doi.org/10.36721/PJPS.2023.36.4.SP.1337-1341.1

Effects of glucosamine hydrochloride combined with non-steroidal anti-inflammatory drugs on symptoms and *HSS scores* in patients with knee osteoarthritis

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Abstract: To investigate the effects of glucosamine hydrochloride combined with non-steroidal anti-inflammatory drugs on symptoms and HSS scores in patients with knee osteoarthritis (KOA). Totally 80 cases of patients with KOA admitted to Cangzhou Hospital of integrated TCM-WM from February 2016 to December 2019 were selected and divided into the Control Group and Observation Group by Random Number Table Method, with 40 cases in each group. After treatment, the Observation Group tends to have lower VAS scores and WOMAC scores than the Control Group (P<0.05). The Observation Group tends to perform better than the Control Group on symptom improvement rate and HSS scores (P<0.05). The expression levels of related inflammatory factors and matrix metalloproteinase (MMPs) are similar before and after treatment in the Control Group (P>0.05). The expression levels of related inflammatory factors and MMPs get lower after treatment in the Observation Group (P<0.05). The evaluation indexes and total scores of the Observation Group are better than those of the Control Group (P<0.05). Glucosamine hydrochloride combined with non-steroidal anti-inflammatory drugs treatment could decrease the expression levels of inflammatory cytokines, relieve knee pain and arthritis symptoms, improve knee function and improve the HSS scores in patients with KOA.

Keywords: Knee osteoarthritis, platelet-rich plasma, sodium hyaluronate, HSS scores.

INTRODUCTION

Knee osteoarthritis (KOA) is an important component in orthopedic diseases, but the pathogenesis remains unclear. Evidence suggests that the degenerative disease of articular cartilage and synovium and imbalance of cartilage matrix synthesis and catabolism play a key role. Its clinical manifestations include knee pain, stiffness, swelling, limited activity, and impaired muscle strength (Cantrell *et al.*, 2020). At present, the main purpose of the treatment is to relieve symptoms and improve knee function (Ishii *et al.*, 2020). Intraarticular hyaluronic acid (HA) injection has been demonstrated effective to relieve pain and improve joint dysfunction and is widely used in KOA (Alekseeva *et al.*, 2020). But it is limited in the widespread use of KOA that it cannot promote the regeneration of damaged cartilage. Non-steroidal anti-inflammatory drugs are the first-line treatments for knee arthritis and have significant effects on relieving joint pain and swelling. Glucosamine hydrochloride is a glycoprotein that can stimulate chondrocytes to produce a normal multimeric structure, which can protect chondrocytes (Gregori *et al.*, 2018). This study, therefore, sets out to assess the effect of glucosamine hydrochloride combined with non-steroidal anti-inflammatory drugs and investigate the effect of the symptoms of knee joint and arthritis and HSS scores.

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MATERIALS AND METHODS

General materials

Totally 80 cases of patients with knee osteoarthritis admitted to Cangzhou Hospital of Integrated TCM-WM from February 2016 to December 2019 were selected as subjects. Inclusion Criteria: a) Diagnosed with KOA (Shresher *et al.*, 2019); b) Radiological degree ≥II according to the Kellgren-Lawrence scale; c) The symptoms of knee pain and/or swelling are not significantly improved after more than half a year of conservative treatment; d) Learn about the study and sign the informed consent. Exclusion Criteria: a) With severe cardiovascular disease; b) With serious knee injury; c) With rheumatoid arthritis, gout, liver and kidney diseases, diabetes, immune system diseases, tumors, etc.; d) With a history of open knee surgery; e) Have received other relevant treatments (intraperitoneal injection of glucocorticoids, ozone, anesthesia, etc.) within a year. All patients were divided into the Control Group and the Observation Group by random number table method, with 40 cases in each group. No statistical significance was observed in the general information of the two groups (P>0.05) (table 1).

Methods

Control Group

Took a non-steroidal anti-inflammatory drug, loxoprofen sodium (Shanghai Daiichi Sankyo Pharmaceutical, SFDA approval no: H20030769) orally, 60mg each time, 3 times a day.

Observation Group

Observational group was given glucosamine hydrochloride capsules (Zhejiang Chengyi Pharmaceutical, SFDA approval No. H20060748) basis on the control group, 0.24g each time, 2 times a day. Weeks were considered a course of treatment and both groups were treated with 2 consecutive courses of treatment.

Observation indicators

All patients were followed up for 3 months after treatment and the following outcomes are assessed. a) VAS (Higuchi *et al.*, 2020). The visual Analogue Scale (VAS) is used to determine the pain intensity experienced by individuals. It includes 10 scales, "0" means "no pain," and "10" means "the worst imaginable pain." b) WOMAC (Leoni *et al.*, 2020). The Western Ontario and McMaster Universities Arthritis Index (WOMAC) is a multidimensional measure of pain, stiffness and physical functional disability, the higher the scores, the more severe the disease. c) Clinical curative effect. Markedly effective, symptoms disappear with normal joint activity; Effective, symptoms progresses with basically joint movement, accompanied by mild limitation; Ineffective, symptoms and joint motion are not significantly improved.

$$\text{Total efficient} = \frac{(\text{markedly effective}+\text{effective})}{\text{Total}} \quad 100\%$$

d) Related factors in peripheral blood. The serum concentrations of IL-1, IL-6, TNF-α, MMP-13, and MMP-9 are detected by enzyme-linked immunosorbent assay prior to treatment and 3 months after treatment. e) HSS (Wang *et al.*, 2019). Hospital Special Surgery knee score (HSS) is used to evaluate knee function. The full score is 100, including pain (30 points), function (22 points), mobility (18 points), muscle strength (10 points), stability (10 points) and flexion deformity (10 points). The higher the score is, the better the function of the knee joint is.

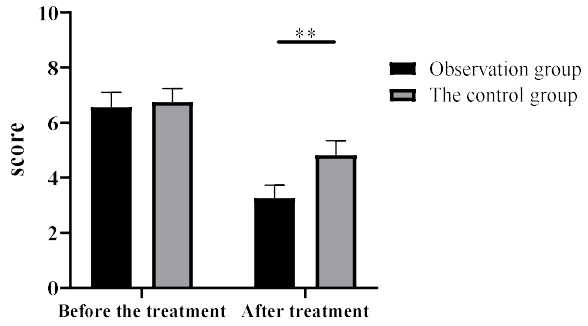

Fig. 1: VAS scores
***P*<0.01: compared with the Control Group.

Ethical approval

The study was approved by the Ethics Committee of Cangzhou Hospital of integrated TCM-WM, No.2015093578, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from patients involved in the study.

STATISTICAL ANALYSIS

All analyses are carried out using SPSS, version 20. Enumeration data is expressed as mean ±standard deviation (mean ±SD) and tested by t test. Qualitative data is expressed as a percentage (%) and tested by the $\chi 2$ test. Differences are considered significant at $P<0.05$.

RESULTS

Comparison of VAS scores

The comparison of VAS scores was shown in fig. 1. Before treatment, the VAS scores of the two groups were comparable with no significant difference ($P>0.05$), while 3 months after treatment, the VAS scores were decreased in all groups and lower in the Observation Group ($P<0.05$).

Comparison of WOMAC scores

The comparison of WOMAC scores was shown in fig. 2. Before treatment, the difference between the two groups in WOMAC scores was not significant (P>0.05). While 3 months after treatment, the WOMAC scores were decreased in all groups and lower in the Observation Group ($P<0.05$).

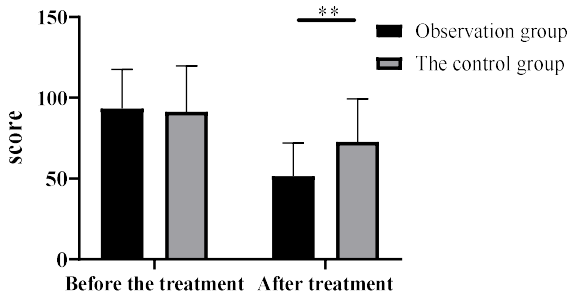

Fig. 2: WOMAC scores
***P*<0.01: compared with the Control Group

Comparison of arthritis symptoms

The Observation Group yielded a higher improvement rate of arthritis symptoms at 3 months after treatment when compared with the Control Group (table 2).

Comparison of arthritis related factors

Before treatment, the serum levels of IL-1β, IL-6, TNF-α, MMP-9 and MMP-13 were comparable between the two groups ($P>0.05$). While 3 months after treatment, all those factors were lower in Observation Group than before treatment and Control Group ($P<0.05$) (tables 3 and 4).

Table 1: General Information

	Gender (n, %)		age ($\bar{x}$±s, year)	Duration ($\bar{x}$±s, year)
	Male	Female		
Observation Group (n=40)	21 (52.50)	19 (47.50)	59.23±3.96	3.29±1.12
Control Group (n=40)	20 (50.00)	20 (50.00)	58.86±4.12	3.52±0.96
χ^2/t	0.050		0.0394	0.9861
P	0.500		0.969	0.327

Table 2: Arthritis symptoms (n, %)

	Special Effect	Valid	Invalid	Total Efficient
Observation Group (n=40)	15 (37.50)	21(52.50)	4 (10.00)	36(90.00)
Control Group (n=40)	9 (22.50)	19 (47.50)	12 (30.00)	28(70.00)
χ^2				5.000
P				0.024

Table 3: Inflammation-Related Factors ($\bar{x}$±s, ng/L)

	IL-1β		IL-6		TNF-α	
	before treatment	after treatment	before treatment	after treatment	before treatment	after treatment
Observation Group (n=40)	25.56±8.02	13.75±6.53*	35.88±8.46	14.89±7.64*	40.37±9.51	21.75±8.62*
Control Group (n=40)	25.78±7.36	25.53±7.94	36.57±8.26	35.83±8.74	39.57±8.72	38.35±9.26
t	0.1278	7.247	0.3691	11.41	0.3921	8.299
P	0.899	<0.001	0.713	<0.001	0.696	<0.001

**P*<0.05 compared with before treatment

Comparison of HSS scores

Before treatment, the difference between the two groups in HSS scores was not significant (*P*>0.05). While 3 months after treatment, higher scores were observed in all groups and significantly higher HSS scores in the Observation Group when compared with the Control Group (*P*<0.05) (table 5).

DISCUSSION

Clinically, trauma, and knee degenerative diseases, are considered the common causes of KOA, which can cause pain, knee swelling, mobility and many other adverse symptoms (Sgroi *et al.*, 2020). It is now well established that HA can reduce the friction between the synovial membrane and the joint, delay the progression of synovial inflammation, which is conducive to promoting the synovial softening and healing (Zhuang *et al.*, 2018). Extensive research has shown that most patients with KOA cannot repair themselves and it is difficult to repair the damaged cartilage themselves (Ha *et al.*, 2019). Non-steroidal anti-inflammatory drugs are anti-inflammatory, antipyretic and analgesic drugs that do not contain glucocorticoids. They are mainly used in the treatment of osteoarthritis (Sun *et al.*, 2020). The mechanism of action is to inhibit the synthesis of prostaglandins in the body, playing an analgesic and anti-inflammatory effect (Blanco *et al.*, 2019). Glucosamine is a compound widely found in nature. One hydroxyl group of glucose is replaced by one amino group (Jevsevar *et al.*, 2018). Glucosamine hydrochloride can be hydrolyzed into amino monosaccharides, which promote the production of proteoglycans and proteoglycans in articular cartilage and inhibits the production of superoxide free radicals, promoting the repair of cartilage cells and the formation of cartilage matrix and preventing the further development of knee osteoarthritis (Armagan *et al.*, 2015) .

Previous studies have established that the peptide growth factors could regulate the synthesis and catabolism of cartilage (Zanotto *et al.*, 2019). Keeping the dynamic balance of the number of decomposable and syngenetic cytokines in vivo could maintain the balance of articular cartilage matrix synthesis and decomposition. As decomposed cytokines, IL-6, IL-1, and TNF-α are involved in the pathogenesis of KOA and are closely related to the degradation of intraarticular cartilage matrix, synovial inflammatory lesions ,and interference of chondrocyte function in osteoarthritis (Yamada *et al.*, 2021). By decomposing the extracellular matrix of articular cartilage, MMPs could cause articular cartilage to well, reduce immunity to the outside world and then lead to further damage to articular cartilage (Pajak *et al.*, 2017). In the early stage of KOA, the difference in the number of decomposed and synthetic cytokines is very

Table 4: Concentration of MMPs ($\bar{x}$±s, ng/L)

	MMP-9		MMP-13	
	before treatment	after treatment	before treatment	after treatment
Observation Group (n=40)	875.62±91.88	582.67±78.36*	852.34±92.56	550.37±84.65*
Control Group (n=40)	865.24±83.49	875.62±91.88	842.68±88.71	853.46±96.42
t	0.5288	13.52	0.4765	14.94
P	0.598	<0.001	0.635	<0.001

**P*<0.05 compared with before treatment

Table 5: HSS scores

		Pain	Function	Mobility	Muscle Strength	Stability	Flexion Deformity	Total
Observation Group (n=40)	before treatment	12.43±2.32	8.12±2.43	4.53±1.26	3.75±1.06	3.24±1.15	4.21±0.89	37.52±2.84
	after treatment	21.95±1.76*	15.83±1.84*	11.35±1.46*	8.24±1.41*	8.02±0.86*	8.13±0.75*	72.63±4.67*
Observation Group (n=40)	before treatment	12.67±2.06	8.41±1.96	4.75±1.39	3.82±1.35	3.48±1.07	4.06±0.78	38.36±2.68
	after treatment	18.31±1.84*	12.67±1.65*	7.13±1.24*	5.67±1.28*	5.47±0.95*	5.87±0.69*	57.39±4.28*
t_{before}		0.4906	0.5875	0.7417	0.2579	0.9663	0.8016	1.361
P_{before}		0.626	0.558	0.460	0.797	0.337	0.425	0.178
t_{after}		9.041	8.087	13.93	8.535	12.59	14.03	15.22
P_{after}		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

**P*<0.05 compared with before treatment

small. If not timely diagnosed and treated, it will come to the middle and late stage, causing degeneration of articular cartilage cells, making decomposed cytokines like IL-1, IL-6,and TNF-α excessively expressed, inducing the synthesis of proteoglycan. This will eventually lead to inhibition of proteoglycan synthesis and chondrocyte division. The pathologically high expression of decomposing cytokines, such as IL-1 and IL-6, would stimulate the over-expression of MMPs, aggravate the imbalance between the synthesis and degradation of extracellular matrix and increase the extent of cartilage damage (Nees *et al.*, 2019). In addition, TNF-α also can stimulate the cartilage cells to produce toxic NO, causing cellular damage (Li *et al.*, 2020). Then, IL-1, IL-6, and TNF-α could aggravate the immune reaction as inflammatory factors (Denstaedt *et al.*, 2020). To sum up, if not diagnosed and treated timely, KOA will come to the middle and late stage, increasing the pathologic secretion of decomposing cytokines, causing the imbalance of MMPs secretion. This is the key link in the development of KOA.

The results showed that after treatment, the VAS scores and WOMAC of the Observation Group were lower than those of the Control Group and the symptom improvement degree and HSS scores of the Observation Group were better than those of the Control Group, significant differences were recorded (P<0.05). Compared with HA treatment, PRP treatment can better relieve patients' pain, joint disorders and other symptoms, facilitate the recovery of patients' joint function and provide a more satisfactory therapeutic effect. This study reported significantly lower levels in the expression of IL-1, IL-6, and TNF-α of KOA patients after PRP treatment. It indicated that the injection of PRP could significantly reduce serum inflammatory factors IL-1, IL-6 and TNF-α expression levels, reduce the secretion of MMP-9, MMP-13 ,and reduce inflammation. Thus, the function of the knee joint can be effectively improved. HA can relieve the pain and inflammation of KOA, but cannot improve the degeneration and injury of articular cartilage.

CONCLUSION

Taken together, these results suggest that glucosamine hydrochloride combined with non-steroidal anti-inflammatory drugs treatment could decrease the expression level of inflammatory cytokines, relieves knee pain and arthritis symptoms, improve knee function and improve the HSS scores in patients with knee osteoarthritis. The findings of this study have several important implications for future practice.

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