

Exploration of the Value of Extract of Wuwei Xiaodu Drink on Rabbit Model of Spinal Infection

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Abstract: *Objective:* To study the therapeutic effect of the Extract of Wuwei Xiaodu Drink on spinal infection and provide the scientific basis for clinical application. *Methods:* By establishing a rabbit model of spinal infection, this paper observed and analyzed the changes in body mass before and after the intervention and the comparison of inflammation-related factors and blood leukocyte counts among the three groups. *Results:* There was a significant difference in the changes in body mass of rabbits before and after intervention in the experimental group, control group and blank group ($P < 0.05$); there was no statistically significant difference in calcitoninogen, C-reactive protein and routine blood leukocyte counts between the experimental group and the control group ($P > 0.05$), and there was a statistically significant difference in calcitoninogen, C-reactive protein and routine blood leukocyte counts between the experimental group and the blank group ($P < 0.05$). *Conclusion:* The Extract of Wuwei Xiaodu Drink can play a protective role by regulating the level of inflammatory factors in blood routine leukocyte count and reducing the inflammatory reaction in the spinal cord injury area.

Keywords: Extract of Wuwei Xiaodu Drink; Spinal infection; Rabbit model

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1. Introduction

The spine, as the central axis structure of the human body, is mainly composed of vertebrae, intervertebral discs and ligaments. In daily life, various factors may lead to spinal infections, such as trauma and bacterial infections. If left untreated, it may cause nerve damage and even affect the patient's life. Therefore, it is of great significance to study the prevention and treatment effects of spinal infections. In recent years, with the deepening of medical research, traditional Chinese medicine (TCM) has shown good therapeutic prospects in the prevention and treatment of spinal infections. Chinese medicine has multi-target and multi-pathway action characteristics and can play an immunomodulatory role by inhibiting the expression of inflammatory cytokines^[1]. Extract of Wuwei Xiaodu Drink is a recipe archived in "Pharmacopoeia of the People's Republic of China (2015 edition)." The main ingredients are honeysuckle, wild chrysanthemum, dandelion, *Viola philippica*, *Begonia fimbripetala*, etc., which

has the efficacy of clearing away heat and detoxicating, dispelling dampness and relieving pain, improving the “Qi” and strengthening the spleen, with astringent effect^[2]. This study conducted a preliminary study on Wuwei Xiaodu Drink in the previous period and found that the formula could effectively reduce the peripheral blood leukocyte count, abdominal macrophage phagocytic index, and serum total protein concentration of rabbits and reduce the peripheral inflammatory response, besides improving the liver index and increase the spleen index of rabbits, and exerted a better anti-inflammatory effect. In this study, the rabbit was used as an animal model, and a spinal infection model was established. By observing and analyzing the changes in body mass before and after the intervention of the three groups and the post-intervention inflammation-related factors and blood leukocyte counts, this study explored the interventional effects of the Extract of Wuwei Xiaodu Drink on spinal infection and its mechanism, to provide the scientific basis for the clinical application.

2. Materials and methods

2.1. General materials

2.1.1. Drugs and reagents

Ninety wild-grade SD rabbits, 8 weeks old, were selected. They were kept in an SPF animal house with free feeding and drinking water, and the room temperature was 25.00 ± 0.33 °C. Extract of Wuwei Xiaodu Drink was prepared by the School of Pharmaceutical Engineering of Traditional Chinese Medicine, Anhui University of Traditional Chinese Medicine, after water extraction and alcohol precipitation, and then vacuum freeze-dried, which contained baicalin and emodin, etc. LPS (Beijing Solepol Science and Technology Co., Ltd., purity $\geq 99\%$); FBS (Beijing Biyuntian Biotechnology Institute); DMEM/F12 medium (Corning, USA); PBS buffer (Beijing Biosun Biotechnology Co., Ltd.); fluorescently labeled TNF- α (Suzhou Desai Biotechnology Co., Ltd.); and albumin (Shanghai Aladdin Biochemical Technology Co., Ltd.).

2.1.2. Materials and instrument

Microscope (Nikon E600i), enzyme labeler (Thermo Scientific, USA), bench-top high-speed cryo-centrifuge (Sartorius AG, Switzerland), automatic biochemical analyzer (Beckman Coulter Inc., USA), and fluorescence quantitative PCR instrument (Bio-Rad Laboratories, USA).

2.1.3. Animal grouping and treatment

In this study, the experimental rabbits were divided into a control group, a blank group, and a test group (Wuwei Xiaodu Drink group) by random number table method, with 30 animals in each group.

2.2. Methods

The experimental group (Wuwei Xiaodu Drink group), blank group and control group were given an extract of Wuwei Xiaodu Drink orally, saline and amoxicillin (State Drug Permit H13021516 Shenwei Pharmaceutical Group Co., Ltd.) 20 mg/kg, dissolved in saline and then orally, respectively. The rabbits were weighed on the day of modeling and 12 weeks after modeling and the related evaluation indexes were measured. Extract of Wuwei Xiaodu Drink is composed of five traditional Chinese medicines: 15 g of honeysuckle, 6 g of wild chrysanthemum, 6 g of dandelion, 6 g of *Viola philippica*, 6 g of *Begonia fimbriatipula* and so on. After the extraction and processing, the extract of Wuwei Xiaodu Drink can better retain the medicinal components and facilitate oral administration.

2.3. Observation indicators

Observe and analyze the changes in body mass before and after intervention, post-intervention inflammation-related factors and blood leukocyte count comparisons in the three groups.

2.4. Statistical methods

SPSS 21.0 statistical software was used to process the data. Measurement data were expressed as mean $\pm$ standard deviation (SD), and a t -test was used, and count data were expressed as a percentage (%), an χ^2 test was used, and the difference was considered statistically significant at $P < 0.05$.

3. Results

3.1. Changes in body mass before and after intervention in three groups of rabbits

The changes in body mass of rabbits before and after intervention in the test group, control group and blank group were significantly different ($P < 0.05$), as shown in **Table 1**.

Table 1. Changes in body mass before and after intervention in three groups of rats

Group	Number of SD rabbits	Pre-intervention (g)	Post-intervention (g)	t	P
Test group	30	236.62 $\pm$ 13.31	311.32 $\pm$ 10.84	23.835	0.000
Control group	30	247.12 $\pm$ 13.41	312.19 $\pm$ 10.32	21.062	0.000
Blank group	30	243.54 $\pm$ 13.32	223.28 $\pm$ 9.51	6.780	0.000

Note: There was no statistical significance in the two-by-two comparison of the experimental group, control group and blank group before intervention ($P > 0.05$); after intervention, there was no statistical difference between the experimental group and the control group ($P > 0.05$); there was a statistical difference between the experimental group and the blank group ($P < 0.05$).

3.2. Inflammation-related factors and blood leukocyte counts in the three groups of rabbits after intervention

There were no statistical differences in calcitoninogen, C-reactive protein, and routine blood leukocyte counts between the test group and the control group ($P > 0.05$), and there were statistical differences in calcitoninogen, C-reactive protein, and routine blood leukocyte counts between the test group and the blank group ($P < 0.05$), as shown in **Table 2**.

Table 2. Inflammation-related factors and routine blood leukocyte counts in three groups of rabbits after intervention

Group	Number of SD rabbits	Calcitoninogen (ng/mL)	C-reactive protein (ng/mL)	Routine blood white blood cell count ($\times 10^9$)
Test group	30	0.32 $\pm$ 0.11	8.19 $\pm$ 0.23	8.21 $\pm$ 0.31
Control group	30	0.33 $\pm$ 0.21	8.08 $\pm$ 0.30	8.10 $\pm$ 0.32
Blank group	30	1.74 $\pm$ 0.22	14.31 $\pm$ 1.48	15.23 $\pm$ 1.17
t_1		0.231	1.594	1.352
P_1		> 0.05	> 0.05	> 0.05
t_2		31.621	22.380	31.767
P_2		0.000	0.000	0.000

Note: t_1 and P_1 indicate the comparison results between the test group and the control group; t_2 and P_2 indicate the comparison results between the test group and the blank group.

4. Discussion

Spinal infections are infectious diseases of the bones and soft tissues of the spine caused by bacteria, fungi or other microorganisms. This infection is usually caused by the invasion of various pathogenic microorganisms such as *Staphylococcus aureus*, *Streptococcus sp.*, etc. into the spinal column, and these microorganisms enter into the vertebral canal through the blood circulation or direct invasion, causing inflammation, necrosis, and abscess formation of the soft tissues and bones. Spinal infections can be triggered by a variety of causes, including, but not limited to, bacterial infections, foreign bodies in the spinal canal, trauma, immunocompromise, and medical infections. Bacterial infections are purulent infections caused by bacteria invading the spinal canal, with common causative organisms being *Staphylococcus aureus* and *Staphylococcus albicans*. Foreign bodies in the spinal canal may cause infection due to compression of the spinal cord, nerve roots, discs and other areas. In addition, trauma to the spine may cause localized blood vessel rupture, which in turn can lead to infection. Immunocompromised and medical infections are also potential causes of spinal infections. Clinical symptoms of spinal infections are varied and typically include back pain, fever, chills, general malaise, and limited mobility. In addition, patients may also experience localized skin erythema, edema and increased skin temperature. In severe cases, the infection may invade the nervous system, leading to symptoms such as numbness and weakness in the limbs and even affecting normal activities. Measures to treat spinal infections mainly include antibiotic therapy and surgical intervention. Depending on the severity of the infection and the type of pathogen, doctors will choose the appropriate antibiotic for treatment. Surgical treatment may be required if the infection is severe and the localized lesion is large. Meanwhile, physiotherapy such as massage, hot packs and hot baths can also be used as an adjunctive treatment to promote blood circulation in the spine area and relieve muscle tension. Spinal infection refers to the exogenous invasion of bacteria, viruses and other pathogens into the human body, disrupting the balance of the body's internal environment and the emergence of local or systemic infection ^[3]. Its pathogenesis is related to host immune dysfunction, which activates neutrophils, monocytes and macrophages under the action of multiple factors, which in turn releases a large number of inflammatory mediators and triggers an inflammatory response in the body.

Firstly, the treatment of spinal infections, as a serious clinical problem, often involves the use of antibiotics, but the long-term use or abuse of antibiotics may lead to the development of drug resistance. Wuwei Xiaodu Drink, as a natural drug, with its broad-spectrum antimicrobial effect may provide a new option for the treatment of spinal infections, especially for drug-resistant strains of bacteria, and it may be of therapeutic efficacy ^[4]. Secondly, the efficacy of Wuwei Xiaodu Drink in clearing heat removing toxins and dissipating boils may help to alleviate the local inflammatory response caused by spinal infections and reduce the pain and discomfort of patients. By regulating the body's immune response, Wuwei Xiaodu Drink may help control the progression of infection and promote the subsidence of inflammation and tissue repair. In addition, Wuwei Xiaodu Drink may also play a role in the prevention of spinal infections ^[5]. By improving the body's resistance, it reduces the invasion and multiplication of pathogenic microorganisms, thus reducing the risk of spinal infection. However, it is worth noting that although Wuwei Xiaodu Drink may have some value in the spinal infection rabbit model, its specific mechanism of action, dose-effect relationship, and the safety of long-term use still need to be further researched and verified. In addition, due to the differences between animal models and humans, the efficacy and safety of Wuwei Xiaodu Drink in humans also need to be confirmed by more clinical trials.

Studies have shown that Wuwei Xiaodu Drink has good antibacterial effects against gram-negative bacilli such as *Staphylococcus aureus*, *Haemophilus influenzae* type A, and *Klebsiella pneumoniae* ^[6]. In this experiment, the tissue sections of the thoracic and lumbar spine of rabbits in the test group showed obvious inflammatory

infiltration, severe vacuolization of nucleus pulposus cells, edema, degeneration and necrosis of neuronal cells, and proliferation of astrocytes. At the same time, there was a statistical difference in calcitoninogen, C-reactive protein, and blood routine leukocyte count between the experimental group and the blank group ($P < 0.05$), and Extract of Wuwei Xiaodu Drink could significantly reduce the number of leukocytes in the serum after the infection, reduce the content of inflammatory markers blood routine leukocyte count, increase the splenic index, and improve the structure of the nucleus pulposus area after the infection. This may be closely related to the molecular mechanism of TCM for spinal infections.

Therefore, the research and development of drugs for spinal infections should focus on their effects on the host immune system and the interactions between different components, to obtain new drugs with higher efficacy. Wuwei Xiaodu Drink has a good bacteriostatic effect and inhibits the expression of LPS-induced inflammatory cytokines blood routine leukocytometer, C-reactive protein and calcitoninogen^[7]. Studies have shown that there are interactions and synergistic effects between multiple components of traditional Chinese medicines, and their mechanisms of action in treating diseases are complex^[8]. Honeysuckle is sweet and cold in nature, can clear heat and detoxify, with its light and clear evacuation, is one of the main herbs in Wuwei Xiaodu Drink, and its dosage is relatively large, which can play the effect of clearing heat and detoxification more effectively; wild chrysanthemum has the effect of dispersing wind and heat, detoxifying and eliminating oedema, and its dosage is moderate so that it can have a synergistic effect with honeysuckle without being too strong; dandelion clears heat and detoxifies, diuretic and diuretic, and its dosage is similar to that of wild chrysanthemum. Dandelion clears heat and removes toxins, induces diuresis and lymphatic drainage, and its dosage is the same as that of wild chrysanthemum, which jointly assists honeysuckle and strengthens the power of clearing heat and removing toxins^[9-10]. This study confirmed the protective effect of Extract of Wuwei Xiaodu Drink on rabbits with spinal cord injury and preliminarily investigated that Extract of Wuwei Xiaodu Drink alleviated spinal cord nerve injury by down-regulating the expression of inflammatory cytokine calcitoninogen, reducing the release of inflammatory mediators, and decreasing the degree of tissue damage.

5. Conclusion

In conclusion, the Extract of Wuwei Xiaodu Drink can effectively alleviate pathological injury after spinal infection in rabbits and regulate the host immune response to play a role in protecting the organism, and its main mechanism of action may be:

- (1) Inhibit the expression of inflammatory cytokines calcitoninogen and C-reactive protein;
- (2) Enhance the proliferation ability of peripheral blood lymphocytes;
- (3) Promote the activity of spleen phagocytes;
- (4) Activate the expression of immune factors in spleen nucleoli;
- (5) Repair damaged spinal cord tissues.

However, it is worth noting that this study failed to exclude the possibility of other interfering factors, such as the animal's factors, feeding conditions, experimental methods, etc. It is necessary to expand the sample size further and repeat the verification.

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Disclosure statement

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