

Research Progress of Tonifying Kidney and Promoting Blood Circulation in the Treatment of Steroid-induced Necrosis of Femoral Head

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ABSTRACT

Osteonecrosis of the femoral head is a common disability disease of the hip joint in China, and osteonecrosis of the femoral head caused by hormone factors is the most common, which is related to the gradual increase in the utilization rate of glucocorticoids in recent years. It is a refractory disease in orthopaedics with a poor prognosis. For this disease, the treatment of traditional Chinese medicine has certain advantages. In view of this, the author reads, analyzes and summarizes its materials by searching China Journal full-text Database and Wanfang Database. This paper reviews the mechanism and clinical research progress of tonifying kidney and activating blood circulation in the prevention and treatment of steroid-induced osteonecrosis of the femoral head, hoping to provide help for the clinical treatment of hormone-related osteonecrosis of the femoral head.

1. Introduction

Osteonecrosis of the femoral head is caused by the interruption or damage of the blood supply of the femoral head due to various factors, resulting in the death of osteocytes and bone marrow components^[1], which leads to local structural changes of the femoral head, collapse of the femoral head, hip pain and functional limitation^[2]. Steroid-induced avascular necrosis of the femoral head is the most common, accounting for 57% of the total incidence of non-traumatic osteonecrosis of the femoral head^[3]. The occurrence of steroid-induced

osteonecrosis of the femoral head is caused by a variety of mechanisms, because the pathogenesis has not been completely determined, so the disease can not be cured^[4]. At present, there are mainly some surgical treatments, such as osteotomy, bone grafting, decompression, hip arthroplasty and so on. Although the operation is gradually mature, it is harmful to the body, and the probability of postoperative complications is high. Patients' acceptance of the operation is low. Therefore, non-operative treatment has been paid more and more attention. Traditional Chinese medicine has been recognized by patients in the treatment of the disease. Clinical guidelines

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also mention that traditional Chinese medicine can effectively prevent the occurrence of osteonecrosis of the femoral head and alleviate the existing symptoms^[5]. Improve the quality of life of patients. Among them, the method of tonifying kidney and promoting blood circulation plays an important role in steroid-induced osteonecrosis of femoral head. This paper discusses its research content in recent years.

2. Understanding of TCM Theory on Steroid-induced Femoral Head Necrosis

In the classical records of traditional Chinese medicine, there is no exact term of “osteonecrosis”. According to the clinical manifestations and characteristics of the disease, osteonecrosis of the femoral head can be attributed to “bone erosion, bone arthralgia” and so on. The compilation of notes on Ling Su Festival said, “the evil of deficiency is also deep in the body.”... Then rotten flesh and rotten muscle is pus, internal injury bone, for bone erosion. Hormone-induced warm heat belongs to the “pure yang product” in traditional Chinese medicine, which is similar to the traditional Chinese medicine “aconite, cinnamon” and so on. Hormone application, resulting in temporary hyperactivity of kidney yang, “hyperactivity of yang is yin absolute”, hyperactivity of yang is bound to burn true yin, bone is not nourished, and then osteonecrosis occurs. Taking hormones for a long time can produce “strong fire”. “always ask about yin and yang should be like a big theory” said: “the qi of strong fire is declining.” Strong fire to eat gas, gas to eat less fire, “strong fire” will damage the vital energy of the human body. Spleen is the acquired foundation, vital qi injury, weak temper, unable to promote blood line, re-feeling the evil of wind, cold and dampness, stagnation of qi and blood, stopping for blood stasis; spleen soil failure, spleen yang weakness, fluid accumulation into dampness, accumulation of dampness into phlegm, phlegm blocking pulse channel, blood stasis, phlegm and blood stasis, qi and blood can not reach the extremities, muscles and muscles have nothing to be proud of. Blood stasis caused by phlegm, phlegm caused by blood stasis, and the combination of phlegm and blood stasis are the most important pathological manifestations in the early stage of the disease. The kidney is the congenital foundation, the main bone produces pulp, hormone is medicine evil, damage the essence of the kidney, lack of kidney essence, bone marrow biochemical passive, bone marrow decreased, bone loss nourishment, no growth, development, repair. Kidney essence also depends on spleen qi and blood nourishment, spleen and stomach weakness can not ascend clear, kidney essence does not

give birth, premature decline, bone withering and waste hair as the disease.

3. Relationship between Tonifying Kidney and Activating Blood and Steroid-Induced Osteonecrosis

The method of tonifying the kidney and invigorating the blood is a flexible application of the method of tonifying the kidney and invigorating the blood, which belongs to the treatment method of “attacking and tonifying at the same time”^[8]. Professor Zhang Daning firstly proposed “kidney deficiency and blood stasis” and “tonifying the kidney and invigorating the blood”^[9]. Hormonal femoral head necrosis is a state of deficiency. Kidney deficiency is the key source of the disease, and “where evil comes from, its Qi must be deficient”. The two are intertwined and affect each other. The “Suwen - Inverse Regulation” says: “Kidney is also water, and born in the bone, kidney does not produce, then the marrow can not be full ... the disease is called bone paralysis”, indicating that the occurrence of bone disease is mostly related to kidney deficiency, the kidney is the main bone marrow, the kidney collects essence, essence produces marrow, marrow nourishes bone, the three are a whole, if the kidney essence is lacking, the marrow transformation and production of no source, the bone is not nourished, then If there is a lack of kidney essence, the marrow has no source of growth and the bone is not nourished, the development is slow. Therefore, the fundamental method is to nourish the kidney. Blood stasis is a pathological factor, especially in paralytic diseases, where the mechanism of blood stasis accompanies the entire development of the disease, and the theory of Chinese medicine mentions that if blood stasis does not go, it is difficult to support kidney energy. Therefore, the treatment of injury diseases lies in the activation of blood. Blood activation includes two kinds, one is “eliminating blood stasis” and the other is “generating new blood”. The method of tonifying the kidney and invigorating the blood is often used to invigorate the blood and move the qi, such as astragalus, Chuanxiong, Danshen, etc., with insects and vines, such as the dragon, scorpion, etc., to break the blood can also solve the function of hormone medicine evil, and at the same time with the medicine to benefit the liver and kidney, such as Eucommia, sequestra, mulberry, can not only benefit the liver and kidney, but also strengthen the tendons and bones. The origin of the disease is in the bone, the source is in the blood, and the root is in the kidney^[10], therefore, the treatment of tonifying the kidney and activating the blood is its basic treatment.

4. Study on the Mechanism of Tonifying Kidney and Activating Blood in Treating Steroid-induced Femoral Head Necrosis

4.1 Intravascular Coagulation Theory

The most common pathological changes of steroid-induced osteonecrosis of the femoral head are intravascular coagulation and thromboembolism. The study found that the patient's hemorheology is abnormal^[11]. In the hypercoagulable state, the blood flow is slow or even interrupted, the blood supply is insufficient, and osteonecrosis occurs. Duan Weifeng et al.^[12] by injecting hormone and endotoxin, the model of osteonecrosis of the femoral head was made and fed with Bushen Quyu recipe suspension in the traditional Chinese medicine group. The experiment shows that Bushen Quyu recipe can alleviate the hypercoagulable state of blood circulation and increase the blood supply of the femoral head. Promote the repair and regeneration of the femoral head. Ran Lei et al.^[13] successfully induced rabbit model of steroid-induced osteonecrosis of the femoral head and fed Quyu Shengxin prescription for 12 weeks. Venous blood samples were collected for hemorheological measurement, including erythrocyte aggregation index, plasma viscosity, hematocrit, and so on. The experimental results show that Quyu Xin recipe can effectively improve blood viscosity, inhibit platelet aggregation and alleviate hemorheology. Intravascular coagulation is the direct cause of osteonecrosis. Tonifying the kidney and activating blood circulation can not only activate blood but also promote blood circulation. However, its specific molecular mechanism and gene expression are not clear, which is only proved by some hematological indicators. Therefore, it is necessary to carry out in-depth discussion.

4.2 Bone Marrow Mesenchymal Stem Cell Differentiation Theory

Bone marrow mesenchymal stem cells (BMSc) is a kind of stem cells with multi-directional differentiation potential, which has the characteristics of self-proliferation and differentiation. It is widely used in tissue engineering technology to repair local osteonecrosis, slow down the progress of disease and improve the quality of life. Some experiments have shown that the proliferation and directional differentiation ability of BMSc decrease due to the necrosis of femoral head caused by hormones. Zhang Ying et al to cultivate good bone marrow mesenchymal stem cells as the experimental object, the dry concentration of kidney-tonifying and blood-activating drugs and femoral head necrosis Yu

capsule water extract dissolved in the experimental object, through MTT to observe the drug regulation of BMSc. The results showed that the expression of BMP-2, Osteonin, Runx-2, OPN and ALP in the experimental group was significantly increased. It can be concluded that Bushen Huoxue medicine combined with Yushui extract of femoral head necrosis can effectively improve the proliferation ability of Ambuscade and increase osteogenic differentiation. Yu et al. obtained the serum containing Bushen Huoxue Decoction by feeding the mouse model. The serum containing different concentrations was used to regulate BMSc. The ALP activity of BMSc was quantitatively analyzed by 4 - nitrophenyl phosphate disodium salt (PNPP) azo method, and the deposition of calcium salt was analyzed by alizarin red staining method. Meanwhile, the osteogenic differentiation gene of MSc was detected by fluorescence quantitative method. Finally, the experimental data show that Bushen Huoxue Decoction promotes osteogenic differentiation of BMSc by enhancing ALP activity, and it can also be concluded that Bushen Huoxue Decoction promotes osteogenic differentiation and mineralization of BMSc.

4.3 Osteoporosis Theory

Long-term use of large doses of hormones can cause osteoporosis. Some studies have shown that glucocorticoid can inhibit the activity of osteoblasts, enhance the activity of osteoclasts and inhibit the absorption of osteoclasts, which not only destroys the structure of the femoral head, but also inhibits its bone turnover^[19,20]. Some scholars have pointed out that excessive hormones can inhibit intestinal calcium absorption and increase renal calcium excretion to affect calcium balance and develop into osteoporosis^[21]. Xu Haibin et al.^[22] used Xianlinggubao capsule combined with calcium D to give the rat model. It is suggested that both of them may effectively improve bone metabolic index and bone structure, promote the activity of osteoblasts and accelerate local bone repair and remodeling by increasing the numerical expression of TGF β 1, p-Smad2/3 and Smad4 and inhibiting Smad7. Li Zhimin et al.^[23] the model experiment of osteonecrosis of the femoral head in rabbits showed that Bushen Huoxue decoction could significantly improve the structural and mechanical indexes of steroid-induced femoral head, reduce bone mass loss, enhance bone hardness and density, and alleviate osteoporosis. prevent osteonecrosis. The method of tonifying the kidney and activating blood circulation is also used as a method for the treatment of osteoporosis, which has a significant improvement in the structural mechanics of bone, but the stress point and load-bearing mode of animals are different from those of

human beings. Whether this method has the same curative effect for patients in the later stage, further comparative study is needed.

4.4 Lipid Metabolism Disorders

One of the causes of steroid-induced osteonecrosis of the femoral head is the disorder of lipid metabolism. At present, it is believed that the use of hormones leads to an increase in blood lipids, resulting in microvascular fat embolism and fat deposition in osteocytes^[24]. Hormones can promote the differentiation of bone marrow mesenchymal stem cells into adipocytes, reduce the differentiation of osteoblasts, and induce osteonecrosis of the femoral head. Liang Xuezheng^[25] used network pharmacology and bioinformatics as theoretical guidance to understand the active components and disease specific targets of Bushen Huoxue capsule, followed by KEGG signal pathway enrichment, and then selected the regulation of lipid metabolism and angiogenesis as the research direction. In the experiment, the experimental group was fed with Bushen Huoxue capsule, and it was found that the protein level of VEGFA in the drug group was higher, while the protein level of PPARG was lower in each group. The data show that Bushen Huoxue capsule can promote angiogenesis and inhibit its adipogenic differentiation. The disorder of lipid metabolism is mainly manifested in the early stage of the disease, and this method has a good effect on balancing lipid homeostasis. However, the depth of the research is insufficient and the specific mechanism is unknown.

4.5 Theory of Osteocyte Apoptosis

Osteocyte apoptosis is one of the most recognized causes of this disease at present. Studies have shown that the use of glucocorticoids can increase the death of osteoblasts and osteocytes and destroy the mechanical sensation of the bone cell network^[26]. Bone trabeculae are sparse, bone mass is reduced, and osteonecrosis occurs. Xu Xilin^[27] used the rabbit model of osteonecrosis of the femoral head and gave Huogu injection and Guanxinning injection to detect the expression of caspase-3 protein. Caspase-3 family plays an important role in transmitting the signal of apoptosis. As a result, both of them inhibit cell apoptosis from multiple targets to achieve bone repair, but the inhibition and repair ability of the method of tonifying kidney and activating blood circulation is stronger than the simple method of activating blood circulation. Zhou Zhengxin et al.^[28] after intragastric administration of Gubitongxiao granule, apoptosis was detected by TUNEL method. The results suggested

that Gubitongxiao granule could effectively inhibit cell apoptosis by reducing blood viscosity, inhibiting platelet aggregation and improving local microcirculation. The method of tonifying kidney and promoting blood circulation is based on the theory of “deficiency from blood stasis”. It has a strong effect on the inhibition of osteocyte apoptosis, but apoptosis is regulated by a variety of different genes and protein synthesis. This method is not clear, and still needs a lot of research.

5. Clinical Study on Treating Steroid-induced Osteonecrosis of Femoral Head by Tonifying Kidney and Activating Blood

Based on the basic pathogenesis of deficiency and blood stasis, the method of tonifying the kidney and promoting blood circulation has become the basic treatment of steroid-induced osteonecrosis of the femoral head. Liu Jinbao et al.^[29] included 80 patients with ARCO stage I and II steroid-induced osteonecrosis of the femoral head, which were divided into Bushen Huoxue capsule treatment group and Xianlinggubao control group. Harris, WOMAC scale score and imaging examination were performed later. It is found that Bushen Huoxue capsule can relieve pain, improve the activity degree and range of hip joint, and effectively reduce the collapse rate of femoral head. Yang Chen et al.^[30] divided the patients with steroid-induced osteonecrosis of the femoral head into treatment group and drug group. The treatment group was treated with Tongluo Shenggu recipe and the control group was treated with high energy shock wave in vitro. Harris, SX-36 scale score and X-ray imaging examination of both hips were performed in the follow-up. According to the Harris scale, Tongluo Shenggu recipe can relieve hip pain, repair hip joint function and reduce deformities. From the SX-36 scale, the quality of life of patients has been improved due to the reduction of pain. Zhang Shenyao^[31] chose Bushen Jianpi Tongluo recipe to treat steroid-induced osteonecrosis of the femoral head. The clinical results showed that the prescription could improve the function of hip joint and increase local bone mineral density. Deng Changcui^[9] analyzed Professor Shen's experience in the use of drugs from the aspects of drug performance, classification and frequency of drugs for the first diagnosis and treatment of “arthralgia syndrome” during Professor Shen Fengjun's 3-year period. It is known that Professor Shen Fengjun uses most drugs for tonifying deficiency, activating blood circulation and removing blood stasis, mainly for *Angelica sinensis*, *Chuanxiong*, *Eucommia ulmoides*, *Shu Di*, etc., which is consistent with Professor Shen Fengjun's point of view, that is, kidney deficiency is the key and blood stasis is

the fundamental for arthralgia disease. Therefore, the treatment is tonifying the kidney and promoting blood circulation.

6. Conclusions

In recent years, with the non-standard use of hormones and the increasingly serious degree of aging, the number of patients with steroid-induced osteonecrosis of the femoral head is increasing. Steroid-induced osteonecrosis of the femoral head belongs to the field of bone arthralgia in traditional Chinese medicine, and kidney deficiency and blood stasis is the basic pathogenesis. Tonifying the kidney and activating blood circulation, as the basic treatment of steroid-induced osteonecrosis of the femoral head, has considerable curative effect in long-term clinical application. Tonifying the kidney and promoting blood circulation were deeply studied from the mechanisms of intravascular coagulation, disorder of lipid metabolism, differentiation of bone marrow mesenchymal stem cells, osteoporosis, osteocyte apoptosis and so on, in order to achieve the purpose of prevention and treatment. However, at present, the mechanism of steroid-induced osteonecrosis of the femoral head is not very clear, and the development of the disease is also a combination of multiple mechanisms, or cross-action, and its molecular mechanism is complex, so our later study can not be limited to a single mechanism. We have to look at it as a whole. From the perspective of evidence-based medicine, the insufficient sample size and observation time of many experiments may affect the experimental results. From the point of view of molecular biology, the signal pathway is also the research direction at present, and the specific mechanism of various signal pathways involved in the development of disease is not very clear. Most of the studies are animal and in vitro experiments, aiming at the potential targets of the pathway. From the perspective of genetics, gene polymorphism has become a research direction, to find the target of genes and diseases, to carry out individual treatment, and to achieve accurate treatment. In clinic, we should closely combine the current classification and staging, and explore the methods of diagnosis and treatment based on the idea of dialectical treatment. We should not use the method of tonifying the kidney and activating blood circulation, but should pay attention to the characteristics of the disease and be closely combined with the clinic.

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