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Research progress of Xuefu Zhuyu decoction in treating angina pectoris of coronary heart disease

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Abstract: Coronary atherosclerotic heart disease (CHD) is one of the common chronic diseases. The clinical incidence of CHD angina pectoris (AP) is extremely high, and the mortality rate is also rising all year round. Xuefu Zhuyu Decoction (XZD) first appeared in "Yilin Gaicuo". It is a famous prescription for treating blood stasis syndrome. Current mechanism studies have shown that XZD can treat AP through multiple targets and multiple pathways, and can also reduce myocardial and arterial damage by interfering with CRP, hs-CRP, TNF-α, and IL-6 inflammatory mediators, and can also affect platelet-activating factor (PAF) to relieve inflammation. Coronary sclerosis and thrombosis etc. Clinical trials have shown that XZD treatment of AP patients can reduce the number of AP attacks, shorten the duration of AP, improve ECG performance, improve hemorheology indicators, improve TCM syndrome scores, reduce the levels of TC, TG, LDL-C and other indicators, and reduce adverse reactions Compared with conventional western medicine, it has fewer side effects and higher safety. This article summarizes relevant literature on XZD treatment of AP in recent years by CNKI, Wanfang, VIP, etc., and reviews its mechanism and clinical research, in order to provide reference for clinical XZD treatment and research on AP.

Coronary atherosclerotic heart disease (CHD) refers to heart disease in which the lumen is narrowed and blocked due to coronary atherosclerosis, and myocardial ischemia, hypoxia or necrosis occurs. It is one of the common chronic diseases in the world today. Studies have shown that[1], cardiovascular disease has become the leading cause of death, of which CHD mainly accounts for about 30% of the total number of deaths. Angina pectoris (AP) is a common type of CHD with a very high clinical incidence. According to the clinical epidemiological research survey, the most common syndrome of AP patients is blood stasis, accounting for about 78.63% [2]. Modern studies have shown that the pathogenesis of AP may be related to IL-6 enhancing local inflammatory response and inducing hepatocytes to synthesize CRP[3], HB-EGF in vascular smooth muscle cells and macrophages is highly expressed and promotes arteriosclerosis[4], MMP -9 digests fibrous membrane components to promote plaque rupture, and significantly increases expression in unstable plaque areas[5], CCL2 factor initiates inflammatory response, and promotes the formation

of atherosclerosis by inducing the release of inflammatory mediators[6]etc. . Patients often take anti-platelet aggregation drugs, β-receptor blockers, CCB, ACEI and other drugs in clinical practice, which can dilate coronary arteries, inhibit platelet aggregation and improve blood circulation, but long-term treatment may damage the nervous system and gastrointestinal tract. The effect of some patients continues to decrease after taking the medicine, and the treatment effect is not satisfactory[7]. With the continuous deepening of research on traditional Chinese medicine, traditional Chinese medicine has certain advantages in the prevention and treatment of CHD[8].

Xuefu Zhuyu Decoction (XZD) was found in "Yilin Gaicuo" written by Wang Qingren, a physician in the Qing Dynasty[9]. Dryness, safflower promoting blood circulation and dispelling blood stasis to relieve pain, is a king drug altogether. Radix Paeoniae Rubra and Rhizoma Chuanxiong help monarch drugs to promote blood circulation and remove blood stasis; Achyranthes bidentata promotes blood circulation to stimulate menstruation, removes blood stasis and relieves pain, draws blood downward, and is a ministerial drug together. Shengdi and Angelica nourish blood and nourish yin, clear heat and activate blood; Bellflower and Citrus aurantium, one rise and one fall, broaden the chest and promote Qi; Stagnant, so that the gas flow then the blood flow, the above are all adjuvant drugs. Platycodon grandiflorum can also carry medicine upwards, and also has the function of making medicine; licorice reconciles various medicines, and is also used as medicine. Modern pharmacological studies[10][11]show that this formula has the functions of anti-inflammation, anti-oxidation, and improving myocardial microcirculation blood perfusion and myocardial contractility, thereby increasing coronary artery perfusion, promoting the establishment of collateral circulation, and improving blood rheology, etc. effect. The current mechanism research shows that XZD can treat AP through multiple targets and multiple pathways, and can intervene in CRP, hs-CRP, TNF-α, IL-6 to reduce their expression, control inflammation, improve cardiovascular disease symptoms, and affect Platelet activating factor (PAF) relieves coronary atherosclerosis and thrombosis to reduce the incidence of AP. Clinical studies have shown that XZD for AP patients can reduce the number of AP attacks, reduce the duration of attacks, improve the patient's ECG performance, improve hemorheology indicators, improve patients' TCM syndrome scores, and reduce the incidence of adverse reactions. The author reviewed the mechanism and clinical research of XZD in the treatment of AP by searching CNKI, Wanfang, VIP and other relevant literature in recent years, in order to provide reference and ideas for clinical XZD treatment of AP.

1. Mechanism research

1.1 XZD Network Pharmacology Research

Based on network pharmacology research, TCMSP was used to retrieve "Peach Kernel", "Safflower", "Glycyrrhizae", "Fructus Citrus Citrifolia", "Red Peony", "Bupleurum", "Chuanxiong", "Greenwort", "Achyranthes bidentata" and "Dihuang" in Xuefu Zhuyu Decoction The active ingredients and targets of CHD were obtained by using databases such as GeneCards to obtain target genes related to CHD, and their intersection targets were screened. Ma Shuhui[12]etc prepared an atherosclerosis model in ApoE-/- mice for verification after analyzing components and targets. The results of GO functional enrichment analysis and KEGG pathway enrichment analysis were sorted and displayed according to the q value. The three items are positive regulation of phosphorus metabolism (q=7.43E-48), positive regulation of intracellular signal transduction (q=3.45E-47), positive regulation of cell movement (q=5.60E- 41), the HIF-1α signaling pathway ranked first. The LDL and TC of the mice in the high-fat model group were higher than those of the low-fat control group, and the HDL was lower than that of the low-fat control group (P<0.05); the LDL and TC of the mice in the low-dose gavage group and high-dose gavage group were lower than those in the

high-fat model group group, HDL was higher than that in the high-fat model group (P<0.05). The area of collagen fibers/total plaque area of aortic tissue in the low-dose gavage group and the high-dose gavage group was higher than that in the high-fat model group, and the total plaque area/vascular lumen area was lower than that in the high-dose model group. High-dose gavage The collagen fiber area/total plaque area of the aortic tissue of mice in the control group was higher than that of the low-dose gavage group, and the total plaque area/vascular lumen area was lower than that of the low-dose gavage group (P<0.05). The positive area of HIF-1α and VEGFR2 in aortic tissue/total plaque area of mice in low-dose gavage group and high-dose gavage group were lower than those in high-fat model group, and HIF-1α and VEGFR2 in aortic tissue of mice in high-dose gavage group The positive area/total plaque area was lower than that of the low-dose gavage group (P<0.05). It shows that the HIF-1αsignaling pathway is one of the core targets of XZD in the treatment of AP. XZD can reduce the area of atherosclerotic plaque and maintain the stability of the plaque by reducing blood lipids and inhibiting the HIF-1α signaling pathway, thereby effectively Treat AP.

1.2 XZD interferes with inflammatory mediators

Inflammation is a key factor in the occurrence of cardiovascular disease (Cardiovascular Disease, CVD). It can affect the progression of CVD by inhibiting growth factors, increasing catabolism and interfering with signal homeostasis[13] . Studies[14]have shown that XZD can reduce myocardial and arterial injury by intervening C-reactive protein (CRP), hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF--α) so as to achieve the purpose of treatment and prevention of AP.

1.2.1 CRP

CRP can directly reflect the inflammation of the body, and high concentration of CRP can promote the proliferation and advance of endothelial cells, promote the formation of atherosclerosis, and then lead to AP[15]. Clinical studies have shown that XZD can effectively reduce CRP. Jiang Wenjun[16] divided 80 patients into treatment group and control group. The treatment group was treated with western medicine combined with XZD. After the course of treatment, the effective rate of the treatment group was 90.0% higher than that of the control group, and the CRP index of the treatment group decreased significantly, indicating that XZD was effective in the intervention of CRP.

1.2.2 Hs－CRP

Hs-CRP is closely related to atherosclerosis. Inflammation can increase the level of hs-CRP, activate the complement system and damage the intima of blood vessels. Hs-CRP is generally regarded as a predictor of the development and prognosis of CHD[17]. 90 patients were divided into treatment group (n = 50) and control group (n = 40) by Xu Yingcai[18]for RCT test. The control group was given routine western medicine and the treatment group was given XZD combined with conventional western medicine. After treatment, it was found that the decrease of hs-CRP concentration in the treatment group was due to the control group, that is, XZD could effectively interfere with hs-CRP.

1.2.3 TNF－α

TNF-αbelongs to polypeptide inflammatory cytokines, which are secreted by activated mononuclear macrophages, which damage vascular endothelial cell system by adhering to vascular endothelial cells, enhance the function of blood coagulation and inhibit fibrinolysis, and are closely

related to CHD[19]. XZD can interfere with TNF- α in AP patients, and the effect is good. 70 patients with AP were divided into observation group (n=35) and control group (n=35) by Li Hongchao[20]. The observation group was treated with XZD and the control group was treated with routine western medicine. After treatment, it was found that the TNF-αindex of AP patients in the observation group was lower than that in the control group.

1.3 Anti-PAF activation

PAF is a bioactive phospholipid secreted by platelets and other inflammatory factors, which can bind to platelet receptors to activate platelets and promote coronary atherosclerosis and thrombosis. The level of its indexes indicates the severity of the patient's condition[21]. Liang Kun[22] divided 300 patients with AP into XZD group and control group. The control group was treated with routine western medicine, and the XZD group was treated with XZD combined with western medicine. After the course of treatment, it was found that the total effective rate of patients in the XZD group (88%) was significantly higher than that in the control group (66.67%), and the level of PAF in the XZD group was significantly lower than that in the control group.

2. Clinical trial study

2.1 Reduce the number of AP attacks

AP is characterized by paroxysmal precordial compression-like pain. Clinical studies have shown that AP patients treated with XZD can relieve the pain of AP and effectively reduce the number of AP attacks. Li Qi[23] divided 64 patients with AP into two groups. 32 patients in the control group were treated with estazolam, and the other 32 patients were treated with XZD plus subtractive prescription on the basis of the control group. The results showed that the clinical effective rate of the observation group was significantly higher than that of the control group, and the number of angina pectoris attacks of the observation group was significantly less than that of the control group. Zhao Shuyan[24] the study showed that the effective rate of XZD combined with trimetazidine in the combination group was 98.00%, which was higher than that in the routine group (84.00%), and the number of AP attacks in the combined group was much less than that in the routine group.

2.2 Shorten AP duration

The duration of attack in patients with AP is related to the treatment and prognosis of the patients. Liu Hongling[25] used isosorbide dinitrate tablets, metoprolol tartrate tablets and captopril tablets to treat AP patients in the control group, and the observation group was treated with XZD combined with western medicine. After treatment, it was found that the AP duration of AP patients in the observation group was 2.53 ±0.55min/ times less than 4.93 ±0.67min/ times in the control group. Xing Fang[26] divided the patients with AP into the control group (n = 53) and the observation group (n = 53). The patients in the control group were treated with routine western medicine and the patients in the observation group were treated with XZD combined with western medicine. The results showed that the total effective rates of the control group and the observation group were 62.26% and 81.13%, respectively. The duration of AP in the observation group was 3.25 ±1.01min/ times, which was better than that in the control group (5.48 ±1.67min/ times).

2.3 Improve ECG performance

ECG is an important method to discover and diagnose AP. Typical ischemic changes can be seen in most patients with AP. In leads dominated by R waves, ST segments depress 0.1mV, sometimes T waves are inverted, and recover after remission. Hou Lina[27] 74 patients with AP were divided into control group (n = 37) and treatment group (n = 37). The control group was treated with routine western medicine, and the treatment group was treated with XZD combined with conventional western medicine. ECG determined that the ECG ST T wave was normal: effective, the ECG ST segment increased ≥ 0.05mV after treatment, and the ECG ST segment did not improve after treatment. The total effective rate of ECG = (effective + effective) / the total number of cases in this group × 100% is the standard. After treatment, the control group was significantly effective 19, effective 10, ineffective 8, the total effective rate was 78.38% ($P < 0.05$), the treatment group was significantly effective 23, effective 13, ineffective 1, the total effective rate was 94.59% ($P < 0.05$). Shang Datao[28] , Hao Wenqing[29], Wang Xiaobai[30] all indicated that the level of ECG in patients with AP treated with XZD or combined with western medicine was better than that in the control group and before treatment, indicating that XZD is effective in the intervention of ECG in patients with AP.

2.4 Improving Hemorheological Indexes

In patients with AP, the blood flow slows down due to the increase of blood viscosity, which leads to the decrease of myocardial blood supply, myocardial ischemia and hypoxia and chest pain, and their hemorheological indexes can be changed obviously. The detection of hemorheological indexes generally includes whole blood specific viscosity, plasma specific viscosity, fibrinogen and prothrombin time. Song Yanqiu[31] 80 patients with AP were divided into the control group (n = 40) and the observation group (n = 40). The control group was treated with aspirin and the observation group was treated with XZD combined with aspirin. The total effective rate of the observation group was 97.5% (39/40), which was significantly higher than that of the control group (80.0%). The whole blood specific viscosity, plasma specific viscosity, fibrinogen L and index in the observation group were significantly lower than those before treatment and those in the control group, and the prothrombin time (s) in the observation group was significantly longer than that in the control group ($P<0.05$).

3. Conclusion

In summary, the mechanism and clinical application of XZD in the treatment of AP have proved that it is effective. Mechanism studies have shown that XZD can treat AP through multiple pathways such as IL6, AKT1, ALB, VEGFA, CCL2, EGF, IL1B, MMP-9, CASP3, MAPK1, AGE-RAGE, HIF-1, TNF, MAPK, NF-kB, PI3K-AKT, JAK-STAT, T cell receptor, B cell receptor, Toll-like receptor, and interfere with CRP, hs-CRP, TNF-α, IL-6 to control inflammation and improve the symptoms of cardiovascular disease. It can also affect platelet activating factor (PAF) to alleviate coronary atherosclerosis and thrombosis to reduce the incidence of AP. Clinical studies have shown that the application of XZD in AP patients can reduce the number of AP attacks, reduce the duration of seizures, improve ECG manifestations, improve hemorheological indexes, improve TCM syndrome scores, reduce the incidence of adverse reactions such as nausea, vomiting and palpitation, and effectively improve the quality of life and medication experience of AP patients. XZD combined with conventional western medicine has great advantages in the treatment of AP, which can make up for the inaccessibility of traditional Chinese and western medicine. With the increasing maturity of the treatment method of integrated traditional Chinese and western medicine,

it has become the clinical choice of the vast majority of doctors. For clinical research, it also needs to carry out large samples and population data collection to further improve the research quality and authority. As for the mechanism research, the theory that XZD interferes with AP through multi-targets, multi-pathways and multi-pathways, there are still some data inaccuracies, so more studies are needed to support it.

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