ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2022 January 7; 10(1): 1-396

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Weekly

EDITORS-IN-CHIEF
Bao-Gan Peng

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
January 7, 2022

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World J Clin Cases 2022 January 7; 10(1): 35-42

DOI: 10.12998/wjcc.v10.i1.35

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Case Control Study

Changes in rheumatoid arthritis under ultrasound before and after sinomenine injection

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Author contributions: Huang YM design the experiment; Zhuang Y drafted the work, Tan ZM collected the data; Huang YM analysed and interpreted data, Zhuang Y and Tan ZM wrote the article.

Institutional review board statement: This study was approved by the Huizhou Central People's Hospital Ethics Committee.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: The authors declared that there is no conflict of interest between them.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Country/Territory of origin: China

Specialty type: Rheumatology

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Abstract

BACKGROUND

Rheumatoid arthritis (RA) is a prevalent clinical autoimmune disease that is commonly treated with diclofenac and methotrexate. In recent years, the application of traditional Chinese medicine in RA has received widespread attention; it promotes blood circulation, strengthens the immune system, and eliminates evil. The sinomenine preparation of Zhingqeng Fengtongning is studied as a possible treatment for patients with RA.

AIM

To explore the value of sinomenine injection into the articular cavity for the treatment of RA.

METHODS

A total of 94 patients with RA treated from January 2019 to January 2021 were selected and divided into the study and control groups with 47 patients each using a simple random number table method. Both groups received conventional treatment with diclofenac sodium and methotrexate tablets. The control group received diproxone and lidocaine by intra-articular administration while the study group received an intra-articular administration of the sinomenine preparation of Zhengqing Fengning and lidocaine. χ^2 test was used to evaluate the therapeutic effect and synovial thickness, degree of pain through the visual analog scale (VAS), blood flow grade, arthroinflammatory indexes [rheumatoid factor (RF), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR)] before and after treatment in the two groups.

RESULTS

The total effective rate of the study group (93.62%) was higher than that of the control group (78.72%) ($P < 0.05$). Before treatment, there were no significant differences between the two groups in terms of synovial thickness, VAS score, blood flow grading, levels of RF, and ESR ($P > 0.05$). After treatment, the synovial

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: August 26, 2021
Peer-review started: August 26, 2021
First decision: September 29, 2021
Revised: October 14, 2021
Accepted: November 26, 2021
Article in press: November 26, 2021
Published online: January 7, 2022

P-Reviewer: Khanna NN, Tanaka M
S-Editor: Wang JL
L-Editor: A
P-Editor: Wang JL

thickness and VAS score were significantly lower ($P < 0.05$) in the study group than in the control group (2.05 ± 0.59 mm *vs* 2.87 ± 0.64 mm and 2.11 ± 0.62 *vs* 2.90 ± 0.79 scores, respectively). The rate of blood flow at grade 0 in the study group (76.60%) was higher than that in the control group (57.45%), and the rate of blood flow at grade I (10.64%) was lower than that in the control group (31.91%) ($P < 0.05$). Furthermore, the levels of RF (55.61 ± 6.13 U/mL), CRP (11.43 ± 3.59 mg/L), and ESR (29.60 ± 5.56 mm/h) in the study group were lower than those in the control group (73.04 ± 9.23 U/mL, 15.07 ± 4.06 mg/L, 36.64 ± 6.10 mm/h, respectively) ($P < 0.05$).

CONCLUSION
Sinomenine administration of Zhengqing Fengtongning in the articular cavity with conventional treatment of RA can improve ultrasonographic blood flow and synovial thickness, reduce pain, regulate inflammation, and enhance therapeutic effect.

Key Words: Rheumatoid arthritis; Articular injection; Sinomenine; Ultrasonic changes; Inflammatory factors; Zhengqing Fengtongning

Core Tip: Sinomenine administration of Zhengqing Fengtongning in the articular cavity can improve blood flow and synovial thickness, reduce pain, regulate inflammation, and enhance therapeutic effect. The drug preparation was administered with diclofenac and methotrexate. Comparison of outcomes was done between a study group and a matched control group.

Citation: Huang YM, Zhuang Y, Tan ZM. Changes in rheumatoid arthritis under ultrasound before and after sinomenine injection. *World J Clin Cases* 2022; 10(1): 35-42
URL: https://www.wjgnet.com/2307-8960/full/v10/i1/35.htm
DOI: https://dx.doi.org/10.12998/wjcc.v10.i1.35

INTRODUCTION

Rheumatoid arthritis (RA) is a prevalent clinical autoimmune disease with symmetrical, chronic, and peripheral joint involvement. It may occur in any age group, and may affect the physical health and quality of life of patients[1-3]. In recent years, there is a continuous increase in the incidence of RA; it has become an important cause of disability. Therefore, studies on safe and effective interventions for RA are essential [4,5].

Currently, glucocorticoids, non-steroidal anti-inflammatory drugs, hydroxychloroquine, and methotrexate are used to treat RA patients. The said medications alleviate clinical symptoms but long-term use increases the risk of adverse reactions, such as peptic ulcer and gastrointestinal discomfort, leading to poor patient compliance and termination of the medication[6-8]. In recent years, the application of traditional Chinese medicine in RA has received widespread attention. Traditional Chinese medicine mainly follows the principle of disease treatment as promotion of blood circulation, strengthening of the immune system, and elimination of evil. Sinomenine has immunosuppressive, analgesic, and anti-inflammatory effects[9,10].

This study explores the effects of sinomenine injection into the articular cavity for the treatment of RA.

MATERIALS AND METHODS

General information

This study was approved by the Ethics Committee of the hospital. A total of 94 patients with RA treated at our hospital between January 2019 and January 2021 were

selected. The inclusion criteria were as follows: (1) Meeting the RA diagnostic criteria in the 2018 Guidelines for the Diagnosis and Treatment of Rheumatoid Arthritis in China[11]; (2) RA in the active stage; (3) good cognitive and communication skills; (4) good cooperation to complete the research; and (5) both the patients and their family members gave their informed consent to participate in this study. Exclusion criteria: (1) Allergic constitution; (2) relevant treatment within 1 mo before participating in the study; (3) gastrointestinal bleeding; (4) mental illness; (5) lactation and pregnancy; (6) blood system lesions; (7) systemic lupus erythematosus and other rheumatic immune system diseases; and (8) severe knee osteoarthritis and joint deformity. Participants were divided into a study group and a control group with 47 patients each according to the simple random number table method. In the study group, there were 21 men and 26 women, aged 35–69 years, with an average age of 51.59 ± 12.87 years old. The course of disease ranged from 8 mo to 7 years, with an average of 3.89 ± 1.37 years. The control group had 18 males and 29 females, aging from 32 to 72, with an average of 53.13 ± 13.55 years. The disease course ranged from 6 mo to 8 years, with an average of 4.01 ± 1.50 years. The clinical data of sex, age, and course of disease were comparable between the two groups ($P > 0.05$).

Methods

Both groups have received conventional treatment with diclofenac sodium tablets (manufactured by Shanxi Jinxin Shuanghe Pharmaceutical Co., Ltd., National Medicine Approval No. H21021130), 75 mg per dose given twice a day and methotrexate tablets (manufactured by Shanghai Shangyao Xinyi Pharmaceutical Co., Ltd., National Medicine Approval No. H31020644), 2.5 mg per dose given thrice a day. The control group received an arthrocavitary injection of 1 mL dexone (Chongqing Huabang Pharmaceutical Co., Ltd., National Medicine Approval No. H20093412) + 1-mL lidocaine (Xi'an Fenghua Pharmaceutical Co., Ltd., National Medicine Approval No. H61020861). In the study group, the patients were treated with 1.4-mL sinomenine Zhengqing Fengtongning injection (Hunan Zhengqing Pharmaceutical Group Co., Ltd., National Medicine Approval No. Z43020279) + 1-mL lidocaine. Both groups were treated for 12 wk.

Indicators

Statistical analysis of the therapeutic effects of the two groups was done after 12 wk of treatment. A "significant effect" was noted when an 80% improvement was observed in the erythrocyte sedimentation rate (ESR) and other laboratory indicators, recovery of normal work and life, and disappearance of joint swelling, tenderness, and other symptoms. It was "effective" when the range of improvement of the ESR and other laboratory examination indexes were at 50%-79%, with partial recovery of work and life, and considerable symptom relief of joint swelling and tenderness. It was "ineffective" when the improvement of the ESR and other laboratory indicators were less than 50%, with difficulty in independent work and life, and without symptom relief of joint swelling and tenderness. The effective rate is computed as (significant effect + effective)/total number of cases × 100%[12]. Another statistical analysis was done to compare the synovial thickness, degree of pain, and blood flow grade of the two groups before and after treatment. The degree of pain was evaluated according to the isual analog scale (VAS) scale, with a score ranging from 0 to 10 points; the higher the score, the stronger the feeling of pain. The synovial thickness was measured by ultrasonic examination. Color Doppler technology was used to detect the intensity of intra-synovial blood flow energy, and the semi-quantitative classification was performed: grade 0 indicated synovial blood flow signal, grade I indicated single blood vessel signal, grade II indicated that the vascular fusion signal was less than 1/2 of the region, and grade III indicated that the vascular fusion signal was larger than 1/2 of the region. Finally, statistical analysis of arthritis indicators was done, including rheumatoid factor (RF), C-reactive protein (CRP), and ESR.

Statistical analysis

SPSS 22.0, was used to analyze the data. Measurement data are expressed as mean ± SD, *t*-test, enumeration data with n (%), and χ^2 test. Statistically significant difference was set at $P < 0.05$.

RESULTS

Comparison of therapeutic effects between the two groups

Table 1 shows that the effective rate of the study group (93.62%) was significantly higher than that of the control group (78.72%) ($P < 0.05$).

Comparison of synovial thickness and VAS scores between the two groups

There was no significant difference ($P > 0.05$) in synovial thickness (5.29 ± 1.44 mm) and VAS score (7.01 ± 1.38) between the study group and the control group (5.50 ± 1.32 mm, 6.89 ± 1.50 mm, respectively). After treatment, synovial thickness (2.05 ± 0.59 mm) and VAS score (2.11 ± 0.62) in the study group were lower than those of the control group (2.87 ± 0.64 mm and 2.90 ± 0.79 scores, respectively, $P < 0.05$) (Table 2).

Comparison of blood flow grading between the two groups

Before treatment, there was no significant difference in blood flow grading between the two groups ($P > 0.05$). After treatment, the rate of blood flow at grade 0 in the study group (76.60%) was higher than that in the control group (57.45%), and the rate of blood flow at grade I (10.64%) was lower than that in the control group (31.91%), with $P < 0.05$ (Table 3).

Comparison of arthro-inflammatory indexes between the two groups

Before treatment, the levels of RF (161.39 ± 15.06 U/mL), CRP (34.10 ± 6.99 mg/L), and ESR (80.71 ± 7.11 mm/h) in the study group were not significantly different from those in the control group (158.91 ± 12.79 U/mL, 32.63 ± 7.29 mg/L, and 78.65 ± 6.70 mm/h, respectively, with $P > 0.05$). After treatment, the levels of RF (55.61 ± 6.13 U/mL), CRP (11.43 ± 3.59 mg/L), and ESR (29.60 ± 5.56 mm/h) in the study group were lower than those in the control group (73.04 ± 9.23 U/mL, 15.07 ± 4.06 mg/L, 36.64 ± 6.10 mm/h, respectively, with $P < 0.05$) (Table 4).

DISCUSSION

RA is an autoimmune disease driven by antigens and co-participated in by multiple cells, including dendritic cells, chondrocytes, fibroblasts, B cells, T cells, and macrophages[13]. The treatment of this disease focuses on improving joint function and controlling disease progression[14]. Methotrexate is a commonly used anti-rheumatic drug to inhibit DNA biosynthesis and to block cell proliferation. It can be used in the S phase of the cell cycle to promote apoptosis, thus exerting therapeutic effects through anti-inflammatory and immune regulation mechanisms[15]. Diclofenac is a non-steroidal anti-inflammatory drug that regulates the inflammatory response in the active stage of RA. However, it is difficult to eliminate the cause of the induced inflammation[16]. Diprospans are widely used in RA. It has anti-inflammatory, anti-allergic, and anti-rheumatic effects. After injection, the diprospan can be rapidly absorbed and can remain in the body for a long time for longer efficiency. However, it is difficult to achieve clinical expectations using these treatment modalities. Traditional Chinese medicine has unique cognitive and therapeutic advantages in RA treatment, which classifies RA into the categories of "Lijiefeng" (uarthritis), "Gubi" (heumatism), and "Bi" (rheumatism). The pathogenesis is explained by congenital deficiency, invasion of the wind-cold-dampness poison, improper diet, stagnation of meridians, and stagnation of qi and blood stasis. Therefore, the basic principles of disease treatment are to promote blood circulation, relieve pain, detoxify and dredge collaterals, dispel wind, and remove dampness[17]. Sinomenine, an alkaloid extracted from *Caulis sinomenii*, can inhibit bone destruction and inflammatory reactions, relax tendons and activate blood, expel wind, and remove dampness without inducing significant side effects[18]. Zhengqing Fengtongning injection is a Chinese medicinal preparation extracted from sinomenine. In this study, the sinomenine preparation of Zhengqing Fengtongning was administered through intraarticular injection to treat RA patients. The results showed that the synovial thickness and VAS score in the study group were lower than those in the control group, and there was better blood flow grade than the control group; the total effective rate was higher than the control group ($P < 0.05$). This indicated that the sinomenine preparation of Zhengqing Fengtongning has a high potential for RA treatment. It could improve blood flow, relieve pain, reduce synovial membrane thickness, and enhance the overall therapeutic effect. Sinomenine has anti-inflammatory and glucocorticoid-like effects that can

Table 1 Comparison of therapeutic effects, *n* (%)

Group	Number of cases	Significantly effective	Improved	Ineffective	Total effective rate
Study group	47	29 (61.70)	15 (31.91)	3 (6.38)	44 (93.62)
Control group	47	21 (44.68)	16 (34.04)	10 (21.28)	37 (78.72)
χ^2 value					4.374
P value					0.036

Table 2 Comparison of synovial membrane thickness and visual analog scale scores

Timing	Group	Number of cases	Synovial thickness (mm, mean ± SD)	VAS score (mean ± SD)
Before treatment	Study group	47	5.29 ± 1.44	7.01 ± 1.38
	Control group	47	5.50 ± 1.32	6.89 ± 1.50
	t value		0.737	0.404
	P value		0.463	0.687
After treatment	Study group	47	2.05 ± 0.59	2.11 ± 0.62
	Control group	47	2.87 ± 0.64	2.90 ± 0.79
	t value		6.458	5.393
	P value		0.000	0.000

VAS: Visual analog scale.

Table 3 Comparison of blood flow classification, *n* (%)

Timing	Group	Number of cases	Grade 0	Grade I	Grade II	Grade III
Before treatment	Study group	47	25 (53.19)	12 (25.53)	7 (14.89)	3 (6.38)
	Control group	47	23 (48.94)	15 (31.91)	5 (10.64)	4 (8.51)
	χ^2 value		0.170	0.468	0.382	0.000
	P value		0.680	0.494	0.536	1.000
After treatment	Study group	47	36 (76.60)	5 (10.64)	5 (10.64)	1 (2.13)
	Control group	47	27 (57.45)	15 (31.91)	3 (6.38)	2 (4.26)
	χ^2 value		3.899	6.351	0.545	0.000
	P value		0.048	0.012	0.460	1.000

selectively inhibit the activity of cyclooxygenase-2, reduce the synthesis of prostaglandin E2, and promote the secretion of adrenocortical hormone. It can also exert nonspecific anti-inflammatory effects, reduce blood viscosity, correct fibrinolysis disorder, improve blood flow velocity, regulate microcirculation, and achieve immunosuppression, anti-inflammatory, analgesic, and antioxidation effects. It can also be used as a histamine release agent. It can regulate the immune system, promote detumescence and analgesia, dispel wind and remove dampness, and activate blood and dredging collaterals. These effects improve vascular permeability and blood circulation, and reduce inflammatory swelling.

Ultrasound is an important diagnostic and therapeutic evaluation measure for RA. In this study, there was an abnormal increase of suprapatellar bursa effusion in the active stage of RA, synovial thickening, and relatively rich blood flow signals in the thickened synovium. After the sinomenine treatment, the inflammation and increase in the synovial fluid were controlled, the exudate in the joint cavity was significantly decreased, the synovial membrane became thinner, and the blood flow signals in the synovial fluid disappeared. Therefore, this study confirmed that sinomenine preparation could also improve ultrasound changes in RA patients.

Table 4 Comparison of arthro-inflammatory indexes (mean ± SD)

Timing	Group	Number of cases	RF (U/mL)	CRP (mg/L)	ESR (mm/h)
Beforetreatment	Study group	47	161.39 ± 15.06	34.10 ± 6.99	80.71 ± 7.11
	Control group	47	158.91 ± 12.79	32.63 ± 7.29	78.65 ± 6.70
	t value		0.861	0.998	1.446
	P value		0.392	0.321	0.152
Aftertreatment	Study group	47	55.61 ± 6.13	11.43 ± 3.59	29.60 ± 5.56
	Control group	47	73.04 ± 9.23	15.07 ± 4.06	36.64 ± 6.10
	t value		10.785	4.605	5.848
	P value		0.000	0.000	0.000

RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Meanwhile, CRP and ESR are important indicators for evaluating RA. CRP is a glycoprotein synthesized by hepatocytes that increases during tissue necrosis or injury/inflammation. It also participates in the non-classical activation pathway of complement, leading to immune regulation, promotion of phagocytosis, and complement activation. The increase in ESR is closely related to the increase in the inflammatory factor content in the body during the active stage of RA. RF is an autoantibody targeting denatured immunoglobulin G in RA patients. It is mostly distributed in the joint fluid and serum of RA patients. It can be used as an important indicator for the diagnosis and efficacy evaluation of RA treatment[19]. The results of this study showed that the levels of CRP, ESR, and RF in the study group after treatment were lower than those in the control group. These laboratory results showed that the sinomenine preparation of Zhengqing Fengtongning injected into the joint cavity has high application value in RA treatment.

CONCLUSION

In summary, the administration of the sinomenine preparation of Zhengqing Fengtongning injection into the articular cavity after the administration of diclofenac and methotrexate tablets can effectively improve blood flow and synovial thickness, relieve pain and inflammation, and improve the overall therapeutic effect. However, this study did not group and compare the treatment of patients with different disease levels. Therefore, the difference in the efficacy of intra-articular injection of sinomenine preparation Zhengqing fengtongning injection in the treatment of RA with different conditions needs further exploration and confirmation.

ARTICLE HIGHLIGHTS

Research background

Rheumatoid arthritis (RA) is a popular clinical autoimmune disease. Diclofenac and methotrexate are usually used for treatment. In recent years, the application of Chinese medicine in RA has received widespread attention. The role of alkali preparations in this field has also received attention.

Research motivation

Explore the treatment methods of RA and broaden the application of Chinese medicine treatment in the field of RA.

Research objectives

This study aimed to study the therapeutic value of sinomenine preparations for RA.

Research methods
A total of 94 RA patients who received treatment from January 2019 to January 2021 were selected for a case-control study.

Research results
The total effective rate of the study group was higher than that of the control group.

Research conclusions
Sinomenine administration of Zhengqing Fengtongning in the articular cavity with conventional treatment of RA can improve ultrasonographic blood flow and synovial thickness, reduce pain, regulate inflammation, and enhance therapeutic effect.

Research perspectives
Sinomenine preparations can have a wider range of applications in the treatment of RA.

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