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Clinical Effect Study of Synovial Inflammation in Knee Osteoarthritis Based on Warming the Yang and Eliminating Blood Stasis

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Abstract: In order to observe the clinical effect of Wuling San and Taohong siwu Decoction combined with western medicines on synovial inflammation of knee osteoarthritis. 60 patients with cold-dampness obstruction type knee osteoarthritis with synovitis treated in Guangyuan Hospital Affiliated to Chengdu University of Traditional Chinese Medicine were randomly divided into experimental group and control group, with 30 cases in each group. The control group was treated by western medicines, and the experimental group was treated with Wuling San and Taohongsiwu Decoction on the basis of control group. After 14 days, VAS score, WOMAC score, knee circumference and functional index of the two groups were observed, and adverse reactions were monitored. Resultly, after treatment, all indexes were improved compared with those before treatment ($P<0.05$). After treatment, all indexes of the experimental group were better than those of the control group ($P<0.05$). There were no obvious adverse reactions during treatment in both groups. In conclusion, Wuling San and Taohongsiwu Decoction combined with western medicines can significantly reduce the pain and swelling of patients with knee osteoarthritis accompanied by synovial inflammation (cold-dampness obstruction type) and improve the joint function.

1. Background

Knee osteoarthritis (KOA) is a chronic knee disease with a distinct stepwise pattern, characterized by cartilage degeneration and synovial inflammatory reaction as the main pathology [1]. Patients with KOA mainly present with clinical symptoms of knee pain, swelling, and dysfunction. According to recent studies, synovitis plays a key role in the development of KOA [2] and may be one of its ultra-early manifestations. Therefore, treatment of synovial inflammation is of great significance for delaying the progression of knee osteoarthritis. In this study, based on the principle of "warming Yang and removing water, promoting blood circulation and removing stasis", Wuling San and Taohongsiwu Decoction were selected to observe the clinical effect of this compound in the treatment of synovitis in the cold and dampness obstruction type knee osteoarthritis.

2. Clinical information

2.1. General information

According to the inclusion and exclusion criteria, 60 patients with cold-dampness arthralgia knee osteoarthritis with synovial inflammation admitted to Guangyuan Hospital Affiliated to Chengdu University of Traditional Chinese Medicine from September 2023 to April 2024 were selected as the study objects. The enrolled patients were randomly divided into the experimental group (30 cases) and the control group (30 cases) according to the order of treatment. The experimental group included 22 females and 8 males, ranging in age from 30 to 70 years old, with an average age of (54.57±9.44) years, and a disease course ranging from 1 to 20 months, with an average disease course of (10.63±5.57) months. The control group included 21 females and 9 males, ranging in age from 24 to 78 years, with a mean age of (54.17±12.91) years, and a mean duration of disease ranging from 2 months to 20 months, with a mean duration of (10.07±5.46) months. Comparison of basic data such as gender, age, and duration of the disease between the two groups showed no statistical difference ($P>0.05$) and were comparable.

2.2. Disease diagnosis

2.2.1. Diagnostic criteria of western medicine

According to the Chinese guideline for diagnosis and management of osteoarthritis (2018 Edition) [3]:(1) Recurrent knee pain in the past 1 month; (2) Age 50 and above; (3) X-ray evidence of joint space narrowing, subchondral osteosclerosis and/or cystic changes, and osteophytes at joint edges; (4) Bone rubbing sensation(friction sounds) on movement; (5) Less than or equal to 30 minutes of morning stiffness. The diagnosis must satisfy (1) and any 2 of (2) ~ (5). Kellgren/Lawrence grading standard [4]: Grade 0, no abnormality; Grade I, slight osteophytes; Grade II, obvious osteophytes, not involving the joint space; Grade III, moderate narrowing of the joint space; Grade IV, obvious narrowing of the joint space and sclerosis of the subchondral bone.

2.2.2. Diagnostic criteria of Chinese medicine

According to the Diagnostic and Therapeutic Efficacy Criteria for Traditional Chinese Medicine [5] and the Guideline for the Diagnosis and Treatment of Knee Osteoarthritis with Traditional Chinese Medicine (2020 Edition) [6], the following are proposed: (1) Main symptoms: knee pain, heavy, aggravated by cold, slow when warm, and unfavorable joint flexion and extension; (2) Secondary disease: waist heavy pain, weather changes aggravated; (3) Tongue and pulse: pale tongue, white and greasy fur; Pulse is moist and slow.

2.3. Inclusion criteria

(1) The subjects meet the above diagnostic criteria; (2) The subjects are aged between 20 and 80 years old; (3) The K-L classification of the subjects is I-III; (4) The subjects have signed the informed consent form.

2.4. Exclusion criteria

(1) The subjects have severe primary medical diseases (circulatory system, urinary system, hematopoietic system, endocrine system, and psychiatric disorders); (2) The subjects are complicated with pulmonary tuberculosis and infected with joint disease; (3) The subjects have a history of severe

related drug allergies; (4) The subjects have used oral medications that may have affected this study within the past month, or received invasive knee joint treatment within the past 6 months.

3. Treatment

Patients in both groups should avoid joint impact and strenuous exercise and eat a balanced diet during treatment.

3.1. Control group

Oral Celecoxib Capsule (Shi Pharmaceutical Group Ouyi Pharmaceutical Co., LTD. Specification: 0. 2g Approval No.:H20203297) 0.2g bid, Diacerein Capsules (TRB Pharma S.A. Specification: 50mg Approval No.: HJ20150130) 50mg qd. Take 2 weeks consecutively for 1 course of treatment, a total of 1 course of treatment is required.

3.2. Experimental group

On the basis of the control group, Wuling San combined Taohongsiwu Decoction (200ml tid) was taken orally every day. Continuous use for 2 weeks is 1 course, a total of 1 course is required. The composition of the decoction is as follows: Alisma 20g, Achyranthes 20g, Grifola 15g, Poria 15g, Salvia miltiorrhiza 15g, Atractylodis Macrocephalae 12g, earthworm 12g, Ramulus Cinnamomi 10g, Peach Kernel 10g, Safflower 10g. The decoction is prepared by the decocting room of Guangyuan Hospital of Traditional Chinese Medicine.

4. Observation of curative effect

4.1. Observation indexes and evaluation criteria of curative effect

(1) Pain score. Visual analogue scale (VAS) was used to evaluate the pain before and after medication. (2) Knee joint function. Knee function was quantitatively assessed by the Western Ontario and McMaster University Osteoarthritis Index (WOMAC score) before and after treatment. (3) Knee swelling. The circumference of the knee joint was measured centered on the superior pole margin, the highest point and the inferior pole margin of the patella and the average of the three values was taken. (4) Improvement of knee function index (hereinafter referred to as “function index”) and evaluation of clinical effect. Formulated in accordance with the Guiding Principles for Clinical Research of New Chinese Medicines [7]. Function index =[(WOMAC score before treatment - WOMAC score after treatment)/WOMAC score before treatment] ×100%. Efficacy was divided into four levels according to functional index and clinical manifestations: Cure (functional index≥95%, pain and other symptoms eliminated, normal joint movement), obvious effect (70%≤functional index < 95%, pain and other symptoms eliminated, joint movement is not limited), effective (25%≤ functional index < 70%, pain and other symptoms basically eliminated, mild joint movement limited) and ineffective (functional index<25%, pain and other symptoms, no significant improvement in joint movement). Total effective rate = (number of effective cases + number of obvious effective cases + number of cured cases)/total number of cases × 100%.

4.2. Statistical processing of data

IBM SPSS Statistics 23.0 was used to analyze the data. Measurement data conforming to normal distribution and homogeneity of variance were represented as ($\bar{x} \pm s$); Non-normal distribution measurement data were expressed as median [P50 (P25, P75)]; The enumeration data were expressed

as [example (%)]. T test and non-parametric test were used for measurement data, and test was used for enumeration data. P < 0.05 was considered statistically significant for all data results.

4.3. Analysis of results

4.3.1. VAS score

The VAS scores of the two groups before and after treatment were compared by Wilcoxon signed-rank test, with P=0.00<0.05 for the experimental group, and P=0.00<0.05 for the control group, which was statistically significant. The VAS scores of the two groups of patients after treatment were statistically different using the Man-Whitney U test, P=0. 01<0.05. In conclusion, both treatment methods can reduce the pain of patients, but the experimental group is better than the control group (see Table 1 for details).

Table 1: Comparison of VAS scores[P50(P25, P75)]

Group	Samples	Before	After	z	P
Experimental group	30	7(6, 7.25)	3(2, 3.25)	-4.954	0.00△
Control group	30	7(6, 7)	3. 5(3, 4)	-4.873	0.00△
z		-1.054	-3.468		
P		0.292	0.01▲		

Note: Compared with the group before treatment, P△<0.05; Compared with control group P▲<0.05 after treatment.

4.3.2. WOMAC score

The WOMAC scores of the two groups before and after treatment were compared by paired-sample T test, with P=0.00<0.05 for the experimental group, and P=0.00<0.05 for the control group, which was statistically significant. The WOMAC scores of the two groups of patients after treatment were statistically different using independent-samples T test, P=0.009<0.05. In summary, both groups can improve the knee joint function, with the experimental group showing better results. (see Table 2 for details).

Table 2: Comparison of WOMAC scores ($\bar{x} \pm s$)

Group	Samples	Before	After	t	P
Experimental group	30	54.73±7.529	20.73±8.395	15.244	0.00△
Control group	30	54.73±7.529	27.07±9.670	12.555	0.00△
t		0.00	-2.709		
P		1.00	0.009▲		

Note: Compared with the group before treatment, P△<0.05; Compared with control group P▲<0.05 after treatment

4.3.3. Knee circumference

The knee circumference of the two groups before and after treatment were compared by Wilcoxon signed-rank test, with P=0.00<0.05 for the experimental group, and P=0.00<0.05 for the control group, which was statistically significant. The circumference of the two groups of patients after treatment were statistically different using the Man-Whitney U test, P=0.001<0.05. Both groups can relieve knee swelling, with the experimental group showing better results. (See Table 3 for details).

Table 3: Comparison of knee circumference [P50 (P25, P75), cm]

Group	Samples	Before	After	z	P
Experimental group	30	36.90(36.38, 37.23)	36.00(36.00, 36.50)	-4.716	0. 00△
Control group	30	37.00(36.40, 37.50)	36.85(36.00, 37.08)	-4.491	0. 00△
z		-1.129	-3.376		
P		0.259	0.001▲		

Note: Compared with the group before treatment, P△<0. 05; Compared with control group P▲<0. 05 after treatment

4.3.4. Comparison of clinical effect

The total effective rate was 93.3% in the experimental group and 83. 3% in the control group. After testing, P=0.137 > 0.05, no statistical difference, indicating that the experimental group and the control group in the treatment of knee joint synovitis clinical effect was similar. (See Table 4 for details)

Table 4: Comparison of effect (samples, %)

Group	Samples	Cure	Obvious effect	Effective	Ineffective	Total effective rate
Experimental group	30	2(6.7%)	5(16.7%)	21(70.0%)	2(6.7%)	93.3%△
Control group	30	0(0.0%)	2(6.7%)	23(76.7%)	5(16.7%)	83.3%
χ^2	4.662					
P	0.137					

Note: Compared with control group, P△>0.05

4.3.5. Safety Assessment

No significant adverse reactions were observed in either group during the treatment.

5. Discussion

Synovitis is a kind of aseptic joint inflammation in which synovial tissue is affected by trauma, joint degeneration and other factors, resulting in synovial cell secretion disorder, leading to excessive joint effusion [8], which plays a key role in the progression of knee osteoarthritis. According to statistics, the proportion of knee osteoarthritis combined with synovitis is as high as more than half [9], which is usually accompanied by the phenomenon of effusion or hemorrhage in the joint cavity, leading to significant swelling of the affected knee and aggravation of pain, and accelerating the progress of knee osteoarthritis. At present, the initial treatment strategy for knee osteoarthritis with synovitis mainly focuses on reducing pain, relieving joint swelling, improving joint mobility, and effectively delaying the further deterioration of the disease [10]. In modern clinical practice, the mainstream treatment methods include oral analgesics, non-steroidal anti-inflammatory drugs, and knee puncture and effusion extraction. Although oral drugs have shown good efficacy in pain relief, they are often accompanied by a greater risk of adverse reactions and the problems of abuse and dependence, so they are not suitable as a long-term treatment. Although joint puncture can remove knee joint effusion in time, it is an invasive operation with the risk of infection and easy to cause fear

of patients. Traditional Chinese medicine (TCM) has been the research direction for the treatment of knee joint synovitis in recent years because of its remarkable efficacy and few adverse reactions [11].

According to its characteristics, synovial inflammation of knee osteoarthritis can be classified into the categories of "Bibing" and "Hexifeng" in traditional Chinese medicine. Tutor Chen Bing believes that the pathogenesis of this disease lies in joint vein damage, wind-cold and damp evil invading the body, resulting in blood overflowing into stasis, dampness and qi fighting, and finally cause cold and damp, water and blood stasis, which are manifested as joint swelling, flexion and extension disadvantage, limb distress. According to its pathogenesis, the main treatment principle is to warm yang and promote diuresis, activate blood circulation and eliminate blood stasis, and facilitate the joints. ”Warm yang and eliminate blood stasis” is derived from Wuling San in the Shanghan Lun and Taohong Siwu Decoction in the Golden Mirror of Medicine. According to years of clinical experience, mentor Chen added and reduced the original formula and summarized this compound, which can vaporise the excess water in the joints of patients and dredge local stasis, so as to achieve the purpose of treating synovial inflammation. In Wuling San, alisma is the monarch medicine, which clear damp and promots diuresis; Grifola, Poria lightly infiltration dampness, for the minister medicine, to assist the monarch medicine pass water in the urine; Ramulus Cinnamomi warm yang and move water, Atractylodis Macrocephalae invigorates spleen and dampness, and strengthens spleen and water with Poria. Peach Kernel and Safflower are the main ingredients of Taohong Siwu Decoction, which have the effects of promoting blood circulation, removing blood stasis, and activating blood circulation. Salviae Miltiorrhizae can promote blood circulation and unblock meridians, while Earthworms can soothe meridians and smooth joints. At the same time, focus on the use of Achyranthes to promote blood circulation, dissipate blood stasis and clear meridians, and strengthen muscles and bones. Modern studies have shown that total saponins of Achyranthes bidentata can reduce the content of cytokines in synovial fluid and play a role in cartilage protection [12]. In recent years, clinical studies have found that Wuling SAN can effectively improve joint swelling, effusion and dysfunction in knee osteoarthritis [13]. At the same time, it can prevent and treat limb swelling after orthopedic surgery [14], and is widely used in orthopedics and traumatology. Modern pharmacology has found that Taohong Siwu decoction can reduce synovial inflammation and protect cartilage matrix by down-regulating the expression of inflammatory factors such as IL-1β, MMP-3, TNF-α, so as to effectively relieve pain and swelling in patients with synovitis and restore joint function [15].

6. Conclusion

The results of this study showed that the total effective rate of the experimental group was higher than that of the control group, but the efficacy of the two groups was similar ($P > 0.05$). The VAS score, WOMAC score and knee joint circumference after treatment were lower than those before treatment in the two groups ($P < 0.05$), and those in the experimental group were lower than those in the control group ($P < 0.05$). Indicating that Wuling San and Taohong Siwu Decoction combined with western medicine in the treatment of knee osteoarthritis with synovitis (cold-dampness obstruction type) can significantly reduce pain, swelling and improve joint function. It is superior to simple western medicine and has no obvious adverse reactions, which is worthy of further study and promotion.

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