

Effects of Perindopril and Amlodipine Combined with Shengmai Injection in Elderly Hypertensive with Heart Failure

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The main objective of this study was to observe the effects of perindopril and amlodipine combined with Shengmai injection on ventricular remodeling, blood pressure control and heart rate variability in elderly hypertensive patients complicated by heart failure. Eighty-six hypertension+heart failure patients treated between January 2021 and January 2023 in our hospital were included and divided into two groups. 43 patients treated with perindopril and amlodipine tablets (perindopril amlodipine group) and based on the perindopril amlodipine group, 43 patients received Shengmai injection (Shengmai injection combination group). Tumor necrosis factor-alpha, high-sensitivity C-reactive protein, angiotensin II, fibroblast growth factor 23, endothelin, left ventricular end diastolic diameter, E peak flow rate/A peak flow rate, left ventricular end-systolic diameter and Minnesota heart failure quality of life scale scores were decreased in the Shengmai injection combination group compared to the perindopril amlodipine group. Besides, nitric oxide, the proportion of number of times successive heartbeat intervals exceed 50 ms divided by the total number of normal-to-normal intervals, standard deviation of normal-to-normal intervals, root-mean-square successive differences and left ventricular ejection fraction were elevated in Shengmai injection combination group vs. perindopril amlodipine group. Lower adverse reaction rate, higher overall response and blood pressure control rates were also identified in the Shengmai injection combination group. Therefore, perindopril and amlodipine plus Shengmai injection enhances vascular endothelial function, ventricular remodeling, cardiac function and heart rate variability, blood pressure control and clinical efficacy while reducing inflammation in elderly hypertension+heart failure patients.

Key words: Perindopril tablets, amlodipine tablets, Shengmai injection, hypertension, heart failure, ventricular remodeling, heart rate variability

Hypertension (HT) is a systemic disorder with arterial pressure elevation characteristics. Persistent HT can easily expand the Left Ventricle (LV), increase ventricular load, gradually reduce cardiac ejection function and ultimately develop into Heart Failure (HF)^[1,2]. Early-stage HT is asymptomatic or symptomatic and typical, and as the disease progresses, there may be clinical symptoms such as headache, dizziness and memory loss^[3]. Uncontrolled blood pressure can lead to progressive involvement of multiple organs in the body, resulting in the failure of corresponding target organs^[4]. Research studies has shown that HT is an important risk factor for HF with a high probability of 28.9 % among hypertensive individuals and it is more common in the elderly

population, seriously affecting the quality of life of patients^[5]. Perindopril and amlodipine are commonly used drugs for patients with HT. While treating HT with these drugs, they can reduce the cardiac function damage to a certain extent^[6]. Among them, perindopril is a third-generation angiotensin-converting enzyme inhibitor that reduces Angiotensin II (Ang II) production, promotes vasodilation and reduces peripheral vascular resistance, thereby improving cardiac and vascular function^[7]. While amlodipine is a class of dihydropyridine calcium antagonists, which can selectively inhibit the transmembrane entry of calcium ions into smooth muscle cells, regulate serum endothelin and improve the function of vascular endothelium, without causing significant

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changes in heart rate in the long-term^[8]. Perindopril or amlodipine alone has a slow onset of action and very limited efficacy. The main pathogenesis of elderly hypertensive patients with HF is qi and yin deficiency, poor qi and blood circulation, insufficient nourishment in the meridians and heart vessels^[9]. Shengmai injection is mainly composed of ginseng, radix ophiopogonis and *Schisandra chinensis*, which is a traditional Chinese medicine used for the treatment of HF. According to the theory of traditional Chinese medicine, Shengmai injection can reinforce qi and nourish yin, promotes blood circulation to remove meridian obstruction, restore the pulse for relieving desertion and nourish the heart, which is widely used to treat vascular diseases and is beneficial to patients with HF^[10]. Therefore, the effect of perindopril and amlodipine combined with Shengmai injection on elderly HT+HF patients was explored and reported in this study.

MATERIALS AND METHODS

General information:

Eighty-six HT+HF patients treated at The Third Central Hospital of Tianjin between January 2021 and January 2023 were selected for study, including 43 patients in the perindopril amlodipine group (24 females and 19 males) and 43 patients in the Shengmai injection combination group (23 females and 20 males). In the perindopril amlodipine group, the age range was 61 y-85 y, mean (69.54±3.23) y and the duration of HT was 3 y-14 y, mean (8.26 ± 1.35) y, with New York Heart Association (NYHA) grade II, grade III and grade IV found in 21, 15, and 7 patients, respectively. In the Shengmai injection combination group, the average age was 60 y-84 y, mean (69.35 ± 3.15) y, and the course of HT was 3 y-15 y, mean (8.52 ± 1.49) y with NYHA grade II, grade III and grade IV found in 19, 16, and 8 patients, respectively. The two groups were not significantly different in general data (p>0.05). This study was approved by the ethics committee of The Third Central Hospital of Tianjin (Ethics approval number: 0025N-0016).

Inclusion criteria:

Patients should meet the diagnostic criteria for primary HT^[11] or chronic HF^[12] and is classified as qi yin deficiency type^[13]; age was 60-85 y old; patients with good compliance; patients who have not received relevant medication treatment within

last 15 d; patient and their family signed a consent form and voluntarily participated in the study.

Exclusion criteria:

Patients with poor compliance; patients with concomitant infectious diseases, congenital heart disease, malignant tumors and immune system diseases; pregnant or lactating women; other cardiovascular diseases such as malignant arrhythmia, active myocarditis, cardiogenic shock, constrictive pericarditis and severe electrolyte disorders; severe liver and kidney dysfunction; HF caused by other factors and individuals with mental disorders.

Research method:

Perindopril amlodipine group: Patients need to eat light diet, control salt intake, take adequate rest and take perindopril tablets (Servier Tianjin Pharmaceutical Co., Ltd., H20100716, 4 mg), once a day, 4 mg each time, amlodipine tablets (Pfizer Pharmaceutical Co., Ltd., H10950224, 5 mg), once a day, 5 mg each time continuously for 3 mo.

Shengmai injection combination group: On the basis of perindopril amlodipine group, patients were given Shengmai injection (Z32021056, 25 ml/tube, Jiangsu Suzhong Pharmaceutical Group Co., Ltd×3 tubes/box), once a day, 25 ml each time, diluted with 250 ml of 5 % glucose injection before intravenous drip continuously for 3 mo.

Observation indicators:

Before and after treatment, 5 ml fasting elbow venous blood was drawn for the determination of the high-sensitivity C-Reactive Protein (hs-CRP), Ang II and Tumor Necrosis Factor alpha (TNF-α), Nitric oxide (NO), Fibroblast Growth Factor 23 (FGF23) and Endothelin (ET) levels by Enzyme-Linked Immunosorbent Assay (ELISA) with all the kits provided by Shanghai Qiaoyu Biotechnology Co., Ltd.

Before and after treatment, the proportion of number of times successive heartbeat intervals exceed 50 ms divided by the total number of Normal-to-Normal (NN) (R-R) intervals (PNN50), Standard Deviation of NN intervals (SDNN), and Root Mean Square of Successive Differences (RMSSD) were measured using a 12 lead dynamic electrocardiogram to determine the Heart Rate Variability (HRV).

Before and after treatment, Left Ventricular End

Systolic Diameter (LVESD), E-peak flow rate/A-peak flow rate (E/A), Left Ventricular Ejection Fraction (LVEF) and Left Ventricular End Diastolic Diameter (LVEDD) levels were quantified using BLS-X8 Color Doppler ultrasound diagnostic instrument.

Patients with qi and yin deficiency mainly present the following adverse reactions include shortness of breath, palpitations, fatigue, night sweating, spontaneous sweating, sweating while moving, dizziness, restlessness, dark red cheeks and dry mouth. Based on the severity level of the Traditional Chinese Medicine (TCM) syndrome, asymptomatic (0 points), mild (2 points), moderate (4 points) and severe (6 points) scores are assigned to patients, respectively^[13].

The Minnesota Heart Failure Quality of Life Scale (MLHFQ) was assessed before and after treatment to estimate the patient's symptoms, activity tolerance, work, etc., with a total score of 105 points, which is negatively correlated with quality of life.

After treatment, the patient will be tested with an ambulatory blood pressure detector. After entering the consultation room, the patient will rest for 5-10 min before testing. After 1-2 min of the first measurement, once again the measurement will be conducted. A third measurement will be carried out if a difference >5 mmHg is determined between the previous two readings and the mean will be taken to calculate the Blood Pressure Control (BPC) rate of each group. The BPC target is <140/90 mmHg^[14].

Clinical efficacy standards:

The patient's heart function has significantly improved and the TCM syndrome score has decreased by 75 % or more, indicating a significant improvement. The patient's heart function has improved and the TCM syndrome score has decreased by 50 %-75 %, which is recorded as effective and meeting none of the

above standards is considered invalid^[13].

Total effective rate (%)=(Significant+effective)/Total×100 %

Statistical analysis:

The obtained statistical data from this study will be analyzed using Statistical Package for Social Sciences (SPSS) 23.0 software (Microsoft, Redmond, USA) and $p < 0.05$ is used as the significance level. Blood indicators, MLHFQ, TCM syndrome score, HRV, LVEF, LVEDD, E/A and LVESD will be expressed in the form of " $\bar{x} \pm s$ ". Paired t-tests will be used to detect intra group data and group t-tests will be used to detect inter group data. Clinical efficacy and BPC rate are analyzed with the Rank sum test and the Chi-square (χ^2) test, respectively.

RESULTS AND DISCUSSION

Before treatment, two groups had similar TNF- α and hs-CRP contents ($p > 0.05$). But after treatment, TNF- α and hs-CRP were reduced in both groups ($p < 0.05$) with lower levels in Shengmai injection combination group ($p < 0.05$) (Table 1).

Ang II, NO, FGF23 and ET were similar in two groups prior to treatment ($p > 0.05$). After treatment, Ang II, FGF23 and ET reduced in both groups ($p < 0.05$), with more notable reductions in Shengmai injection combination group ($p < 0.05$). NO was elevated in both groups but higher in Shengmai injection combination group compared with perindopril amlodipine group ($p < 0.05$) (Table 2).

PNN50, SDNN and RMSSD were compared between the two groups of patients. Before treatment, two groups were similar in PNN50, SDNN, and RMSSD ($p > 0.05$). After treatment, PNN50, SDNN and RMSSD of both groups increased ($p < 0.05$), with even higher levels in Shengmai injection combination group ($p < 0.05$) (Table 3).

TABLE 1: COMPARISON OF TNF- α AND hs-CRP CONTENTS BETWEEN THE TWO GROUPS OF PATIENTS ($\bar{x} \pm s$)

Groups	n	TNF- α (ng/l)		hs-CRP (mg/l)	
		Before treatment	After treatment	Before treatment	After treatment
Perindopril amlodipine	43	81.02 \pm 13.12	61.35 \pm 8.23 ^a	9.45 \pm 2.35	4.08 \pm 1.23 ^a
Shengmai injection combination	43	81.65 \pm 12.66	45.61 \pm 6.54 ^a	9.67 \pm 2.50	2.14 \pm 0.57 ^a
t		0.227	9.819	0.42	9.394
p		0.812	<0.001	0.675	<0.001

Note: ^a $p < 0.05$ vs. before treatment in this group

TABLE 2: COMPARISON OF ANG II, NO, FGF23 AND ET LEVELS BEFORE AND AFTER TREATMENT BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Clinical characteristics	Treatment	Group		t	p
		Perindopril amlodipine (n=43)	Shengmai injection combination (n=43)		
Ang II (ng/l)	Before treatment	12.55±3.12	12.09±3.45	0.648	0.518
	After treatment	7.44±2.03 ^a	4.62±1.12 ^a	7.976	<0.001
NO (μmol/l)	Before treatment	45.67±7.23	45.32±7.05	0.227	0.821
	After treatment	58.53±10.12 ^a	70.39±13.10 ^a	4.698	<0.001
FGF23 (ng/l)	Before treatment	684.06±19.15	685.92±18.68	0.456	0.65
	After treatment	501.33±23.17 ^a	477.61±25.25 ^a	4.539	<0.001
ET (pg/ml)	Before treatment	88.86±8.42	88.49±8.15	0.207	0.836
	After treatment	73.23±10.52 ^a	59.41±12.37 ^a	5.581	<0.001

Note: ^ap<0.05 vs. before treatment in this group

TABLE 3: COMPARISON OF PNN50, SDNN, AND RMSSD LEVELS BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Group	PNN50 (%)		SDNN (ms)		RMSSD (ms)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Perindopril amlodipine	5.23±0.85	6.41±1.04 ^a	117.45±2.32	121.56±3.13 ^a	31.56±3.52	38.12±4.16 ^a
Shengmai injection combination	5.06±0.81	7.66±1.15 ^a	117.12±2.40	124.63±3.85 ^a	31.29±3.45	44.61±5.12 ^a
t	0.949	5.286	0.648	4.062	0.359	6.451
p	0.345	<0.001	0.519	<0.001	0.72	<0.001

Note: ^ap<0.05 vs. before treatment in this group

Before treatment, there were no statistically difference in LVEF, LVEDD, E/A, and LVESD values between the two groups ($p>0.05$). After treatment, LVEF of both groups was increased and was higher in Shengmai injection combination group than in perindopril amlodipine group ($p<0.05$). LVEDD, E/A and LVESD were reduced in both groups, with even further lower levels in Shengmai injection combination group ($p<0.05$) (Table 4).

Before treatment, the two groups showed no marked differences in adverse reactions and TCM syndrome scores ($p>0.05$). After treatment, the adverse reactions and TCM syndrome score in the two groups was reduced significantly ($p<0.05$) and were even lower in the Shengmai injection combination group ($p<0.05$) (Table 5).

Before treatment, the MLHFQ score was similar in two groups ($p>0.05$). After treatment, the MLHFQ score of patients in both groups reduced statistically

($p<0.05$) and was much lower in Shengmai injection combination group compared to perindopril amlodipine group ($p<0.05$) (Table 6).

Clinical efficacy and BPC rate was compared between the two groups of patients. The Shengmai injection combination group showed higher total effective rate and BPC rate than the perindopril amlodipine group ($p<0.05$) (Table 7).

HT is a common chronic disease in clinical practice and persistent HT can easily lead to HF in the body. Elevated arterial pressure can increase the LV afterload of the body. In order to maintain normal systolic ventricular wall stress, myocardial cells gradually undergo hypertrophy, thereby increasing the volume of myocardial cells resulting in abnormal myocardial contraction and relaxation function. The degeneration and proliferation of vascular smooth muscle cells can reduce the lumen area of coronary arteries, reduce their responsiveness to

vasodilators and cause functional damage to vascular endothelial cells^[15,16]. Myocardial hypertrophy can reduce capillary density, abnormal microcirculation function, exacerbate metabolic abnormalities and cause myocardial ischemia. The increase of pressure load in hypertensive patients is the initiating factor for ventricular remodeling. High pressure load can increase the weight of the LV, promote myocardial cell apoptosis and myocardial fibrosis, reduce myocardial contractility, continuously increase the work of the heart to maintain cardiac output, ultimately reduce cardiac output and induce HF^[17]. Perindopril is an angiotensin converting enzyme inhibitor that can reduce the body's production of Ang II, activate phosphatase C, release intracellular calcium ions, promote the body's production of NO by activating NO synthase, dilating blood vessels and producing a blood pressure lowering effect. High levels of NO can relax blood vessels, reduce myocardial oxygen consumption, inhibit the release of sympathetic neurotransmitters, reduce myocardial damage and improve cardiac function. Amlodipine is a long-term dihydropyridine calcium antagonist, which can dilate the blood vessels and coronary vessels, promote the increase of coronary blood flow and reduce blood pressure. Along with that its half-life is long, its vasodilator and antihypertensive effect is stable, which can prevent rapid blood pressure drop, reduce LV afterload and reduce the occurrence of LV hypertrophy^[18].

HF belongs to the category of “chest obstruction” in TCM, which is often caused by the patient's prolonged illness, weak physical condition and insufficient heart qi. Qi deficiency cannot promote blood circulation, resulting in blood stasis. If the patient's emotional state was not smooth and overworked, it

can lead to qi stagnation and blood stasis. Long-term qi deficiency can cause insufficient yin and blood, coupled with unfavorable blood flow, exacerbating blood flow obstruction, internal stasis and loss of nourishment in the heart^[19]. Shengmai injection is a TCM with simple preparation in which red ginseng is used to replenish vital energy, restore the pulse to firm off, replenish qi and absorb blood, activate blood to remove stasis, strengthen the heart and relieve pain. *Ophiopogon japonicus* is used to moisturize the lungs and clear away the heart fire, nourish yin to generate body fluids and remove annoyance. *Schisandra chinensis* is used to enhance qi while nourishing fluid and calm the heart. The combination of the three can achieve the functions of replenishing qi and yin, restoring the pulse to firm off, activating blood and dissolving stasis and nourishing the heart. Research has shown that Shengmai injection can reduce Ang II levels, inhibit aldosterone production, block the renin angiotensin aldosterone system and reverse ventricular remodeling. It can also inhibit inflammatory damage, improve vascular endothelial function, ventricular repolarization and cardiac function^[20]. In addition, Shengmai injection also has the effect of dilating blood vessels and controlling patient blood pressure^[21].

Inflammatory reactions participate in the onset and development of HT+HF. hs-CRP can promote inflammation, accelerate atherosclerosis formation in arteries and TNF- α induced inflammation can also exacerbate vascular damage^[22]. Shengmai injection combination group showed lower TNF- α and hs-CRP contents than perindopril amlodipine group, which indicates that perindopril and amlodipine combined with Shengmai injection can reduce inflammatory damage in elderly HT+HF patients.

TABLE 4: COMPARISON OF LVESD, LVEF, E/A AND LVEDD BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Clinical characteristics	Treatment	Groups		t	p
		Perindopril amlodipine (n=43)	Shengmai injection combination (n=43)		
LVESD (mm)	Before treatment	65.72 \pm 4.75	65.27 \pm 4.32	0.56	0.647
	After treatment	59.25 \pm 3.92 ^a	55.24 \pm 3.15 ^a	5.229	<0.001
LVEF (%)	Before treatment	36.09 \pm 4.22	36.35 \pm 4.40	0.28	0.78
	After treatment	46.54 \pm 5.11 ^a	55.81 \pm 5.75 ^a	7.902	<0.001
E/A	Before treatment	1.05 \pm 0.22	1.02 \pm 0.21	0.647	0.52
	After treatment	0.56 \pm 0.13 ^a	0.33 \pm 0.09 ^a	9.539	<0.001
LVEDD (mm)	Before treatment	57.61 \pm 5.48	57.13 \pm 5.32	0.412	0.681
	After treatment	54.30 \pm 4.05 ^a	50.12 \pm 3.22 ^a	5.298	0

Note: ^ap<0.05 vs. before treatment in this group

TABLE 5: COMPARISON OF ADVERSE REACTIONS AND TCM SYNDROME SCORE BETWEEN THE TWO GROUPS OF PATIENTS BEFORE AND AFTER TREATMENT ($\bar{x}\pm s$)

Adverse reaction and TCM syndrome score	Treatment	Group		t	p
		Perindopril amlodipine	Shengmai injection combination		
Shortness of breath	Before treatment	3.95±0.96	3.90±1.01	0.235	0.815
	After treatment	1.76±0.46 ^a	1.01±0.25 ^a	9.394	<0.001
Palpitations	Before treatment	3.93±1.01	4.01±1.05	0.36	0.712
	After treatment	1.81±0.47 ^a	1.03±0.26 ^a	9.523	<0.001
Fatigue	Before treatment	3.96±1.02	3.91±0.98	0.232	0.817
	After treatment	1.65±0.40 ^a	0.98±0.26 ^a	9.209	<0.001
Night sweating and spontaneous sweating	Before treatment	3.90±0.93	3.94±0.89	0.204	0.839
	After treatment	1.68±0.50 ^a	0.93±0.21 ^a	9.069	<0.001
Sweating while moving	Before treatment	3.84±1.03	3.93±1.10	0.392	0.696
	After treatment	1.76±0.45 ^a	1.01±0.21 ^a	9.04	<0.001
Dizziness and restlessness	Before treatment	1.85±0.52	1.88±0.55	0.26	0.796
	After treatment	1.09±0.36 ^a	0.48±0.19 ^a	9.827	<0.001
Dark red cheeks	Before treatment	1.82±0.50	1.86±0.52	0.364	0.717
	After treatment	0.79±0.23 ^a	0.45±0.13 ^a	8.439	<0.001
Dry mouth	Before treatment	1.86±0.48	1.81±0.50	0.473	0.637
	After treatment	0.81±0.23 ^a	0.43±0.11 ^a	9.774	<0.001

Note: ^ap<0.05 vs. before treatment in this group

TABLE 6: COMPARISON OF MLHFQ SCORES BETWEEN THE TWO GROUPS ($\bar{x}\pm s$)

Group	n	MLHFQ	
		Before treatment	After treatment
Perindopril amlodipine	43	80.04±13.34	65.15±10.45 ^a
Shengmai injection combination	43	79.25±13.51	55.46±8.12 ^a
t		0.273	4.801
p		0.786	<0.001

Note: ^ap<0.05 vs. before treatment in this group

TABLE 7: COMPARISON OF CLINICAL EFFICACY AND BPC RATE BETWEEN THE TWO GROUPS OF PATIENTS

Group	n	Significantly effective	Effective	Invalid	Total effective rate, n (%)	BPC rate, n (%)
Perindopril amlodipine	43	18	17	8	81.4	25 (58.14)
Shengmai injection combination	43	29	13	1	97.67	36 (83.72)
Z/ χ^2					4.468	6.824
p					0.035	0.009

High concentrations of FGF23 can cause endothelial dysfunction and ventricular remodeling, Ang II can cause the body to secrete a large amount of ET, inhibit NO and cause vascular endothelial damage^[23]. Lower Ang II, FGF23 and ET levels and higher NO levels were found in Shengmai injection combination group compared with perindopril amlodipine group, indicating that perindopril and amlodipine combined with Shengmai injection can improve the vascular endocutaneous function in elderly HT+HF patients. The higher PNN50, SDNN, RMSSD and LVEF and lower LVEDD, E/A and LVESD in Shengmai injection combination group compared with perindopril amlodipine group suggests that perindopril, amlodipine combined with Shengmai injection can improve HRV, ventricular remodeling and cardiac function in elderly HT+HF patients. The TCM syndrome and MLHFQ score of Shengmai injection combination group were lower and the total effective rate and BPC rate were higher compared with perindopril amlodipine group, which indicated that perindopril and amlodipine combined with Shengmai injection could improve the BPC rate and clinical efficacy in treating elderly patients with HT complicated with HF. The limitations of this study are few cases are included in this study, and the period of study time is short, that makes it not possible to observe the long-term curative effect of patients. Hence, future research work needs to be improved.

In summary, perindopril and amlodipine combined with Shengmai injection can reduce inflammatory damage, improve vascular endothelial function, ventricular remodeling, cardiac function, HRV and improve BPC rate and clinical efficacy in elderly patients with HT complicated by HF.

Conflict of interests:

The authors declared no conflict of interest.

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This article was originally published in a special issue, "Exploring the Role of Biomedicine in Pharmaceutical Sciences" Indian J Pharm Sci 2024;86(1) Spl Issue "56-63"