

Comparison between Spironolactone and Eplerenone on LV Systolic Function in Patients with Chronic Heart Failure

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Abstract

Background: Chronic heart failure (CHF) is the most common and prognostically unfavorable outcome of many diseases of the cardiovascular system. Clinical trials have demonstrated mortality and morbidity benefits of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. These studies have used either eplerenone or spironolactone as the MRA. Eplerenone is a selective aldosterone antagonist expected to have a lower incidence of hormonal side effects than spironolactone. The present study is designed to compare these two drugs in chronic heart failure patients as no head to head trial between these two drugs is found regarding improvement of systolic function, tolerability and safety. The aim of this study is to compare the effects of eplerenone and spironolactone on LV systolic function in patients with chronic heart failure in a single center.

Methods: It was a randomized clinical trial single blind study. A total of 224 cases of chronic heart failure with reduced ejection fraction and NYHA class III or IV were selected by random sampling, from July 2017 to June 2018. Each patient was randomly allocated into either of the two arms, and was continued receiving treatment with either spironolactone (Arm-I) or eplerenone (Arm-II). Each patient was evaluated clinically, biochemically and echocardiographically at the beginning of treatment (baseline) at 1 month and at the end of 6th month. Echocardiography was performed to find out change in left ventricular systolic function.

Result: After 6 months of treatment, ejection fraction was found higher in the eplerenone arm (40.3 ± 6.5 versus $38.3 \pm 4.6\%$; $P < 0.05$). Ejection fraction (EF) changes were 6.2% in eplerenone group and 4.1% in spironolactone arm. A significant reduction in left ventricular end-systolic volume (21.9 ± 2.5 in group I versus 14.9 ± 5.7 in group II; $P < 0.05$) and left ventricular systolic diameter (48.7 ± 4.0 in arm I versus 45.2 ± 4.9 in arm II; $P < 0.05$) occurred after 6 months of treatment. But no significant differences were observed in left ventricular end-diastolic volume (187.8 ± 37.4 versus 184.5 ± 33.9 ; $P = 0.101$) and left ventricular diastolic diameter (60.1 ± 4.5 versus 61.0 ± 4.9 ; $P = 0.0818$) between arms. Assessment of blood pressure six months after treatment shows, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were improved in both arms but difference between two arms were statistically non-significant ($p > 0.05$).

Conclusion: In this study, the improvement in systolic function was more in eplerenone arm, which also had fewer adverse side effects when compared to spironolactone arm. So, it can be concluded that eplerenone can be advised in patient with chronic heart failure in addition to other drugs that are used to treat heart failure.

Keywords: Chronic Heart Failure, Spironolactone, Eplerenone, LV Systolic Function.

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Introduction

Heart failure (HF) is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood (Yancy et al. 2013). Pathophysiology of heart failure involves the activation of a number of neurohormonal systems in response to any form of cardiac injury.

HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved ejection fraction (EF) to

those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF.

EF is considered important in classification of patients with HF because of differing patient demographics, comorbid conditions, prognosis, and response to therapies (Drazner et al. 2001).

In chronic HF predominantly the sympathetic nervous system and the renin-angiotensin aldosterone system

(RAAS) systems become upregulated. Specific agents that target the RAAS are angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists (Miller., 2007).

Clinical trials have demonstrated mortality and morbidity benefits of mineralocorticoid receptor antagonists (MRAs) in patients with heart failure. These studies have used either eplerenone or spironolactone as the MRA. (Zannad et al., 2004, Juurlink et al., 2004).

Spironolactone (or its metabolite, potassium canrenoate) and eplerenone are the currently licensed MRAs for clinical use. However, studies have reported that compared to placebo, eplerenone was associated with significant improvement in systolic function (Marrs, et al., 2018).

Eplerenone is a selective aldosterone antagonist and has been shown to have fewer incidence of hormonal side effects than spironolactone. Evidence from trials shows that eplerenone improves survival and reduces cardiovascular mortality and hospitalization, compared with standard treatment alone. Eplerenone was found to be more effective but also more costly than standard treatment (Nadin, 2005).

Previously spironolactone and eplerenone was studied separately with placebo arm. Upon journal review no head to head trial between these two drugs is found regarding improvement of systolic function, tolerability and safety. Aim of our study was to compare the left ventricular systolic function in chronic heart failure patient treated with spironolactone and eplerenone in our setting.

Methods

Study design and patients

This randomized single blind clinical trial was conducted at the University Cardiac Center, Bangabandhu Sheikh Mujib Medical University, Dhaka. The centre is currently being ranked as one of the top hospital in Bangladesh. Total duration was 1 year from July, 2017 to June, 2018. We studied 224 adult patients (age >15 years) of heart failure with reduced EF. All patients had New York Heart Association class III or IV symptoms for ≥ 3 months and an LV ejection fraction < 40% by echocardiography. Patients were excluded if serum creatinine was > 2.5mg/dl on previous medical records, serum potassium level > 5mmol/L on previous medical records, systolic blood pressure < 85 mm Hg or prior history of aldosterone antagonist hypersensitivity. The protocol was approved by the Institutional Review Board (IRB). Written informed consent was obtained from all study patients after careful explanation of the study procedures.

Study Procedure

All patients with chronic heart failure were enrolled purposively following the inclusion and exclusion criteria. Detailed history, physical examination and an echocardiogram were done on admission and outpatient consultation. After enrollment the study subject were divided into 2 arms randomly by using online graph pad software: spironolactone (arm I) and eplerenone (arm II). In addition to study drug, standard treatments for CHF according to the ACC/AHA HF Guideline 2013 were permitted. Up and down titration of the index drug was done according to patients need. Up and down titration of drug dose was done according to patients need. At the end of the 1st month of treatment, patients were followed up using serum creatinine and serum electrolytes and dose adjustment was done accordingly. At the end of the 6th month LV systolic function of all cases was compared with their baseline echocardiographic data. Detail clinical evaluation for improvement of symptoms including adverse effects of medications and echocardiographic assessment of LV systolic function of all the cases were performed at baseline and after 6 months of treatment with spironolactone or eplerenone arm. Echocardiographic assessment was done by using 2D and M-mode echocardiography. The LV ejection fraction (LVEF) was calculated using a standard method (modified Simpson method) in Vivid E9 (GE Healthcare) echo machine with 3.5 MHz transducer. During echocardiography the following parameters were assessed; left ventricular end diastolic dimension (LVIDd), left ventricular end systolic dimension (LVIDs), left ventricular end diastolic volume and left ventricular end systolic volume. Two independent, blinded observers reviewed these echocardiograms. After completion of the data collection, comparison was done between two (baseline and after 6 months of treatment) echocardiographic finding and inference was drawn.

Statistical analysis

The primary end point of the study was LV study: Left ventricular end diastolic dimension (LVIDd), Left ventricular end systolic dimension (LVIDs), Left ventricular end diastolic volume (EDV), Left ventricular end systolic volume (ESV), The LV ejection fraction (LVEF). Secondary efficacy end point variable was the effect on blood pressure.

Keeping the research topic in concern, a preset easily understandable data sheet was used for data collection. After collection of all information, these data were checked, verified for consistency and edited for finalized result. Data cleaning validation and analysis was

performed using the software SPSS (Statistical Package for Social Science) version 23.0. Descriptive statistics were used to summarize data using means, standard deviation and median for continuous variables. Categorical data were summarized by calculating percentages which were presented as frequency tables and charts. Symmetrical continuous data by t-test and asymmetrical data by Mann-Whitney U Test was compared. Significance was defined as P value less than 0.05.

Results

A total 224 patients were selected for study. Each patient was allocated into one of the two arms, and continued receiving treatment with either spironolactone (ARM-I) or eplerenone (ARM-II). Each patient was evaluated clinically and echocardiographically at the beginning of treatment (baseline) and at the end of 6th month. The number of patients who lost to follow-up was 7 in spironolactone arm and 10 in eplerenone arm.

As shown in Table 1, there were no significant differences between the two arms in terms of socio-demographic data including age, gender, body weight, hypertension, diabetes mellitus, hyperlipidemia and smoking at baseline.

With regard to cardiac medications, administration of diuretics, angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta blockers, nitrates, statins and antiplatelet was similar in both arms.

Left ventricular volume, dimension and function

Left ventricular volumes and function data are presented in Table 2. After 6 months of treatment, significant improvement of left ventricular ejection fraction was observed in eplerenone treated arm (38.3 ± 4.6 in arm I versus 40.3 ± 6.5 in arm II; $P < 0.05$). Ejection fraction (EF) changes were 6.2% in eplerenone arm and 4.1% in spironolactone arm.

A significant reduction in left ventricular end-systolic volume (7.0 ± 1.9 ml in arm I versus 18.3 ± 6.3 ml in arm II; $P < 0.05$) and left ventricular systolic diameter (2.4 ± 0.9 mm in arm I versus 6.8 ± 0.1 mm in arm II; $P < 0.05$) occurred after 6 months of treatment. But no significant differences were observed in reduction of left ventricular end-diastolic volume (3.1 ± 0.3 ml versus 14.2 ± 1.8 ml; $P = 0.101$) and left ventricular diastolic diameter (1.2 ± 0.8 versus 1.7 ± 0.1 ; $P = 0.081$) between arms.

Table-I
Baseline characteristics of study patients

| | Spironolactone (n=112) | Eplerenone (n=112) | P-value |
|--------------------------|---------------------------|-----------------------|---------------------|
| Age (mean±SD) | 53.1±7.9 | 52.9±8.2 | 0.219 |
| Sex | | | |
| Male (%) | 76(67.8%) | 72(64.2%) | 0.283 |
| Female (%) | 49(34.1%) | 40(35.7%) | |
| Blood Pressure (mean±SD) | | | |
| Systolic | 109.8±11.1 | 108.6±12.9 | 0.09 ^{ns} |
| Diastolic | 73.1±7.8 | 72.3±8.5 | 1.00 ^{ns} |
| Medication | | | |
| Diuretics | 112(100.0%) | 144(100.0%) | 0.119 ^{ns} |
| B-blocker | 54(48.2%) | 48(42.8%) | 0.149 ^{ns} |
| ACEI | 63(56.2%) | 68(60.7%) | 0.207 ^{ns} |
| ARB | 38(33.9%) | 42(37.5%) | 0.296 ^{ns} |
| Nitrate | 21(18.7%) | 18(16%) | 0.116 ^{ns} |
| Statin | 7(6.9%) | 73(65.1%) | 0.223 ^{ns} |
| Antiplatelet | 85(75.8%) | 82(73.2%) | |

Table-II*Changes in left ventricular function, volumes and dimensions after 6 months of treatment.*

| | Spironolactone | | Mean of Difference | Eplerenone | | Mean of Difference | p-value |
|------------------------------|----------------|----------------|--------------------|-------------|----------------|--------------------|----------------------|
| | Baseline | After 6 months | | Baseline | After 6 months | | |
| LVIDd (mm) | 61.3(5.3) | 60.1(4.5) | 1.2(0.8) | 62.4(5.0) | 61.0(4.9) | 1.7(0.1) | 0.0818 ^{ns} |
| LVIDs (mm) | 51.1(4.9) | 48.7(4.0) | 2.4(0.90) | 52.0(4.8) | 45.2(4.9) | 6.8(0.1) | 0.002 ^s |
| LV end systolic volume (ml) | 125.9(18.2) | 118.9(16.3) | 7.0(1.9) | 131.1(27.6) | 112.8(26.8) | 18.3(6.3) | 0.007 ^s |
| LV end diastolic volume (ml) | 190.9(37.7) | 187.8(37.4) | 3.1(0.3) | 198.7(35.7) | 184.5(33.9) | 14.2(1.8) | 0.101 ^{ns} |
| LVEF(%) | 34.7(2.9) | 38.3(4.6) | 3.6(1.7) | 34.1(3.6) | 40.3(6.5) | 6.2(2.9) | 0.001 ^s |

Table-III*Changes of blood pressure amongst the study patients*

| | Spironolactone | | Mean of Difference | Eplerenone | | Mean of Difference | p-value |
|------------|----------------|----------------|--------------------|-------------|----------------|--------------------|---------|
| | Baseline | After 6 months | | Baseline | After 6 months | | |
| SBP (mmHg) | 115.7(13.3) | 109.8(11.1) | 5.9(2.2) | 116.3(14.8) | 108.6(12.9) | 7.7(1.9) | 0.09 |
| DBP (mmHg) | 73.7(9.3) | 73.1(7.8) | 0.6(1.5) | 75.5(10.1) | 72.3 (8.5) | 3.2(1.6) | 1.00 |

Table-IV*Adverse effects of medications*

| | Spironolactone (n=112) | Eplerenone(n=112) | P-value |
|-----------------------|------------------------|-------------------|---------|
| Gynecomastia | 11(10.4%) | 0 | 0.320 |
| Mastalgia | 6(5.7%) | 0 | 0.114 |
| Menstrual disturbance | 4(3.8%) | 1(0.9%) | 0.170 |
| Dizziness | 12(11.4%) | 4(3.9%) | 0.001 |

Effects on blood pressure

Assessment of blood pressure after six months of treatment shows, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were improved in both group but difference between two groups were statistically non-significant ($p>0.05$) Table 3.

Adverse effect of medication

Although no significant differences of adverse event observed between arms, arm I or patients receiving spironolactone had experienced more adverse profile than eplerenone arm. Adverse profile of medication shows that, in arms I patients, gynecomastia occurred in 10.4% of patients, dizziness in 11.4%, mastalgia in 5.7% and menstrual disturbance in 3.8% patients. In arms II patient's dizziness in 3.9% of patients and menstrual disturbance in 0.9% patients. None of patient observed developed mastalgia, orgynecomastia. Difference between two arms was statistically non-significant ($p>0.05$) except for dizziness which is significant ($p<0.05$) Table 4.

Discussion

The main objective of the study was to compare the left ventricular systolic function in chronic heart failure

patients treated with spironolactone and eplerenone. In the present study, the baseline characteristics of the two treatment arms were same; therefore, the effectiveness of spironolactone and eplerenone is clearly comparable.

The present study demonstrates that eplerenone improves cardiac performance to a greater extent than spironolactone during the 6 months treatment of patients with chronic heart failure. When compared with the spironolactone arm, the eplerenone group showed larger increases in LV ejection fraction and LV systolic dimension (volume and diameter) at rest. In contrast, no significant difference of improvement was observed in left ventricular diastolic dimension (LVIDd and LVEDV) and blood pressure between 2 arms. But the 2 drugs improved symptoms, exercise tolerance, and quality of life to a similar extent.

Swedberg et al., recommends aldosterone receptor antagonists in addition to ACE inhibitors, beta blockers and diuretics. Study reported that aldosterone antagonist spironolactone has been shown to improve survival in patients with chronic, severe heart failure. Eplerenone is a selective aldosterone antagonist expected to have a lower incidence of hormonal side effects than spironolactone. (Nadin et al., 2005)

In this study although no significant differences of adverse drug reactions were observed between arms, arm I or patients receiving spironolactone had experienced more adverse profile than eplerenone arm. Adverse profile of medication shows that, in arm I patients, gynecomastia occurred in 10.4% of patients, dizziness in 11.4%, mastalgia in 5.7%. In arm II patient's dizziness occurred in 3.9% of patients, none of patients observed developed mastalgia, gynecomastia. The difference between the two arms was statistically non-significant except for dizziness which was significant.

Most previous studies that evaluate the hemodynamic response in 3 to 6 months of MRA therapy have reported benefits, including improvements in left ventricular ejection fraction and reduced ventricular volumes. Our findings are consistent with most of these studies, as measures of left ventricular end-diastolic volume, left ventricular end systolic volume, and

ejection fraction tend to improve in both arms but more with eplerenone, although the reductions in end-diastolic volume did not reach statistical significance.

Our findings in accordance with result of other studies, which reported that in both arms, LVEF, improved significantly.

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