Clinical efficacy of celecoxib for osteoarthritis and bone anchor assisted knee extensor reconstruction

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Abstract: Celecoxib is the most recent non steroidal anti-inflammatory analgesic, and has been gradually used in the treatment of acute pain, rheumatism and osteoarthritis. This paper analyzes the analgesic effect of celecoxib in the treatment of knee osteoarthritis and put forward a new mechanism of knee joint extensor reconstruction assisted by bone anchor. The experimental group was given celecoxib 200 mg/ time and 1 time /d. The results showed that VAS (Visual Analogue Scale) decreased gradually in both groups on the 1st, 3rd and 7th day of treatment and VAS in experimental group was lower than that in control group at the same time point ($P<0.05$). At the 1 year follow-up, experience group had a significant improvement on the Lysholm (69.33 ± 8.38 preoperatively and 88.65 ± 12.93 postoperatively) and Kujula (69.33 ± 8.38 preoperatively and 88.65 ±12.93 postoperatively) knee scores ($P<0.05$). The results showed that celecoxib had a good analgesic effect in patients with knee osteoarthritis and reducing the release of inflammatory factors may be its mechanism.

Keywords: Celecoxib, inflammatory reaction, TNF-α, patellofemoral instability, anchor technique.

INTRODUCTION

Osteoarthritis (OA) is a degenerative disease of the knee joint. The main clinical manifestations of OA are joint pain and joint dysfunction (Kita *et al*., 2014). At present, non-steroidal anti-inflammatory drugs are commonly used in the treatment of OA (Arendt, 2009). Celecoxib is one of the commonly used drugs, but the mechanism of action is not clear. At present, drug therapy is still the first choice in clinic, mainly immunosuppressive agents, anti-inflammatory drugs and glucocorticoids (Biyani *et al*., 2014). Glucosamine hydrochloride is a kind of glucocorticoid. It enhances bone nutrition level and synovitis secretion by activating mucopolysaccharide synthesis and calcium absorption, thereby enhancing joint lubrication, reducing bone friction, alleviating pain and increasing mobility (Paccez *et al*., 2014). Celecoxib is the most novel non-steroidal anti-inflammatory and analgesic drug. It has been gradually used in the treatment of acute pain, rheumatism and osteoarthritis (Li *et al*., 2016). Scholars have confirmed that Celecoxib and placebo are used in patients at the same time. Celecoxib can significantly improve joint pain. Some scholars pointed out that glucosamine hydrochloride can interact with non-steroidal anti-inflammatory drugs (Barber *et al*., 2008). It can greatly improve the treatment effect, play a multiplier effect with half the effort and shorten the treatment cycle. In order to investigate the clinical effect of glucosamine hydrochloride combined with celecoxib in the treatment of knee osteoarthritis, the author made a clinical observation on the patients in our hospital (Liu *et al*., 2017). The results showed that celecoxib can significantly improve the symptoms of knee joint.

Patellofemoral instability is a common knee disease which is notorious for its complicated etiology, diversified treatment methods and difficulty to assess the curative effect (Balcarek *et al*., 2014; Nayir *et al*., 2015). MPFL (Medial patellofemoral ligament) reconstruction shows effective treatment for patellofemoral instability). However, adolescents with immature epiphysis who are undergone this operation may have the risk of epiphysis damage and finally results in the abnormal bone growth (Liu *et al*., 2017). Furthermore, for the patients with TT-TG (tibial tubercle trochlear groove) value greater than 20 mm, distal realignment operation is required (Becher *et al*., 2014). The realignment operations especially the transposition of tibial tubercle may have the risk of damaging the epiphysis and then result in knee recurvatum (Ostojic *et al*., 2015). On the contrary, the soft tissue procedure has no such risk. Some classical soft tissue procedures give a satisfactory result for the reconstruction with bone anchor. Bone anchor technique shows excellent effect in bone and ligament healing (Kujala *et al*., 1993; Cheung *et al*., 2012). On this basis some classical soft tissue procedures are carried out on the adults, but the indications have seldom been studied. Between January 2010 and December 2016, 166 patients with patellofemoral instability were treated with bone anchor assisted extensor mechanism reconstruction.

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Curative effect analysis and logistic regression analysis with some related indexes were performed in this study.

MATERIALS AND METHODS

General data

166 patients were participated in this study. 108 male and 58 female patients suffered an average disease course of 9 years with an average age of 24 years (range, 13-53 years). They were randomly divided into 2 groups, the experimental group and the control group, 54 cases in each group. The patients in the control group were treated with routine treatment, while the experimental group was treated with celecoxib capsules. Celecoxib is currently the most new non-steroidal anti-inflammatory and analgesic drug, has been gradually used in the treatment of acute pain, rheumatism and osteoarthritis, has been confirmed that celecoxib and placebo in patients at the same time, celecoxib can significantly improve joint pain. All patients were approved by ethics committee. This study was approved by Ethics Committee of Kunming Medical University, Approval number as 10KMUEC2D.

All of the patients had knee pain with unstable gait and suffered subluxation of the patella with flexion deficiency. For the physical examination, patients suffered the tenderness on the gap of the patellofemoral joint, the margin of the bone and the lateral patellar-femoral ligament. Positive results were obtained in Patellar push examination and Patellar declination examination. Preoperative Lysholm knee score) and Kujula anterior knee score) was 69.33±8.38 and 67.05±8.43, respectively. Meniscal and other ligamentous injuries were excluded by MRI (Magnetic Resonance Imaging). The CT examination indicated the distance from tibial tubercle to femoral trochlea (TT-TG) was 18.5-25.6 mm with an average of 21.6 mm. X-ray examinations excluded the obvious varus and valgus deformity and showed normal osseous structure of the knee. MRI imaging indicated lateral trochlear inclination was 4-29° with an average of 16.7°. Standard knee X-ray on 30° of flexion showed that Insall-Salvati ratio was 0.68-1.56 with an average of 1.12. An Insall-Salvati index greater than 1.2 has been defined as patella alta).

Related indicators observed

(1) The degree of joint pain: VAS was performed at rest before treatment and on the 1^{st}, 3^{rd} and 7^{th} day of treatment in both groups to evaluate the degree of joint pain. (2) Serum levels of inflammatory factors: Peripheral venous blood 10 ml was collected before treatment and at the end of treatment, and serum was centrifuged. IL-6 and TNF-a were detected by ELISA.

Exclusion criteria

(1) In the last week, patient has received western medicine or acupuncture (including needle knife, massage, etc.) treatment such as NSAIDs. (2) Psychiatric patients, or accompanied by serious cardiovascular and cerebrovascular diseases, gastrointestinal, hematopoietic system, liver and kidney dysfunction, as well as with infectious or systemic infectious diseases. (3) Diabetic patients had poor glucose control. (4) There are skin ulcerations in the knee joint. (5) Patients with secondary arthritis, such as acute trauma, fracture, psoriatic arthritis or knee replacement. (6) There are other diseases that affect knee joint symptoms, such as lumbar disc herniation, hip joint disease and so on. (7) Rheumatism and rheumatoid arthritis do not belong to osteoarthritis patients.

Operation procession

Operation methods: After subarachnoid block anesthesia tourniquet was applied to the patients in the supine position, microtubule excision forward knee excision was carried out. Excised the skin and superficial fascia, took lateral retinaculum loosened, and exposed the internal oblique muscle of quadriceps femoris. Internal oblique muscle of quadriceps femoris was rearranged according to the Madigan method and was fixed to 1/3 of the lateral side of the patella and pavilion of the quadriceps femoris. Seperated the patellar ligament, cut it into two parts and separated the lateral half of the patellar ligament from the tibial tubercle and fixed it to the pes anserinus with a bone anchor, making sure that the exterior margin of the patella was in the line of the exterior margin of the fermoral lateral condyle. At last, flushed and sutured the excision routinely.

Postoperative treatment

Antibiotics were routinely used to prevent infection before and after surgery. The long plaster splints or external immobilizations were applied postoperatively to stabilize the affected limb into full extension position for 3 weeks. Patients were guided to take patella loosening and fermoris forceps muscule contraction exercise, but no knee joint flexion and extension exercise was carried out. 4 weeks after surgery, CPM (continuous passive motion) of 0-90° was carried out on the injured knee. 2 months after surgery, the knee flexion extended to 120°, and quadriceps femoris strengthening exercises were applied.

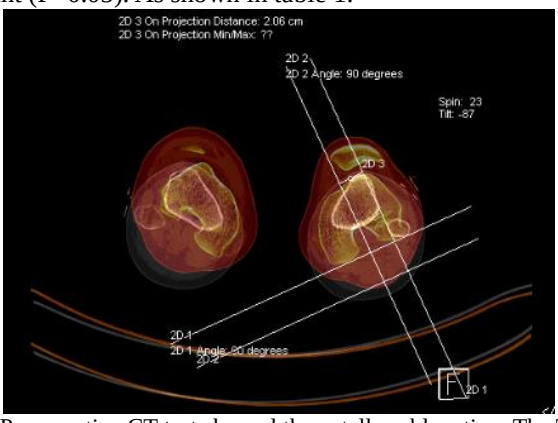
STATISTICS ANALYSIS

Data were analyzed using SPSS22.0. All data were expressed as mean ± S.D. P-value of the difference between preoperation and postoperation was evaluated using paired t-test. $P<0.05$ was considered statistically significant. For the logistic regression, age (>18 years old, mature; <18 years old, immature), Insall-Salvati index (> 1.2, patella alta; <1.2, non-patella alta) and lateral trochlear inclination (>15°, normal; <15°, abnormal) were defined as independent variables. 1-year postoperative Insall score) was defined as a dependent variable.

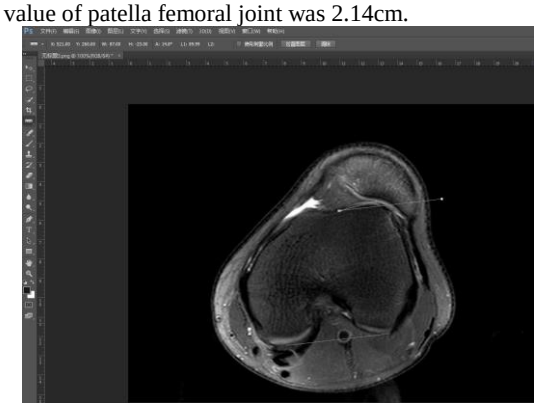
RESULTS

Comparison of joint pain before and after treatment

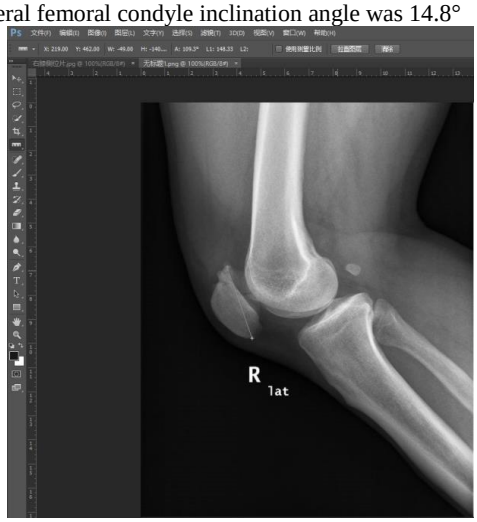
There was no significant difference in VAS between the two groups before treatment (P>0.05); VAS of the two groups decreased gradually on the first, third and seventh day after treatment, and VAS of the observation group was lower than that of the control group at the same time point (P<0.05). As shown in table 1.



(a) Preoperative CT test showed the patella subluxation. The TT-TG value of patella femoral joint was 2.14cm.



(b) Lateral femoral condyle inclination angle was 14.8°



(c) Insall-Salvati value was 1.26. These parameter values were detected by Photoshop CC 2015 Preoperatively.

Fig. 1: Logistic regression indexes of patient's injured (right) knee.

Comparison of serum IL-6 and TNF- alpha levels

Before treatment, there was no significant difference in serum IL-6 and TNF-alpha levels between the two groups (P>0.05). After treatment, serum IL-6 and TNF-alpha levels in the two groups decreased, and the observation group decreased more significantly (P<0.05). As shown in table 2.

Surgical treatment results

All the excisions healed well and no operation complications such as nerve injury occurred. The postoperative follow-up time ranged from 1 to 12 months. After symptomatic treatment, significant pain relief was reported among 13 patients who suffered knee pain. For 13 patients, the pain of the knee did not relief postoperatively but relieved by symptomatic treatment. 8 weeks after surgery, knee X-ray on 60° of flexion showed the correct location of the patella. The anatomic relations of the patellofemoral joint recovered well. No signs of nerve injury, visible development of pseudoarthrosis, fixation failure, postoperative patellar subluxation or any other complications were observed. For adolescent patients, there were no injuries of epiphysis.

After 4 week of follow-up, the Lysholm score of the experience group patients (89.13±10.24) improved significantly compared with preoperative values (t= -13.64, P=0.00) (table. 3). The Kujula score (88.55 ± 12.28) was also improved significantly (t= -14.91, P= 0.00) (table. 4). All the patients had a significant improvement on the Lysholm knee scores (P<0.05). 1 months after surgery, the Insall Ceriterion was applied to evaluate curative effects (Standard descriptions: Excellent: no knee pain, no unstable symptom, normal knee joint movement; Good: mild discomfort, accidental discomfort, no influence on daily activities; Acceptable: pain on the patellofermoral joint, slight instability of patellofermoral joint, restricted range of motion, incapable of taking part in some activities; Bad: recurrent dislocation or even further deformity, incapable of taking part in any activities, required further operations.). Results showed that 56 patients were "Excellent", 10 patients were "Good", 9 patients were "Acceptable" and 8 patients were "Bad". Ratio of "Excellent" and "Good" was 79.5%. The logistic regression results were analyzed by taking age, TT-TG value, Insall index and lateral trochlear inclination as independent variables and taking the Insall score as a dependent variable. But the lateral trochlear inclination and Insall-Salvati index were excluded from the logistic regression analysis. Age and Insall score in experience group were analyzed using $\chi 2$ test, the results were shown in table 5. Typical case was shown in fig. 1 and logistic regression factors of this patient's injured (right) knee were shown in fig. 1.

DISCUSSION

The pathological changes of osteoarthritis are destruction

Table 1: VAS comparison between the two groups before and after treatment (x ±s)

Group	N	VAS(Visual Analogue Scale/Score)			
		Before treatment	Treatment for first days	Treatment for third days	Treatment for seventh days
Control group	83	4.5±0.7	2.8±0.2	2.5±0.4	2.2±0.3
Experience group	83	4.6±0.8	4.2±0.7	3.7±0.6	3.3±0.5

Table 2: Comparison of serum IL-6 and TNF- alpha levels

Group	n	IL-6(μg /mL)	TNF-α(μg /L)
Control group	83		
	Before treatment	324.5±42.7	25.8±3.6
	After treatment	279.6±48.8	21.3±4.8
Experience group	83		
	Before treatment	330.7±44.8	26.1±4.2
	After treatment	225.1±40.5	16.8±3.7

Table 3: Lysholm score of pre-operation and post-operation

Group	Preoperation	4 weeks post-operation	8 weeks post-operation	t value	P value
Control group	69.33±8.38	88.65±12.93	91.65±12.93	-13.64	0.00
Experience group	69.79±7.34	89.13±10.24	92.57±13.27	-6.24	0.05

Table 4: Kujula score of pre-operation and post-operation

Group	Preoperation	8 weeks post-operation	t value	P value
Control group	67.05±8.43	88.55±12.28	-14.91	0.00
Experience group	66.91±7.63	89.24±10.71	-7.28	0.00

Table 5: χ^2 test analysis of age and Insall score for experience group

Insall score (1 year post-operation)	Age		Total
	< 18	> 18	
Approve and bad	0(5.1)	17(11.9)	17
Excellent and good	25(19.9)	41(46.13)	66
Total	25	58	83

of articular cartilage and formation of subchondral osteophyte, which can lead to joint deformity for a long time (Pan *et al*., 2011). Pain and joint dysfunction are the main clinical symptoms of osteoarthritis. Joint pain further aggravates dysfunction. Long-term pain can also induce and aggravate local inflammatory reaction of articular cartilage and aggravate cartilage injury (Rhee *et al*., 2012). NSAIDS is a first-line treatment for osteoarthritis, and it relieves joint pain by inhibiting inflammation (Saggin *et al*., 2012). The main mechanism of NSAIDS in treating osteoarthritis is to inhibit cyclooxygenase (COX), which is related to prostate synthesis. COX includes COX-1 and COX-2. COX-1 mainly exists in gastric mucosa, platelets and kidneys, and participates in prostaglandin synthesis. COX-2 is an inducible enzyme, which is related to inflammation (Stefanik *et al*., 2013).

Celecoxib is a COX-2 specific inhibitor with anti-inflammatory and analgesic effects, can improve the knee joint mobility of patients with knee osteoarthritis, increase mobility, promote the absorption of joint effusion, so that joint swelling subsided, but its mechanism of action is rarely reported (Shi *et al*., 2015). Diclofenac is a non-steroidal anti-inflammatory and analgesic drug derived from phenylacetic acid. Its mechanism is to inhibit the activity of cyclooxygenase, thereby blocking the conversion of arachidonic acid to prostaglandin, promoting the combination of arachidonic acid and triglyceride, reducing the concentration of intracellular free arachidonic acid, and indirectly inhibiting the synthesis of leukotrienes (Sun *et al*., 2015). Diclofenac is one of the most potent drugs in NSAIDS, and its inhibitory effect on prostaglandin synthesis is stronger than that of aspirin and indomethacin (Wang *et al*., 2008). The VAS of the observation group was significantly lower than that of the control group on the 1st, 3rd and 7th day, suggesting that the analgesic effect of celecoxib on patients with articular cartilage inflammation was better than that of diclofenac (Nayir *et al*., 2015).

Promoting the synthesis and release of inflammatory mediators is an important mechanism of pain perception in patients with osteoarthritis, and persistent pain will further amplify the inflammatory response and increase the synthesis of inflammatory mediators (Yang *et al*., 2014). IL-6 and TNF-alpha are important inflammatory mediators *in vivo*. The former is an important multifunctional cytokine *in vivo*, which can not only directly mediate inflammatory reaction and cause tissue damage, but also have the function of pain-causing factors, and can cause and aggravate joint pain (Balcarek *et al*., 2014). TNF-alpha is the earliest inflammatory factor that changes in inflammatory response (Becher *et al*., 2014). It can not only directly mediate the inflammatory injury of tissue, but also locally recruit inflammatory cells and promote the cascade amplification of inflammatory response. The results showed that the serum levels of IL-6 and TNF-alpha in the observation group were significantly lower than those in the control group, suggesting that celecoxib can alleviate arthritis (Cheung *et al*., 2012).

The bone anchor assisted extensor mechanism reconstruction is a classical operation (Cheung *et al*., 2012). In our study, this operation assisted with bone anchor could harvest an "Excellent" and "Good" ratio as 79.5%, which was lower than that (95%) of the medial patellofemoral ligament reconstruction18 (Kita *et al*., 2014). But we found that the patients with poor curative effects suffered a long disease course and patellofemoral arthritis resulted from patellofemoral instability, while the patients (children and adolescents with immature epiphysis) with short disease course and no obvious patellofemoral arthritis harvested an "Excellent" and "Good" ratio as 90% (Li *et al*., 2016). It was also reported that the pressure of patellofemoral joint would increase after the operation. But for the children and adolescents with immature epiphysis, this operation would improve the femoral condyle development (Becher *et al*., 2014). This operation, a kind of soft tissue operation, would not damage epiphysis. There was no dysplasia of the epiphysis and genu recurvatum in the postoperative follow-up.

Logistic regression is a multifactor correlation analysis. In this study, age was selected as a factor because the postoperative follow-up showed a better clinical effect in younger patients (Ostojic *et al*., 2015). Insall index and lateral trochlear inclination were selected as factors because they were widely reported as important parameters for prediction of patellofemoral instability (Yang *et al*., 2014). In addition, TT-TG is a well-known parameter for the rearrangement of the distal tissue. In this study, the postoperative follow-up showed worse curative effects when TT-TG value increased (>20mm) (Becher *et al*., 2014).

CONCLUSION

To sum up, celecoxib can alleviate joint pain in patients with knee osteoarthritis, inhibit bone TLR4 / NF - kappa B signaling pathway and reduce the release of inflammatory factors may be its mechanism. Celecoxib can significantly alleviate acute pain and osteoarthritis symptoms in patients with osteoarthritis, and its combination with glucosamine hydrochloride can make the patient's joint pain symptoms get accurate treatment, thus shortening the treatment time. At the same time, the use of bone anchor assisted extensor mechanism reconstruction offers a good option for patellofemoral instability with a satisfactory short-term effect and fewer complications. It seems to be relatively easy and reliable. This method is helpful to recover the patellofemoral instability, with a satisfactory early clinical effect and fewer complications. However, further follow-up analysis is required for long-term clinical results. This operation was better carried out on the adolescents. And patella alta and flat lateral femoral condyle had little influence on the curative effect of this operation.

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