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Effect of celecoxib combined with glucosamine hydrochloride in promoting the functional recovery and decreasing the inflammatory factor levels in patients with knee osteoarthritis

Jin Zhang, Ruiyi Ge and Ziquan Yang*
Sport Medicine, Second Hospital of Shanxi Medical University, Taiyuan Sports, PR China

Abstract: To explore the role of celecoxib with glucosamine hydrochloride on functional recovery and reduction of inflammatory factors in patients with knee osteoarthritis. Altogether 128 patients with knee osteoarthritis in the middle and early stage admitted to our hospital from January 2018 to July 2019 were selected and grouped into the control group (CG) (celecoxib tablet therapy) and the combination group (ComG) (celecoxib combined with glucosamine hydrochloride therapy). Blood routine indexes and inflammatory factor levels before and after intervention, Lequesne score, VAS pain and adverse reactions of the two groups of patients before and after intervention were explored. Before intervention, there was no evident difference between the two groups in each index ($P>0.05$). After intervention, the blood routine index IgM rheumatoid factor, albumin/globulin, erythrocyte sedimentation rate and inflammatory factors TNF-α, IL-6, IL-1β, hs-CRP levels in the ComG were evidently better than those in the CG, while Lequesne score and VAS pain score were lower than those in the CG ($P<0.01$). The total incidence of adverse reactions in the ComG was evidently lower than that in the CG. Celecoxib combined with glucosamine hydrochloride is effective in the treatment of knee osteoarthritis and has little adverse reactions.

Keywords: Celecoxib, glucosamine hydrochloride, knee osteoarthritis, functional recovery, inflammatory factor.

INTRODUCTION

Knee osteoarthritis (KOA) is a chronic degenerative joint disease, which is mainly characterized by articular cartilage destruction, changes and hyperosteogeny. Its clinical manifestations are joint pain, limited activity, swelling and pain (Lespasio *et al*., 2017). With the extension of time, the patient's symptoms are gradually worsen, the joint deformation is obvious in the late stage, dysfunction occurs, which seriously affects the activity and quality of life, and the disability rate is very high (Hussain, *et al*. 2018). The earliest and most important pathological changes occur in articular cartilage, which is surrounded by proteoglycan matrix and ollagen can maintain the stability of chondrocytes. There is a balance of synthesis and degradation between chondrocytes and matrix, while reversible metabolic disorder is one of the earliest signs of cartilage damage and degradation (Madry, *et al*., 2016). Patients with early knee osteoarthritis mainly relieve local symptoms through anti-inflammatory and analgesic drug therapy combined with physical therapy and quadriceps functional exercise, while patients with middle and advanced stage need osteotomy or joint replacement (Benner *et al*., 2019). Conservative treatment has been used clinically for a long time. Besides physical therapy, drug therapy has been the main treatment method for the disease, among which the most important ones are non-steroidal anti-inflammatory and analgesic drugs (Charlesworth, *et al*., 2019), glucosamine hydrochloride (Blanco, *et al*., 2019) and intra-articular injection of glucocorticoid (Parisi *et al*., 2019). However, long-term administration of non-steroidal anti-inflammatory drugs will also increase the incidence of interstitial nephritis and even lead to renal function damage, and gastrointestinal reactions are the most common adverse reactions (Moore *et al*., 2019).

Non-steroidal anti-inflammatory drugs act an anti-inflammatory and analgesic role by hindering the activity of cyclooxygenase, thus hindering arachidonic acid from eventually producing prostacyclin, and are commonly used drugs for treating arthritis (Ricciotti *et al*., 2018). At present, two isozymes of cyclooxygenase are known, namely cyclooxygenase -1 and cyclooxygenase -2. Cyclooxygenase -1 is mainly used to protect gastrointestinal tract, regulate platelet aggregation, regulate peripheral vascular resistance and maintain renal blood flow. Cyclooxygenase -2 mainly affects the synthesis of prostaglandins, which can mediate inflammation and pain. The inhibitory effect of non-steroidal anti-inflammatory drugs on cyclooxygenase -2 is the basis of its therapeutic effect. The effect on cyclooxygenase -1 is the cause of its adverse reactions (Anwar, *et al*. 2015; Radi and Khan 2019). Celecoxib is a cyclooxygenase -2 inhibitor and has been listed in China for many years. The application of it on treatment of arthritis has definite curative effect and little side effect. Therefore, it has been widely used clinically (Al-Rashed, *et al*., 2018). Glucosamine hydrochloride is a natural amino monosaccharide and an important component necessary for the synthesis of proteoglycan in human

**Corresponding author*: e-mail:1252254199@qq.com

articular cartilage matrix. It has affinity for articular cartilage, can diffuse into articular soft matrix, reach chondrocytes, supplement substances required for cartilage matrix proteoglycan synthesis, stimulate and restore the biosynthesis of hyaluronic acid and proteoglycan, thus blocking the pathological process of osteoarthritis, delaying the progress of diseases, improving joint activity and relieving pain (Bruyere *et al*. 2016; Sterzi *et al*., 2016). In-vitro glucosamine usually exists in the form of N- acetylate, sulfuric acid or hydrochloric acid, and can be completely dissolved in gastric acid and absorbed in small intestine in the original state of glucosamine, while the absorbed glucosamine has no relation with the previous acid radical, but has the same *in vivo* activity (McCarty *et al*., 2019). At present, glucosamine sulfate has been widely used in clinical treatment in various countries, but the use time of glucosamine hydrochloride is still short.

In this paper, the therapeutic effect of celecoxib combined with glucosamine hydrochloride on knee osteoarthritis patients, the function recovery and the influence of serum inflammatory factor level were studied and the efficacy of celecoxib combined with glucosamine hydrochloride was evaluated, which provided certain basis for clinical treatment of knee osteoarthritis.

MATERIALS AND METHODS

Research participants

Altogether 128 patients with knee osteoarthritis from January 2018 to July 2019 were obtained. All patients were knee osteoarthritis of middle and early stage and were divided into 2 groups by random fig. table method. There were 60 cases in the control group (CG), including 33 men and 27 women, with an average age of (54.6± 4.9) years. There were 68 cases in the combination group (ComG), including 37 men and 31 women, with an average age of (55.7±4.7) years. There was no evident difference in the basic data (P>0.05). Inclusion criteria: The patient had persistent knee pain for more than one month, and X-ray examination showed osteophyte at the joint edge; the patient's age was not less than 40 years, and no other drugs were used for treatment within 15 days. Exclusion criteria: patients had coagulation dysfunction, liver, heart, kidney and other important organ dysfunction, gout and inflammatory arthritis; patients were allergic to drug used in this research. The study was approved by the Ethics Committee and all patients have signed informed consent forms.

Method

CG: Celecoxib tablets (200mg), once every 24 hours, oral treatment for 4 weeks. Com G: Glucosamine hydrochloride (480mg) was added on the basis of the CG, once every 12 hours and oral treatment was carried out for 4 weeks.

Outcome measures

The liver and kidney function, urine routine and blood of the two groups were tested routinely before treatment, and the levels of inflammatory factors before and after intervention were compared, including IL-6, hs-CRP, TNF-α. The levels of IgM rheumatoid factor, albumin/globulin (A/G) and erythrocyte sedimentation rate before and after intervention were compared between the two groups. Efficacy was scored by Lequesne standard index. VAS score method was applied to evaluate the pain degree of 20m walking before and after intervention in the two groups, with a total score of 10 points. The high score was closely related to the pain. Adverse reactions of the two groups were observed.

STATISTICAL ANALYSIS

SPSS21.0 was applied to test the data. The measurement data were represented as Mean ± SD and compared by t test. The counting data was expressed as (n, %) % and was analyzed by chi-square test. GraphPad Prism 6 was applied for visualizing the fig. 1.

Ethical approval

Written informed consent for publication of this paper was obtained by all authors.

RESULTS

Comparison of blood routine indexes

The changes of blood routine indexes before and after intervention were compared between the two groups. The results showed that before treatment, there was no evident difference in IgM rheumatoid factor, albumin/globulin and erythrocyte sedimentation rate between the two groups after intervention, the indexes of the ComG were evidently better than those of the CG (P<0.01).

Comparison of inflammatory factors

In order to explore the role of different drug treatments, the levels of inflammatory factors were compared in patients' serum. The results showed that there was no evident difference in TNF-α, IL-6, IL-1β and hs-CRP between the two groups before treatment after intervention, each index level of the two groups of patients decreased, but each index level of the ComG was evidently lower than that of the CG, it was shown in table 1.

Comparison of Lequesne scores

In order to test the role of drugs on knee joint function recovery, the Lequesne score showed that before intervention, there was no evident difference (P>0.05). After intervention, all indexes of Lequesne score in the two groups of patients improved and the score decreased, but all indexes in the ComG were evidently better than those in the CG (P<0.01), it was shown in table 2.

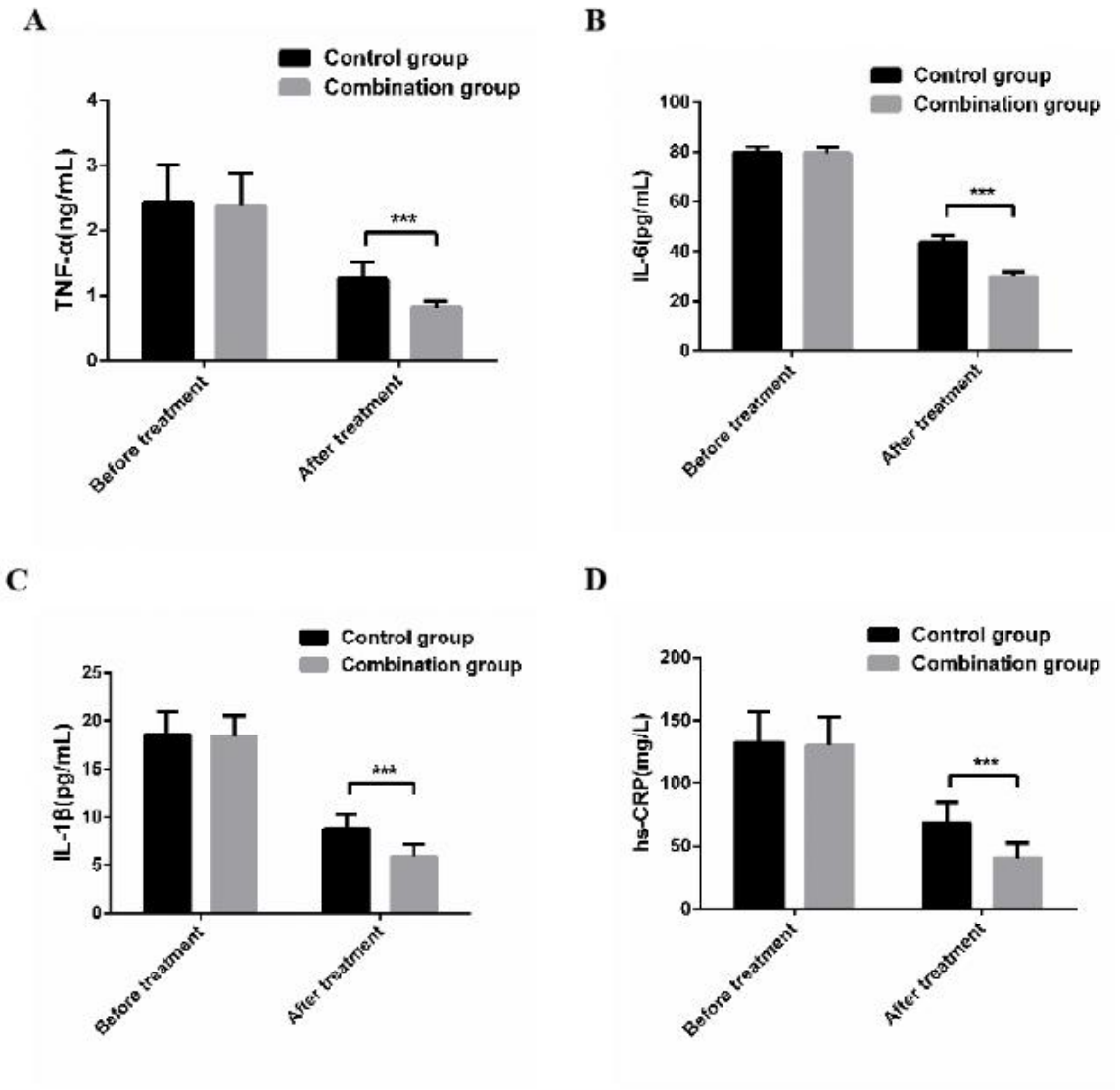

Fig. 1: Comparison of inflammatory factor levels before and after intervention between the two groups.
(A: Comparison of TNF-α levels between the two groups before and after intervention; B: Comparison of IL-6 levels before and after intervention between the two groups; C: Comparison of IL-1β levels before and after intervention between the two groups; D: Comparison of hs-CRP levels between the two groups before and after intervention; *** indicates compared with the CG, P<0.01).

Table 1: Comparison of blood routine indexes

	IgM rheumatoid factor (IU/mL)		A/G		ESR (mm/h)	
	Before treatment	after intervention	Before treatment	after intervention	Before treatment	after intervention
CG (n=60)	79.8±2.35	43.5±3.05	3.75±1.13	2.94±0.63	18.6±0.32	12.1±0.19
ComG (n=68)	79.5±2.31	29.5±1.98	3.78±1.08	2.21±0.52	18.5±0.28	15.8±0.22
χ2/t	0.7273	31.1451	0.1535	7.1785	1.8857	101.162
P	0.4684	<0.0001	0.8783	<0.0001	0.0616	<0.0001

Comparison of VAS pain score

By comparing the pain score of 20m VAS before and after intervention, there was no evident difference. After intervention, the pain was relieved, but the score of the ComG was lower than that of the CG (P<0.01), it was shown in table 3.

Table 3: Comparison of VAS pain score

	Before treatment	One week after intervention	Three weeks after intervention	Six weeks after intervention	Twelve weeks after intervention
CG (n=60)	6.91±1.43	6.51±1.32	5.72±1.25	4.23±1.03	3.42±0.98
ComG (n=68)	6.93±1.48	5.45±1.28	4.13±1.15	3.02±0.82	1.97±1.01
$\chi 2/t$	0.0775	4.6075	7.4940	7.3909	8.2187
P	0.9383	<0.0001	<0.0001	<0.0001	<0.0001

Table 4: Comparison of adverse reaction rates

	Nausea and vomiting	Diarrhea	Stomach upset	Dizzy	Skin allergy	Total incidence
CG (n=60)	3(5)	2(3.33)	2(3.33)	1(1.67)	1(1.67)	9(15)
ComG (n=68)	1(1.47)	1(1.47)	1(1.47)	0(0)	0(0)	3(4.41)
$\chi 2/t$						4.2061
P						0.0403

Comparison of adverse reaction rates

By observing the occurrence of adverse reactions of patients during treatment, the incidence rate in the CG was 15%, and that in the ComG was 4.41%, with statistically evident difference (P<0.01), it was shown in table 4.

DISCUSSION

Among the various types of osteoarthritis, knee osteoarthritis is the most common in clinic. Due to violent trauma or long-term chronic injury induction, knee joint suffers from persistent inflammatory injury, resulting in the formation of hypertrophy and hydrops joint cavity. Daily activity restriction and pain are the main symptoms of the disease, which have a serious impact on the life and work of patients. Drug therapy has always been the main treatment method for osteoarthritis (Taylor 2018).

In this study, celecoxib alone and celecoxib combined with glucosamine hydrochloride therapy were applied to two groups of knee osteoarthritis patients, and the changes of indexes and functional recovery before and after intervention were observed. The results revealed that before intervention, there was no evident difference in the indexes (P>0.05). After intervention, the blood routine indexes IgM rheumatoid factor, albumin/globulin and erythrocyte sedimentation rate in the ComG were evidently better than those in the CG, and TNF-α, IL-6, IL-1β and hs-CRP were evidently lower than those in the CG. Studies have shown in table 2 that inflammatory cytokine IL-1β can promote the decomposition of articular cartilage. Under pathological conditions, in vivo IL-1β can promote cartilage cells to produce a large amount of matrix metalloproteinases, and it has no effect on tissue inhibitors of metalloproteinases, making the two out of balance and causing cartilage progressive destruction (Kosloski *et al*. 2016). TNF-α can stimulate chondrocytes and synovial synovial cells to secrete inflammatory transmitters, degrade articular cartilage and collagen, thus damaging marginal bone and further aggravating the patient's condition (Zhao *et al*., 2019). hs-CRP is a sensitive detection index among inflammatory factors, while IgM rheumatoid factor is a specific detection item for patients with rheumatoid arthritis, and its level is correlated with disease outcome (Arntz *et al*., 2018). Glucosamine hydrochloride can stimulate articular disc to produce proteoglycan, repair damaged tissues, improve metabolism and collagen content of bone and cartilage, inhibit enzyme synthesis in cartilage, inhibit oxidation degree of damaged cells, reduce production of inflammatory factors, relieve pain of patients and promote recovery of joint motion function. Glucosamine hydrochloride enters the blood circulation in the form of glucosamine, rapidly combines with proteins in plasma, and is easy to absorb (Bhathal *et al*., 2017). Celecoxib is a new generation compound with unique mechanism of action, namely, specific inhibition of cyclooxygenase -2. Inflammatory stimulation can induce the production of cyclooxygenase -2, thus leading to the synthesis and accumulation of inflammatory prostaglandins, especially prostaglandin E2, which can cause inflammation, edema and pain. Celecoxib can inhibit the production of inflammatory prostaglandins by inhibiting cyclo-oxygenase -2, thus achieving anti-inflammatory, analgesic and antipyretic effects (Kim *et al*., 2018; Puljak *et al*., 2017). At the same time, Lequesne score and VAS pain score of the ComG were lower than those of the CG after intervention. Glucosamine hydrochloride is a natural component in articular cartilage and an indispensable synthetic substance of aminoglycan. The substance can play a specific role in articular cartilage, maintain cartilage structure and hinder prostaglandin synthesis, so as to prevent chondrocytes from being damaged by harmful substances, relieve pain and slow down the degeneration speed of osteoarthritis (Bascoul-Colombo *et al*., 2016). The total incidence of adverse reactions of patients in the ComG was evidently lower than that in the CG. Celecoxib, as a specific inhibitor, has many similarities with non-steroidal anti-inflammatory drugs in

curative effect. Because of its short half-life (van Midwoud *et al*., 2018), it is difficult to accumulate *in vivo*, so it can effectively reduce adverse reactions of gastrointestinal tract. This study focused on the therapeutic effect of glucosamine hydrochloride combined with celecoxib on knee osteoarthritis. In recent years, other studies have focused on the therapeutic effect of glucosamine hydrochloride combined with other drugs on knee osteoarthritis, such as chondroitin sulfate. Studies have shown (Puigdellivol *et al*., 2019) that glucosamine hydrochloride combined with chondroitin sulfate can also reduce pain index and improve motor function of osteoarthritis patients. At the same time, glucosamine and chondroitin sulfate have shown strong effects on delaying the progression of knee osteoarthritis (Messina *et al*., 2019). A double-blind experiment pointed out (Navarro *et al*., 2020) that glucosamine hydrochloride combined with chondroitin sulfate reduced circulating IL-6 (an inflammatory cytokine), but in other aspects, the effect on other circulating protein biomarkers was similar to that of celecoxib. It can be seen that glucosamine hydrochloride combined with celecoxib has the same curative effect on knee osteoarthritis as other methods, which is worthy of clinical promotion.

To sum up, the combined treatment of celecoxib and glucosamine hydrochloride for knee osteoarthritis patients can evidently improve clinical symptoms, improve the effect of cartilage repair, have a good effect on functional recovery, and reduce the level of inflammatory factors, which is worthy of clinical application.

CONCLUSION

Celecoxib with glucosamine hydrochloride has a significant effect on the treatment of knee osteoarthritis, which can effectively reduce the level of inflammatory factors, improve the motor function of patients and relieve their pain, and has little adverse reactions. It is an effective way to treat knee osteoarthritis clinically.

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