The Post-Operative Analgesic Efficacy of Celecoxib Compared with Placebo and Parecoxib after Total Hip or Knee Arthroplasty

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Background: *Nonsteroidal antiinflammatory drugs (NSAIDs) in combination with opioids is a model of multimodal analgesia. NSAIDs have the oral and parenteral forms.*

Objective: *The aim of the present study was to evaluate the efficacy of celecoxib compared with placebo and parecoxib after total hip or knee arthroplasty.*

Material and Method: *A total of 120, ASA 1-2, aged 18-75 years, patients were randomly assigned to receive one of the three groups: Group I (control) received placebo (n = 40), group II received 400 mg celecoxib orally (n = 40) and group III received 40 mg parecoxib intravenously (n = 40). The present study medication was administered 1 hour before surgery. All patients had access to patient-controlled analgesia (PCA) with intravenous morphine. Patients were studied at 0,1,6,12 and 24 hours postoperatively for verbal numerical rating scale (VNRS), morphine consumption,satisfaction score and side effects.*

Results: *The intraoperatively fentayl requirement were similar among the three groups ($p < 0.00$). Celecoxib and parecoxib significantly decreased the amount of morphine requirement after total hip or knee arthroplasty compared to placebo at 1, 6, 12 and 24 hours ($p < 0.00$). The celecoxib group required more morphine than the parecoxib group at 1, 6, 12 and 24 hours ($p < 0.00$). The VNRS score in parecoxib group was significantly lower than the celecoxib and control groups at 1,6,12 but not at 24 hours. The VNRS score was lower in the celecoxib group compared to the control group at 1 and 6 hours postoperatively ($p = 0.01$, $p < 0.01$ respectively). The placebo group had a higher sedation score ($p = 0.008$) but not for nausea vomiting ($p = 0.36$) and pruritus ($p = 0.12$) compared to the treatment groups.*

Conclusion: *Within 12 hours after total hip and knee arthroplasty, pre-operative administration of parenteral parecoxib 40 mg was more effective than oral celecoxib 400 mg and placebo in terms of morphine consumption and VNRS score.*

Keywords: *Parecoxib, Celecoxib, Postoperative pain*

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Postsurgical pain has commonly been managed with opioid analgesics. However, they are associated with adverse effects such as respiratory depression, sedation, nausea, vomiting, constipation, and intestinal ileus[1]. An effective drug which would be co-administered with morphine to reduce the amount of opioids used is recommended. Nonsteroidal antiinflammatory drugs (NSAIDs) have been used adjunctively in the management of pain after surgical procedures[2,3]. The mechanism of action of NSAIDs is related to inhibition of the cyclooxygenase (COX) enzyme[1], which exists as two distinct isoforms: COX-1 and COX-2[4,5]. COX-1 is constitutively active throughout the body and is responsible for mediating routine physiologic functions, such as maintaining gastric mucosal integrity and vascular hemostasis. However, the inducible COX-2 enzyme is expressed in association with inflammation and pain[5].

Celecoxib is an oral COX-2 specific inhibitor. Doyle et al[6] compared celecoxib with the classical NSAIDs in terms of post-dental surgery pain reporting similar analgesic effects. Reuben et al[7] demonstrated significant opioid sparing effects with celecoxib and rofecoxib when used in conjunction with patient-controlled analgesia (PCA) with morphine after spinal fusion surgery.

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Parecoxib sodium, an intravenous high-selective COX-2 inhibitor, is effective in treating postoperative oral surgery, orthopedic surgery, and abdominal hysterectomy pain[6-8]. However, the analgesic efficacy of both celecoxib and parecoxib on postoperative pain might not be comparable in terms of verbal numerical rating scale (VNRS) and amount of opioids usage. The aim of the present study was to compare analgesic efficacy of prospective administated single-dose oral celecoxib with intravenous parecoxib in patient undergoing total hip or knee arthroplasty.

Material and Method

The present study was approved by the hospital research ethics committee and written informed consent from all patients, a total of 120, age 18-75 years, American Society of Anesthesiologist Physical Status (ASA) classification I and II patients undergoing elective total knee or hip arthroplasty. The patients could operate patient-controlled analgesia (PCA) device after presurgical instruction. Exclusion criteria were known allergy, sensitivity, asthma or contraindication to opioids, sulfonamide, NSAIDs, history of GI bleeding, peptic ulcer, coagulation disorder, renal impairment, liver disease, heart disease, cerebrovascular disease, psychosis, current pregnancy or breast feeding, history of known or suspected drug abuse and NSAIDs use within 24 hours before surgery.

120 patients were randomized into three groups. Group C (n = 40) received celecoxib 400 mg orally, group D (n = 40) received parecoxib 40 mg intravenously, and group P (n = 40) received placebo orally. The present study medications were administered one hour before induction. The anesthetists who provided the anesthesia and evaluated the postoperative pain scores were blind to the group assignment. Anesthesia was induced with intravenous thiopental 3-5 mg/kg, fentanyl 2 mcg/kg and maintained with sevoflurane, 66% nitrous oxide in oxygen. Supplemental bolus doses of intravenous fentanyl were administered as nessessary. All the patients were allowed access to a PCA pump (IVAC: PCAM (ALARIS Medical System)) in the post anesthesia care unit (PACU). The PCA device was programmed to deliver 1 ml bolus dose of morphine (1 mg/ml) "on demand", with a lock out interval of 5 minutes and total morphine dose not exceeding 30 mg during any 4 hours interval. If the analgesic remained inadequate after one hour the incrementable dose of morphine was increased to 2 mg. No other analgesia supplement was given. The patients with severe pain that was not adequately controlled by PCA morphine could be withdrawn from the present study. Any patient in this category would not be replaced with a newly enrolled patient.

The pain score, the total amount of morphine, sedation score, nausea and vomiting and pruritus were assessed at 0, 1, 6, 12 and 24 hours after operation. The satisfaction score with pain management was evaluated by using a VNRS at 24 hours after arthoplasty. Postoperative pain was assessed using the VNRS ranging from "0" (no pain) to "10" (worst imaginable pain). Sedation scores were used (1 = awake, 2 = asleep but easily arouse, 3 = drowsy, rousable, 4 = somnolence, difficult to arouse).

Statistical analysis

Sample size of 38 patients per group was calculated for a power of 0.8 and $\alpha = 0.05$ to detect a 20% difference in PCA morphine usage among three groups. The authors enrolled 40 patients per group in the present study. Data are present as mean (SD). To assess for normal, the Kolmogorov-Smirnov (KS) test was performed on the data set.

Demographic data, sedation, nausea and vomiting and pruritus were analysed by the non parametric test (Kruskal-Wallis H test). Pain score and mophine consumption were analyzed by ANOVA. $P < 0.05$ was considered statistically significantly different.

Results

Demographic data, duration of operation and the total amount of intraoperative fentanyl usage were similar among the three groups (Table 1). Mean 24 hour morphine consumption of 10.73 ± 3.20 mg in the parecoxib group and 25.28 ± 5.39 mg in the celecoxib group were significantly lower than that of 37.50 ± 6.78 mg in the placebo group ($p < 0.00$) (Fig. 1). The total morphine consumption at 24 hours postoperative period of the parecoxib and celecoxib groups were reduced by 71.39% ($p < 0.01$) and 32.59% ($p < 0.01$) respectively when compared to the control group. The VNRS score in the parecoxib group was significantly lower than the celecoxib and control groups at 1, 6, 12 ($p < 0.001$) but was similar at 24 hours ($p = 0.121$). The VNRS score was lower in the celecoxib group compared to the control group at 1 and 6 hours after operation ($p = 0.36$, $p = 0.12$ respectively). Pruritus and nausea vomiting were similar but was significantly different for sedation among the three groups ($p = 0.362$, $p = 0.122$ and $p = 0.008$ respectively) (Table 1). The mean satisfaction scores of the parecoxib, celecoxib

Table 1. Demographic characteristics and side effects

Group	Placebo (n = 40)	Parecoxib (n = 40)	Celecoxib (n = 40)
Sex, n (%)			
Male	8 (20.00)	13 (32.50)	11 (27.50)
Female	32 (80.00)	27 (67.50)	29 (72.50)
Age	64.00 ± 7.41	68.05 ± 9.75	68.33 ± 7.59
Duration of operation (min), mean ± SD	128.50 ± 19.22	119.25 ± 23.11	117.50 ± 14.68
Intra operative fentanyl usage (mcg), mean ± SD	132.50 ± 27.85	111.25 ± 21.15	128.75 ± 30.25
Side effect, n (%)			
Sedation	8 (20.00)	0 (0.00)	3 (7.50)
Nausea	8 (20.00)	9 (22.50)	5 (12.50)
Vomiting	0 (0.00)	3 (7.50)	0 (0.00)
Pruritus	2* (5.00)	0 (0.00)	1* (2.50)

* Low grade of pruritus

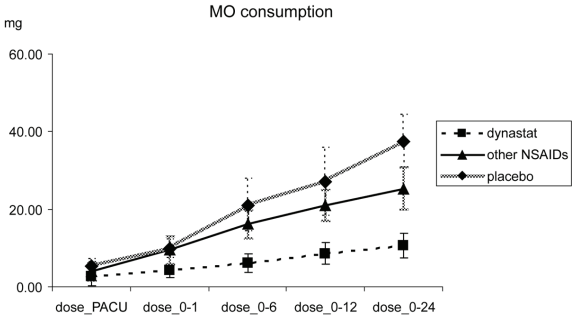

Fig. 1 The mean ± SD morphine consumption at PACU, 1, 6, 12 and 24 hours after operation

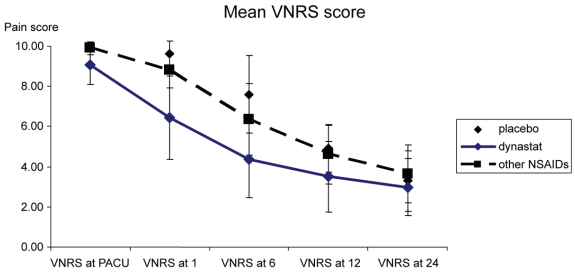

Fig. 2 The mean ± SD VNRS at PACU, 1, 6, 12 and 24 hours after operation

and control group were 9.1 ± 0.3, 9.3 ± 0.2 and 9.2 ± 0.2 respectively which were not significantly different among the three groups.

Discussion

A multimodal analgesic approach is recommended for the management of perioperative pain[1,4,5]. NSAIDs expecially COX-2 inhibitor play an increasing role in the treatment of postoperative pain either on its own or in combination with opioids.

Celecoxib is an oral COX-2 inhibitor, which has a 22% to 40% bioavailability, an analgesic onset of 30-60 minutes. A time to peak concentration of 2 hours after oral administration and the elimination half-life is approximately 11 hours [10]. Parecoxib, a water-soluble prodrug of valdecoxib, is a high-selective COX-2 inhibitor that is available for intravenous administration. The efficacy and duration of analgesia of parecoxib appears to be dose dependent. The time to onset of analgesia occurs 7 to 14 minutes after IV administration of parecoxib 40 mg. Clinically meaningful pain relief (50% reduction in pain) occurs within 17 minutes. The peak analgesic effect occurs within 2 hours, and the duration of analgesia is 5 to 22 hours[10].

Both celecoxib and parecoxib, COX-2 selective inhibitors, have demonstrated opioid-sparing effects following surgery. Elia et al[11] studied a meta-analysis of addition of COX-2 inhibitors to standard PCA morphine for pain control after surgery provided an opioid-sparing effect of 15-55%. Previous studies of 200 mg celecoxib demonstrated analgesic efficacy in patients undergoing dental, orthopedic, and otolaryngological procedures[7,9-14]. Recart et al[15] studied in otolaryngologic surgery showed that celecoxib 400 mg was more effective than 200 mg in reducing severe postoperative pain and the need for rescue analgesic medication in the postoperative period.

Previous studies of addition 40 mg intravenous parecoxib sodium resulted in a significant

reduction of approximately 27-40% in the amount of PCA morphine consumption after operation[16-19]. Barton et al[19] concluded that parecoxib sodium 20 mg and 40 mg have comparable analgesic effects and is as effective as intravenous ketorolec 30 mg after gynecologic laparotomy surgery. Soltesz et al[20] found that parecoxib 40 mg twice daily provides postoperative pain relief equivalent to that of dipyrone 4 g daily during the first 48 hours in patients after hysterectomy.

Gan et al[21] used parecoxib and then valdecoxib in addition to opioids via PCA after laparoscopic cholecystectomy. The present study showed that the use of parecoxib resulted in a reduction of 20% opioids requirement and a reduction in pain severelity by 33%. Desjardins et al[22] demonstrated the median time to rescue medication for patients receiving parecoxib 40-mg was more than 24 hours in dental surgery. The present study found the administration of a 40-mg dose of parecoxib resulted in a significant reduction in VNRS and morphine consumption postoperative period.

The decreasing in opioids consumption is benefit to reduce opioids-related adverse effects. Marrett et al[23] did a meta-analysis of randomized controlled trials to evaluate the risk of morphine adverse effects in patients treated with NSAIDs. NSAIDs decreased significantly postoperative nausea & vomiting and sedation. Pruritus, urinary retention, and respiratory depression were not significantly decreased by NSAIDs. Straube et al[24] studied the effects of preoperative COX-2 selective NSAIDs inhibitor on postoperative outcomes. The study showed no significant decrease in postoperative nausea/vomiting. The present study did not show any reduction of pruritus, urinary retention, nausea/ vomiting or respiratory depression.

Malan et al[25] and Desjardins et al[26] demonstrated both parecoxib and celecoxib admistration resulted in significant improving quality of recovery and patient satisfaction during postoperative period. The present study showed the improvement of postoperative analgesia with parecoxib and celecoxib but failed to influence patient satisfaction and side effects.

One concern regarding the perioperative use of NSAIDs is the possible deleterious effect on osteogenesis. A large body of literature derived from laboratory animal studies suggests that COX-2 inhibitors either delay or inhibit bone healing[27-29]. It suggested that the deleterious effects of COX-2 inhibitors on fracture healing may be reversible with short-term treatment[30]. Gerstenfeld et al[31] have concluded that the management of fracture-associated pain with inhibitors of COX-2 should neither impair nor delay healing as long as the duration of treatment is consistent with current standards of care. In addition to limiting the usage of NSAIDs for short period of time, physicians should prescribe the lowest effective dose for bone surgeries.

In conclusion, within 12 hours after total hip and knee arthroplasty, pre-operative administration of parenteral parecoxib 40 mg is more effective than oral celecoxib 400 mg and placebo in terms of morphine consumption and VNRS score.

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การศึกษาเปรียบเทียบฤทธิแก้ปวดของยา celecoxib และ parecoxib ที่ให้ก่อนผ่าตัด ในผู้ป่วยที่มารับการผ่าตัดเปลี่ยนข้อสะโพกหรือข้อเข่า

วิชัย อิทธิชัยกุลฑล, นฤมล ประจันพาณิชย์, ชุติมา โฆษิตชัยวัฒน์, ธีรยุทธ อินทปัญญ์

ภูมิหลัง: *เทคนิคการนำ nonsteriodal anti inflammatory drugs (NSAIDs) มาใช้ร่วมกับ opioids สามารถบรรเทาปวดหลังผ่าตัดได้ดี และลดอาการข้างเคียงของยาลงได้ NSAIDs มีทั้งชนิดรับประทาน ฉีดเข้ากล้าม และหลอดเลือดดำ*

วัตถุประสงค์: *ทำการศึกษาเปรียบเทียบฤทธิ์แก้ปวดของยา celecoxib และ parecoxib ที่ให้ก่อนผ่าตัด ในผู้ป่วยที่มารับการผ่าตัดเปลี่ยนข้อสะโพกหรือข้อเข่า*

วัสดุและวิธีการ: *โดยทำการศึกษาในผู้ป่วย 120 ราย มีอายุระหว่าง 18 ถึง 75 ปี สภาพผู้ป่วยแบ่งตาม American Society of Anesthesiologists classification ระหว่าง 1 ถึง 2 แบ่งผู้ป่วยเป็น 3 กลุ่ม กลุ่มที่ 1 ผู้ป่วยรับประทาน celecoxib 400 มก. กลุ่มที่ 2 ได้รับ parecoxib 40 มก. ทางหลอดเลือดดำ และกลุ่มควบคุมได้รับยาหลอกรับประทานทั้ง 3 กลุ่ม ได้ยาก่อนผ่าตัด 1 ชั่วโมง หลังผ่าตัดผู้ป่วยได้รับมอร์ฟีน ด้วยเครื่อง patient-controlled analgesia (PCA) ทำการศึกษาระดับความปวด (verbal numerical rating scale, VNRS) จำนวนมอร์ฟีน, ภาวะแทรกซ้อน และความพึงพอใจของผู้ป่วยต่อการบำบัดความปวด*

ผลการศึกษา: *พบว่าจำนวนของการใช้มอร์ฟีนในผู้ป่วยกลุ่ม celecoxib และ parecoxib (กลุ่มศึกษา) มีค่าน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ ($p < 0.01$) ระดับคะแนนปวด (VNRS) ของกลุ่มศึกษามีค่าน้อยกว่ากลุ่มควบคุมที่ 1, 6 และ 12 ชั่วโมง ($p < 0.01$) แต่ไม่แตกต่างกันที่ 24 ชั่วโมง หลังผ่าตัด ($p = 0.32$) ผู้ป่วยกลุ่ม celecoxib ต้องการมอร์ฟีนมากกว่ากลุ่ม parecoxib ทุกช่วงเวลาของการศึกษา ผู้ป่วยกลุ่มควบคุมพบอาการง่วงซึมมากกว่ากลุ่มศึกษาผู้ป่วยทุกกลุ่มมีอาการคลื่นไส้อาเจียน และอาการคันไม่แตกต่างกัน*

สรุป: *ผลการศึกษาการฉีด parecoxib 40 มก. สามารถลดการใช้มอร์ฟีน และระดับความปวดได้ดีกว่าการรับประทาน celecoxib 400 มก. หรือ ยาหลอกในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนข้อสะโพกหรือข้อเข่าภายในระยะเวลา 12 ชั่วโมงหลังผ่าตัด*