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Original Research Article

Combined moxibustion/adalimumabin treatment of ankylosing spondylitis, and its influence on related functional indicators

Longfei Han[1], Jianying Zhang[2]*, Hui Liang[2]
[1]Shandong Traditional Chinese Medicine University, [2]Traditional Chinese Medicine External Treatment Center of Shandong Provincial Hospital of Traditional Chinese Medicine, Jinan, Shandong, China

For correspondence: **Email: caojingrang184744@163.com; **Tel:** +86-13066035253*

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Abstract

Purpose: *To study the clinical efficacy of the combination of du-moxibustion and adalimumab in the treatment of ankylosing spondylitis, as well as its influence on related functional indicators.*
Methods: *From 2019 to 2020, 90 ankylosing spondylitis patients treated in Shandong Traditional Chinese Medicine University Hospital were assessed for eligibility and recruited. They were assigned, based on the order of admission, to receive either conventional treatment (control group) or du-moxibustion plus adalimumab (study group). Clinical treatment efficacy, levels of inflammatory indices, and spinal mobility in the two groups were determined and compared. Numerical Rating Scale (NRS) was employed for pain assessment, while Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used for disease status evaluation. Bath Ankylosing Spondylitis Functional Index (BASFI) was used for assessing functional limitation.*
Results: *Du-moxibustion plus adalimumab was associated with significantly higher treatment efficacy and lower levels of inflammatory factors when compared to conventional treatment ($p < 0.05$). Comparable NRS scores before treatment and 2 weeks after treatment were observed in the two groups ($p > 0.05$). The eligible patients given du-moxibustion plus adalimumab showed lower NRS scores, higher BASDAI scores, and lower BASFI scores versus those receiving conventional treatment ($p < 0.001$).*
Conclusion: *Treatment of ankylosing spondylitis patients with the combination of du-moxibustion and adalimumab mitigates symptoms and clinical indicators of the disease and relieves pain in the patients. Therefore, the combined treatment should be subjected to further clinical trials prior to its use in clinical practice.*

Keywords: *Du-moxibustion, Adalimumab, Ankylosing spondylitis, Numerical rating scale, Inflammatory factors, BASDAI, BASFI*

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INTRODUCTION

Ankylosing spondylitis, a disease frequently seen in orthopedic clinics, refers to chronic spinal lesions [1,2]. Although the etiology of ankylosing spondylitis remains unelucidated, it is believed to be related to the interaction of immune and genetic factors, and it presents clinical manifestations such as morning stiffness, spinal stiffness, and back pain [3-5]. Delayed or

ineffective treatment measures may result in various complications such as kidney disease and heart disease which can be life-threatening and may also compromise the quality of life of the patient [6-8]. Currently, no drugs have been developed for radical treatment and control of ankylosing spondylitis in order to prevent incidents of joint deformities. Unfortunately, it has been clinically confirmed that not only does conventional treatment produce unsatisfactory outcomes, it is also accompanied by various limitations [9,10]. On the other hand, combined treatment of ankylosing spondylitis with adalimumab and du-moxibustion is considered a more effective therapy for the disease. Accordingly, the present study was to assess the clinical efficacy of du-moxibustion plus adalimumab in the treatment of ankylosing spondylitis and its influence on related functional indicators.

METHODS

General information on patients

From 2019 to 2020, 90 ankylosing spondylitis patients treated in Shandong Traditional Chinese Medicine University Hospital were assessed for eligibility and recruited. They were assigned via the order of admission to either a control group or a study group.

Inclusion criteria

Patients in the following categories were included: those who met the diagnostic criteria of spondyloarthritis, patients who had morning stiffness for ≥ 1 h, and patients whose lumbar spines were limited in lateral flexion and anteroposterior movement.

Exclusion criteria

The excluded patients were those with severe diseases in heart, brain, and lung, as well as patients who had other system diseases. Patients undergoing lactation or pregnancy, and patients participating in other clinical trials, were also excluded.

Ethical approval

This study was approved by the ethics committee of Shandong Traditional Chinese Medicine University (approval no. 2018-12-20). The patients and their family members were fully informed of the purpose of the study and provided written informed consent. The protocol followed the Declaration of Helsinki [11] guidelines for human studies in this study.

Treatments

The control group received conventional treatment. For this purpose, the patients were given 0.10 g imrecoxib tablet (Jiangsu Hengrui Pharmaceutical Co. Ltd.; NMPA approval number: H20110041; specification: 0.10 g x 10 tablets), 0.10 twice daily, and 50 mg of thalidomide tablets (Changzhou Pharmaceutical Factory Effective Company; NMPA approval number: H32026129; specification: 25 mg x 20 tablets), twice daily.

The study group was given du Moxibustion powder, comprised of the following:

(a) Drugs including *Duhuo, Qianghuo,* and *Cantharidin,* were ground and mixed with 1.0 g musk.
(b) Ginger paste: This was prepared by crushing 2000 g of ginger into a paste and the juice of the paste was lightly squeezed out.
(c) One piece of white mulberry root-bark, one towel, pure moxa, and an appropriate amount of dry cotton balls.

Specific treatment procedures

Each patient was instructed to lie in the prone position, and the Du Channel from *Dazhui* to *Yaoshu* was routinely disinfected and smeared with ginger juice. The du-moxibustion powder was sprinkled evenly into a thin strip with a width of about 5 mm, from top to bottom, and then the mulberry paper was applied to it. Then, the ginger paste was placed on it to form a trapezoid with a width of 40 mm and a height of 20 mm, with a narrow top and a wide bottom. The top was pressed to make the middle slightly concave, and finally, the cone-shaped moxa (25 mm at the bottom, and 20 mm high) was spread on the top of the ginger paste and connected from the end to the end. The upper, middle, and lower points were ignited simultaneously: complete combustion was considered one moxa-cone. After moxibustion for 3 consecutive moxa-cones, the ginger mud and moxa ash were gently removed with a hot and humid towel. After moxibustion, the skin was ruddy, and a few blisters slowly developed into a pearl-like shape after 4 - 6 h. The blisters were healed on the next day, and the moxibustion scabs fell off after 3-5 days. The treatment was performed once a month, with 3 performances comprising a course of treatment. Moreover, the patients were given a subcutaneous injection of 40 mg of adalimumab (Vetter Pharma-Fertigung GmbH & Co. KG; NMPA approval number: S20170019; specification: 40 mg/0.8 mL x 1) once in 2 weeks.

Treatment for all eligible patients spanned 3 months.

Measurement of treatment indicators

The levels of clinical effectiveness in the two treatments groups were compared. Treatment effectiveness was categorized as *markedly effective, effective,* or *ineffective*. If the patient's clinical symptoms basically disappeared, treatment was markedly effective. In the effective category, the clinical symptoms of the patients were appreciably reduced. However, treatment outcome was deemed ineffective if the clinical symptoms in the patients remained unremitted, or if they became worsened.

Early morning fasting cubital venous blood samples were taken from all the eligible patients, and sera were separated after centrifugation. The serum samples obtained were kept frozen at -80 °C, prior to analysis for levels of tumor necrosis factor (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) using ELISA kits per the kit instructions.

The Numerical Rating Scale (NRS) with a total score of 10 points, was used for pain assessment of patients [12]. A higher score indicates higher pain severity. The time points before treatment, and 2 weeks, 1 month, 2 months, and 3 months after treatment were designated T0, T1, T2, T3, and T4, respectively, and the pain levels of patients in the two groups at the various time points were compared.

A portable muscle strength test and joint mobility meter (Shenzhen Greens Instrument Co. Ltd; model: Hoggan MicroFET) was employed for spinal mobility evaluation before and after treatment. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used for disease condition assessment. The score is proportional to the severity of the condition. Bath Ankylosing Spondylitis Functional Index (BASFI) was applied for the evaluation of functional limitation, with a total score of 10 points. The score is proportional to the severity of functional limitation.

Statistical analysis

The SPSS 20.0 data processing software was used for statistics in this research, while GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for graphics plotting. Counting data are expressed as numbers and percentages [n, (%)], and were compared using the chi-square (χ^2) test. Measurement data are represented as mean ± standard deviation (SD) and were statistically compared by *t*-test. Statistical significance of difference was assumed at $p < 0.05$.

RESULTS

General profile of patients

The two groups of patients showed comparable general profiles ($p > 0.05$) (Table 1).

Clinical efficacy

Du-moxibustion plus adalimumab was associated with significantly higher treatment efficacy versus conventional treatment ($p < 0.05$) (Table 2).

Table 1: Comparison of general profile between the two groups of patients (mean ± SD, n = 45)

Parameter	Study (n=45）	Control (n=45）	χ^2 or *t*	*P*-value
Age (years)	36.25±3.32	36.33±3.29	0.115	0.909
BMI (kg/m^2)	26.27±1.59	25.89±1.63	1.119	0.266
Gender				
Male	23（51.11）	21（46.67）	0.178	0.673
Female	22（48.89）	24（53.33）	1.533	0.129
SAS score (points)	47.33±0.51	47.17±0.48	0.258	0.797
SDS score (points)	52.13±1.61	52.21±1.32	0.045	0.832
Smoking				
Yes	20（44.44）	21（46.67）		
No	25（55.56）	24（53.33）		
Drinking			0.178	0.673
Yes	22（48.89）	24（53.33）		
No	23（51.11）	21（46.67）		
Place of residence				
Urban	31(68.89)	30(66.67)		
Rural	14(31.11)	15(33.33)		

Table 2: Comparison of clinical efficacy between the two groups [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effectiveness
Study	66.67（30/45）	31.11（14/45）	2.22（1/45）	97.78（44/45）
Control	46.67（21/45）	26.67（12/45）	26.67（12/45）	73.33（33/45）
χ^2				10.879
P-value				< 0.05

Table 3: Comparison of levels of serum inflammatory factors between the two groups (mean ± SD)

Variable		Study	Control	*T*	*P*-value	
TNF-α（**ng·L^{-1}**）	***Before treatment***	235.88±24.36	235.45±24.67	0.083		0.934
	After treatment	21.36±10.98	56.22±12.11	14.306	<0.001	
CRP（**mg·L^{-1}**）	***Before treatment***	36.88±11.37	36.69±11.52	0.079		0.937
	After treatment	3.21±1.02	9.36±1.45	23.271	<0.001	
IL-6（**ng·L^{-1}**）	***Before treatment***	39.25±4.53	39.35±5.11	0.098		0.922
	After treatment	23.27±1.35	35.25±3.23	22.956	＜0.001	

Serum inflammatory factor levels

There were significantly lower serum levels of inflammatory factors in the study group than in the control group ($p < 0.05$; Table 3).

NRS scores

At T_0 and T_1, there were no marked disparities in NRS scores between the two treatment groups. The NRS scores of patients in the experimental group at T0, T1, T2, T3, and T4 were 9.58 ± 0.22, 8.66 ± 0.35, 5.23 ± 0.1, 3.27 ± 0.25 and 1.13 ± 0.02 points, respectively. However, the patients given joint therapy had significantly lower NRS scores versus those given conventional treatment at T_2, T_3, and T_4 ($p < 0.001$) (Figure 1).

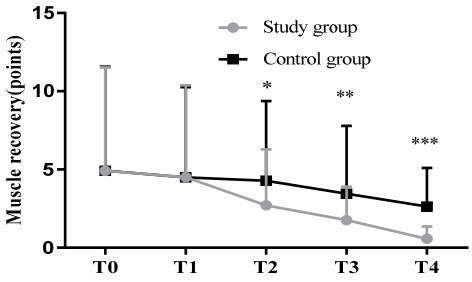

Figure 1: Comparison of NRS scores between the two groups before and after treatment. *$P < 0.001$, NRS score of experimental vs that of control at T2; **$p < 0.001$, NRS score of experimental vs that of control at T3; ***$p < 0.001$, NRS score of experimental vs that of control at T4

Spinal mobility

The spinal mobility values of the experimental group of patients before and after treatment were 34.58 ± 4.89° and 54.02 ± 11.23°, respectively. The spinal mobility values of the control group before and after treatment were 35.01 ± 4.95° and 44.24 ± 6.89°, respectively. Du-moxibustion plus adalimumab showed better enrichments in spinal mobility benefits versus conventional treatment ($p < 0.05$; Figure 2).

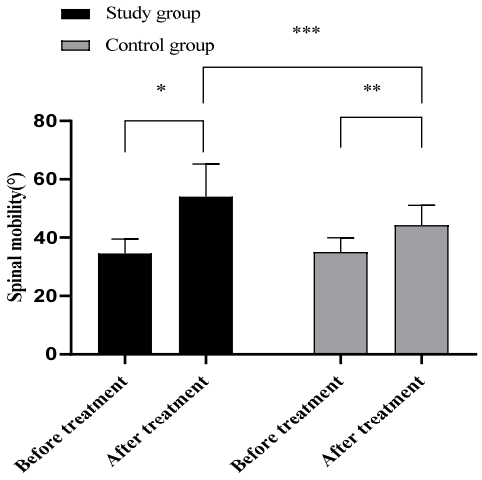

Figure 2: Comparison of spinal mobility before and after treatment between the two groups. *$P < 0.001$, spinal mobility values of the experimental group before and after treatment; **$p < 0.001$, comparison of spinal mobility values of the control group before and after treatment, ***$p < 0.001$, spinal mobility value of experimental group vs that of control group after treatment

BASDAI scores

The BASDAI scores of patients in the experimental group before and after treatment were 6.11 ± 1.53 and 2.32 ± 0.89 points, respectively, while the BASDAI scores of the control group before and after treatment were 6.09 ± 1.48 and 3.85 ± 1.21 points, respectively.

After treatment, the study group had markedly higher BASDAI scores than the control group ($p < 0.05$, Figure 3).

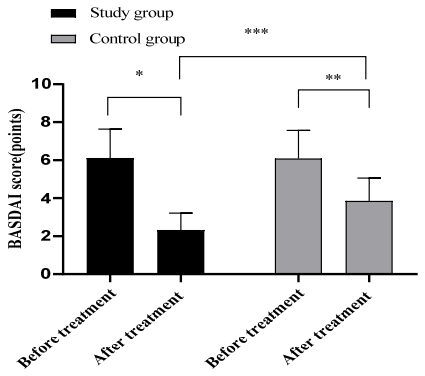

Figure 3: Comparison of BASDAI scores between the two groups. *$P < 0.001$, BASDAI scores of the experimental group before treatment vs scores after treatment; **$p < 0.001$, BASDAI scores of the control group before and after treatment; ***$p < 0.001$, BASDAI score of the experimental vs that of the control patients after treatment

BASFI scores

The BASFI scores of patients in the experimental group before and after treatment were 7.23 ± 1.11 and 2.05 ± 0.56 points, respectively. The BASFI scores of the control group before and after treatment were 7.28 ± 1.08 points and 3.84 ± 0.93 points, respectively. The post-treatment BASFI scores of patients in the study group were significantly lower than the corresponding scores of patients in the control group ($p < 0.05$) (Figure 4).

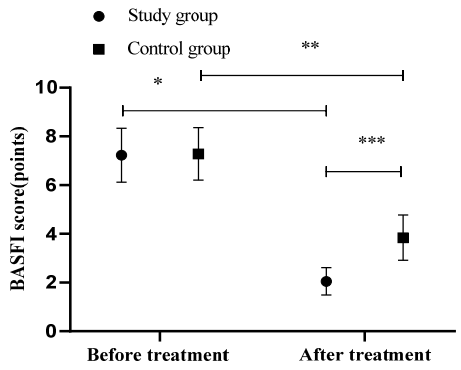

Figure 4: Comparison of BASFI scores between the two groups. *$P < 0.001$, comparison of BASFI scores of the study group before and after treatment; **$p < 0.001$, BASFI scores of the control group before and after treatment; ***$p < 0.001$, comparison of BASFI scores of the study vs that of the control patients after treatment

DISCUSSION

Ankylosing spondylitis is characterized by high prevalence, especially in young and middle-aged men [13-15]. Previous studies have demonstrated that the pathogenesis of the disease is related to genetics and infections [16]. The conventional treatment strategy used for ankylosing spondylosis involves the combination of parecoxib and thalidomide, which is aimed at suppressing the disease and the associated inflammation. Imrecoxib effectively relieves pain in ankylosing spondylosis patients, while thalidomide exerts an anti-inflammatory effect, reduces levels of inflammatory factors, and improves remission [12]. Nonetheless, the clinical effects of these treatments are far from satisfactory.

In the present study, du-moxibustion plus adalimumab was associated with significantly higher treatment efficacy and lower levels of inflammatory factors versus conventional treatment. This indicates that the combination treatment produced a superior efficacy in bringing down the inflammatory response. This finding may be attributed to the fact that adalimumab has a high affinity for TNF-α. Thus, adalimumab effectively prevented the binding of TNF-α to the cell surface TNF-α receptors P55 and P57, thereby blocking its deleterious effect [17]. Du-moxibustion alleviated pain in the patients, thereby enhancing their recovery. In traditional Chinese medicine, ankylosing spondylitis is categorized as *bone palsy*, and the disease affects the lumbosacral region and the spine [18]. Since the spine is in the *Du meridian* route, and the waist is closely related to renal function, the etiology of ankylosing spondylosis is thought to be related to deficiency of kidney *qi*, *invasion of cold*, and *stagnation of qi* [19]. Du-moxibustion clears the *Du meridian* and removes spinal paralysis, thereby optimizing the clinical efficacy of adalimumab therapy.

In this study, the NRS scores of patients given joint treatment at T2, T3, and T4 were significantly lower than those receiving conventional treatment, indicating that the combination of du-moxibustion and adalimumab quickly relieved pain in the patients. In addition, du-moxibustion plus adalimumab was associated with higher BASDAI scores and lower BASFI scores versus conventional treatment herein. This indicates that, relative to conventional treatment, the combined use of du-moxibustion and adalimumab substantially mitigated the disease condition and improved the mobility of the patients, thereby enhancing disease prognosis.

Adalimumab, a new type of biological agent, inhibits ankylosing spondylitis-induced abnormal expressions of tumor necrosis factor, thereby reducing the inflammatory response and suppressing the disease. However, adalimumab monotherapy does not result in a radical cure for ankylosing spondylitis. Therefore, du-moxibustion was introduced into the treatment regimen to ameliorate clinical symptoms and clinical indicators in patients, and to ensure higher treatment effectiveness [20]. Here, du-moxibustion plus adalimumab yielded better efficacy versus conventional treatment, which is consistent with the research results in a previous report [21]. In that publication, there was significantly higher total treatment effectiveness in the study group (90.63 %) than in the control group (65.63%). Thus, the results obtained in this study confirm the merit of this combined treatment method for ankylosing spondylitis [22].

CONCLUSION

The treatment of ankylosing spondylitis patients with the combination of du-moxibustion and adalimumab mitigates symptoms and clinical indicators of the disease and relieves pain in patients. Therefore, the treatment strategy should be further subjected to clinical trials for validation for use in clinical practice.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Longfei Han, Jianying Zhang and Hui Liang wrote and reviewed the manuscript.

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