Multimodal Pain Management Following Minimally Invasive Total Knee Arthroplasty: An Experience in 3-Dose Parecoxib

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Objective: *To report the results of multimodal pain control with the use of parecoxib following minimally invasive total knee arthroplasty (MIS-TKA).*
Material and Method: *A consecutive series of 103 patients who underwent 122 MIS-TKAs in 120 episodes of admission by a single surgical team was included in the study. A uniform multimodal pain management protocol was used; including 3-dose regimen of parecoxib in patients who had no contraindication. From 12 hours after complete surgery, early ambulation was started according to patient ability. Serial pain scores were recorded, postoperatively. Intravenous tramadol was prescribed for pain rescue as needed.*
Results: *Mean age was 67.5 $\pm$ 7.8 years and 68% of patients had medical co-morbidities. Twelve patients (10%) did not receive parecoxib. Eighty-nine patients of the studied group (86%) could ambulate within 24 hours after surgery. The mean preoperative and postoperative pain scores of the group at 6 hours, 12 hours, 24 hours and 36 hours were 6.9, 2.5, 2.4, 2.2 and 1.8, respectively. The postoperative pain following TKA was rated as satisfied pain relief (pain score < 3), of which, the parecoxib group had less need of tramadol than that of non-parecoxib group (10.2% vs. 33%). There was no fluctuation of postoperative blood pressure, as well as no complication related to the use of 3-dose intravenous parecoxib. The serum creatinine level after the second dose in the parecoxib group was found 0.1 mg/dL higher than those who did not take parecoxib (Δ, 0.3 vs. 0.2 mg/dL). With a variable intravenous fluid rate to maintain adequate hourly urine, the parecoxib group had more volume of 24-hour fluid intake after surgery (3658 vs. 2918 mL).*
Conclusion: *Multimodal postoperative pain control after MIS-TKA provided satisfied postoperative pain relief, and patients receiving parecoxib had less injectable narcotic administration. Although we prevented perioperative inadequate fluid intake, the serum creatinine level was found slightly higher in parecoxib group. Thus, appropriate fluid intake should be considered when parecoxib is prescribed for postoperative pain in TKA.*

Keywords: *Parecoxib, Pain, Postoperative pain, Minimally invasive, MIS, Total knee arthroplasty, TKA, Multimodal*

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Opioids have been using as a high potency analgesics for the treatment of postoperative pain following major orthopedic surgeries. Among them, total knee arthroplasty (TKA) may be considered as one of the most painful procedures. Due to the intensity of pain after the conventional TKA, patients usually require opioids or theirs derivatives for several days to several weeks. While opioids are effectively analgesics, their common adverse effects, such as dizziness, nausea and vomiting may delay patient's ambulation.

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After Tria and Coon[1] introduced the minimally invasive surgery-total knee arthroplasty (MIS-TKA), this less invasive approach has provided very satisfactory results, in terms of patient ambulation and recovery, as it has a shorter skin incision and less muscle cut. Several studies have also shown that the MIS approach decreases postoperative pain[1-6]. Besides the surgical technique, specific anesthetic method and postoperative pain control also play important roles on the early postoperative ambulation of the minimally invasive arthroplasty[2,3]. To accommodate a rapid patient ambulation, a multimodal drug treatment strategy that combines two or more analgesics with different modes of action has been proposed in order to avoid the requirement for intravenous opioids or the use of too much opioids on the day of ambulation. Among medications used in the multimodal analgesia, the selective cyclooxygenase-2 (COX-2) inhibitors are one of them[1-5].

We have started the MIS-TKA since late 2002 with non-specific pain control protocol. Following the learning curve of the MIS-TKA[6], the surgical technique has been modified[7] and the multimodal postoperative pain control with oral COX-2-specific inhibitors has been used for the postoperative pain management[8]. However, due to a decrease of appetite on the postoperative day 0 (POD 0) to day 1 (POD 1), the oral form COX-2 specific inhibitor might not be administered efficiently. Parecoxib[9] is an injectable prodrug formulation of the orally administered COX-2 specific inhibitor, valdecoxib, which is available for short-term management of postoperative pain during the first 24 hours after MIS-TKA. Although two previous trials[10,11] reported its high pain relief efficacy with relatively safe, the risk of adverse events (AEs) or major complications regarding the use of parecoxib after major surgeries, which patients undergo a major physical stress and major hemodynamic change, are still being concerned by many surgeons, especially orthopedic surgeons who perform major surgeries in the elderly who usually have medical co-morbidities.

The objective of this study was to evaluate the results of multimodal pain management with the use of parecoxib in patients who underwent MIS-TKA.

Material and Method

Between February 2004 to August 2007, 103 patients who had late stage of primary knee osteo-arthritis and underwent MIS-TKAs at a single hospital were evaluated. Among 103 patients, 120 episodes of patient admission occurred in 122 MIS-TKA surgeries (17 patients had 2 admissions for staged bilateral TKA, and 2 patients had one-stage bilateral TKA). Patients with one-stage bilateral TKA were determined as a single episode of admission. As patients who underwent staged bilateral TKA had different severity of arthritis or leg alignment, different admissions with a minimum of 4-month interval and different results of blood tests, we considered these different admissions as different episodes of admission for MIS-TKA.

Surgical technique

All surgeries were performed by a single surgical team including anesthesiologist, internist and surgeon. The single MIS-TKA surgical technique included a limited skin incision, minimal quadriceps tendon incision (2-cm tendon splitting), no patella eversion and the use of a mobile skin window. The posterior stabilized knee implant (NexGen-Flex, Zimmer, Warsaw, IN, USA) was used in all knees. In all surgeries, a tourniquet was used and the knee was inserted with a vacuum drain before wound closure. The drain was removed at 12 hours after the surgery.

Anesthesia and postoperative pain management

Epidural analgesia was the primary selected method. Alternatively, for patients who had previous lower back surgery, general anesthesia (GA) was used. Additionally, spinal anesthesia was added with morphine at a 0.2-0.3 mg/dose, only if there was a failed attempt for epidural analgesia. At the end of surgery, the epidural group received an additional epidural fentanyl at the dose of 1 μg/kg, while fentanyl at the dose of 1 μg/kg/hr was given intravenously for 6 hours in the GA group. For the spinal morphine group, no medication was added.

Following the multimodal postoperative pain control standing order, all patients received oral acetaminophen 1,000 mg every 6 hours for 7 doses starting from 6 hours after surgery. Similarly, parecoxib sodium 40 mg was administered intravenously for 3 consecutive doses every 12 hours after skin closure. Parecoxib is contraindicated in patients with a history of sulfonamide allergy, serum creatinine level > 1.5 mg/dL or for the treatment of postoperative pain following coronary artery bypass graft (CABG) surgery. The standing order for intravenous fluid intake was at a variable rate of 100-140 mL/hr in order to keep the urine flow between 20-40 mL/hr. Pain rescue medication was permitted at any time when requested by the patients. Patients in need pain rescue medication were given parenteral tramadol by intravenous injection, 50-75 mg

every 4-6 hours as needed (50 mg/dose for patients with body weight ≤ 70 kg and 75 mg/dose for patients with body weight > 70 kg). Time and dose of pain rescue medication were recorded. To prevent nausea and vomiting, an intravenous drip of metoclopramide was administered for 6 hours.

To avoid an analgesic effect from the anesthesia or from the additional narcotic at the end of surgery, the evaluation of pain which related to the use of parecoxib was determined beginning at 12 hours after completion of surgery and continuing at 24 hours, 36 hours after surgery and at discharge, as well as the evaluation of patient ambulation. The degree of post-operative pain was rated by independent observer (ST) using a visual analog scale; VAS (0 = no pain, 10 = worst possible pain). The pain score at ≤ 3 was defined as a satisfied pain relieving. Safety and tolerability were assessed by monitoring adverse events (AEs). Data of all AEs occurring throughout the study were obtained by observation and indirect question of patients and by assessing changes from baselines in physical examination, vital signs, and clinical laboratory values. Renal function was measured by serum creatinine (Cr) and blood urea nitrogen (BUN).

Postoperative ambulation

Patients were encouraged to move the operated foot and ankle immediately when they could control their lower limbs. As all surgeries were finished around 6 PM, a voluntary upright sitting was evaluated in the morning of POD 1, at 12-hour postoperative period. If patients were able to sit and stand up without dizziness, patients were allowed to walk with a walking aid. The total walking time was started from a minimum of 15 minutes on the first day of ambulation, then a minimum of 30 minutes on the second day and a minimum of 1 hour on later days. More daily activities were continued until patients were allowed to discharge, which usually occurred between POD 3 and POD 5. Discharge criteria included ability to flex the operated knee to 90 degrees and ability to walk independently with a walking aid with a minimum of 1 hour per day.

Statistical analysis

The demographic and perioperative data, ambulation ability, pain scores, and routine postoperative blood tests were evaluated by an independent observer (ST). The descriptive statistics was applied for all variables by means and standard deviations or percentage.

Results

Demographic data

Of the 103 patients enrolled into this study, 90 were females and 13 were males. The average age at the time of surgery was 67.5 ± 7.8 years (range, 46-85). The mean Body Mass Index (BMI) was 27.5 ± 3.8. Sixty-eight percent of patients had medical co-morbidities (Fig. 1), which hypertension was the most common co-morbidities found in 38% patients (n = 39). The mean preoperative range of knee motion was 7.5-116.3 degrees. In 120 episodes of admissions, the epidural anesthesia, the spinal anesthesia with morphine and the GA were provided in 93 cases, 20 cases and 7 cases, respectively. The mean total operative time was 105 ± 38 min. The average blood collected from the drain was 408 ± 292 mL. Mean baseline pain scores as measured on the VAS were 6.9 (range, 4-9).

Postoperative ambulation

Two patients could ambulate at 10 hours after surgery (less than 12-hour postoperative period), while 87 patients (84%) could ambulate at 12-hour postoperative period. All patients could achieve ambulation according to the protocol (sit-stand-walk) within 24 hours, postoperatively. There was no surgical complication; however, 10 cases developed slightly wound drainage up to 5 days without any further evidence of infection. At discharge, all patients went home with self rehabilitation educational program. No complication occurred during the 12-month follow-up period, as well as readmission for any reason.

Parecoxib group vs. Non-parecoxib group

Parecoxib was not given in 12 of 103 patients (10%) because of contraindication. After surgery, serial pain scores of the studied group were classified as satisfied (≤ 3) from 12-hour postoperative period to the day of discharge (Fig. 2). There was decreasing of serial pain scores in both groups; however, patients receiving parecoxib had more decreased serial pain

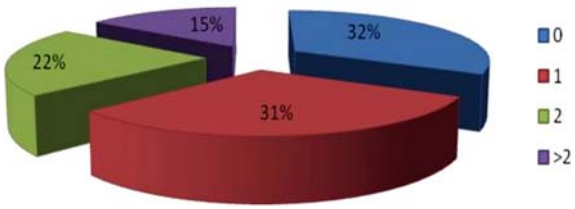

Fig. 1 Medical co-morbidities in studied patients (n = 103)

score than those who did not receive parecoxib (Fig. 3). The proportion of patients who took pain rescue medication (intravenous tramadol) in the parecoxib and non-parecoxib group was 10.2% and 33.0%, respectively. There was no serious adverse event reported related to parecoxib.

During 36-hour period after the administrative 3-dose parecoxib, no abnormal fluctuation of blood pressure was observed in patients. Base on the variable intravenous fluid rate to keep urine at a minimum 20 mL/hr, the average 24-hour fluid intake/output after surgery of the parecoxib group was found higher than that of the non-parecoxib group (Fig. 4). In both groups, there were increased BUN and creatinine level from baseline (Fig. 5). However, the elevated creatinine level in the parecoxib group was averaged 0.1 mg/dL higher than the changed level of the non-parecoxib group. These changes were not considered to clinically meaningful.

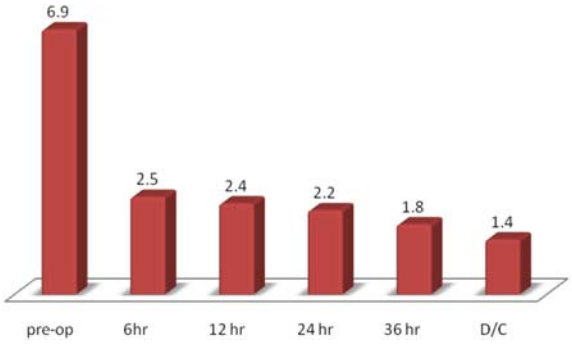

Fig. 2 Mean pain scores from the preoperative period to the postoperative period at 6 hours, 12 hours, 24 hours, 36 hours and at the day of discharge of the studied group

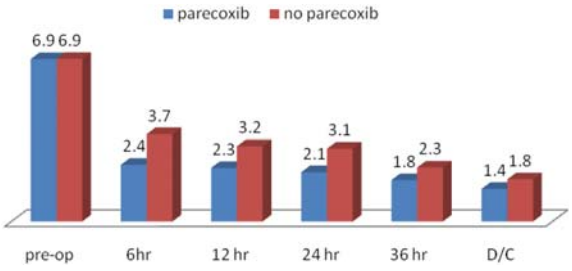

Fig. 3 Comparison of pain score changes in parecoxib and non-parecoxib group from the preoperative period to the immediate postoperative period and POD 1 to POD 3 and at discharge

Among 17 patients who had staged bilateral TKA, 13 of them had parecoxib administration. Table 1 shows the transient raising in BUN and creatinine levels monitored at the first and the second pre- and postoperative admission in 13 patients treated with parecoxib.

Discussion

Recently, multimodal pain control has been recommended in order to minimize the amount of strong narcotics. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly medication used in multimodal postoperative pain control; however, the use of traditional NSAIDs are limited by side-effects which include impaired coagulation, gastrointestinal complications, cardiac side-effects and renal dysfunction. Cyclooxygenase (COX)-2 specific inhibitors[13] were developed in an attempt to obtain the therapeutic benefits of NSAIDs while decreasing gastrointestinal side-effects. Parecoxib[9] is the first injectable COX-2-specific inhibitor approved for short-term treatment of postoperative pain. Although previous short-term studies of noncardiac surgical patients receiving

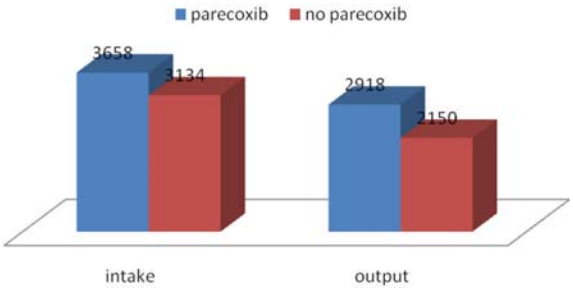

Fig. 4 Comparison of average 24-hour fluid intake and output in mL of parecoxib and non-parecoxib group

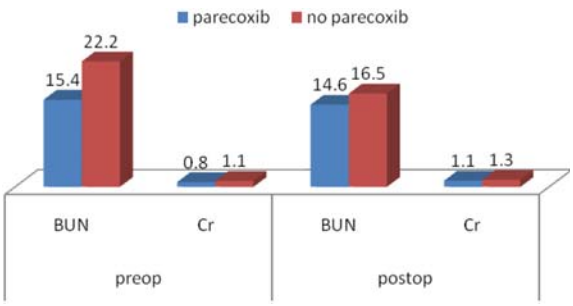

Fig. 5 Pre- and postoperative changes in BUN and Cr of parecoxib and non-parecoxib groups

Table 1. Transient changes in BUN and Cr during preoperative and postoperative periods of the first and second admissions in 13 parecoxib patients

1st admission				2nd admission				Value difference (1st vs. 2nd preoperative)		Time difference
Preoperative		Postoperative		Preoperative		Postoperative				
BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	BUN	Cr	Month
26.6	0.95	24.1	0.92	18.1	0.7	15.4	0.68	-8.5	-0.25	3
14.1	0.66	19	0.75	16	0.69	20.6	0.93	1.9	0.03	4
8.5	0.62	10	0.65	10	0.61	13.1	0.67	1.5	-0.01	14
33.4	1.82	26.4	1.44	29	1.51	30	1.55	-4.4	-0.31	7
19	0.7	13.3	0.77	11.8	0.52	12.2	0.84	-7.2	-0.18	3
12.1	0.72	15.5	0.9	11.3	0.75	10.3	0.69	-0.8	0.03	5
15.2	0.84	18.5	1.04	20.2	0.99	15	1.01	5	0.15	13
20.5	1.21	22.3	1.25	19.8	1.23	22.1	1.17	-0.7	0.02	12
15.7	0.79	14.5	0.99	16.1	0.71	15.8	0.84	0.4	-0.08	9
17.1	0.75	16.6	0.81	16.7	0.68	17.1	0.7	-0.4	-0.07	7
10.6	1.07	12.6	1.15	11.3	0.99	15.4	1.1	0.7	-0.08	4
14.8	0.69	18.8	0.71	10.4	0.68	12	0.9	-4.4	-0.01	12
12	0.62	12	0.74	14.6	0.68	16.9	0.7	2.6	0.06	4

parecoxib for orthopedic procedures have not revealed any serious adverse effects[14-18], complications related to COX-2 inhibitor which may compromise postoperative patient conditions are still being concerned.

In the present study, we used multimodal pain control regimen including prolonged local anesthetic methods (spinal or epidural analgesia) or intravenous narcotic (fentanyl), NSAID (parecoxib) and simple analgesic (acetaminophen). As prolonged local anesthesia or the intravenous narcotics was discontinued for an approximately 6 hours prior to starting of ambulation, it minimized dizziness, nausea or vomiting at the time of ambulation. In addition, patient functions were found to improve until discharge corresponding to the decreasing pain scores. Although the serial mean postoperative pain scores and the percentage of tramadol needed in the parecoxib group were lower than those of non-parecoxib group, the patients in the non-parecoxib group were relatively less physical fit than that of parecoxib group. Because the number of the non-parecoxib group was too small, thus the comparative statistical test was not performed as we considered the data of both groups were not comparable.

According to the present study, the postoperative level of creatinine increased in both groups, and the parecoxib group had a 0.1 mg/dL higher level than that of the non-parecoxib group. As the most total knee replacements are performed with the bloodless filed, the fluid replacement according to bloodless field and visible blood loss at the perioperative period may not be adequate. Postoperatively, the visible blood collected in the vacuum drain is about 300-1000 mL[19,20], which is approximately 51% of the total blood loss[21]. Thus, it could be possible that patients had some degree of dehydration after TKA. The COX-2 inhibitor administration can impair the renal blood flow due to the decrease of prostacyclin[22]. Additionally, the recent study[23] demonstrated that parecoxib related to reduction of renal blood flow in the elderly who underwent orthopedic surgery. Therefore, it was explainable why patients in the parecoxib group had a higher level of serum creatinine. However, increasing serum creatinine level was a transient effect after patients returned to adequate hydration. We found that, in patients who came at the second admission for the contralateral knee replacement, the serum creatinine levels were decreased from those of the postoperative level of the first admission.

Prescription of parecoxib for acute postoperative pain control after TKA may draw surgeon's major concern of renal problem from combined effect of COX-2 inhibitors and inadequate hydration. As the variable intravenous fluid rate to achieve a minimum of 20 mL/hr of urine output demonstrated that the overall 24-hour intravenous fluid in the parecoxib group was much higher than that of non-parecoxib group without any adverse events, we propose that 3-dose parecoxib

for acute postoperative pain after TKA should be prescribed with adequate fluid intake for keeping a proper urine output in order to avoid renal impairment.

According the intention for a short-term usage, the analgesic effect of 3-dose parecoxib in multimodal pain control decreased pain rescue medication. The first dose of parecoxib, which was injected at the time of wound closure, provided an additive pain control effect to any one of 3 anesthetic methods. The second and the third doses were administered when the patient started to ambulate which the pain control effect would cover for a 24-hour period. On the POD 2, when the pain was decreased and all patients could have normal appetite, the oral form of pain medication could be applied.

The limitation of this study was a case series, which preselected patients whether to receive parecoxib or not. According to the strict indication to use parecoxib, the number of patients who did not take parecoxib was too small to be compared with that of parecoxib group. Thus, the comparative statistical test on parecoxib and non-parecoxib groups was not done in this study. However, the strength of this study is a consecutive series of few variable factors in terms of surgical team and technique, pain management protocol, and early ambulation protocol, which reported results of the use of parecoxib injection in elderly patients who usually have medical co-morbidity.

Conclusion

The multimodal postoperative pain control combined with 3 doses of parecoxib in MIS-TKA for selected elderly patients provided satisfied results, in terms of pain relief, early ambulation and adverse events. Due to more fluid intake at the first 24 hours after surgery observed in parecoxib group without any adverse event, adequate hydration should be considered when parecoxib is prescribed.

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การควบคุมอาการปวดด้วยวิธี Multimodal หลังจากการผ่าตัดเปลี่ยนข้อเข่าเทียม: ประสบการณ์การใช้ยา Parecoxib แบบ 3 ครั้งต่อเนื่องกัน

อารี ตนาวลี, สาธิต เที่ยงวิทยาพร

วัตถุประสงค์: *เพื่อรายงานผลการควบคุมอาการปวดหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม วิธีเนื้อเยื่อบาดเจ็บน้อย โดยวิธีการให้ยาระงับปวดแบบผสมผสาน (multimodal pain management) โดยใช้ยา parecoxib ร่วมกับยาตัวอื่น*

วัสดุและวิธีการ: *ทำการติดตามผู้ป่วยอย่างเรียงลำดับจำนวน 103 ราย ซึ่งได้พักรักษาตัวที่โรงพยาบาล 120 ครั้ง เพื่อทำการผ่าตัดข้อเข่า 122 เข่า โดยคณะศัลยแพทย์ชุดเดียวกัน และใช้วิธีการควบคุมอาการปวด หลังการผ่าตัดแบบเดียวกันโดยผู้ป่วยที่ไม่มีข้อห้ามใช้ยา parecoxib จะได้รับยาแบบ 3 ครั้งติดต่อกัน ตั้งแต่เวลา 12 ชั่วโมง หลังการผ่าตัดเป็นต้นไป ผู้ป่วยเริ่มการฝึกนั่ง ยืน จนถึงการเดิน ตามความสามารถของผู้ป่วย โดยผู้ป่วยได้รับยาฉีดแก้ปวด tramadol หากยังมีอาการปวดมาก*

ผลการศึกษา: *ผู้ป่วยมีอายุเฉลี่ย 67.5 ปี และร้อยละ 68 ของผู้ป่วยทั้งหมดมีโรคร่วม (medical co-morbidity) ผู้ป่วยจำนวน 12 ราย (ร้อยละ 10) ไม่ได้รับยา parecoxib จากการศึกษาพบว่าผู้ป่วย 89 ราย (ร้อยละ 86) เดินได้ภายใน 24 ชม. หลังการผ่าตัด ค่าเฉลี่ย pain score ก่อนการผ่าตัดของผู้ป่วยทั้งหมด คือ 6.9 และหลังการผ่าตัด ที่ 6, 12, 24 และ 36 ชม. คือ 2.5, 2.4, 2.2 และ 1.8 ตามลำดับ โดยกลุ่มที่ได้รับ parecoxib ต้องการยาแก้ปวด tramadol ชนิดฉีดน้อยกว่ากลุ่มที่ไม่ได้รับ parecoxib (ร้อยละ 10.2 กับ ร้อยละ 33) ไม่พบการแปรปรวนของความดันเลือด หรือภาวะแทรกซ้อนจากการใช้ยา parecoxib แบบ 3 doses อย่างไรก็ตามค่าเฉลี่ย serum creatinineในผู้ป่วยที่ได้รับยา parecoxib ครั้งที่ 2 มีค่าสูงกว่ากลุ่มที่ไม่ได้รับยา parecoxib อยู่ 0.1 มิลลิกรัมต่อเดซิลิตร (D, 0.3 กับ 0.2 มิลลิกรัมต่อเดซิลิตร) ทั้งที่ได้รับสารน้ำมากกว่ากลุ่มที่ไม่ได้รับยา parcoxib*

สรุป: *ในการระงับอาการปวดหลังการผ่าตัด MIS-TKA ด้วยวิธีการให้ยาแบบผสมผสานได้ผลเป็นที่พอใจ โดยผู้ป่วยที่ได้รับยา parecoxib ชนิดฉีดติดต่อกัน 3 ครั้ง มีความต้องการยาแก้ปวด narcotic น้อยกว่าผู้ป่วยที่ไม่ได้ parecoxib แต่เนื่องจากผู้ป่วยกลุ่มที่ได้รับ parecoxib มีค่า creatinine ในซีรัมหลังการผ่าตัดเพิ่มขึ้นสูงกว่ากลุ่มที่ไม่ได้รับยาอยู่เล็กน้อย คณะผู้วิจัยมีความเห็นว่าควรให้สารน้ำในปริมาณที่เพียงพอ เมื่อมีการใช้ parecoxib สำหรับรับอาการปวดหลังการผ่าตัดเปลี่ยนข้อเข่าเทียม*