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Study on the Regulation of ROS by Acupuncture and Moxibustion to Relieve Inflammation in the Treatment of Sciatica

Xuqing Zhang#, Jinying Wang, Hanqing Tang*, Xiaofei Xing, Shumin Zhang, Meiye Song

School of Basic Medicine, Youjiang Medical University for Nationalities, Baise, China
Email: *phdtanghanqing@163.com

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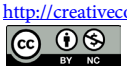

Abstract

Objective: To observe the analgesic effect of acupuncture and moxibustion on chronic constriction injury (CCI) pain model rats, and to investigate the mechanism of constriction constriction injury. **Methods:** 32 SPF SD rats were divided into Control Group, Sham Surgery Group, Model Group and Acupuncture and moxibustion Group, with 8 rats in each group. The Model Group, Acupuncture and moxibustion Group and sciatic nerve ligation were used to establish the CCI pain rat model. The sham operation group only separated the nerve, and the control group did not do any treatment. After modeling, the Acupuncture and moxibustion Group was given acupuncture treatment, while the control group and the Model Group did not do any intervention. 7 days for 1 course of treatment, continuous treatment for 3 courses of sampling and detection. Paw withdrawal mechanical threshold (PWMT) and Paw withdrawal thermal latency (PWTL) were observed. Biochemical detection of reactive oxygen species (ROS), malondialdehyde (MDA), Super Oxide Dismutase (SOD), glutathione (GSH); Serum, tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) levels were detected by ELISA. **Results:** Compared with the control group, PWMT and PWTL in the Model Group were decreased ($P < 0.05$), ROS, MDA, TNF-α, IL-1β and IL-6 levels or contents were increased ($P < 0.05$), SOD and GSH contents were decreased ($P < 0.01$ or $P < 0.05$). Compared with Model Group, PWMT and PWTL in acupuncture and moxibustion group were increased ($P < 0.05$), ROS, MDA, TNF-α, IL-1β and IL-6 levels or contents were decreased ($P < 0.05$), SOD and GSH contents were increased ($P < 0.01$ or $P < 0.05$). **Conclusion:** Acupuncture and moxibustion can reduce the ROS level, enhance the antioxidant capacity of the body, reduce the damage of sciatic nerve caused by inflammation, and relieve sciatic pain.

Keywords

Oxidative Stress, Inflammatory Factors, Acupuncture, Pain

1. Introduction

Pain is known as the fifth vital sign and is a common feature of many diseases. Neuropathic pain (NPP) is chronic pain caused by sensory nerve injury [1].

The etiology and mechanism of NPP are complex, and the relationship between the disease and the cause of pain is complex. Sciatica is a kind of neuropathic pain with a very common incidence in China [2], which not only damages the physical and mental health of patients but also creates a burden on the economy of patients. In addition, patients often reduce work efficiency due to radiation pain with varying durations of sudden attacks and leg paraesthesia [3].

Modern medicine often uses non-opioid drugs, sedation and other analgesic and neurotrophic drugs for treatment, in addition to epidural injection and intervertebral disc surgery and other treatment methods [4] [5] [6]. Although medication or surgery can reduce patients' pain, the long-term effect is not exact, and long-term application has serious side effects [7] [8] [9] [10]. Therefore, it is urgent to find a way to relieve sciatica and ease the economic burden of patients. ROS is closely related to the occurrence and development of sciatica [11] [12] [13] [14]. The increase of ROS expression leads to the increase of TNF-α, IL-1β and IL-6, and inflammatory factors are important key factors in the pathophysiological mechanism of sciatica [15] [16]. At present, acupuncture and moxibustion are commonly used in the clinical treatment of nerve pain [17], which has been proven to be an effective and safe treatment in clinical practice, and has achieved good results in reducing pain and improving patients' quality of life [18] [19] [20]. Acupuncture and moxibustion, with their low price, and quick effect, can be combined with other treatment methods, and the incidence of adverse reactions after treatment is low, so it has become the choice of routine treatment for sciatica [20].

Acupuncture can stimulate acupuncture points, activate the antioxidant oxidase system [21], inhibit the production of ROS, reduce cell damage, alleviate inflammation, reduce nerve sensitization, and reduce sciatica, but little is known about its mechanism. By establishing CCI rat models, this study observed and explored the mechanisms related to pain relief through acupuncture and moxibustion regulating ROS to reduce inflammatory factors from the perspective of antioxidants.

2. Materials and Methods

2.1. Experimental Animals

In this experiment, 32 SD rats with the mass (165 - 195) g were selected. The experimental animal production license number was SCXK (Xiang) 2019-0014, provided by Changsha Tianqin Biotechnology Co., LTD. The animals were kept

in cages at (23 ± 2)˚C humidity (48 ± 2)% and had free access to water and food. All the animals were put into the experiment after 7 days of adaptation. This experiment was approved by the Ethics Committee of Youjiang Medical College for Nationalities.

2.2. Drugs and Reagents

Serum Reactive Oxygen Species (ROS) detection kit (lot number: 20221201-RXSH0845-100); lL-1β, lL-6, TNF-a detection kits (Elabscience company, batch number: PA0340DD6682, PA04ZZPH8715, PA068ZRL0781) GSH, MDA, SOD kits were selected from Nanjing Jiancheng Bioengineering Institute (batch number: 20230201).

2.3. Instrument

Von Frey filament (Stoelting); PL-200 Hot string instrument (Chengdu Caimeng Software Co., LTD.); Spark multi-function microplate detector; ME204E electronic balance (Ohaus Electronic Instrument Co., LTD.); Intelligent thermostatic water tank (Gongyi City Yingyu high-tech instrument Factory).

2.4. Animal Grouping and Modeling

A total of 32 rats were divided into 4 groups (8 rats per group) by computer random number table method: control group, Sham Surgery Group Model Group, Acupuncture and moxibustion Group.

Molding method: The rat was anesthetized by intraperitoneal injection of 20% uratane, and the left hind limb was disinfected. The skin was cut longitudinally along the sciatica side at the junction of femur and buttock along the muscle to bluntly separate the subcutaneous fascia from the muscle, expose the sciatic nerve, free the surrounding tissue, and make four ligation rings around the sciatic nerve trunk. Each ligation ring is separated by about 1 mm and slightly dents the nerve, but does not block blood flow. In the sham group, only the sciatic nerve was exposed and the sciatic nerve was not ligate. In the model group, PWMT and PWTL decreased and positive behaviors such as paw retraction were observed.

2.5. Intervention Mode

7 days after the CCI model was established, the medicine thread was lit, the flame was extinguished, and the remaining star-shaped fire point was set in Zusanli (ST36) until the star-shaped fire point was extinguished once. The moxibustion was started 3 times a day, and the left Yanglingquan (GB34) and Huantiao Point (GB30) were selected for routine disinfection. The fiber tissue was picked out by oblique piercing under the skin with a sewing needle or a three-edged needle. In addition, the acupoint was punctured vertically and quickly 3 times, about 1mm into the skin, and disinfected after puncturing, once a day at each point, moxibustion and acupuncture were taken as a course of treatment for 7 days, and the next course of treatment was continued at an in-

terval of 1 day for a total of 3 consecutive courses. The control group, the sham operation group and the model group did not intervene, and samples were taken for detection at the end of the last course of treatment.

2.6. Detection Method

PWMT and PWTL were detected 1d before surgery, 1d after surgery, 3d after surgery, 5d, 7d, 9d, 11d, 15d.

2.6.1. PWMT Detection

Before the start of the experiment, the experimental environment should be kept at a constant 24˚C, and the rats underwent adaptive training in a glass box for 30 minutes a day for three days to reduce the stress response caused by environmental changes. During the formal test, the skin of the lateral plantar edge of the affected foot of the rats was subjected to gradually increasing vertical pressure with Von Frey wire. Observe for painful behaviors (e.g. retraction, foot licking, foot lifting, etc.). Record the pressure value of the first positive reaction, which is PWMT. To ensure data accuracy, each rat was tested three times, and the average value was taken as the final PWMT value. The interval between the two tests should be at least 5 minutes.

2.6.2. PWTL Detection

When measuring the thermal pain threshold, set the infrared intensity and temperature of the thermal radiometer, usually 50˚C, and control the heating time within 30 seconds. A heating plate was placed under the hind foot of the animal, the reaction time of the animal to lift the foot due to pain was recorded, and three tests were averaged to evaluate the sensitivity to heat pain.

2.6.3. Biochemical Index Detection

The contents of ROS, MDA, SOD, GSH, TNF-α, L-1β and IL-6 in the serum of rats in each group were measured. After the venous blood of the rats was extracted, the test tube was put into a centrifuge to extract serum, and the supernatant was taken for testing. The operation was conducted in strict accordance with the instructions. The colorimetric method, WST-1 method, microplate method, ABTS and ELISA were used respectively, and the samples were added and incubated successively.

2.7. Draw Materials

After the intervention, blood was taken from the abdominal aorta and placed at room temperature for 1h, then placed in a centrifuge for 10 min (4000 r/min), the supernatant was taken and stored in the refrigerator at −80˚.

2.8. Statistical Analysis

SPSS 26.0 software was used for statistical analysis of the data, and the measurement data were in line with normal distribution and homogeneous variance,

expressed as mean ± standard deviation (x ± s). Comparison between groups was conducted by one-way ANOVA and LSD, and $P < 0.05$ was considered statistically significant.

3. Result

3.1. PWMT and PWTL Test Results

Compared with before modeling, PWMT in the Model Group decreased significantly on day 1 after modeling, and reached the lowest level on day 7, and PWMT and PWTL were significantly different from those in the sham operation group ($P < 0.05$ or $P < 0.01$), indicating that the modeling of CCI model rats was successful. From the 7th day of acupuncture operation intervention to the 15th day, PWMT and PWTL were significantly different from those in the modeling group ($P < 0.05$) in Figure 1.

3.2. Biochemical Index Detection Results

As shown in Figure 2, ROS, MDA, TNF-α, IL-1β and IL-6 contents of rats in the Model Group were higher, and SOD and GSH contents were lower than those in the Sham Surgery Group with statistical significance ($P < 0.05$), while there was no significant difference between the sham operation group and the control group. The contents of ROS, MDA, TNF-α, IL-1β and IL-6 of rats in acupuncture and moxibustion group were lower, and the contents of SOD and GSH were higher than those in Model Group, with statistical significance ($P < 0.05$).

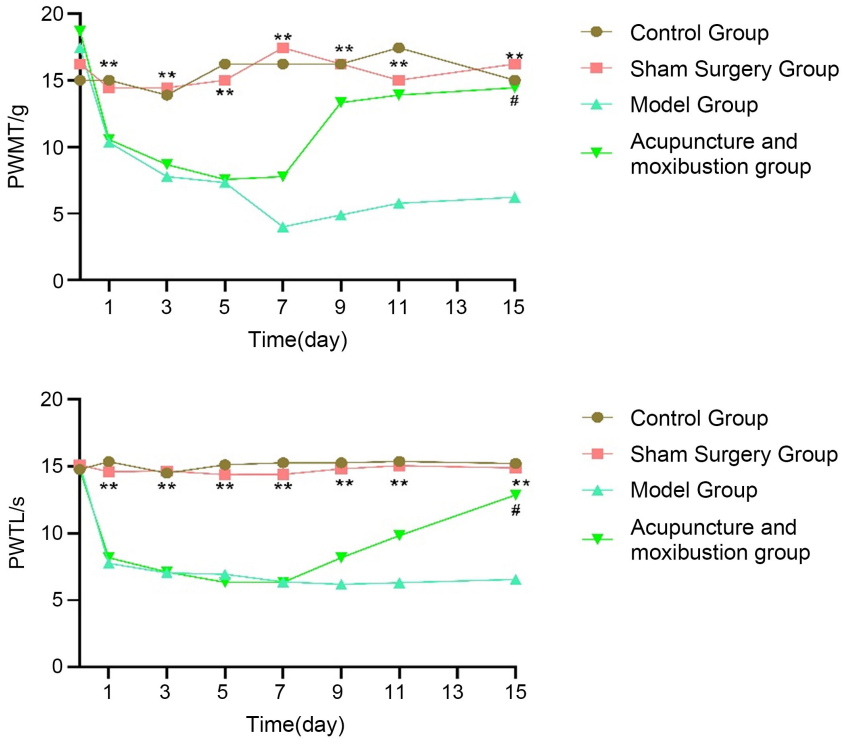

Figure 1. P** < 0.01; P* < 0.05; P## < 0.01; P# < 0.05; n = 3.

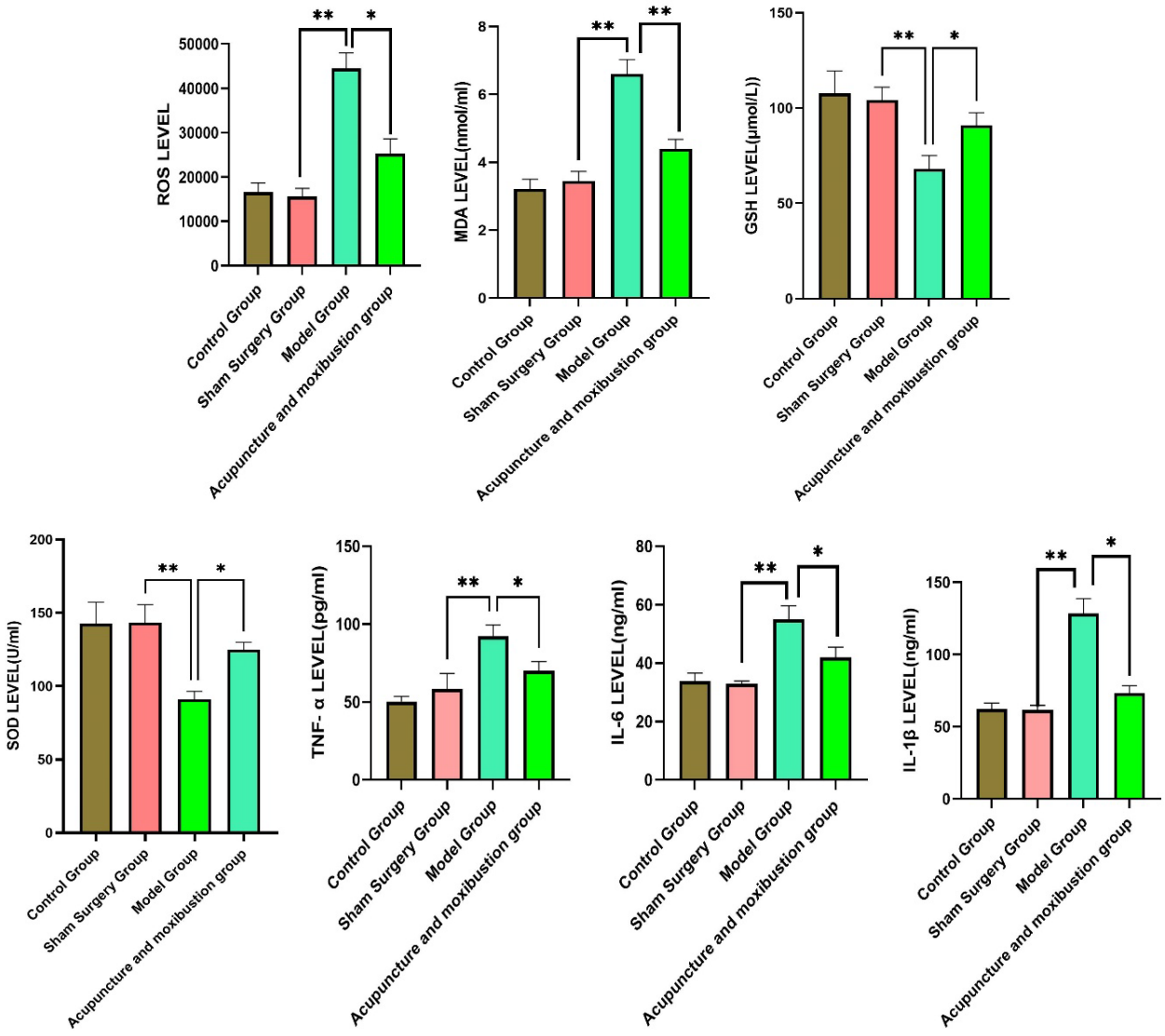

Figure 2. P** < 0.01; P* < 0.05; n = 3.

4. Discussion

Sciatica is a common clinical condition often associated with degenerative disc changes. Intervertebral disc degeneration was caused by ROS, TNF-α, IL-1β, IL-6 and other influences [22] [23] [24], and the central nucleus pulposus bulked out, resulting in intervertebral disc herniation. If the protrusion compresses the adjacent sciatic nerve, the patient may experience pain, decreased sensation, or a pinprick sensation at the nerve route site. These symptoms are collectively called sciatica.

The activity of inflammatory factors such as ROS and TNF-α is closely related to sciatica. In the pathological process of sciatica, ROS, as a medium of oxidative stress, can cause damage to nerve tissue, affect the normal function of cells, and indirectly promote inflammation and TNF-α production. ROS can also affect intracellular signaling pathways such as NF-κB activation through oxidative

stress, which in turn affects cytokine production and release. As a result, the overproduction of ROS leads to uncontrolled inflammatory responses and tissue damage.

TNF-α is a key inflammatory mediator, which induces the production of IL-1β and IL-6, increases vascular permeability, attracts more inflammatory cells to gather in the damaged area, and exacerbates local inflammation and pain [25] [26]. In TNF-mediated signal transduction, ROS is catalyzed by activation of oxidase [27]. ROS and TNF-α are mutually promoting, ROS can stimulate the production of TNF-α, while TNF-α can promote the production of ROS, forming a vicious cycle.

Inflammatory factors such as IL-1β, IL-6 and TNF-α play a key role in neurosensitization [28] [29]. By acting directly on nerve cells, they activate signal transduction pathways and increase neuronal excitability; Promote the release of neurotransmitters and enhance the transmission of nerve signals; Changes in the neural microenvironment, as well as entering the blood circulation and reaching the central nervous system, activate and sensitize pain processing pathways, resulting in central sensitization. In addition, ROS oxidative damage promotes the production of pro-inflammatory mediators and inflammation sensitizes nerve nociceptors to cause pathological pain [30]. These mechanisms are involved in pain transmission and amplification from the periphery to the center, and are important factors in the occurrence and maintenance of chronic pain.

No matter in normal or pathological conditions, the body metabolizes and produces ROS [31], and the excessive production of ROS tilts the balance between oxidation and antioxidants and leads to oxidative stress [32]. SOD treats oxidized substances in the body [33]. When SOD is unable to deal with over-generated ROS, lipid peroxidation is triggered and lipid peroxides are generated. As the end product of lipid peroxidation and degradation [34], MDA easily reacts with phospholipids on the cell membrane, leading to oxidative damage of tissues, further consumes SOD, induces the production of oxygen free radicals, weakening the antioxidant capacity of rats, and thus aggravates sciatic nerve injury. GSH, another major antioxidant in the body, fights oxidation by converting hydrogen atoms into reduced glutathione, clearing free radicals and IL-1β in the body [35], which not only helps to maintain the REDOX balance in cells but also prevents the damage caused by inflammatory factors to cells.

This suggests that the reduction of ROS contributes to the recovery of sciatica in this model, and further reduces the contents of TNF-α, IL-1β, IL-6, etc [36]. Acupuncture is often used to treat all kinds of acute and chronic pain [37] [38]. The results of this experiment showed that PWMT and PWTL of rats in the Model Group were decreased 1 day after CCI modeling, and it was not until the end of the experiment that the rats showed obvious hyperalgesia after modeling. PWMT and PWTL increased significantly, indicating that acupuncture indeed increased the pain tolerance of rats, alleviated the injury induced by ROS, TNF-α, IL-1β and IL-6, reduced the swelling degree of sciatic nerve fibers, and improved central pain sensitization. Acupuncture at Yanglingquan and Huantiai

can reduce inflammatory mediators [39] [40] [41]. Moxibustion "Zusanli" can significantly reduce the content of ROS and MDA in serum, increase antioxidant substances, balance oxidative stress in the body [42] [43], and reduce cell apoptosis and necrosis caused by ROS. According to the significant differences in the contents of TNF-α, IL-1β and IL-6 between the Acupuncture and moxibustion Group and the Model Group, it has been proved that acupuncture can interrupt TNF-α, promote the mutual promotion between ROS, improve mitochondrial damage, and weaken the release of IL-1β and IL-6 [44].

In summary, this study revealed that acupuncture intervention can effectively relieve sciatica, and its initiation mechanism is related to the inhibition of the ROS signaling pathway. However, there are still some limitations in this experiment. The results of acupuncture in reducing inflammatory factors in rat models cannot be directly generalized to humans, because the physiological differences between animals and humans, the control of experimental environment and the potential bias of clinical studies may affect the accuracy of the results. Therefore, it is necessary to verify its effect in humans through well-designed clinical trials, as well as the impact of inflammation on the dorsal horn of the middle spinal cord during the unverified analgesic process. Later experiments can be further verified from this aspect, providing more evidence for clinical acupuncture treatment of sciatica and scientific support for the development of acupuncture.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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