

Study on The Treatment of Osteonecrosis of The Femoral Head Based on The Classic Theory of “Blood Stasis Removal - Regeneration - Bone Fusion”

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Abstract: Objective Based on Traditional Chinese Medicine (TCM) classics, this paper, by searching the literature on the treatment of femoral head necrosis with TCM, aims to explain the essence of the theory of “blood stasis removal - regeneration - bone fusion”, analyze the development of modern Chinese medicine in the treatment of osteonecrosis of femoral head (ONFH), and provide new ideas for the treatment of ONFH with integrated traditional Chinese and western medicine. **Methods** CNKI, PubMed, Wanfang and VIP databases were searched by computer to collect literature research on the theory of “blood stasis removal - regeneration - bone fusion” and the treatment of ONFH with integrated TCM Western medicine. Based on content analysis and bibliometric analysis, the modern integrated traditional Chinese and western medicine literature database of treating ONFH with the theory of “removing blood stasis and generating bone” was established and analyzed. **Results** Based on the theory of “blood stasis removal - regeneration - bone fusion”, this paper found that the TCM treatment of ONFH has the clinical effect of promoting blood circulation and removing blood stasis. The essence of the modern medicine of the theory of “blood stasis removal - regeneration - bone fusion” is to eliminate the microcirculation disorders caused by microvascular regeneration and hypoperfusion, so as to promote bone regeneration, which coincides with the treatment of ONFH by western medicine. **Conclusions** The theory of “blood stasis removal - regeneration - bone fusion” in modern Chinese medicine has a certain scientific and valuable value, which is worth more scientific research in the future.

1 INTRODUCTION

ONFH refers to a disease in which venous vessels are blocked or arterial blood supply is damaged, and the secondary increase of bone pressure leads to osteoblast necrosis, which leads to structural changes and collapse of the femoral head, and ultimately leads to hip joint pain and dysfunction (Wei-dong, Yong-qiang & Liang, 2016). There are different opinions on the pathogenesis of ONFH. Most scholars believe that the fundamental mechanism of ONFH may be related to the blood flow disturbance caused by blood flow in the blood vessels (Carmen, Adina & et al., 2018), but the exact etiology and pathogenesis have not been fully clarified. It is an important method to improve the hemorheology of femoral head and promote the repair of damaged bone cells. In ancient Chinese medicine, blood stasis was not only the direct cause of disease formation, but also the key to treating disease. In Qing Dynasty, Shiduo Chen summarized the process of fracture healing into three stages: “blood stasis removal”, “regeneration” and “bone consolidation” (Lei-lei, Xiao-bo, Guo-ju & et al., 2016), which can be applied to guide the treatment of ONFH with integrated traditional Chinese and western medicine. By searching the literature on the treatment of ONFH with modern TCM, the research on the

mechanism of the treatment of ONFH with TCM guided by the theory of “blood stasis removal - regeneration - bone fusion”. This research aims to provide new methods and new ideas for the treatment of ONFH with integrated traditional Chinese and western medicine.

2 CLARIFICATION OF ONFH

2.1 The definition of TCM

The exact name of ONFH is not directly recorded in traditional Chinese medicine, but some descriptions of “Gubi”, “Gushi” and “Guwei” are consistent with the pathogenesis, symptoms and location of ONFH. In *Suwen Chang Ci Jie Lun*, Gubi was described as a bone disease that “the body was too heavy to lift, and the bones ached”. In *Pipa Lun*, it is recorded that Gushi is caused by the restriction among five elements and spleen diseases affect kidney diseases, leading to “bone weakness, bone marrow emptiness”, and the symptom of “foot inability to walk”.

2.2 Pathogenesis of TCM

“Blood stasis” is the pathologic core of all diseases and the

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key to treatment, which is basically the consensus of doctors. *Warriors of the Yuan Dynasty: Luo Chuang Sun Shanghou* proposed that Qi can drive blood to flow around the body, and blood usually does not stay in one place to accumulate. However, if a fall occurs, the blood will lose its original regularity and stop accumulating at the injury site. According to the *Annals of Arthralgia Syndrome*, “poor blood flow inside or outside the blood vessels, which stays in the local area, resulting in poor local blood flow and loss of muscle vein support, leading to Arthralgia syndrome”. Therefore, removing blood stasis should be taken as the treatment method in syndrome differentiation and treatment, and a hypothesis should be put forward that all incurable diseases may be caused by doctors who are not good at removing blood stasis by removing blood stasis.

3 THE THEORY OF “BLOOD STASIS REMOVAL - REGENERATION - BONE FUSION”

3.1 Classic Theory Basis

Suwen Tiaojing pointed out that the meridian is not only the intermediary of organs, but also the way to run Qi and blood. The formation and change of various diseases are based on the imbalance of Qi and blood. According to Yang Yi Da Quan: “... we should first activate the blood to remove blood stasis. If the blood is not active, the blood is not stasis, and the bones are not connected... we should activate the blood to remove stasis, and new bones are formed”. To put it simply, if the veins are not unobstructed, there will be stasis; if blood stasis is formed, new blood will be difficult to flow. If new blood cannot flow, bone is difficult to regenerate. Vice versa. Therefore, the theory of “blood stasis removal - new birth - bone combination” has been gradually developed and improved on the basis of combining the support of classical theories of TCM and the clinical efficacy of “removing blood stasis method”.

3.2 The History of Development

According to Zhiwen: the interpretation of Li Hezhen, “this is an attack on pathogens, and it should be timely stabbed into the blood to restore vital energy”, pointing out that blood stasis should be removed to restore vital Qi. Fu Qingzhu Gynecology recorded that, “...It is not known that new blood cannot be generated, old blood cannot be consumed, blood replenishing can generate new blood, and blood activating can drive old blood away”. It is proposed that new blood cannot coexist with old blood, when Qi is prosperous, new blood will rise automatically, accompanied by the natural decline of old blood and other stagnant substances. According to this book, the improvement of blood stasis syndrome is closely related to the formation of new blood. It is mentioned in Du Yi’s essay that, “there must be endless blood stasis in the meridians. If it is not removed, the newborn blood cannot flow...”. If blood stasis formed, it will affect the operation of the original blood and the formation and distribution of

new blood. The formation of new substances is the power of removing blood stasis. Therefore, removing blood stasis and collaterals can replenish the body, and Qi and blood are infused into the tendons, veins, flesh, skin, bones and pulp. The limbs can be restored with Qi and blood, and the function can be restored automatically (Xiang, Wei-zhuo, Jian-li & et al., 2018).

3.3 The Theory of “Blood Stasis Removal - Regeneration - Bone Fusion” and Modern Medicine

3.3.1. Understanding of TCM and Western medicine

At present, most TCM doctors mainly treat femoral head necrosis from the perspective of “Yu”, and believes that venous stasis plays a key role (De-xi, Xiu-yang, Kai-you & et al., 2009) (Chun-xiang, 2019) and “removing blood stasis” is the main treatment method. TCM “Xueyu” syndrome is a pathological state formed by the stagnation and local accumulation of “Xueyu” syndrome, the pathological product of the pathogenic factor “Xueyu” syndrome. According to the experimental results of classical theory of TCM and modern scientific research, the discussion of “Xueyu” in TCM is basically the same as the pathological study of modern medicine on “blood stasis”. The significance of the theory of “blood stasis removal - regeneration - bone fusion” corresponds to the elimination of pathological products, promoting vascular regeneration and blood supply repair, promoting the absorption of dead bone and the formation of new bone (Dewei, Feng & Benjie, 2020). The following will also be discussed from these three aspects.

3.3.2. The theory of “blood stasis removal – regeneration” and modern medicine

Previous studies (Zhenhua, Kangle & Xiangyang, 2017) (Liang, Junhai, Zhilie & et al, 2019) (Guicheng & Yongjun, 2019). have shown that vascular endothelial growth factor (VEGF) can promote vascular regeneration, improve microcirculation in necrotic areas, promote cell migration and so on, which can be used as one of the reference materials of “blood stasis removal – regeneration”. In addition, regulating the level of VEGF in bone is one of the potential strategies for treating damaged bone repair and promoting bone regeneration (Kun-chi, Xiong-gang, Jiang-tao & et al., 2019). Sun et al. (2021) took traditional Chinese medicine for removing blood stasis (such as Taohong and Chuanxiong, etc.) or prescriptions for removing blood stasis (such as Xuefu Zhuyu Tang and Taohong Siwu Tang, etc.) as examples, and selected 40 rabbits for experiments. They concluded that traditional Chinese medicine for activating blood circulation and removing blood stasis can promote angiogenesis and allogeneic of allograft bone. Chen et al. (2019) used the long bones of the limbs of newborn red rabbits and established a stable bone marrow stromal cell line. 24 big ear rabbits were randomly divided into the control group (normal saline group) and the experimental group (Jiawei Taohong Siwu Tang group), and it is found that 3, 5, 7, 14

days after treatment, the expression of vascular endothelial growth factor in experimental group was stronger than that in control group. It is suggested that Jiawei Taohong Siwu Tang can induce bone marrow stromal cells to divide into vascular progenitor cells, and promote the expression of related growth factors, which further indicates that TCM for activating blood circulation and removing blood stasis can promote fracture healing.

3.3.3. The theory of “blood stasis removal - bone fusion” and modern medicine

The guidelines for clinical diagnosis and treatment of adult femoral head necrosis (2019 version) (Fu-wen & Yu-bao, 2012) mentioned that the local formation of venous thrombosis in ONFH led to local ischemia, and femoral head collapse and subchondral fracture can be seen. The healing process of fracture can be simply described as the process of “blood stasis removal - regeneration - bone fusion” (Qiu-shi, Wei, Qing-wen & et al, 2013), which is a process of clearing necrotic tissue and repairing new parts. New bone formation and angiogenesis are interrelated processes. In the TCM treatment of bone diseases, removing blood stasis and generating new blood is one of the important principles of treatment. The effect of removing blood stasis helps to clear the blood stasis in the lesion, dredge the meridians, promote the recovery of blood circulation, and improve the hypoxia state. The neogenesis effect is mainly in promoting angiogenesis to improve blood supply, which together create a good internal environment for bone regeneration and bone healing. Sun et al. (2022) evaluated the Harris score, serum osteocalcin (BGP) and insulin growth factor-1 (IGF-1) before and after treatment in the treatment group (taking Huoxue Shenggu Tang) and the control group (only external blood stasis removal herbs) to evaluate the therapeutic effect of TCM. The results showed that the pain of affected parts in the treatment group was relieved after treatment. To sum up, the application of traditional Chinese medicine for activating blood circulation and removing blood stasis or (and) external application with the effect of activating blood circulation and removing blood stasis can effectively relieve ONFH pain, and can promote bone formation and growth in ONFH lesion areas by regulating bone metabolism.

4 MATERIALS AND METHODS

4.1 Literature Search

The clinical literature related to the efficacy of TCM in the treatment of osteonecrosis of the femoral head was retrieved, including CNKI (from 2010 to March 2022), PubMed (from 2010 to March 2022), Wanfang Data Knowledge Service Platform, VIP Chinese science and technology journal database, and the attached references. At the same time, through manual access to relevant magazines, professional materials and network information was also retrieved to add more detailed information. The search terms are “Traditional Chinese Medicine”, “Osteonecrosis of Femoral Head”, “huoxue”,

“quyu”, “shengxin”, and others.

4.2 Inclusion Criteria

- (1) Study type: randomized controlled trial or clinical controlled trial;
- (2) Subjects: ONFH patients;
- (3) Intervention measures: The treatment group, on the basis of the control group, was given TCM, other TCM treatments or some western medicine therapy as intervention measures;
- (4) Outcome index: Harris score of hip function.

4.3 Exclusion Criteria

- (1) Documents with inconsistent inclusion criteria;
- (2) Review, clinical research, experimental progress and other non-clinical efficacy studies;
- (3) Non-randomized controlled trial or clinical controlled trial;
- (4) Studies based on simple data statistics, small sample size, or evaluation method that are not rigorous enough.

4.4 Statistical Methods

RevMan 5.4 software was used for literature data integration and meta-analysis. For continuous data, the mean and standard deviation were extracted to calculate the weighted mean difference and 95% confidence interval.

5 RESULTS

5.1 The Clinical Literature Retrieval and Basic Characteristics

A total of 143 relevant articles were initially retrieved, and 37 duplicate articles were excluded through NoteExpress 3.2 software, 106 articles were obtained, 29 review articles, online pharmacological research articles, 41 articles unrelated to research content and 12 articles with inconsistent interventions were excluded, 24 articles were obtained. After reading the full text, 17 literatures without Harris score as outcome index were excluded, and a total of 7 literatures were finally included in the meta-analysis (Wojciech, Tomasz, Andrzejński & et al, 2022) (Peng & Ying, 2019) (Feng, 2014) (Jinlong, Haibo & Shaoqiu, 2019) (Zhi-yong, Jian-min & Yun-fei, 2017) (Mingwang, Yifei, Xing & et al, 2020).

5.2 Harris Score Meta-Analysis of Clinical Literature

In the seven articles included, 529 patients were included in the study, including 274 in the control group and 277 in the observation group, which showed the clinical efficacy of TCM in treating osteonecrosis of the femoral head. When Harris score was used as the outcome index, the above 7 studies were pooled and the heterogeneity test

showed statistical heterogeneity ($P < 0.00001$, $I^2 = 97\%$). The results showed that there was a significant difference in Harris score between the two groups after treatment ($Z = 23.91$, $P < 0.00001$), suggesting that the intervention of TCM in the treatment of osteonecrosis of the femoral head has a significant clinical effect.

6 DISCUSSION

It can be seen from the above analysis that the main mechanism described in the theory of “blood stasis removal - regeneration - bone fusion” is to promote angiogenesis and new bone formation by improving the blood flow status of femoral head vessels, which is very similar to the treatment and recovery process of femoral head necrosis in modern medicine. This theory refers to the application of “removing blood stasis” method, and the use of blood activating and stasis removing drugs to achieve the purpose of removing blood stasis, so that the blood circulation is normal. According to the relevant clinical research literature on the intervention of TCM in modern medical treatment of ONFH, and by comparing the hip joint function evaluation system represented by Harris score between the observation group and the treatment group, this paper proves that this method is effective, scientific and feasible, and more intuitively and clearly shows the clinical efficacy of TCM in treating ONFH. The results of this paper provide a new idea and direction for the future treatment of ONFH with integrated traditional Chinese and western medicine.

7 CONCLUSION

The theory of “blood stasis removal - regeneration - bone fusion” refers to the use of drugs to promote blood circulation and remove stasis in the complexions, so that the blood can follow the original path, regenerate new blood, dredge the meridians, and achieve the balance of Qi, blood, Yin and Yang. The theory of ONFH treatment in modern Chinese medicine has a certain scientific and valuable value, which is worth more scientific research in the future.

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