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# Do Nonsteroidal Anti-Inflammatory Drugs Affect Tissue Healing After Arthroscopic Anterior Cruciate Ligament Reconstruction?

Authors' Contribution:  
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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** Experimental studies have reported nonsteroidal anti-inflammatory drugs (NSAIDs) could impair tendon healing. The purpose of this study was to investigate whether NSAIDs could affect recovery of knee joint function in patients after anterior cruciate ligament (ACL) reconstruction.

**Material/Methods:** We enrolled 40 patients treated with celecoxib and 40 patients treated with tramadol, who underwent ACL reconstruction from January 2011 to December 2017. Visual analogue scale (VAS) and functional outcomes were collected and evaluated. The follow-up period was 12 months.

**Results:** In both groups, all patients obtained pain release after surgery, compared with that before surgery. But no significant differences were observed between the 2 groups in VAS scores. We also did not find any differences between the 2 groups at 1 year of follow-up, in terms of anterior drawer test, Lachman test, side-to-side laxity assessed by KT-2000, IKDC score, Lysholm score, and Tegner scale. However, the celecoxib group showed a reduced incidence of nausea compared to the tramadol group ( $P=0.048$ ).

**Conclusions:** The use of NSAIDs after ACL reconstruction is relatively safe and could decrease adverse side effects which were caused by opioid drugs.

**MeSH Keywords:** **Anterior Cruciate Ligament Reconstruction • Anti-Inflammatory Agents, Non-Steroidal • Tendon Injuries**

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## Background

Anterior cruciate ligament (ACL) tear is a common injury among people who take an active part in sports, with an incidence of about 8 per 10 000 person-years in the general population [1]. Among various treatment options, ACL reconstruction has become the top choice of orthopedics doctors, for ligament reconstruction could help patients re-obtain relatively normal knee function and potentially delay consequent osteoarthritis [2–4]. It has been estimated that there are 329–435 per 1 000 000 person each year from 1994 to 2006 who receive ACL reconstruction in the United States [5]. Although numerous studies have reported excellent subjective and objective outcomes after ACL reconstruction, satisfactory results require careful postoperative nursing and rehabilitation. During the early postoperative period, effective control of postoperative pain could obtain good results through rehabilitation, which might achieve better shoulder function and return to normal life as soon as possible.

Many treatment methods, including drug therapy, cryotherapy, and regional nerve block, have been introduced to control pain. Among these methods, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are the 2 commonest types of oral medications used to control pain [6,7]. However, adverse side effects caused by oral medications are an annoying problem. Opioid drugs could result in nausea, sedation, constipation, vomiting, and respiratory depression [8]. On the other hand, due to inhibition of cyclooxygenase (COX)-1 and disturbance of platelet function, traditional nonselective NSAIDs might lead to gastrointestinal toxicity and bleeding [9,10].

In recent years, selective COX-2 inhibitors, including celecoxib, have become more popular because they can provide similar effect in pain control and reduce incidence of side effects of traditional NSAIDs and opioid [11]. However, recent basic science studies have reported selective COX-2 inhibitors could impair tendon-to-bone healing, weakening mechanical stability of joints [12,13]. Whether selective COX-2 inhibitors postpone healing of ACL resulting in reduced functional outcomes remains unclear. Therefore, we performed this study to compare the clinical outcomes between celecoxib (a selective COX-2 inhibitor) and tramadol (an opioid drug) in patients undergoing ACL reconstruction.

## Material and Methods

The present study was approved by the Clinical Ethics Committee of Shanghai Tenth People's Hospital affiliated with Tongji University. Written informed consent was obtained from each study participant.

In this study, we enrolled a total of 80 patients older than 18 years old who received single-bundle ACL reconstruction using hamstrings tendon autografts from January 2011 to December 2017. All patients with ACL ruptures were diagnosed with magnetic resonance imaging images and positive physical examination and confirmed by arthroscopy. Exclusion criteria was as follows: 1) insufficient data regarding patients' medical records; 2) revision due to infection; and 3) other knee ligament injury requiring surgical treatment. Among 80 patients, there were 40 patients who received celecoxib (200 mg twice a day, oral) and 40 patients who took tramadol (50 mg twice a day, oral).

All surgical procedures were performed by the same senior surgeon. All patients received the same rehabilitation protocol. Normal daily activities with brace were allowed from postoperative day 1. Full range of motion was allowed at an average of 4 to 6 weeks postoperatively. Straight line running was allowed after postoperative at half a year. Return to full sports participation was allowed after 9 months post-surgery. All patients took the initial postoperative oral medications at 3 hours after surgery. Subsequent medications were assigned according to the instructions.

### Outcome assessments

All perioperative data were collected. All patients were followed up at 1, 3, 6, and 12 months after operation. At these time points, we evaluated clinical outcomes, including visual analogue scale (VAS), anterior drawer test, Lachman test, Pivot shift test, knee stability using KT-2000, and functional assessments. Functional assessments included International Knee Documentation Committee (IKDC) subjective evaluation form, Lysholm score, and Tegner scale [14–16].

### Statistical analysis

All statistical analyses were conducted with SPSS software (version 18.0). Frequencies and descriptive statistics were used for all data of demographics and outcomes. Continuous variables were presented as mean  $\pm$  standard deviation (SD). Comparison of continuous variables between the 2 groups was analyzed using Student's *t*-test. Comparison of categorical outcomes between the 2 groups was determined using chi-square test. A  $P < 0.05$  was considered to be statistically significant.

## Results

All demographics of patients in this study are listed in Table 1. Among a total of 80 patients, 40 patients were included in the celecoxib group and 40 patients in the tramadol group. There was no significant difference between the celecoxib group and tramadol group in terms of age, gender, body mass index

**Table 1.** Demographic and baseline clinical characteristics of patient in this study.

	Celecoxib (n=40)	Tramadol (n=40)	P value
Age, y	29±8.9	27±9.2	0.326
Gender, Male/Female	29/11	27/13	0.626
Body mass index	24.6±3.12	25.1±2.91	0.461
Side of injury, right/left	24/16	26/14	0.644
Associated meniscal injury	13	14	0.813
Associated chondral defect	1	2	0.556
Time from injury to surgery in months	5.6±4.7	6.2±5.1	0.586
Follow-up in months	12	12	–

**Table 2.** VAS Scores pre- and post-operation.

	Celecoxib (n=40)	Tramadol (n=40)	P value
Preoperative VAS score	6.4±2.1	6.1±2.3	0.544
VAS score at 3 days after surgery	4.6±1.9	4.3±2.0	0.494
VAS score at 2 weeks after surgery	3.3±1.6	3.1±1.8	0.601
VAS score at 3 months after surgery	2.2±1.4	2.4±1.3	0.510
VAS score at 6 months after surgery	1.1±0.8	1.2±1.1	0.643
VAS score at 1 year after surgery	0.9±0.8	0.7±1.1	0.355

(BMI), and side of injury. There were 13 patients in the celecoxib group and 14 patients in the tramadol group who had ACL rupture associated with meniscal injury. Regarding to the associated chondral defect, there were 1 patient in the celecoxib group and 2 patients in the tramadol group, suggesting no difference. All participants had followed up for at least 1 year after surgery. At 12 months, no patient was lost in follow-up of this study.

We used VAS scores to evaluate the pain degree of the patients (Table 2). In both groups, the mean VAS scores were decreased after surgery, compared with that before surgery. However, there were no significant differences between the 2 groups in VAS scores at 3 days, 2 weeks, 3 months, 6 months, or 12 months after ACL reconstruction.

We next assessed knee stability of patients after ACL reconstruction. Table 3 presents the evaluation of knee instability at postoperative 1 year. The proportions of patients who had positive anterior drawer test in the celecoxib and tramadol groups were 22.5% (9 out of 40) and 27.5% (11 out of 40), indicating no significant difference. With regard to the Lachman test (positive, 25% in the celecoxib group and 20% in the tramadol group;  $P=0.592$ ) and pivot shift test (positive, 17.5% in the celecoxib group and 22.5% in the tramadol group;  $P=0.781$ ), no

significant differences were observed between the 2 groups. We also used KT-2000 to assess knee stability. There were no patients in both groups who revealed a side-to-side difference greater than 5 mm. A total of 29 (72.5%) in the celecoxib group and 27 (67.5%) in the tramadol group showed a side-to-side difference of less than 3 mm. All patients in both groups obtained normal knee stability. However, no significant difference was revealed in side-to-side laxity assessed by KT-2000 between the 2 groups. Table 4 lists subjective functional outcomes at 1 year after surgery. We still found no significant difference between the 2 groups, in term of IKDC score, Lysholm score, and Tegner scale.

Finally, we compared the adverse side effects of the 2 drugs (Table 5). We found that patients who took tramadol had higher incidence of nausea compared to those who received celecoxib ( $P=0.048$ ).

## Discussions

The purpose of this study was to investigate the effect of a selective COX-2 inhibitor on the clinical outcomes, in view of its inhibitory role on tendon-to-bone healing which was reported previously in basic research. The findings of the current

**Table 3.** Evaluation of knee instability at postoperative 1 year.

	Celecoxib (n=40)	Tramadol (n=40)	P value
Anterior drawer test, positive (%)	9 (22.5%)	11 (27.5%)	0.605
Lachman test, positive (%)	10 (25%)	8 (20%)	0.592
Pivot shift test, positive (%)	7 (17.5%)	9 (22.5%)	0.781
KT-2000 (mm)			0.626
<3mm	29 (72.5%)	27 (67.5%)	–
3–5 mm	11 (27.5%)	13 (32.5%)	–
>5 mm	0	0	–

**Table 4.** Postoperative outcomes at 12 months after surgery.

	Celecoxib (n=40)	Tramadol (n=40)	P value
IKDC score	81.7±12.1	80.2±12.8	0.592
Lysholm score	88.6±6.9	87.1±5.9	0.299
Tegner scale	6.8±1.4	7.1±1.5	0.358

**Table 5.** Incidence of adverse effects.

	Celecoxib (n=40)	Tramadol (n=40)	P value
Postoperative 3 days			
Nausea	1	6	0.048
Somnolence	2	4	0.395
Gastrointestinal disorders	4	2	0.395
Pruritus	0	1	0.314
Bruising	0	0	–
Postoperative 2 weeks			
Nausea	1	4	0.165
Somnolence	1	2	0.556
Gastrointestinal disorders	5	4	0.723
Pruritus	0	0	–
Bruising	0	0	–

study showed that celecoxib did not affect clinical outcomes for patients undergoing ACL repairs, similar to tramadol. Furthermore, celecoxib could lead to less adverse side effect than tramadol. Therefore, celecoxib seemed to be more satisfactory than tramadol.

The ACL is an important structure providing anterior and rotational stability of the knee joint [17,18]. ACL rupture could lead to pain, a popping sound during injury, instability of the knee, and joint swelling. Without effective treatment, ACL rupture

could develop osteoarthritis of knee in future. Numerous studies in recent years have reported excellent outcomes in patients undergoing ACL reconstruction [17,19,20]. However, it is a major concern that failure rate of ACL reconstruction was reported from 1.4% to 18% [21–24]. Many factors might affect outcomes after ACL reconstruction, including surgeon's technique, perioperative nursing, and postoperative rehabilitation. Among these factors, postoperative pain and inflammatory control are very crucial for tendon healing during perioperative period or postoperative rehabilitation period. Although various studies have

demonstrated that pain patients experienced less pain after arthroscopic surgery than that after open surgery, pain is still of significance after arthroscopic surgery [25]. It is well established that NSAIDs is applied in modern multimodal pain therapy [26]. In addition, NSAIDs are commonly reported to prevent those common adverse side effects of opioids, including sweating, dizziness, nausea, vomiting, loss of appetite and dysuria [27].

Although NSAIDs have so many advantages, these drugs have been reported to potentially impair musculoskeletal healing in several previous basic experimental studies [12,13,28,29]. These experimental studies found that NSAIDs could have a negative effect in decreasing inflammatory cell signaling during inflammatory and proliferative phase of tendon healing. Furthermore, selective COX-2 inhibitors have been recently very popular because they could avoid inhibitive effects on COX-1 preventing adverse side effects of traditional NSAIDs. However, the performance of selective COX-2 inhibitors used in clinic remains unclear. Several experimental studies of NSAID treatment on rats have revealed NSAID could impair healing of supraspinatus reattachment, patellar tendon reattachment, and the Achilles tendon [30–33]. To our knowledge, our study is the first time to investigate whether celecoxib could affect functional healing in patients undergoing ACL reconstruction. Our study did not reveal an impaired effect of celecoxib on tendon healing, with excellent functional healing in patients at 1 year after ACL reconstruction. Therefore, celecoxib could reduce those adverse side effects of tramadol.

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Several limitations in the present study should be concerned. First, this is a retrospective study carried out at a single institution, and thus it is inevitable to lead to a selection bias. Second, we should expand the sample size to do further research because sample size in this study is relatively small. Finally, additional analgesia was required 2 weeks after surgery that could affect the outcomes in this study.

## Conclusions

This is the first study to investigate the effect of use of NSAIDs on tissue healing after arthroscopic anterior cruciate ligament reconstruction. The findings from our study indicated that use of celecoxib in the short term after ACL reconstruction is safe and could release postoperative pain. Furthermore, celecoxib could lead to less adverse side effect than tramadol. Therefore, celecoxib seemed to get more attention in the clinic. However, in view of some limitations, further studies involving randomized controlled design with larger sample size will be urgently needed.

## Competing interests

None.

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