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Original Article

The effects of warm acupuncture combined with sodium hyaluronate on the pain, joint function, and joint inflammation in knee osteoarthritis patients

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Abstract: Objective: To explore the clinical efficacy of warm acupuncture combined with intra-articular injections of sodium hyaluronate in treating knee osteoarthritis (KOA) and the combination's effect on the recovery of joint function. Methods: From April 2018 to September 2019, 184 patients with KOA who received treatment in our hospital were recruited as the research cohort, and they were separated into two groups according to the treatment methods each received. In the monotherapy group (MG), the patients (n=86) were treated with intra-articular injections of sodium hyaluronate in the knee, while the patients in the combined group (CG) (n=98) were treated with acupuncture in addition to the treatment given to the MG. The clinical effects after the treatment, the adverse reactions during treatment, the visual analogue scale pain (VAS) scores, the Lysholm knee joint system (LKSS) scores, the knee joint McMaster University osteoarthritis index (WOMAC) levels, the quality of life scores, the tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, and vascular endothelial growth factor (VEGF) levels in the joint fluid were compared in the two groups. Results: The clinical treatment rate in the CG was higher than it was in the MG ($P < 0.05$), and there were no significant adverse reactions in the two groups during the treatment. Compared with the MG, the VAS and WOMAC scores were lower in the CG, but the Lysholm and quality of life scores were higher after the therapy ($P < 0.05$). After the treatment, the TNF-α, IL-1β, IL-6, and VEGF joint fluid levels were significantly decreased in both groups, and the corresponding levels in the CG were lower than they were in the MG ($P < 0.05$). Conclusion: Warm acupuncture combined with intra-articular injections of sodium hyaluronate can safely and effectively improve the clinical symptoms of KOA patients, an improvement that may be related to the treatment's ability to effectively reduce the release of the inflammatory factors and the VEGF content in the affected joints.

Keywords: Warm acupuncture, sodium hyaluronate, knee osteoarthritis, VEGF

Introduction

Knee osteoarthritis (KOA) is a disabling disease that impacts about 250 million people worldwide [1]. This disease is related to many factors such as age, obesity, strains, and trauma [2]. KOA mostly develops in middle-aged and elderly people, its incidence rate increases yearly due to the aging population, and it has become a serious public health problem [3]. KOA is characterized by pain, swelling, knee joint stiffness, limited walking ability, and even disability in severe cases, conditions that seriously affect patients' quality of life [4]. For now, the treatment for KOA mainly includes conservative therapy or surgery. For some patients with KOA who have not progressed to the end stage, the conservative treatment is often used to relieve their symptoms, delay the progress of the disease, and improve their quality of life [5]. However, the conservative treatment can only relieve the disease or the pain, but it cannot effectively control the progression of the disease at present. Moreover, many drugs easily cause various adverse reactions, so it is difficult to use them over the long term [6, 7]. Therefore, it is necessary to find a more effective conservative treatment for KOA.

Sodium hyaluronate is a type of macromolecular polysaccharide biomaterial formed by the repeated alternation of N-acetyl glucuronic

acid, which is a common component of the extracellular matrix [8]. Sodium hyaluronate plays a lubricating role in the joint cavity, and it can cover and protect articular cartilage, ameliorate joint contracture, suppress cartilage degeneration, change the surface, improve the pathological joint fluid, and increase the lubricating function [9]. Previous studies revealed that sodium hyaluronate is a safe, ideal, and effective drug to treat KOA [10]. Acupuncture is an important part of Chinese medicine, and it has been used in China for thousands of years. At present, acupuncture is considered to be a safe and effective method to relieve pain, and it is suitable for treating various types of musculoskeletal pain including KOA [11]. It is reported that more than 10% of adults in Israel use acupuncture to treat chronic pain [12]. Nowadays, many different acupuncture techniques have been developed, such as traditional manual acupuncture (MA), electroacupuncture (EA), transcutaneous electrical acupoint stimulation (TEAS), laser acupuncture, and warm acupuncture [13]. Warm acupuncture is a combination of acupuncture and moxibustion, that is, during the needle retention, the moxa wool is rubbed or the moxa strip is directly placed on the needle handle to ignite it, and the heat is transmitted to the acupuncture point through the needle body [14]. It has been reported that warm acupuncture has a better analgesic effect on KOA than ordinary acupuncture [15].

This study was designed to investigate the clinical efficacy and safety of warm acupuncture combined with intra-articular injections of sodium hyaluronate in treating KOA, and to analyze the treatment mechanism, aiming to find a safer and more effective treatment scheme for patients with KOA.

Materials and methods

Research cohort

From April 2018 to September 2019, 184 patients with KOA who received treatment at the Beijing Gulou Hospital of Traditional Chinese Medicine were recruited as the study cohort.

Inclusion criteria: Patients who met the diagnostic standard for osteoarthritis established by the American College of Rheumatology [16] and who were confirmed to have KOA through x-rays or CT scans, patients who were 40-75 years old, patients who signed an informed consent form, patients who had no communication barriers and who were able to cooperate with the study, and patients with mild or medium KOA (a Kellgren-Lawrence score of 1-2).

Exclusion criteria: Patients with other diseases affecting their knee joint function, patients with incomplete clinical data, patients with a previous history of knee surgery, patients who had used non-steroidal anti-inflammatory drugs, chondroprotective drugs, or analgesics in the most recent three months patients with severe brain, cardiovascular, or kidney diseases, and patients who were pregnant or lactating.

The 184 patients were separated into two groups according to the treatment method each patient received. Among the patients, 86 received intra-articular injections of sodium hyaluronate in the knee as the MG, and the other 98 patients were treated with intra-articular injections of sodium hyaluronate combined with acupuncture in the knee as the CG. This study conformed to the Declaration of Helsinki, and it was approved by the Ethics Association of our hospital.

Treatment methods

In the MG, the patients were injected with sodium hyaluronate in their knee joint cavities. The steps were as follows: The patient was in a sitting or supine position with his or her knees bent at 90°. Next, the affected knee was routinely disinfected. The medial side of the patellar ligament below the patella of the knee was selected as the puncture point, and the puncture was about 10 cm. Next, the sodium hyaluronate was injected into the knee joint cavity (if there was effusion, it was drained before the injection). After the injection, the patient's joints were moved slightly so that the liquid was evenly distributed in the joint cavity, and the patient was advised to avoid a large range of knee joint movements as much as possible. The treatments were given one time per week for 4 weeks.

In the CG, the patients were treated with acupuncture in addition to the injections given in the MG. The main points were Xuehai, Heding, Xiyan, Dubi, Yinlingquan, Yanglingquan, and Zusanli, and the adjunct points were Guanyuan, and Qihai. The specific procedure was as fol-

lows: The patient's skin was routinely disinfected , and the patient assumed a supine position. A two-inch needle was selected, and the needle was placed at the above acupuncture points. After the acuesthesia, the appropriate depth was retained, and then a round piece of paper was placed under the needle to avoid scalding the skin. During the needle retention period, the pure moxa was wrapped on the needle handle, or a moxa stick with a length of about 2 cm was placed on the needle handle 2-3 cm away from the skin. Next, the pure moxa or the moxa stick was ignited to perform the acupuncture starting near the skin. Three moxa sticks were ignited each time, 30 min/time, 1 time/d. The eight times constituted one course of treatment, with a course interval of 3 days. The patient was treated consecutively for 3 courses, for a total of 4 weeks.

All the acupuncturists were licensed in Chinese medicine for at least 20 years, and they received the same training under the clinical therapeutic program before the research.

Outcome measures

After four weeks of treatment, the short-term clinical effects were evaluated in the two groups and classified into one of three levels: Markedly effective: After the treatment, the knee joint pain, stiffness, and swelling basically disappeared, and the patients could carry out their basic daily activities. Effective: After the treatment, the above clinical symptoms of the patients were significantly improved, but there was still some discomfort or fricative sounds heard during basic activities, and the knee joint function was improved. Ineffective: The patient's condition did not meet the above criteria. The effectiveness rate of the therapy (%) = (cases with markedly effective + cases with effective)/total cases × 100%.

The adverse reactions were recorded during the treatment, such as gastrointestinal discomfort, dizziness, broken needles, and bleeding.

Before and after the four weeks of treatment, the visual analogue scale (VAS) [17] was used to assess each patient's degree of pain, with a total possible score of 10. The higher the score, the more severe the pain.

Before and after the four weeks of treatment, the patients' knee function was assessed using the Lysholm Knee Score Scale (LKSS) [18] and the McMaster University Osteoarthritis Index (WOMAC) [19]. The LKSS was used to evaluate the symptoms such as claudication, knee flexion angle, swelling degree, ability to get up and down stairs, and locking. The lower the score, the more serious the dysfunction. The WOMAC includes stiffness (2 items), pain (5 items), and joint function (17 items). The total possible scores are 8, 20, and 68, respectively. The higher the score, the more severe the symptoms.

After the four weeks of treatment, the quality of life (QLQ-C30) questionnaire [20] was used to assess the patients' quality of life, including disease control, living behavior, exercises, and psychological and emotional changes. The total possible score of each item was 100 points. The higher the score, the better the quality of life.

Before and after the four weeks of treatment, 2 mL of knee joint fluid was extracted and stored at -80°C to test the TNF-α, IL-1β, IL-6, and VEGF levels. The ELISA was used to determine the levels, and the assay was conducted in strict accordance with the kit's specifications.

Statistical analysis

SPSS 21.0 was used for statistical analysis, and GraphPad Prism 7 was used to draw the figures. The enumeration data were expressed as percentages (%), and the comparison were conducted using chi square tests. The quantitative data were represented as ($\bar{x}$ ± sd). Independent t tests were used for the comparisons between two groups. Paired t tests were applied for the comparisons before and after the treatment within the group. One-way ANOVA analyses were used for the comparison among multiple groups, and back-tests were used to verify the correctness of the statistical values. A difference was statistically significant when $P < 0.05$.

Results

Comparison of the baseline data

There were no significant differences in the basic clinical data such as gender, age, body mass index (BMI), course of the disease, smoking history, alcoholism history, working status, location of the disease, or the Kellgren-Lawrence classification in the two groups ($P > 0.05$) (**Table 1**).

Table 1. Comparison of the basic data in the two groups ($\bar{x} \pm sd$), [n (%)]

Grouping	MG (n=86)	CG (n=98)	χ^2/t	P
Gender			1.454	0.228
Female	59 (68.60)	75 (76.53)		
Male	27 (31.40)	23 (23.47)		
Age/years old	58.51±8.92	59.23±9.23	0.460	0.647
BMI (kg/m^2)	24.21±2.86	23.86±2.72	1.003	0.318
Course of disease (years)	4.89±2.95	5.21±2.68	0.782	0.277
Smoking history			0.553	0.457
Yes	48 (55.81)	60 (61.22)		
No	38 (44.19)	38 (38.78)		
Alcoholism history			1.199	0.274
Yes	32 (37.21)	29 (29.59)		
No	54 (62.79)	69 (70.41)		
Working or not			0.102	0.749
Yes	30 (34.88)	32 (32.65)		
No	56 (65.12)	66 (67.35)		
Location of disease			0.095	0.758
One knee	70 (81.40)	78 (79.59)		
Knees	16 (18.60)	20 (20.41)		
Kellgren-Lawrence			0.197	0.657
1	37 (43.02)	39 (39.80)		
2	49 (56.98)	59 (60.20)		

Table 2. Comparison of the clinical curative effect [n (%)]

Grouping	Markedly effective	Effective	Ineffective	Effective treatment
MG (n=86)	23 (26.74)	44 (51.16)	19 (22.09)	67 (77.91)
CG (n=98)	38 (38.78)	51 (52.04)	9 (9.18)	89 (90.82)
χ^2				5.917
P				0.015

Comparison of the clinical efficacy

By evaluating the clinical efficacy in the two groups, it was found that 23 cases (26.74) were markedly effective, 44 cases (51.16) were effective, and 19 cases (22.09) were ineffective in the MG, for an effective rate of 77.91%. In the CG, 38 cases (38.78) were markedly effective, 51 cases (52.04) were effective, and 9 cases (9.18) were ineffective, for an effective rate of 90.82%. The effectiveness rate in the CG was higher than it was in the MG ($P < 0.05$) (**Table 2**).

Comparison of the adverse reactions

We looked for any adverse reactions during the treatment, but we found that there was no gastrointestinal discomfort, bleeding, broken needles, needle syncope, or other adverse reactions in either group.

Comparison of pain degree

By evaluating the pain before and after the treatment, it was found that there were no significant differences in the VAS scores in both groups before the therapy ($P > 0.05$). After the therapy, the VAS scores were significantly reduced in the two groups, and the VAS scores in the CG were significantly lower than the VAS scores in the MG ($P < 0.05$) (**Figure 1**).

Comparison of the knee joint function scores

By evaluating the knee joint function scores, it was found that the LKSS and WOMAC scores were similar in both groups before the therapy, and there were no significant differences ($P > 0.05$). After the therapy, the patients' LKSS scores increased significantly in both groups, but the WOMAC scores decreased ($P < 0.05$). In addition, compared with the MG, the LKSS scores were higher and the WOMAC scores were lower in the CG after the treatment ($P < 0.05$) (**Figure 2**).

Comparison of the quality of life scores

By assessing the patients' quality of life, it was found that the QLQ-C30 disease control, life behavior, exercise, and psychological emotion scores in the CG were significantly better than the corresponding scores in the MG ($P < 0.05$) (**Figure 3**).

Comparison of the inflammatory factors and VEGF levels in the synovial fluid

By measuring the inflammatory factor and VEGF levels in the joint fluid before and after the treatment, it was found that there was no significant difference in the TNF-α, IL-1β, IL-6, or VEGF levels in the two groups before the therapy ($P > 0.05$). After the therapy, the TNF-α,

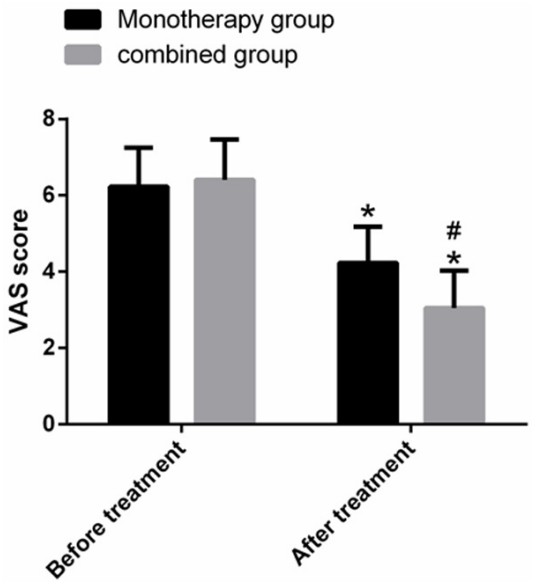

Figure 1. Comparison of the VAS scores before and after the treatment. Note: * means compared with before the treatment in the same group, $P < 0.05$; # means that compared with MG, $P < 0.05$.

IL-1β, IL-6, and VEGF levels in the joint fluid were significantly decreased in both groups, and the corresponding levels in the CG were lower than they were in the MG ($P < 0.05$) (**Figure 4**).

Discussion

This study was designed to investigate the clinical curative effect and safety of warm acupuncture combined with intra-articular injections of sodium hyaluronate in treating KOA. The results showed that warm acupuncture combined with intra-articular injections of sodium hyaluronate could not only provide a better curative effect for patients with KOA, but it also had significant advantages in reducing pain, improving joint function, improving the quality of life, and reducing joint inflammation compared with sodium hyaluronate injections alone.

KOA is one of the primary causes of disability in middle-aged people, and there is no cure [5]. Clinically, local analgesics, glucosamine, non-steroidal anti-inflammatory drugs, sodium hyaluronate and surgical treatment are mainly used to relieve patients' symptoms, but these methods are usually accompanied by many side effects, so they don't meet patients' needs [21]. Acupuncture is a non-operative method commonly used in the eastern world to relieve KOA, and it has been used for thousands of years [22]. There are many acupuncture methods, among which warm acupuncture is the combination of acupuncture and moxibustion, so it has the advantages of both and can more effectively relieve the clinical symptoms of KOA [14, 15]. The intra-articular injection of sodium hyaluronate is a common way to treat KOA, as it can effectively relieve patients' symptoms [23]. This study was designed to investigate the clinical curative effect of warm acupuncture combined with intra-articular injections of sodium hyaluronate in treating KOA. Compared with the MG, the treatment efficiency was higher, the VAS scores were lower, the LKSS scores were higher, and the WOMAC scores were lower in the CG after the treatment. During the treatment, there was no gastrointestinal discomfort, bleeding, broken needles, needle syncope, or other adverse reactions in the two groups. Therefore, warm acupuncture combined with intra-articular injections of sodium hyaluronate has a better clinical effect in treating KOA and without significant side effects. This suggests that warm acupuncture combined with intra-articular injection of sodium hyaluronate has a significant synergistic effect.

The pathogenesis of KOA is unclear, but it is thought that synovitis is one of its main causes, so reducing inflammation in patients is also one of the main treatment directions for KOA [24]. TNF-α can participate in pathological processes such as synovitis and cartilage destruction by inhibiting the synthesis of cartilage collagen and promoting the degradation of the cartilage matrix [25]. IL-1β can promote the proliferation of the cartilage and synovial cells, and it also can produce a synergistic effect with TNF-α to accelerate the degradation of the cartilage matrix [26]. IL-6 can aggravate cartilage inflammatory injury by blocking the synthesis of cartilage proteoglycan and promoting the degradation of the cartilage matrix [27]. Previous studies have shown that acupuncture can improve the symptoms of patients with KOA by suppressing the release of inflammation cytokines such as TNF-α, IL-1β, and IL-6 [19]. In this study, the inflammatory factor levels in the joint fluid were measured in both groups. The results revealed that the TNF-α, IL-1β, and IL-6 levels in the joint fluid were significantly decreased in both groups after the therapy, and the three

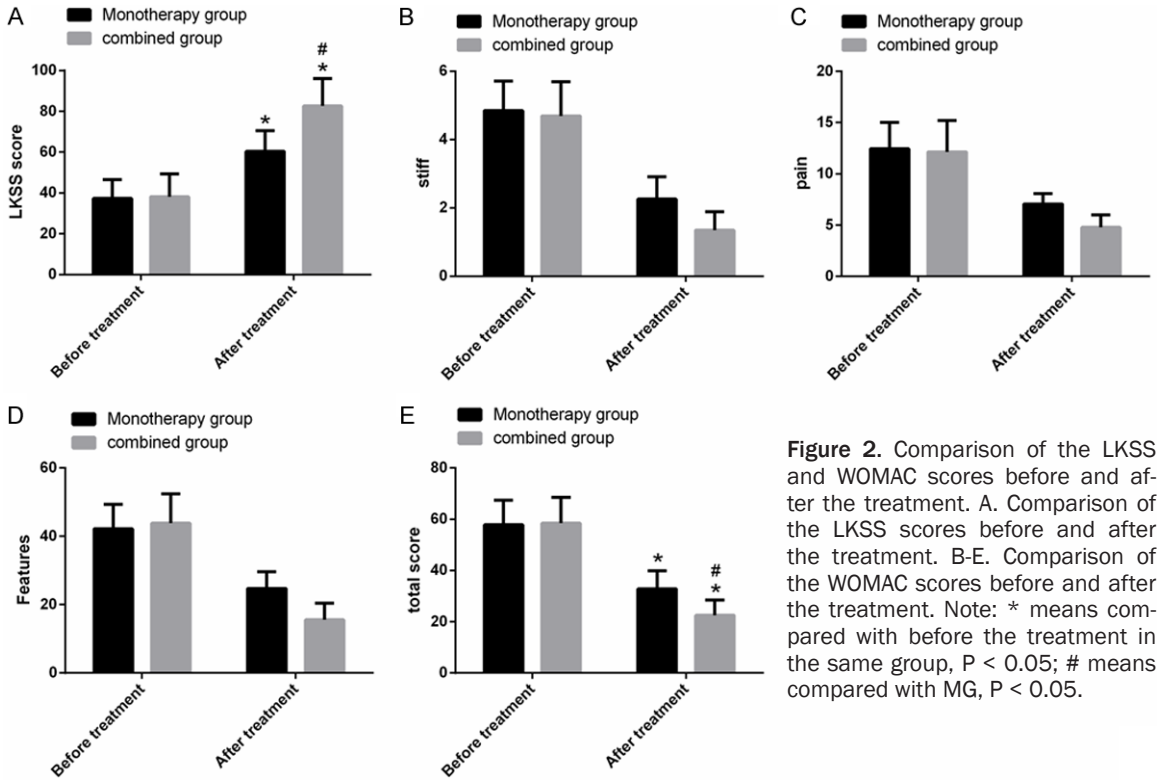

Figure 2. Comparison of the LKSS and WOMAC scores before and after the treatment. A. Comparison of the LKSS scores before and after the treatment. B-E. Comparison of the WOMAC scores before and after the treatment. Note: * means compared with before the treatment in the same group, $P < 0.05$; # means compared with MG, $P < 0.05$.

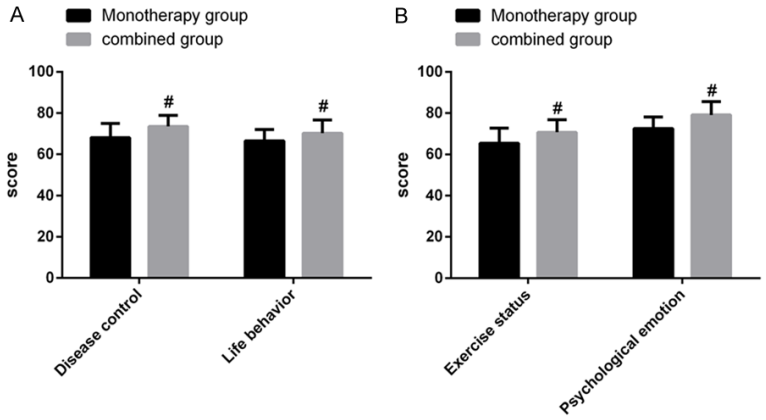

Figure 3. Comparison of the quality of life scores. A. Comparison of the disease control and life behavior scores in the two groups after the treatment. B. Comparison of the exercise and psychological emotions in the two groups after the treatment. Note: # means compared with the MG, $P < 0.05$.

levels in the CG were lower than they were in the MG. This indicated that warm acupuncture combined with intra-articular injections of sodium hyaluronate can improve the symptoms of patients with KOA by inhibiting the release of inflammatory cytokines. VEGF is a cytokine that promotes angiogenesis, and it is an important angiogenesis factor and an important angiogenesis regulator in the process of bone development and bone remodeling [28]. Studies have shown that the content of VEGF is abnormally elevated in the articular cartilage of patients with KOA, and it actively participates in the development of KOA [29, 30]. Previously, an animal experiment revealed that acupuncture and sodium hyaluronate can improve the condition of rabbits in a KOA rabbit model by reducing the VEGF content in the cartilage and subchondral bone [31]. In this study, the VEGF joint fluid changes in the patients were measured in the two groups, and it was found that the VEGF level was decreased significantly after the treatment, and the VEGF level in the CG was lower than it was in the MG. This suggests that warm acupuncture combined with intra-articular injections of sodium hyaluronate can also control disease progression by reducing the VEGF content in the affected joints. This might be due to the fact that acupuncture combined with sodium hyaluronate can effectively reduce

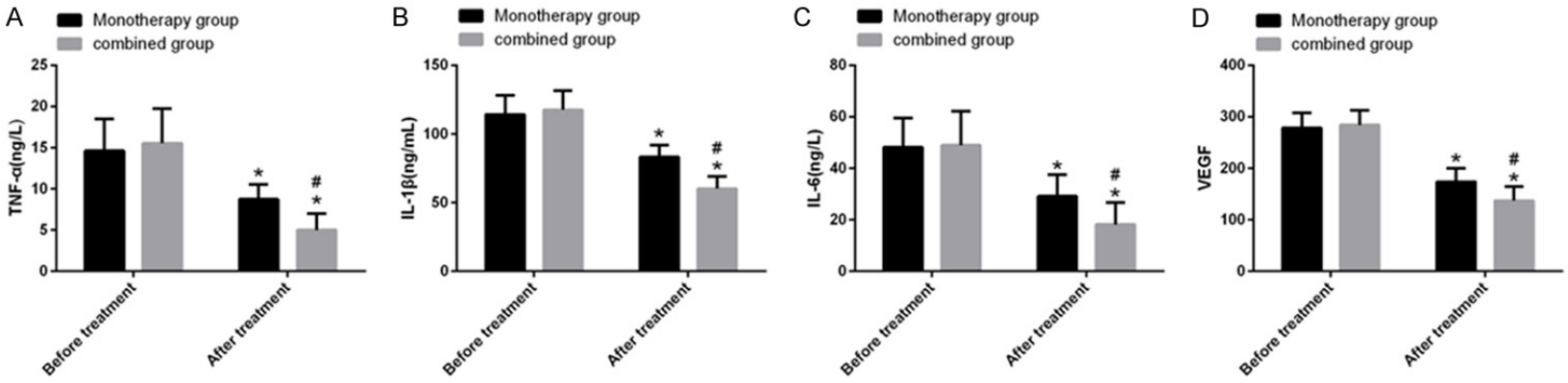

Figure 4. Comparison of the inflammatory factors and the VEGF levels in the synovial fluid. A. Comparison of the TNF-α levels in the synovial fluid before and after the treatment. B. Comparison of the IL-1β levels in the synovial fluid before and after the treatment. C. Comparison of the IL-6 levels in the synovial fluid before and after the treatment. D. Comparison of the VEGF levels in the synovial fluid before and after the treatment. Note: * means compared with before the treatment in the same group, $P < 0.05$; # means compared with the MG, $P < 0.05$.

joint pressure and improve venous stasis and hypoxia, thus reducing the expression of VEGF.

There are some deficiencies in this study. For example, the members of the study cohort are all from the same region, but KOA is a global disease, so the results of this study may not be applicable to patients in other regions. Secondly, KOA is a chronic disease. However, the treatment and follow-up durations in this study were short, so the longer-term efficacy of warm acupuncture combined with intra-articular injections of sodium hyaluronate in treating KOA were not explored.

To sum up, this study has preliminarily revealed shown that warm acupuncture combined with intra-articular injections of sodium hyaluronate can safely and effectively improve the clinical symptoms of patients with KOA, which may be related to the fact that it can effectively reduce the release of inflammatory factors and the VEGF content in the affected joints.

Disclosure of conflict of interest

None.

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