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Original Article

Study on the clinical efficacy of Mongolian medicine in the treatment of osteoarthritis

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Abstract: Objective: The object of this paper was to evaluate the clinical efficacy and safety of Mongolian medicine in the treatment of osteoarthritis (OA). This was completed by offering evidence to provide a clinical basis for the treatment of OA. We explored the mechanism of the sticking application of Mongolian medicine. Method: A total of 123 patients with OA diagnosed in the Affiliated Hospital of Inner Mongolia Medical University from January 2017 to December 2017 were enrolled. The clinical data of the patients were retrospectively analyzed. Patients were divided into three groups according to the medication they were using at the time: The strapping group, the glucosamine hydrochloride group, and the Mongolian medicine group, with 41 patients in each group. The treatment indicators of the included patients 2 weeks after the treatment and 4 weeks after the treatment were fully recorded in our hospital. The levels of CGRP, TNF-α, MMP-3, VEGF, and IL-10 before and after treatment were measured by ELISA. The auxiliary diagnostic index was X-ray film. Results: Compared with the control group, the Mongolian medicine group improved the symptoms of pain, swelling, limited movement, and daily life quality of patients to different degrees. There was a significant decrease in the VAS score at each time point of the Mongolian medicine group ($P < 0.05$). ŧThe scores of bodily pain in SF-36 QOL were significantly higher in the Mongolian medicine group at different time points ($P < 0.05$). After treatment, the levels of MMP-3, TNF-α, VEGF, and CGRP in the Mongolian medicine group were significantly lower than those before the treatment ($P < 0.05$). Conclusion: Mongolian medicine can inhibit the expression of MMP-3, TNF-α, VEGF, and CGRP in serum, and up-regulate the trend of IL-10, alleviating the inflammatory reaction. It has a good curative effect in the treatment of OA patients. It is better than western medicine in pain, swelling, and improving bone and joint function index.

Keywords: Mongolian medicine, osteoarthritis, randomized contrast, WOMAC pain score

Introduction

Osteoarthritis (OA) is a chronic degenerative osteoarthritis characterized by a degeneration of articular cartilage and pathological changes of synovial and subchondral bone [1]. Many factors, including inflammation, heredity, and trauma, can lead to OA [2]. In recent years, the overall incidence rate has increased, the age of the patients has decreased, the disability rate of the disease has become higher, and the control of the disease has been poor, which has caused pain and a severe economic burden to the majority of patients [3]. In the treatment of OA, modern medicine includes non-steroidal anti-inflammatory drugs and surgical treatment. The treatment has been relatively mature, but there are gastrointestinal and cardiovascular disease risks and postoperative complications. These can bring patients certain troubles including not alleviating the progress of OA [4]. Exploration for the prevention and treatment of OA in the early and middle stages is a hot topic of global concern.

In Mongolian medicine, OA belongs to the category of "joint yellow hemolymph disease" [5], which is characterized by joint pain, swelling,

and limited mobility. It is believed that wind, cold, dampness, and injury can lead to the imbalance of the "three roots" of the human body, resulting in excessive yellow hemolymph, stasis in the bones and joints so that the movement of Qi and blood in the joints is blocked [6]. The Mongolian medicine sticking therapy has a long history in treating yellow hemolymph disease. It inhibits Heyi, dispels Xila, relieves pain and detoxification, and is highly effective, safe, without side effects, is simple and easy to operate, and does not produce drug dependence [7].

The long term prevention and treatment effect of OA is not ideal. Most people believe that the clinical symptoms, course, and progression of OA cannot be controlled or significantly improved with drugs and other combined therapies [8]. More efforts are needed to strengthen the research on OA, enhance the level of prevention and treatment, strengthen the public's correct understanding of OA, reduce the disability rate, and improve patients' quality of life. For the western treatment of OA, the primary treatment is symptomatic treatment, including non-steroidal anti-inflammatory drugs or analgesics to reduce pain. These auxiliary instruments can reduce the burden of the affected knee [9].

The doctor of traditional Chinese medicine (TCM) has its unique theoretical system. TCM believes that the pathogenesis of OA includes liver and kidney deficiency, blood stasis, and phlegm wetness. Treatment including tonify deficiency, lethargy, dispelling stasis, dehumidification, and inside and outside governance, has obtained good curative effect. It is worth promoting in clinical practice [10].

Mongolian medicine (Mongolian name: Yashuneridun) is a Mongolian medicine patch for external use, often used in clinical osteoporosis, rheumatoid arthritis, and waist and leg pain. It is a commonly used essential treatment method for the clinical treatment of OA in Mongolian medicine and is suitable for the current needs of treatment [11]. The study of clinical efficacy and the research on the mechanism of the application therapy is not comprehensive. Yashuneridun has been used in clinical practice, but the advantages of Yashuneridun in treating OA and the specific mechanism of action are unknown. This study's most significant innovation is exploring the inflammatory mechanism involved. Mongolian medicine was selected to stud the Mongolian medicine sticking therapy in this paper. The clinical trial designed a treatment group and two control groups for the randomized trials of a large sample. The quantitative scoring tables were used to test the biomarkers to evaluate the positive effect of Mongolian medicine sticking therapy on OA.

Method

Subject sources

A total of 123 patients with OA treated in the Affiliated Hospital of Inner Mongolia Medical University from January 2017 to December 2017 were retrospectively enrolled and divided into three groups, with 41 patients randomly assigned for the study. The testing program was approved by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University and approved for clinical trial.

Medicine and reagents

Mongolian medicine group

Mongolian medicine (Inner Mongolia Horqin Pharmaceutical Co., Ltd., batch number: 18060503). Mongolian treatment consisted of 6 g of Asiatica, 9 g of monkshood-tuber, 9 g of rhizoma typhoid, 9 g of prepared kusnezoff monkshood root, 9 g of preparemonkshd motor root, 9 g of rhizoma arisaematis, 9 g of lignum millettiae, 6 g of menthol, 6 g of borneol, and 4 g of camphor. Usage: clean the skin of the affected area and apply daily for 28 days of treatment.

Tianhe strapping group

Tianhe Gutong Strapping (Guilin Huarun Tianhe Pharmaceutical, batch number: 20170710). It consisted of obtuse leaf erycibe stem, ephedra, angelica Sinensis, dried ginger, angelica dahurica, pepper stem, frankincense, Panax notoginseng, Curcuma, pepper, camphor, cinnamon oil, and menthol. Usage: clean the skin of the affected area and apply daily for 28 days of treatment.

Conventional drug group

Glucosamine hydrochloride (Jiangsu Zhengda Qingjiang Pharmaceutical Co., Ltd., batch num-

ber: 180502). Take 0.75 g once daily, 2 times a day for 28 days.

Subject selection

Inclusion criteria

(1) Meeting the criteria of *OA Classification of American Rheumatology Society* in 1995, the *Radiological Classification of OA* and *Functional Classification of OA* [12]; (2) Patients who conformed to the diagnostic criteria of "Joint Yellow Hemolymph Disease" in the *Chinese Medical Encyclopedia Mongolian Medicine Chapter* and *Mongolian Traditional Therapeutics* in the Mongolian textbook of national colleges and universities in 2014 [13]. (3) Mongolian medical syndromes and clinical symptoms and signs scored below the severity of the score, OA radiological classification criteria below IV (excluding IV), OA functional classification below IV (excluding IV). (4) The age of 40 to 75 years (including 40 and 75 years), gender free. (5) The duration of the disease not limited. (6) Those who had not used glucocorticoid for arthritis or received surgery within a month before. (7) Willing to sign informed consent to participate in the research voluntarily. (8) During his treatment in our hospital, he took one of the Gutong Strapping, glucosamine hydrochloride, and Mongolian medicine, and no crossover existed; (9) After 2 weeks and 4 weeks of treatment, all the indicators of treatment effect were completely recorded in our hospital.

Exclusion criteria

(1) Mongolian medicine syndrome and clinical symptoms and signs score above moderate, OA radiological classification standard above IV, OA function classification above IV. (2) Bone and joint diseases (e.g. rheumatoid diseases, trauma, bone tuberculosis, tumors, gout, hemochromatosis, hemophilia, neuropathy, ankylosing spondylitis, osteochondral lesions, and post-infectious arthritis. (3) Patients with chronic severe diseases such as cardiovascular and cerebrovascular diseases, liver, kidney, and hematopoietic system, thyroid dysfunction, calcium, and phosphorus metabolism and mental illness. The criterion is whether the patients are regularly treated with drugs. (4) Pregnant women, nursing women, or women who may become pregnant, critically ill or advanced patients. (5) Glucosamine, rubber allergy, hypersensitive constitution, and skin allergy. (6) Using glucocorticoid, arthritis, or other drugs for treatment or surgery 1 month before the test. (7) Long-term oral administration can affect the efficacy and safety. (8) Those who do not comply with the relevant provisions of medical clinical trials of the medical ethics committee of Inner Mongolia Medical University. (9) The records of various indicators of treatment effect are incomplete.

Observation indicators

Evaluation index

Main curative effect index: (1) VAS: applied in various pain evaluation indicators; 0 point indicates no pain; 3 points below indicate endurable slight pain; 4 to 6 points indicate pain and affecting sleep, endurable; 7 to 10 points suggest that the patient has sharp pain, which affects appetite and affects sleep. The degree of pain relief before and after the treatment was observed as an objective criterion for curative effect evaluation.

(2) Mongolian medicine syndrome and clinical symptoms and signs score: the primary index is the effective rate of treatment. The criteria refer to the criteria for judging the curative effect of OA syndrome in the *Guiding Principles for Clinical Research of New Drugs of Traditional Chinese Medicine* (2002) and the requirements for improving the symptoms of Joint yellow hemolymph Disease in the *Traditional Therapeutics of Mongolian Med*icine [14]. Clinical recovery: the clinical symptoms and signs of Mongolian medicine disappeared. The score of syndromes decreased by 95%. Significantly effective: the clinical symptoms and signs of Mongolian medicine improved and the score of syndromes decreased by 70% and remained less than 95%. Effective: the clinical symptoms and signs of Mongolian medicine improved, and the score of syndromes decreased by 30%, and less than 70%. Invalid: Mongolian medicine clinical symptoms, signs were not significantly improved or even aggravated, syndrome scores reduced by less than 30%.

The formula (Nimodipine) is: [(score before treatment - score after treatment) ÷ score before treatment] ×100%.

(3) The criteria for evaluating the efficacy of JOA for the cervical spine and the criteria for assessing the effectiveness of modified JOA for low back pain [15]; the highest JOA score of the cervical spine was 17 points, with a minimum score of 0 points; the highest JOA score for the lumbar spine is 29 points, with a minimum score of 0 points; the improvement of the cervical spine and lumbar function before and after treatment was assessed by improving index.

(4) Harris score [16]: it is commonly used to evaluate the effect of hip arthroplasty and arthroplasty. A total score of 100 points, 90 points or above is excellent, 80 to 89 points are good, 70 to 79 points are acceptable, and less than 70 points are wrong.

(5) WOMAC OA scale: widely used in patients with OA [17]. Joint pain, stiffness, and daily activity function are used to evaluate the OA of the knee.

The objectivity of the data can be guaranteed by comparing the alleviation of pain, the effective rate of clinical symptoms of Mongolian medicine, the functional grading of OA, and the cross-comparison with the scoring tables of various parts.

Secondary efficacy indicators: (1) Liver function, kidney function, blood routine, urine routine, and electrocardiogram (ECG) test were used to detect the toxic and side effects of drugs during the reaction period. An X-ray examination was used to assist with the diagnosis.

(2) SF-36 [18]: SF-36 scale is the primary evaluation of life quality, including daily activities, and emotional and disease impact degree. The scores before and after treatment were considered objective criteria for curative effect evaluation.

(3) Assessment of shoulder joint dysfunction: the assessment of joint dysfunction is usually based on its sound limb function as the primary reference standard [19]. When evaluating the degree of limb joint function loss, calculating the degree of motion of the affected limb joint and the degree of the typical healthy stem is necessary. The degree of limb function loss of the affected limb is obtained by using the weight index formula to evaluate the degree and grade of limb disability.

(4) Mayo Elbow Joint Function Scale (MEPS) [20]: the score was 100 points, including 45 points for pain, 20 points for motor function, 10 points for stability, and 25 points for daily activities. The scoring system has been widely used in the evaluation of elbow fractures.

(5) Kofoed Evaluation system [21]: the result evaluation is that a score of 85 to 100 points is excellent; a score of 75 to 85 is good; a score of 70 to 74 is acceptable; a score below 70 points is wrong. It is used to reflect ankle function.

(6) AOFAS Ankle-Hindfoot Scale [22]: this standard evaluates the ankle joint, subtalar joint, talus joint, and heel joint.

(7) Functional classification of OA [23]: activity limitation grading is often used to evaluate the severity of bone and joint function objectively. Level I can do various activities; level II is moderately restricted. One or more joints are discomforting or restricted, but they can perform normal activities; level III is limited and can take care of oneself without engaging in general activities; level VI is to lie in bed or sit only without taking care of oneself. This is used for grading and screening.

Baseline indicators

Sex, age, course of the disease, location of bone and joint, VAS, Mongolian medical syndrome and clinical symptoms and signs scoring table, cervical vertebra JOA efficacy evaluation standard, shoulder joint dysfunction evaluation, MEPS, modified JOA low back pain evaluation standard, Harris table, Xi'an outline-McMaster University WOMAC OA Scale, Kofoed Evaluation system, and AOFAS Ankle-Hindfoot Scale, SF-36; CGRP, TNF-α, MMP-3, VEGF, IL-10, and liver and kidney function, blood routine, urine routine, electrocardiogram examination; X-ray examination before treatment.

Statistical analysis

SPSS22.0 software was used for statistical analysis. All data were expressed as mean ± standard deviation ($\bar{x} \pm s$). Paired t-test was used for comparison before and after treatment, one-way ANOVA was used for comparison between multiple groups, and the x^2 test was used for grade data. Analysis of covariance was used to analyze various time points. The test level was set as $\alpha=0.05$.

Ethical review

The testing program was approved by the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University (No. KY2018004) and approved for the clinical trial. WHO China Clinical Trial Registration Center registered this test with the registration number ChiCTR1800015660.

Results

Completion of the test

A total of 210 patients were selected according to inclusion and exclusion criteria. Through preliminary screening, 50 cases (Thirty patients had incomplete data, 15 people with other serious chronic diseases, 5 people under the age of standard) were excluded. Thirty-seven patients were banned from the clinical screening (5 had soft tissue injuries; 14 had reached surgical treatment level and were in serious condition; 7 had to rule out rheumatoid arthritis; and 11 had other diseases). There were 123 patients selected. A total of 210 patients were chosen to be enrolled, 41 each taking precisely the three drugs (**Figure 1**).

Baseline analysis

Baseline analysis of the basic characteristics and clinical characteristics of social demography

The three groups' essential and clinical characteristics' baseline data were statistically analyzed. The results showed no significant difference between the three groups in age, duration, body mass index, and sex ratio. They were compared, as shown in **Table 1**.

Baseline analysis of illness severity

Through comparing the baseline severity of VAS, Mongolian medical syndrome, and clinical symptoms and signs score, cervical JOA curative effect evaluation standard, shoulder joint dysfunction evaluation, MEPS, improved JOA low back pain evaluation standard, Harris score, WOMAC score, Kofoed evaluation system and AOFAS Ankle-Hindfoot Scale, SF-36 score of the three groups, there was no significant difference between the indexes ($P > 0.05$). The comparability was good as shown in **Table 2**.

Results of efficacy evaluation

Main therapeutic indicators

VAS, Mongolian medical syndrome and clinical symptoms and signs score: As shown in **Figure 2A**, in the VAS aspect, the Mongolian medicine group decreased significantly two weeks and four weeks after treatment ($P < 0.01$), and four weeks of follow-up ($P < 0.05$) compared with that before treatment. It showed that Mongolian medicine can significantly improve the pain symptoms of patients with OA, with short-term and long-term effects. Compared with the control group, after two weeks, four weeks of treatment, and four weeks of follow-up, the Mongolian medicine group showed a better relief effect on bone and joint pain than the control group.

In the **Figure 2B-D**, it showed that there was no significant difference in the scores of symptoms and signs between the time points of the Mongolian medicine group ($P > 0.05$), but the cure rate and efficiency after four weeks of treatment were higher than those after two weeks of treatment. The cure rate and efficiency after four weeks of follow-up were higher than those after four weeks of treatment. This suggested that with the prolongation of the treatment period, Mongolian medicine can improve the pain, chills, tenderness, swelling, morning stiffness, walking ability, and other daily quality of life in patients with OA.

WOMAC pain, stiffness, and joint function score: As shown in **Figure 3A-C**, in the aspects of WOMAC pain, stiffness, and joint function score, there was a significant decrease between two weeks ($P < 0.01$) and four weeks ($P < 0.05$) after treatment. There was no significant difference between 4 weeks after treatment and four weeks after follow-up ($P > 0.05$). The scores of pain, stiffness, and function decreased significantly. This suggested that Mongolian medicine can relieve knee pain, stiffness, and joint motor function in a short period, and has a long-term effect. WOMAC pain score was significantly lower in the Mongolian medicine group than in the control group ($P < 0.05$), confirming the relief effect of Mongolian medicine on pain. The WOMAC stiffness score and joint function score showed that Mongolian medicine was like or superior to the control group.

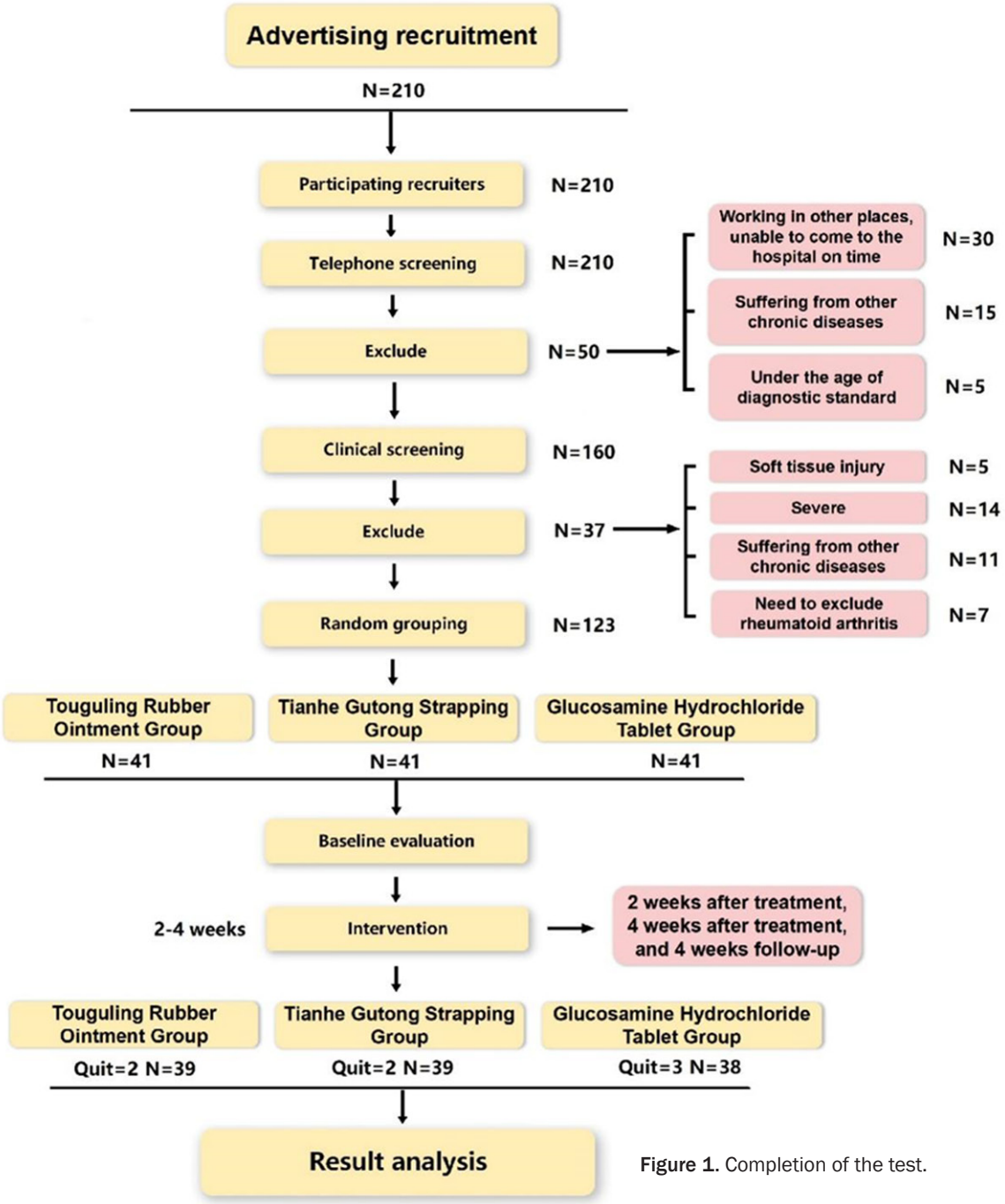

Figure 1. Completion of the test.

As shown in **Figure 3D-F**, there was no significant difference in the total effective rate of WOMAC scores at each time point ($P > 0.05$). The actual effective rate after four weeks of treatment was higher than that after two weeks, and the total effective rate after four weeks of follow-up was higher than that after four weeks. The real effective rate and the degree of improvement of each dimension integral showed that Mongolian medicine positively affected knee OA.

JOA curative effect evaluation standard and Harris score: **Figure 4A**, **4B** showed that the JOA scores of the Mongolian medicine group were significantly higher after two weeks of treatment than before, four weeks after treatment, and two weeks after treatment ($P <$

Table 1. Baseline analysis of the basic characteristics and clinical characteristics of social demography

Characteristics		Mongolian medicine Group (N=39)	Tianhe Strapping group (N=39)	Glucosamine Hydrochloride Tablet Group (N=38)	*P* value
Age (year)		56.40±9.09	56.03±8.22	56.35±8.78	> 0.05
Sex - no.	Male	8	9	10	> 0.05
	Female	31	30	28	> 0.05
BMI		24.70±3.78	24.45±3.10	24.4±3.76	> 0.05
Course of disease (month)		8.19±7.99	7.79±6.27	7.94±7.85	> 0.05
Knee osteoarthritis (case)		20	21	19	> 0.05
Cervical osteoarthritis of the facet joint (case)		3	4	3	> 0.05
Lumbar osteoarthritis (case)		9	7	9	> 0.05
Osteoarthritis of shoulder joint (case)		3	2	3	> 0.05
Osteoarthritis of ankle joint (case)		1	1	1	> 0.05
Osteoarthritis of hip joint (case)		1	1	1	> 0.05
Osteoarthritis of the hand (case)		1	3	2	> 0.05
Osteoarthritis of elbow joint (case)		1	0	0	> 0.05
Temperature (°C)		36.45±0.31	36.44±0.29	36.48±0.28	> 0.05
Respiration (second/min)		18.45±1.80	18.28±1.75	18.48±1.91	> 0.05
Heart rate (sub/min)		73.85±8.83	72.13±7.74	73.40±9.37	> 0.05

Note: P > 0.05, there was no significant difference between the three groups.

Table 2. Baseline analysis of Illness severity

Index		Mongolian medicine Group (N=39)	Tianhe Strapping group (N=39)	Glucosamine Hydrochloride Tablet Group (N=38)	*P* value
VAS		5.625±1.81	5.325±1.82	5.35±1.94	> 0.05
Mongolian medical syndrome and clinical symptoms and signs score		5.98±1.31	5.70±1.49	5.60±1.66	> 0.05
Cervical JOA curative effect evaluation standard		10.00±1.00	11.25±1.26	11.50±1.73	> 0.05
Shoulder joint dysfunction evaluation		25.67±0.58	25.50±0.71	25.33±1.53	> 0.05
MEPS		64.28±0.00	0	0	> 0.05
Waist JOA evaluation standard		22.22±1.72	22.71±1.60	22.67±1.58	> 0.05
Harris table		60.42±0.00	62.27±0.00	60.98±0.00	> 0.05
WOMAC	Pain score	5.50±1.36	4.70±1.59	5.45±0.90	> 0.05
	Stiffness score	2.95±0.22	2.95±0.22	2.77±0.37	> 0.05
	Functional score	17.65±3.30	15.67±1.93	16.16±2.50	> 0.05
Kofoed evaluation system		75.00±0.00	76.00±0.00	75.00±0.00	> 0.05
AOFAS		77.00±0.00	76.85±0.00	77.00±0.00	> 0.05
SF-36 table	Physiological function	60.31±3.51	59.46±2.62	59.54±3.01	> 0.05
	Social function	56.82±21.19	55.64±20.93	51.28±24.20	> 0.05
	Physical limitations	58.97±25.32	67.95±25.62	66.03±23.05	> 0.05
	Somatic pain	72.67±14.20	75.74±11.91	74.21±11.37	> 0.05
	Mental health	68.72±16.82	70.97±17.26	69.85±15.70	> 0.05
	Emotional intelligence	55.62±32.85	56.46±31.78	57.31±24.48	> 0.05
	Vitality	70.77±13.93	72.18±16.30	73.21±13.98	> 0.05
	Overall health	65.90±14.37	64.74±14.60	65.64±15.05	> 0.05

Note: P > 0.05, there was no significant difference between the three groups.

0.05). Comparing four weeks of follow-up with four weeks of treatment, the scores were improved and there was no significant difference (P > 0.05). Comparing the total curative effect of cervical JOA, there was an upward trend with the prolongation of the treatment period. The curative effect of the three groups was similar, suggesting that Mongolian medi-

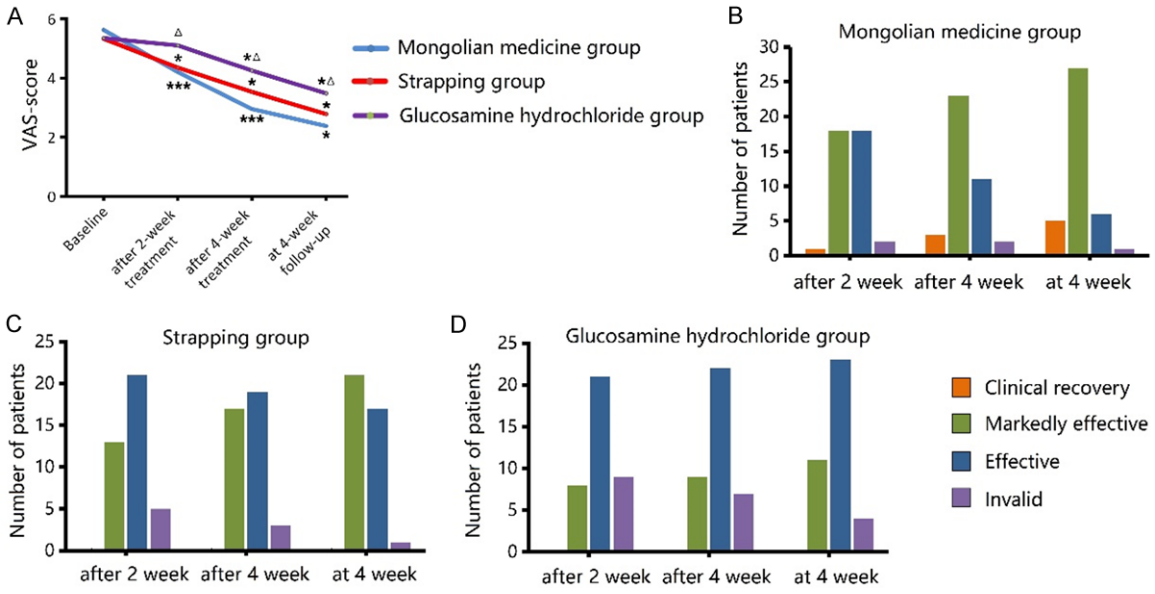

Figure 2. Comparison of VAS time difference, baseline difference, and curative effect at different time points. A: The patients in the treatment and follow-up period were compared within the group. There was a significant decrease ($P < 0.01$) after 2 weeks and 4 weeks of treatment in the Mongolian medicine group, and a significant decrease ($P < 0.05$) after 4 weeks of follow-up ($P < 0.05$). There was significant difference at each time point. Compared with the glucosamine hydrochloride group, there were significant differences in each time points between the two groups. B-D: There was no significant difference between the three groups at each time point ($P > 0.05$), but the cure rate and efficiency of the three groups increased significantly. Compared with baseline at each time point, * indicated $P < 0.05$, ***$P < 0.001$, Δ indicated that the comparison of the control group with the Mongolian medicine group was $P < 0.05$. Note: After 2 weeks: after 2-week treatment; after 4 weeks: after 4-week treatment; at 4 weeks: at 4 week follow-up.

cine was effective in treating cervical OA of facet joints.

Figure 4C, **4D** showed that the JOA score in the modified JOA low back pain group was significantly higher two weeks after treatment than before, four weeks after therapy than that two weeks after treatment ($P < 0.05$). There was no significant difference between 4 weeks after treatment and four weeks follow-up ($P > 0.05$), but the score differed. In the aspect of lumbar vertebra JOA, from the comparison between the groups and the total effective rate, the group of Mongolian medicine was better than the other two groups, confirming the curative effect of Mongolian medicine on lumbar OA. **Figure 4E** shows that there was 1 case in each group of Harris. It was impossible to compare between the groups and within the groups.

Secondary efficacy indicators

Kofoed and shoulder/elbow joint function evaluation system: **Figure 5A**, **5B** showed that there was 1 case in each group of the Kofoed evaluation system and the AOFAS Ankle-Hindfoot Scale. There was no comparison between the two groups or within the group. In the Mayo elbow function score criteria, there was one case in the Mongolian medicine group. There was no comparison between the two groups or within the group. The total effective rate of the elbow joint in the Mongolian medicine group was better than that in the other two groups (**Figure 5D**). As for the evaluation of shoulder collective loss, there was a significant increase in the treatment group ($P < 0.05$) after two weeks compared with that before treatment, four weeks after therapy than that two weeks after treatment ($P < 0.05$), and there was no significant difference between 4 weeks after treatment and four weeks after follow-up ($P > 0.05$). In terms of the improvement rate of shoulder joint loss, with the extension of treatment time, Mongolian medicine can improve the degree of shoulder collective loss (**Figure 5E**).

SF-36 life quality assessment form: In **Figure 6A-H**, it showed that in terms of bodily pain and

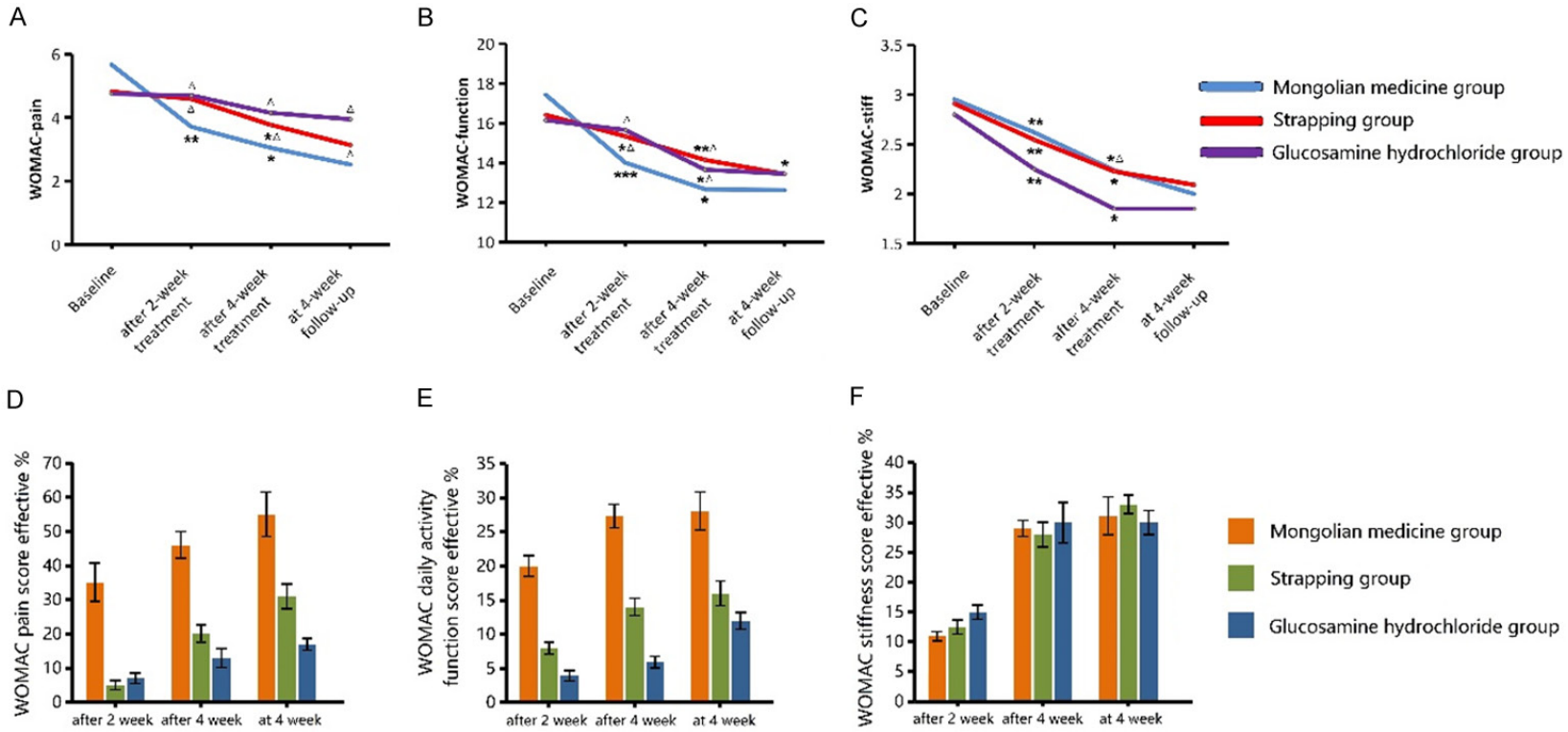

Figure 3. The difference of WOMAC scores, baseline, and the total efficiency at each time point. A: WOMAC pain score was significantly decreased in the Mongolian medicine group after 4 weeks of treatment ($P < 0.05$), and significantly decreased in the Mongolian medicine group than in the control group at all time points ($P < 0.05$). B: There was a significant difference in the WOMAC score in the Mongolian medicine group 4 weeks after treatment ($P < 0.05$). C: The stiffness score of WOMAC decreased significantly after 4 weeks of treatment ($P < 0.05$). D-F: The total effective rate of Mongolian medicine group in terms of pain, stiffness, and functional score showed an increasing trend at all time points. There were 20 cases in the Mongolian medicine group, 21 cases in the strapping group and 19 cases in the glucosamine hydrochloride group. (Comparing with baseline at each time point, * means $P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Δ means that the comparison of the control group and the Mongolian medicine group were $P < 0.05$).

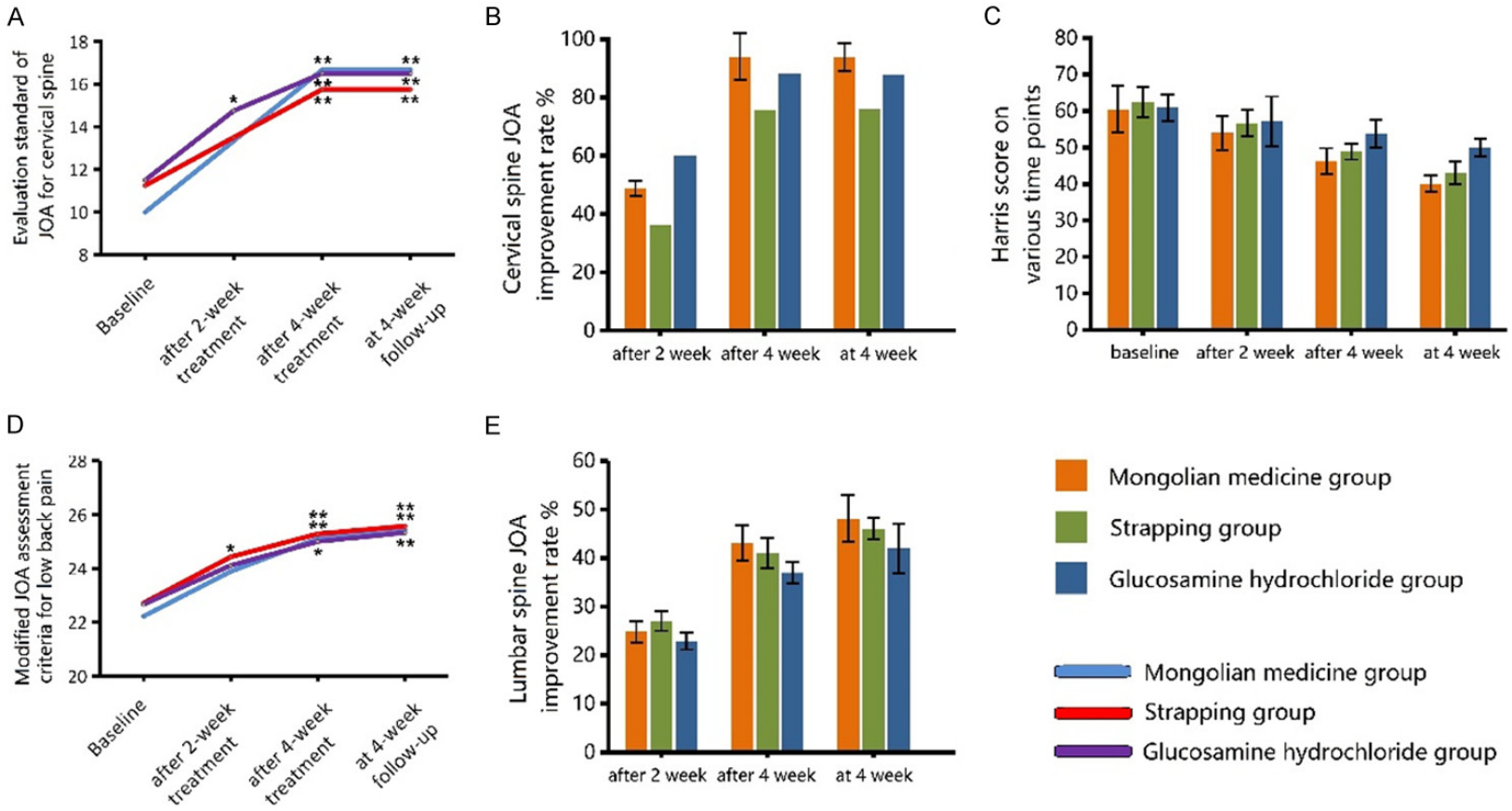

Figure 4. JOA curative effect evaluation standard and Harris score. A, B: After 2 weeks of treatment and 4 weeks of treatment, there was a significant increase in the Mongolian medicine group ($P < 0.05$). There was no significant difference between the control groups ($P > 0.05$). C, D: There was no significant difference within the Mongolian medicine group or between the groups ($P > 0.05$), but the total curative effect increased with the prolongation of treatment time. E: From the improvement of indicators, three groups of patients showed an improving trend. Each time point is compared with baseline, and * indicates $P < 0.05$.

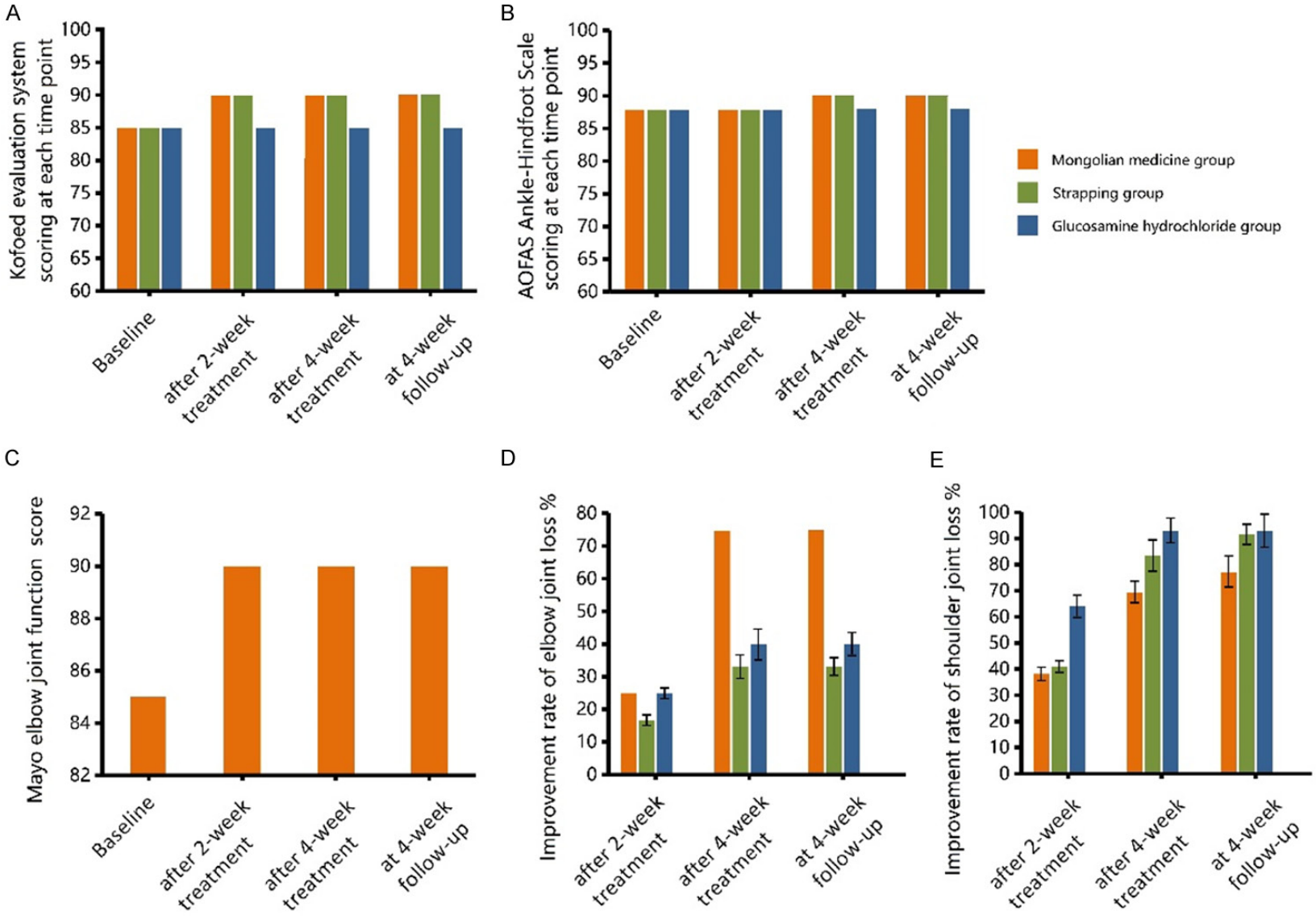

Figure 5. Kofoed and shoulder/elbow joint function evaluation system. A, B: The Kofoed evaluation system and AOFAS Ankle-Hindfoot Scale showed that there was no comparison among the three groups, but from the improvement of indicators, the three groups showed a trend of improvement. C, D: Through comparing the three groups of patients with hand osteoarthritis at each time point, the total effective rate of hand joint in the Mongolian medicine group was better than the other two groups. E: In terms of the improvement rate of shoulder joint loss, with the extension of treatment time, Mongolian medicine can better improve the degree of shoulder joint loss.

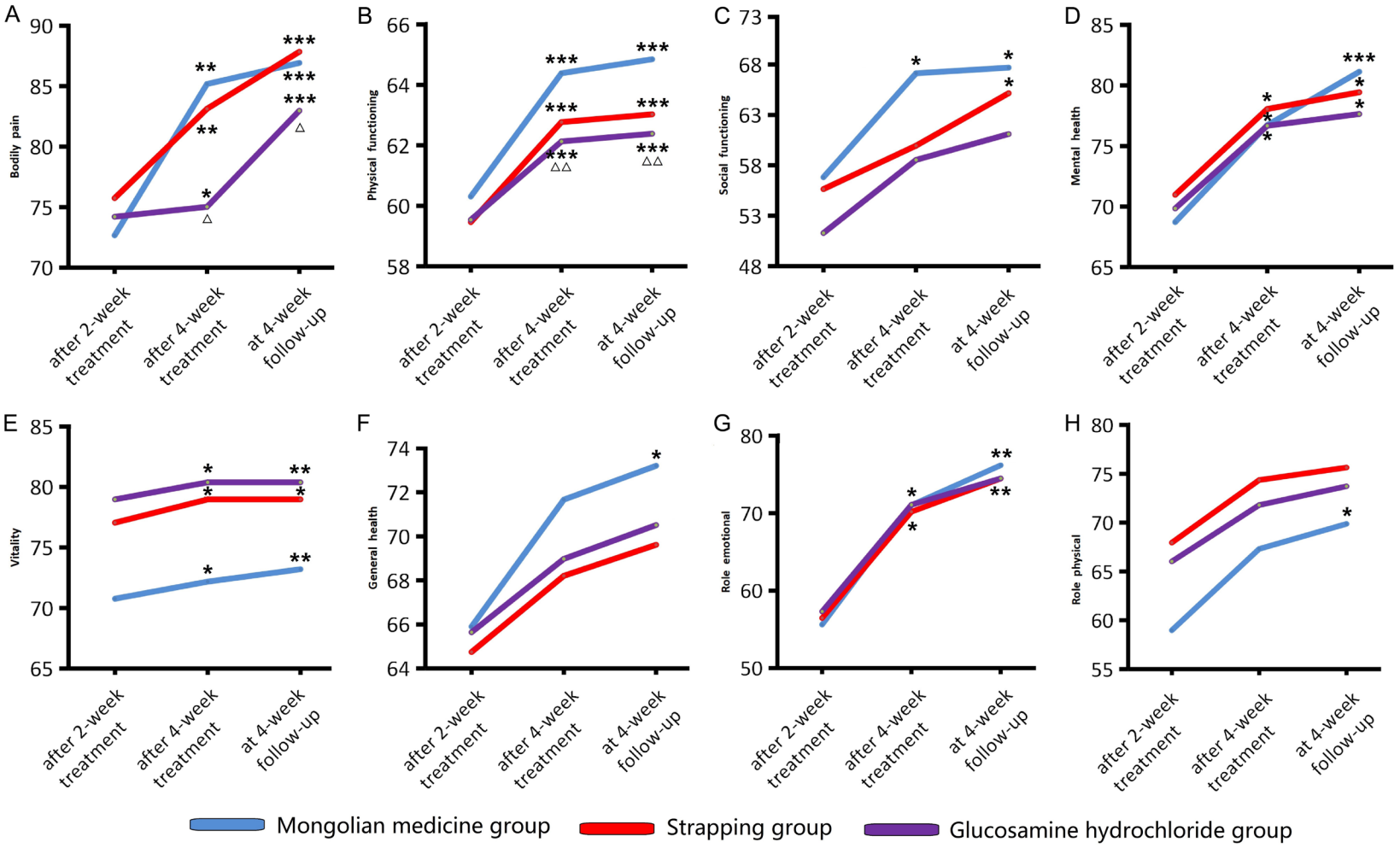

Figure 6. Comparison of SF-36 life quality assessment form with baseline differences. A: In terms of SF-36 pain, there was a significant increase in 4 weeks after the treatment in Mongolian medicine group ($P < 0.01$). B: Physiological function of the three groups was significantly higher after 4 weeks of treatment ($P < 0.01$). There was a significant difference between the Mongolian medicine group and the glucosamine hydrochloride group at each time point ($P < 0.05$). C: In terms of social function, there was a significant increase in 4 weeks after treatment Mongolian medicine group ($P < 0.05$). D, E: Mental health and vitality were significantly increased in the three groups after 4 weeks of treatment ($P < 0.05$). F, G: There was no significant difference in life health and life function among the three groups at each time point after treatment ($P > 0.05$). H: In terms of emotional intelligence, there was a significant increase in the Mongolian medicine group and strapping group after 4 weeks of treatment ($P < 0.05$). (Comparing with baseline at each time point, * means $P < 0.05$, **$P < 0.01$, ***$P < 0.001$, Δ means that the comparison of the control group and the Mongolian medicine group were $P < 0.05$).

physiological function, the scores of the Mongolian medicine group were significantly higher after four weeks of treatment than before ($P < 0.01$), and there was a significant increase after four weeks of follow-up compared with four weeks of treatment ($P < 0.05$). In terms of mental health, vitality, and emotional function, there were significant differences between the two groups after four weeks of treatment and before treatment ($P < 0.05$). There was no significant difference between 4 weeks of treatment and four weeks of follow-up ($P > 0.05$). Regarding social function, there was a substantial increase in the score index between 4 weeks after treatment and four weeks after follow-up ($P < 0.05$). There was no significant difference in physiological function and general health ($P > 0.05$). Compared with the glucosamine hydrochloride tablet group, Mongolian medicine's body pain and physiological function were significantly higher at each time point ($P < 0.05$), and other aspects were better than the control group. From the data analysis, Mongolian medicine can interfere with the scores of each dimension of the SF-36 Quality of Life Scale and has a good effect on pain, joint motor function, emotional anxiety, and the improvement of quality of daily life.

Detection results of OA-related biomarkers: **Figure 7A-E** showed that the MMP-3 level in the Mongolian medicine group decreased significantly after four weeks compared with that before the treatment ($P < 0.01$). The MMP-3 level in the two control groups reduced significantly ($P < 0.05$). After treatment for four weeks, the TNF-alpha of the three groups decreased, especially compared to before treatment ($P < 0.05$). The VEGF of the three groups had a significant decrease after four weeks of treatment compared with that before treatment ($P < 0.05$). The IL-10 of the three groups increased after four weeks of treatment compared with that before the treatment ($P > 0.05$), but the IL-10 index had a distinct upward trend. After four weeks of treatment, there was a significant decrease in CGRP in the Mongolian medicine group compared to before the treatment ($P < 0.05$).

Discussion

OA is the most common bone and joint disease, which can cause joint pain, swelling, limited movement, and even disability [24]. With the population's aging, the disease's overall incidence has increased, and the age of the disease has become younger. It was reported to become one of the fourth major disability diseases in 2020 [25]. There are many treatments for OA, but there remain some problems, such as unsatisfactory results or toxic side effects. Mongolian medical paste therapy has a long history and is widely used in the treatment of OA. The curative effect is widely recognized, but there are some problems, such as the unclear mechanism of action [26]. According to the above characteristics, this experiment selected the sticking therapy, designed two control groups of western medicine and Chinese medicine, and used VAS scores to compare between groups. They used CGRP, TNF-α, MMP-3, VEGF, and IL-10 index changes to observe the mechanism of the medicine. Two control groups were designed, including Gutong plaster. According to the reports, glucosamine hydrochloride were recognized as bone protectors with fewer side effects [27]. The efficacy and biological impact of Mongolian medicine in the treatment of OA is observed objectively.

The analysis of the research results showed that Mongolian medicine can relieve pain symptoms, improve joint movement, improve mental anxiety and swelling, and improve the quality of life. 1. Pain evaluation results showed that Mongolian medicine played a role in the short-term and long-term pain relief effect. The overall effect was better than that of the control group. 2. Joint function evaluation results showed that Mongolian medicine can directly improve joint movement and joint movement ability. 3. It plays a vital role in social, mental health, vitality, and emotional functions. 4. According to the scores of clinical symptoms and signs of Mongolian medicine, Mongolian medicine can improve the symptoms of joint swelling. 5. JOA scores and other scales cross-repeated results showed that Mongolian medicine could improve the overall efficacy of OA. The improvement in pain, swelling, emotion, and quality of life was better than that of the two control groups. 6. The Mongolian medicine can reduce the indexes of CGRP, TNF-α, MMP-3, VEGF, up-regulate IL-10, and play an anti-inflammatory role.

The OA is called "joint yellow hemolymph disease" in Mongolian medicine. "Three Roots, Seven Elements, and Three Pollutants" is an

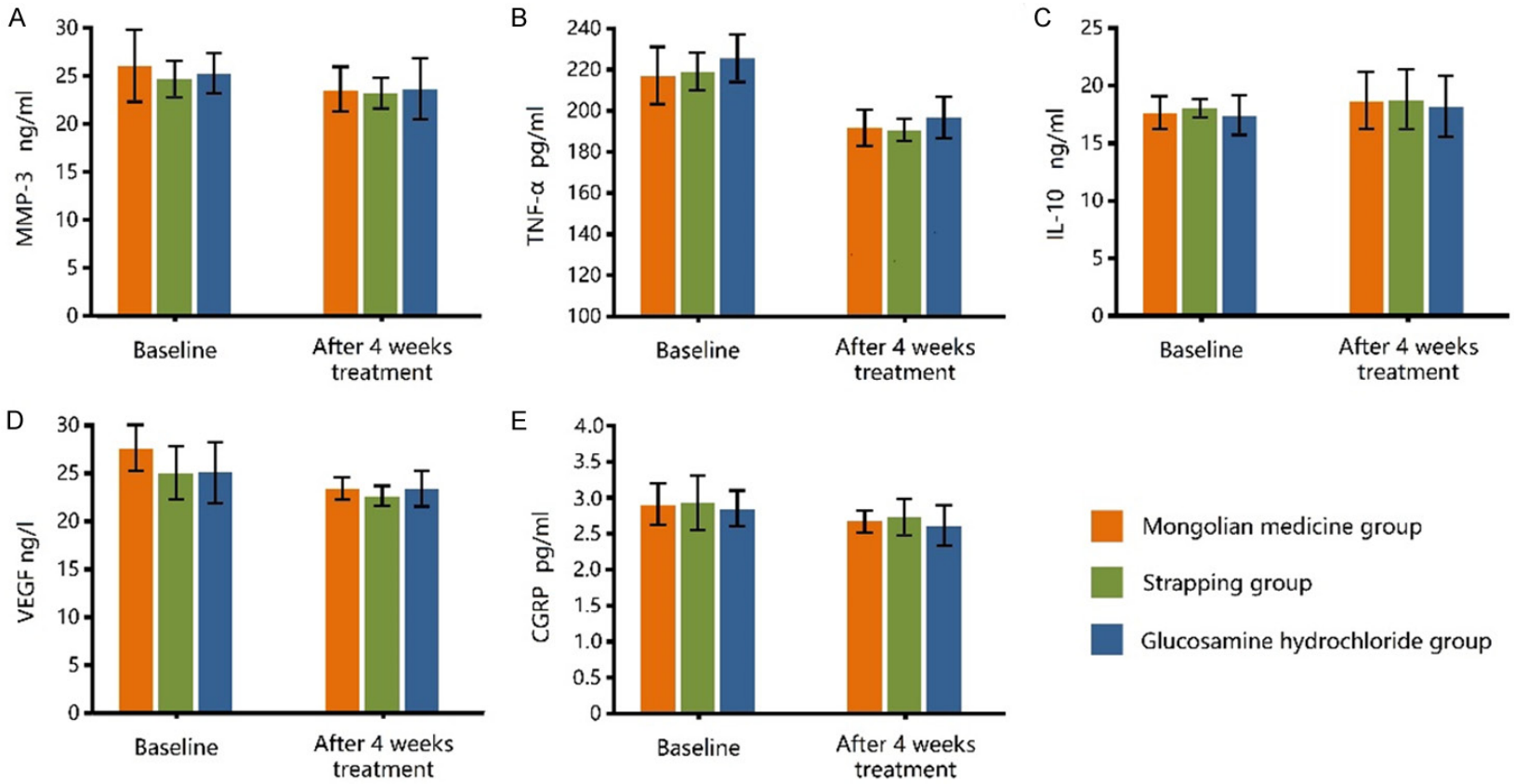

Figure 7. Detection results of osteoarthritis related biomarkers. A: On MMP-3 index, after 4 weeks of treatment, there was a significant decrease in the Mongolian medicine group ($P < 0.01$). B: After treatment for 4 weeks, the Mongolian medicine group showed a significant decrease in TNF-alpha ($P < 0.05$). C: On VEGF index, after 4 weeks of treatment, there was a significant decrease in the Mongolian medicine group ($P < 0.05$). D: After treatment, the IL-10 index increased in the Mongolian medicine group. E: On the CGRP index, after 4 weeks of treatment, there was a significant decrease in the Mongolian medicine group ($P < 0.05$). Between the five groups, there was no significant difference between the three groups ($P > 0.05$). (Each time point was compared with the baseline, * indicates $P < 0.05$, ** indicates $P < 0.01$).

essential theoretical system of Mongolian medicine. It is believed that the human body is a whole that carries out life activities under the interdependence and restraint of three roots and seven elements. It is nourished continuously by the conversion of clean and dirty, a metabolic process in the body [28]. Yellow hemolymph is produced in the transformation of clean and dirty. It is distributed throughout the body, especially in joints and skin, with the functions of lubricating joints, coordinating joint movement, and lubricating the skin. The yellow hemolymph's overflow, decay, or fighting can cause disease [29]. Joint yellow hemolymph disease is caused by wind, cold, dampness, intense activity, injury, turbid heat, perspiration, and cold. Yellow hemolymph is directly overflowing or caused by the disorder of three roots (Heyi, Xila, Badakan) with stasis in bone and joint, so that the Qi and blood circulation of the joint is blocked and the disease occurs [30]. In the early stage of yellow hemolymph disease, there were symptoms of fever that through the course of the disease formed into the cold yellow hemolymph disease. Mongolian medicine can improve symptoms and signs and treat OA by dialectical treatment of "dredging Heyi blood, drying yellow hemolymph, and balancing three roots" [31]. Using the sticking therapy with a bandage, fixed tissue effect, added with the pharmacodynamics, physical factors, and acupoint medication treated the OA by sticking plaster in the pain part. It was found that Mongolian medicine could relieve swelling and improve pain symptoms and joint activity. This indicated that Mongolian treatment could dry yellow hemolymph, and improve microcirculation (dredge Heyi blood) by improving human resistance and balance the three roots, to cure the disease.

In this study, the therapeutic effect of paste therapy on OA was taken as a starting point for the first time. A large sample of randomized controlled clinical trials was conducted. The levels of OA-related cytokines and biomarkers were measured, effectively assessing the positive effect of Mongolian medicine sticking therapy on OA [32]. There were some problems in this study. 1. We chose a randomized controlled trial to observe the therapeutic effect of Mongolian medicine on OA. The OA of eight parts were studied, including a cervical vertebra, shoulder, elbow, hand, hip, lumbar vertebra, knee, and ankle joint. This created a problem of having a small sample size. 2. The study cycle was relatively short. According to the principle of glucosamine hydrochloride treatment, the recommended treatment course is 3 months so that the comprehensive efficacy can be worse than that of the two groups [33].

According to the above results, it was confirmed that Mongolian medicine had a positive effect on OA, and the overall effect was satisfactory. The curative effect was close to that of two control groups or even better than that of the control group, especially in pain, apokatastasis, and emotion, which can improve the quality of life. The study found that the sticking therapy for OA had the advantages of significant efficacy, safety, simple, and economics.

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Disclosure of conflict of interest

None.

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