Research Paper

Clinical Study on the Treatment of Acute Coronary Syndrome in Remission with Shexiang Baoxin Pill Combined With Metoprolol Succinate

YUHUI LI, JIALE WANG, MIN YANG, LINLIN ZHANG AND YING CHEN[1]*

College of Traditional Chinese Medicine, Changchun University of Chinese Medicine, [1]Branch of National Clinical Research Center for Chinese Medicine Cardiology, Affiliated Hospital of Changchun University of Chinese Medicine, Changchun 130011, China

We attempt to investigate the clinical efficacy and safety of Shexiang Baoxin pill combined with metoprolol succinate in acute coronary syndrome at remission stage patients. We randomly selected 72 patients in remission stage of acute coronary syndrome in our cardiology department from March 2021 to December 2021, then divided them into observation group (36 cases with Shexiang Baoxin pill combined with metoprolol succinate treatment) and control group (36 cases with metoprolol succinate treatment). Besides, both groups treated with standardized Western medicine, anti-platelet, lipid-lowering drugs, etc. Compared both groups on the clinical effective rate, cardiac function indexes changes and plasma endothelial function indexes (angiotensin II, endothelin-1 and nitric oxide) changes before and after treatment. Left ventricular end-diastolic dimension and left ventricular end-systolic dimension value of observation group decreased remarkably higher than control group after treatment ($p<0.01$); observation group possessed remarkably higher value than control group ($p<0.01$). After 1 mo treatment, in serum, angiotensin II and endothelin-1 concentration of observation group decreased more than control group ($p<0.05$), but nitric oxide concentration in serum increased more than control group ($p<0.05$). The total effective rate of observation group was 88.9 %, it was remarkably higher than control group (55.5 %) ($p<0.05$). The incidence of cardiovascular events in observation group (8.33 %) was remarkably lower than control group (13.89 %) ($p<0.05$). Shexiang Baoxin pill combined with metoprolol succinate can obviously improve the acute coronary syndrome remission patients' angina symptoms, improve heart function, and reduce the serum angiotensin II and endothelin-1, at the same time increase the nitric oxide concentration level, effectively reduce the incidence of cardiovascular events, can provide clinical guidance value for effective treatment in acute coronary syndrome remission patients.

Key words: Shexiang Baoxin pill, metoprolol succinate, acute coronary syndrome, angina, myocardial infarction

Acute Coronary Syndrome (ACS) remains one common disease in cardiovascular medicine. In 2015, there were nearly 170 ACS deaths per 100 000 people in developed North America and 298 deaths per 100 000 people in developing Asia, it has become a serious public health problem, threatening people's health[1]. According to different clinical manifestations, we divided ACS into three different clinical types Unstable Angina (UA), Non ST segment Elevation Myocardial Infarction (NSTEMI) and ST segment Elevation Myocardial Infarction (STEMI), it must be distinguished in terms of diagnosis, prognosis and optimal treatment strategy[2]. Because of the widespread and early Percutaneous Coronary Intervention (PCI) use, and innovations in antithrombotic and anticoagulant regimens using more potent P2Y12 receptor antagonists and fondaparinux and bivalirudin, prognosis and ischemic events reduction of ACS patients can be achieved over the past couple of years[3]. Nevertheless, the increased bleeding rate, especially when using these new materials, remains a serious challenge for current treatment[4]. Despite Western medicine develops rapidly in treating Cardiovascular Disease (CVD), the mortality rate of CVD remains high, at present, traditional Chinese

***Address for correspondence**
E-mail: chenying66323@163.com

medicine combined with Western medicine has become a common treatment method for various chronic diseases such as coronary heart disease and chronic lung disease[5]. Many clinical studies have indicated that the combination of traditional Chinese medicine and Western medicine can obtain more clinical benefits in patients with coronary heart disease[6].

Shexiang Baoxin Pill (SBP) is a classic prescription of Dynasty Song in China; it has been widely used for preventing and treating CVD, such as UA, Myocardial Infarction (MI) and Heart Failure (HF). SBP contains seven kinds of Chinese medicinal materials, artificial musk, ginseng, bezoar, cinnamon (cinnamon bark), storax, senso and borneol[7]. SBP can exert clinical therapeutic effects on CVD through various mechanisms such as regulating angiogenesis and coronary dilation, inhibiting inflammation and oxidative stress, improving lipid metabolism and protecting vascular endothelium[8]. Moreover, in clinical practice, multiple randomized controlled trials and expert consensus on SBP for CVD treatment has confirmed SBP protecting cardiovascular effect.

Angiotensin converting enzyme inhibitor, angiotensin receptor blocker and beta (β) receptor blocker have been proved to have effect on reducing mortality and morbidity in all stages of HF and preventing the transition from asymptomatic to symptomatic Left Ventricle (LV) dysfunction[9]. Metoprolol succinate is one of the common treatment drugs for ACS. We attempt to discuss the clinical efficacy of SBP combined with metoprolol succinate in ACS in remission patient's treatment.

MATERIALS AND METHODS

General information:

We randomly selected 72 patients in remission stage of ACS in our cardiology department from March 2021 to December 2021 as study cohort.

Inclusion criteria: Meet the diagnostic criteria of 'Guidelines for the diagnosis and treatment of non ST segment elevation ACS', after coronary angiography and Index of Microcirculatory Resistance (IMR) test, diagnosed as ACS in remission patient; ages were from 18 y to 75 y old; patients with complete basic information, physical and chemical examination and the patient himself or his family had signed the informed consent.

Exclusion criteria: Severe cardiac arrhythmias patients; patients combined with hemorrhagic cerebrovascular accident and gastrointestinal bleeding; patients with coagulation disorder; severe diabetes complications; severe liver and kidney function impairment (serum alanine aminotransferase >3 times the upper normal limit and/or serum creatinine levels, 265 μmol/l); malignant tumor, psychiatric patient and allergy to SBP and metoprolol succinate. General information of both groups had comparability ($p>0.05$) as shown in Table 1.

Methods:

Treated both groups with regular Western medicine, including anti-ischemia (nitrates), antiplatelet (aspirin), anticoagulation (heparin), regulating lipid (statins), etc. Specific drugs included, Bayaspirin 100 mg, 1/d, orally; Plavix (Sanofi Aventis Pharmaceutical Co., Ltd): 75 mg, 1/d, orally; low molecular weight heparin calcium (Tianjin Chase Sun Pharmaceutical Co., Ltd.): 6000 IU, 2/d, subcutaneous injection; nitroglycerin: 0.5 mg orally, repeated use within 5 min in severe cases; atorvastatin calcium: 20 mg, 1/d, orally every day. Diagnosis and treatment of blood pressure or hypoglycemia are also given to individual patients. Treated control group with metoprolol succinate (Astrazeneca AB National License Medical Number J20100098), 23.75 mg-45.7 mg, orally, once daily; after receiving the same control group treatment, gave observation group SBP (Shanghai Hehuang Pharmaceutical Co., Ltd, National License Medical Number Z31020068), 22.5 mg-45 mg, orally, Three Times a Day (TID). The course of treatment was 4 w and did not use other traditional Chinese medicines in the diagnosis and treatment stage.

Observation indicators:

Detection of Angiotensin II (Ang II), Endothelin-1 (ET-1) and Nitric Oxide (NO) in peripheral blood serum: Collected the fasting elbow vein 5 ml of both groups' patients in the early morning of the 2nd d of hospitalization and placed them into two centrifuge tubes respectively, 3 ml each. Left one of the tubes at room temperature for 30 min, then centrifuged at 3500 r/min (4°) for 10 min, extracted supernatant. Adopted Enzyme-Linked Immunosorbent Assay (ELISA) to test Ang II, ET-1 and NO concentration in peripheral blood serum. After 1 mo treatment, tested Ang II, ET-1 and NO concentration in serum.

Cardiac function measurement: Monitored the cardiac function of both groups before and after treatment, and the main monitoring indicators were Left Ventricular End Diastolic Diameter (LVEDD), Left Ventricular Ejection Fraction (LVEF), Stroke Volume (SV) and Left Ventricular End Systolic Diameter (LVESD), the

monitor machine was M-type echocardiogram monitor (Purchased from Philips Corporation, USA).

Efficacy evaluation criteria refer to literature standards:

According to the "Guidelines for the Diagnosis and Treatment of Non ST segment Elevation ACS"[10] jointly issued by the National Health Commission and the State Administration of Traditional Chinese Medicine in 2019, the criteria for evaluating the efficacy, clinical efficacy was judged according to symptoms, signs and Electrocardiogram (ECG) indicators.

Markedly effective: Under the same physical labor intensity, the number of angina pectoris symptoms decreased by more than 80 %.

Effective: The number of angina pectoris symptoms decreased by 50 % to 80 %.

Ineffective: The number of angina pectoris episodes had not improved significantly and even the number of angina pectoris or symptoms had worsened.

Cardiovascular adverse events:

Cardiovascular events including primary endpoints, secondary endpoints and combined endpoints. Endpoint events included sudden cardiac death and shock, arrhythmia, secondary MI and secondary revascularization (including PCI and Coronary Artery Bypass Grafting (CABG)); secondary endpoints included readmissions due to ACS, recurrent myocardial ischemia, cardiac insufficiency, non-fatal stroke and all kinds of thrombosis (including in stent restenosis, lower extremity arterial occlusion) and the combined endpoint is the combination of the primary and secondary endpoints.

Statistical analysis:

Adopted Statistical Package for the Social Sciences (SPSS) 25.0 to process and analyze data. Expressed the enumeration data by percent (%) and compared between groups by Chi square (χ^2) test. Measurement data (cardiac function and serum indexes, etc.) accorded with normal distribution and homogeneous variance, expressed by ($\bar{x}\pm s$), compared by t test and $p<0.05$, showing that the divergence was of statistical significance.

RESULTS AND DISCUSSION

Both groups possessed no obvious difference on age, gender, blood pressure, number of coronary lesions, etc. ($p>0.05$), both groups had comparability as shown in Table 1.

Comparison of cardiac function indexes (LVEDD, LVESD, LVEF (%), SV) between both groups before and after treatment was done. After 1 mo of SBP combined with metoprolol succinate, LVEDD and LVESD value decreased more than metoprolol succinate group, it was of statistical significance ($p<0.05$); SV value increased more than metoprolol succinate group, it was of statistical significance ($p<0.05$) as shown in Table 2.

TABLE 1: COMPARISON OF BOTH GROUPS ON GENERAL INFORMATION

	Observation group (n=36)	Control group (n=36)	t/ ^{2}	p
Age	62.7±9.09	63.11±8.77	-0.19	0.84
Gender (male)	16 (44.4 %)	15 (41.7 %)	0.06	0.81
BMI (kg/m^2)	25.68±4.63	26.08±4.51	-0.35	0.72
Diastolic pressure (mmHg)	86.5±18.60	86.05±14.69	0.11	0.9
Systolic pressure (mmHg)	171.05±20.31	164.5±22.35	1.3	0.19
Vasculopathy			0.31	0.86
Single vessel lesion (case (%))	14 (38.9 %)	12 (33.3 %)		
Double vessel lesion (case (%))	12 (33.3 %)	14 (38.9 %)		
Triple vessel lesion (case (%))	10 (27.8 %)	10 (27.8 %)		
Undergoing PCI (case (%))	17 (47.22 %)	19 (52.7 %)	0	1

TABLE 2: COMPARISON OF CARDIAC FUNCTION INDEXES (LVEDD, LVESD, LVEF (%), SV) BETWEEN BOTH GROUPS BEFORE AND AFTER TREATMENT

ITEM	Before and after treatment	Observation group (n=36)	Control group (n=36)	t	p
LVEDD (MM)	Before treatment	59.25±6.95	59.56±87.71	-0	0.98
	After treatment	46.08±5.12	49.42±5.20	-2.7	0.007
LVESD (MM)	Before treatment	41.31±6.71	43.28±5.86	-0.7	0.51
	After treatment	30.19±6.11	34.19±4. 14	-3.3	0.002
LVEF (%)	Before treatment	54.06±6.98	54.22±7.06	-0.1	0.92
	After treatment	54.69±7.41	54.00±7.91	0.38	0.7
SV (ML)	Before treatment	73.64±7.06	71.72±7.88	1.08	0.28
	After treatment	79.63±10. 24	73.31±7.95	2.92	0.04

Compared both groups on Ang II, ET-1 and NO concentration levels before treatment, they had no remarkable difference, it was no of statistical significance ($p>0.05$); after 1 mo treatment, Ang II and ET-1 concentration levels decreased remarkably, SBP combined with metoprolol succinate group decreased higher than control group, the obvious difference was of statistical significance ($p<0.05$); NO concentration levels of both groups increased, SBP combined with metoprolol succinate group increased greater than control group, the obvious difference was of statistical significance ($p<0.05$) as shown in Table 3.

After 1 mo treatment for both groups, observation group had 32 cases markedly effective and effective patients, the total clinical efficacy was 88.9 %; control group had 21 cases markedly effective and effective patients, the total clinical efficacy was 55.5 %, the total clinical efficacy possessed statistical significance ($p<0.05$) as shown in Table 4.

After one course of treatment, observation group had 3 cases adverse events, cardiovascular event rate was 8.33 %; control group had 5 cases adverse events, cardiovascular event rate was 13.89 %, the cardiovascular event rate possessed statistical significance ($p<0.05$) as shown in Table 5.

TABLE 3: COMPARISON OF SERUM CONCENTRATION LEVELS OF ANG II, ET-1 AND NO IN BOTH GROUPS BEFORE AND AFTER TREATMENT

Item	Before and after treatment	Observation group (n=36)	Control group (n=36)	t	p
Ang II (pg/ml)	Before treatment	187.64±49.58	190.35±49.21	-0.2	0.8
	After treatment	96.08±28.75	170.78±45.54	-8.3	0
ET-1 (ng/l)	Before treatment	121.22±16.11	122.54±13.73	-0.4	0.7
	After treatment	74.45±6.07	95.39±21.81	-5.5	0
NO (μmol/l)	Before treatment	60.86±11.42	58.78±12.22	0.74	0.5
	After treatment	96.67±14.34	88.67±15.76	2.52	0

TABLE 4: COMPARISON OF BOTH GROUPS ON CLINICAL EFFICACY AFTER TREATMENT

	Markedly effective	Effective	Ineffective	Total clinical efficacy
Observation group	10 (27.7 %)	22 (61.1 %)	4 (2.78 %)	32 (88.9 %)
Control group	5 (13.8 %)	16 (44.4 %)	15 (27.7 %)	20 (55.5 %)
				8.98
p				0.011

TABLE 5: THE INCIDENCE OF ADVERSE CARDIOVASCULAR EVENTS IN BOTH GROUPS

Group	Case	Sudden death	HF	PCI	HF	CABG	Cardiovascular event rate (%)
Observation group	36	0	1	1	0	1	8.33
Control group	36	0	2	2	1	0	13.89

Note: As for the cardiovascular event rate; p>0.05, it had no statistical significance

ACS is a potential disease which threatens life; it affects millions of people each year. Despite MI hospitalization rates decrease, but how to identify and prevent ACS remains an important public health issue[11]. In the past couple of years, researchers have gained a better understanding of the pathophysiology of ACS, along with great advances in medical management. Initial ACS management should contain risk stratification, appropriate drug management (including Dual Antiplatelet Therapy (DAPT), anticoagulation and appropriate adjuvant therapy), and a decision to adopt an early invasive or regular treatment strategy. Long term management after an ACS event should be tailored according to each patient's circumstances[12]. This study also explores the effect of SBP combined with metoprolol succinate on clinical efficacy of ACS in remission patients; it significantly improves the clinical efficacy of ACS in remission patients and has great clinical reference value in the long term treatment and patient's management.

Previous studies have shown that SBP can improve endothelial dysfunction. Since endothelial dysfunction is a key factor in cardiovascular system diseases development, restoring and maintaining endothelial cells normal function has been considered as an effective treatment for ACS[13]. When the coronary arteries stimulated, the endothelial barrier injured, the permeability increased and the accumulation of lipids and leukocytes into the intima accelerated, promoting vascular stenosis, then ischemic heart disease and stroke happened. At the same time, endothelial dysfunction leads to decreasing endothelium-dependent vasoactive substances such as NO, vasodilation properties impairment and increasing related vascular stiffness, thereby increasing blood pressure and aggravating hypertension[14]. Reactive Oxygen Species (ROS) and oxidative stress are considered major pathological factors associated with endothelial damage. SBP has been reported to increase NO production by enhancing NO activity, considering that NO plays a key effect in regulating anti-apoptotic and antioxidant capacity, this is also the mechanism that SBP protects coronary vessels from ROS induced damage. In cerebral ischemia-reperfusion injury experimental model, we found SBP increased B-cell lymphoma 2 levels, decreased caspase-3 levels to protect brain cells, SBP may be involved in ameliorating endothelial dysfunction through the regulation of related apoptotic pathways[15]. Furthermore, SBP can protect endothelial function in ACS patients by increasing NO and SOD and decreasing ET-1 and Malondialdehyde (MDA) [16]. This study also confirmed that SBP can effectively improve endothelial function in patients with ACS, which is consistent with previous studies.

Due to mature cardiomyocytes's limited regenerative capacity, functional cardiomyocytes loss results in a decreased ability of remaining cardiomyocytes to compensate for systolic function, simultaneous production of excess extracellular matrix, it leads to cardiac hypertrophy, structural disorder and fibrosis and cardiac remodeling[17]. One study monitoring SBP's role in diabetic rats' cardiac pathological changes shows that SBP remarkably reduces myocardial interstitial fibrosis, reverses fiber disorder and mitochondrial swelling and, improves systolic and diastolic function. Studies have found that SBP can inhibit Transforming Growth Factor-beta 1 (TGF-β1)/SMAD pathway activation, thereby hindering hypertension induced myocardial fibrosis development[18]. Moreover, studies have shown that SBP gavage increases LVEF and improves cardiac function in rats with myocardial ischemia[19]. This study also confirmed that SBP can effectively improve the cardiac function indicators in patients with ACS, which is consistent with previous studies.

SBP is derived from ancient Chinese medicine formula, it has been shown to have a direct therapeutic effect on CVD, promotes angiogenesis, inhibits inflammation, improves endothelial function and dyslipidemia, and interferes with vascular smooth muscle cell growth and cardiac remodeling[20]. In view of the above pharmacological and therapeutic characteristics of cardiovascular system, SBP is worthy of promotion and application in clinic further. Meanwhile, we need more experiments and clinical trials in the future to

support SBP use by providing more reliable evidence. This study also confirmed that SBP combined with metoprolol succinate can significantly improve cardiac function and intravascular function. The study also has shortcomings, first of all, the study sample size is small, which will lead to biased results, secondly, the comparison of adverse reactions was not included in this study, which needs to be further improved in future research.

The results of this study confirmed that the incidence of cardiovascular events, the efficacy of angina pectoris, the ECG score, the high-sensitivity C-reactive protein in both groups, results showed $p<0.05$, they possessed statistical significance, observation groups possessed higher total effective rate than control group, indicating the clinical effect of metoprolol succinate sustained-release tablets combined with SBP in treating UA of coronary heart disease is exact and should be widely used in clinical.

Conflict of interests:

The authors declare no conflict of interests.

REFERENCES

1. Cavallari I, Cannon CP, Braunwald E, Goodrich EL, Im K, Lukas MA, *et al.* Metabolic syndrome and the risk of adverse cardiovascular events after an acute coronary syndrome. Eur J Prev Cardiol 2018;25(8):830-8.
2. Derumeaux G, Ternacle J. Layer-specific strain in acute coronary syndrome: Back to the future! Eur Heart J Cardiovasc Imaging 2018;19(12):1325-6.
3. Gach O, El HZ, Lancellotti P. Acute coronary syndrome. Rev Med Liege 2018;73(5-6):243-50.
4. Granville Smith I, Parker G, Rourke P, Cvejic E, Vollmer-Conna U. Acute coronary syndrome and depression: A review of shared pathophysiological pathways. Aust N Z J Psychiatry 2015;49(11):994-1005.
5. Makki N, Brennan TM, Girotra S. Acute coronary syndrome. J Intensive Care Med 2015;30(4):186-200.
6. Okajima F, Kurihara O, Takano M. Acute coronary syndrome and postprandial delayed hyperchylomicronemia. Aging (Albany NY) 2019;11(9):2549.
7. Sun ML, Qu C, Guo SY. Clinical efficacy of Shexiang Baoxin pill in treatment of coronary microcirculation disorders. Chin J Emerg Resusc Disaster Med 2022;17(1):98-1016.
8. Salvo F, Bezin J, Bosco-Levy P, Letinier L, Blin P, Pariente A, *et al.* Pharmacological treatments of cardiovascular diseases: Evidence from real-life studies. Pharmacol Res 2017;118:43-52.
9. Ueland T, Aukrust P, Caidahl K. CCL21 and prognosis in acute coronary syndrome. Aging (Albany NY) 2019;11(21):9225.
10. Ge JB. Interpretation of guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndrome. Chin Circul J 2017;32(z2):5-6.
11. Cottel D, Montaye M, Marécaux N, Amouyel P, Dallongeville J, Meirhaeghe A. Comparison of the rates of stroke and acute coronary events in northern France. Eur J Prev Cardiol 2018;25(14):1534-42.
12. Tang AR, Rabi DM, Lavoie KL, Bacon SL, Pilote L, Kline GA. Prolonged hypothalamic-pituitary-adrenal axis activation after acute coronary syndrome in the GENESIS-PRAXY cohort. Eur J Prev Cardiol 2018;25(1):65-72.
13. Agwa SH, Elzahwy SS, El Meteini MS, Elghazaly H, Saad M, Abd Elsamee AM, *et al.* ABHD4-regulating RNA panel: Novel biomarkers in acute coronary syndrome diagnosis. Cells 2021;10(6):1512.
14. Canto JG, Canto EA, Goldberg RJ. Time to standardize and broaden the criteria of acute coronary syndrome symptom presentations in women. Can J Cardiol 2014;30(7):721-8.
15. Galappatthy P, Bataduwaarachchi VR, Ranasinghe P, Galappatthy GK, Wijayabandara M, Warapitiya DS, *et al.* Management, characteristics and outcomes of patients with acute coronary syndrome in Sri Lanka. Heart 2018;104(17):1424-31.
16. Henri C, Rouleau JL. Acute pulmonary edema and acute coronary syndrome: Mostly a trigger or an associated phenomenon? Can J Cardiol 2016;32(10):1200-2.
17. Parker GB, Cvejic E, Vollmer-Conna U, McCraw S, Granville Smith I, Walsh WF. Depression and poor outcome after an acute coronary event: Clarification of risk periods and mechanisms. Austr N Z J Psychiatry 2019;53(2):148-57.
18. Fan XR, Zhang XS, Huang ZJ. Effect of Shexiang Baoxin pill on aortic fibrosis induced by aldosterone in rats. Chin J Int Med Cardio Cerebrov Dis 2022;20(6):988-90.
19. Qanitha A, de Mol BA, Pabittei DR, Mappangara I, van der Graaf Y, Dalmeijer GW, *et al.* Infections in early life and premature acute coronary syndrome: A case-control study. Eur J Prev Cardiol 2016;23(15):1640-8.
20. Chen BZ, Feng MJ, Chang FY. Effect of Shexiang Baoxin pill on vascular endothelial function in patients with coronary artery microcirculation disorder. Chin J Integr Med Cerebrovasc Dis 2022;20(1):182-4.

This article was originally published in a special issue, "Modern Applications in Biomedical Research and Pharmaceutical Sciences" Indian J Pharm Sci 2022:84(3) Spl Issue "13-18"