery. Approximately a century ago, Crile et al [28] demonstrated the inherent relationship between intraoperative tissue injury and aggravation of acute pain and forward postoperative pain, which is currently referred to as central sensitization. The rationale was to minimize intraoperative nociception through pre-emptive analgesia and prevent relevant changes in the central nervous system as well as formation of painful scars [29]. Parecoxib, a selective COX-2 inhibitor, has been proved to be effective for various kinds of operation, such as cardiopulmonary bypass, hernioplasty, appendectomy, gynecologic laparoscopy, and open cholecystectomy [30]. It was well established that pre-emptive parecoxib analgesia was more effective than postoperative administration for overall pain management in certain general surgical procedures [31]. In this study, we detected that VAS scores for leg pain and ODI scores were less in parecoxib group than those of placebo group at each time point, which was in accordance with previous studies. There is evidence that the intravenously administered parecoxib prior to operation resulted in a decreased sum of rescue analgesics [32]. Consistently, our study showed that patients in the parecoxib group consumed less sum of rescue analgesics during the first 5 days compared with those in the placebo group, the difference was significant. In our series, complication rate was lower in the parecoxib group (5.0%) than that of placebo group (7.5%), while no significant difference was detected, two patients in the placebo group showed dysesthesias, this symptom was alleviated by increased dosage of medication. There was no other major complication during the follow-up.

Opioids are quite efficient analgesic in the disposal of postoperative pain, yet their use is associated with many adverse effects, such as

respiratory inhibition, mental state remodeling, sicchasia, emesis and astriction [33]. Non-steroidal anti inflammatory drugs (NSAIDs) have been utilized in the treatment of various kinds of acute or chronic pain [34]. Nevertheless, the NSAIDs are often contraindicated in the remedy of acute traumatic or operative pain on account of platelet inhibition and bleeding tendency. In the present study, patients treated with pre-emptive parecoxib showed greater improvements in pain scores and patients' satisfaction. No significant differences were detected regarding perioperative bleeding in the two groups, which indicates that parecoxib did not affect perioperative bleeding. Systematic reviews indicate that COX-2 inhibitors such as parecoxib are effective for the treatment of acute postoperative pain [35]. The lack of platelet suppression enables parecoxib to be injected intravenously or intramuscularly with good patient tolerance [36].

There still remains controversy and confusion in regard to the effectiveness of pre-emptive parecoxib analgesia. A few reports suggested that pre-emptive parecoxib did not lighten the degree of pain after operation [37, 38]. This discrepancy might be attributed to the mode of administration and subjective judgment of pain scores. One of these studies was processed with a single dose of parecoxib [39]. According to our experience, the clinician should also conduct a thorough preoperative evaluation of the patient history, including former pain reactions, analgesia medicine employments and any other relevant information. Such an evaluation contributes to comprehensive consideration of influential factors of pain perception and patient's response to it. Besides, pain stands for an uncomfortable sensorial and emotional experience, direct measurement of this subjective feeling is inaccurate and challenging, particularly assessing it through a single tool. To minimize the variations, the symptom was evaluated with two independent grading systems coupled with a modified Macnab's criteria in the present study. Prospective study project is an effective method for this sort of research, so we conducted the present study accordingly. A double blinded strategy and randomization of the patients by software were also adopted in order to minimize the possibility for bias.

Although our findings encourage us to adopt pre-operative parecoxib to get a more ideal

anesthetic effect after percutaneous endoscopic lumbar discectomy, there were certain limitations in our study. One limitation is that we did not address length of return to work and cost-effectiveness, which may limit the conclusions we can make from our results. Another limitation of our study we excluded two or more segmental disc herniation with expected difficult operation to control confounding variables; generalization of this result should be exercised with caution. And we did not investigate the effects of pre-emptive parecoxib on C-reactive protein level and stress response in more detail. This study may be more persuasive if we had accessed these parameters.

The current study showed that the application of pre-emptive parecoxib significantly alleviated early postoperative pain decreased the sum of rescue analgesics and improved patient satisfaction after percutaneous endoscopic lumbar discectomy. Therefore, pre-emptive parecoxib may be useful in pain relief of the percutaneous endoscopic lumbar discectomy.

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### Disclosure of conflict of interest

None.

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