

Effect of moxibustion plus *Duhuo Jisheng* decoction on hs-CRP, IL-1 β and TNF- α levels in middle-aged and elderly patients with knee osteoarthritis

艾灸加独活寄生汤对中老年膝关节炎患者hs-CRP、IL-1 β 和TNF- α 的影响

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Abstract

Objective: To observe the clinical effect of moxibustion combined with *Duhuo Jisheng* decoction for middle-aged and elderly patients with knee osteoarthritis (KOA) and its impact on serum high sensitive C-reactive protein (hs-CRP), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) levels.

Methods: A total of 90 eligible KOA patients were randomized into an observation group ($n=45$) and a control group ($n=45$). Cases in the observation group received moxibustion plus oral administration *Duhuo Jisheng* decoction, while cases in the control group received *Duhuo Jisheng* decoction. Then the hs-CRP, IL-1 β and TNF- α levels were examined and the clinical effect was evaluated.

Results: Before treatment, the hs-CRP, IL-1 β and TNF- α levels showed no between-group statistical differences (all $P>0.05$). After 8 weeks of treatment, the hs-CRP, IL-1 β and TNF- α levels all dropped significantly in both groups ($P<0.01$ or $P<0.05$), and the treatment group showed more substantial changes than the control group (all $P<0.05$). The total effective rate was 97.8% in the treatment group, versus 86.7% in the control group, showing a statistical difference ($P<0.05$).

Conclusion: Moxibustion plus *Duhuo Jisheng* decoction has a good clinical effect for middle-aged and elderly KOA patients, and the effect may relate to the decreased hs-CRP, IL-1 β and TNF- α levels.

Keywords: Moxibustion Therapy; Osteoarthritis, Knee; C-reactive Protein; Interleukin-1beta; Tumor Necrosis Factor-alpha

【摘要】目的：探讨艾灸联合独活寄生汤对中老年膝骨性关节炎(KOA)患者血清超敏C-反应蛋白(hs-CRP)、白细胞介素-1 β (IL-1 β)和肿瘤坏死因子- α (TNF- α)水平的影响，并观察临床疗效。**方法：**共纳入90例 KOA 患者，按随机数字表法分为观察组和对照组，每组45例。对照组予以口服独活寄生汤治疗，观察组在对照组治疗的基础上加用艾灸治疗，观察两组患者治疗前后炎性因子 hs-CRP、IL-1 β 和 TNF- α 水平的变化并比较其临床疗效。**结果：**治疗前两组患者的 hs-CRP、IL-1 β 和 TNF- α 水平均无统计学差异(均 $P>0.05$)。治疗8星期后，两组的 hs-CRP、IL-1 β 和 TNF- α 水平均明显下降($P<0.01$ 或 $P<0.05$)，且观察组下降幅度较对照组更明显(均 $P<0.05$)。观察组总有效率97.8%，明显优于对照组的86.7% ($P<0.05$)。**结论：**艾灸联合独活寄生汤治疗中老年 KOA 具有良好的临床疗效，其机理可能与降低患者的炎性因子 hs-CRP、IL-1 β 和 TNF- α 有关。

【关键词】 灸法；关节炎，膝；C-反应蛋白；白细胞介素-1 β ；肿瘤坏死因子- α

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Knee osteoarthritis (KOA) is a common degenerative joint disease among the middle-aged and elderly people. It is generally caused by strain of peripheral ligament, and subsequent lesion of the joint cartilage may lead to swelling, pain, osteoproliferation or even movement dysfunction^[1]. The cause of KOA is complicated and requires further investigation.

Currently, in traditional Chinese medicine (TCM), there is much progress in treating KOA, such as medicinal herbs, which can activate blood and resolve stasis and non-pharmaceutical therapy. They all showed a good clinical effect, in which, moxibustion especially shows a more substantial effect. We've treated KOA patients with moxibustion plus *Duhuo Jisheng* decoction and the levels of high sensitive C-reactive protein (hs-CRP), interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) were examined. The results are summarized as follows.

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1 Clinical Materials

1.1 Diagnostic criteria

1.1.1 Diagnosis in Western medicine

It was based on the diagnosis criteria in *Guiding Principles for Diagnosis and Treatment for Osteoarthritis* (2007 version)^[2]: frequent knee joint pain during the recent 1 month; X-ray reveals a narrowed joint space, subchondral bone sclerosis and (or) cystic degeneration, the presence of osteophyte around joint facet; a clear, thick synovial fluid (≥ 2 times) with white blood count (WBC) $< 2\ 000/\text{mL}$; aged 40 or above; morning stiffness ≤ 3 min; bone crepitus (feelings) during joint movement. The presence of item 1, 2 or 1, 3, 5, 6 or 1, 4, 5, 6 at once can be diagnosed with KOA.

1.1.2 Diagnosis in Chinese medicine

This was based on the *Guiding Principles for Clinical Study of New Chinese Medicines*^[3]: a dull pain with impaired flexion and extension during early onset, aggravation during weather change, a long course with frequent relapse. A hidden onset, a gradual development, usually occurs in middle-aged or elderly people; a slight swelling, fluid retention and crepitus on active motion during joint movement; X-ray reveals osteoporosis, narrowed joint space, subchondral bone sclerosis, a lip-shaped margin, or formation of osteophyte; a normal erythrocyte sedimentation rate (ESR).

1.2 Inclusion criteria

Accorded with the diagnosis criteria in Chinese and Western medicine; willing to participate in this study and sign the informed consent.

1.3 Exclusion criteria

Severe cardiopulmonary disease, high blood pressure or mental disorders; tear of meniscus, loose bodies in the knee joint or locked joint facet, or KOA patients in late stage; rheumatic arthritis, rheumatoid diseases, gout or other diseases which may lead to knee pain; a history of knee trauma or surgery; patients who have received other treatment which may affect indicators in this study; failed to make an objective evaluation of the scales in this study.

1.4 Statistical methods

The SPSS 17.0 version software was employed for statistical analysis. The measurement data conforming to normal distribution were expressed by mean \pm standard deviation ($\bar{x} \pm s$), paired sample *t*-test was used for inter-group comparison, and the independent sample *t*-test was used for intra-group comparison. $P < 0.05$ indicated a statistical significance.

1.5 General data

A total of 90 KOA patients in Orthopedics Clinic between March 2014 and March 2016 were randomly allocated into a treatment group ($n=45$) and a control group ($n=45$). There were 23 males and 22 females in the treatment group, aged between 45 and 71 years,

averaged at (57.8 ± 6.3) years, and their duration lasted from 1.5 to 5 years, averaged at (2.97 ± 0.49) years. There were 21 males and 24 females in the control group, aged between 46 and 70 years, averaged at (58.3 ± 6.1) years, and their duration lasted from 1.2 to 5.5 years, averaged at (3.01 ± 0.55) years. There were no drop-out cases during treatment, and no significant between-group differences in age, gender and duration (all $P > 0.05$), indicating that the two groups were comparable.

2 Treatment Methods

2.1 Treatment group

2.1.1 Moxibustion

Acupoints: Xuehai (SP 10), Liangqiu (ST 34), Weizhong (BL 10), Yanglingquan (GB 34), Neixiyan (EX-LE 4), Dubi (ST 35) and Ashi points.

Methods: Patients took a supine position and a moxibustion box suitable for the size of the affected leg was selected, and then the knee was put into the box. The moxa supporters were adjusted properly. Moxa sticks were then fixed and pointing to the acupoints. Made sure the distance between the stick and skin was around 3-5 cm. Adjust the distance if any discomfort or pain occurred. The treatment lasted for 30 min each time, once a day, and 7-treatment constituted a course, 8 courses in total.

2.1.2 Oral intake of *Duhuo Jisheng* decoction

Constitution: *Sang Ji Sheng* (*Herba Taxilli*) and *Dang Shen* (*Radix Codonopsis*) 20 g, *Du Huo* (*Radix Angelicae Pubescentis*), *Dang Gui* (*Radix Angelicae Sinensis*), *Fu Ling* (*Poria*), *Bai Shao* (*Radix Paeoniae Alba*), *Shu Di Huang* (*Radix Rehmanniae Preparata*), *Du Zhong* (*Cortex Eucommiae*) and *Huai Niu Xi* (*Radix Achyranthis Bidentatae*) 15 g, *Fang Feng* (*Radix Saposhnikovia*) and *Qin Jiao* (*Radix Gentianae Macrophyllae*) 10 g, *Rou Gui* (*Cortex Cinnamomi*), *Xi Xin* (*Herba Asari*), *Chuan Xiong* (*Rhizoma Chuanxiong*) and *Gan Cao* (*Radix Glycyrrhizae Preparata*) 6 g.

Differentiation: *Fu Zi* (*Radix Aconiti Lateralis Preparata*) and *Gan Jiang* (*Rhizoma Zingiberis*) were added for cold syndrome; *Fang Ji* (*Radix Stephaniae Tetrandrae*), *Yi Yi Ren* (*Semen Coicis*) and *Cang Zhu* (*Rhizoma Atractylodis*) were added for dampness syndrome; *Dan Shen* (*Radix Salviae Miltiorrhizae*) and *Yan Hu Suo* (*Rhizoma Corydalis*) were added for stasis syndrome.

Method: Boiled with 300 mL water, and taken in morning and evening separately, one dose a day, 5 doses a week, for 8 weeks in total.

2.2 Control group

Orally took *Duhuo Jisheng* decoction only, with the same component, usage and courses as those in the treatment group.

3 Therapeutic Efficacy Observation

3.1 Observation items

Took 4 mL plasma sample from all patients before and after treatment. The venous blood was collected on empty stomach in the early morning, then centrifuged at 1 500 r/min for 10 min. The hs-CRP was tested with immunoturbidimetry. The enzyme-linked immunosorbent assay (ELISA) was used for testing IL-1 β and TNF- α .

3.2 Therapeutic efficacy criteria

This was based on the *Guiding Principles for Clinical Study of New Chinese Medicines*^[3].

Recovery: Almost absence of clinical signs and symptoms, with normal joint function.

Marked effect: Remarkable alleviation of clinical signs and symptoms, basically restored of joint function, and able to participate in normal labor activity.

Improvement: Alleviated clinical signs and symptoms, basically restored joint function, unable to take care of themselves or partially recovered ability for labor activity.

Failure: No improvement at all.

3.3 Results

3.3.1 Comparison in hs-CRP, IL-1 β and TNF- α level

There were no significant between-group differences in hs-CRP, IL-1 β and TNF- α levels before treatment (all $P > 0.05$); after treatment, the hs-CRP, IL-1 β and TNF- α levels were significantly decreased in both groups and there were significant between-group differences ($P < 0.05$ or $P < 0.01$), (Table 1).

3.3.2 Comparison in therapeutic efficacy

The total effective rate was 97.8% in the treatment group, higher than 86.7% in the control group, showing a statistical difference ($P < 0.05$), (Table 2).

Table 1. Comparison in hs-CRP, IL-1 β and TNF- α levels ($\bar{x} \pm s$)

| Group | <i>n</i> | Time | hs-CRP (mg/L) | IL-1 β (ng/L) | TNF- α (μ g/L) |
|-----------|----------|------------------|---------------------------------|----------------------------------|---------------------------------|
| Treatment | 45 | Before treatment | 10.94 \pm 2.33 | 24.02 \pm 3.29 | 9.02 \pm 1.89 |
| | | After treatment | 6.50 \pm 2.17 ¹⁾³⁾ | 13.94 \pm 1.67 ¹⁾³⁾ | 4.03 \pm 0.92 ¹⁾³⁾ |
| Control | 45 | Before treatment | 10.63 \pm 2.51 | 24.41 \pm 3.77 | 8.93 \pm 1.97 |
| | | After treatment | 8.59 \pm 2.65 ²⁾ | 16.23 \pm 1.44 ²⁾ | 6.43 \pm 1.40 ²⁾ |

Note: Intra-group comparison, 1) $P < 0.01$, 2) $P < 0.05$; compared with the control group after treatment, 3) $P < 0.05$

Table 2. Comparison in therapeutic efficacy (case)

| Group | <i>n</i> | Recovery | Marked effect | Improvement | Failure | Total effective rate (%) |
|-----------|----------|----------|---------------|-------------|---------|--------------------------|
| Treatment | 45 | 22 | 14 | 8 | 1 | 97.8 ¹⁾ |
| Control | 45 | 16 | 13 | 10 | 6 | 86.7 |

Note: Compared with the control group, 1) $P < 0.05$

4 Discussion

Clinically, KOA mainly manifests as swelling, pain and restricted movement of the knee joint. In Chinese medicine, it falls under the category of 'Bi-impediment syndrome', 'bone-impediment' or 'tendon-impediment'^[4], which results from retention of wind, cold or dampness and subsequent qi stagnation and blood stasis^[5]. Contributing factors may include aging, deficiency of the liver and kidney, malnourishment of the bones and tendons and disorder between qi and blood. As a result, the treatment strategies are to resolve dampness, unblock meridians, reinforce the liver and kidney, tonify qi and blood and remove wind cold. Pathologically, KOA mainly manifests as cartilage degeneration and synovitis. More and more studies have indicated that inflammation may play an important role in KOA. The role of cytokines in KOA initiation and progression can be explained by their effect on cartilage matrix degradation and synthesis. Studies in recent years have shown that inflammatory

cytokines TNF- α , IL-1 β and hs-CRP are initiating factors involved in the pathogenesis of KOA^[6-7].

Duhuo Jisheng decoction is originated from *Bei Ji Qian Jin Yao Fang* (Important Formulas Worth a Thousand Gold Pieces for Emergency) by Sun Si-miao, Tang dynasty. Being a commonly used decoction for wind-dampness Bi-impediment syndrome, it has a good therapeutic effect for KOA^[8-9]. *Shu Di Huang* (*Radix Rehmanniae Preparata*), *Bai Shao* (*Radix Paeoniae Alba*), *Du Zhong* (*Cortex Eucommiae*), *Sang Ji Sheng* (*Herba Taxilli*) and *Huai Niu Xi* (*Radix Achyranthis Bidentatae*) can tonify liver and kidney, strengthen waist and knee, coupled with *Qin Jiao* (*Radix Gentianae Macrophyllae*), *Fang Feng* (*Radix Saposhnikoviae*), *Xi Xin* (*Herba Asari*), *Du Huo* (*Radix Angelicae Pubescentis*) and *Rou Gui* (*Cortex Cinnamomi*) to dispel wind-cold and dampness evils and relax sinews and activate collaterals, with *Dang Gui* (*Radix Angelicae Sinensis*) and *Chuan Xiong* (*Rhizoma Chuanxiong*) to circulate the blood and dissipate stasis, with *Dang Shen* (*Radix Codonopsis*), *Fu Ling* (*Poria*) and *Gan Cao* (*Radix Glycyrrhizae Preparata*)

to boost qi and tonify spleen. The whole constitution can dispel wind-dampness, relieve pain, tonify qi and blood, which is in accordance with KOA treatment^[10]. Cheng W, *et al*^[11] proved that *Duhuo Jisheng* decoction can decrease TNF- α , IL-1 β and hs-CRP levels in joint fluid of KOA patients, inhibit cartilage destruction by inflammatory factors, and thus postpone the degeneration of joint cartilage.

As a traditional Chinese rehabilitation therapy, moxibustion combines heat, light and medication stimulation on particular acupoints. Mugwort leaf is the main ingredient of moxibustion. It owns a pleasant fragrance and is good at penetration. When applied locally, it can dredge meridians and dispel cold evil. Moxibustion at acupoints can dredge meridians and debond adhesion, improve blood circulation around knee joint, facilitate absorption of inflammatory factors and thus alleviate symptoms including pain or swelling^[12-15]. Besides, moxibustion can relieve the pressure between joints and bones, facilitate synthesis of joint cartilage matrix and accelerate the rehabilitation process of joint damage^[16-17]. Ji H, *et al*^[18] proved that moxibustion can decrease serum inflammatory IL-1 and TNF- α levels.

In this study, there were no significant between-group differences in hs-CRP, IL-1 β and TNF- α levels before treatment, indicating that the states of KOA in the two groups were comparable. After 8 weeks of treatment, the overall effect in the treatment group was substantially higher than that in the control group; serum inflammatory cytokine levels in both groups all dropped significantly, while the change in the treatment group was higher than that in the control group, indicating that moxibustion combined with *Duhuo Jisheng* decoction has a better therapeutic effect than oral intake of *Duhuo Jisheng* decoction alone. It also shows that this therapy can relieve pain on one hand, and inhibit inflammation on the other hand, thus worth popularization.

Conflict of Interest

There was no potential conflict of interest in this article.

Statement of Informed Consent

Informed consent was obtained from all individual participants included in this study.

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