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A retrospective study on the short-term effect of high-dose spironolactone (80 mg/d) on chronic congestive heart failure

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Abstract

To explore the short-term effect of high-dose spironolactone (80 mg/d) on chronic congestive heart failure (CHF).

The general clinical data of 211 patients with CHF from February 2016 to August 2019 were collected and analyzed. Patients were divided into Low-dose group (taking 40 mg/d spironolactone) and High-dose group (taking 80 mg/d spironolactone) according to the patient's previous dose of spironolactone. The changes of B-type brain natriuretic peptide (BNP), NT-pro BNP (N terminal pro B type natriuretic peptide), echocardiography, 6-minute walking test (6MWT), and comprehensive cardiac function assessment data were collected for analysis.

Compared with before treatment, the blood potassium of the two groups increased significantly ($P < .05$), but the blood potassium did not exceed the normal range. Compared with before treatment, BNP, NT-pro BNP, LVEDD, LVEDV and NYHA grading were significantly decreased ($P < .05$), LVEF and 6-MWT were significantly increased ($P < .05$). Compared with the Low-dose group, the high-dose group BNP (117.49 ± 50.32 vs 195.76 ± 64.62, $P < .05$), NT-pro BNP (312.47 ± 86.28 vs 578.47 ± 76.73, $P < .05$), LVEDD (45.57 ± 5.69 vs 51.96 ± 5.41, $P < .05$), LVEDV (141.63 ± 51.14 vs 189.85 ± 62.49, $P < .05$) and NYHA grading (1.29 ± 0.41 vs 1.57 ± 0.49, $P < .05$) were significantly reduced, but, 6-MWT (386.57 ± 69.72 vs 341.73 ± 78.62, $P < .05$), LVEF (41.62 ± 2.76 vs 36.02 ± 2.18, $P < .05$) and total effective rate (92.68% vs 81.39%, $P < .05$) increased significantly.

Compared with 40 mg spironolactone, 80 mg spironolactone can rapidly reduce BNP and NT-pro BNP concentration, enhance exercise tolerance, improve clinical signs and cardiac function classification, and has better efficacy.

Abbreviations: 6MWT = 6-minute walking test, BNP = B-type brain natriuretic peptide, CHF = congestive heart failure, LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular end systolic diameter, LVESV = left ventricular end-systolic volume, NT-pro BNP = N terminal pro B type natriuretic peptide, NYHA = New York Heart Association, RAAS = renin-angiotension-aldosterone system.

Keywords: aldosterone, brain natriuretic peptide, chronic congestive heart failure, renin-angiotension-aldosterone system, spironolactone

1. Introduction

The incidence of chronic congestive heart failure (CHF) in the global population is about 0.4% to 2.0% and the 5-year mortality rate is as high as 21% to 50%, which seriously endangers people's life and health.[1,2] The etiology and pathogenesis of CHF are complex, in which renin-angiotension-aldosterone system (RAAS) is activated, peripheral blood vessels and left ventricular remodeling play an important role in the development of CHF.[3–5] As CHF worsens, the left ventricular tension increased, and the levels of B-type brain natriuretic peptide (BNP) and N-terminal pro brain natriuretic peptide precursor (NT-pro BNP) synthesized by cardiomyocytes also increased significantly.[6] At present, BNP and NT-pro BNP have become internationally recognized markers for the diagnosis of heart failure. The concentrations of BNP and NT-pro BNP and the speed of their growth are the objective indexes to judge the degree of CHF.[6–8]

The commonly used therapeutic drugs for CHF include ACEI, β receptor and aldosterone receptor antagonists. Studies have found that during the application of ACEI, plasma aldosterone levels decrease in a short period of time, but can still increase after long-term treatment. This phenomenon is called "aldosterone escape phenomenon".[9,10] At present,about 38% of patients have "aldosterone escape phenomenon".[9,10] It is suggested that the addition of spironolactone on the basis of conventional CHF treatment can not only reduce the phenomenon of aldosterone escape, but also improve the cardiac function and quality of life of patients by diuresis, edema elimination and myocardial fibrosis inhibition.[9,10] It is suggested that the addition of spironolactone on the basis of conventional CHF treatment can not only reduce the phenomenon of aldosterone escape, but also improve the cardiac function and quality of life of patients by diuresis, edema elimination, and myocardial fibrosis inhibition.[9–11] At present, there are few reports on the short-term effect of

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

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high-dose spironolactone on CHF and its effect on plasma BNP and NT-pro BNP. Therefore, this paper aims to explore the short-term therapeutic effect of high-dose spironolactone on CHF and its effect on BNP and NT-pro BNP, so as to provide reference for clinical intervention in CHF.

2. Materials and methods

2.1. Case collection

The general clinical data of 211 patients with CHF failure from February 2016 to August 2019 were collected and analyzed. Inclusion criteria: diagnosis of chronic CHF; New York Heart Association (NYHA) cardiac function grade III; patients with BNP (200–871ng/L); normal liver and kidney function. Exclusion criteria: acute myocardial infarction; implantation of artificial pacemaker; hyperthyroid heart disease; severe arrhythmia; pericardial disease; blood potassium is greater than 5.0 mmol/l; patients with hepatic insufficiency (continuous increase of serum transaminase more than 3 times of the upper limit of normal level) or renal insufficiency (creatinine clearance rate <30 ml/min); patients with hematological diseases; patients with primary aldosteronism. Cardiac function diagnostic criteria according to NYHA cardiac function classification: Level I, there is no heart failure symptom in daily activities; level II, there is heart failure symptom in daily activities (dyspnea, fatigue); level III, there is heart failure symptom lower than daily activities; level IV, there is heart failure symptom at rest.[12] The relationship between BNP value and NYHA classification is as previously reported: NYHA Class I BNP value is 83.1 ng/L; Class II is 235 ng/L (137–391 ng/L); Class III is 459 ng/L (200–871 ng/L); Level IV is 1119 ng/L (728–1300 ng/L).[13] The study was approved by the ethics committee of Chongqing Bishan District People's Hospital. All patients knew about the study and signed the informed consent.

2.2. Clinical data collection

All patients were treated with rest, oxygen inhalation, salt restriction, cardiotonic, nitrates, β-blockers, ACEI and other basic treatments. According to the amount of spironolactone taken by the patients, they were divided into: low-dose group (taking 40 mg/d spironolactone); high-dose group (taking 80 mg/d spironolactone), 10 days as a course of treatment. Blood potassium, BNP and NT Pro BNP were collected before and10 days after spironolactone treatment. The blood indexes were detected by Olympus (Japan) automatic biochemical analyzer and ELISA Kit (produced by America Jingmei company). Color Doppler echocardiography has been completed by senior ultrasound doctors who are not aware of the study. Color Doppler echocardiography was used to detect left ventricular end systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and left ventricular ejection fraction (LVEF) of the two groups before and10 days after spironolactone treatment. Six-minute walking test (6MWT) and NYHA cardiac function classification were collected before and10 days after spironolactone treatment. 6MWT refers to the previous literature, and the walking distance of patients is divided into four grades.[14,15]

2.3. Efficiency evaluation

The therapeutic effect was evaluated by the method of comprehensive cardiac function efficiency. According to the classification of clinical signs, 6-minute walking test and NYHA cardiac function classification, the comprehensive evaluation of cardiac function was carried out (see Table 1 for the specific evaluation). Marked efficiency and effective efficiency are called total efficiency. The classification standard of clinical signs is as previously reported.[16–18] Lung sounds: severe: wet lung sounds in both lungs account for 80% to 100% of the lungs; moderate: Wet rales in the middle and lower lung fields account for 30% to 60% of the lungs below the lower scapular angle; mild: Wet murmur at the base of both lungs is less than 30%. Filling of bilateral jugular vein (in supine position): severe: upper 1/3 of the distance from the upper edge of the clavicle to the jaw angle; moderate: within 2/3 of the distance from the upper edge of the clavicle to the mandibular angle; mild: Within the lower 1/3 of the distance from the upper edge of the clavicle to the mandibular angle. Grade of degree of edema of both lower limbs: severe: above knee joint; moderate: below the knee joint, more than 1/3 below the tibia; mild: No edema in the lower limbs or anterior lower tibia.

2.4. Statistical Processing

SPSS 19.0 software was used for data analysis. The continuous or categorical data are presented as mean ± standard deviation (SD), frequency, percentile, and range, as appropriate. K-S single sample test was used to calculate the normal distribution of continuous variables before doing further comparison. Student's t test and the Wilcoxon test were used to compare clinical characteristics between UHLL and UPL groups. Variables in the contingency table were analyzed by the χ^2 test (or the Fisher exact test). When $P < .05$, the difference was significant was used to calculate the normal distribution of continuous variables before doing further comparison. Student's t test and the Wilcoxon test were used to compare clinical characteristics between UHLL and UPL groups. Variables in the contingency table were analyzed by the χ^2 test (or the Fisher exact test). When $P < .05$, the difference was significant.

3. Result

3.1. Baseline characteristics

A total of 211 patients included in the study (low-dose group, n = 129; high-dose group, n = 82), during the 10-day drug treatment, no patient stopped taking medicine due to adverse drug reactions.

Table 1

Comprehensive evaluation of cardiac function.

Item	NYHA cardiac function Classification	Clinical signs	6MWT
Markedly effective	increased 2 grade	improved 2 grade	extended distance over level 2
Effective	improved 1 grade	improved 1 grade	extended distance over level 1
Invalid	no improvement	no improvement	no distance extension

6MWT = six-minute walking test, NYHA = New York Heart Association.

Table 2

Clinical characteristics of baseline before treatment in two groups.

Parameter	Low-dose group (n = 129)	High-dose group (n = 82)	*P* Value
Age, years	61.94 ± 12.67	62.64 ± 11.02	.637
Gender, M/F (n, %)	75/54 (58.14/41.86)	48/34 (58.54/41.46)	.845
Hypertension (n, %)	81 (62.79)	53 (64.63)	.137
Diabetes (n, %)	26 (20.15)	18 (21.95)	.432
Smoking (%)	51 (39.53)	32 (39.02)	.557
Hypertensive heart disease	57 (44.18)	38 (46.34)	.135
FBS (mg/dL)	5.71 ± 1.86	5.81 ± 1.77	.314
Coronary heart disease	42 (32.56)	25 (30.49)	.438
Dilated heart disease	12 (9.31)	8 (9.75)	.654
Rheumatic heart disease	18 (13.95)	11 (13.41)	.732
ALT, (U/L)	30.52 ± 9.24	31.61 ± 8.98	.579
AST,(U/L)	31.07 ± 8.91	30.40 ± 9.57	.297
Serum Creatinine (μmol/L)	130.62 ± 30.12	137.62 ± 23.56	.675
Serum Urea (mmol/L)	6.84 ± 1.42	6.72 ± 1.38	.457

ALT = alanine aminotransferase, AST = aspartate aminotransferase, FBS = Fasting blood glucose.

Among the 211 patients, 95 cases of hypertension heart disease, 67 cases of coronary heart disease, 20 cases of dilated heart disease, and 19 cases of rheumatic heart disease. As shown in Table 2, there was no statistical difference in age, gender, comorbidity, case type, liver and kidney function between the two groups ($P > .05$).

3.2. Changes of blood potassium, BNP, and NT-pro BNP

As shown in Table 3, compared with before treatment, the blood potassium of the two groups increased significantly after treatment ($P < .05$), but the blood potassium did not exceed the normal range (3.50~5.50mmol/L). These results suggest that high-dose spironolactone has little effect on blood potassium in a short time, and its safety is similar to that of low-dose spironolactone. There was no significant difference between the two groups in blood potassium (3.74 ± 0.47 vs 3.85 ± 0.36, $P > .05$). Compared with before treatment, BNP and NT-pro BNP in the two groups decreased significantly ($P < .05$). Compared with low-dose group, BNP (117.49 ± 50.32 vs 195.76 ± 64.62, $P < .05$) and NT-pro BNP (312.47 ± 86.28 vs 578.47 ± 76.73, $P < .05$) decreased more significantly in high-dose group.

3.3. Echocardiographic changes

As shown in Table 4, there was no significant difference in LVESD, LVESD, LVESV, LVEDV and LVEF between the two groups before treatment ($P > .05$). Compared with that before treatment, LVEF ($P < .05$) was significantly higher, LVEDd and LVEDV were significantly lower ($P < .05$) in the two groups after 10 days of treatment. Compared with the low-dose group, the LVEF (41.62 ± 2.76 vs 36.02 ± 2.18, $P < .05$) of the high-dose group was significantly higher, and the LVEDD (45.57 ± 5.69 vs 51.96 ± 5.41, $P < .05$) and LVEDV (141.63 ± 51.14 vs 189.85 ± 62.49, $P < .05$) were significantly lower.

Table 3

Changes of blood potassium, BNP and NT-pro BNP.

Parameter		Low-dose group (n = 129)	High-dose group (n = 82)
Blood potassium (μmol/L)	Before treatment	3.17 ± 0.42	3.23 ± 0.37
	After treatment	3.74 ± 0.47*	3.85 ± 0.36*
BNP (pg/ml)	Before treatment	569.72 ± 272.36	575.54 ± 246.92
	After treatment	195.76 ± 64.62*	117.49 ± 50.32*,†
NT-pro BNP (pg/ml)	Before treatment	2795.76 ± 454.82	2857.76 ± 414.61
	After treatment	578.47 ± 76.73*	312.47 ± 86.28*,†

* Indicates a significant difference compared Before treatment ($P < 0.05$).
† Indicates a significant difference compared Low-dose group ($P < 0.05$).

Table 4

Changes of echocardiography results before and after treatment in two groups.

Parameter		Low-dose group (n = 129)	High-dose group (n = 82)
LVESD (mm)	Before treatment	45.05 ± 4.67	44.55 ± 4.38
	After treatment	43.36 ± 5.05	42.51 ± 5.27
LVEDD (mm)	Before treatment	61.58 ± 7.24	62.32 ± 6.56
	After treatment	51.96 ± 5.41*	45.57 ± 5.69*,†
LVESV (ml)	Before treatment	165.20 ± 68.24	161.35 ± 77.26
	After treatment	156.84 ± 75.87	152.11 ± 81.72
LVEDV (ml)	Before treatment	214.44 ± 57.50	222.56 ± 53.95
	After treatment	189.85 ± 62.49*	141.63 ± 51.14*,†
LVEF (%)	Before treatment	33.48 ± 1.95	32.65 ± 2.14
	After treatment	36.02 ± 2.18*	41.62 ± 2.76*,†

LVEDD = left ventricular end-diastolic diameter, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, LVESD = left ventricular end systolic diameter, LVESV = left ventricular end-systolic volume.
* indicates a significant difference compared Before treatment ($P < .05$).
† indicates a significant difference compared Low-dose group ($P < .05$).

3.4. 6-minute walking test and NYHA heart function grading changes

As shown in Table 5, there was no significant difference in 6-MWT and NYHA grading between the two groups before treatment ($P > .05$). Compared with that before treatment, 6-MWT ($P < .05$) increased significantly and NYHA grading ($P < .05$) decreased significantly in the two groups after 10 days of treatment. Compared with low-dose group, high-dose group 6-MWT (386.577 ± 69.72 vs 341.73 ± 78.62, $P < .05$) was significantly higher, NYHA grading (1.29 ± 0.41 vs 1.57 ± 0.49, $P < .05$) was significantly lower.

3.5. Comprehensive assessment of cardiac function

As shown in Table 6, compared with low-dose group, the total effective rate of high-dose group (92.68% 3 vs 81.39%, $P < .05$) is significantly higher, which suggests that short-term and high-dose use of spironolactone can significantly improve the heart function of patients.

Table 5

6-minute walking test and NYHA heart function grading changes.

Parameter		Low-dose group (n = 129)	High-dose group (n = 82)
6-MWT	Before treatment	235.73 ± 46.62	229.53 ± 52.42
	After treatment	341.73 ± 78.62*	386.577 ± 69.72*,†
NYHA grading	Before treatment	3.00 ± 0.00	3.00 ± 0.00
	After treatment	1.94 ± 0.49*	1.51 ± 0.41*,†

6-MWT = 6-minute walking test, NYHA = New York Heart Association.
* indicates a significant difference compared Before treatment ($P < .05$).
† indicates a significant difference compared Low-dose group ($P < .05$).

Table 6

Changes in comprehensive evaluation of cardiac function.

Grouping	Marked effect	Effective	Invalid	Total effect
Low-dose group (n = 129)	47 (36.43%)	58 (44.96%)	24 (18.60%)	105 (81.39%)
High-dose group (n = 82)	42 (51.22%)	34 (41.46%)	6 (7.31%)	76 (92.68%)
χ^2	–	–	–	7.231
P value	–	–	–	.027

4. Discussion

In CHF, the concentration of aldosterone in the blood increased significantly (up to 20 times). In addition to sodium retention and potassium excretion, A large number of aldosterone can promote the growth of fibroblasts, especially the proliferation of fibroblasts, stimulate the synthesis of protein and collagen, cause the remodeling of atria, ventricles and large blood vessels, and accelerate the deterioration of heart failure.[16,17] ACEI drugs can effectively block renin-angiotensin I in CHF treatment, while angiotensin II type 2 (AT2) and aldosterone often escape, which greatly reduces the therapeutic effect of CHF.[18,19] At present, spironolactone can inhibit the conversion of AT1 to AT2 in the treatment of CHF, greatly reduce the aldosterone escape phenomenon, can eliminate edema, inhibit myocardial fibrosis and improve the cardiac function and quality of life of patients.[20,21] Therefore, the combination of ACEI and aldosterone inhibitors can effectively block the renin-angiotension-aldosterone system, significantly improve heart failure and reduce mortality.[22,23] Foreign scholars claim that spironolactone should be maintained in large dose (> 50 mg/d) only for CHF patients with refractory or severe pulmonary edema or peripheral edema.[24] In China, scholars advocate long-term use of low-dose spironolactone (20 mg or 40 mg), which can prevent ventricular remodeling of CHF and improve the quality of life of patients.[17] In this study, we used high-dose spironolactone (80 mg/d) to treat CHF with NYHA heart function grade III, we found that 80 mg of spironolactone was more effective than 40 mg of spironolactone in improving clinical signs, exercise tolerance and cardiac function. The results suggest that the short-term application of 80 mg spironolactone in CHF can quickly correct the heart failure and improve the quality of life of patients.

When kidneys fail, they can no longer remove excess potassium, so the level builds up in the body. High potassium in the blood, also called hyperkalemia, represents impaired renal function. Spironolactone has a similar structure to aldosterone, and it can competitively bind to aldosterone receptors. It can fight water and sodium retention of aldosterone, but the use of spironolactone can lead to the occurrence of hyperkalemia, with an incidence rate of 8.6% to 26%.[25] In this study, we found that the serum potassium values of both 40 mg and 80 mg doses of spironolactone increased, of which the 80 mg blood potassium increased higher, but the blood potassium value remained within the normal range. The results showed that the safety of 40 mg and 80 mg spironolactone in correcting CHF in a short time is similar. BNP and NT-pro BNP are mainly derived from the ventricle. When left ventricular dysfunction occurs, it is quickly released into the blood due to myocardial dilatation, which helps regulate cardiac function.[6–8] Both BNP and NT-pro BNP are important markers for the diagnosis of heart failure. The release of both is proportional to the degree of cardiac insufficiency, which has important clinical value for the detection and prognosis of cardiac function.[6–8] In previous studies, CHF patients (NYHA III, LVEF $\leq$ 40%) were randomly divided into placebo group (standard treatment + placebo) and spironolactone group (standard treatment + spironolactone). After treatment, the BNP and NT-pro BNP concentration of both groups decreased, but the decrease of spironolactone group was more significant.[26–28] In this study, we found that BNP and NT-pro BNP decreased significantly in low-dose group and high-dose group after treatment with spironolactone, but BNP and NT Pro BNP decreased more significantly in high-dose group. The results indicate that the dose of spironolactone is closely related to the decrease rate of BNP and NT Pro BNP. The possible mechanism is that high-dose spironolactone can more effectively inhibit the conversion of AT1 to AT2 in a short period of time, antagonize the aldosterone system, prevent aldosterone escape, reduce water and sodium retention, reduce cardiac preload, reduce ventricular wall tension, reduce myocardial cell BNP and NT-pro BNP secretion. In the prospective study, patients with CHF (NYHA III, LVEF$\leq$40%) were treated with 25 mg spironolactone, and compared with the control group, the spironolactone group had significantly lower left ventricular end systolic volume index, left ventricular mass index, and significantly improved cardiac function and LVEF.[29,30] Spironolactone can significantly improve the heart function and exercise tolerance of CHF, improve the clinical symptoms and reduce the mortality of patients, which has been confirmed in several studies.[29–32] In this study, we found that compared with low-dose spironolactone, high-dose spironolactone can significantly improve the cardiac function and labor tolerance of patients, mainly manifested in the significant increase of LVEF, the significant decrease of NYHA heart function grading, LVEDD and LVEDV, and the extension of 6MWT distance. The results showed that high-dose of spironolactone could significantly reduce left ventricular preload, improve left ventricular systolic function, improve clinical symptoms and exercise tolerance in a short period of time. In conclusion, Short-term administration of 80 mg spironolactone to CHF patients can significantly reduce BNP and NT-pro BNP concentration, improve heart function and clinical symptoms. During the treatment period, patients will not appear hyperkalemia, which has better efficacy.

However, there are still some limitations to this study. First, this study is a retrospective study and is not a double-blind randomized controlled trial in design. Second, the sample size of the study is small and cannot fully represent the actual situation in all cases. Third, this study has all the limitations and risks of bias inherent in the study design. Fourth, The treatment of CHF is long-term, and research suggests that long-term use of ACEI has the risk of hyperkalemia, which requires great attention.[33,34] But, this study is a short-term study of high-dose spironolactone, without long-term exploration and the results of this study can only represent the research conclusions of this unit, and can not be extended to different populations.

Author contributions

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