Int J Clin Exp Med 2016;9(10):19454-19460
www.ijcem.com /ISSN:1940-5901/IJCEM0028816

Original Article

Efficacy of parecoxib on the level of IL-6, CRP, and postoperative pain relief after percutaneous nephrolithotomy

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Received March 21, 2016; Accepted June 12, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: The purposes of this study were to investigate the efficacy of parecoxib on postoperative inflammatory response, and to assess serum levels of acute phase reactants, for example cytokine (IL)-6 and C-reactive protein (CRP) in patients who have undergone percutaneous nephrolithotomy (PCNL). Methods: One hundred and twenty patients undergoing PCNL were randomly divided into control group and parecoxib group. All patients were managed by a propofol-based general anesthesia with a fixed continuous intravenous remifentanil. Parecoxib group received a single dose of parecoxib 40 mg on the day of surgery, and followed 40 mg every 12 hours for 48 hours. During the first 72 hour, pain visual analog scales were recorded daily. To measure serum IL-6 and CRP level, blood samples were collected before surgery and at 24, 48 and 72 hour after surgery. Results: The serum IL-6 and CRP levels increased significantly in both groups at 24 hour after PCNL. IL-6 levels differed significantly between two groups at 24 and 48 hour after surgery ($P<0.05$). CRP levels in parecoxib group were significantly lower than control group at the same day ($P<0.05$). Visual analog scale in parecoxib group was significantly lower at 3 hour after extubation and 24 hour postoperatively ($P<0.05$). Conclusions: Patients undergoing PCNL with parecoxib adding to systemic analgesic therapy revealed reduced mean additional analgesic consumption, postoperative pain, and serum IL-6 and CRP levels. Analgesia with anti-inflammatory drug may contribute to the relief of the postoperative inflammatory response and pain in patients undergoing PCNL.

Keywords: Parecoxib, postoperative pain, percutaneous nephrolithotomy, inflammatory response

Introduction

The postoperative pain can be distressing, so many doctors now consider pain to be the fifth vital sign, and the pain control is a significant concern in hospitalized patients [1]. A variety of analgesic drugs and techniques with favorable results have been used to relieve pain after PCNL surgery [2].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in pain states by suppressing the cyclooxygenase enzyme responsible for the release of mediators of inflammation [3]. NSAIDs are related with gastrointestinal bleeding, inhibition of platelet aggregation, and renal toxicity, limiting their applications in medical practice. Parecoxib, an injectable COX-2 selective NSAID, is currently the only available nonopioid analgesic and anti-inflammatory agent indicated for parenteral use that does not interfere with platelet aggregation [4, 5]. Clinical trials have reported a benefit in reducing pain following oral, orthopedic, gynecologic, and cardiac surgeries [6]. Recently, parecoxib was selected for pain relief in patients with acute renal colic, and significantly improves patients' perceived analgesia following radical open prostatectomy [7, 8].

As parecoxib is intended for the short-term treatment of the postoperative pain following PCNL, therefore it may offer advantages in the treatment; however, to date, no clinical studies have evaluated the use of parecoxib in postoperative pain relief following PCNL. The primary aim of this study was to investigate and compare the efficacy of parecoxib for postoperative

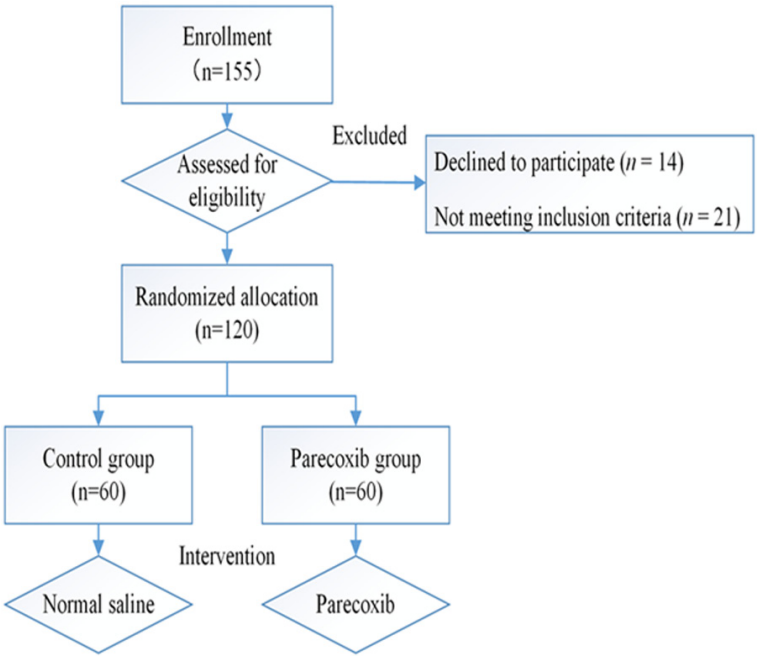

Figure 1. The consort flow diagram of the design for PCNL surgery study.

pain relief after PCNL in first 72 h of the postoperative period. Secondary aim was to assess the serum levels of acute phase reactants, such as interleukin-6 (IL-6) and C-reactive protein (CRP) in patients with PCNL and to elucidate the efficacy of parecoxib on postoperative inflammatory response.

Patients and methods

A double-blind randomized comparative study was conducted prospectively from January 2013 to December 2014 in 155 adult patients posted for PCNL surgery after Institutional Ethics Committee's approval and informed consent. They were randomly divided into two equal groups with 60 patients in each group by closed envelope method. Patient's inclusion criteria were 18-60 years of age, 35-85 kg weight having body mass index <30, with nephrostomy tube (18 F) and duration of surgery <3 h. Study drug was prepared by person blinded to the actual study and findings recorded by a third person. The consort flow diagram of this study was showed in **Figure 1**.

All patients were managed by a propofol-based general anesthesia with a fixed continuous intravenous remifentanil 0.1 μg/kg/min. All patients were pre-medicated with intravenous propofol 60 mg. Balanced general anaesthesia was administered, induction done using midazolam 4 mg, and intubation facilitated by atracurium 20 mg. After endotracheal intubation, patients were maintained with O_2/N_2 O with atracurium and isoflurane. All surgeries were performed by the one senior surgeon to reduce surgical interference. Surgery was performed in the prone position as previously described [9]. Patients were extubated and kept in post-anaesthesia care unit under observation for 30 min. After leaving the recovery room, a single dose of parecoxib 40 mg on the day of surgery followed 40 mg every 12 hours for 48 hours is the standard dosage recommended by the manufacturers for IV application in adults. Patients having supracostal puncture, excessive bleeding, and a PCA pump were excluded from the study.

During follow up, patients were assessed for pain and side-effects by an independent observer blinded to the administration. The pain score was assessed using 0-10 point visual analogue scale (VAS). When VAS score >4, the patient in all groups was administered intravenous bucinnazine 100 mg slowly as a rescue analgesia when the patients requested in the ward by the experienced nurses blinding to the investigation, and the patient was reassessed. Total consumption of bucinnazine required in 24 h were noted. To measure serum IL-6 and CRP level, blood samples were collected before surgery and at 24, 48 and 72 hour after surgery. The levels of IL-6 and CRP were measured using an ECLIA (Roche Diagnostics GmbH, Mannheim, Germany) for all the patients.

Statistical analysis

The sample size was estimated as 60 patients in each group. All parametric results were showed as mean ± standard deviation (SD). Statistical analysis was performed with SPSS 19.0 software. The differences of categorical variables and continuous variables between groups were analyzed by Fisher's exact test and Student's t-test.

Table 1. Patient characteristics, surgical information, side effects in the postoperative period

	Group Placebo (*n* = 60)	Group Parecoxib (n = 60)
Sex (M/F)	25/35	27/33
Age (yr)	39.3 ± 10.2	41.7 ± 13.6
BMI (kgm^{-2})	24.1 ± 6.3	23.0 ± 4.7
Number of nephrostomy tubes (1/2 tube)	47/13	50/10
Total remifentanil consumption (mg)	0.66 ± 0.18	0.58 ± 0.15
Duration of anesthesia (min)	85 ± 14	96 ± 19
Total consumption of bucinnazine in 24 h (mg)	54.3 ± 58.7	56.4 ± 29.0
Postoperative hospital stay (day)	6.7 ± 2.4	7.1 ± 1.9
Side-effects (number of patients)	Nausea-2 Vomiting-1	Nausea-1 Vomiting-1

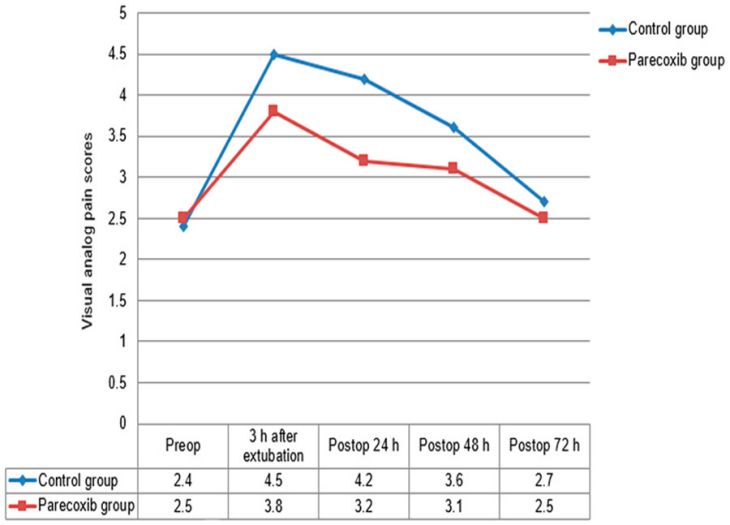

Figure 2. Postoperative pain scores as assessed by Visual Analogue Scale in the study groups.

Results

There were 35 dropouts from the 155 patients enrolled in the study, 120 patients accorded with the study criteria were enrolled in the trial. The demographic data regarding age, sex, and BMI were comparable and insignificant. The number of nephrostomy tubes between two groups has no significant differences (**Table 1**).

Mean postoperative hospital stay length was 6.7 ± 2.4 days in control group and 7.1 ± 1.9 days in parecoxib group. No significant differences were found between two groups (P = 0.177). Mean consumption of bucinnazine in first 24 h, remifentanil consumption and duration of anesthesia were 54.3 ± 58.7 mg, 0.66 ± 0.18 mg and 85 ± 14 min in control group and 56.4 ± 29.0 mg, 0.58 ± 0.15 mg and 96 ± 19 min in parecoxib group. Similarly, no significant differences were found between two groups (P = 0.194).

Visual analog scale reached to the peak at 3 h after extubation, then declined gradually in both groups. However, the visual analog scale was significantly lower at 3 h after extubation and postoperative 24 h in parecoxib group (P<0.05) (**Figure 2**). Whereas, no significant differences in visual analog scale were found between the two groups at postoperative 48 h and 72 h.

Postoperative growth in serum IL-6 and CRP concentrations were showed in both groups. The CRP value peaked on the postoperative 72 h in control group, whereas IL-6 values peaked on the postoperative 24 h in both groups. However, IL-6 level was significantly lower in parecoxib group than in control group at postoperative 24 h. There were no significant differences in serum IL-6 levels between the groups at postoperative 72 h. Meanwhile, serum CRP differed significantly between the groups at postoperative 24 h and 48 h (**Figures 3**, **4**).

No major complication occurred in any groups. Gastrointestinal adverse reactions, mostly such as nausea and vomiting, were defined as the most common events in both groups. The side-effects like nausea and vomiting were less and insignificant in both groups. No patients in both groups quit the research because of severe adverse reactions (**Table 1**).

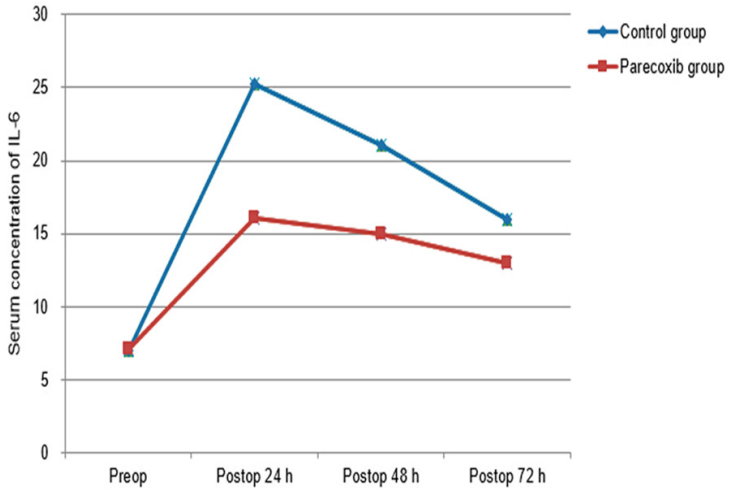

Figure 3. Changes in serum concentration of IL-6 before and after PCNL in the study groups.

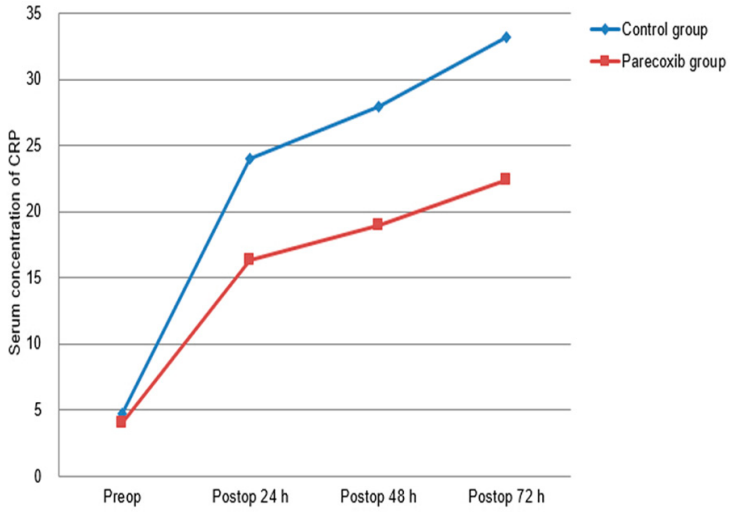

Figure 4. Changes in serum concentration of CRP before and after PCNL in the study groups.

Discussion

Since it has been performed by Fernstrom and Johannson in the 1970s, PCNL has been considered as an effective and standard treatment alternative that is commonly used to manage patients with large or complex upper urinary tract calculi [10]. After completion of stone fragmentation and removal, placement of nephrostomy tube is a standard practice with the intention to drain the urine and clots, tamponade of tract bleeding, and preserve the reentry tract for a staged procedure [11].

In traditional PCNL surgery, the nephrostomy tube leads to local inflammatory reaction which produces the postoperative pain and discomfort in PCNL. In our study, the postoperative pain was most intense immediately after recovering from remifentanil-based anesthesia for PCNL surgery and subsequently declined to low levels in all groups within 72 h after surgery in our study. Patients in the parecoxib group felt less severe postoperative pain, whereas those in the control group showed higher VAS scores in our study. The COX-2 inhibitor parecoxib exerts its analgesic effect on surgical pain through the inhibition of neuronal ERK activation in the spinal cord [12]. The results of the present investigation showed the VAS pain scores were significantly lower in the parecoxib group as compared to the control group at 3 h after extubation and 24 h following surgery under general anesthesia. The high pain score in all patients following PCNL would be prevented if parecoxib was administered intravenously. These findings are in accordance with previous study assessing effects of on analgesia benefit [13]. Parecoxib provides effetive pain relief in the initial postoperative period, suggesting the advantage of preventive analgesia for post-operative pain control.

PCNL stands for a crucial surgical stress, which is associated with an obvious increase in the postoperative circulating levels of plasma inflammatory markers [14]. Prostanoids, synthesized by two isoforms of COXs, are important mediators in many important physiological responses, such as inflammation and thrombosis. Meanwhile, inhibition of prostanoids synthesis has related to the anti-inflammatory effects of COX inhibitors. Previous study has demonstrated that the up-regulation of COX-2 was contributed to the synthesis of PGE_2 which resulted in the production of IL-6 [15]. During the acute inflammatory response that follows the surgery, a plenty of pro-inflammatory and anti-inflammatory cytokines are released. Among those cytokines, the serum IL-6 is con-

sidered to be a sensitive marker of the degree of surgical stress [16]. Meanwhile, CRP is an indicator of inflammation, such as TNF-α and IL-6, which produced on stimulation by monocyte related cytokines [16]. Our results confirmed that the levels of serum IL-6 and CRP increased in all patients after surgery, IL-6 values peaked at 24 h after surgery in the both group, and CRP level ascended continuously after surgery. IL-6 elevation was significantly less pronounced in the parecoxib group than the control group at 24 h following surgery. While the IL-6 level determined at reference value in parecoxib group, it was remained over reference range in control group at postoperative 72 h. In addition, Postoperative serum CRP level in parecoxib group was obviously lower than control group. Our findings implied that parecoxib can relive pain by attenuating the inflammatory response.

Besides increases in the levels of serum CRP and IL-6 postoperatively, Opioid-induced hyperalgesia (OIH) may partly contribute to increased pain scores postoperatively in all groups [17]. Our patients received a remifentanil-based anaesthesia. Hyong et al found that remifentanil added to propofol anesthesia causes pain sensitization in the immediate postoperative period and has been shown to be associated with OIH [18]. Parecoxib provides effective pain relief in the initial postoperative period in our study. Many reports suggests a role for COX-2 inhibitors in the modulation of OIH in humans and COX-2 inhibitors antagonize NMDA receptor function in the central nervous system by inhibition of prostaglandin synthesis [17]. Thus, it has been hypothesized parecoxib might attenuate or prevent the expression of opioid-induced tolerance and hyperalgesia in the immediate postoperative period. Treatment with parecoxib prevents this pronociceptive effect and so this may be useful for the management of acute postoperative pain when remifentanil and propofol are used as anesthetics.

At the end of a remifentanil infusion, patients may have increased opioid requirements due to opioid-induced increased pain sensitivity. Therefore, the initial requirement of opioids may not only be related to the intraoperative trauma, but also reflect a remifentanil-associated hyperalgesia. Previously published studies indicate that no significant difference in regard opioid sparing effect by administering additional non-analgesics parecoxib while VAS scores were significantly lower in the parecoxib groups after surgery [19-21]. Although parecoxib analgesia resulted in an average reduction of cumulative bucinnazine requirements by 4% compared to placebo in patients undergoing PCNL in our present study, we observed a similar small difference that no significant differences in cumulative bucinnazine administration were measured between the two groups after surgery. However, opioid sparing is not by itself considered a clinically meaningful endpoint. Thus, we examined other measurements assessing patients' benefits from multi-modal analgesia. Many other studies have confirmed parecoxib reduced opioid consumption postoperatively and opioid sparing effects of parecoxib may translate into clinical benefit in patients' analgesia [8, 15, 22, 23]. The results of investigations may depend on the type of surgery performed and the dosages used and could be an incentive for other researchers to re-evaluate different dosages of non-opioid analgesics in patients undergoing PCNL.

Previous studies have questioned the safety of the selective COX-2 inhibitors or the COXIBS [24, 25]. Use of selective COX-2 inhibitors or the COXIBS was found to be related to significant risk of arterial thrombosis, renal toxicity, cerebrovascular and myocardial infarction. In spite of compelling evidence on the adverse effects of the selective COX-2 inhibitors or the COXIBS that have been investigated in previous studies, the vast majority of this evidence is associated to their long term usage. On the contrary, there were some studies focused on their short term use when started intra-operatively or even postoperatively. Their results showed no significant differences in the frequency of postoperative complications between the NSAIDS and control group, which showed a similar tendency the same as in our study [15, 26]. In our study, serious adverse events were not observed. The incidence of side effects like nausea and vomiting were minimum and insignificant in both groups. No drug reactions apart from mild nausea and vomiting, which were treated with antiemetics, occurred in our study.

There are some limitations in our study. Firstly, this is a single centre research study with limited samples, so a multiple centre study with sufficient samples should be performed to

increase the conviction in future. In addition, we excluded patients with supracostal puncture, thus being unable to evaluate the efficacy of our study when supracostal puncture was involved.

Conclusions

In conclusion, our study observed that patients undergoing PCNL experienced reduced postoperative pain, serum CRP and IL-6 levels, when parecoxib was used to the systemic analgesic therapy. Analgesia with anti-inflammatory drug may conduced to the relief of the postoperative inflammatory response and pain in patients undergoing PCNL.

Disclosure of conflict of interest

None.

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