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Progress in the Treatment of Neurogenic Cervical Spondylosis by Guizhi Decoction with Gegen

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Abstract: ***Neurogenic cervical spondylosis is a disease in which the nerve roots are compressed due to herniated intervertebral discs or bony hyperplasia, thus causing symptoms such as pain, abnormal sensation, or loss of muscle strength in the distribution area of the corresponding nerves, and it is a common type of cervical spondylosis, which seriously affects the quality of life of patients. Guizhi decoction with Gegen is one of Zhang Zhongjing's prescription, composed of Gui Zhi, Paeoniae Alba, Ginger, Jujubes, Radix et Rhizoma Glycyrrhizae, Pueraria Mirifica, which is made of Guizhi decoction with Pueraria Mirifica. It has the efficacy of relieving muscle release, generating fluids to relieve tendons, and harmonising camps to pass through the channels and collaterals, and can be used widely for rheumatoid arthritis, gout, and other diseases in addition to good treatment of wind-cold colds and flu. It is found that Guizhi decoction with Gegen can achieve the purpose of treating neurogenic cervical spondylosis by improving microcirculation, regulating the autonomic nerves as well as immune anti-inflammatory and analgesic effects. This paper summarises the mechanism of action and clinical application of Guizhi decoction with Gegen and the active ingredients of single herbs in the treatment of neurogenic cervical spondylosis, with the aim of providing references for the treatment of neurogenic cervical spondylosis with traditional Chinese medicine.***

Keywords: Guizhi decoction with Gegen, Neurogenic cervical spondylosis, Research progress**.**

1. Introduction

Cervical Spondylotic Radiculopathy (CSR) is a degenerative disease caused by degenerative disc changes, cervical joint instability, and spinal stenosis. These lesions cause compression of the peripheral nerve roots, which leads to a series of symptoms such as pain and numbness in the neck, upper extremities, and shoulders. This type of cervical spondylosis is very common and frequent, and is one of the most common types of cervical spondylosis in clinical practice [1]. In recent years, due to the increasing pressure of people's work, especially office workers or students, who have their heads lowered for long periods of time to carry out work and study, the number of people suffering from the disease is increasing day by day, which has caused a great deal of impact on the patients' life and work.

2. Etiology and Pathogenesis of CSR

2.1 Modern Medicine's Perception of CSR

The pathogenesis of CSR radicular pain is complex and not caused by a single mechanism; each mechanism is intersecting, interconnected, and interacting with each other, mainly involving mechanical compression, inflammatory response, autoimmunity, and metabolic disorders [2,3]. Wu Zilong et al. concluded that the mechanisms that play a crucial role in CSR radicular pain are mechanical compression and inflammatory response [4]. Xia Bin et al. examined 38 patients by multilayer spiral CT (MSCT) and found that the patients had manifestations of anterior and posterior margin osteophytes, cervical intervertebral disc protrusion, and ossification of the posterior longitudinal ligament combined with spinal stenosis, and concluded that mechanical compression leading to intervertebral foraminal stenosis was most relevant to the pathogenesis of CSR radicular pain [5].

2.2 Chinese Medicine's Understanding of CSR

According to Chinese medicine, CSR belongs to the category of ‘paralysis’, which can be called ‘paralysis of the neck’ according to the site of onset. The Yellow Emperor's Internal Canon, ‘Su Wen - Paralysis’, says: ‘Wind, cold and dampness are mixed together and become paralysis’. Wind, cold, dampness three evils invade to the body, easy to cause skin and muscle loss of nourishment, injected into the meridians, affecting the normal operation of the meridians and smooth, stagnant joints and bones, hindering the operation of qi and blood, and ultimately lead to qi and blood paralysis and paralysis of the hair for paralysis disease [6]. ‘Suwen - to true to be a great theory’ cloud: ’Yin paralysis, lumbar vertebrae head and neck pain, sometimes dizziness, the disease originated in the kidney.’ If the old body is weak, the organism is not cured for a long time, when feeling the cold and damp external evil attack, it will lead to the obstruction of qi and blood operation, and the symptoms of cold skin, numbness and pain in the neck will appear, and the wind, cold and damp evil attacking the organism is the symptom, and the liver and kidneys are weak, and qi and blood loss is the basis [7]. The evidence of the ‘quintessence’ said: ‘Neck pain is not wind, that is, the gas is frustrated, but also pillow from the pain..., from the frustration of flash and sedentary loss of pillow to the neck can not be shifted, all by the kidney can not be born of the liver, the liver is not in order to raise the tendons, so the organs are not conducive to, ’ that is, with the strain-related. Therefore, it can be seen from the literature over the ages that both external and internal causes can lead to poor qi and blood circulation, and pain when there is no circulation, causing the onset of CSR pain.

3. Theoretical Basis for the Treatment of CSR with GuiZhi Decoction Plus Pueraria Mirifica

Guizhi decoction with Gegen is from Article 14 of The Treatise on Typhoid Fever, written by Zhang Zhongjing during the Eastern Han Dynasty. 'If you are sick with the Sun, with a strong neck and back, and you are sweating and have a bad wind, Guizhi decoction with Gegen is the mainstay of the soup.' It consists of Gui Zhi, Paeoniae Alba, Ginger, Jujube, Roasted Licorice and Pueraria Mirifica. The Chinese medicinal herb Pueraria Mirifica promotes sweating and detoxification of the exterior, detoxifies the muscles and generates body fluid; the subject's medicinal herb Gui Zhi warms the meridians and passes through the channels; white peony nourishes the blood and softens the liver, eases the urgency of the problem and relieves pain; ginger detoxifies the exterior and disperses the cold, removes dampness and relieves pain; jujube benefits the vital energy and nourishes the blood, while licorice eases the urgency of the problem and relieves pain and benefits vital energy to nourish the middle. This formula is made of Guizhi decoction adding Gegen, and the combination of all the medicines has the efficacy of detoxifying the muscles and releasing, generating fluid and soothing the tendons, and harmonising the camps and collaterals, which can effectively improve the muscle spasms of neck and shoulder, and alleviate the pain [1].

4. Study on the Modern Pharmacological Effects of the Single Herb of Guizhi Decoction with Gegen

4.1 Pueraria Mirifica

Pueraria lobata has a long history and wide range of applications as a traditional Chinese herbal medicine, and is the dried root of the leguminous plant Wild. The main bioactive components in Pueraria Mirifica are isoflavonoids, including geraniol and soy glycosides. These components have a wide range of pharmacological activities, such as antioxidant, anti-inflammatory, and immunomodulatory effect [8-9]. It was found that the isoflavone compounds in Pueraria Mirifica exert their good anti-inflammatory effects through multiple mechanisms. Firstly, isoflavones can not only inhibit the production and release of inflammatory cytokines such as IL-1β and TNF-α, thus reducing inflammatory responses, but also inhibit important inflammatory signalling pathways such as NF-κB and MAPK, thus preventing the expression of inflammatory genes [9-10]; secondly, isoflavones have good antioxidant activity, which can scavenge free radicals, reduce oxidative stress damage, and then suppress the occurrence and development of Inflammation occurs and develops [11]; at the same time, isoflavones can regulate the function of immune cells, such as macrophages and T cells, and inhibit the generation of inflammatory immune responses [11-12]. In addition, Pueraria lobata also has a certain analgesic effect, which can reduce the pain feeling of patients with cervical spondylosis and improve the quality of life of patients. Chu Limei [13] and other rats using intrathecal injection of Pueraria lobata combined with dorsal root nerve ligation surgery compared with the control group in order to observe the analgesic effect of Pueraria lobata on rats with dorsal root neuropathic pain, the results show that the dorsal root ganglion of rats in the expression of IL-6, IL-1β protein significantly increased, and the expression of its significant decrease after a week of continuous use of the drug, suggesting that pueraria lobata can be inhibited by inhibition of the production of inflammatory factors, on the neuropathic pain by inhibiting the production of inflammatory factors.

4.2 Gui Zhi

Cinnamon sticks are the shoots of the Chinese medicine cinnamon, which is widely used in Chinese medicine clinics. Its chemical composition mainly includes volatile components, such as cinnamaldehyde (also known as cinnamaldehyde) as the main component, as well as organic acids and glycosides. Cinnamaldehyde is one of the most important active components in the volatile oil. The volatile oil components in cinnamon sticks can inhibit the release of inflammatory mediators, reduce the inflammatory response, and have a certain analgesic effect. At the same time, cinnamon sticks have the effect of dilating blood vessels and promoting blood circulation, which is effective for pain and diseases caused by cold condensation and blood stasis [14]. In addition, the flavonoids in cinnamon sticks have strong antioxidant capacity, which can scavenge free radicals and effectively resist the attack of free radicals, thus protecting cells from oxidative damage [15].

4.3 Paeonia Lactiflora and Liquorice

Paeonia lactiflora is the dried root of Paeonia lactiflora, family Buttercupaceae, and its chemical constituents include terpenoids, volatile oils, flavonoids, and polyphenols. Paeoniflorin is a water-soluble monoterpene glycoside compound with a wide range of pharmacological effects, and it has good therapeutic effects in inflammatory diseases, immunological diseases, and neurological diseases. Liu Juntong et al [16] found that paeoniflorin can inhibit inflammatory responses, hinder leukocyte infiltration, and inhibit the release and expression of inflammatory factors IL-1β and TNF-α. Its analgesic mechanism may be related to the elevation of beta-endorphin (β-EP) levels in serum and cerebral cortex, and the reduction of prostaglandin E2 production or release in cerebral cortex [17]. The main components of liquorice are triterpenoid saponin compounds such as glycyrrhizin and glycyrrhizic acid, with additional flavonoids and glycyrrhizic polysaccharides. Its pharmacological effects mainly cover various aspects such as anti-inflammatory, antibacterial, antiviral, antioxidant and immunomodulatory [18]. It has been found that the pairing of white peony with liquorice can help the active ingredients in the drug to dissolve better, thus improving the efficacy, and even the best anti-inflammatory and analgesic effect was achieved when peony: roasted liquorice = 1: 1 pairing [19].

4.4 Ginger and Jujube

Ginger is the fresh rhizome of ginger, family Zingiberaceae. Ginger contains volatile oil (gingerol, gingerene, gingerenol, etc.), gingerol, diphenylheptane-like components, etc., which have antibacterial, anti-inflammatory and analgesic, antioxidant and other pharmacological effect [20]. Dates are rich in nutrients, mainly including sugars, vitamins, proteins, minerals, as well as some amino acids and polyphenolic compounds, especially polyphenolic compounds such as flavonoids and phenolic acid compounds in jujube, which have strong antioxidant and anti-inflammatory effects [21].

The pairing of ginger and jujube has a synergistic effect and integrates their respective pharmacological effects.

5. Study on the Mechanism of Action of Guizhi Decoction with Gegen in the Treatment of CSR

5.1 Anti-inflammatory and Analgesic Effects

Inflammatory response is a protective response of the body's immune system to injury or infection in the body. The inflammatory response in CSR mainly involves the tissues and structures around the cervical nerve roots, which typically show a localised response of pain or fever; a systemic response of headache, neck stiffness, prolonged general malaise and pain; and an immune response of increased inflammatory markers such as C-reactive protein. Stimulated by pathological factors, damaged nerve roots and surrounding tissues release inflammatory mediators, such as interleukin-1 (IL-1), prostaglandin E2 (PGE2), tumour necrosis factor-α (TNF-α), etc. IL-1β and TNF-α are able to activate inflammation-related signalling pathways, including NF-κB, MAPK, and other pathways, which can promote the transcription and expression of inflammatory genes, and are also able to activate immune cells such as monocytes or macrophages, T cells and B cells, promoting their value-added and the release of inflammatory mediators [22-23]. Li Yang et al [24] investigated the effects of Guizhi decoction with Gegen on apoptosis and inflammatory factors in fibrocytic ring cells of rabbits with cervical spondylosis model, and found that compared with the blank group and the model group, the expression of TNF- mRNA and IL-1 mRNA in the group of Guizhi decoction with Gegen was decreased, while the expression of Bcl-2 mRNA was elevated, so Guizhi decoction with Gegen may inhibit apoptosis by suppressing the expression of inflammatory factors and modulating the expression level of apoptosis-related factors. expression levels to inhibit apoptosis and inflammatory responses, thereby delaying disc degeneration and playing a role in protecting the intervertebral disc. Chen Huibin [25] et al. found that Guizhi decoction with Gegen could effectively reduce the pain perception of CSR rats, significantly improve their pain symptoms, and improve their tolerance of forelimb pain, and suggested that its mechanism may involve the regulation of SIRT1/NF-κB-p65 and BDNF/TrkB signalling pathways, which in turn reduces inflammatory responses and pain sensitivity..

5.2 Improvement of Microcirculation

The vertebral artery of the cervical spine is one of the important blood vessels supplying the cervical spine and the surrounding nerve tissues. When the cervical spine undergoes degenerative diseases, bone spur formation or disc herniation, and the nerve root is compressed, it may lead to insufficient blood supply or reduced local blood flow of the vertebral artery, which in turn leads to nerve root ischemia. It was found that Guizhi decoction with Gegen can reduce serum nitric oxide (NO) levels, increase serum endothelin (ET) levels, improve patients' vascular endothelial dysfunction, with the effects of vasodilatation and promotion of local blood circulation, and increase the oxygen supply and nutrient supply to the cervical muscles and neural tissues, so as to alleviate the local ischemic and hypoxic state [26-27].

5.3 Regulation of Immune Function

Clinical studies have confirmed that the nucleus pulposus of the intervertebral disc is immunoreactive [28]. As the disc degenerates, the nucleus pulposus material may herniate or rupture, compressing the nerve root. In the case of a ruptured disc, the nucleus pulposus material is exposed to the immune system. This material is normally isolated inside the disc, and the immune system sees it as ‘foreign’ and triggers an immune response. If disc degeneration and nerve root compression persist, a chronic inflammatory response develops, leading to continued immune system activation, and the continued autoimmune response leads to further tissue damage and neurological dysfunction, forming a vicious cycle [22]. Guizhi decoction with Gegen can regulate the body's immune function, enhance the immune system's ability to resist disease, reduce inflammation and injury caused by abnormal immune responses, and reduce autoimmune attacks and damage to the nerve roots by regulating the immune balance. The study of Dong Yongli et al [29] revealed the mechanism of action of Guizhi decoction with Gegen in anti-inflammatory immunity through a network pharmacological approach. The remedy exerts its immune anti-inflammatory effects by regulating a series of key target genes, such as serine/threonine protein kinase and interleukin 6, which intervene in the processes of binding to DNA and RNA, interaction with cytokine receptors, modulation of cytokine activity, regulation of enzyme activities, and anti-oxidative stress.

6. Guizhi Decoction with Gegen Combined with Other Therapies for CSR

6.1 Combined Acupuncture and Moxibustion Therapy

Acupuncture, as a safe and effective Chinese medicine therapy, can play an active role in the comprehensive treatment of CSR, such as by stimulating specific acupoints, relieving pain and numbness, relaxing muscles, and promoting the recovery of neurological function and other advantages, to help patients relieve their symptoms and improve their quality of life. Huang Bo et al [30] found that the CASCS score, quality of life, and nursing satisfaction of the study group (acupuncture Tianzong and Fengchi points combined with Guizhi decoction with Gegen treatment) were higher than those of the control group (conventional care). If Guizhi decoction with Gegen combined with warm acupuncture therapy is adopted on the basis of conventional western medicine treatment, needling Baihui, Daxi, Houxi, Sanyinjiao, Cervical Bairao, and Hangzhong can help to alleviate the patients‘ neck pain and numbness, and at the same time improve the aseptic inflammation, and enhance the cervical vertebrae's flexibility and mobility, which can promote the patients’ recovery and improve their quality of life [31]. Now, several studies have shown that the combination of Guizhi decoction with Gegen and acupuncture therapy for CSR can significantly improve the relevant clinical symptoms of patients, and the selection of acupuncture points and techniques are gradually enriched more.

6.2 Combined Orthopaedic and Massage Therapy

Orthopaedic Tuina is a kind of Chinese medicine manipulative treatment, which corrects the derangement of the cervical vertebrae and the surrounding tissues, improves the blood circulation, and reduces the pressure on the nerve roots, so as to achieve the effect of relieving the symptoms. Conventional massage methods include pushing, holding, moxibustion, pinching and shaking. By observing the six-step massage method (deep penetration to the skin, deep penetration to the veins, deep penetration to the flesh, deep penetration to the tendons, deep penetration to the bone joints, and relaxation and closure) combined with Guizhi decoction with Gegen for the treatment of CSR, Pan Xiaoqian [32] found that the combination of Guizhi decoction with Gegen for the treatment of CSR and the combined use of either the conventional massage method or the six-step massage method resulted in a favourable clinical therapeutic effect and safety. However, compared with combining conventional massage therapy, combining the six-step massage method can better relieve the pain level, more favourable to the recovery of cervical spine function, and more obviously improve the symptoms and signs. The six-step massage method may play a more positive role in supporting the positive and correcting the imbalanced state of muscles and bones. Sun Sidong et al [33] concluded through their study that the combination of Guizhi decoction with Gegen and cervical chiropractic has significant effects in improving neck health, effectively relieving patients' neck and shoulder pain, helping to restore cervical spine function, eliminating activity limitation, and having the comprehensive therapeutic effects of dispersing cold and relieving muscle, warming yang and transforming dampness, and relieving pain and relieving tendons.

6.3 Combined Traction Therapy

Traction therapy is a common non-surgical treatment for CSR. It stretches the cervical vertebrae through mechanical force, increases the intervertebral space, reduces the compression of disc herniation on the nerve root, relieves pain, numbness and other related symptoms, regulates the nutrient supply of the cervical disc, and promotes the repair of damaged tissues. The traction force should be gradually increased to avoid excessive traction leading to neck injury, pay attention to neck warmth during treatment, and closely monitor the patient's response, if there is any discomfort, the traction force should be adjusted in time or stop the treatment. According to Xiao Liangxing et al [34], Guizhi decoction with Gegen has a reinforcing effect on the efficacy of traction, which can improve the neck problems from multiple aspects, not only solving the metabolic problems of the intervertebral discs themselves, but also strengthening the neck muscle strength, so as to better protect the spinal nerves of the neck.

6.4 Combined Microneedle Therapy

Small-needle knife treatment for CSR can precisely loosen the adhesions at the nerve roots, effectively reduce the highly bulging disc, improve the mobility of the cervical spine, eliminate local inflammation, and promote tissue repair, which is a common clinical treatment method. Modified Guizhi Plus Gegen Decoction combined with mini-needle knife for CSR can further enhance the effect of treatment, has obvious advantages, and is worth promoting [35].

In addition, Guizhi decoction with Gegen combined with extracorporeal shock wave therapy, external application of traditional Chinese medicine, minimally invasive surgical treatment, and emotion therapy [36] all have good results. Among them, emotion therapy is particularly important in the treatment of CSR. Painful stimuli and sensory abnormalities often have a negative impact on patients' mental health, triggering emotional problems such as anxiety and depression. For patients with chronic pain, physical discomfort is not only physiological suffering, but may also cause a range of emotional and psychological responses.

7. CSR Prevention and Health Care

‘Treating the disease before it occurs’ is one of the core ideas of Chinese medicine health care, which first appeared in the Yellow Emperor's Classic of Internal Medicine, and refers to taking measures to prevent disease before it occurs in order to maintain good health. This philosophy emphasises the concept of prevention and positive health, which focuses on the harmony of human beings in the natural environment, and advocates holistic health rather than a single means of treatment. This is different from the Western medical concept of ‘treating the already sick’, which focuses on treating diseases after they have occurred [37,38].

7.1 Correct Posture

Maintaining good sitting, standing and sleeping postures can help prevent CSR. Correct sitting posture should be with feet flat on the floor, back straight, spine naturally curved, shoulders naturally drooping and head neutral; correct standing posture should be with feet naturally separated, slightly wider than shoulder width, centre of gravity evenly distributed over the feet, head straight, field of vision looking straight ahead, shoulders relaxed, back straight and arms naturally drooping; correct sleeping posture should be with pillows of moderate height, keep spine naturally curved, legs naturally straight and relaxed, avoid crossing legs; it is recommended to choose a slightly more comfortable mattress. Sleeping posture should choose a pillow of moderate height, keep the natural curvature of the spine, legs naturally straight and relaxed, avoid cross legs, it is recommended to choose a slightly harder mattress. Poor posture can lead to excessive bending or straightening of the cervical vertebrae, compressing the nerve roots and thus triggering CSR.

7.2 Combination of Work and Rest

Maintaining the same posture for a long period of time, especially with a low or crooked head, will lead to strain of the neck muscles and herniation or deformation of the cervical discs, which will compress the nerve roots and trigger cervical spondylosis. It is recommended to take regular breaks, get up and move around every 30-60 minutes, do some simple stretching exercises to relax the neck muscles, and also carry out some neck and back muscle trainin.

7.3 Cold Protection and Warmth of the Neck

The neck is exposed to the outside of the body for a long

period of time and is susceptible to external evils. When the neck is exposed to cold, blood vessels will constrict, resulting in slowing down of local blood circulation and muscle stiffness and spasm, and the muscle spasm will compress the cervical nerve roots, causing the symptoms of CSR. Therefore, focusing on keeping the neck warm is an important measure to prevent CSR.

8. Conclusion

In conclusion, Guizhi decoction with Gegen can regulate nerve function, improve blood circulation, anti-inflammatory and analgesic effects through multiple pathways, so as to achieve the purpose of treating CSR. When using Guizhi decoction with Gegen for treatment, the dose and composition of the drug should be adjusted according to the specific conditions of the patient, and attention should be paid to the interaction between traditional Chinese medicine and western medicine to avoid adverse reactions. The treatment of CSR may take a long time, and comprehensive treatment should be adhered to in order to avoid the recurrence of symptoms. It has been found that Guizhi decoction with Gegen combined with other therapies can target the lesions more precisely, enhance the efficacy, regulate the whole body, alleviate the symptoms, and significantly improve the quality of life and functional status of patients. Moreover, Chinese medicine has the advantages of fewer toxic side effects, better efficacy, simple operation and affordability compared with western medicine, which makes it suitable for long-term use.

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