Cellular and Molecular Biology

Journal homepage: www.cellmolbiol.org

Effect of Qingre Jiedu Huoxue Huayu Recipe on blood stasis and toxin syndrome in patients with non-ST segment elevation acute coronary syndrome, serum Lp-PLA2, TNF- α, and PIGF expression level

Tan Zifu, Li Jiaquan*, Zhang Juan

Department of Cardiovascular Diseases,The National Hospital of Enshi Hubei 445000 China

ARTICLE INFO

Original paper

Article history:
Received: August 09, 2021
Accepted: November 29, 2021
Published: December 01, 2021

Keywords:
Huoxue Huayu Prescription; Lp-PLA2; TNF- α; PIGF

ABSTRACT

The pathological basis of non-ST-segment elevation acute coronary syndrome (NSTE-ACS) is severe coronary stenosis, unstable plaque erosion, and rupture, resulting in coronary blood flow reduction and myocardial ischemia, leading to acute thrombosis cardiovascular disease events. This subject intends to study the treatment of NSTE-ACS patients with blood stasis and toxin syndrome by Qingre Jiedu Huoxue Huayu Decoction, observe its clinical efficacy, and explore the effects of serum lipoprotein phospholipase A2 (Lp-PLA2) and tumor necrosis factor- α (TNF- α), the effect of placental growth factor (PIGF) expression. In this study, 100 patients with blood stasis and toxin syndrome of NSTE-ACS treated in the cardiovascular department of Enshi National Hospital from August 2020 to August 2021 were selected as the research object. They were randomly divided into traditional Chinese medicine comprehensive treatment groups and conventional western medicine control groups, with 50 cases. The conventional western medicine control group was treated with hydroclopidogrel tablets orally, and the comprehensive treatment group of traditional Chinese medicine combined with Qingre Jiedu Huoxue Huayu formula orally. The patients in both groups were treated for four weeks. The results showed that after treatment, the practical clinical rate of the comprehensive treatment group was significantly higher than that of the conventional western medicine control group. After treatment, the TCM syndrome score, angina pectoris attack duration, and angina pectoris attack frequency, myocardial zymogram index level, serum Lp-PLA2 and TNF of the two groups were measured- α. The levels of PIGF were significantly lower than those before treatment. The decline of the above indexes in the comprehensive treatment group of traditional Chinese medicine was significantly better than that in the control group of conventional Western Medicine ($P<0.05$). The incidence of MACE events in the TCM Comprehensive treatment group was significantly lower than that in the conventional western medicine control group ($P <0.05$).

DOI: http://dx.doi.org/10.14715/cmb/2021.67.4.14

Introduction

Acute coronary syndrome (ACS) is a group of clinical syndromes based on the rupture or erosion of coronary atherosclerotic plaque and secondary complete or incomplete occlusive thrombosis (1). It is a series of clinical symptoms including unstable angina pectoris, ST segment elevation myocardial infarction and non-ST segment elevation myocardial infarction (2). Most studies have shown that inflammatory response and inflammatory mediators play an important role in the rupture of unstable plaque. The increase of oxidized lipid, angiotensin, arterial pressure and blood glucose can bring inflammatory cell infiltration. In addition, the potential infection of vascular wall and the activation of immune response can promote plaque rupture. In the process of plaque rupture, there is an imbalance between inflammatory cells and normal tube wall cells, especially between activated macrophages and smooth muscle cells (3). Activated macrophages produce excessive metalloproteinases and secrete vasoactive substances and coagulation factors, resulting in vasoconstriction and thrombosis. Activated T lymphocytes produce proinflammatory cytokines such as interferon- γ. It can prevent the synthesis of extracellular matrix proteins (ECMP) such as collagen and elastin (4). The damaged smooth muscle cells also reduce the production of ECMP, weaken the superstructure of the tube wall, enhance the inflammation and immune response in the plaque,

*Corresponding author. E-mail: tanzf2021@163.com

make the fibrous cap on the plaque surface thinner, and the rupture of unstable plaque is induced by shear stress and wall penetrating pressure. Studies have shown that local or systemic inflammation of coronary artery plays an important role in the occurrence and development of as and its complications (5, 6). There are a large number of inflammatory cells in vulnerable plaque and plaque rupture. The activation of inflammatory response is the main factor leading to plaque instability, and the degree of inflammatory cell infiltration is closely related to the degree of plaque stability (7). Relevant markers have been used in the diagnosis, treatment and prognosis of ACS. The pathological basis of non-ST segment elevation acute coronary syndrome (NSTE-ACS) is severe coronary stenosis and unstable plaque erosion and rupture, resulting in coronary blood flow reduction and myocardial ischemia, leading to acute thrombosis and acute cardiovascular events (8). NSTE-ACS can progress to acute myocardial infarction or sudden death, which seriously threatens human life, health and quality of life.

Vascular endothelial growth factor (VEGF) is a growth factor that specifically promotes the mitosis of vascular endothelial cells. It can promote the proliferation of endothelial cells and accelerate the formation of new blood vessels (9, 10). At the same time, it can aggravate the aggregation, phagocytosis and secretion of various inflammatory factors of intravascular macrophages, so as to cause vascular injury and promote the formation, growth and rupture of as plaque (11). Placental growth factor (PIGF) is one of the members of VEGF family. PlGF plays an important role in the occurrence and development of atherosclerosis. It can promote the chemotactic aggregation of monocytes and macrophages promote inflammatory response, promote the progress of atherosclerosis, cause plaque instability and lead to the occurrence of ACS. Plasma PlGF level can be used as a biological marker of poor prognosis in patients with ACS. Lipoprotein associated phospholipase A2 (Lp-PLA2) is a newly studied inflammatory response mediator (12). In recent years, more and more evidence show that it can promote as and is a new inflammatory response marker in as. Lp-PLA2 is mainly synthesized and secreted by mature macrophages and lymphocytes and regulated by inflammatory mediators (13). Lp-PLA2 in human circulation exists in the form of binding to lipoprotein particles, of which 2/3 binds to low density lipoprotein (LDL), and 1/3 binds to high density lipoprotein (HDL) and very low-density lipoprotein (VLDL). In the early studies on Lp-PLA2, Lp-PLA2 was also called platelet activating factor acetylhydrolase (PAF-AH) because it can hydrolyze inflammatory factors such as platelet activating factor (PAF) and structurally related oxidized phospholipids, so it was considered to inhibit inflammatory response and even the formation of atherosclerosis (14). As an inflammatory factor, TNF-α directly leads to the acceleration of coronary atherosclerosis, and at the same time, it plays an important role in the pathophysiological process of coronary vascular disease (15). People have studied TNF-α in depth, and its role. The understanding of the mechanism is mainly in the following two aspects: first, TNF-α can cause cell necrosis and angiogenesis. This is because it can activate mononuclear macrophages, which can release a large amount of cytotoxicity after being activated (16). These toxic substances can directly cause cell necrosis, and necrotic cells will be repaired immediately, thereby promoting angiogenesis. Second TNF-α can cause coronary artery intima thickening and atherosclerotic plaque formation. This is due to TNF-α can stimulate the expression of endothelial cell adhesion molecules (17, 18). These adhesion molecules can release platelet growth factors from platelet endothelial cells and platelets, causing the proliferation of smooth muscle cells. The excessive proliferation of smooth muscle cells can cause coronary luminal stenosis and accelerate the occurrence of coronary atherosclerosis (19).

Studies have shown that patients with NSTE-ACS often have pathological conditions of multi-site plaque rupture, and a variety of markers of inflammatory reaction, thrombosis and coagulation system activation are increased, including lipoprotein phospholipase A2 (Lp-PLA2) and tumor necrosis factor-α (TNF-α), inflammatory factors such as placental growth factor (PIGF) are closely related to the instability of sclerotic plaque, and can be used as an important index to evaluate cardiovascular adverse events and prognosis (20). At this stage, percutaneous coronary intervention or drug-enhanced antithrombotic therapy are mostly used for the

treatment of NSTE-ACS (21). Antiplatelet therapy is the cornerstone of drug treatment of NSTE-ACS. The early use of antiplatelet therapy can effectively reduce the occurrence of thrombotic events and improve the prognosis of patients with NSTE-ACS. Traditional Chinese medicine believes that the theory of "blood stasis and toxin causing disease" and "blood stasis and toxin Conghua" is in line with the pathological mechanism of NSTE-ACS, and a series of compound traditional Chinese medicine preparations with detoxification and blood circulation have been proved to have definite clinical efficacy in the treatment of coronary heart disease and acute coronary syndrome. The purpose of this study was to observe the clinical effect of Jiedu Huoxue Recipe on patients with blood stasis and toxin syndrome of NSTE-ACS and its effect on serum Lp-PLA2 and TNF- α, In order to provide clinical basis for the treatment of NSTE-ACS.

Materials and methods

Basic data

All cases in this study were from 100 patients with blood stasis and toxin syndrome of NSTE-ACS in the cardiovascular department of Enshi National Hospital from August 2020 to August 2021. Understand the research content and enter the clinical trial after signing the informed consent.

The diagnostic criteria of Western medicine were formulated according to the guidelines for the diagnosis and treatment of non ST segment elevation acute coronary syndrome, and confirmed by ECG or echocardiography; The diagnostic criteria of TCM syndrome differentiation are formulated with reference to the research data of academician Chen Keji's team, that is, retrosternal pain, bitter mouth and dry throat, upset insomnia, chest tightness and palpitation, red face and fever, yellow red urine, secret stool knot, yellow or dry tongue coating, dark red tongue and astringent pulse.

45 ≤ age ≤ 70; It meets the diagnostic criteria of blood stasis and toxin syndrome of NSTE-ACS; the clinical data were complete, and they volunteered to participate in the study and signed the informed consent form.

Complicated with severe heart failure, severe hypertension and malignant arrhythmia; Complicated with serious primary diseases such as liver, kidney, hematopoietic system and malignant tumor; Coronary artery bypass grafting or percutaneous coronary intervention were performed within 3 months; Those who have allergy or clinical intolerance to the drugs in this clinical trial; Pregnant or lactating women.

Research methods

100 patients with blood stasis and toxin syndrome of NSTE-ACS treated in the cardiovascular department of Enshi National Hospital from August 2020 to August 2021 were selected as the research object. They were randomly divided into traditional Chinese medicine comprehensive treatment group and conventional western medicine control group, with 50 cases in each group. The conventional western medicine control group was treated with hydroclopidogrel tablets orally, and the comprehensive treatment group of traditional Chinese medicine combined with Qingre Jiedu Huoxue Huayu formula orally. The patients in both groups were treated for 4 weeks. The TCM syndrome score, angina pectoris score, myocardial zymogram index level, major adverse cardiovascular events (MACE), serum Lp-PLA2 and TNF were compared between the two groups- α、 PIGF level. The specific road map is shown in figure 1.

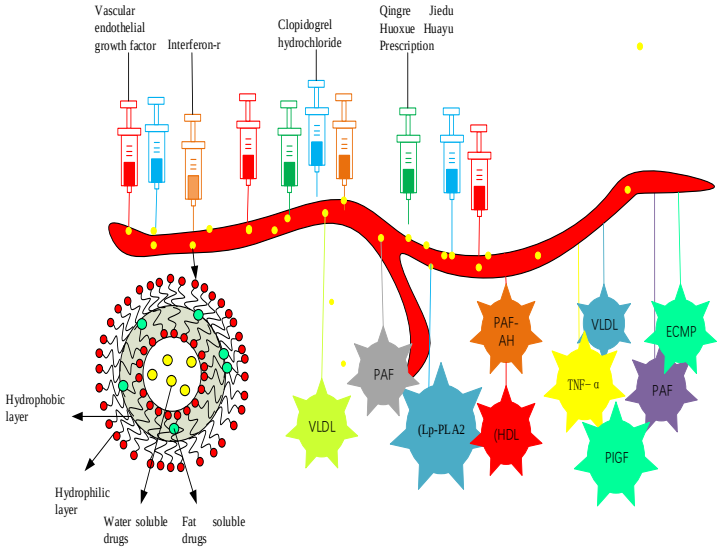

Figure1. Treatment schematic of NSTE-ACS

Index detection

TCM syndrome score and clinical efficacy criteria are formulated with reference to the guiding principles for clinical research of new traditional Chinese medicine. According to the quantitative standard of

TCM symptom classification, the TCM syndrome scores of the two groups before and after treatment were recorded. Efficacy criteria: significant effect: clinical symptoms and signs basically disappeared, and the efficacy index ≥ 70%; Effective: clinical symptoms and signs were improved, 30% ≤ efficacy index < 70%; Ineffective: clinical symptoms and signs are not significantly improved or even worsened, and the curative effect index is less than 30%, in which the curative effect index = (total score before treatment - total score after treatment) / total score before treatment × 100%。 Clinical effective rate = (number of markedly effective cases + number of effective cases) / total number of cases × 100%。

The incidence of angina pectoris in the two groups before and after treatment was recorded, including the frequency and duration of angina pectoris every week.

The levels of serum myocardial enzymes before and after treatment were measured by automatic blood analyzer, mainly including troponin T (cTnT), creatine kinase (CK) and creatine isozyme (CK-MB).

Serum Lp-PLA2 and TNF- α, PIGF level

Using double antibody sandwich enzyme-linked immunosorbent assay, venous blood samples of the two groups were collected at week 0 and week 24 respectively to detect serum Lp-PLA2 and TNF- α, PIGF expression level.

Statistical method

Using IBM SPSS 25.0 software, the measurement data are expressed by (mean± standard deviation), the t-test is used for inter group comparison, and the rank sum test can be used when the variance is uneven; The counting data were expressed by (frequency or frequency), the covariance test was used for baseline inequality, and the chi square test was used for inter group comparison. The difference was statistically significant (P<0.05).

Results and discussion

Comparison of basic conditions of patients

A total of 100 patients were included in this study, including 55 male patients, aged from 45 to 80 years, and 45 female patients, aged from 46 to 76 years. In the TCM Comprehensive treatment group, there were 50 patients, 26 female patients and 24 male patients, with an average age of 61.25 ± 6.83 years. In the conventional western medicine control group, there were 50 patients, 23 males and 27 females, with an average age of 61.8 ± 6.12 years; There was no significant difference in age and gender between the two teams (P > 0.05) (table 1).

Table 1. Comparison of age and sex; group (A), Number of people (B), Gender (male/ female) (C) and Age (years) (D)

A	B	C	D
TCM Comprehensive treatment group	50	24/26	61.25±6.83
Conventional western medicine control group	50	23/27	61.8±6.12
P	0.987	0.412	0.671

There was no significant difference between the two groups in the past diseases such as hypertension, type 2 diabetes, arrhythmia, heart failure and smoking history (table 2).

Table 2. Comparison of past medical history; Past history (A), TCM Comprehensive treatment group (B), Conventional western medicine control group (C)

A	B	C	P
Hypertension	16	15	0.443
Type 2 diabetes mellitus	14	12	0.341
Arrhythmia	6	7	0.758
Heart failure	4	3	0.675
Smoking history	14	15	0.889
PCI history	3	8	0.187

Comparison of TCM syndrome scores

It can be seen from the data in figure 2 and figure 3 that there is no statistically significant difference between the two groups in the details of symptom scores before treatment. Compared with before and after treatment, the scores of TCM comprehensive treatment group after treatment were less than those before treatment; After treatment, there was significant difference between the two groups in chest pain, chest tightness, palpitation, shortness of breath and other items, and the average value of the TCM comprehensive treatment group was lower than that of the conventional treatment group, indicating that the treatment effect of the TCM comprehensive treatment group was better than that of the conventional treatment group.

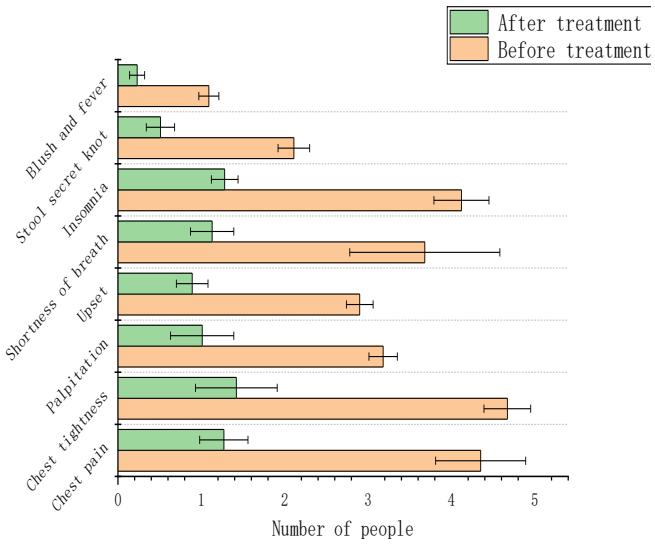

Figure 2. Comparison of TCM syndrome scores before and after treatment in TCM Comprehensive treatment group

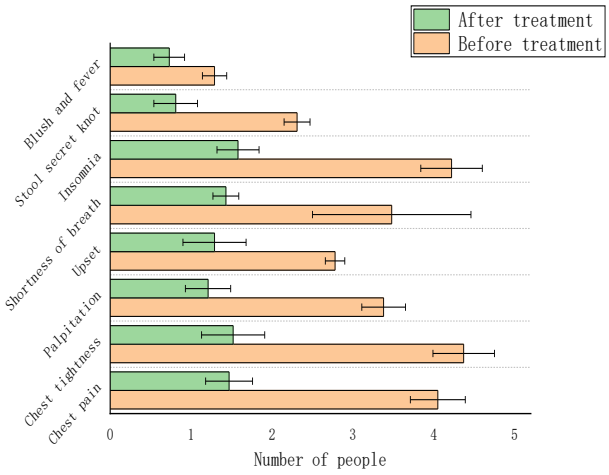

Figure 3. Comparison of TCM symptom scores before and after treatment in conventional western medicine control group

Comparison of angina pectoris attack

After treatment, the duration and frequency of angina pectoris in the two groups were significantly lower than those before treatment, and the decline of angina pectoris duration and frequency in the comprehensive treatment group of traditional Chinese medicine was significantly better than that in the control group of conventional Western Medicine. The specific results are shown in figure 4.

Comparison of myocardial zymogram indexes

After treatment, the levels of Serum cTnT, CK and CK-MB in the two groups were significantly lower than those before treatment, and the decline of Serum cTnT, CK and CK-MB in the comprehensive treatment group of traditional Chinese medicine was significantly better than that in the control group of conventional western medicine. See figure 5 for specific results.

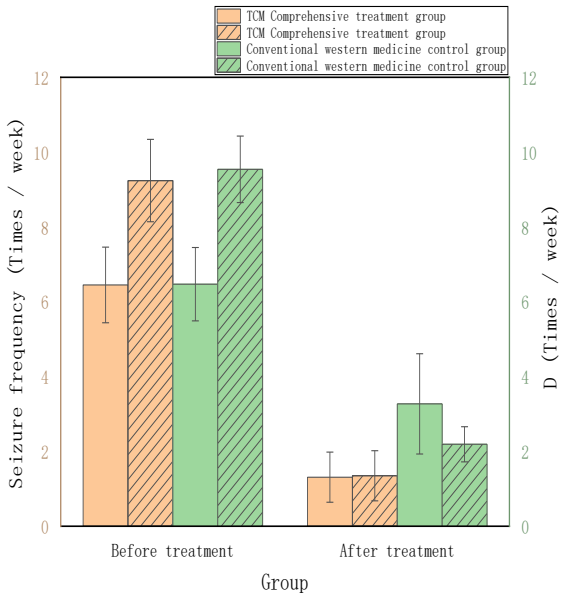

Figure 4. Comparison of angina pectoris attack between the two groups

Serum Lp-PLA2 and TNF- α, Comparison of PIGF levels

After the treatment, the serum levels of Lp-PLA2, TNF-α, and PIGF in the two groups were significantly lower than before treatment. The levels of serum Lp-PLA2, TNF-α, PIGF levels in the NSTE-ACS patients with stasis syndrome in the comprehensive treatment group of traditional Chinese medicine were significantly lower than those in the conventional western medicine control group. The specific results are shown in figure 6, figure 7, and figure 8.

Comparison of MACE events

There was no significant difference in the incidence of ischemic chest pain readmission, acute myocardial infarction, cardiogenic shock, heart failure and all-cause death between the two groups within 3 months of follow-up ($P>0.05$); The incidence of MACE events in TCM comprehensive treatment group was significantly lower than that in conventional western medicine control group ($P<0.05$). See table 3 for specific results.

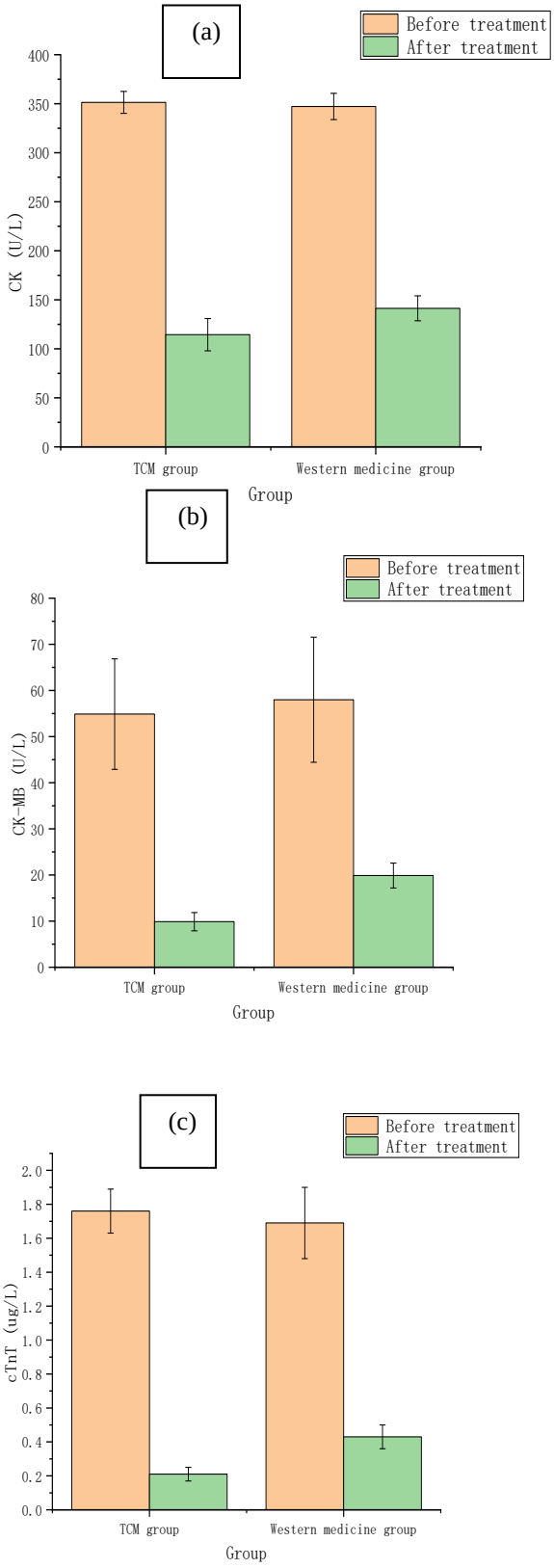

Figure 5. Comparison of myocardial zymogram indexes between the two groups

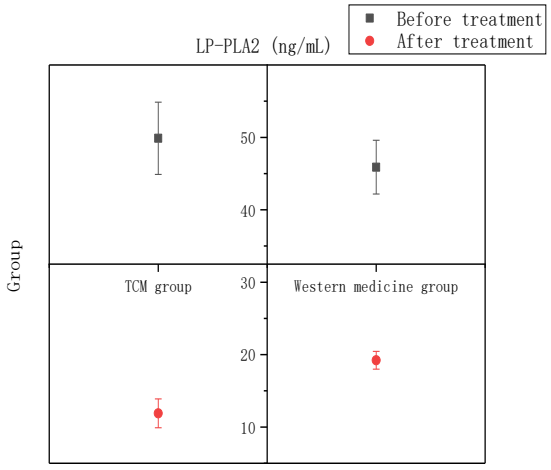

Figure 6. Comparison of serum Lp-PLA2 levels between the two groups

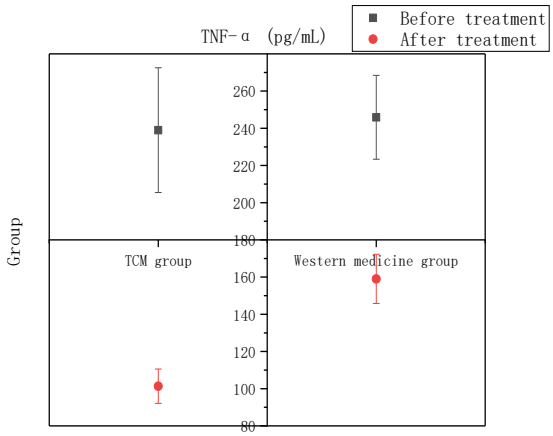

Figure 7. Serum TNF in two groups- α Level comparison

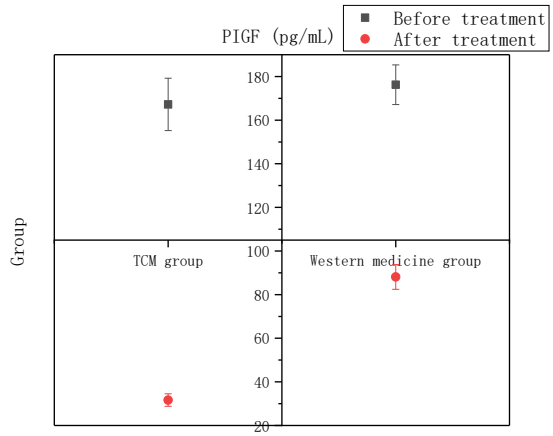

Figure 8. Comparison of serum PIGF levels between the two groups

Table 3. Comparison of MACE events between the two groups; TCM Comprehensive treatment group (A) and Conventional western medicine control group (B)

Group	A	B	P
Miocardial infarction	2	7	P<0.05
Cardiogenic shock	1	5	P<0.05
Heart failure	0	3	P<0.05
Death	2	4	P<0.05
Ischemic chest pain	2	5	P<0.05

NSTE-ACS is a common cardiovascular emergency in clinic (22). It has the characteristics of rapid onset, rapid progress, many complications and high mortality. It has a high probability of recurrence of cardiovascular events (22, 23). The main pathogenesis is the rupture of coronary atherosclerotic plaque, which makes platelet adhesion and activation, promotes vasoconstriction, forms thrombus, blocks the coronary artery, causes coronary artery stenosis to varying degrees, seriously affects the normal metabolic function of myocardial tissue, further reduces the blood supply of myocardium, and gradually presents the symptoms of myocardial ischemia and hypoxia (24). Therefore, how to effectively resist platelet aggregation and reduce blood viscosity is the key to the treatment of NSTE-ACS, and reducing long-term cardiovascular events is the long-term strategy for the treatment of NSTE-ACS (17, 22, 24).

The results showed that the clinical effective rate of TCM comprehensive treatment group was significantly higher than that of conventional western medicine control group. The incidence of MACE events in TCM Comprehensive treatment group was significantly lower than that in conventional western medicine control group (P<0.05); Moreover, the decline of TCM syndrome score, angina pectoris attack and myocardial enzyme spectrum index level in the comprehensive treatment group of traditional Chinese medicine were significantly better than those in the control group of conventional western medicine, indicating that Jiedu Huoxue decoction has a significant clinical effect in the treatment of patients with NSTE-ACS blood stasis syndrome, and can effectively improve TCM symptoms, angina pectoris attack duration and attack frequency, Reduce the index of Myocardial Zymogram and the incidence of mace. Inflammatory response plays an important role in the occurrence and development of NSTE-ACS. Changes in inflammatory factor levels are closely related to changes in NSTE-ACS. Lp-PLA2, also known as platelet activating factor acetylhydrolase, is a newly discovered vascular inflammatory factor that can cause arterial thrombosis and vascular inflammation. Related studies have found that Lp-PLA2 levels and NSTE-ACS patients have long-term major The risk of cardiovascular events is closely related and has important value in predicting the risk stratification of NSTE-ACS patients. TNF-α is the initiating factor of the inflammatory response. Under abnormal conditions, it promotes the body to synthesize and secrete CRP and other inflammatory factors. The function is overactive to increase the inflammatory response. It can also further induce the body's oxidative stress level dysfunction to aggravate myocardial injury and necrosis to a certain extent. PIGF can induce the synthesis of tissue factors in the body to accelerate the inflammatory response. It can also affect the stability of coronary atherosclerotic plaques and cause ischemia and eventually thrombosis. It is expected to become a risk predictor of risk stratification and cardiovascular adverse events in patients with NSTE-ACS. It can be seen that the detection of serum levels of Lp-PLA2, TNF-α, PIGF and other inflammatory factors can effectively reflect the changes in the development of the disease in NSTE-ACS patients to a certain extent, and is of great significance for the evaluation of clinical treatment effects. The results of this study showed that the level of serum Lp-PLA2, TNF-α and PIGF levels in the NSTE-ACS patients with blood stasis syndrome in the NSTE-ACS comprehensive treatment group was significantly lower than that of the conventional western medicine control group. Jieduhuoxue Decoction can effectively reduce NSTE-ACS blood stasis. The level of serum Lp-PLA2, TNF-α, PIGF in patients with syndrome can inhibit inflammation.

In summary, Jieduhuoxue Decoction has a significant clinical effect in treating NSTE-ACS patients with stasis syndrome. It can effectively improve the symptoms of TCM, the duration and frequency of angina pectoris, reduce myocardial enzyme spectrum indexes and the incidence of MACE, and also reduce serum Lp- PLA2, TNF-α, PIGF levels to inhibit inflammation, clinical application safety is high, and has a certain promotion value.

References

1. Linde JJ, Kelbæk H, Hansen TF et al. Coronary CT angiography in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2020; 75(5): 453-463.

2. Kofoed KF, Kelbæk H, Hansen PR et al. Early versus standard care invasive examination and treatment of patients with non-ST-segment elevation acute coronary syndrome: VERDICT randomized controlled trial. Circulation 2018; 138(24): 2741-2750.

3. Tarantini G, Mojoli M, Varbella F et al. Timing of oral P2Y12 inhibitor administration in patients with non-ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2020; 76(21): 2450-2459.

4. Zhao Q, Zhang T-Y, Cheng Y-J et al. Impacts of triglyceride-glucose index on prognosis of patients with type 2 diabetes mellitus and non-ST-segment elevation acute coronary syndrome: results from an observational cohort study in China. Cardiovasc Diabetol 2020; 19(1): 1-19.

5. Kazemi E, Zargooshi J, Kaboudi M et al. A genome-wide association study to identify candidate genes for erectile dysfunction. Brief Bioinformatics 2021; 22(4): bbaa338.

6. Bueno H, Rossello X, Pocock SJ et al. In-hospital coronary revascularization rates and post-discharge mortality risk in non–ST-segment elevation acute coronary syndrome. J Am Coll Cardiol 2019; 74(11): 1454-1461.

7. Jeong HS, Hong SJ, Cho S-A et al. Comparison of ticagrelor versus prasugrel for inflammation, vascular function, and circulating endothelial progenitor cells in diabetic patients with non–ST-segment elevation acute coronary syndrome requiring coronary stenting: a prospective, randomized, crossover trial. JACC Cardiovasc Interv 2017; 10(16): 1646-1658.

8. Ofori-Asenso R, Zomer E, Chin KL et al. Prevalence and impact of non-cardiovascular comorbidities among older adults hospitalized for non-ST segment elevation acute coronary syndrome. Cardiovasc Diagn Ther 2019; 9(3): 250.

9. Raziei Z, Kahrizi D, Rostami-Ahmadvandi H. Effects of climate on fatty acid profile in Camelina sativa. Cell Mol Biol 2018; 64(5): 91-96.

10. Chen J-Y, He P-C, Liu Y-H et al. Association of Parenteral Anticoagulation Therapy with Outcomes in Chinese patients undergoing percutaneous coronary intervention for non–ST-segment elevation acute coronary syndrome. JAMA Int Med 2019; 179(2): 186-195.

11. Zhao Q, Zhang T-Y, Cheng Y-J et al. Triglyceride-Glucose Index as a Surrogate Marker of Insulin Resistance for Predicting Cardiovascular Outcomes in Nondiabetic Patients with Non-ST-Segment Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. J Atheroscler Thromb 2020: 59840.

12. Bueno H, Rossello X, Pocock S et al. Regional variations in hospital management and post-discharge mortality in patients with non-ST-segment elevation acute coronary syndrome. Clin Res Cardiol 2018; 107(9): 836-844.

13. Bardaji A, Barrabés JA, Ribera A et al. Revascularisation in older adult patients with non-ST-segment elevation acute coronary syndrome: effect and impact on 6-month mortality. Eur Heart J Acute Cardiovasc Care 2020; 9(4): 358-366.

14. Stepien K, Nowak K, Skorek P et al. Baseline indicators of coronary artery disease burden in patients with non-ST-segment elevation acute coronary syndrome. Minerva Cardioangiol 2019; 67(3): 181-190.

15. Furtado RH, Nicolau JC, Guo J et al. Morphine and cardiovascular outcomes among patients with non-ST-segment elevation acute coronary syndromes undergoing coronary angiography. J Am Coll Cardiol 2020; 75(3): 289-300.

16. Pollack Jr CV, Davoudi F, Diercks DB et al. Relative efficacy and safety of ticagelor vs clopidogrel as a function of time to invasive management in non–ST-segment elevation acute coronary syndrome in the PLATO trial. Clin Cardiol 2017; 40(6): 390-398.

17. Darvishi E, Aziziaram Z, Yari K et al. Lack of association between the TNF-Î±-1031genotypes and generalized aggressive periodontitis disease. Cell Mol Biol 2016; 62(11): 63-66.

18. Sarma AA, Braunwald E, Cannon CP et al. Outcomes of women compared with men after non–ST-segment elevation acute coronary syndromes. J Am Coll Cardiol 2019; 74(24): 3013-3022.

19. Wang A, Kwee LC, Grass E et al. Whole blood sequencing reveals circulating microRNA associations with high-risk traits in non-ST-segment elevation

acute coronary syndrome. Atherosclerosis 2017; 261: 19-25.
20. Morici N, Savonitto S, Ferri LA et al. Outcomes of elderly patients with ST-elevation or non-ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention. Am J Med 2019; 132(2): 209-216.
21. Chan MY, Neely ML, Roe MT et al. Temporal biomarker profiling reveals longitudinal changes in risk of death or myocardial infarction in non–ST-segment elevation acute coronary syndrome. Clin Chem 2017; 63(7): 1214-1226.
22. Elzanaty A, Maraey A, Khalil M et al. Coronary computed tomography angiography vs. standard of care for evaluation of NSTE-ACS: a systematic review and meta-analysis. Euro Heart J 2021; 42(Supplement_1): ehab724. 0192.
23. Ercisli MF, Lechun G, Azeez SH, Hamasalih RM, Song S, Aziziaram Z. Relevance of genetic polymorphisms of the human cytochrome P450 3A4 in rivaroxaban-treated patients. Cell Mol Biomed Rep 2021; 1(1): 33-41.
24. Yamamoto K, Natsuaki M, Morimoto T et al. Coronary Artery Disease Without Standard Cardiovascular Risk Factors. Am J Cardiol 2021.