

## Effect and Mechanism of Traditional Chinese Medicine HuoLou Gukang Pill Combined with Simvastatin on Steroid-induced Necrosis of Femoral Head

### Abstract:

**Aims:** To explore the effect and mechanism of traditional Chinese medicine HuoLou Gukang pill combined with simvastatin on steroid-induced necrosis of femoral head.

**Methods:** A total of 130 patients with steroid-induced necrosis of femoral head treated in our hospital from January 2016 to April 2017 were randomly divided into control group and study group. Each group had 65 cases. Control group were treated with simvastatin, patients in study group were treated with traditional Chinese medicine HuoLuo GuKang pill on the basis of control group. Before and after treatment, patients were tested for adiponectin, TNF- $\alpha$ , blood lipid and blood glucose. Harris score and VAS score were also measured.

**Results:** There was no significant difference in adiponectin, TNF- $\alpha$ , blood glucose, CH, TG, HDL-C and LDL-C between two groups before treatment ( $P>0.05$ ). After treatment, the levels of adiponectin and HDL-C in study group were significantly higher than those in control group ( $P<0.05$ ), but the levels of TNF- $\alpha$ , blood glucose, CH, TG and LDL-C in study group were significantly lower than those in control group ( $P<0.05$ ). There was no significant difference in Harris score and VAS score between two groups before treatment ( $P>0.05$ ). The Harris score of study group was significantly higher than that of control group after treatment ( $P<0.05$ ). The VAS score of study group was significantly lower than that of control group ( $P<0.05$ ). After follow-up comparative analysis, there was no significant difference between Harris score and VAS score in study group ( $P>0.05$ ), but there was significant difference in control group ( $P<0.05$ ). The efficacy of two groups was analyzed based on Harris scores: The total effective rate was 96.9% in study group and 86.2% in control group ( $P<0.05$ ). The efficacy of two groups was analyzed based on VAS scores: The total effective rate of study group was 95.4%, significantly higher than that of control group (84.6%), and the difference was statistically significant ( $P<0.05$ ). **Conclusion:** The treatment effect of Chinese medicine HuoLou Gukang pill combined with simvastatin on steroid-induced necrosis of femoral head is better than that of simvastatin. Chinese medicine HuoLou Gukang pills combined with simvastatin can intervene the development of steroid-induced necrosis of femoral head effectively, prevent malignant progress and reduce incidence of patients by reducing blood lipid and improving hemodynamic mechanism, thus it is worthy being popularized and applied.

**Keywords :** Simvastatin; HuoLou Gukang pills; Steroid-induced necrosis of femoral head; Treatment ; Mechanism

### Introduction

Steroid-induced necrosis of femoral head is very common in clinic and is one of the most difficult diseases in orthopedics <sup>[1]</sup>. Most patients were young adults aged 30-50 years old, and the disease progressed rapidly. If they did not take proper treatment measures, about 80% patients would suffer from femoral head collapse, dysfunction of hip joints and even disability within 1-3 years. Steroid-induced necrosis of femoral head is difficult to recover and has a high disability rate. Most patients need to take hormones for a long time, which has irreversibly injured femoral head in the long run <sup>[2-3]</sup>. It is considered that <sup>[4]</sup> excessive long-term use of hormones can lead to abnormal lipid metabolism, resulting in steatosis and necrosis of osteocytes, which may be the pathogenesis of steroid-induced necrosis of femoral head. Because patients are young, service life of prosthesis is limited, many patients with osteonecrosis involving proximal femur, replacement mechanism of bone necrosis persists, and the prosthesis prone to loosening, it is generally believed that artificial joint replacement is not the ideal treatment on steroid-induced necrosis of femoral head. At present, there is no special remedy to treat steroid-induced necrosis of femoral head. In recent years, statins lipid-lowering drugs become a hot research topic in prevention of steroid-induced necrosis of femoral head. Statins (Such as simvastatin, lovastatin and pravastatin, etc.), inhibitors of methylglutaryl coenzyme A reductase (HMG-CoA reductase), became the primary drug for lipid-lowering therapy in the late 1980s <sup>[5]</sup>. Chinese medicine HuoLou Gukang pill is a kind of Chinese patent drug composed of Myrrh, Angelica, Astragalus, Chuanxiong, Drynaria, Eupolyphaga,

Frankincense, Salvia, Polygonum multiflorum, Antlers, Millettia, Rehmanniae, Pberetima and other Chinese herbal medicines. In recent years, the treatment effect of traditional Chinese medicine HuoLou Gukang pill combined with simvastatin on steroid-induced necrosis of femoral head was satisfactory in our hospital. This study summarizes and analyzes the effect of traditional Chinese medicine HuoLou Gukang pill combined with simvastatin on steroid-induced necrosis of femoral head, in order to reveal its therapeutic mechanism.

## **1 Material and Methods**

### **1.1 Normal information**

A total of 130 patients with steroid-induced necrosis of femoral head treated in our hospital were selected as cases from January 2016 to April 2017. Their clinical symptoms are mainly pain in thighs, hips and knees, claudication, dislocation of hip joint and tenderness around hip joint. Inclusion criteria were: ① all patients should be in accordance with diagnostic criteria<sup>[3]</sup> steroid-induced necrosis of femoral head. In special inspection of hip joint, "4" test, independent single leg and Arey's syndrome experiment was positive; ② all patients had a history of taking hormonal medications, patients and their families had right to information and consent to treatment before enrollment. Exclusion criteria were: ① patients with malignant tumors or other more serious somatic diseases; ② steroid-induced necrosis of femoral head due to other causes; ③ patients and their families did not agree to treatment. All 130 patients underwent X-ray examination according to the International Society of Bone Circulation International Staging Methods, including 90 cases of stage I, 30 cases of stage II and 10 cases of stage III. They were divided into study group and control group by random number table method. Each group had 65 cases. There were 23 males and 22 females in study group. The patients' ages ranged from 29 to 73 years with an average of  $38.3 \pm 1.5$ , and their courses ranged from 3 months-5 years with an average of  $3.4 \pm 0.7$ . There were 22 males and 23 females in control group. The patients' ages ranged from 28 to 72 years with an average of  $38.1 \pm 1.8$ , and their courses ranged from 3 months-5 years with an average of  $3.2 \pm 0.6$ . The general characteristics of patients between two groups did not differ significantly ( $P > 0.05$ ).

### **1.2 Methods**

The control group was given simvastatin tablets (Beijing Wansheng Pharmaceutical Co., Ltd.), each time 10 mg, once daily, orally, for 12 weeks.

The study group was given traditional Chinese medicine HuoLou Gukang pill based on control group (Zhengzhou Orthopedic Hospital hospital preparations, Henan medicine system Z20120433), each time 6g, 3 times a day, orally, 30d for a course of treatment, and even served 3 courses.

### **1.3 Observation index**

① Detection of adiponectin and TNF- $\alpha$ <sup>[5]</sup>: Venous blood was extracted from patients before and after treatment, placed 30min, centrifuged 560r/min for 20min, and took the serum at  $-80^{\circ}\text{C}$  to be tested. Adiponectin and TNF- $\alpha$  were measured using an ELISA kit (Assay Pro, USA). ② Blood glucose and blood lipids detection: Fasting blood lipids and blood glucose levels were measured using 7600 automatic biochemical analyzer (Hitachi, Japan).

### **1.4 Evaluation standard**

After 3 months of follow-up, Harris score and VAS score of 2 groups were compared.

① Harris score: Harris scores were performed on patients respectively before and after treatment. After treatment, it was judged according to the standard of the relevant literature. Cured: Harris scores were between 90-100, clinical symptoms of the patients disappeared, detection of trabecular bone under bursal reproduction area inspected by MRI, CT and X-ray examination had obvious signs of improvement or disappearance. Valid: Harris scores were between 70 and 89, the clinical symptoms of patients (such as joint dysfunction, pain and claudication) were significantly improved, lesion area in patients inspected by MRI, CT and X-ray examination were absorbed or stabilized. Invalid: Harris scores were less than 70 points, the patient's clinical symptoms and signs were improved, and results of MRI, CT and X-ray examination did not change.

② VAS score: A horizontal line was draw on paper, one end of the horizontal line is 0, indicating no pain, the other end is 10, indicating a sharp pain, and the middle part indicated varying degrees of pain. Let patients marked on the line according to their own feelings, indicating the degree of pain. Cured: Clinical

symptoms and signs disappeared, function returned to normal, and the improvement rate was higher than 90%. Markedly effective: Clinical symptoms disappeared or significantly reduced, signs improved significantly, function returned to normal, and the improvement rate was between 75%-90%; Valid: Clinical symptoms and signs were alleviated, but some symptoms and signs still remained, and the improvement rate was between 30%-75%. Invalid: Symptoms and signs did not change or worsen before and after treatment, and the improvement rate was less than 30%.

### 1.5 Statistical methods

All statistical analyses were performed using SPSS 21.0 software. Measurement data was used ( $\bar{x} \pm s$ ) and tested by student's t-test. Quantitative data was tested by  $X^2$ . A p-value of  $<0.05$  was considered statistically significant.

## 2 Results

### 2.1 Comparison of adiponectin, TNF- $\alpha$ , blood glucose and blood lipid levels in two groups before and after treatment

There was no significant difference in adiponectin, TNF- $\alpha$ , blood glucose, CH, TG, HDL-C and LDL-C between two groups before treatment ( $P>0.05$ ). After treatment, the levels of adiponectin and HDL-C in study group were significantly higher than those in control group ( $P<0.05$ ), but the levels of TNF- $\alpha$ , blood glucose, CH, TG and LDL-C in study group were significantly lower than those in control group ( $P<0.05$ ). (Table 1)

(Table 1) Comparison of adiponectin, TNF- $\alpha$ , blood glucose and blood lipid levels in two groups before and after treatment ( $\bar{x} \pm s$ )

Group	Study group (n=65)	Control group (n=65)	T	P
<b>Adiponectin /mg·L<sup>-1</sup></b>				
Before treatment	4.95±0.25	5.02±0.21	-1.341	0.276
After treatment	9.55±0.14	6.01±1.02	6.457	0.000
<b>TNF-<math>\alpha</math> / <math>\mu</math>g·L<sup>-1</sup></b>				
Before treatment	1.82±0.67	1.79±0.73	0.209	0.821
After treatment	0.88±0.11	1.52±0.64	7.253	0.011
<b>Blood sugar /mmol·L<sup>-1</sup></b>				
Before treatment	6.47±1.32	6.36±1.18	0.903	0.727
After treatment	5.07±0.31	6.08±0.76	7.415	0.042
<b>CH/mmol·L<sup>-1</sup></b>				
Before treatment	5.11±0.86	5.07±0.49	0.205	0.493
After treatment	4.13±0.17	4.87±0.55	8.009	0.015
<b>TG/mmol·L<sup>-1</sup></b>				
Before treatment	1.85±0.12	1.77±0.36	0.594	0.653
After treatment	0.66±0.03	1.66±0.32	12.672	0.005
<b>HDL-C/mmol·L<sup>-1</sup></b>				
Before treatment	0.72±0.72	0.85±0.53	0.604	0.593
After treatment	1.67±0.04	1.21±0.36	11.007	0.004
<b>LDL-C/mmol·L<sup>-1</sup></b>				
Before treatment	3.15±0.18	3.08±0.63	0.165	0.398
After treatment	1.88±0.23	2.69±0.46	6.051	0.037

### 2.2 Comparison of Harris and VAS scores in 2 groups

There was no significant difference in Harris and VAS score between two groups before treatment ( $P>0.05$ ). After treatment, the Harris score of study group was significantly higher than that of control group ( $P<0.05$ ), and the VAS score of study group was significantly lower than that of control group ( $P<0.05$ ). (Table 2)

(Table 2) Comparison of Harris and VAS scores in 2 groups ( $\bar{x} \pm s$ , score)

Group	Harris score		VAS score	
	Before treatment	After treatment	Before treatment	After treatment
Study group	67.46±3.62	94.52±2.17	7.55±0.84	4.21±0.07

(n=65)				
<b>Control group</b> (n=65)	67.51±2.96	76.78±4.03	7.57±1.02	6.94±1.14
<b>T</b>	0.606	5.127	0.713	6.089
<b>P</b>	0.913	0.024	0.526	0.022

### 2.3 Comparison of follow-up score in two groups

After follow-up comparative analysis of scores, there was no significant difference between Harris and VAS scores in study group ( $P>0.05$ ), but there was significant difference in scores of control group ( $P<0.05$ ). (Table 3)

(Table 3) Comparison of follow-up score in two groups ( $\bar{x} \pm s$ , score)

Group	After treatment	After follow-up	T	P
<b>Harris score</b>				
Study group (n=65)	94.52±2.17	93.09±1.87	0.209	0.453
Control group (n=65)	76.78±4.03	43.27±3.95	5.082	0.031
<b>VAS score</b>				
Study group (n=65)	4.21±0.07	4.17±0.06	0.337	0.416
Control group (n=65)	6.94±1.14	9.12±1.07	4.956	0.034

### 2.4 Comparison of efficacy in 2 groups

The efficacy of two groups was analyzed based on Harris scores: The total effective rate was 96.9% in study group and 86.2% in control group ( $P<0.05$ ). (Table 4)

The efficacy of two groups was analyzed based on VAS scores: The total effective rate of study group was 95.4%, significantly higher than that of control group (84.6%), and the difference was statistically significant ( $P<0.05$ ). (Table 5)

(Table 4) Comparison of efficacy with Harris score in two groups (Case)

Group	Case	Cured	Valid	Invalid	Total effective rate/%
Study group	65	52	11	2	96.9
Control group	65	43	13	9	86.2
Z					-3.257
P					0.003

(Table 5) Comparison of efficacy with VAS score in two groups (Case)

Group	Case	Cured	Markedly effective	Valid	Invalid	Total effective rate /%
Study group	65	44	12	6	3	95.4
Control group	65	32	14	9	10	84.6
Z						-2.913
P						0.005

### Conclusion:

There was no significant difference in adiponectin, TNF- $\alpha$ , blood glucose, CH, TG, HDL-C and LDL-C between two groups before treatment ( $P>0.05$ ). After treatment, the levels of adiponectin and HDL-C in study group were significantly higher than those in control group ( $P<0.05$ ), but the levels of TNF- $\alpha$ , blood glucose, CH, TG and LDL-C in study group were significantly lower than those in control group ( $P<0.05$ ). There was no significant difference in Harris and VAS score between two groups before treatment ( $P>0.05$ ). After treatment, the Harris score of study group was significantly higher than that of control group ( $P<0.05$ ), and the VAS score of study group was significantly lower than that of control group ( $P<0.05$ ). After follow-up comparative analysis of scores, there was no significant difference between Harris and VAS scores in study group ( $P>0.05$ ), but there was significant difference in scores of control group ( $P<0.05$ ). The efficacy of two groups was analyzed based on Harris scores: The total effective rate was 96.9% in study group and 86.2% in control group ( $P<0.05$ ). The efficacy of two groups was analyzed based on VAS scores: The total effective rate of study group was 95.4%, significantly higher than that of control group (84.6%), and the difference was statistically significant ( $P<0.05$ ). The treatment effect of Chinese medicine HuoLou Gukang pills combined with simvastatin on steroid-induced necrosis of femoral head is better than that of simvastatin. This indicates that Chinese medicine HuoLou Gukang pills combined with simvastatin can intervene the development of steroid-induced necrosis of

femoral head effectively, prevent malignant progress and reduce incidence of patients by reducing blood lipid and improving hemodynamic mechanism, thus it is worthy being popularized and applied.

### 3 Discussion

Hormonal necrosis of the femoral head is often found in young and middle-aged. The course of disease is developing faster. If there is no effective treatment in time, the femoral head may collapse and cause hip dyskinesia. Patients should be treated with hip replacement after 3-4 years of diagnosis<sup>[6]</sup>. Replacement therapy of artificial hip joint has good effect in improving function and alleviating pain. However, due to large amount of daily activities, complications of subsidence, fracture, loosening may occur in the early total hip replacement, which required repeated refurbishment, causing patients suffer more<sup>[7-8]</sup>. At present, the use of hormone is the leading cause of non-traumatic hormone induced osteonecrosis in China. Steroid induced osteonecrosis of the femoral head, which is caused by hormones, is called aseptic osteonecrosis or avascular osteonecrosis. Its pathogenesis has not yet been fully elucidated, but the mechanism of disorder of lipid metabolism has been widely recognized<sup>[9-10]</sup>.

Kaushik AP et al<sup>[11]</sup> carried out a long-term follow-up study on patients with high-dose corticosteroids and oral statins. MRI and other imaging findings were used as evaluation criteria for osteonecrosis. It was found that only 3 patients had osteonecrosis, much lower than those reported in the literature (single glucocorticoid induced osteonecrosis of 3%-20%), suggesting that statins can prevent steroid induced osteonecrosis of the femoral head effectively.

Nozaki Y et al found<sup>[12]</sup> that pravastatin can inhibit steroid-induced osteonecrosis of the femoral head in rats. This may be pravastatin has the function of regulating lipid metabolism, can reduce the number of fat cells in femoral head bone tissue to achieve protection.

Chinese medicine HuoLou Gukang pill is composed of Myrrh, Angelica, Astragalus, Chuanxiong, Drynaria, Eupolyphaga, Frankincense, Salvia, Polygonum multiflorum, Antlers, Millettia, Rehmannia, Pberetima and other Chinese herbal medicines. Angelica can remove blood stasis and activate collaterals, moisten spleen and muscle, and enrich blood and activate blood, which is the most important medicine for enriching blood and activating blood. Chuanxiong can make qi-stagnation, promote blood circulation and relieve pain. Earthworm activates collaterals; Corydalis Corydalis activates blood and disperses stasis; Scorpion dispels wind and relieves pain; Astragalus improves immune system and enhances the immunity of human body; Salvia circulates blood and removes blood stasis. Modern medical research has found that<sup>[13]</sup> Angelica and Chuanxiong have the effects of correcting lipid metabolism disorder, improving capillary permeability, improving blood rheology and promoting the expression of vascular endothelial growth factor in femoral head indirectly. Antlers, Rhizoma Drynariae can enlarge the number of osteoblasts, inhibiting bone loss. All these drugs are used with the effect of activating blood circulation to dissipate blood, nourishing liver and kidney, relaxing vein and relieving pain. They also have the effect of repairing osteonecrosis, relieving the pain of hip joint effectively, promoting bone repair and improving the function of joint. However, the therapeutic effect of a single drug on steroid necrosis of femoral head is often poor in clinical.

This study used Chinese medicine HuoLou Gukang pill to intervent treatment based on simvastatin. Harris score analysis showed that the total effective rate and Harris score of study group were significantly better than those of control group; VAS score showed that the total effective rate and VAS score of study group were significantly different from those of control group. The results of the two methods, Harris score and VAS score, were very similar. This showed that the occurrence and development of HuoLou Gukang pill combined with simvastatin could inhibit steroid induced necrosis of femoral head. After comparing follow-up scores, we found that there was no significant difference between Harris score and VAS score in study group, compared with scores after treatment was not statistically significant ( $P < 0.05$ ). The results showed that Chinese medicine HuoLou Gukang pill combined with simvastatin could effectively interfere the malignant progress of steroid-induced femoral head necrosis. Adiponectin, a type of adipose-derived cytokine, is found mainly in body's adipose tissue. Adiponectin has effects of anti-atherosclerosis, improving insulin resistance and reducing hypolipidemic and blood glucose, which is a protective factor in inflammatory response. It is considered that<sup>[14]</sup> steroid induced necrosis of femoral head is associated with hyperlipidemia resulting from the use of a large number of hormones. A large amount of fat is accumulated in bone marrow cavity, causing venous return

to be blocked, which eventually causes liver to release fat embolus and attach to blood vessel wall. After thrombolytic releases a large number of inflammatory factors, permeability of blood vessels and interstitial fluid increases, resulting in increased pressure of intraosseous and joint, forming osteofascial compartment syndrome. The above situation further aggravates the occlusion of veins, leading to steroid-induced necrosis of the femoral head after a longer period of intraosseous ischemia. In addition, glucocorticoids can also make epiphyseal degeneration, resulting in bone fatigue and trabecular bone fracture, while increasing the rate of apoptosis of osteoblasts, increased osteoclast activity, and accelerated the occurrence of osteonecrosis. TNF- $\alpha$  is likely to be the main cause of hormonal necrosis of femoral head. Adiponectin has a strong biological role, can inhibit TNF- $\alpha$  and reduce the level of inflammatory factors in joints, thereby inhibiting the destruction of inflammation on joints, which plays an interfering role in occurrence of steroid-induced femoral head necrosis<sup>[15]</sup>. This study found that, compared with the control group, adiponectin of patients in study group with adiponectin increased significantly, but TNF- $\alpha$ , blood lipids and blood glucose decreased significantly. This suggests that traditional Chinese medicine HuoLou Gukang pill combined with simvastatin can competitively inhibit HMG-CoA reductase function to increase the content of adiponectin in body, so as to decrease the content of triacylglycerol and cholesterol in blood circulation, and then plays the role of lowering blood fat and blood sugar. At the same time, it can reduce the blood fat within thrombus formation, so as to alleviate vascular embolism, decrease intraosseous pressure and joint bursal pressure, ease damaged vascular bed and restore venous blood flow, but also alleviate fat deposition in bone cells to improve its necrosis and degeneration. In addition, traditional Chinese medicine HuoLou Gukang pill combined with simvastatin on steroid-induced necrosis of femoral head may also have the following mechanisms: ① It can alleviate high viscosity and high blood stagnation, and recover damaged capillaries. Chinese medicine HuoLou Gukang pill combined with simvastatin can effectively reduce LDL-C and increase sensitivity of platelet nitric oxide, reducing patient's blood and plasma viscosity, thereby reducing the deposition of platelet aggregation, and is conducive to the recovery of blood supply, reducing bone cell necrosis rate. ② It resists osteoporosis and promotes bone reconstruction. Traditional Chinese medicine HuoLou Gukang pill combined with simvastatin can maintain the role of bone volume, and reduce hormones caused by osteoporosis and necrosis. ③ The regulation of gene level induces an increase in expression of related anti apoptotic proteins.

In conclusion, Chinese medicine HuoLou Gukang pill combined with simvastatin can intervene the development of steroid-induced necrosis of femoral head effectively, prevent malignant progress and reduce incidence of patients by reducing blood lipid and improving hemodynamic mechanism, thus it is worthy being popularized and applied.

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