

Comparison of the metabolic effects of eplerenone and spironolactone via plasma galectin-3 level in patients with heart failure

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ABSTRACT

Objectives: This study aims to compare the metabolic effect of eplerenone and spironolactone, mineralocorticoid receptor blockers, in patients with heart failure via galectin-3 plasma level.

Patients and methods: Between March 2018 and July 2018, 20 heart failure patients (12 males, 8 females; mean age 65.2±7.6 years; range, 58 to 73 years) diagnosed based on clinical parameters and echocardiographic findings were randomized (1:1) to either spironolactone (25 mg/day) or eplerenone (50 mg/day). All patients were also given standard heart failure treatment. We measured plasma levels of galectin-3 with biochemically. Galectin-3 levels were compared before the study and four months after both spironolactone and eplerenone treatment.

Results: The mean ejection fraction of the patients was 25.0±4.6% in the eplerenone group and 25.0±4.7% in the spironolactone group. Demographic and hemodynamic characteristics of the patients were comparable between the groups. In both groups, plasma galectin-3 levels were not significantly different prior to initiation of mineralocorticoid receptor antagonist therapy (p=0.307). In patients receiving eplerenone, the mean plasma galectin-3 levels decreased from 898.6±23.4 to 99.7±7.9 four months after the treatment (p=0.0004). In the spironolactone group, galectin-3 levels prior to and after treatment did not change significantly (p=0.201).

Conclusion: Galectin-3 concentration, which is an emerging marker of cardiac fibrosis, statistically decreased in the eplerenone group rather than spironolactone group. Based on this finding, we can speculate that eplerenone is more effective than spironolactone in preventing fibrosis and inflammation in patients with heart failure.

Keywords: Eplerenone, fibrosis, Galectin-3, heart failure, spironolactone.

Heart failure (HF) is a common and highly morbid cardiovascular disorder associated with perturbations in cardiac structure and function. The incidence of HF has been gradually increasing in recent years. For individuals aged >40 years, the lifetime risk for developing HF has been estimated to be approximately 20%.^[1,2] The incidence of HF is the highest in population aged >65 years, which has been rapidly growing, ensuring an epidemic of HF that is expected to continue to grow as the population ages.^[1,2] According to Boon et al.,^[3] the prevalence of HF rises from approximately 1% among patients aged 50 to 59 years to 5 to 10% among those aged 80 to 89 years.

Galectin-3, a member of the galactic family, is a 30 kDa protein. It is an emerging marker of cardiac fibrosis, which is an outcome of HF.^[4-6] There is increasing evidence in consensus with the use of plasma galectin-3 as a diagnostic and prognostic biomarker for HF.^[6]

Mineralocorticoid receptor antagonists (MRAs), represented by the non-selective agents spironolactone^[7] and selective eplerenone^[8,9] have been shown to improve survival in patients with symptomatic chronic HF and acute myocardial infarction associated with left ventricular (LV) systolic dysfunction. These clinical benefits have been related to the improvement of LV remodeling and the reduction of cardiac fibrosis.^[10,11] Activation of mineralocorticoid receptor promotes myocardial fibrosis, inflammation, cardiomyocyte death, and LV hypertrophy,^[12] although the molecular

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mechanisms which specifically underlie their clinical benefits have not been completely elucidated, yet. In addition, spironolactone and eplerenone differ in their molecular structure, pharmacodynamics, and pleiotropic effects;^[13,14] however, meaningful differences between the two agents are not clearly present, and clinical practice guidelines do not discriminate between agents while recommending the use of an MRA in this setting.^[15,16]

In the present study, we, therefore, aimed to evaluate the differences of plasma galectin-3 levels in patients receiving either eplerenone or spironolactone for the treatment of HF and to assess the effectiveness of these treatments.

PATIENTS AND METHODS

In this prospective study, all patients were selected based on echocardiographic and clinical findings. Eligibility criteria were as follows: having the New York Heart Association (NYHA) functional Class III symptoms, an LV ejection fraction (LVEF) of <30%, and receiving treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin-receptor blocker and a beta-blocker, furosemide, digoxin (unless contraindicated) at the recommended dose or maximal tolerated dose. Exclusion criteria were renal failure, non-cardiac fluid overload, thyroid disorders, hepatic disorders, or atrial fibrillation. Finally, a total of 20 HF patients (12 males, 8 females; mean age 65.2±7.6 years; range, 58 to 73 years) were included between March 2018 and July 2018. A written informed consent was obtained from each patient. The study protocol was approved by the Ethics Committee of Bicard Clinic of Bishkek, Kyrgyzstan. The study

was conducted in accordance with the principles of the Declaration of Helsinki.

The patients were randomized (1:1) to either spironolactone (25 mg/day) or eplerenone (50 mg/day). Ten patients received eplerenone 50 mg/day (Group 1), while the other 10 patients received spironolactone 25 mg/day for four months (Group 2). Blood samples were aseptically collected from each patient at the beginning of treatment and after four months, and plasma was eventually separated for the measurement of plasma galectin-3 using the galectin-3 assay (BG Medicine (BG Medicine Inc., Waltham, MA, USA). This assay quantitatively measures the concentration of human galectin-3 levels in ethylenediaminetetraacetic acid plasma. It has a high sensitivity (lower limit of detection, 1.13 ng/mL) and exhibits no cross-reactivity with collagens or other members of the galectin family. Commonly used HF medications such as ACE inhibitors, beta-blockers, furosemide, acetylsalicylic acid, warfarin, coumarins, and digoxin do not show interference with this assay.^[7]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard error of the mean (SEM), median (min-max), or number and frequency. Univariate analysis was performed using the Student's t-test. Categorical data were compared using the chi-square test. A linear regression analysis was used to identify the relationship between continuous variables. A *p* value of <0.05 was considered statistically significant.

Table 1
Demographic and hemodynamic characteristics of patients

	Eplerenone Group (n=10)	Spironolactone Group (n=10)	<i>p</i>
	Mean±SD	Mean±SD	
Age (year)	65.7±7.7	64.6±7.6	>0.05
Left ventricular ejection fraction (%)	25±4.6	25±4.7	>0.05
Duration of heart failure (year)	5.8±3.4	5.7±3.6	>0.05
Blood pressure systolic (mmHg)	123±17	120±15	>0.05
Blood pressure diastolic (mmHg)	75±10	74±8	>0.05
Plasma galectin-3 level (pg/mL) (before treatment)	898.6±23.4	864.4±28.5	>0.05

SD: Standard deviation.

Table 2 Comparison of Galectin-3 levels			
	Before treatment galectin-3 (pg/mL)	After treatment galectin-3 (pg/mL)	<i>p</i>
	Mean±SD	Mean±SD	
Group 1 (Eplerenone)	898.6±23.4	99.7±7.9	0.0004
Group 2 (Spironolactone)	864.4±28.5	798±25	0.201
<i>p</i> -value	>0.05	0.001	

SD: Standard deviation.

RESULTS

The mean LVEF of the patients was 25.0±4.6% in the eplerenone group and 25.0±4.7% in the spironolactone group. Demographic and hemodynamic characteristics of the patients including baseline galectin-3 levels were comparable between the groups (Table 1).

In both groups, plasma galectin-3 levels were not significantly different prior to initiation of MRA treatment ($p=0.307$). In patients receiving eplerenone, the mean plasma galectin-3 levels significantly decreased from 898.6±23.4 to 99.7±7.9 four months after the treatment ($p=0.0004$). In the spironolactone group, however, galectin-3 levels prior to and after treatment did not change significantly ($p=0.201$). In patients receiving eplerenone, the mean plasma galectin-3 level was statistically significantly lower than the patients receiving spironolactone four months after the treatment (99.7±7.9 pg/mL vs. 798±25 pg/mL; $p=0.001$) (Table 2).

DISCUSSION

Biomarkers such as galectin-3 which reflect ongoing remodeling may provide complementary information regarding the natriuretic peptides used in the management of chronic HF with regard to risk stratification for future adverse cardiac events including death, myocardial infarction, and need for heart transplantation.^[10] Plasma galectin-3 measurement is cost-effective, readily available, easily interpretable, and suitable for low-income individuals similar to those included in our study.

The physiological importance of spironolactone is indirect regulation of blood volume and blood pressure by sodium retention. However, spironolactone also plays an essential role in the pathogenesis of HF.^[17]

By antagonizing spironolactone, MRAs can prevent the pathophysiological effects of sodium retention, cardiac hypertrophy, and cardiac fibrosis.^[12]

Currently, the success of several MRAs has been already established in HF. First, the Randomized Aldactone Evaluation Study (RALES) trial determined the efficacy of co-therapy with spironolactone in patients with severe HF (LVEF ≤35%) compared to placebo.^[18] The primary efficacy end-point was all-cause mortality and secondary endpoints included cardiovascular death and hospitalization and change in the NYHA class. Spironolactone treatment proved to be successful in reducing the risk for all-cause mortality (30% risk reduction) and prespecified secondary outcomes, compared to placebo, regardless of age. Second, The Eplerenone in Patients with Heart Failure Due to Systolic Dysfunction Complicating Acute Myocardial Infarction (EPHESUS) trial investigators investigated the efficacy of eplerenone treatment in addition to optimal treatment in a multi-center, double-blind, randomized trial in patients with LV dysfunction (LVEF ≤40%) after acute myocardial infarction. Treatment with eplerenone led to a reduction of overall mortality (by 15%) and to a reduction of cardiovascular death and hospitalization (by 13%) compared to placebo. The Effect of Eplerenone versus Placebo on Cardiovascular Mortality and Heart Failure Hospitalization in Subjects with NYHA Class II Chronic Systolic Heart Failure (EMPHASIS-HF) trial also investigated the effectiveness of eplerenone in patients with systolic HF (LVEF ≤35%) and mild HF symptoms.^[19,20]

In the present study, plasma galectin-3 concentration in clinical groups were identical at the beginning of treatment. Upon randomization, in the eplerenone group, plasma galectin significantly decreased after four months than in patients receiving spironolactone.

In the patients receiving spironolactone, plasma galectin-3 level did not significantly change. Although eplerenone and spironolactone have the same effect on the treatment of HF,^[21,22] they have different molecular structures, pharmacodynamics, and pleiotropic effects.^[16] Clinical practice guidelines do not specifically discriminate between these two agents for the use of an MRA in this setting.^[21,22] There may be slight differences in the MRAs' metabolic activities. We can detect these differences via new emerging biochemical markers, such as galectin-3. In our study, we showed that, there was a significant difference in reducing galectin-3 levels in favor of the eplerenone group. Eplerenone treatment differs from spironolactone in this setting. Although there is no clear discrimination in the clinical practice guidelines so far, we can obtain new data with metabolic studies to clarify the difference of these agents.

The main limitation of our study is its limited sample size. In addition, we were unable to test clinical outcomes. Nevertheless, this study provides evidence regarding the superiority of eplerenone to spironolactone in reducing galectin-3 levels.

In conclusion, our study findings indicate that the metabolic effects of eplerenone are different from those of spironolactone and eplerenone may be superior to spironolactone in the way of metabolic aspect in patients with HF. Additional large-scale studies are still needed to clarify the relationship of eplerenone treatment and plasma galectin-3 levels in adjusting HF treatment.

Declaration of conflicting interests

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