Exploring the Treatment Effect of Leihuo Moxibustion "Zusanli" Combined with Intradermal Needle on Rheumatoid Arthritis According to the "Cytokine-Inflammation-Immunity" Network

Pingguo Chen, Ruitao Zhang, Yan Tao, Lunjian Luo*

Department of traditional Chinese medicine, The Second People's Hospital of Xiangtan City, Xiangtan 411000, Hunan, China

**Corresponding Author.*

Abstract: In order to find out the treatment effect of the "Zusanli" point combined with the press needle on rheumatoid arthritis and its effect on inflammatory factors, this comprehensive investigation of rheumatoid arthritis (RA) involved the enrollment of a total of 60 confirmed patients, who were randomly assigned to either a control or a treatment group through a meticulous randomization process, with 30 patients in each group. The control group served as the baseline for no specific therapeutic intervention, while the treatment group received a customized treatment regimen. The objective was to accurately evaluate the actual effect of this treatment program on the control of RA disease to provide strong support for clinical practice and future research directions. The control group received standard treatment using Western medicine, and the treatment group added thunder fire moxibustion combined with press needle "Zusanli" point treatment on the basis of Western medicine treatment. The changes in patient visual analog scores (VAS), the serum levels of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and the disease activity score-28 (DAS 28) were assessed prior to and following the treatment. In comparison to the control group, the treatment group exhibited a significant decrease in VAS scores ($P < 0.05$). Additionally, serum levels of IL-1, IL-6, and TNF-α, along with the DAS 28 score, were considerably lower than those observed in the control group. The overall response rate for rheumatoid arthritis was 60% in the control group and 83% in the treatment group, with a significant difference ($P < 0.05$). The findings indicate that Western medicine, combined with thunder fire moxibustion, demonstrates significant effectiveness. "Zusanli" combined with press needle treatment is better than Western medicine alone, which can reduce inflammatory cytokines and relieve symptoms.

Keywords: Thunder-fire Moxibustion; Press Needle; Rheumatoid Arthritis

1. Introduction

Rheumatoid arthritis (RA) is a complex and multifactorial chronic autoimmune inflammatory disease whose exact etiology remains unclear. The disease is typified by chronic, progressive synovial inflammation of the joint, accompanied by the deterioration of articular cartilage and bone, leading to joint malformation and impaired function. The development of rheumatoid arthritis (RA) is a multifaceted process that encompasses the interplay of various factors, including genetic susceptibility, environmental influences, aberrant immune system activation, and other contributing elements. Among the factors contributing to the pathogenesis of RA is the immune system's erroneous identification of joint tissues as foreign invaders, resulting in the release of a multitude of inflammatory factors that inflict damage upon the joints. Furthermore, the disease frequently presents with systemic symptoms, including fatigue, low-grade fever, weight loss, and the formation of subcutaneous nodules (rheumatoid nodules), which significantly impact the quality of life and prognosis of patients. It is of great significance to conduct further research into the pathogenesis of rheumatoid arthritis, to explore effective treatment strategies and to improve disease

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management, with the aim of improving the quality of life of patients and reducing the social medical burden. Data show that rheumatoid arthritis can occur at any age, with 80% of the disease in 35~50 years old, female patients 2~3 times more than men, and the incidence of rheumatoid arthritis in China ranges from 0.32% to 0.36%. It is predicted that 31.7 million people worldwide will have rheumatoid arthritis by 2050[1]. The causes and mechanisms involved in the onset of rheumatoid arthritis are complex and not yet fully elucidated. Nevertheless, the majority of research suggests that the pathogenesis of rheumatoid arthritis is linked to genetic predispositions, hormonal influences, environmental factors, and other variables. The main treatments for rheumatoid arthritis are medication, physical therapy and surgery. Among them, medication is the mainstay of rheumatoid arthritis treatment. Frequently utilized medications encompass glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and various other options that can relieve pain and inflammation but have limited symptom control; glucocorticoids can reduce inflammation and relieve symptoms, but prolonged use could result in adverse effects, including osteoporosis and metabolic disorders; and disease-modifying drugs can control inflammation and slow down disease progression but need to be taken for a long time and monitored for side effects. Therefore, it is particularly important to find treatments with fewer side effects and reliable efficacy.

Studies have shown that large amounts of proinflammatory cytokines mediate inflammatory responses in rheumatoid arthritis patients[2,3]. As pivotal cytokines, IL-1, IL-6, and TNF-α exert intricate and significant influences on immune system regulation and inflammatory responses. The investigation of these cytokines not only advances our comprehension of the immune system's operational mechanisms but also offers novel insights and techniques for the diagnosis and treatment of associated pathologies. They are often used to observe changes in inflammation. In this study, by observing the changes of several important inflammatory cytokines and the changes of DAS 28 before and after treatment to evaluate the inflammation of the disease and to explore the clinical efficacy of thunder fire moxibustion "Zusanli" joint press the clinical curative effect of needle treatment of rheumatoid arthritis.

2. Clinical Data

2.1 General Information

The causes and mechanisms involved in the onset of rheumatoid arthritis are complex and not yet fully elucidated. Nevertheless, the majority of research suggests that the pathogenesis of rheumatoid arthritis is linked to genetic predispositions, hormonal influences, environmental factors, and other variables. The treatment group consisted of 30 patients, which included 14 males, accounting for 46.7% of the total cohort and 16 female patients (53.3%), indicating a relatively balanced gender distribution. The age range of patients is considerable, spanning from 35 to 70 years old. This encompasses a diverse range of ages, from middle to advanced age, which reflects the disease's incidence across different age groups. The median age of the patients was 55 years old, which not only indicates the average age of patients in the treatment group but also suggests that middle-aged and older adults may be a high-incidence group for the disease. Overall, the composition of patients in the treatment group showed a certain representation in terms of gender and age, which provided strong support for the universality and promotion value of follow-up research results. The research received approval from the Ethics Committee of Xiangtan Second People's Hospital (No. 2021 002). This study was performed and drafted according to the STROBE statement.

2.2 Inclusion Criteria

In this study, we conducted a meticulous screening of all patients who met the criteria for classifying rheumatoid arthritis as outlined by the American College of Rheumatology in collaboration with the European League Against Rheumatism. This standard considers the patient's clinical presentation, laboratory tests, and imaging evidence to guarantee the scientific rigor of the study and the reliability of the results and the relevant diagnostic standards outlined in the Guiding Principles for Clinical Research in New China Medicine (Patients with dampness-heat obstruction were

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not included in the inclusion criteria); DAS 28 were active[4,5]; All of the patients gave their affirmative consent.

2.3 Exclusion Criteria

Individuals suffering from advanced cardiac, neurological, hepatic, and renal conditions; females during pregnancy and lactation; patients with inactive psychiatric disorders; excessive doses of corticosteroids or biological agents within 2 weeks prior to enrollment.

2.4 Shedding Standards

Subjects who cannot complete the experiment on time due to some reason or accident, who cannot complete the experiment due to changes in their condition, subjects with severe dizzy moxibustion reaction and skin allergic reaction at the fixed point of the press needle.

2.5 Treatment Methods

The control group used Western medicine treatment: ① methotrexate (methotrexate) (Shanghai Shangyao Xinyi Pharmaceutical Co., LTD.): administer 10 mg at each occurrence, on a weekly basis; ② folic acid (Tianjin Lisheng Pharmaceutical Co., LTD.), 10 mg per administration, once a week; ② leflunomide (Suzhou Changzheng-Xinkai Pharmaceutical Co., LTD.): 10mg each time, once a day. If the pain is obvious, add the nonsteroidal anti-inflammatory drug ③ Arexib (Chengdu Shengdi Pharmaceutical Co., LTD.) once or twice a day, no more than seven days.

Alongside receiving the same intervention as the control group, the treatment group added thunder fire moxibustion combined with press needle "Zusanli" point treatment. Thunder-fire moxibustion treatment: after the patient's supine position, exposed lower limbs, and adequate positioning (the outside of the calf, 3 inches below the leading edge of the tibia), the thunder-fire moxibustion with a diameter of 6c m was ignited, using mild moxibustion and moxibustion for 30 minutes. Press needle treatment: thunder fire after moxibustion treatment, we will perform the conventional skin disinfection on bilateral foot sanli point, choose 0.22mm×1.5mm disposable sterile press needle, one hand fixed skin, another hand sterile tweezers will press the needle on the acupoints. Then, we will press stab after smoothing the press needle fixed on the skin. Each acupoint pressure is pressed with the needle, with pressure strength at a level where patients experience a slight sour swelling sensation. Intermittent press 3~5 times a day, keep for 24 hours and remove the press needle. The above treatment was observed 3 times a week and observed after 8 weeks.

2.6 Observation Indicators

The criterion of therapeutical effect: In accordance with the "New Guiding Principles for Clinical Research of Traditional Chinese Medicine" (2002), this study employed a rigorous scientific and systematic approach to determine the efficacy of the treatment program. This entailed a comprehensive evaluation of the improvement of clinical symptoms, changes in physical signs, and the necessity of medical examination results. The primary objective of this study is to ensure the accuracy and reliability of the results obtained, a pursuit rooted in rigorous adherence to scientific research methods and careful consideration of data processing[3]. In evaluating clinical recovery, efficacy criteria are clearly defined. If the improvement rate of major signs and symptoms reaches or exceeds 75%, and the levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the body have returned to the normal range or significantly converge to the normal standard, the treatment effect is considered significant, or "clinical recovery." A treatment is deemed "effective" if the patient's major signs and symptoms demonstrate an improvement rate between 30% and 75%, accompanied by a corresponding decline in CRP and ESR levels. Conversely, if the improvement rate of major signs and symptoms is less than 30%, and there is no appreciable improvement in CRP and ESR levels, the treatment is considered "ineffective." The establishment of these criteria provides a quantitative basis for the objective and comprehensive evaluation of treatment effects, thereby ensuring the scientific and repeatable conclusions of the study.

Safety observation: We need to observe whether there is dizziness, chest tightness, shortness of breath, allergic reaction and other phenomena in the treatment process and whether the treatment can be continued.

Visual analog scoring (VAS) method[4]: Patients self-score their pain according to their

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own pain conditions.

The Disease Activity Score 28 (DAS-28)[4,5] serves as a standardized metric to assess rheumatoid arthritis activity, categorized as follows: remission is indicated by a DAS-28 score below 2.6; low disease activity falls within the range of 2.6 to less than 3.2; moderate activity is denoted by scores from 3.2 up to but not including 5.1; whereas, high activity is marked by a DAS-28 exceeding 5.1. The DAS-28 scores were recorded before and after treatment.

Fasting blood from two groups was drawn before and after laboratory testing for CRP, ESR, IL-1, IL-6 and TNF- α.

2.7 Statistical Methods

The collected data were subjected to statistical analysis utilizing SPSS version 20.0. Quantitative measurements are presented as mean ± standard deviation ( ), whereas frequency data rates were analyzed using the chi-square test, with a significance threshold established at $P < 0.05$

3. Results

3.1 The Treatment Effect in the Two Patient Groups

After 8 weeks, according to the efficacy judgment criteria, there were 12 clinical recoveries, 8 effective, and five were ineffective, resulting in an overall effectiveness rate of 83% within the treatment group; there were 2 clinical recoveries, 10 effective, 6 effective, 12 ineffective, the overall effectiveness rate in the control group was 60%. The comparison between the treatment group and the control group yielded statistically significant results ($P < 0.05$) (see Table 1).

Table 1. The Treatment Efficacy in Two Groups[n/N(%)]

Group	N	clinical recovery(n)	excellence(n)	valid(n)	of no avail	total effective rate
Control group	30	5	12	8	5	83%
Treatment group	30	2	10	6	12	60%※

Note: N denotes the overall number of cases within the group, while n indicates the count of clinically recovered, effective, and ineffective cases. The comparison with the control group is significant at $P < 0.05$.

3.2 Comparison of Adverse Effects in the Two Groups

One individual in the control group experienced dizziness, while in the treatment group, a solitary patient reported experiencing dry mouth. Statistical analysis revealed no noteworthy disparity in this adverse event occurrence between the two groups, with a P-value exceeding 0.05, indicating a lack of significant difference.

3.3 VAS Score Comparison

After 8 weeks of treatment, the VAS score was less than the control group, and the VAS scores between the two groups were significantly different ($P <0.05$) (Table 2).

Table 2. The VAS Scores Prior to and Following Treatment in Both Groups (x ± s)

Group	N	Before	After
Control group	30	6.67±0.79	2.75±0.35△
Treatment group	30	6.88±0.63	1.25±0.40△※

Note: N denotes the overall count of cases within the group; when compared to the control group, ※$P < 0.05$; in contrast to the pre-treatment phase, △$P < 0.05$.

4. Discussion

This study aimed to analyze and compare the changes in inflammatory cytokines IL-1, IL-6, and TNF-α in the two groups of patients before surgery. This was done in order to reveal the dynamic trend of these indicators before surgical intervention and provide a scientific basis for optimizing treatment strategy and predicting postoperative recovery and after treatment. The results demonstrated that patients in the specific treatment group exhibited significantly diminished levels of these cytokines post-treatment, indicating that the treatment regimen effectively suppressed the inflammatory response. Conversely, the other group of patients demonstrated comparatively limited improvement, thereby revealing discrepancies in how different treatment regimens regulate the inflammatory response. This finding provides a crucial reference point for evaluating the therapeutic effect and optimizing the therapeutic strategy.

The findings of this study indicated that no statistically significant differences were

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observed in the levels of inflammatory cytokines—specifically interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)—as well as in the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), both of which are critical markers of inflammation, between the two patient groups prior to treatment ($P > 0.05$). This outcome suggests that the inflammatory response of patients in both groups was similar at baseline before treatment commenced, thereby providing a robust foundation for subsequent observation and analysis regarding the effects of therapeutic interventions on these indicators. Furthermore, it underscores the appropriateness and validity of this study's methodology in sample selection, grouping, and baseline data collection, thereby establishing a strong basis for the interpretation and extrapolation of future results. However, following eight weeks of treatment, these inflammatory markers exhibited a marked decline in the treated group compared to the control group ($P < 0.05$), suggesting that the employed treatment regimen was highly efficacious in mitigating inflammation (Table 3).

Table 3. The Changes in Inflammatory Indexes before and after Treatment in the Two Groups (x ± s)

Group	n	Time	IL-1(pg/mL)	IL-6(pg/mL)	TNF-(ng/mL)	ESR (mm/h)	CRP (mg/L)
Control group	30	Pretherapy	36.23±17.56	37.37±6.74	32.48±19.42	56.26±19.03	54.63±18.89
		Post-treatment	19.04±3.61$^{\triangle※}$	21.73±5.32$^{\triangle※}$	19.72±4.19$^{\triangle※}$	32.16±12.59$^{\triangle※}$	35.26±10.57$^{\triangle※}$
Treatment group	30	Pretherapy	35.31±16.52	35.15±9.32	30.32±17.81	55.26±18.46	56.53±17.79
		Post-treatment	13.18±3.21$^{\triangle}$	12.49±3.94$^{\triangle}$	10.75±3.59$^{\triangle}$	26.16±6.83$^{\triangle}$	17.90±8.26$^{\triangle}$

Note: Compared with the control group $^{※}P<0.05$; Compared with the pretherapy $^{\triangle}P<0.05$.

Comparison of DAS 28 scores between the two groups before and after treatment revealed that, prior to treatment, the DAS 28 scores for both groups were comparable ($P > 0.05$). However, after 8 weeks of treatment, the scores in the treatment group were significantly lower than those in the control group ($P < 0.05$) (see Table 4).

Table 4. Comparison of DAS 28 Scores before and after Treatment in Group II Patients (x ± s)

Group	n	Before treatment	After the treatment
Control group	30	5.48±0.81	3.25±0.38$^{\triangle}$
Treatment group	30	5.56±0.81	2.58±1.11$^{\triangle※}$

Note: In comparison to the control group, $^{※}P < 0.05$; in relation to the pre-treatment measurements, $^{\triangle}P < 0.05$

4. Discussion

At present, when Western medicine treats RA, the drugs mainly include NSAIDs, anti-rheumatic drugs to improve the condition, glucocorticoids, biological agents and so on. Clinically, the remission rate of rheumatoid arthritis is not ideal. Many patients with rheumatoid arthritis find it difficult to achieve the standard treatment only by Western medicine treatment. There are gastrointestinal reactions, liver and kidney function damage and other side effects. Traditional Chinese medicine(TCM) classifies rheumatoid arthritis as "arthralgia", "calendar wind," and "puppet". TCM believes that the cause of rheumatoid arthritis is mainly "Six Evils" and "Qi-deficiency". Among them, "Qi-deficiency" is the first cause, "Huangdi Neijing: "healthy qi" stored inside, evil can not do, evil gathered, its qi must be empty", Chinese medicine emphasizes the leading role of vital qi in the process of disease development." Fuzheng Quxie" is an important treatment for the management of rheumatoid arthritis conditions involves various therapeutic approaches. Traditional Chinese Medicine utilizes acupuncture as a primary therapeutic approach for rheumatoid arthritis, moxibustion and so on[6,7]. Rheumatoid arthritis is refractory and difficult to cure, and disease remission and continuous remission are the treatment goals agreed upon by clinicians and scholars. From the current clinical treatment effect, it is difficult to control the rheumatoid arthritis condition with simple drugs or only traditional Chinese medicine treatment. Therefore, it is necessary to seek a more ideal combination treatment method. Increasing clinical experience suggests that[8] the integration of

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traditional Chinese medicine with Western medicine can mutually benefit from collaboration and serve to enhance one another. In this study, the moxibustion "Zusanli" point was introduced based on Western medicine, which serves as the primary approach to enhancing the body's resilience. Zusanli is the joint point of the stomach and the lower joint point of the stomach. In the moxibustion material, the selection of its radiation, firepower, and penetration are stronger than in ordinary moxa moxibustion. In addition, to strengthen the lasting effect, the press needle was combined to stimulate the "Zusanli" point. Press needle therapy belongs to intradermal needles, which are easy to operate and painless, with the characteristics of shallow thorns for a long time. "Quiet to stay for a long time", with weak and long-term stimulation to achieve a sustained effect. The results of this study demonstrate that the therapeutic approach involving the "Zusanli" acupuncture point, when used in conjunction with needle pressure, yields more favorable results than Western medicine treatment administered in isolation.

Modern medicine points out that rheumatoid arthritis mainly presents as joint synovial inflammation and vascular abnormalities, resulting in the degradation of cartilage and bone within the joints and ultimately causing joint deformities and a decline in functionality. Research has identified that a variety of proinflammatory cytokines are present in the synovial tissue of affected individuals, with IL-1, IL-6, and TNF-α identified as significant contributors, which activate immune cells to produce antibodies and activate T lymphocytes through signaling to trigger autoimmune disorders[9]. It can be reasonably deduced that the onset of rheumatoid arthritis is closely associated with the complex interactions within the "cytokine-inflammation-immune" network. In this study, on the basis of Western medicine treatment, the thunder fire moxibustion "Zusanli" point was combined with a press needle to treat rheumatoid arthritis. Yu N et al.[10] found the analgesic and anti-inflammatory properties of acupuncture in the treatment of rheumatoid arthritis operate via enhancing Treg cell populations and inhibiting M1 macrophage polarization, emphasizing the potential therapeutic benefits of acupuncture in managing pain and improving inflammatory conditions. This study revealed that moxibustion Zusanli combined with thunity-fire moxibustion and press acupuncture technology could significantly reduce the levels of inflammatory factors such as IL-1, IL-6 and TNF-α in the body, effectively reduce the inflammatory response, and thus regulate the body's immunity, demonstrating the unique value and application potential of traditional Chinese medicine in modern medicine.

5. Conclusion

Rheumatoid arthritis (RA) is a multifaceted, long-term autoimmune inflammatory disorder that chiefly targets the joints and adjacent soft tissues, resulting in pain, swelling, stiffness, and impaired function. Additionally, it may impact multiple systems throughout the body, significantly impacting patients' quality of life. Its management necessitates a multidisciplinary approach to alleviate symptoms, delay disease progression, and enhance patients' quality of life. Drug therapy is the main treatment for rheumatoid arthritis. Commonly used drugs incorporate nonsteroidal anti-inflammatory agents (NSAIDs), glucocorticoids, and medications that modify disease progression. NSAIDs relieve pain and inflammation with limited symptom control; corticoids reduce inflammation and symptoms, but long-term use may lead to side effects. Therefore, it is particularly important to find treatments with fewer side effects and reliable efficacy. In this research, "Zusanli" combined with acupressure was employed alongside conventional Western medical treatment to address rheumatoid arthritis. The findings indicate that the combination of "Zusanli" and traditional treatment yields superior results compared to Western medicine alone, demonstrating a reduction in inflammatory cytokines and alleviation of symptoms.

Acknowledgments

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