

# Do Different Cyclooxygenase Inhibitors Impair Rotator Cuff Healing in a Rabbit Model?

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## Abstract

**Background:** The effect of selective and non-selective cyclooxygenase (COX) inhibitors on tendon healing was variable. The purpose of the study was to evaluate the influence of non-selective COX inhibitor, ibuprofen and flurbiprofen axetil and selective COX-2 inhibitor, celecoxib on the tendon healing process in a rabbit model.

**Methods:** Ninety-six New Zealand rabbits were used as rotator cuff repair models. After surgery, they were divided randomly into four groups: Ibuprofen ( $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), celecoxib ( $8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), flurbiprofen axetil ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), and control group (blank group). All drugs were provided for 7 days. Rabbits in each group were sacrificed at 3, 6, and 12 weeks after tendon repair. Tendon biomechanical load failure tests were performed. The percentage of type I collagen on the bone tendon insertion was calculated by Picric acid Sirius red staining and image analysis. All data were compared among the four groups at the same time point. All data in each group were also compared across the different time points. Qualitative histological evaluation of the bone tendon insertion was also performed among groups.

**Results:** The load to failure increased significantly with time in each group. There were significantly lower failure loads in the celecoxib group than in the control group at 3 weeks ( $0.533 \text{ vs. } 0.700, P = 0.002$ ), 6 weeks ( $0.607 \text{ vs. } 0.763, P = 0.01$ ), and 12 weeks ( $0.660 \text{ vs. } 0.803, P = 0.002$ ), and significantly lower percentage of type I collagen at 3 weeks ( $11.5\% \text{ vs. } 27.6\%, P = 0.001$ ), 6 weeks ( $40.5\% \text{ vs. } 66.3\%, P = 0.005$ ), and 12 weeks ( $59.5\% \text{ vs. } 86.3\%, P = 0.001$ ). Flurbiprofen axetil showed significant differences at 3 weeks (failure load:  $0.600 \text{ vs. } 0.700, P = 0.024$ ; percentage of type I collagen:  $15.6\% \text{ vs. } 27.6\%, P = 0.001$ ), but no significant differences at 6 and 12 weeks comparing with control group, whereas the ibuprofen groups did not show any significant difference at each time point.

**Conclusions:** Nonsteroidal anti-inflammatory drugs can delay tendon healing in the early stage after rotator cuff repair. Compared with nonselective COX inhibitors, selective COX-2 inhibitors significantly impact tendon healing.

**Key words:** Biomechanical; Cyclooxygenase Inhibitors; Healing; Histological; Rotator Cuff

## INTRODUCTION

The rotator cuff tear is among the most common tendinopathy diseases. "How to guarantee tendon healing" has become one of the challenges after tendon repair. The inflammatory reaction is considered mandatory for tendon healing. Any factors that progress or delay inflammation will affect the tendon healing process.<sup>[1-3]</sup>

Although nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly administered during the postoperative period of rotator cuff repair because of their ability to reduce pain, their influence on tendon healing has come under investigation. Previous studies have shown that NSAIDs inhibit soft tissue healing.<sup>[1,2]</sup>

To our knowledge, however, few studies have examined the effect of different cyclooxygenase (COX) inhibitors on rotator cuff healing. The purpose of this research was to evaluate the effect of different COX inhibitors on the tendon healing process, based on an animal rotator cuff repair model.

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## METHODS

### Study design

The rabbit rotator cuff was chosen for this study because of its anatomical similarities to the human shoulder. After approval from our Institutional Animal Care and Use Committee, we obtained 96 mature, male New Zealand white rabbits with a mean preoperative weight of 2.5 kg. They were fed and housed for 1 week preoperatively. The right supraspinatus tendon of each rabbit was then detached as a massive tear and then repaired by the bone tunnel suture technique. Postoperatively, the animals were divided randomly into four groups: ibuprofen, celecoxib, flurbiprofen axetil, and control group (blank group). The animals were sacrificed at 3, 6, and 12 weeks, and the tissues were analyzed using histological and biomechanical testing.

### Surgical technique

According to our previous animal models,<sup>[3]</sup> the rabbits were anesthetized by intraperitoneal injection of xylazine hydrochloride (0.2 ml/kg). The supraspinatus was identified through the deltoid splitting approach. The tendon was dissected from the greater tuberosity (GT), and 5 mm × 5 mm tendon tissue was removed from the end. The tuberosity was gently roughened and debrided. Bone tunnels were created at the anterior and posterior extents of the insertion. A modified Mason-Allen stitch using an Orthocord suture (Johnson and Johnson, Piscataway, NJ, USA) was placed into the supraspinatus tendon. The suture ends were then passed through the bone tunnels and tied, which repaired the supraspinatus tendon to the GT. The incision was closed in

layers. Penicillin was administered intramuscularly in the first 3 days post-operatively at a dose of  $0.8 \times 10^6$  U/d [Figure 1a-c].

### Animal experimentation

The rabbits were randomly assigned to 4 groups postoperatively (24 rabbits per group). The first group received ibuprofen ( $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), the second group received celecoxib ( $8 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), the third group received flurbiprofen axetil ( $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ ), and the fourth group received no drug for control. The ibuprofen and celecoxib were mixed into a standard diet, and the flurbiprofen axetil was administered intravenously. All drugs were provided for 7 days postoperatively. The rabbits were then sacrificed at 3, 6, and 12 weeks. Within each group of 8 rabbits, 4 specimens were used for biomechanical testing, and 4 were used for histological analysis. Both shoulders of each rabbit were thawed at room temperature before biomechanical testing.

### Biomechanical testing

The humerus with attached supraspinatus was meticulously dissected from the surrounding tissues. The specimen was then placed into an MTS-858 biomechanical testing system (MTS Co., USA) and secured in a custom designed jig. The distal humeral end was embedded in denture base resin. The specimen was preloaded to 2.5 N and then loaded to failure at a speed of 1 mm/s. The maximum load at failure in both sites of each specimen was recorded, and the percentage of maximum load on the repair side compared with the normal side was calculated and compared among different groups [Figure 1d].

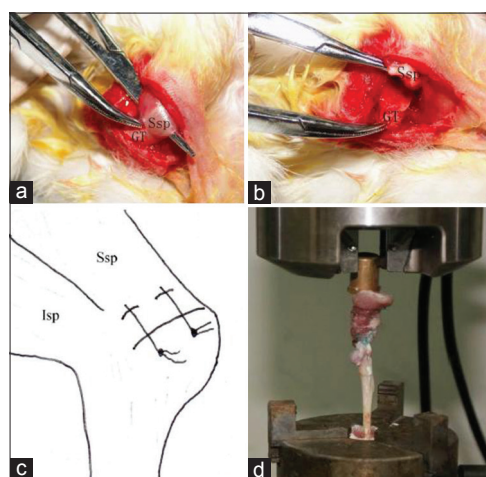
### Histological analysis

The tissue specimens were fixed in 10% neutral buffered formalin for 76 h and then decalcified, dehydrated, and embedded in paraffin. Five-micrometer-thick sections that included the repaired supraspinatus tendon and the GT were cut in the coronal plane and then stained with hematoxylin and eosin. The appearance of the repair site was then evaluated qualitatively.

Picric acid sirius red staining was used for quantitative analysis of the collagen content in the bone tendon insertion. Collagen I appeared to be yellowish red, and collagen III appeared to be green with polarized light illumination. By quantifying different colors in one image using the Image-Pro Plus 6.0 software (Media Cybernetics, MD, USA), the distribution and maturation of the two types of collagens in the bone tendon insertion could be calculated and compared among different groups. Three different areas in the bone tendon insertion were selected and examined to reduce sampling error.

### Statistical analysis

Statistical analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Comparisons among groups were performed using one-way analysis of variances (ANOVA) and Dunnett's test with significance set at  $P < 0.05$ .



**Figure 1:** The surgical procedure and biomechanical testing. (a) The supraspinatus was identified through the deltoid splitting approach; (b) The tendon was dissected from the greater tuberosity, and 5 mm × 5 mm tendon tissue was removed from the end. The tuberosity was gently roughened and debrided; (c) A modified Mason-Allen stitch using an Orthocord suture (Johnson and Johnson, Piscataway, NJ, USA) was placed into the supraspinatus tendon. The suture ends were then passed through the bone tunnels and tied, which repaired the supraspinatus tendon to the greater tuberosity; (d) The specimen was then placed into an MTS-858 biomechanical testing system (MTS Co., USA) and secured in a custom designed jig. Ssp: Supraspinatus; GT: Greater tuberosity; Isp: Infraspinatus.



## RESULTS

### Biomechanical testing

All specimens failed at the tendon bone attachment site during biomechanical testing. In each group, the percentage of maximal load to failure on the surgery side compared with the value on the normal side increased significantly over time.

At 3 weeks after surgery, the percentage of maximal load to failure in the ibuprofen, celecoxib, flurbiprofen axetil, and control group was shown in Table 1. There were significantly lower failure loads in the celecoxib and flurbiprofen axetil groups compared with the control group ( $P = 0.002$  and  $0.024$  separately), but there was no significant difference between ibuprofen and the control group ( $P = 0.133$ ). At 6 weeks after surgery, there was a significantly lower failure load in the celecoxib group than in the control group ( $P = 0.010$ ), but there was no significant difference

in the ibuprofen or flurbiprofen axetil groups compared with the control group ( $P = 0.285$  and  $0.679$ , respectively). These significant differences persisted at 12 weeks. There was significantly lower failure loads in the celecoxib group compared with the control group ( $P = 0.002$ ), but no significant difference in the ibuprofen or flurbiprofen axetil groups compared with the control group ( $P = 0.921$  and  $0.556$ , respectively) [Table 1].

### Histological analysis

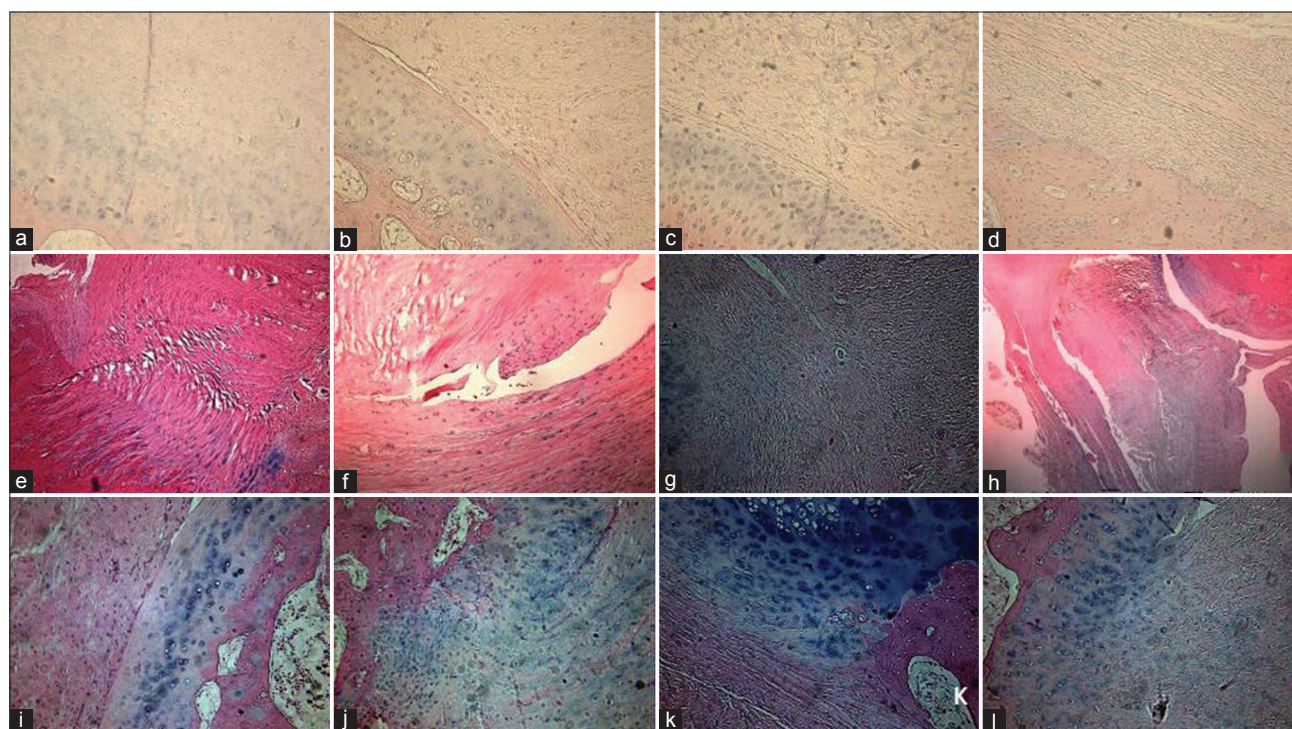
#### Qualitative evaluation

At 3 weeks, there was poorly organized fibrovascular granulation tissue at the tendon bone insertion in all three groups. In the ibuprofen and control groups, a little osteoclastic activity and cartilage formation could be found [Figure 2a-d]. At 6 weeks, mutual fibrocartilage formation and some Sharpey's fibers were observed in the ibuprofen, flurbiprofen axetil, and control groups, but

**Table 1: Biomechanical testing results (failure load) among different group in each time point ( $n=12$ )**

Time point	Flurbiprofen axetil group	Celecoxib group	Ibuprofen group	Control group	$t^*$	$P^*$	$t^{1\ddagger}$	$P^{1\ddagger}$	$t^{2\S}$	$P^{2\S}$	$t^{3\parallel}$	$P^{3\parallel}$
At 3 weeks	$0.600 \pm 0.017$	$0.533 \pm 0.037$	$0.640 \pm 0.045$	$0.700 \pm 0.062$	2.55	0.010*	2.11	0.024*	3.41	0.002*	0.21	0.133
At 6 weeks	$0.743 \pm 0.068$	$0.607 \pm 0.032$	$0.710 \pm 0.080$	$0.763 \pm 0.032$	1.82	0.040*	0.11	0.679	2.17	0.010*	0.26	0.285
At 12 weeks	$0.783 \pm 0.050$	$0.660 \pm 0.033$	$0.800 \pm 0.036$	$0.803 \pm 0.040$	4.73	0.006*	0.18	0.556	3.06	0.002*	0.01	0.921

\*Significant difference;  $t^*$ ,  $P$ : ANOVA test of three groups;  $\ddagger t^1, P^1$ : Flurbiprofen axetil group versus control group;  $\S t^2, P^2$ : Celecoxib group versus control group;  $\parallel t^3, P^3$ : Ibuprofen group versus control group.



**Figure 2:** The qualitative evaluation of HE staining images, original magnification  $\times 200$ . At 3 weeks, there was poorly organized fibrovascular granulation tissue at the tendon bone insertion in all three groups. In the ibuprofen and control groups, a little osteoclastic activity and cartilage formation could be found. (a-d) At 6 weeks, mutual fibrocartilage formation and some Sharpey's fibers were observed in the ibuprofen, flurbiprofen axetil, and control groups, but not in the celecoxib group. The continuity of the tendon was still poor in the celecoxib group. (e-h) By 12 weeks, in the ibuprofen, flurbiprofen axetil, and control groups, the tendon was hypercellular and contained a mixture of fibroblastic cells. The four zones of the bone tendon interface could be found. In the celecoxib group, no cartilage or new bone formation could be observed, and the collagen orientation remained disorderly (i-l).

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### Quantitative analysis

All groups exhibited progressively increasing collagen I with time, indicating improving collagen maturity and organization. At 3 weeks, all groups showed collagen III dominating at the bone tendon insertion. The percentage of collagen I in the ibuprofen, celecoxib, flurbiprofen axetil, and control groups was  $26.2 \pm 1.7\%$ ,  $11.5 \pm 3.5\%$ ,  $15.6 \pm 4.4\%$ , and  $27.6 \pm 0.5\%$ , respectively. There was significantly less collagen I in the celecoxib and flurbiprofen axetil groups than in the control group (the  $P = 0.001$  in both cases), but there was no significant difference between the ibuprofen and control groups ( $P = 0.577$ ). At 6 weeks, the percentage of collagen

I in the ibuprofen, celecoxib, flurbiprofen axetil, and control groups was  $67.2 \pm 3.5\%$ ,  $40.5 \pm 3.5\%$ ,  $63.8 \pm 4.4\%$ , and  $66.3 \pm 3.2\%$ , respectively. There was significantly less collagen I in the celecoxib group than in the control group ( $P = 0.005$ ), but there was no significant difference in the ibuprofen or flurbiprofen axetil groups compared with the control group ( $P = 0.905$  and  $0.714$ , respectively). This collagen I increase was clearly apparent at 12 weeks. The percentage of collagen I in the ibuprofen, celecoxib, flurbiprofen axetil and control groups was  $82.6 \pm 2.9\%$ ,  $59.5 \pm 5.5\%$ ,  $80.4 \pm 2.4\%$ , and  $86.3 \pm 1.9\%$ , respectively. There was significantly less collagen I in the celecoxib group than in the control group ( $P = 0.001$ ), but there was no significant difference between the ibuprofen or flurbiprofen axetil groups and the control group ( $P = 0.237$  and  $0.075$ , respectively) [Table 2 and Figure 3].

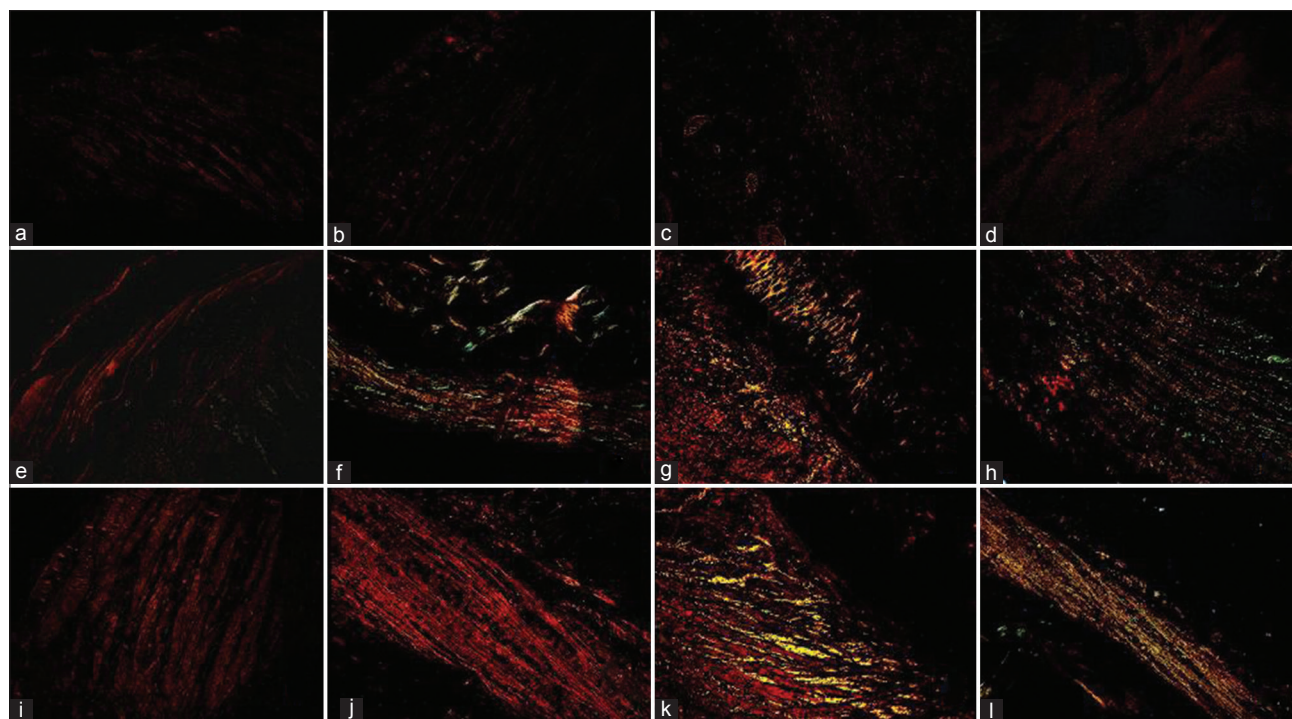
### DISCUSSION

NSAIDs are commonly used for pain control after rotator cuff repair procedures. They function by inhibiting the enzyme COX, which catalyzes the conversion of

**Table 2: The percentage of collagen I among three time point in each group (n=12)**

Time point	Flurbiprofen axetil group (%)	Celecoxib group (%)	Ibuprofen group (%)	Control group (%)	$t^*$	$P^*$	$t\ 1^\ddagger$	$P\ 1^\ddagger$	$t\ 2^\S$	$P\ 2^\S$	$t\ 3^\parallel$	$P\ 3^\parallel$
At 3 weeks	$15.6 \pm 4.4$	$11.5 \pm 3.5$	$26.2 \pm 1.7$	$27.6 \pm 0.5$	7.71	0.001*	7.96	0.001*	4.01	0.001*	0.23	0.577
At 6 weeks	$63.8 \pm 4.4$	$40.5 \pm 3.5$	$67.2 \pm 3.5$	$66.3 \pm 3.2$	5.29	0.001*	0.15	0.714	3.91	0.005*	0.10	0.905
At 12 weeks	$80.4 \pm 2.4$	$59.5 \pm 5.5$	$82.6 \pm 2.9$	$86.3 \pm 1.9$	3.41	0.012*	1.68	0.075	6.52	0.001*	1.06	0.237

\*Significant difference;  $^*t, P$ : ANOVA test of three groups;  $^\ddagger t\ 1, P\ 1$ : Flurbiprofen axetil group versus control group;  $^\S t\ 2, P\ 2$ : Celecoxib group versus control group;  $^\parallel t\ 3, P\ 3$ : Ibuprofen group versus control group.



**Figure 3:** (a-l) The quantitative analysis of Sirius red staining images, original magnification  $\times 200$ . All groups exhibited progressively increasing collagen I with time, indicating improving collagen maturity and organization. At 3 weeks, all groups showed collagen III dominating at the bone tendon insertion.



arachidonic acid to prostaglandins and thromboxane, which are main factors in algogenesis.<sup>[4,5]</sup> Two forms of COX have been identified. COX-1 is a constitutively expressed enzyme that is found in most tissues and organs, in which the production of normal prostaglandin levels is vital to tissue homeostasis. COX-2 is an inducible enzyme that is produced by inflammatory cells and tissues. Nonselective NSAIDs such as ibuprofen and flurbiprofen axetil inhibit both the COX-1 and COX-2 enzymes. Selective COX-2 inhibitors, such as celecoxib, have the advantage of selectively inhibiting the inflammation reaction with minimal gastrointestinal side effects.<sup>[6,7]</sup>

However, the inflammation reaction is the main step in the tendon healing process. Theoretically, COX inhibitors will then affect rotator cuff healing. In 2007, Ferry *et al.*<sup>[8]</sup> transected rat patellar tendons and found, in the load to failure mechanical test, that the ibuprofen group was significantly stronger than the celecoxib group, but not significantly different from the control group. Connizzo *et al.*<sup>[9]</sup> later reported that the early administration of ibuprofen during the postoperative period was detrimental to tendon healing but that delayed administration was not. We administered ibuprofen during the early repair stage because most pain killing drugs would be used soon after surgery.

Because the side effects of nonselective COX inhibitors are not uncommon, there is a tendency to use COX-2 selective inhibitors, such as celecoxib, as an alternative pain control method. However, to date, the reported effect of selective COX-2 inhibitors on tendon healing has been variable. Forslund<sup>[10]</sup> found that NSAIDs diminish the cross-sectional area and collagen content in healing tendons but showed no relation to load to failure. However, Elder *et al.*<sup>[11]</sup> treated rats with celecoxib for 6 days after medial collateral ligament transaction and reported a 32% lower load to failure in the celecoxib group. For ibuprofen, the nonselective COX-2 inhibitor, Virchenko *et al.*<sup>[12]</sup> examined the impact of the timing of COX-2 inhibitor on rat tendon healing and demonstrated that the early administration of the drug would negatively affect the biomechanical properties, but that the late administration would significantly increase them.

Although some studies reported that both nonselective NSAIDs and selective COX-2 inhibitors inhibit the healing of tendon, which appeared to be linked to the enzyme COX-2, the details of the mechanism remain to be investigated. In 2006, Cohen *et al.*<sup>[13]</sup> compared the effects of celecoxib and indomethacin, a traditional nonselective NSAID, after rat rotator cuff repair. Animals were sacrificed at 2, 4, and 8 weeks and evaluated by biomechanical testing and histological analysis. He found significant differences in failure loads, collagen organization and maturation in the celecoxib and indomethacin groups compared with the control group at each time point, but found no significant difference between the drug groups. To our knowledge, there are few studies to compare the effect of different COX inhibitors on rotator cuff healing. Unfortunately, the author only quantitatively analyzed the failure loads between two

groups. In addition, indomethacin is seldom used as pain control medicine in recent years because of its well-known side effects.

In our study, both nonselective COX inhibitors and a selective COX-2 inhibitor showed a tendency to delay the healing process during the early repair stage. The results were found through quantitative biomechanical and histological analysis. Both the celecoxib and flurbiprofen axetil groups showed significantly lower maximal failure load compared with the control group, which is compatible with histological change at 3 weeks. In normal bone tendon insertion, type I collagen is the main structure continuity between the bone and the tendon in the alignment arrangement. After repair of the torn tendon, type III collagen appeared in a disordered arrangement and was then gradually replaced by type I collagen. Eventually, type I collagen dominated in the insertion area, and collagen fibers were reestablished. Fewer normal collagen fibers and a disordered arrangement would make the bone tendon insertion less durable under mechanical stress.<sup>[14-16]</sup> In our study, at all-time points, a close relationship between biomechanics and histological change could be found. However, in the ibuprofen group, in our study, the load failure and percentage of type I collagen are lower than the control group but not to a statistically significant degree. This result may be due to gastrointestinal digestion minimizing the drug effect.

Compared with ibuprofen, flurbiprofen axetil has an advantage in intravenous administration. This lipid microsphere nonselective COX inhibitor can be delivered targeting the inflammation site.<sup>[17,18]</sup> In our study, flurbiprofen axetil delayed tendon healing significantly compared with ibuprofen at 3 weeks after tendon repair, although both drugs are nonselective COX inhibitors. This significance difference disappeared by 6 weeks after surgery, which means that different routes of administering drugs have limited effects on tendon healing at the very early stage. Because the celecoxib group showed a significant difference from the control group from 3 weeks until 12 weeks, when the control tendon was almost healed, the COX-2 enzyme seems to be the main factor in the tendon healing process.

Clinical studies demonstrated that complete healing of a rotator cuff tendon repair results in superior function.<sup>[19,20]</sup> It is important to identify factors that might interfere with the biological healing process. Because the impact of NSAIDs on soft tissue healing remains poorly understood, our results have important implications for drug administration as pain control after rotator cuff tendon repair.

From our study, we can draw the conclusion that NSAID drugs can delay tendon healing in the early stage after rotator cuff repair. Compared with nonselective COX inhibitors, selective COX-2 inhibitors significantly impact tendon healing.

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### Conflicts of interest

There are no conflicts of interest.

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