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Original Research Article

Efficacy of Wushaoshe Qufeng Tablet and leflunomide combination therapy in the management of rheumatoid arthritis, and its influence on incidence of adverse drug reactions

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Abstract

Purpose: *To study the effectiveness and safety of combined use of Wushaoshe Qufeng tablets and leflunomide in the treatment of rheumatoid arthritis patients.*
Methods: *A retrospective trial was conducted among 120 patients with rheumatoid arthritis hospitalized in Heyuan Hospital of Traditional Chinese Medicine, Heyuan, from February 2020 to February 2021. The patients were equally divided into study group (n = 60) and control group (n = 60). Both groups received conventional treatment. in addition, the control group received leflunomide, whereas the experimental group received Wushaoshe Qufeng tablets. The two groups were compared with respect to laboratory indicators, TCM syndrome scores, and adverse events.*
Results: *The post-treatment TCM syndrome scores was lower in the experimental group versus control group ($p < 0.001$). After treatment, the study group was superior to the control group in terms of their biochemical indicators ($p < 0.001$). Safety profile was better in the study group than in the control group ($p < 0.05$). Treatment effectiveness was significantly higher in the study group than in the control group ($p < 0.05$).*
Conclusion: *Combined treatment of rheumatoid arthritis patients with Wushaoshe Qufeng tablets and leflunomide shows improved biochemical indicators, mitigates clinical symptoms, and enhances treatment effectiveness. Moreover, the combination therapy is safe, and therefore, should be considered for the management of rheumatoid arthritis patients.*

Keywords: *Wushaoshe Qufeng Tablets, Leflunomide, Rheumatoid arthritis*

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INTRODUCTION

Rheumatoid arthritis is a chronic and systemic autoimmune disease which produces early arthritis-like symptoms, soft tissue swelling and pain. As the disease becomes exacerbated, joint deformities may arise in severe cases, thereby threatening the patient's life and health [1]. At present, the pathogenesis of rheumatoid arthritis is not clearly understood, and there are no long-

term treatments for the disease. Thus, the affected patients are prone to recurrence after routine medication. Moreover, non-steroidal anti-inflammatory drugs (NSAIDs) immunosuppressive drugs easily triggers liver and kidney dysfunctions, thereby leading to difficulties in treatment of patients [2]. Therefore, there is need for safer and more effective drugs for treatment of rheumatoid arthritis. Some clinical researchers have used combinations of Chinese and Western medicine for patients with rheumatoid arthritis, based on the perspective of holistic TCM treatment and syndrome differentiation. It was found that combination of *Sanhan Qushi Decoction* and *wind-dispelling* drugs, *dampness-removing,* blood circulation-enhancing and *dampness-removing* drugs; and combination of *Qufeng Tongluo Decoction* with leflunomide, produced outstanding effects and lower degree of adverse reactions, thereby considerably enhancing the overall effectiveness of treatment [3]. In addition, it has been reported that *black snake* hydrolysate reduces the levels of serum inflammatory factors in collagen-induced arthritic rats, which indicates its potential benefit in prevention and treatment of rheumatoid arthritis [4]. Traditional Chinese medicine believes that snake preparations penetrate the bones and *remove wind*, with no side effects, and that they are useful in the treatment of patients with rheumatoid arthritis. However, not much has been reported on the effect of combination of black snake hydrolysate and leflunomide on rheumatoid arthritis. The present study investigated the effect of combined application of black snake hydrolysate and leflunomide on rheumatoid arthritis by retrospectively analyzing data on 120 patients.

METHODS

General patient profile

A retrospective study was conducted based on the data of rheumatoid arthritis patients who hospitalized in Heyuan Hospital of Traditional Chinese Medicine, Heyuan, from February 2020 to February 2021. The study received ethical approval from the ethical committee of Heyuan Hospital of Traditional Chinese Medicine, Heyuan, and followed international guidelines for human studies.

Inclusion criteria

The included subjects were: (1) patients who were aware of the processes involved in the research, and who signed informed consent form, or had their family members sign for them; (2) patients diagnosed as having rheumatoid arthritis after examination in accordance with the *Diagnostic Criteria for Internal Medicine* [5]; (3) patients who had obvious clinical symptoms of rheumatoid arthritis, i.e., at least 3 of the 12 joint areas including the knee joints, ankle joints, and elbow joints on both sides developed arthritis or joint swelling and pain, with persistent morning stiffness for at least 1 h per day [6]; (4) subjects who had subcutaneous nodules; (5) patients with positive rheumatoid factor [7], and (6) those who showed bone erosion in the wrist joint during image examination.

Exclusion criteria

The excluded patients were those who had: (1) mental problems or communication problems, and (2) other serious diseases such as systemic lupus erythematosus, malignant tumors, acute and chronic hepatitis, and liver and kidney dysfunction [8]. Moreover, pregnant or lactating patients, and those who were allergic to *Wushaoshe Qufeng* tablets and leflunomide, were excluded from the study.

Finally, 120 patients were included in the study, and they were assigned to study and control groups at a ratio of 1:1, based on the order of admission. The general information were homogeneous in the two groups ($p > 0.05$; Table 1).

Withdrawal criteria

Those whose conditions deteriorated during the study, and patients with some serious co-morbidities or complications, were withdrawn from the study. In addition, subjects who requested to be withdrawn due to their unwillingness to continue participating in the clinical trial, were withdrawn. In the above situations, if the researchers adjudged that it was not suitable for the affected patients to continue with the clinical trial, regardless of the reason, their case record forms were kept, and their last test results were taken as the final results which were used for full data analysis.

Treatments

Both groups received conventional treatment; the control group received leflunomide (20 mg/day, Jiangsu Yabang Epson Pharmaceutical Co. Ltd, National Medicine Standard H20080420), but the dose was changed to 50 mg/day after 3 consecutive days. The drug was administered for a total period of 12 weeks.

Table 1: Comparison of general patients' profile

Variable	Study group (n=60)	Control group (n=60)	χ^2/t	*P*-value
Gender			0.147	0.702
Male	20	22		
Female	40	38		
Age (years)				
Range	45-76	46-74		
Mean age	57.65±3.54	57.35±3.44	0.471	0.639
Mean weight (kg)	56.65±2.10	56.59±2.32	0.149	0.882
BMI (kg/m^2)	22.10±1.23	22.05±1.20	0.225	0822
Course of disease (years)	1.62±0.54	1.65±0.57	0.296	0.768
Joint function score	8.65±1.10	8.57±1.05	0.407	0.684
Joint function classification				
Ⅰ	25	26	0.034	0.853
Ⅱ	25	24	0.035	0.853
Ⅲ	10	10	0.000	1.000
Joint X-ray staging				
Ⅰ	10	9	0.063	0.803
Ⅱ	41	40	0.038	0.845
Ⅲ	9	11	0.240	0.624
Place of residence			0.134	0.715
City	30	32		
Rural area	30	28		
Monthly income (Yuan)			0.302	0.583
≥4000	34	31		
<4000	26	29		
Underlying illness				
Diabetes	16	17	0.042	0.838
Hypertension	22	24	0.141	0.707

In addition to the treatment given to the control group, the study group was treated with *Wushaoshe Qufeng* tablets (Guangzhou Zhixin Pharmaceutical Co. Ltd., Guangdong 20160108) 3 times a day (6 tablets each dose) for a total period of 12 weeks.

Evaluation of indices

TCM syndrome score

In the *Guiding Principles for Clinical Research of New Chinese Medicines*, clinical symptoms and scores are divided into 4 grades according to their severity viz: normal (0 point), mild (1 point), moderate (2 points) and severe (3 points). After treatment, symptoms such as joint pain, morning stiffness, swelling, and chills 6 weeks after treatment, and 12 weeks after treatment were compared between the two groups [9].

Biochemical indicators

Fasting venous blood (5 ml) was drawn from each patient in the two groups before treatment, 6 weeks after treatment, and 12 weeks after treatment. The blood samples were centrifuged at 4000 rpm at 4 °C, and the immunoturbidimetric method was used to determine levels of rheumatoid factor (RF) and C-reactive protein (CRP) with reagent kits (Nanjing Jidan Biotechnology Co. Ltd., Suzhou approval number 2012 No. 2400146), while levels of anti-cyclic citrullinated peptide antibodies (anti-CCP) were measured with enzyme-linked immunosorbent assay (ELISA) kits (Beijing Kewei Clinical Diagnosis Reagent Co. Ltd.; approval number: S20060028).

Incidence of adverse reactions

The number of cases of adverse drug reactions such as skin rash, gastrointestinal problems, mild decreases in number of white blood cells, mild increases in transaminase, oral ulcers and dizziness, were determined.

Treatment efficacy

If the patient's symptoms disappeared, and joint function and serological indicators returned to normal, the treatment was regarded as resulting in *cure*. If the symptoms basically disappeared, or the main symptoms disappeared, and joint function and serological indicators basically returned to normal, the treatment was regarded as *markedly effective*. If the patient's symptoms were alleviated, with improvements in joint function and serological indicators, and the patients could take care of themselves, the

treatment was considered *effective*. However, if the patient did not experience improvement in any of above aspects, the treatment was deemed to be *ineffective* [10].

Statistical analysis

The data analysis was done with SPSS 20.0 software, while graphics were prepared with GraphPad Prism 7 (GraphPad Software, San Diego, USA). Enumeration data and measurement data were processed via χ^2 test and *t*-test, respectively. The significance for all tests was set at $p < 0.05$.

RESULTS

TCM syndrome scores

Markedly lower TCM syndrome score was noticed in experimental group vs. control group after treatment ($p < 0.001$; Table 2).

Levels of laboratory indicators

Better post-treatment values of laboratory indicators was observed in the experimental group in relative to the control group ($p < 0.001$). These results are presented in Figure 1, Figure 2 and Figure 3. There was no significant difference in the RF levels at T1 between the two groups (149.65 ± 21.65 vs 150.57 ± 20.88, $p > 0.05$). However, the RF levels at T2 and T3 in the experimental group were significantly lower than the corresponding values in the control group (114.26 ± 21.25 vs 140.98 ± 20.41, and 99.68 ± 12.57 vs 119.68 ± 15.68, respectively; $p < 0.001$).

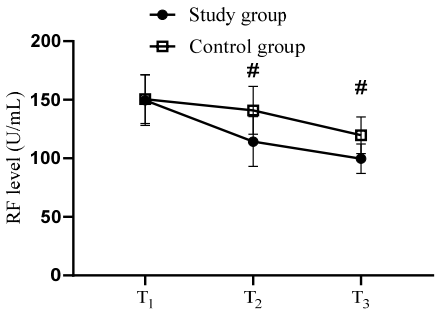

Figure 1: Comparison of patients' RF levels. Values are mean ± SD

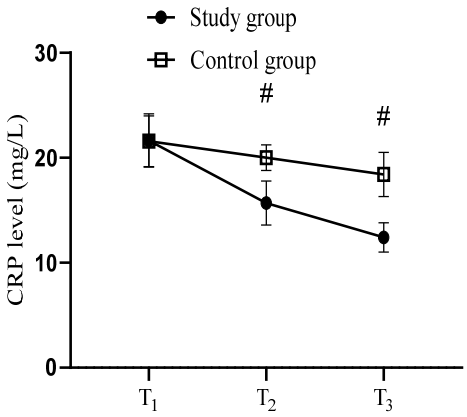

Figure 2: Comparison of CRP levels in patients. Values are expressed as mean ± SD

Table 2: Comparison of TCM syndrome scores of patients in the 2 groups (mean ± SD)

Variable	Control group (n=60)		Study group (n=60)		*T*	*P*-value
Joint pain	Before treatment	2.78±0.12	Before treatment	2.76±0.13	0.876	0.383
	6 weeks after treatment	1.45±0.14	6 weeks after treatment	2.10±0.15	24.538	<0.001
	12 weeks after treatment	1.05±0.14	12 weeks after treatment	1.69±0.15	24.161	<0.001
Morning stiffness	Before treatment	2.41±0.20	Before treatment	2.43±0.21	0.534	0.594
	6 weeks after treatment	1.65±0.23	6 weeks after treatment	1.98±0.25	7.525	<0.001
	12 weeks after treatment	1.29±0.12	12 weeks after treatment	1.49±0.14	8.402	<0.001
Swelling	Before treatment	2.26±0.23	Before treatment	2.30±0.24	0.932	0.353
	6 weeks after treatment	1.44±0.20	6 weeks after treatment	2.05±0.21	16.293	<0.001
	12 weeks after treatment	0.98±0.10	12 weeks after treatment	1.75±0.23	23.782	<0.001
Chills	Before treatment	2.65±0.23	Before treatment	2.62±0.24	0.699	0.486
	6 weeks after treatment	1.34±0.21	6 weeks after treatment	2.11±0.23	19.151	<0.001
	12 weeks after treatment	0.95±0.10	12 weeks after treatment	1.54±0.15	25.350	<0.001

There was no significant difference in CRP levels at T1 between the two groups (21.65 ± 2.54 vs 21.58 ± 2.41; $p > 0.05$). However, CRP levels at T2 and T3 in the experimental group were significantly lower than the corresponding values in the control group (15.68 ± 2.10 vs 20.01 ± 1.23, and 12.41 ± 1.41) vs 18.42 ± 2.10, respectively; $p < 0.001$).

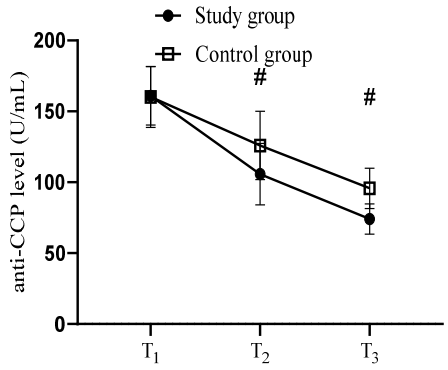

Figure 3: Comparison of patients' anti-CCP levels. Values are expressed as mean ± SD. There was no significant difference in anti-CCP levels at T1 between the two groups (160.98 ± 20.54 vs 160.25 ± 21.55, $p > 0.05$). However, anti-CCP levels at T2 and T3 in the experimental group were significantly lower than the corresponding control values (105.68 ± 21.68 vs 125.98 ± 24.10, and 74.11 ± 10.68 vs 95.68 ± 14.21, respectively; $p < 0.001$)

Incidence of adverse reactions in patients

As shown in Table 3, the experimental group experienced notably lower incidence of adverse reactions than the control group ($p < 0.05$).

Treatment efficacy

Table 4 shows that the study group yielded higher total treatment effectiveness than the control group ($p < 0.05$).

DISCUSSION

Rheumatoid arthritis is an aggressive joint inflammation which originates from the small joints of the hands and feet. The major early symptoms of the disease are joint swelling and morning stiffness. If effective treatment is not provided, the condition might become life-threatening. Advancements in medical research have led to development of several drugs for the treatment of rheumatoid arthritis. To date, the commonly used drugs in clinical practice are non-steroidal drugs, glucocorticoids, biological monoclonal antibodies, as well as Chinese medicine preparations [11]. Non-steroidal drugs and immunosuppressive drugs are widely preferred because they are effective in controlling the progression of the disease. Nevertheless, a prior trial reported that long-term usage of these drugs resulted in gastrointestinal reactions, or impairment of liver and kidney functions [12]. This poses a serious challenge in the treatment of rheumatoid arthritis. Therefore, it is critically important to use drugs with lower side effects.

Recent studies have shown that traditional Chinese medicines such as *Qufeng Tongluo Decoction*, *Sanhan Qushi Decoction, and Jiawei Shengyang Decoction* produced desirable effects on rheumatoid arthritis, with lower probability of adverse reactions [13]. Therefore, these drugs may be superior to conventional Western medicines in terms of mild toxicity. In TCM, it is believed that rheumatoid arthritis belongs to rheumatism disease which results from the interplay of three *qi* of wind, dampness and

Table 3: Comparison of incidence of adverse reactions between the two groups of patients [n (%)]

Group	Skin rash	Gastrointestinal reactions	Mild decrease in white blood cells	Mild increases in transaminases	Oral ulcers	Dizziness	Adverse reactions
Study	3 (5.0%)	3 (5.0%)	0 (0.0%)	2 (3.3%)	3 (5.0%)	1 (1.7%)	48 (80.0%)
Control	4 (6.7%)	6 (10.0%)	2 (3.3%)	4 (6.7%)	3 (5.0%)	5 (8.3%)	36 (60 %)
χ^2							5.023
P-value							0.034

Table 4: Comparison of treatment efficacy between the two groups of patients [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effectiveness
Study	12(20.0)	18(30.0)	18(30.0)	48(80.0)
Control	6(10.0)	12(20.0)	20(33.3)	38(63.3)
χ^2	2.353	1.600	0.154	4.104
P-value	0.125	0.206	0.695	0.043

coldness. In TCM, it is believed that the patients often present with *cold evil invasion.* Thus, the treatment of rheumatoid arthritis follows the rules of Chinese medicine by *dispelling dampness* and relieving pain; promoting blood circulation and removing blood stasis. The main component of the *Wushaoshe Qufeng* tablets used in this study was black snake, which was recorded in the *Compendium of Materia Medica* in the Ming Dynasty as a non-toxic drug with sweet and flat smell which was effective for *curing stubbornness of the wind* [14]. This drug is used in TCM for *dispelling wind*, relieving pain, and *eliminating evil*, and it is appropriate for diseases with high recurrence. The improvement of clinical indicators in the two groups after treatment may be attributed to the fact that leflunomide inhibited the activation of nuclear factor-KB, reduced the expressions of cytokines and adhesion factors, and slowed down the production of antibodies, thereby exerting an anti-inflammatory effect.

After treatment, better TCM syndrome scores and levels of laboratory indicators was witnessed in the experimental group, which is presumably because that black snake type II collagen induced immune tolerance, thereby reducing inflammatory factor levels in the patients, enhancing lymphocyte action, mitigating inflammatory injury, and alleviating clinical symptoms of rheumatoid arthritis.

It has been reported that the hydrolysate of black snake significantly reduced collagen-induced arthritis in rats and enhanced the level of anti-bovine type II collagen [15]

This indicated that the physicochemical properties of black snake are similar to those of anti-bovine type II collagen, and that it inhibited the development of rheumatoid arthritis [16]. Similarly, in another study, it was found that the 28-joint disease scores of patients with rheumatoid arthritis were reduced by snake preparation, with significantly higher total treatment effectiveness [17,18]. The present study also found that patients who took *Wushaoshe Qufeng tablets* had markedly higher overall treatment effectiveness than control patients, as well as minor adverse reactions. After one week of symptomatic treatment, all the adverse reactions were no longer noticeable, indicating that *Wushaoshe Qufeng tablets* are safe. However, it is worth noting that the snake preparations currently in practice include *black snake* wine and black snake powder. Thus, there is need to investigate whether there is consistent safety amongst the different snake preparations.

CONCLUSION

Treatment of rheumatoid arthritis patients with A combination of *Wushaoshe Qufeng tablets* and leflunomide improves their biochemical indices, relieves clinical symptoms, and improves treatment efficacy. Moreover, the treatment is highly safe, and thus may suitable for the management of rheumatoid arthritis.

DECLARATIONS

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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