

Original Research Article

Effects of the combination of loxoprofen sodium and sodium hyaluronate on osteoarthritis and knee function

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Abstract

Purpose: To determine the treatment efficacy of the combination of loxoprofen sodium and sodium hyaluronate in osteoarthritis (OA), and its role in knee joint function.

Methods: 98 patients with OA admitted to Guang'an People's Hospital, Sichuan, China were allocated into control group (CNG, given loxoprofen sodium $n = 51$) and study group (SG, given loxoprofen sodium and sodium hyaluronate, $n = 47$). Both groups were compared in terms of the levels of inflammatory factor, Lysholm, VAS, WOMAC scores, treatment effects, serum MDA, NO, SOD levels, adverse effects, and blood rheology indices.

Results: The study group had higher SOD levels, and higher BALP and BGP than CNG ($p < 0.05$). SG had lower TRACP-5b and blood rheological indices than CNG ($p < 0.05$). The difference in the incidence of adverse reactions was not statistically significant between the two groups ($p > 0.05$).

Conclusion: The combination of loxoprofen sodium and sodium hyaluronate effectively improves the function and blood rheological indices of knee joints. It reduces the occurrence of adverse reactions and the level of pain in patients with OA, and improves OA prognosis. However further clinical trials are required prior to application in clinical practice.

Keywords: Loxoprofen sodium, Sodium hyaluronate, Osteoarthritis, Knee joint function

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INTRODUCTION

Knee osteoarthritis (OA) is characterized by the presence of osteophytes, bone destruction and degeneration, and there are many factors that trigger the occurrence of this disease, including genetics, age, trauma, obesity, etc [1]. Several studies have shown that oxidative stress is evident in OA patients during OA progression, and the treatment option are joint cavity

injections and oral medications being the main treatment options [2]. Although there are a wide range of treatment options for OA with the progress and development of medical technologies, there is no clear direction on the treatment path for OA. In terms of OA and pain, ozone therapy plays a crucial part in improving the function of the knee joint and relieving pain in patients [3]. However, it has been confirmed through animal model experiments that the *in*

vivo stress response index is significantly higher after ozone treatment, which is not conducive for clinical treatment [4].

The present study was undertaken to determine the effects of the combination of loxoprofen sodium and sodium hyaluronate on osteoarthritis and knee function.

METHODS

General patient information

Ninety-eight OA patients treated in Guang'an People's Hospital, Sichuan, China, were randomly assigned to two groups. The control group (CNG) (n = 51) included 26 male and 25 female patients, 30 - 80 years of age, with a mean age 56.3 ± 3.9 years and disease duration of 1 - 11 years. Mean duration was 5.4 ± 1.3 years. The number of cases of bilateral and unilateral knee disease was 32 and 19, respectively, and the K-L classifications: grade III, grade II, and grade I were 12, 26, and 13, respectively. The study group (SG) (n = 47) included 25 male and 22 female patients, 30 - 82 years of age with a mean age of 56.5 ± 4.0 years, and disease duration of 1 - 12 years with a mean duration of 5.3 ± 1.4 years. The cases of bilateral and unilateral knee were 28 and 19, respectively, and the K-L classification: 11, 24, and 12 patients with grade III, grade II, and grade I, respectively. The general data were comparable ($p > 0.05$) in the two groups. All subjects agreed to join in the study. The study was approved by the hospital Ethics Committee (approval no. 2021-011), and all the procedures used followed the guidelines of The Declaration of Helsinki [5].

Inclusion criteria

These were patients who met the diagnostic criteria for OA, complete data and signed informed consent, had K-L classification: grade I-III and those with high compliance and adherence to follow-up [16].

Exclusion criteria

Excluded from the study were patients with depression and schizophrenia, somatic diseases such as hyperthyroidism and coronary heart disease, autoimmune system diseases, kidney function disorders or cardiopulmonary insufficiency and those treated with antipsychotic drugs in the 6 months before admission, pregnant or lactating.

Drug administration procedure

Loxoprofen sodium tablets (60 mg, H20052275, Chongqing Kerry Pharmaceutical (Group) Co., Ltd.) was orally administered every 8 h for a total of 8 weeks. Sodium hyaluronate (H20113379, Huaxi Fruida Biomedical Co. Ltd.) was administered by intra-articular injection. The silver needle used was routinely sterilized; then patient bends the knee at 90° , locates the puncture point in the depression of the lateral knee, punctures at an angle of 45° , and slowly injects the drug into the joint cavity, 25 mg/dose once a week for 8 weeks.

Evaluation of parameters/indices

Inflammatory factor levels

The fasting elbow venous blood (3 mL) of the study subjects was taken and centrifuged at 3500 rpm for 10 min. Tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6 levels were determined using enzyme-linked immunosorbent assay, with kits provided by Shanghai Enzyme Link Biotechnology Co (Shanghai, China) [17].

Lysholm, VAS, and WOMAC scores

The Lysholm Knee Function Rating Scale was applied to assess the improvement of knee function, with scores ranging from 0 - 100. Visual analogue scale (VAS) was applied to assess the pain level of patients, ranging from 0 - 10, with 10 referring to severe pain and 0 to no pain. The WOMAC scale was applied to evaluate the range of physical function, pain, and morning stiffness of the patients ranging from 0 - 100; the higher the score, the more significant the improvement in all functions [18].

Treatment effectiveness

Treatment effectiveness (TE) was calculated using Eq 1. The higher the effectiveness, the greater is the number of patients who were healed or showed improvement [19].

$$\text{Effectiveness} = \frac{\text{no. of effective cases}}{\text{total no. of cases}} \times 100\% \quad \dots (1)$$

Serum MDA, NO, SOD levels [10]

Serum malondialdehyde (MDA), nitric oxide (NO), and superoxide dismutase (SOD) levels were determined, and the more the values approached normal values, the better the treatment outcome.

Adverse effects

Patients with joint deformation, subcutaneous bleeding, joint swelling and osteophytes were counted, and the incidence was calculated.

Blood rheology indices [11]

Erythrocyte sedimentation rate, erythrocyte aggregation index, and fibrinogen level were determined using a blood rheometer, which was operated according to manufacturers' instructions.

Statistical analysis

GraphPad Prism 8 was used to plot the graphs. The data were analyzed with Statistical Package for the Social Sciences (SPSS) 22.0 software. For data conforming to normal distribution, the count data were described by (n (%)) and analyzed by chi-square test. Measurement data were presented as mean \pm standard deviation (SD) and analyzed by *t*-test. Logistic regression analysis was conducted to influence factor analysis. $P < 0.05$ was taken as statistically significant.

RESULTS

Levels of inflammatory factors

Both groups had no significant difference in the levels of inflammatory factors before treatment ($p > 0.05$). The TNF- α , IL-1 β and IL-6 levels were significantly decreased in two groups after

treatment, and were much lower in the SG than in the CNG ($p < 0.05$; Table 1).

Lysholm, VAS, and WOMAC scores

Both groups had no significant difference in Lysholm, VAS, and WOMAC scores before treatment ($p > 0.05$). The scores of Lysholm, VAS, and WOMAC were significantly reduced in two groups after treatment, and were much lower in the SG than in the CNG ($p < 0.05$, Table 2).

Treatment effects

There was no significant improvement in joint activity and the symptom score reduced to 30%. However, there was mild limitation of joint activity, significant improvement in imaging findings and clinical symptoms, and a reduction in the symptom score which ranged from 30 - 70%. Also, the clinical symptoms basically disappeared, and symptom score reduced to 70%. The treatment efficiency values were 82.4 and 97.9% in the CNG and the SG, respectively, and the SG exhibited higher treatment efficiency than the CNG ($p < 0.05$) (Table 3).

Serum MDA and NO levels and SOD activity

Both groups had no significant difference in serum MDA, NO and SOD levels before treatment ($p > 0.05$). The MDA and NO levels were significantly reduced, while SOD levels were increased in both groups after treatment. But in comparison with the CNG, the levels of MDA and NO were lower, while the SOD levels were higher in the SG ($p < 0.05$, Figure 1).

Table 1: Comparison of inflammatory factor (mean \pm SD, $\mu\text{g/mL}$)

Group	Number of cases	TNF- α		IL-1 β		IL-6	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	51	32.2 \pm 7.7	16.5 \pm 4.4	69.8 \pm 10.5	45.8 \pm 6.9	29.5 \pm 3.3	12.1 \pm 2.9
Study	47	32.5 \pm 7.5	12.8 \pm 3.2	69.6 \pm 10.4	33.7 \pm 5.8	29.6 \pm 3.4	7.8 \pm 2.7
T		0.638	16.754	1.427	15.028	0.792	18.524
P-value		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 2: Comparison of Lysholm, VAS, and WOMAC scores (mean \pm SD)

Group	Number of cases	Lysholm scores		VAS score		WOMAC score	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Control	51	54.2 \pm 10.6	77.2 \pm 8.5	6.7 \pm 0.9	4.8 \pm 1.8	57.4 \pm 6.3	39.5 \pm 5.1
Study	47	53.8 \pm 10.8	72.6 \pm 6.7	6.8 \pm 1.0	3.2 \pm 1.2	57.2 \pm 6.5	36.2 \pm 5.4
T		0.863	18.025	1.842	16.854	0.968	17.423
P-value		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Table 3: Comparison of treatment effects (mean ± SD)

Group	Number of cases	Ineffective	Effective	Significantly effective	Total Effective
Control	51	9 (17.6)	11 (21.6)	31 (60.8)	82.4%
Study	47	1 (2.1)	9 (19.1)	37 (78.7)	97.9%
χ^2					6.523
P-value					<0.05

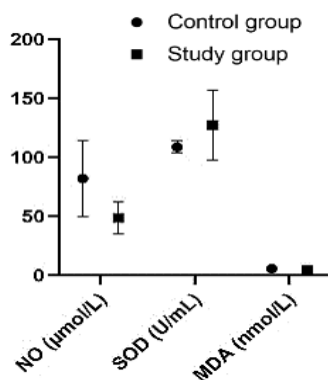


Figure 1: Comparison of serum MDA, NO and SOD levels. After treatment, the study group had lower MDA and NO, and higher SOD levels than the control group ($p < 0.05$)

Incidence of adverse reactions

The incidence of adverse reactions was 19.6 % in the CNG and 21.3 % in the SG respectively, exhibiting no significant difference ($p > 0.05$) (Figure 2).

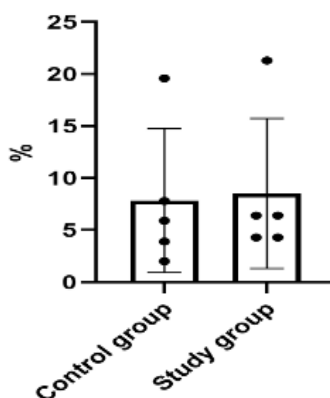
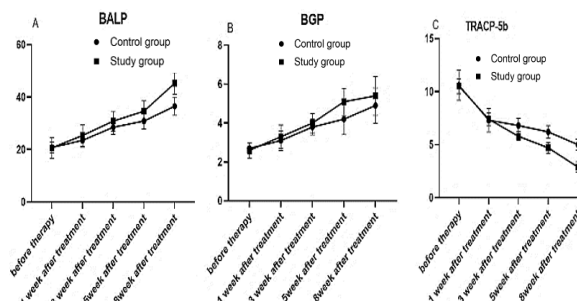


Figure 2: Comparison of adverse reactions ($p > 0.05$)

Bone metabolic indices

Both groups had no significant difference in BALP, BGP and TRACP-5b before treatment ($p > 0.05$). However, after 1, 3, 5 and 8 weeks of treatment, BALP and BGP in both groups increased significantly, and TRACP-5b decreased significantly, but in contrast to the CNG, BALP and BGP were higher, while TRACP-5b were lower in the SG ($p < 0.05$) (Figures 3 A, B and C).



Figures 3: Comparison of bone metabolic indices. After 1, 3, 5 and 8 weeks of treatment, (A) BALP, (B) BGP (C) TRACP-5b. SG versus CNG ($p < 0.05$)

Levels of blood rheological indices

Both groups showed no significant difference in the erythrocyte sedimentation rate, erythrocyte aggregation index and fibrinogen level before treatment ($p > 0.05$). The blood rheological indices were significantly reduced in the two groups, and were much lower in the SG than in the CNG ($p < 0.05$) (Figure 4).

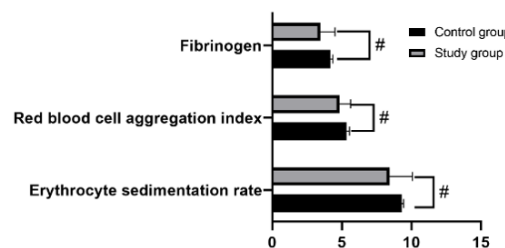


Figure 4: Comparison of blood rheological indices ($\#p < 0.05$)

DISCUSSION

Inflammation plays a significant role in OA, where chondrocytes are primarily affected. Studies show a higher prevalence of OA in women compared to men [12]. Patients with abnormal cartilage metabolism develop deposits of calcium salt crystals and a significantly high incidence of synovitis [13]. Inflammatory factors accelerate the rate of disease progression and are involved in pain, cartilage degeneration, and synovitis [14]. Synovitis has an impact on the manifestation of OA, accelerating disease progression [15]. The differentiation, secretion and proliferation of chondrocytes are relatively

stable under normal conditions. If accompanied by inflammatory reaction, the internal environment will be changed, abnormal cell secretion and metabolism will appear, and it will gradually lead to cartilage tissue degradation [16]. In this study, the combination of loxoprofen sodium and sodium hyaluronate was effective in the treatment of patients with OA. Intra-articular injection of sodium vitrate provides lubrication of the joint cavity as well as increased elasticity [17]. Loxoprofen sodium treatment protects the articular cartilage, facilitates regeneration and healing, and may further improve joint and knee function [18]. The IL-1 β affects cell membrane receptors, and nociceptive sensitivity and kinase activity are greatly altered [19]. Pain is the primary symptom of patients with knee arthritis, and TNF- α antibody relieves the pain caused by OA, thereby improving allodynia [20,21]. Studies have confirmed the correlation between inflammatory pain and IL-6.

This study investigated the effect of the combination of loxoprofen sodium and sodium hyaluronate in the management of OA and associated inflammatory factor levels in patients with OA. After treatment, the SG had lower levels of inflammatory factors than the CNG. It indicated that the combination reduced the level of inflammatory factors to a greater extent and facilitated the improvement of the disease when compared with the monotherapy of loxoprofen sodium. The results of this study showed that both groups exhibited significantly reduced Lysholm, VAS, and WOMAC scores, with the SG much lower than the CNG. The results confirmed that the combination of loxoprofen sodium and sodium hyaluronate improved the knee function and reduced the level of pain of patients, which further improved their treatment compliance.

NO is a highly reactive free radical that inhibits matrix synthesis and chondrocyte proliferation, which makes chondrocyte apoptosis faster [22]. SOD is an antioxidant enzyme, capable of scavenging superoxide anion radicals, and SOD levels were determined clinically to evaluate the ability to scavenge oxygen radicals. The MDA can reflect on the degree of free radical attack on healthy cells, and is a lipid peroxidation product [23,24].

This study investigated the effect of loxoprofen sodium and sodium hyaluronate on the stress response of OA patients, and the results suggested that after treatment, both groups had noticeably reduced MDA and NO, and significantly increased SOD levels, and the SG had lower MDA and NO, as well as higher SOD levels than the CNG. The results confirmed that

the combination of loxoprofen sodium and sodium hyaluronate did not increase the stress response, and the treatment was safe and conveniently improved patients' prognosis.

CONCLUSION

Loxoprofen sodium in combination with sodium hyaluronate improves knee joint function and blood rheological indices in patients with OA. There is a further reduction in the occurrence of adverse reactions and the level of pain. The treatment leads to a better disease prognosis. Therefore, the combination of loxoprofen sodium and sodium hyaluronate should be further investigated on a large scale before clinical application can be recommended.

DECLARATIONS

Funding

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Ethical approval

The study was approved by the Ethics Committee of Guang'an People's Hospital, Sichuan, China (approval no. 2021-011).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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