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Investigating the effectiveness and mechanism of Xinbao pill in micro vascular angina treatment

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Abstract: Coronary micro vascular dysfunction is attracting increasing attention, yet effective treatments remain inadequate. This study analysed the clinical efficacy and potential mechanisms of Xinbao pill in patients with microvascular angina (MVA). 200 MVA patients admitted from January 2020 to June 2021 were randomly divided into the control group (n = 100) and an observation group (n=100). Both groups received standard treatment, the observation group added Xinbao pill treatment. The clinical outcomes and angina symptoms were evaluated in both groups. The total clinical effective rate, angina symptom SAQ score, NO level, CFR and treadmill exercise test total exercise time of the two groups were considerably increased after treatment and the observation group was remarkably higher than the control group (P<0.05). Meanwhile, the number of exertional angina pectoris attacks, ET-1 levels, serum inflammatory factor levels and the maximum depression degree of ST segment were considerably lower after treatment, and the observation group was remarkably lower than the control group (P<0.05). The use of Xinbao pills in the treatment of MVA is significantly effective in reducing the symptoms of angina pectoris, reducing the levels of inflammatory factors and ET-1, which can further improve the efficacy and safety.

Keywords: Micro vascular angina, Xinbao pill, clinical efficacy, CFR.

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INTRODUCTION

Micro vascular angina (MVA) is a special type of stable angina pectoris, which refers to a group of clinical syndromes with exertional angina or angina-like symptoms, positive electrocardiogram exercise test, but normal coronary arteries or no obstructive lesions on coronary angiography (Smilowitz *et al.*, 2023). According to research statistics that there are approximately 112 million individuals with angina pectoris globally (Kunadian *et al.*, 2021). With rapid advancements in coronary heart disease diagnosis and treatment, particularly through widespread use of coronary angiography, fractional flow reserve (FFR) technology and intracavitary imaging, significant advancements have been made in the treatment of angina (Crea and Lanza, 2016; Sidik *et al.*, 2020). However, clinical practice continues to encounter difficulties: while some patients exhibit classic angina pectoris symptoms and noticeable ischemic alterations on the electrocardiogram, coronary angiography does not show substantial narrowing of the epicardial coronary arteries (Aldiwani *et al.*, 2021). Most of these individuals have coronary micro vascular disease (CMVD), which is defined by angina pectoris with a positive treadmill exercise test. However, the findings from coronary angiography are normal and coronary spasm can be ruled out (Chen *et al.*, 2023; Ullrich *et al.*, 2023).

Currently, the underlying mechanisms of micro vascular angina are not well understood and clinical management primarily focuses on alleviating symptoms and improving patients' quality of life to prolong survival and reduce the occurrence of cardiovascular complications (Yu *et al.*, 2023). Although drugs such as nitrates and β-blockers can provide some degree of symptomatic relief, they still have significant limitations. There are no data to support the prognostic improvement of nitrates in patients with chronic stable angina, while the vasodilatory effect of nitrates is independent of endothelial integrity, the mechanism of which has not been fully elucidated. β-blockers cannot be used in vasospastic angina and their efficacy in micro vascular disease is controversial. (Lanza *et al.*, 2014; Seitz *et al.*, 2022). The effect of calcium antagonists is even more controversial. Some studies have shown that they can reduce chest pain, but some studies have shown that they are ineffective (Suzuki, 2015). Research shows that intracoronary application of anisodamine has a significant effect on enhancing coronary no-reflow and sluggish blood flow during acute myocardial infarction and can improve myocardial perfusion, reduce coronary microcirculation spasm and dredge coronary microcirculation (Dong *et al.*, 2022; Zhang *et al.*, 2023). Furthermore, endothelial dysfunction plays a crucial role in the development of cardiovascular disease. Endothelial cells are a layer of cells in the inner wall of blood vessels, which not only form the interface between blood and tissues, but also maintain vascular

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homeostasis by regulating processes such as vascular tone, inflammatory response, thrombosis and cell proliferation. When endothelial cell function is impaired, endothelial dysfunction occurs, causing decreased bioavailability of nitric oxide, increased oxidative stress, and an inflammatory response, which in turn leads to the development of cardiovascular and metabolic disorders, such as including atherosclerosis and hypertension (H. Sun *et al.*, 2020; Zuchi *et al.*, 2020).

Compared with the single active ingredient of Western medicine, Chinese herbal medicine has a variety of active ingredients, and has the advantage of multi-target synergy in the treatment of MVA (M Wang *et al.*, 2021; Yu *et al.*, 2023). Xinbao Pill is a Chinese patent medicine, the ingredients of which are mainly Yang Jin Hua, ginseng, cinnamon, radix et rhizoma ginseng, panax ginseng and many other Chinese herbs combined together, containing atropine, hydroxylamine, polyamine and other ingredients. Due to its effects of warming the heart and kidneys, benefiting qi and yang and activating blood circulation, it is often used to treat yang deficiency of the heart and kidneys, chronic cardiac insufficiency caused by stasis of the heart veins, bradycardia caused by sinus node insufficiency, pathological sinus node syndrome, and angina pectoris caused by ischemic heart disease (Y. Wang, Liu*, et al.*, 2022). Moreover, the existing studies have confirmed that the components contained in Xinbao Pills play an important role in regulating blood lipids, increasing anti-platelet aggregation, dilating cardiovascular and cerebrovascular vessels and eliminating oxygen free radicals.

It can significantly improve the hemorheology and blood lipid levels of patients, and has high clinical application value (Pan *et al.*, 2024). There are more studies on the treatment of chronic heart failure with Xinbao Pills, mostly analysing the related vascular endothelial function and inflammatory factor levels, etc., and the research indexes on the treatment of MVA are similar to them, but the study on the treatment of MVA with oral Xinbao Pills has not been reported, based on which, we analyse the efficacy of Xinbao Pills in the treatment of MVA by combining these indexes.

This research was to assess the therapeutic impact of Xinbao pill by comparing and analyzing the vascular endothelial function index and serum inflammatory marker levels, the occurrence and symptoms of MVA, the results of the treadmill exercise assessment and the variations in coronary flow reserve (CFR) in patients with MVA before and after treatment. This research not only offers a fresh perspective for treating MVA but also establishes a significant clinical foundation for enhancing patient quality of life, increasing survival rates, decreasing acute cardiac events, and alleviating economic burdens.

MATERIALS AND METHODS

Research design

This study is a systematic evaluation and integration aimed at analyzing the clinical efficacy and potential mechanisms of Xinbao Pill in MVA. The design of this study was a randomized controlled trial design conducted in multiple clinical centres. From January 2020 to June 2021, a total of 200 patients including 73 males and 127 females, aged from 39 to 76 years, with a disease duration of 1 to 13 years, 55 cases with diabetes, 77 cases with hypertension and 68 cases with hyperlipidemia admitted for MVA at our institution were selected. They were divided into two groups, 100 cases in each group. The Hebei Engineering University Affiliated Hospital ethics committee granted approval for this research endeavor, and all participants, along with their respective families, provided their assent and affixed their signatures on the informed consent forms.

Diagnostic, inclusion and exclusion criteria (Y. Sun et al., 2021)

Diagnostic criteria: Diagnosis was made according to the international standard for diagnostic criteria of MVA (Ong *et al.*, 2018): (1) Typical symptoms of exertional angina pectoris, poor efficacy of nitrates in the case of attack; (2) There was tangible proof of myocardial ischemia; (3) Coronary micro vascular function was impaired, CFR was impaired, CFR <2.5 or 2.0; (4) Cardiac catheterization did not reveal any notable stenosis within the subepicardial coronary arteries (<20%); (5) Exclude other heart diseases and non-cardiogenic chest pain.

Inclusion criteria: (1) Conform to the diagnostic criteria of coronary micro vascular disease; (2) 18-80 years old; (3) Cardiac function grade 1-2; (4) Voluntary signing of informed consent; (5) Ability to make regular return visits.

Patient exclusion criteria: (1) Atypical angina symptoms; (2) No ischemic changes in electrocardiogram; (3) Definite stenosis in coronary angiography; (4) Coronary spasm and coronary myocardial bridge; (5) Failure to cooperate with follow-up, lack of clinical data.

Therapies

Patients in both groups received standard secondary medications for coronary heart disease, which included aspirin, isosorbide mononitrate tablets, atorvastatin, and metoprolol tartrate. Alongside this therapy, individuals in the observation group received Xinbao Pills at a dosage of 2 pills each time, administered three times a day. Both groups were treated for a duration of 6 months. During this treatment phase, they were not permitted to use other similar traditional Chinese medicines or patent remedies for coronary heart disease. Patients were also instructed to adhere to a low-fat, low-salt diet, maintain regular routines and refrain from smoking and alcohol to prevent fatigue. Those with hypertension or diabetes were advised

to follow their physician's recommendations for managing blood pressure and blood sugar levels. After 6 months, the outcomes were evaluated and compared.

Clinical efficacy evaluation

The occurrence rate of angina pectoris episodes was utilized as the criterion for assessing clinical effectiveness (Rayegani *et al.*, 2021). Markedly effective: clinical symptoms disappeared or significantly reduced, the frequency and degree of angina pectoris decreased by more than 80%, or no angina pectoris occurred, without nitroglycerin. Effective: clinical symptoms were relieved, the occurrence rate and degree of angina pectoris were reduced by 50% ~ 80%, and the dosage of nitroglycerin was reduced by more than 50%. Invalid: no improvement or aggravation of clinical symptoms, angina pectoris attack frequency decreased by less than 50%, nitroglycerin dosage decreased by less than 50%.

Symptoms of MVA

The Seattle Angina Questionnaire (SAQ) assessed the symptoms of MVA before and after 6 months of treatment (Thomas *et al.*, 2021). The scale included five dimensions: (1) level of restriction in physical activity; (2) stable condition of angina pectoris; (3) episodes of angina pectoris; (4) satisfaction with treatment; (5) understanding of the disease. The standard score is calculated as follows: (actual score - minimum score in this category)/ (maximum score in this category - minimum score in this category) × 100. A higher score indicates improved quality of life and physical functioning for the patients.

Observation indicators and detection methods

CFR detection

The sulfur hexafluoride microbubble contrast agent (Bracco, Italy, Sonovue) was administered via the anterior cubital vein at a speed of 1.5mL/s. The cross-sectional images of the apical hearts were observed by the Philips UltrasoundIE 33 echocardiography system. The system supporting software was used to analyze the myocardial plateau strength (A) and the average refilling velocity (β). CFR = A × β, CFR ≤2.5 indicates that there is impaired coronary blood flow reserve function.

Electrocardiogram treadmill exercise test

The electrocardiogram treadmill exercise test was carried out to record the total time of the exercise test and the maximum degree of ST segment depression before and after treatment, and to evaluate the risk of angina pectoris.

Vascular endothelial function index detection

A volume of 2mL of fasting venous blood was obtained from all patients. The collected whole blood was left to stand for 1 hour and then centrifuged at a low speed (2000 rpm for 10 minutes) to separate the serum for future use. The Endothelin-1 (ET-1) and Nitric Oxide (NO) levels were detected according to the steps in the instructions of ET-1 assay kit and NO assay kit (Nanjing Jiancheng Bioengineering Institute, item No. were H093-1-1 and A012-1).

Detection of serum inflammatory markers

In the fasting state of the patient, 3 mL of venous blood was taken and centrifuged for 10 min at a rotational speed of 2000 rpm/min and the serum was absorbed for use. The levels of tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) in the serum were measured using enzyme-linked immunosorbent assay. The kits were supplied by Shanghai Enzyme-linked Biotechnology Co., Ltd., with item numbers ml077385, ml062891, and ml058097.

Observation of adverse reactions

The routine blood and urine tests, coagulation function assessment, and liver and kidney function evaluations were conducted prior to and following treatment in both groups. The incidence of palpitations, sweating, appetite loss, nausea, vomiting, dizziness and headaches after treatment was documented.

Ethic Approval

The Hebei Engineering University Affiliated Hospital ethics committee granted approval for this research endeavor vide reference No.2019 [K] 021.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 27.0 statistical software. Measurements data conformed to normal distribution were (x±s) and comparisons among groups were made using independent samples t-test and count data were expressed as rate (%) using x^2 test, with P<0.05 meaning the discrepancy was statistically significant.

RESULTS

Comparison of general clinical data between the two groups of patients

No notable differences were observed in age, gender distribution, risk factors, or medical history between the two groups (P>0.05) (table 1).

Comparison of clinical efficacy

According to statistics, the total effective rate of the control group was 64%, which was significantly lower than that of the observation group (86%) (P<0.05), indicating that the treatment mode of the observation group was superior (table 2).

Comparison of SAQ scores of angina pectoris symptoms

The angina symptoms findings revealed that the scores of the SAQ scale for angina symptoms in both groups after treatment were considerably higher than those prior to treatment, with the observation group scoring higher than the control group (P<0.05) (table 3).

Table 1: Comparison of general clinical data between two groups

	Control group (n=100)	Observation group (n=100)	t/χ^2	P
Age (Year)	60.80±9.44	54.39±9.74	1.063	0.763
Gender (Male/Female)	32/68	41/59	1.747	0.186
Course of disease (Year)	6.24±3.42	6.05±3.17	1.169	0.439
BMI (kg/m^2)	23.18±4.37	24.27±4.12	1.127	0.554
Diabetes	29 (29%)	26 (26%)		
Hypertension	36 (36%)	41 (41%)	0.547	0.761
Hyperlipidemia	35 (35%)	33 (33%)		

Table 2: Two groups of patients after clinical curative effect comparison

Group	Excellent	Effective	Invalid	Total effective rate	Z	P
Control (n=100)	30	34	36	64.0%	-2.926	0.003
Observation (n=100)	41	45	14	86.0%		

Table 3: Comparison of SAQ scale scores of angina symptoms between the two groups before and after treatment.

Group		①	②	③	④	⑤
Control	Before treatment	45.28±5.61	35.74±5.00	43.28±6.98	23.32±3.56	37.33±7.28
(n=100)	After treatment	50.07±6.26[a]	65.95±4.90[a]	72.09±8.68[a]	44.62±3.79[a]	49.06±6.78[a]
Observation	Before treatment	46.07±4.50	38.70±3.68	40.64±7.44	22.44±3.64	38.36±6.50
(n=100)	After treatment	64.81±6.19[ab]	71.94±4.20[ab]	77.91±9.58[ab]	48.80±2.89[ab]	56.47±8.12[ab]

Note: a: compared to the same group before treatment P<0.05; b: compared to the after treatment control group P<0.05. (1) indicates level of restriction in physical activity; (2) indicates stable condition of angina pectoris; (3) indicates episodes of angina pectoris; (4) indicates satisfaction with treatment; (5) indicates understanding of the disease.

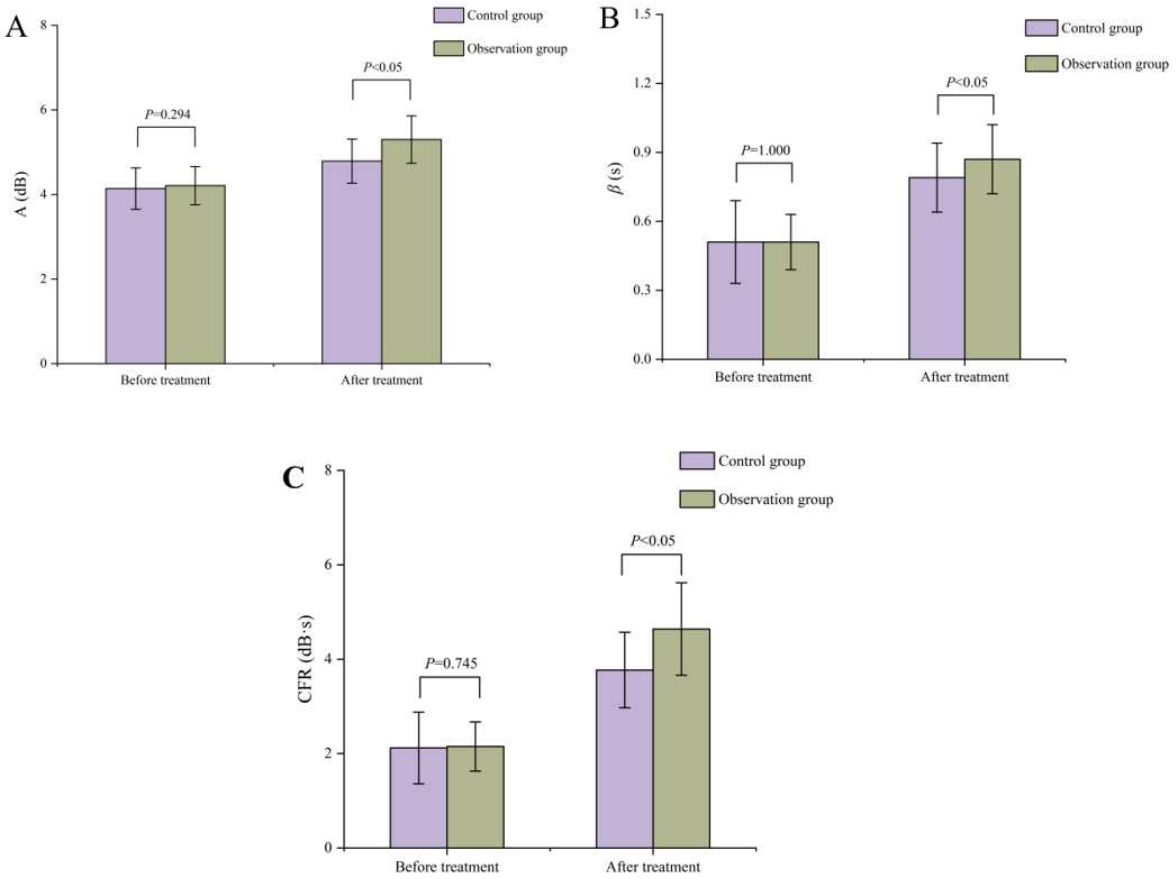

Fig. 1: Comparison of A, β and CFR levels. (A) Comparison of A levels, A indicates myocardial plateau strength. (B) Comparison of β levels, β indicates average refilling velocity. (C) Comparison of CFR levels, CFR indicates coronary flow reserve.

Table 4: Occurrence of the adverse reaction

Group	*n*	Nausea and vomiting	palpitation	Loss of appetite	Dizziness and headache
Control	100	2	3	5	2
Observation	100	3	2	6	4

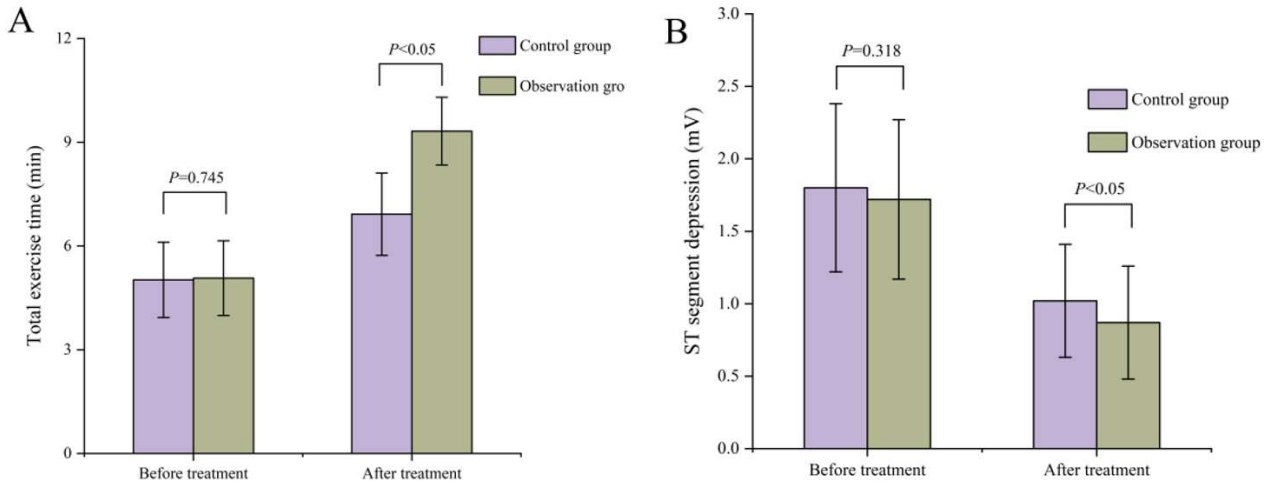

Fig. 2: Comparison of treadmill exercise test results. (A) Comparison of total exercise time. (B) Comparison of ST segment depression.

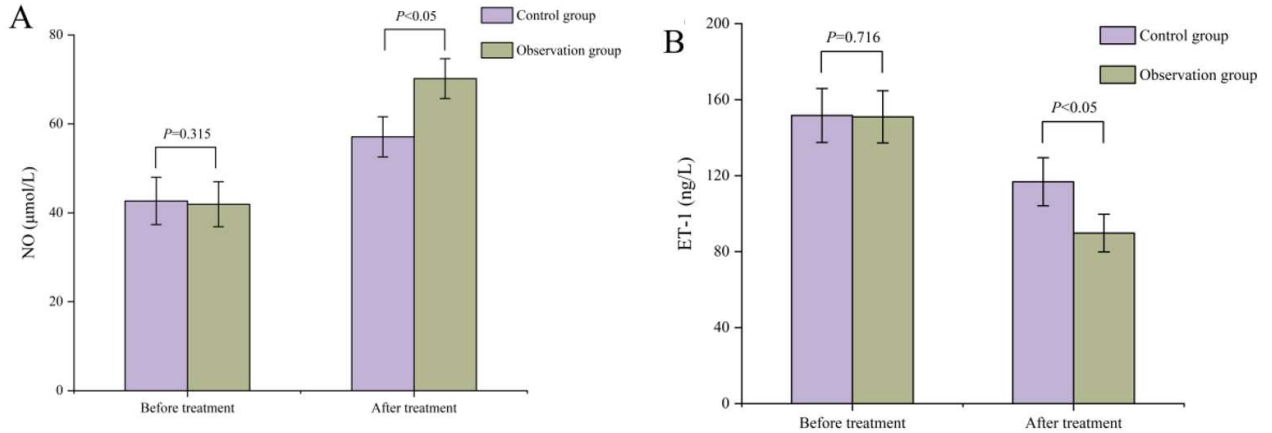

Fig. 3: Comparison of vascular endothelial function indexes. (A) Comparison of NO level, NO indicates Nitric Oxide. (B) Comparison of ET-1 level, ET-1 indicates Endothelin-1.

Comparison of A, β and CFR between the two groups before and after treatment

There was no significant difference between the two groups before treatment (P>0.05). After treatment, serum levels of A, β and CFR were increased in both groups, and the levels in the observation group were higher than those in control group (P<0.05) (fig. 1).

Comparison of moving plate test results

The comparison of treadmill exercise test outcomes that indicated no significant differences in total exercise duration and ST segment depression prior to treatment (P>0.05). After treatment, the observation group demonstrated a noteworthy greater total exercise duration compared to their before treatment values and the control group, while the ST segment depression was notably reduced compared to the control group (P<0.05) (fig. 2).

Comparison of vascular endothelial function indexes

The results showed no significant differences in NO and ET-1 levels between the groups before treatment (P> 0.05). After treatment, the NO level in the observation group was greater than it before treatment value and that of the control group, whereas the ET-1 level was lower than both its before treatment value and that of the control group (P<0.05) (fig. 3).

Comparison of serum inflammatory markers

No significant differences in serum hs-CRP, IL-6 and TNF-α levels were observed between the groups prior to treatment (P>0.05). After treatment, the serum concentrations of hs-CRP, IL-6 and TNF-α in both groups decreased compared to their before treatment levels, with the observation group exhibiting lower levels than the control group (P<0.05) (fig. 4).

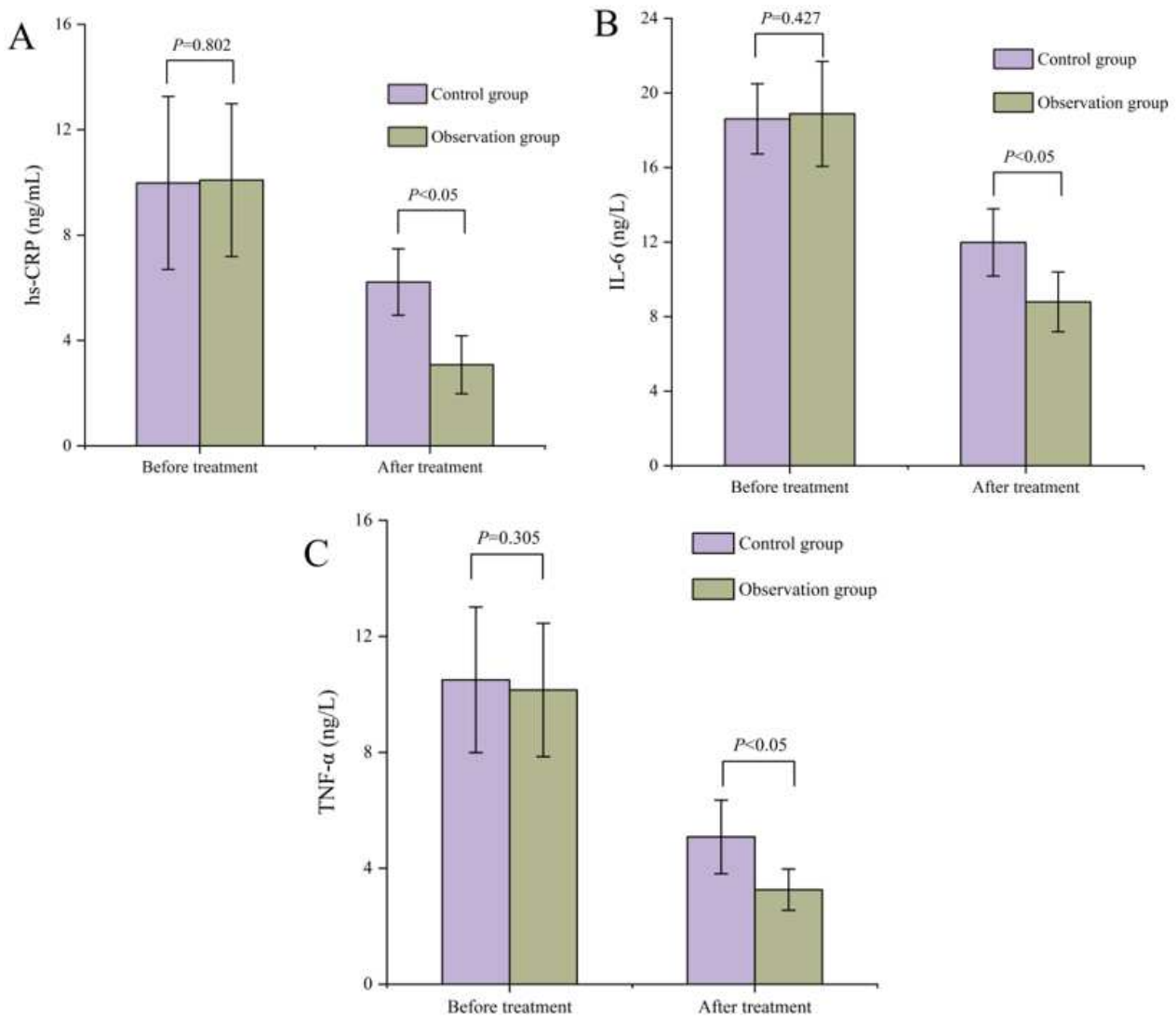

Fig. 4: Comparison of serum inflammatory factor levels between the two groups before and after treatment. (A) Comparison of hs-CRP concentration, hs-CRP indicates high-sensitivity C-reactive protein. (B) Comparison of IL-6 concentration, IL-6 indicates interleukin 6. (C) Comparison of TNF-*α* concentration, TNF-*α* indicates tumor necrosis factor-*α*.

Comparison of adverse reactions between two groups

During the course of treatment, both groups showed no abnormalities in blood and urine analyses, coagulation function, or liver and kidney performance. The incidence of adverse effects in the control group was 12%, whereas the observation group reported a rate of 15% having no significant differences ($P>0.05$) (table 4).

DISCUSSION

This is an initial clinical study conducted by the researchers, assessing the clinical effectiveness of Xinbao Pills in individuals with MVA. The clinical research on the pathogenesis of MVA is mainly due to microvascular dysfunction, endothelial dysfunction, chronic inflammatory response and other factors that not meet the normal myocardial metabolism, resulting in myocardial ischemia and hyperalgesia (Yang and Lerman, 2005). The key to its treatment is to reduce microvascular injury, improve myocardial microcirculation, and maintain normal myocardial blood supply. For MVA, the clinical treatment is mainly based on conventional cardiology treatment, in which aspirin can play an antithrombotic role and inhibit platelet aggregation and rosuvastatin can help regulate blood lipids and improve coronary artery stenosis (Aldiwani *et al.*, 2021; Wu *et al.*, 2015). Combination therapy can reduce the impact of clinical symptoms, but the impact of this treatment on vascular endothelial function is restricted, and it is difficult to obtain an ideal curative effect.

Compared with western medicines, Xinbao Pills, which is a Chinese herbal medicine, has certain advantages in the treatment of MVA. The main components of Xinbao pills

include datura flower, antler, ginseng, aconite, cinnamon, borneol, notoginseng, musk, toad venom, etc. (Tian *et al.*, 2023). Among them, the main drug Daturae Flos contains active ingredients such as hyoscyamine and scopolamine. Clinical studies have found that hyoscyamine can improve coronary circulation, acute myocardial infarction, myocardial blood perfusion, reduce coronary microcirculation spasm and dredge coronary microcirculation (Kochiadakis *et al.*, 1996; Renner *et al.*, 2005). Velvet antler can maintain the activity of myocardial mitochondrial calcium pump, effectively dilate blood vessels and improve cardiac microcirculation (Clifford *et al.*, 1979). This research revealed that standard basic treatment combined with Xinbao Pill can considerably reduce clinical symptoms in patients and enhance the treatment effectiveness rate after 6 months. The findings indicated that the overall effectiveness rate in the group using Xinbao Pill was higher. Additionally, both groups improved SAQ scale scores after treatment in comparison. After treatment, the total exercise duration on the treadmill and ST segment depression in the observation group demonstrated notable improvement. Simultaneously, the CFR in the observation group also significantly improved post-treatment. These findings may be associated with the effectiveness of Xinbao Pills in enhancing arterial microcirculation, providing evidence for the role of Xinbao Pills in MVA treatment to some extent.

Coronary vascular endothelial cell dysfunction may be one of the pathogenesis of MVA (Hoffmann *et al.*, 1998; Wennmalm, 1994). Endothelial cells act on coronary smooth muscle by releasing diastolic and contractile factors, thereby regulating lumen diameter and blood flow (Gurzău *et al.*, 2021). Microvascular lesions can cause continuous contraction of small blood vessels and aggravate the accumulation of adenosine, lactic acid and other metabolites in myocardium, thus causing chest pain and chest tightness (Nagib El-Kilany *et al.*, 2004). Therefore, the main way to treat MVA is the timely and continuous repair of vascular endothelial cell function. NO and ET-1 are two important cytokines involved in vasodilation and vasoconstriction, and they have antagonistic functions (Ford *et al.*, 2020). Related research has indicated that fluctuations in NO and ET-1 levels are integral to the entire pathophysiological progression of cardiovascular diseases (Porro *et al.*, 2014). This research revealed that after 6 months of treatment with Xinbao Pills, serum NO levels in both groups significantly rose, while ET-1 levels notably declined, with the treatment group showing more pronounced improvements in vascular endothelial cell parameters. It is suggested that Xinbao Pill may improve myocardial ischemia and hypoxia by improving the function of cardiac microvascular endothelial cells, regulating the secretion balance of endothelial cell vasomotor factors, reducing coronary microcirculation resistance, increasing coronary microcirculation blood flow, and improving myocardial ischemia and hypoxia. Y. Wang, Li*, et al.* (2022) analyzed the efficacy of cardioprotection pills in chronic heart failure in a controlled trial and reported similar findings. This is mainly due to the fact that Cinnamon water extract and cinnamon oil in Xinbao Pills can increase the myocardial blood supply, positively influence the rise in left ventricular diastolic pressure and coronary artery pressure, and help to promote the opening of myocardial collateral circulation (Mohammadabadi and Jain, 2024; Sedighi *et al.*, 2018); Musk can effectively dilate coronary arteries and reduce myocardial oxygen consumption (Y. Yang *et al.*, 2022); bufonis venenum can increase myocardial nutrient blood flow, improve microcirculation, and improve myocardial ischemia and hypoxia (Huang *et al.*, 2022).

The hs-CRP is a commonly used inflammatory marker protein for cardiovascular diseases. It is synthesized by IL-6 to stimulate liver cells and promotes its production during inflammation and tissue damage. It is the most valuable cardiovascular risk and strong predictor of all inflammation and blood lipid markers (Badimon *et al.*, 2018). Survey research has pointed out that there is a close relationship between inflammatory response and MVA (Anzai, 2018). Therefore, serum inflammatory factors are also the key to evaluating the therapeutic effect of MVA. In this research, the serum concentrations of IL-6, TNF-α, and hs-CRP in two groups after treatment were reduced, and the observation group exhibited lower levels. Ma and Ma (2023) reported similar findings in a clinical study of Xinbao Pills combined with sacubitril valsartan in the therapy of chronic heart failure. This is attributed to that Ginseng and Aconite in Xinbao Pills can effectively promote the uptake and utilization of glucose by cells, enhance glycolysis and aerobic decomposition capacity, increase myocardial energy supply, inhibit the content of myocardial lactate under hypoxic conditions, suppress the formation of oxygen free radicals, lower myocardial lipid peroxide levels, and elevate superoxide dismutase in ischemic myocardium, thus exerting anti-myocardial ischemia effects (Cui *et al.*, 2013). Borneol and Panax notoginseng can inhibit myocardial contraction, slow down heart rate, decrease peripheral vascular resistance, lower myocardial oxygen demand, and improve hypoxia resistance of myocardial tissue through anti-lipid peroxidation (Liu *et al.*, 2021; Song *et al.*, 2017). This suggests that the combination of Xinbao Pills with standard Western medicine is effective in mitigating the inflammatory response in MVA patients. Xinbao Pills can modulate the release of inflammatory mediators, enhance the phagocytic function of macrophages, and lessen inflammatory damage.

CONCLUSION

In summary, for individuals suffering from MVA, the addition of Xinbao Pills to standard treatment can more effectively decrease the frequency of angina attacks,

alleviate symptoms, enhance clinical outcomes, and reduce ST segment depression on electrocardiograms. This approach significantly raises ET-1 levels while inhibiting NO levels, lowers serum inflammatory markers, and increases survival rates for patients with MVA. However, this research is a single-center sample, and the treatment and follow-up time is short, so there are certain limitations. In the future, the sample source can be further expanded and the duration of the study can be extended to explore the long-term effects of Xinbao Pills for MVA at one time.

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