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Original Research Article

Effect of modified Buyang huanwu decoction on hemorheology, myocardial remodeling, serum soluble CD40 ligand and serum soluble P-selectin in patients with acute myocardial infarction after percutaneous coronary intervention

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Abstract

Purpose: *To investigate the effect of modified Buyang Huanwu decoction on hemorheology and myocardial remodeling in patients with acute myocardial infarction (AMI) after conventional percutaneous coronary intervention (PCI), and its relationship with serum levels of soluble CD40 ligand (sCD40L) and soluble P-selectin (sP-sel).*

Methods: *After PCI, 80 patients seen from February 2021 to February 2022 in Shijiazhuang Fourth Hospital, China with AMI were enrolled in the study. Subjects were assigned to study and control groups. Control group received standard conventional medical treatments, while study group received modified Buyang Huanwu decoction, in addition to the same standard treatment, orally twice a day (morning and night) for 3 months). The effect of modified Buyang Huanwu decoction was determined by comparing the post-treatment clinical outcomes and levels of hemorheology indices and myocardial remodeling-associated indices (myocardial injury markers) in both groups of patients.*

Results: *The clinical outcome in study group was significantly better, and the hemorheology indices were significantly improved when compared to control subjects ($p < 0.05$). Serum levels of myocardial injury markers (cardiac troponin (cTnI), cardiac markers (CRP), and brain natriuretic peptide (BNP)), and inflammatory markers (sCD40L and sP-sel) in study group were significantly decreased to varying degrees, relative to control group ($p < 0.05$).*

Conclusion: *Modified Buyang Huanwu decoction reduces inflammatory marker levels, cardiac inflammatory response and myocardial remodeling, and improves the prognosis of AMI in patients after PCI. Therefore, it may be beneficial to develop other methods for treating acute myocardial infarction after percutaneous coronary intervention.*

Keywords: *Modified Buyang Huanwu decoction, Acute myocardial infarction, percutaneous coronary intervention*

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INTRODUCTION

Acute myocardial infarction (AMI), a common clinical cardiovascular disease with a 3 % incidence rate in the USA is caused by acute necrosis of myocardial cells, resulting in post-sternal compression pain, nausea and vomiting, amongst other symptoms [1]. If the patient does not get timely treatment after myocardial infarction, complications such as arrhythmia, cardiac rupture, cardiac insufficiency and ventricular aneurysm may occur, all of which adversely affect treatment effectiveness and survival of the patient [2]. Acute myocardial infarction (AMI), with myocardial ischemia and necrosis as the main pathological changes, is caused by embolism due to a variety of predisposing factors. Two characteristics of AMI are acute onset and high death rate. Fortunately, studies have demonstrated that percutaneous coronary intervention (PCI) rapidly opens the infarct-related vessels (IRA) and effectively produces reperfusion of myocardial tissue in the infarct area [3]. Percutaneous coronary intervention (PCI) is a non-surgical procedure used for treating blockage in a coronary artery. A catheter is inserted into a blood vessel in the wrist or groin and threaded through the blood vessels to the affected artery. Then, a small balloon is inflated to open up the artery and restore blood flow to the heart. In some cases, a stent may be inserted to help keep the artery open. However, PCI may lead to vascular endothelial damage, platelet adhesion and thrombosis. Moreover, the patients are prone to adverse events such as dyspnea, arrhythmia, and myocardial ischemia, resulting in myocardial injury after PCI [4].

The complex structural changes in early-infarcted and non-infarcted areas may lead to secondary acute left ventricular enlargement which readily induces ventricular remodeling after AMI, thereby making it an important risk factor for poor prognosis after PCI. Therefore, clinical research on AMI is focused on strategies for enhancing myocardial perfusion, reducing myocardial injury and reversing ventricular remodeling after PCI.

The modified *Buyang Huanwu* decoction prescription [5] comprised *Astragalus membranaceus* and *Salvia miltiorrhiza* (30 g each); angelica tail and red peony (18 g each), and earth-worm, motherwort, Chuanxiong, safflower, dwarf lilyturf tuber, peach kernel, and pilose asiabell root (15 g each). The prescription also contained sub-erect spatholobus stem, long-stamen onion bulb, rosewood, and Chinese magnolia vine fruit (10 g each), as well as 6 g of licorice roots.

Traditional Chinese medicine (TCM) has a rich reservoir of clinical records in the treatment of AMI. It is currently widely believed that most patients with AMI have *qi* deficiency syndrome and blood stasis. Percutaneous coronary intervention (PCI), commonly known as angioplasty, is a non-surgical method for opening up blocked coronary arteries. It is performed using a catheter and a balloon or stent to compress, dilate or remove the blockage. Although it is beneficial for the removal of blood stasis, interventional treatment results in further damage to *vital qi*, thereby regenerating the blood stasis, and eventually leading to heart vessel obstruction and cardiovascular events. Therefore, the treatment of *qi* deficiency and blood stasis after PCI should be based on invigorating *qi* and removing blood stasis [6]. However, the decoction focuses mostly on invigorating *qi*, in addition to activating blood circulation and *dredging collaterals*, all of which are consistent with pathologies seen after PCI [7]. Therefore, the role of the decoction in AMI after PCI is worthy of further studies to investigate its effect on AMI patients.

This study aimed to determine the therapeutic impact of modified *Buyang Huanwu* decoction on AMI patients after PCI. By comparing the hemorheological changes, changes in myocardial remodeling and serum levels of inflammatory response indices in patients exposed to the modified decoction, the effect of the herbal product on the clinical treatment was unraveled. The study was intended to provide important reference data on myocardial injury following PCI for AMI and other diseases related to myocardial injury.

METHODS

Subjects and general information

Eighty (80) AMI patients who underwent PCI at Shijiazhuang Fourth Hospital, China from February 2021 to February 2022 were enrolled in this study. This research was approved by the Ethical Committee of Shijiazhuang Fourth Hospital according to the declaration of Helsinki promulgated in 1964 as amended in 1996, as per the approval number SJZ2022003. Patients were divided into two groups: study and control, based on the treatment methods used. There were 40 patients in each group.

Inclusion criteria

Patients who were confirmed as having AMI based on persistent chest pain, coronary angiography, ischemic ST-T changes on

electrocardiogram, and elevated cardiac troponin I, in line with the criteria of AMI in the Rapid Diagnosis and Treatment Guidelines for Acute Coronary Syndromes of 2022, were enrolled in this research. Those who had *qi* deficiency and blood stasis based on the TCM syndrome differentiation and efficacy criteria were also included. Patients who had onset signs of AMI were also included. The symptoms of interest were tingling in the chest, tightness in the chest, fatigue, shortness of breath, sweating, palpitations, dark tongue or petechiae, kinking and tortuous sublingual veins, thin and white coating on the tongue and weak pulse with onset time less than 12 h. In addition, patients who successfully received emergency PCI treatment, those with Killip classification in grades Ⅰ-Ⅲ, patients aged 30 to 80 years, and those who submitted signed informed consent to participate in the study, were all included.

Exclusion criteria

The excluded patients were subjects who had severe dysfunction in important organs such as liver and kidney; patients with hematological diseases, and those with diseases of the endocrine system. Moreover, patients with long-standing myocardial infarction, cardiogenic shock, cardiac tamponade, chronic heart failure, congenital heart disease, complete atrioventricular block and other cardiovascular diseases were excluded. Patients with malignant tumors, hematopoietic and coagulation disorders, and patients with severe complications such as severe dissection, shock, and aggravated hematoma after PCI, were excluded. In addition, patients who had no-reflow or slow flow of infarct-related artery after PCI; those who withdrew as a result of adverse reactions to drugs or severe allergies; patients who had long-term use of anticoagulants or who used other medications likely to affect the results of the study, and those who were taking part in other studies, were excluded.

Treatment methods

Patients in control group were given standard conventional medical treatments after PCI, continuously for 3 months. These treatments involved use of antiplatelets (Aspirin (Bayer, Germany), 3-5g per day, taken orally in 4 doses; 25-50 mg of β-blocker Atenolol (AstraZeneca, USA) orally once daily, and angiotensin-converting enzyme inhibitor Benazepril (Novartis, USA) (10 mg per day). The modified *Buyang Huanwu* decoction (Keda Pharmaceutical Co. Ltd., China) (Keda Pharmaceutical Co., Ltd., China) was given to patients in study group, in addition to the same standard therapy given to control patients. The mixture was decocted once daily and taken twice in the morning and twice in the evening (200 mL each time) for 3 months. No other Chinese patent medicine or Chinese herbal decoction was allowed during the treatment.

Evaluation of parameters/indices

Clinical efficacy of treatment

After 3 months of treatment, clinical efficacy was evaluated [8]. Treatment effectiveness comprised 4 categories: *cured (C), significantly efficacious (ME), efficacious (E)*, and *poor (P)*. Patients were *cured* if TCM syndrome score decreased by ≥ 90 %, ECG returned to normal, Killip heart function returned to normal or improved more than Ⅱ grade; TCM symptom score decreased by 75 – 89 %, ECG ST segment was close to the baseline with more than 0.05 mV, but did not reach the normal level, and the Killip heart function classification increased by Ⅰ - Ⅱ. Treatment outcome was deemed *effective* if TCM symptom score decreased by 50 – 74 %, and Killip cardiac function classification increased by Ⅰ grade. However, treatment was *poor/ineffective* if the TCM symptom score decreased by less than 50 %, with no significant change in heart function. Total treatment effectiveness (T%) was calculated using Eq 1.

T (%) = ((C+ME+E)/N)100 …… (1)
where N is the total number of cases

Hemorheology

Whole blood high shear viscosity (WBHSV) and low shear viscosity (WBLCV), viscosity of plasma (PV), erythrocyte aggregation index (AI), fibrinogen (Fg), and other hemorheology-related indicators were measured using automatic hemorheology instrument and automatic hemagglutination instrument, before and after PCI in AMI patients [9].

Determination of ventricular remodeling

Blood (5 - 10 mL) was collected from the median elbow vein of each patient. The blood samples were centrifuged at 3,000 rpm for 10 min. Serum levels of creatine kinase isoenzyme-MB (CK-MB), cardiac troponin (cTnI), and brain natriuretic peptide (BNP were assayed using enzyme-linked immunosorbent assay (ELISA). Ultra-sensitive C-reactive protein (CRP) was measured with an ultra-sensitive immune-turbidimetric assay. The levels of soluble P-selectin (sP-sel) and soluble CD40 ligand (sCD40L) were determined with ELISA kits [10].

Statistical analysis

The SPSS 20.0 statistical software was used for data analysis. Chi-square test was used for the comparison of count data between the two groups. Measurement data are expressed as mean ± standard deviation (SD), and comparison between groups was done with Student's *t*-test. Differences were assumed to be statistically significant at $p < 0.05$.

RESULTS

Basic data of patients

Control group had 28 males and 12 females of ages 27 - 75 years (average age = 54.6 ± 2.8 years). The location of myocardial infarction in 27 patients was in the middle anterior wall, while 27 subjects had myocardial infarction in the inferior wall. The Killip classification [11] showed that there were 31 patients in grade I, and 9 patients in grade II. In study group, there were 26 men and 14 women aged 30 - 72 years (average age = 55.1 ± 3.9 years). Myocardial infarction occurred in the middle anterior wall in 23 subjects, but it was present in the inferior wall in 17 participants. Using the Killip classification, 32 patients were rated as grade Ⅰ, while 8 patients were in grade Ⅱ. As shown in Table 1, general data were comparable (sex, age, location of myocardial infarction, and cardiac function classification) between both cohorts.

Treatment efficacy

The results showed a significantly higher number of people in cured, very efficacious, and efficacious categories in study group than in control group. The total effectiveness values in study and control groups were 92.5 and 80 %, respectively. These results are shown in Figure 1.

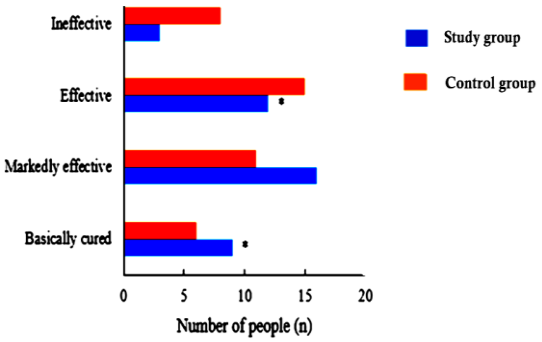

Figure 1: Comparison of clinical efficacy between the two groups. ***Note:*** **P* < 0.05 vs. control group

Hemorheological indices

The pre-treatment levels of hemorheology indices were comparable in both groups ($p > 0.05$). However, after 3 months of administration of modified *Buyang Huanwu* decoction, the levels of WBHCV, WBLCV, PV, AI, and Fg in the two groups were significantly reduced, with significantly lower values in study group, as shown in Table 2.

Levels of myocardial injury markers CK-MB and cTnI

After treatment, there were marked increases in serum levels of CK-MB in the two groups, but the serum levels of cTnI were significantly decreased, with significantly lower values of the 2 parameters in study group (Figure 2)

Table 1: Basic data of patients in both cohorts (n=40)

Group	Gender		Mean age	SIM		Killip	
	M	*F*		*Middle anterior*	*Inferior*	*Ⅰ*	*Ⅱ*
Study	26	14	55.1±3.9	23	17	32	8
Control	28	12	54.6±2.8	27	13	31	9
χ^2/t	0.739		0.271	1.246	1.075	0.053	0.084
P	0.213	0.307	0.063	0.277	0.267	0.472	0.513

Sim: Site of myocardial infarction

Table 2: Values of hemorheological indices in the two groups (n=40)

Group		WBHCV (mPa·sec)	WBLCV (mPa·sec)	PV (mPa·sec)	AI	Fg (g/L)
Study	Before treatment	5.53±0.46	13.62±1.73	2.53±0.41	4.02±0.38	4.18±1.04
	After treatment	4.21±0.35*#	8.24±1.51*#	2.2±0.13*#	2.14±0.19*#	2.72±0.25*#
Control	Before treatment	5.62±0.48	13.65±1.76	2.5±0.39	3.91±0.33	4.17±1.06
	After treatment	4.95±0.38*	9.37±1.62*	1.8±0.15*	3.05±0.27*	2.72±0.25*

**P* < 0.05, vs. pre-treatment, #*p* < 0.05, vs. control

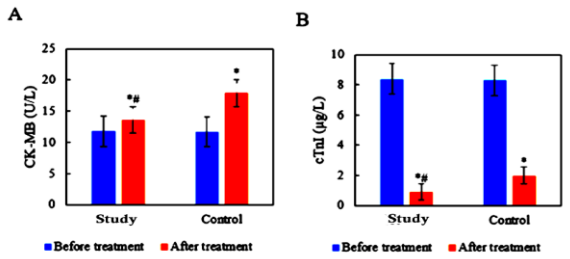

Figure 2: Comparison of (A) CK-MB and (B) cTnI levels between the two groups (n=40). ***Note:*** **P* < 0.05, vs. pre-treatment; #*p* < 0.05, vs. control. CK-MB: creatine kinase isoenzyme-MB; cTnI: cardiac troponin

Serum levels of cardiac markers CPR and BNP

Treatment with modified *Buyang Huanwu* decoction led to significant decreases in the serum levels of high-sensitivity CRP and BNP in study group when compared to control group (*p* < 0.05; Table 3).

Table 3: Comparison of serum CRP and BNP levels (n=40)

Group	CRP (mg/L)	BNP (ng/L)
Control	27.23±2.54	173.47±23.33
Study	11.25±1.65*	58.52±8.74*

Note: **P* < 0.05, vs control group

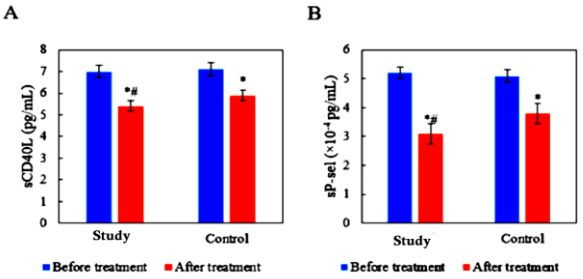

Figure 3: Serum levels of (A) sCD40L and (B) sP-sel in the two groups (n=40). ***Note:*** **P* < 0.05, vs. pre-treatment, #*p* < 0.05, vs. control. sP-sel: soluble P-selectin; sCD40L: soluble CD40 ligand

Values of inflammatory response indices sCD40L and sP-SEL

Treatment with modified *Buyang Huanwu* decoction led to significant decreases in serum sP-sel and sCD40L in study group when compared to control group (*p* < 0.05; Figures 3 A and B).

DISCUSSION

This study was carried out to investigate the effect of modified *buyang huanwu* decoction on hemorheology, myocardial remodeling, and sCD40L and sP-SEL after PCI in patients with AMI. The results showed that treatment of AMI patients (after PCI) with the decoction resulted in improvements in hemorheology indices and reduction in the degree of myocardial remodeling when compared to patients who received conventional medications. These findings suggest that the modified decoction therapy may be beneficial to patients with AMI after PCI, through reduction of myocardial injury, mitigation of myocardial inflammation, and decrease in myocardial remodeling.

Modified *Buyang Huanwu* decoction is mainly used for the treatment of *qi* deficiency syndrome and blood stasis. Results from previous studies suggest that *Buyang Huanwu* decoction may reduce blood viscosity and promote cardiovascular recovery in patients [12]. In the present study, it was observed that after 3 months of treatment with the modified decoction, the levels of WBHCV, WBLCV, PV, AI, and Fg in the two groups were significantly decreased, with lower values seen in patients treated with modified decoction than in those treated with general medical treatment. Although there was similarity in PV in the two groups following treatment, the treatment was nonetheless effective, when compared with pre-treatment.

It is known that patients with AMI often have heart failure, heart rate disorders, and shock, and most of them have mitochondrial damage. Investigations outside China have indicated that approximately one-quarter of such patients have no obvious medical history and clinical manifestations of the disease, and more than 50 % of patients have no obvious abnormal changes in electrocardiogram [13]. Other studies have shown that the sensitivity of AMI is 40 – 60 %. Due to the ease of measurement and high degrees of sensitivity as cardiac markers, troponin, creatine kinase isoenzyme and myoglobin have been widely used in clinical diagnosis, and have become the "gold standards" in the clinical examination of AMI [14]. In this study, it was found that the serum level of cTnI in patients with AMI treated with the modified decoction after undergoing PCI, was lower than that of AMI patients with PCI who received general medical surgery, while an opposite pattern was seen for serum CK-MB. However, post-treatment level of CK-MB was lower in study cohort. Thus, modified *Buyang Huanwu* decoction was effective in reducing the serum levels of cTnI and CK-MB, indicating that it was more effective in reversing heart injury.

An attack of AMI may cause changes in the structure and function of myocardial cells,

resulting in myocardial remodeling, as well as changes in collagen deposition and inflammatory response [15]. Therefore, cardiac markers are used for evaluating the degree and progression of myocardial remodeling after AMI, and for predicting the long-term prognosis of AMI in patients. C-reactive protein (CRP) is an inflammatory marker whose level is often increased after AMI due to the resultant myocardial damage and inflammatory response [16]. The hormone, BNP is produced in the heart and its level increases during cardiac dilatation and load. Thus, following AMI, BNP levels are often elevated due to myocardial damage and increased cardiac load [17]. Previous studies have shown that TCM has great potential in mitigating ventricular remodeling [18].

This study selected these two indicators for analysis of the histological changes in myocardial tissues of patients with AMI following PCI, who were treated with the modified *Buyang Huanwu* decoction, as well as the myocardial repair process after AMI. The results revealed that after treatment, the serum levels of high-sensitivity CRP and BNP were significantly reduced, indicating that the modified decoction improved heart function. Thus, the modified decoction treatment has potential for reducing cardiac load after AMI, and for decreasing myocardial remodeling. It is known that sCD40L is a cytokine that plays an important regulatory function, while sP-sel, a soluble form of selectin P on the surface of platelets, is an indicator of inflammatory response. These two indicators may be elevated during myocardial infarction, thereby triggering an inflammatory response and platelet activation. In previous studies [19,20], it was demonstrated that *Buyang Huanwu* decoction improved blood circulation and enhanced metabolism in myocardial tissue. Some of the components of the decoction may have anti-inflammatory effects, and may also have regulatory effects on immune function, which may be beneficial in suppressing the production of mediators of inflammation while activating the immune cells. In this study, the serum levels of sP-sel and sCD40L in patients with AMI on PCI after treatment with modified *Buyang Huanwu* decoction were lower than in those treated with general medication. This suggests that the modified decoction treatment improved platelet activation reduced the inflammatory response caused by myocardial infarction, and decreased the abnormal aggregation of platelets and the release of inflammatory mediators after myocardial infarction.

Study limitations

A relatively small sample size was used in the study. There is need for an expanded sample size in subsequent studies. Moreover, this study was done in a single center. If the scope of its application is to be expanded, a multi-center study is required.

CONCLUSION

This study has demonstrated that treatment of patients with AMI using modified *Buyang Huanwu* decoction after PCI leads to significant reductions in hemorheological indices, as well as reductions in serum levels of cTnI, CPR, BNP, sCD40L, sP-sel, and other indices, when compared to pre-treatment and post-treatment levels, relative to the control. These findings indicate that the modified decoction therapy is beneficial for reducing blood viscosity, enhancing cardiovascular recovery, reducing inflammatory response, and mitigating ventricular remodeling. These findings provide a new guide for the prognosis of PCI. However, the specific mechanism involved in the effect of the modified decoction on AMI needs to be further studied.

DECLARATIONS

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None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities

pertaining to claims relating to the content of this article will be borne by the authors. All authors read and approved the manuscript for publication. Xiaolong Li and Haijun Zhao conceived and designed the study. Xiaoxu Li, Xingrui Zheng and Hua Shi collected and analyzed the data, while Juanxia Li1 and Fanhua Meng wrote the manuscript. Xiaolong Li and Haijun Zhao contributed equally to this work as co-corresponding authors. Juanxia Li1 and Fanhua Meng contributed equally to this work as co-first authors.

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