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Original Article

Meridian-sinew release therapy for the treatment of refractory rheumatoid arthritis

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Abstract: Objective: To evaluate the efficacy and safety of Meridian-sinew Release therapy in Chinese patients with refractory active Rheumatoid Arthritis (RA). Summary of Background Data: Few studies focused on the effect of combination of Meridian-sinew Release therapy and Methotrexate (MTX) on refractory active RA of Chinese patients. Methods: Eighty refractory active rheumatoid arthritis patients were randomized to receive Meridian-sinew Release+MTX 10 mg (n=40), MTX 10 mg (n=40) every week for 12 weeks. The primary end point was the proportion of patients achieving ≥20% improvement in the American College of Rheumatology criteria (ACR20) at week 12. Secondary efficacy endpoints included 28-joint disease activity score with ESR (DAS28-ESR), simplified disease activity index (SDAI), clinical disease activity index (CDAI) and Health Assessment Questionnaire-Disability Index (HAQ-DI). Results: Week 12 ACR20 response rates were significantly greater in Meridian-sinew Release+MTX group (30/38 (78.9%)) than in MTX group (19/37 (51.3%)), (P<0.001), as were ACR50 and ACR70 response rates. Patients treated with Meridian-sinew Release+MTX were significantly more likely to achieve clinical remission, using various definitions, at 12 weeks versus MTX alone. A larger percentage of Meridian-sinew+MTX patients than MTX alone patients were in states of low disease activity or remission for DAS28-ESR, SDAI and CDAI after 12 weeks of treatment. Conclusion: Our study suggests that Meridian-sinew Release therapy was well tolerated and efficacious in improving clinical outcomes in Chinese patients with refractory active RA.

Keywords: Meridian-sinew release therapy, rheumatoid arthritis, meridian-sinew scope, meridian-sinew knife

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that primarily affects joints. Characterized by inflammation and destruction of joints, RA casts an immense influence on health and living qualities of the afflicted, deactivating patients and the society with enormous economic burden [1-3]. Its morbidity rate is 0.5%~1% across the world [4] and about 0.3%~0.4% in China. It is estimated that over 50% of the patients would suffer from severe disability in the first 10 years of affliction with the disease and only 40% of the patients can carry on their work after 15 years' affliction [5]. Early diagnosis of RA is the basis of early treatment. In the first two years of affliction, most patients may undergo severe radiographic damage, during which both bone and tissue structures would suffer from rapid damage [6]. Therefore, the sooner the treatment begins, the more probable it will be to control the inflammatory process and reduce bone and tissue damage [7]. So far, there is no effective method to completely cure RA. Aiming to achieve complete remission [8], release treatments may control and prevent the pain and functional loss of damaged joints. Pharmacological therapy, which is still the principal approach to treat RA, mainly includes nonsteroidal anti-inflammatory drugs, slow acting anti-rheumatism drugs, glucocorticoid, biological agents, etc. However, these often cause discomfort and even serious side effects to patients, including peptic ulcer, hepatic toxicity, renal toxicity, blood cell reduction, blood coagulation dysfunction and allergic reactions. Nowadays in China, the treatment of RA is expensive, time-consuming, accompanied with severe side effects, leading to a relatively

low patient compliance. Having a special curative effect for easing pain, traditional Chinese medicine has been used to heal RA and other joint lesions for several thousand years [9-12]. As the understanding of limitations and side effects of Western medicine deepens, an increasing number of people began to focus on complementary and alternative medicine. Hence, it is quite necessary to search for safe and effective alternative therapies for RA.

Meridian-sinew release therapy is originated from the meridian-sinew theory and the nine needles therapy in Inner Classic. Through release, removal, lavement and other operations on diseased tissuesunder visual conditions, it treats swelling, pain and functional limitation of joints, tendons and fascia via a meridian-sinew scope and a meridian-sinew knife. As a new alternative therapy, it has been used to treat various rheumatic joint swelling and pain, especially RA [13-16]. In the process of our clinical treatments of RA with this therapy, we discovered that it can effectively ease the pain and swelling of the afflicted joints, soothe morning stiffness, improve arthral function, reduce inflammatory markers such as blood sedimentation rate (ESR) and C reactive protein (CRP) [14-16]. This therapy shows its unique strengths as its alteration of the patient organs remains within microscopic structures without any damage to the whole body structure, minimizing organic tissue damage and allowing a fast recovery.

This research aims to evaluate the curative effects and safety of meridian-sinew release therapy for refractory active RA, providing objective evident for the clinical application of meridian-sinew release therapy. Therefore, this research is of essential clinical value, promising as a new, safe and effective alternative therapy to treat refractory active RA.

Materials and methods

Subjects

Patients hospitalized in Guangzhou General Hospital of Guangzhou Military Command from January 2008 to December 2013 were recruited. The diagnosis of RA was made according to the RA Diagnostic Standard revised by American College of Rheumatology in 1987 [17], as well as the Disease Activity Standard regulated by European League against Rheumatism [18]. We recruited the subject patients in accordance with the following criteria: (i) diagnosed as RA at a medium or above active level according to the above RA Diagnostic Standard; (ii) aged between 18 to 70 years old; (iii) at least one of the afflicted joints of the patient shows a joint tenderness count ≥10, a joint swelling count ≥8; (iv) with Westergren method, CRP ≥2 mg/dl or ESR ≥28 mm/h; (v) willing and able to complete the research program. The exclusion criteria were intra-articular corticosteroid injection within 4 weeks preceding the study and severe, infectious arthritis, unstable chronic illness (including but not limited to congestive heart failure, chronic renal failure, and tumors in the joint), other autoimmune diseases such as ankylosing spondylitis, systemic lupus erythematosus, and gout. This research study was approved by the Ethics Committee of Guangzhou General Hospital of Guangzhou Military Command Area and all patients involved have signed paper copies of Informed Consent Form.

Estimation of sample size was based on the results of previous studies and then calculated according to the calculation formula for sample size estimation, with a clinical efficacy increase of 25% from the original level. The calculation formula was as follows: $n=(U_{\alpha}+U_{\beta})^2\ 2P\ (1-P)/(P_1-P_0)^2$ as to calculate the content of every sample [19].

Interventions and randomization

Before the patients participating in the study, they were informed that this research was aimed to evaluate the curative effects and safety of meridian-sinew release therapy for active RA and that they would be required to give up other forms of treatment for the duration of the study. Patients were randomly assigned to the meridian-sinew release therapy group or control group through computer-generated random numbers. Patients in the meridian-sinew release therapy group were treated with Methotrexate tablets 10 mg once per week, (produced by Shanghai Hualian Pharmaceutical Factory, nationally approved as H31020644), and Celecoxib Capsule 100 mg twice daily (manufacturer: Pfier Pharmaceuticals LLC, USA, approval number: J20080059), as well as meridian-sinew release treatment oper-

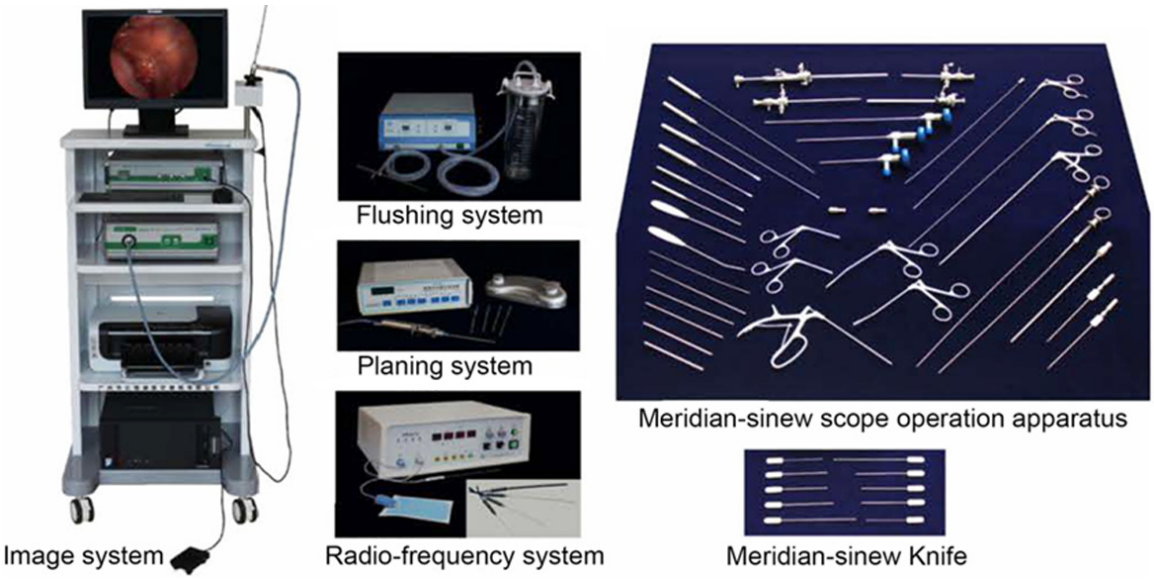

Figure 1. Meridian-sinew minimally Invasive therapy system (meridian-sinew scope, meridian-sinew knife).

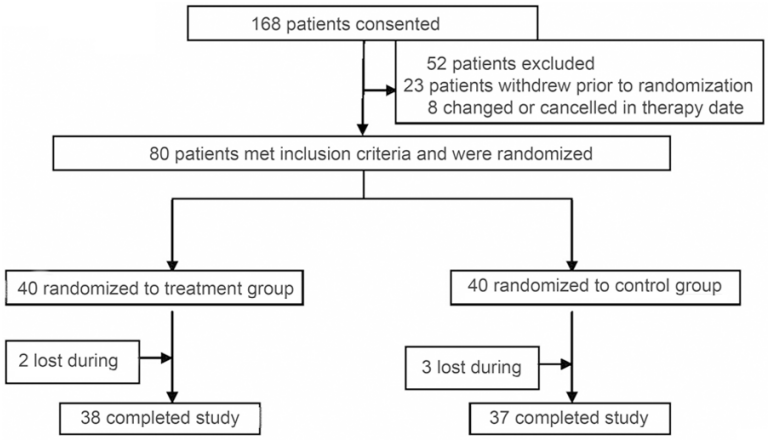

Figure 2. Flow chart of the distribution of the study cohort.

ated with meridian-sinew knife and needle-knife scope, while the control group patients were treated with Methotrexate tablets 10 mg once per week, Celecoxib Capsules 100 mg twice daily.

Treatments in detail

Meridian-sinew release group: The patients in this group were treated with Methotrexate tablets 10 mg once per week, Celecoxib Capsules 100 mg twice daily for a duration of 12 week, along with meridian-sinew release therapy. The meridian-sinew release therapy applies a meridian-sinew minimally invasive treatment system (**Figure 1**) including Meridian-sinew scope and meridian-sinew knife, to release and peel off the afflicted joints and tissue as to alleviate the swelling pain and dysfunction of joints, tendon and fascia.

The meridian-sinew scope and meridian-sinew knife technology is a modern Chinese medical operative technology for rheumatoid diseases guided by the meridian-sinew theory of Inner Classic, based on the concept and description of the traditional "Nine Needles". The course of treatment for meridian-sinew release therapy treatment lasted for 6 weeks. In the first week, with the assistance of meridian-sinew scope, meridian-sinew knife was used to release the adhesions of the afflicted joints for once. The procedure is as follows: a surgery incision was located on the lesion joint and after given a local infiltration anesthesia of 2% lidocaine, a small incision was slit open with a scalpel. A straight knife was used to peel off the subcutaneous fascia, muscular layer, cut through the joint capsule to crave up a meridian-sinew scope passage. The drive pipe of the meridian-sinew scope was inserted into body and then the core of the drive pipe was removed and taken out.

Table 1. Demographics and baseline characteristics

Parameter*	Meridian-sinew release group (n=38)	Control group (n=37)
Age ± SD (year)	51.0±12.9	51.0±13.0
Females (n (%))	34 (85.0)	33 (82.5)
RA duration ± SD (year)	1.0±0.6	1.0±0.6
Weight ± SD (kg)	55.3±9.5	55.9±10.3
ESR (mm/h)	61.1±29.8	60.8±29.3
CRP (mg/dl)	3.0±3.1	3.0±3.2
Swollen joint count (n ± SD)		
0-28	10.9±5.1	11.1±5.0
0-66	16.9±6.5	17.1±7.1
Tender joint count (n ± SD)		
0-28	13.1±6.0	13.0±6.1
0-66	20.9±9.9	21.0±10.1
DAS28-ESR	6.6±1.0	6.6±0.9
DAS28-CRP	5.9±1.1	5.8±1.0
HAQ-DI score	1.1±0.6	1.2±0.5
SDAI score	40.9±12.5	41.1±13.1
CDAI score	38.1±11.5	38.3±12.1
Patient's global assessment of diseaseactivity ± SD (mm)	65.2±24.1	66.0±23.9

*Data are mean ± SD unless otherwise indicated; DAS28-CRP, disease activity score using a 28-joint count and CRP level.

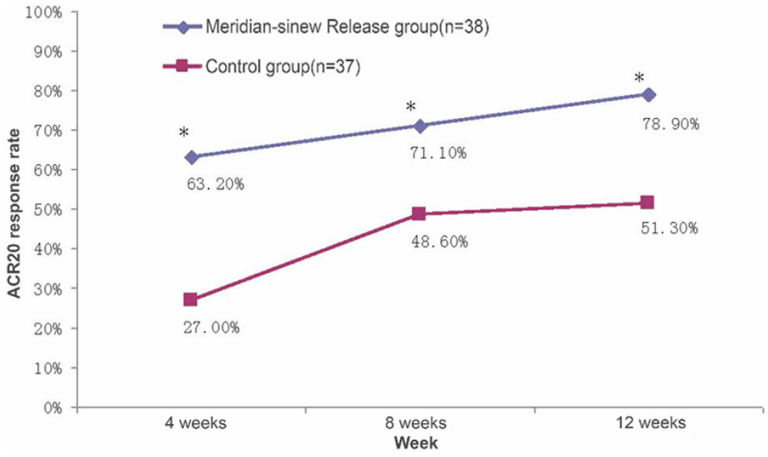

Figure 3. Percentage of patients with an ACR20 response. *P<0.001 versus Control group.

The meridian-sinew scope was inserted into the incision and the introducing passage for perfusate was installed. After perfusate fluid was injected into the lesion area, relative tissue structures within the joint were given close observation sequentially, during which process, operations such as release, peeling-off, cartilage repair, foreign substance elimination, synovium planning were conducted accordingly. Meanwhile, the joint would be under constant purge of perfusate infusion with inserted laveur draining the circulation of perfusate until the joint flushing fluid became clear and clean. As for treatments from the 2nd to the 6th week, the targeted body section was chosen based on the meridian-sinew acupoint searching guidance in China Meridian Sinews [20]. Surrounding the afflicted joint, outward and inward the joint spaces, meridian-sinew focus sites (namely acupoints of the meridian-sinew network). We marked the focus points with methylene blue and implemented a local infiltration anesthesia with 2 ml 2% lidocaine. We inserted the meridian-sinew knife into the marked area vertically to penetrate the deeper tissue layer and reach the bone surface. We release the adhesions with horizontal movements and opened the meridian-sinew pathways with vertical movements. This treatment was performed once a week for a whole five-week course.

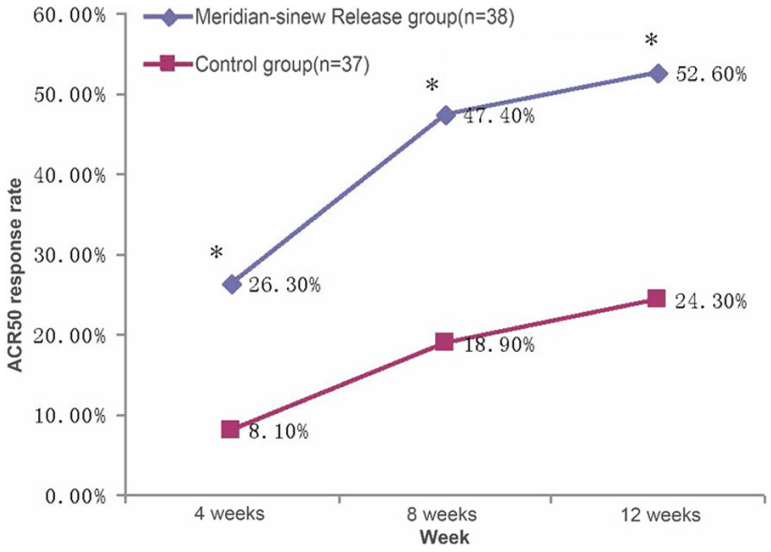

Figure 4. Percentage of patients with an ACR50 response. *P<0.001 versus Control group.

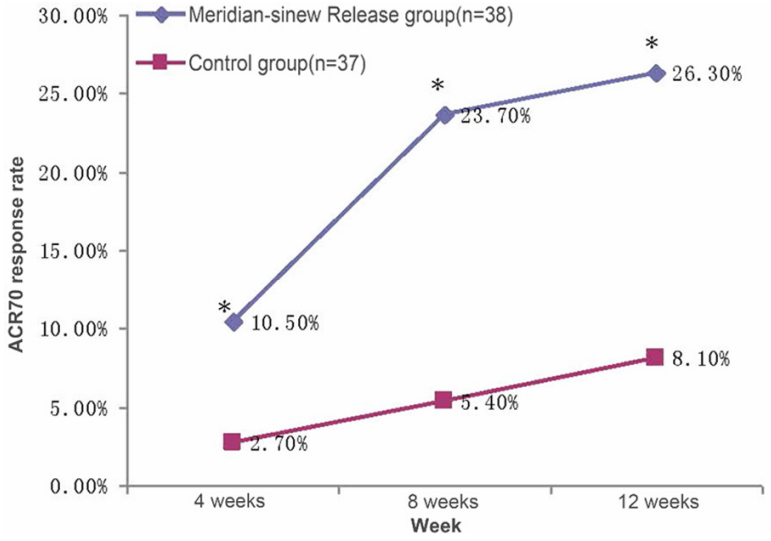

Figure 5. Percentage of patients with an ACR70 response. *P<0.001 versus control group.

Control group

The patients of this group were prescribed with Methotrexate tablets 10 mg once per week, Celecoxib Capsules 100 mg twice daily for a 12-week course.

Outcome evaluations

The follow-up and outcomes evaluations were performed by independent blinded assessors. The primary end point was the proportion of patients achieving ≥20% improvement in the American College of Rheumatology criteria at week 12 [21, 22]. ACR50 and ACR70 response rates were also measured. Secondary efficacy endpoints included the 28-joint disease activity score with ESR [23], simplified disease activity index [24], clinical disease activity index [25]. Physical function was evaluated with the Health Assessment Questionnaire Disability Index [26]. Clinical remission, defined as DAS28-ESR< 2.6 [23], SDAI ≤3.3 [27], CDAI ≤2.8 [28] at week 12. Low, medium and high disease activity was also determined using DAS28-ESR, SDAI and CDAI. Patients were monitored for adverse events, including the treatment site reactions and abnormal routine laboratory values during the study.

Statistical analysis

The collected statistics were analyzed by the Stata/SE 9.2 Statistical software. Differences between the treatment groups in ACR response rates were assessed using a X^2 test. Secondary endpoints were analyzed using the Fisher's exact test and Wilcoxon rank sum test for discrete variables and continuous variables, respectively. Univariate logistic regression analysis was performed, applying 14 baseline demographics and disease characteristics. With a p value<0.05, the difference in group results was verified as of statistical significance.

Results

Patient disposition and baseline characteristics

Between January 2008 and December 2013, we identified 168 patients with a diagnosis of

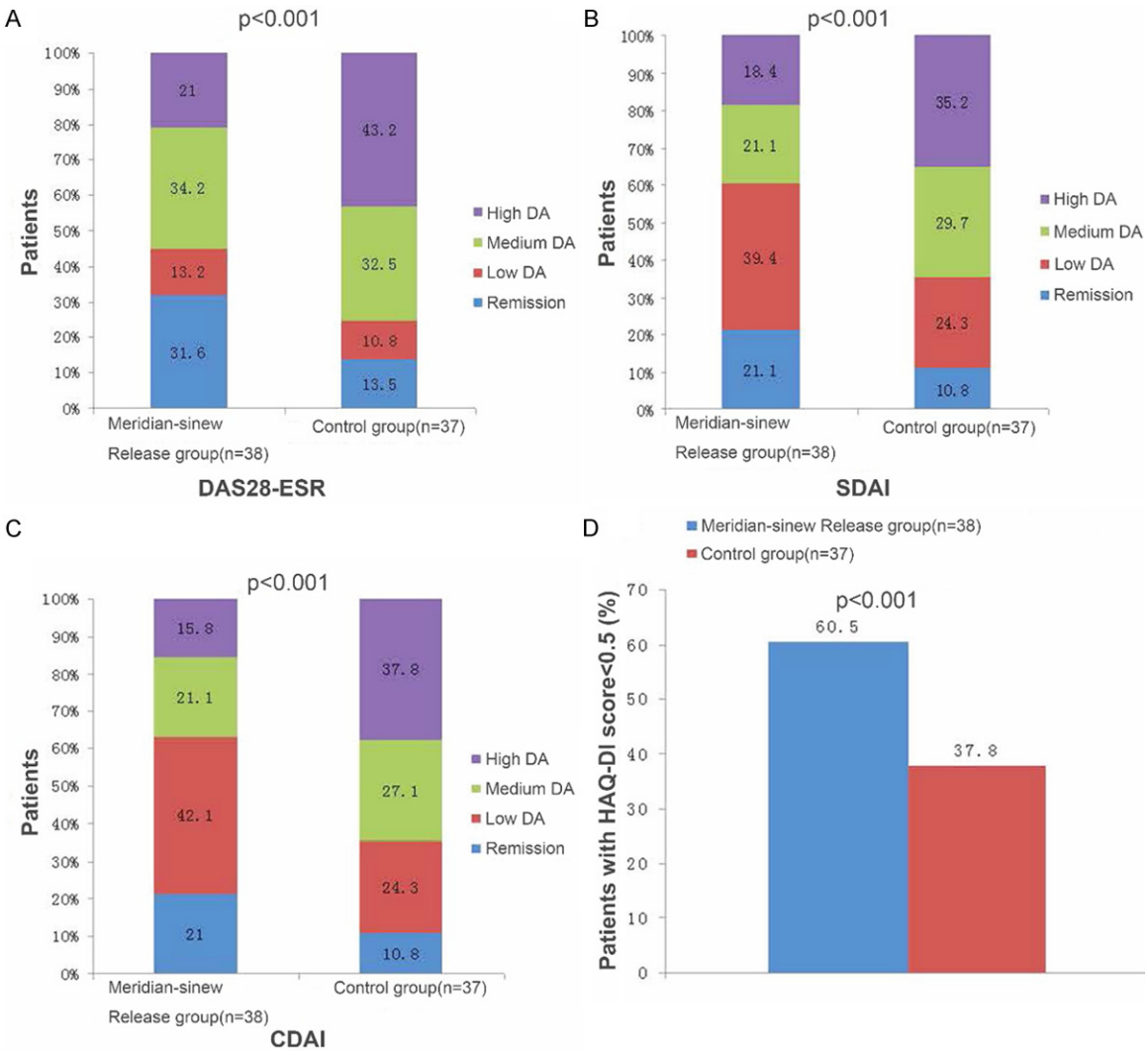

Figure 6. A-C. The percentage of patients with low, medium or high disease activity at week 12. D. The percentage of patients achieving functional remission (HAQ-DI score<0.5) at week 12. The following values were used to identify remission, low, medium and high disease activity for each clinical assessment: DAS28-ESR (<2.6, ≥2.6-<3.2; ≥3.2-≤5.1, >5.1, respectively), SDAI (≤3.3, >3.3-≤11.0, >11.0-≤26.0, >26.0, respectively), and CDAI (≤2.8, >2.8-≤10.0, >10.0-≤22.0, >22.0, respectively).

active RA. We excluded 88 patients because they did not meet the inclusion criteria, were not willing to participate in the study, or did not strictly adhere to the requirements of the research program. In total there were 80 patients participating in this research study. **Figure 2** shows the patient recruitment, allocation, follow-up losses and the exclusion. **Table 1** describes the baseline characteristics of the patients. 2 patients in the meridian-sinew release therapy group dropped out, one due to pain and the other due to personal reasons; 3 patients in the control group dropped out, one due to pain, two due to personal reasons. Patient demographics and baseline disease characteristics were well balanced across two groups (**Table 1**). Among all patients, the mean RA disease duration was 1.0 years, 83.75% were female, the mean age was 51 years, the mean CRP level was 3.0 mg/dl and the mean ESR level was 61 mm/h.

Efficacy results

The main curative effect indexes of the evaluation include ACR20, ACR50, ACR70, DAS28-ESR, SDAI, CDAI and HAQ-DI. Among these, ACR20, ACR50 and ACR70 were evaluated in

Table 2. Comparison of adverse reactions of the two groups [case (%)]

Group	Amount of events	AST/ALT increasing	Leukocyte decreasing	Gastrointestinal discomfort	Hair loss	Event/time
Meridian-sinew release group	38	1	0	1	1	3 (79)
Control group	37	1	1	1	0	3 (81)

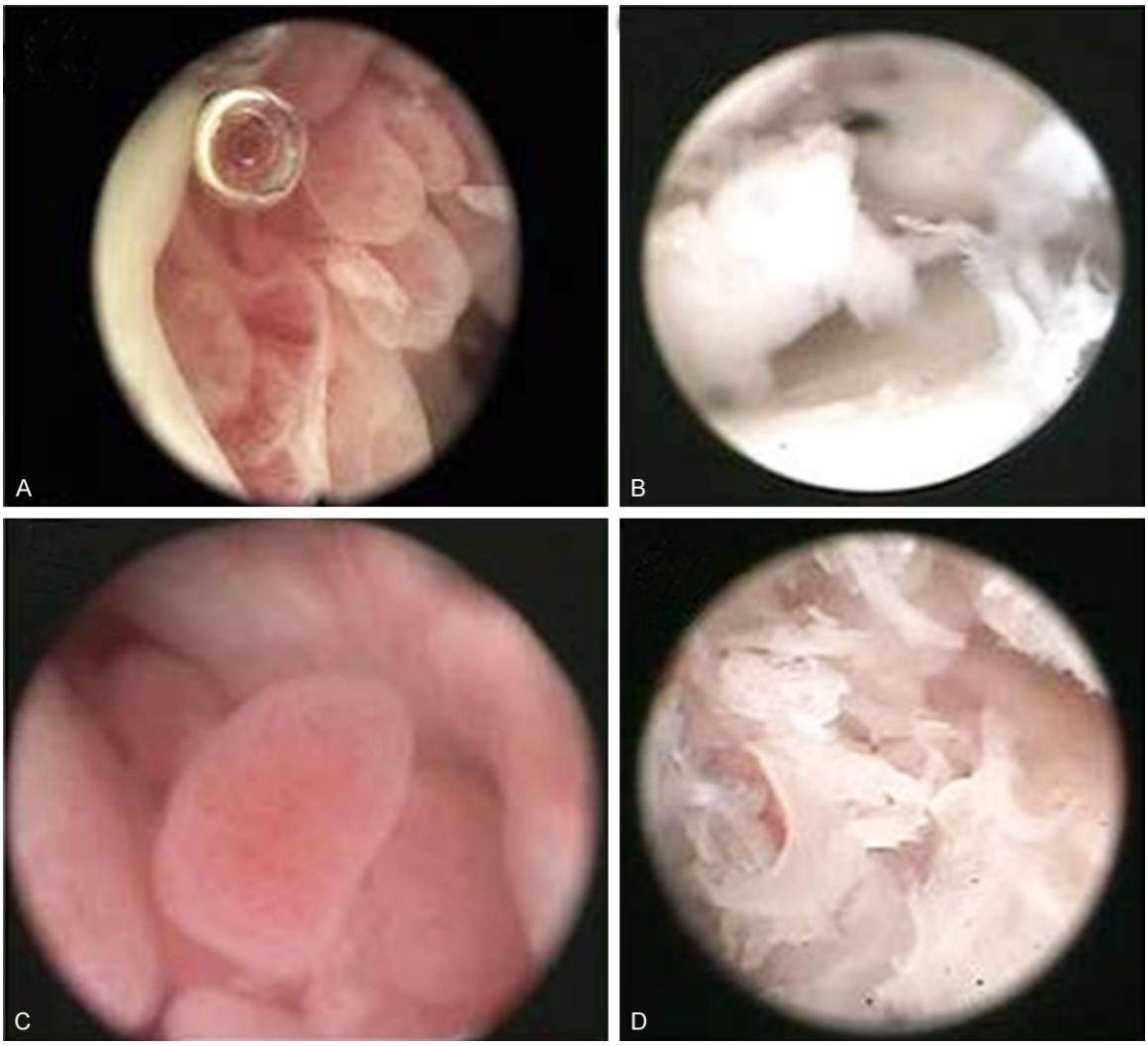

Figure 7. Characteristics inside RA afflicted joints through meridian-sinew scope. A. Synovial hyperplasia. B. Cellulose effusion. C. Formation of pannus. D. Cartilage damage.

the fourth, eighth and twelfth weeks; DAS28-ESR, SDAI, CDAI and HAQ-DI were evaluated before the treatment and 12 weeks after the treatment. A significantly higher percentage of Meridian-sinew Release+MTX patients achieved ACR responses versus MTX alone patients at each assessment (**Figures 3**-**5**). Significant differences between treatment groups, observed as early as week 4, were maintained through week 12. At week 12, a significantly larger percentage of Meridian-sinew+MTX patients versus MTX alone patients achieved ACR20, ACR50 and ACR70 responses (**Figures 3**-**5**). Significant differences in favor of Meridian-sinew+MTX were also observed for DAS28-ESR, SDAI and CDAI. A larger percentage of Meridian-sinew+MTX patients than MTX alone patients were in states of low disease activity or remission after 12 weeks of treatment (**Figure 6A-C**). A significantly larger

decrease from baseline in mean HAQ-DI score, which is indicative of an improvement in physical function. The percentage of patients achieving normal functionality (HAQ-DI score<0.5) after 12 weeks of treatment was also significantly higher with Meridian-sinew+MTX. Improvements from baseline in physical function (HAQ-DI) after 12 weeks of treatment were also significantly greater in Meridian-sinew Release group than in Control group (**Figure 6D**).

Safety

The adverse event occurrence rates of the two groups were not of statistical significance (**Table 2**, P>0.05). Adverse reactions such as liver function damages, gastrointestinal discomfort and hair loss were caused by methotrexate medicines, which could be alleviated by expectant treatment, and allows the former treatment be maintained.

Discussion

This research was designed to evaluate the efficacy and safety of Meridian-sinew Release in Chinese patients with RA. This is the first description of a clinical trial of Meridian-sinew+MTX versus MTX alone with active RA. Moreover, Meridian-sinew+MTX significantly improved a wide array of clinical and functional disease activity measures and responses versus MTX alone, with improvements observed as early as the first assessment (week 4) and maintained through the 12-week random trial. Those treated with Meridian-sinew+MTX had significant improvements from baseline to week 12 in clinical measures of efficacy, including ACR20, ACR50, ACR70 response rates, and percentage of DAS28-ESR, SDAI and CDAI, in comparison with those who received MTX alone.Physical function was also significantly improved from baseline in the Meridian-sinew+MTX groups compared with MTX alone. By comparing the adverse event occurrence rates of the two groups during the whole courses of treatment, we found their differences were of no statistical significance, basically proving the safety of meridian-sinew release therapy.

RA is a chronic autoimmune disease caused by unknown etiology with arthral lesions as the main symptom. Its development is quick and its affliction, inveterate, showing a serve damage to joints in the early stage [29, 30]. So far, without a thorough understanding of RA pathophysiological process and since joint damage leads to most RA disabilities, researchers at home and abroad generally regard synovial lesion as the critical factor in the process of RA joint damage. Synovium is the first layer of tissue that is invaded within the joint structure. The early lesions take place within the joint synovial area, then synovial damages occur sequentially in other area, eventually leading to the stiffness and malformation of the joints [30,31]. The current RA treatments are incapable of repairing the damaged joints completely. Therefore, to effectively control the development of synovial inflammation is a crucial measurement to alleviate joint cartilage damage, provide utmost protection to arthral functions, which is impossible to be fulfilled with pharmaceutical therapy merely.

According to traditional Chinese medicine theory, RA is classified as rheumatological disease. Its etiology and pathogenesis are explained as the stagnation of perverse force within the meridian-sinew network, forming morbid clusters and contracture, blocking the circulation of energy and blood, resulting in coagulation of blood and blockage of energy, which are manifested as symptoms of sore muscles, pain, numbness, contracture and limitation of motions, showing a particular connection with the malfunctioned meridian-sinew system. Meridian-sinews, also known as the 12 meridian-sinews, are a body system that is formed when Qi from the twelve meridians is distributed in the muscles, tendons, bones and joints, primarily supporting the bone structures and assisting to facilitate the junctions. The regular functioning of meridian-sinew system is rudimental to maintain the smoothness of the meridian-sinew pathways and the regular functions of the joints structures. Symptoms of contracture or congestion in the system would definitely lead to and enforce the blockage of the meridian-sinew, triggering swelling and pain in joints. Inner Classic suggests “horizontal congestion” is the key factor that causes abnormality in meridian-sinew structures and functions. As quoted from Lingshu, Cijiezhenxie, there is a statement saying “patients who show excess in the upper body and deficiency in the

lower trunk are suffering from horizontal congestion in their meridian-sinew pathways, which should be unclogged and drain away". There are horizontal congestions inside and outside the joints. Inside the joints, the horizontal congestions are mainly hypertrophic joint capsules, tissue adhesion cord, hyperplastic synovial tissues, cellulose effusion, dismantled cartilage etc. which are the pathological products of the rheumatological process as well as a crucial inducement of rhematological lesion. Horizontal congestions outside the joints are mainly found tissues around the joints in the form of abnormal dissection or functional changes, such as painful nodules or strap-shaped masses in muscle, tendon, mucous bursa and ligament structures, as well as trembling chill and numbness in the meridian-sinew circulation. With the use of meridian-sinew scope in this research, we discovered typical pannus, synovial hyperplasia, cellulose effusion and cartilage damage inside RA afflicted joints, which shows consistent characteristics of horizontal congestion described in Inner Classic (**Figure 7**). Therefore we believe that, the numbing pain and joint malfunction of RA are caused by horizontal congestions in the form of synovial hyperplasia, pannus formation and cellulose effusion, which entrap and impede the circulation of meridian-sinew Qi and blood. Mr. Zhang [32] found that there were pathways of lower resistance within the organic body, through which the mesenchyme fluid flows. Such pathways were enveloped by meridian-sinew fascia and under influence of the fascia's movement. Whenever strap-shaped masses or nodules are formed, they impede the smooth flow of interstitial fluid and result in the accumulation of inflammatory substances in gaps between tissues, causing painful feeling or hyperalgesia.

The key to resolve RA pain and malfunction is to release the entrapment and pressure on the meridian-sinew Qi-blood circulation imposed by horizontal congestions inside and outside the afflicted joints. The pathogenesis of RA lies in local stagnancy of Qi and blood caused by various etiological factors. The blockage in Qi circulation leads to painful feeling. Mr. Zhang claims that peeling off the abnormal adherence of muscular and bone structures and breaking down hyperplastic cellulose to unclog the space of the pathways can recover the flow of interstitial fluid and lymphatic fluid, purge and clean up the congested pathways by washing away the accumulating metabolic waste, realizing the effect of easing pain and inflammation [33]. Under the guidance of the meridian-sinew theory, there is clinical research report that successfully remove the horizontal congestion's entrapment and pressure on the meridian-sinew system, reducing or eliminating the stagnancy of Qi-blood circulation after the removal of congestion and hence relieving the numbing pain of the joints [15, 16]. According to various conditions of horizontal congestions in different parts of the body, on the basis of big needle and long needle characteristics described in Nine Needles, Twelve Source Acupoints, Mr. Wei has invented meridian-sinew scope and meridian-sinew knife as instruments in unhitching congested knots in the meridian-sinew network, which have garnered satisfying curative effects in the field of RA treatment in the recent years [13-16]. The result of this research has also revealed that with the use of meridian-sinew scope and meridian-sinew knife, the meridian-sinew release therapy can fulfill the treatment of active RA by releasing, peeling off and planning the hyperplastic synovium, pannus, effused cellulose inside the patients' afflicted joints, removing lesion issues such as dismantling cartilage around the afflicted joints, as to unclog the Qi-blood circulation inside and outside the joints, removing the congestion's entrapment and pressure on the meridian-sinew flow. After a 12-week meridian-sinew therapy course, the patients achieved a standard status of curative effect markers such as ACR20, ACR50, ACR70 while showing obvious improvement in other markers that was DAS28-ESR, SDAI, CDAI and HAQ-DI etc. in comparison with patients in the control group. Meridian-sinew release therapy is a kind of mechanical stimulation too. Its functional mechanism can improve the blood capillary activeness of local tissues and organs, stimulate lymphatic circulation, enhance the metabolic capability of the lesion area, enlarge the pathways for interstitial fluid, increase the volume of the fluid and reduce the fluid pressure, prompting the absorption of lesion and substance; lesion absorption allows local swelling, which accelerates the lymphatic circulation of mesenchyma [34].

The result of this research indicates with the use of meridian-sinew scope and meridian-sinew knife to remove horizontal congestion in the meridian-sinew circulation network, the meridian-sinew release therapy for the treatment of RA is relatively safe. It can rapidly improve various symptoms of RA, improving physical signs and lab inflammatory activity indexes. An invasive procedure may influence the data uncontrollable and hence the conclusions drawn by factors as expectation bias and others. A sham procedure can eliminate theses bias, but it will result in ethical challenges. The major limitation of this study was the small sample size and the relatively short observation period (12 weeks) as well as the lack of iconographical processive observation. But it was just a pilot case study, we are planning a meridian-sinew release therapy of RA clinical research with a larger sample size, longer observation period (24-48 weeks), supplemented with an iconographical processive observation.

Conclusion

This experimental research shows that meridian-sinew release therapy for the treatment of RA, with the use of meridian-sinew scope and meridian-sinew knife to remove horizontal congestion in the meridian-sinew circulation network and unclog the pathways for Qi-blood circulation, shows a better effect than the pure oral medication therapy. It can effectively relieve swelling, pain and malfunction of the RA-afflicted joints, decrease the disease activity with a satisfying safety level. All in all, meridian-sinew release therapy is a safe, effective alternative therapy for refractory active RA treatment.

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Disclosure of conflict of interest

None.

Abbreviations

RA, Rheumatoid Arthritis; MTX, Methotrexate; ACR, American College of Rheumatology; DAS-28-ESR, 28-joint disease activity score with ESR; DAS28-CRP, disease activity score using a 28-joint count and CRP level; SDAI, simplified disease activity index; CDAI, clinical disease activity index; HAQ-DI, Health Assessment Questionnaire-Disability Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate.

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