

Comparison of the Therapeutic Effects of Spironolactone at Doses of 25 and 50 mg in Patients with Systolic Heart Failure: A Randomized Clinical Trial

Ahmad Reza Assareh¹ , Habib Haybar¹ , Khaled Hamid² , Saeed Hesam³ , Nehzat Akiash^{1*} 

1. Atherosclerosis Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

2. Dept. of Cardiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

3. Dept. of Biostatistics and Epidemiology, Faculty of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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Corresponding Information:

Nehzat Akiash,

Atherosclerosis Research Center,
Ahvaz Jundishapur University of
Medical Sciences, Ahvaz, Iran

E-Mail: akiash.n@gmail.com

ABSTRACT

Background & Objective: Heart failure (HF), as the final stage of cardiovascular disease, is a prevalent cause of mortality, disability, and recurrent hospitalization. Effective treatment of systolic HF is crucial for reducing patient disability and preventing repeated hospital admissions. In this context, we aimed to conduct a comparative study of spironolactone at doses of 25 mg and 50 mg in patients with systolic HF.

Materials & Methods: This randomized clinical trial was performed on 100 patients with systolic HF. The patients were randomly divided into two treatment groups receiving 25 and 50 mg of spironolactone. Subsequently, changes in ejection fraction, frequency of hospitalization, performance capacity, quality of life, and electrolyte disorders were examined.

Results: There was no significant difference between the groups in terms of age, sex, cardiovascular risk factors, history of cerebrovascular accidents, readmission rate, and EF changes ($P>0.05$). At the end of the study, the mean scores of performance capacity and quality of life in patients receiving 50 mg of spironolactone were 204.3 ± 28 and 32 ± 3.1 , respectively. These values were statistically higher than those reported in patients receiving 25 mg of spironolactone (178.9 ± 30 and 36.7 ± 3.3 , respectively) ($P<0.001$). In patients who received 50 mg of spironolactone, the average levels of potassium and blood urea nitrogen were 0.68 ± 0.08 and 6.1 ± 1.4 , respectively. These levels were significantly higher compared to those in patients receiving a 25mg dose, where the levels were 0.39 ± 0.17 and 4.7 ± 2.8 , respectively ($P<0.05$). However, it is important to note that the maximum values observed did not exceed the normal range for these parameters

Conclusion: Compared to the 25mg dose, the 50mg dose of spironolactone was observed to enhance both the quality of life and performance capacity in patients with systolic HF. Therefore, it can be prescribed as the initial daily dosage for managing patients with HF.

Keywords: Heart Failure, Spironolactone, Readmission, Quality of life



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Introduction

As a result of advancements in medical technology improving the survival rates of cardiovascular patients, coupled with increased life expectancy and a decrease in the prevalence of cardiovascular disease, heart failure (HF) has become the terminal stage of cardiovascular disease. It is now a leading cause of death, disability, and frequent hospital admissions (1-3). The treatment of this disease is of paramount importance, not only to reduce the disability of patients, but also to prevent recurrent hospitalizations, as this condition can place a substantial

physical, psychological, and financial strain on patients, their families, and society as a whole (4, 5).

Regulation of neurohormonal activity in patients with HF is a key treatment strategy for these individuals. This approach plays a crucial role in managing their condition effectively (6). Among various medications prescribed for HF, aldosterone inhibitors have been found to have a significant impact on the pathophysiology of this condition (7, 8). Studies have shown that these agents can alleviate clinical symptoms in patients, reduce the rate of

hospital readmissions, and enhance the quality of life for those living with HF (9, 10). According to previous research, the administration of spironolactone has been associated with a reduction in both mortality and hospital readmission rates among patients with severe HF (11). In addition, research has indicated that the use of spironolactone can lead to improvements in the left ventricular function for patients suffering from chronic HF (12).

Materials and Methods

Patients

This randomized controlled triple-blind clinical trial (IRCT2015010520563N1) was conducted on 100 systolic HF patients referred to Imam Khomeini Hospital, Ahvaz, Iran. The study was conducted using a triple-blind protocol. In this approach, the participants, clinicians, and data analysts were all unaware of the specific intervention each patient was receiving until the conclusion of the clinical trial. The participants of this study were patients diagnosed with systolic HF, with an ejection fraction (EF) of less than 40, over a six-month period (14, 15). The exclusion criteria for the study were as follows: pregnant women, patients with renal disorders, patients with blood potassium levels >5.1 mmol, patients with severe hypotension, and patients unable to tolerate the aldosterone receptor antagonist. This study was carried out following the acquisition of written informed consent from all participating patients. Additionally, the study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, ensuring that all procedures adhered to ethical guidelines.

Sample size

We estimated that a total of 100 patients with systolic HF would be needed to detect a significant difference between the groups. This was based on a two-tailed alpha of 0.05 and a power ($1-\beta$) of 0.85 for evaluating two independent relationships. The sample size was determined based on previous studies (12), taking into account that a 4% difference between the two groups is clinically significant. According to our statistical advisor, the sample size in each group should be 41. However, considering a potential 20% reduction in the composite outcome measure, we decided to increase the sample size in each group to 50.

Study design

The patients were randomly assigned into two equal intervention groups using simple randomization (based on a table of random numbers corresponding to the drug dosage). Each group consisted of 50 patients. The case group consisted of patients who received a daily dose of 50 mg of spironolactone for six months. The control group consisted of patients who received a

Given the potential side effects of aldosterone inhibitors on renal function and blood potassium levels, they should be administered with caution and at the lowest effective dose (13). Therefore, in the present study, for the first time, we aimed to investigate the safety and efficacy of a higher dose of spironolactone on the quality of life, hospital readmission, and renal electrolytes of HF patients who were admitted to Imam Khomeini Hospital of Ahvaz, Iran, and to compare the effects observed with a lower dose of the same medication.

Daily dose of 25 mg of spironolactone for the same duration. During their hospitalization, all patients underwent echocardiography. The EF was measured using the Simpson method and visual assessment (16). In terms of monitoring the electrolyte status of patients taking spironolactone, renal function assessments were conducted on the 3rd and 7th days following the onset of treatment. All patients were provided with the standard HF treatment upon discharge, which included spironolactone. At the time of discharge, all paraclinical data, including echocardiography results and clinical test findings, were documented for each patient. Additionally, each patient participated in a 6-Minute Walk Test (6MWT) as part of their evaluation (17).

The patients' quality of life was assessed and documented by the researcher through interviews, using the Minnesota Satisfaction Questionnaire (MSQ), a tool whose validity has been confirmed in previous studies (18). This questionnaire consists of 21 questions, which are divided into three categories. Eight questions focus on physical factors, five on emotional factors, and the remaining eight on other factors. The questionnaire has a total of 105 points, with each question scored based on the patient's response, ranging from "very high ability" (5 points) to "inability" (0 point). These variables were reassessed six months after the patient's hospitalization. Ultimately, the percentage of change in the patients' EF, improvements in quality of life, number of hospitalizations, electrolyte disorders, and performance capacity were compared between the two patient groups.

Statistical analysis

Upon completion of data collection, descriptive statistics, including the mean $\pm$ standard deviation (SD) and frequency, were calculated. Given the normal distribution of the quantitative variables, statistical tests, such as the independent sample t-test and Chi-square test, were employed to compare the means of the variables between the two groups. A P-value of less than 0.05 was deemed statistically significant. The results were analyzed and reported using SPSS Version 20 for Windows. This study was carried out following the acquisition of written informed consent from the patients and the receipt of the ethics code from the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1394.67).

Results

In this study, we included 100 patients with systolic HF. The participants had a mean age of 58.2 ± 8.6 years,

ranging from 39 to 77 years. Of these patients, 59% were male, and 41% were female. The demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic characteristics and comorbidities of the two groups

Variables	25mg Spironolactone	50mg Spironolactone	Mean of the two groups	P-value
Age	57.9 $\pm$ 9.1	58.6 $\pm$ 8.2	58.2 $\pm$ 8.6	0.71
Sex (female)	36%	46%	41%	0.2
Diabetes	28%	36%	32%	0.26
High blood pressure	44%	42%	43%	0.5
Hyperlipidemia	26%	30%	28%	0.41
Smoking	36%	28%	32%	0.26
History of CVA	10%	16%	13%	0.27

In terms of cerebrovascular accident (CVA) risk factors among the participants, the following frequencies were observed: 32% had a history of diabetes, 28% had hyperlipidemia, 43% had hypertension, 32% had a history of smoking, and 13% had a history of CVA. During the six-month follow-up period, the average readmission rate in both groups was 1.3 ± 0.8 times. The frequency of hospitalization for patients with systolic HF was as

follows: 12.6% of patients had no history of readmission, 44.2% had one readmission, 35.8% had two readmissions, and 7.4% had three readmissions. Before the study, the average distance covered in the 6MWT for patients receiving 25 mg and 50 mg of spironolactone was 167.9 ± 29.6 and 172.1 ± 26.7 , respectively. However, a significant difference was observed at the end of the study (Table 2).

Table 2. Pre- and posttest evaluation of spironolactone

Variables	Pretest			Posttest		
	25mg Spironolactone	50mg Spironolactone	P- value	25mg Spironolactone	25mg Spironolactone	P-value
EF	26.8 $\pm$ 6.6	27.2 $\pm$ 6.4	0.77	27.6 $\pm$ 6.4	30.1 $\pm$ 5.1	0.051
6MWT distance	167.9 $\pm$ 29.6	172.1 $\pm$ 26.7	0.45	178.9 $\pm$ 30	204.3 $\pm$ 28	<0.001
MQLF score	39.4 $\pm$ 3.5	38.9 $\pm$ 3.2	0.48	36.7 $\pm$ 3.3	32 $\pm$ 3.1	<0.001
BUN	16.2 $\pm$ 2.6	16.7 $\pm$ 2.8	0.36	21	22.8	0.04
K	3.9 $\pm$ 0.2	3.8 $\pm$ 0.15	0.17	4.39 $\pm$ 0.3	4.56 $\pm$ 0.15	0.04
Cr	1.3 $\pm$ 0.13	1.26 $\pm$ 0.1	0.08	1.4 $\pm$ 0.12	1.46 $\pm$ 0.1	0.36
Na	135.9 $\pm$ 1.6	136.6 $\pm$ 1.7	0.19	134.4 $\pm$ 2.4	134.8 $\pm$ 2.2	0.44
Readmission	---	---	---	1.5 $\pm$ 0.8	1.2 $\pm$ 0.6	0.08

Abbreviations: EF: Ejection fraction; 6MWT: Six-Minute Walk Test; MQLF: Minimal Quality of Life Form; BUN: Blood urea nitrogen; K: Potassium; Cr: Creatinine; Na: Sodium. P-values ≤ 0.05 were considered significant.

Furthermore, the pretest Minimal Quality of Life Form (MQLF) scores were 39.4 ± 3.5 and 38.9 ± 3.2 for 25 mg and 50 mg of spironolactone, respectively. By the end of the study, a significant difference was observed in the MQLF score (Table 2).

The patients' age in the case group was not significantly different from that of the control group ($P=0.2$). Similarly, the history of diabetes, hypertension, hyperlipidemia, smoking, and CVA in the case group did not significantly differ from the group receiving 25 mg of spironolactone ($P \geq 0.05$). There was no significant difference in the mean EF and readmission rate between the two groups of patients who received 25 mg and 50 mg of spironolactone ($P \geq 0.05$). However, patients in the 50mg spironolactone group covered a significantly longer

distance in the 6MWT at the end of the study, compared to the 25mg spironolactone group, with an increase of 26 meters observed in the 50mg spironolactone group.

In terms of renal function laboratory parameters, patients who received 50 mg of spironolactone exhibited higher serum potassium and BUN levels compared to those in the 25mg spironolactone group. However, these maximum values did not exceed the normal range, and notably, hyperkalemia was not observed in any of the patients. Furthermore, there was no significant difference in the levels of serum sodium and creatinine between the two groups under study (Table 3).

Table 3. Significant pre- and posttest differences in parameters under study

Mean differences between pre- and posttest	25mg Spironolactone	50mg Spironolactone	P-value
6MWT distance	12.4 ± 5	29.8 ± 14	<0.001
EF	1.41	1.96	0.055
K	0.39 ± 0.17	0.68 ± 0.08	<0.001
BUN	4.7 ± 2.8	6.1 ± 1.4	0.006

Abbreviations: EF: Ejection fraction; 6MWT: Six-minute walk test; BUN: Blood urea nitrogen; K: Potassium. P values ≤ 0.05 were considered significant.

Discussion

HF often represents the final stage of numerous cardiovascular conditions. The incidence of HF is on the rise, and despite advancements in medicine, its treatment continues to pose significant challenges (19, 20). Consequently, this research assessed the impact of administering 25mg and 50mg doses of spironolactone to patients suffering from systolic HF. The results indicated that a higher dosage of spironolactone significantly enhanced both the quality of life and performance capacity of these patients, as evidenced by the 6MWT. In addition, a meta-analysis revealed that treating HF patients with preserved EF using mineralocorticoid antagonists, such as spironolactone, enhances their quality of life and triggers a reversal of cardiac remodeling (21). This evidence corroborates the validity of our findings.

In this study, the impact of spironolactone on the patients' EF was examined. It was observed that administering a 50mg dose of spironolactone led to an increase in the mean EF of patients compared to a 25mg dose. However, this difference was not statistically significant. Other research, including a study by Vizzaedi et al. (22), demonstrated that spironolactone enhances EF in HF patients, which

aligns with the findings of our study. Furthermore, the study found that the administration of two distinct doses of spironolactone did not influence the readmission rate of HF patients. This result aligns with the findings of a study by Inampudi et al. (23), which suggested that spironolactone does not affect the readmission of HF patients. However, it contradicts the results of studies by Pitt et al. (24) and Hoyt et al. (25), who reported the beneficial effect of spironolactone on the patients' readmission rates. The discrepancy may be attributed to the limited sample size of the current study. Future research involving larger participant groups may help resolve this issue.

Impaired renal function is a common occurrence in patients with chronic HF and serves as a definitive predictor of mortality in these individuals (26). Our findings revealed that, compared to the 25mg dose, the 50mg dose of spironolactone led to an increase in serum potassium and BUN levels in patients. However, it is crucial to note that these values did not exceed the respective normal ranges. Moreover, spironolactone treatment did not affect changes in the patients' sodium and creatinine levels. This is in line with the results of a study by Svensson et al. (13), which reported an

increase in serum potassium levels due to spironolactone therapy. However, our study diverges from these findings as the higher dose of spironolactone did not result in hyperkalemia in the patients studied. Additionally, a study by Stubnova et al. (27) demonstrated that while spironolactone increased serum potassium levels in patients with chronic HF, it improved their two-year survival rate.

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Conclusion

In summary, high doses of spironolactone were found to enhance the quality of life and performance capacity in patients with systolic HF. However, these doses also resulted in elevated serum potassium and BUN levels, although it is crucial to note that these values remained within the normal range. Spironolactone did not influence the readmission rate of patients. While other studies have demonstrated the impact of spironolactone on mortality rates, further research into the effects of varying doses of spironolactone (including 25. mg and 50 mg) on patient mortality could provide valuable insights into the clinical use of spironolactone in treating HF. Given the observed improvements in the patients' quality of life and the safety of renal function with higher doses of

spironolactone, it is proposed that an initial daily dose of 50mg spironolactone could be prescribed for managing HF patients. However, it is important to note that in this study, we did not evaluate the mortality rates of the patients, which constitutes a limitation of our research.

Authors' Contribution

Design of the work:AA, HH.Data Collection , Design and Preparation of the table Tabales:KHH, Data Anyalysis & Interpretation: SH,NA.Drafting of the Article :AA,KHH.Critical revision of the article:NA

Conflict of Interest

The authors declare that they have no conflict of interest.

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Ethics Approval

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