

# Comparison of Eplerenone and Spironolactone in Treatment of Patients with Congestive Heart Failure Visiting a Tertiary Hospital in North India

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## Abstract

**Background:** Congestive heart failure (CHF) is a serious clinical condition, with not many established treatment options. Eplerenone (Inspra) is the second aldosterone antagonist commonly used (in preference to Spironolactone) for treatment of hypertension and CHF in the US. Literature for its effectiveness in India is lacking, hence the need for the present study.

**Methodology:** The present cross-sectional, observational study was done among 100 adult patients (>20 years) (50 patients in each study group: Eplerenone and Spironolactone), diagnosed with chronic CHF and poor left ventricle function (ejection fraction <40%) unknown of their blood pressure status. Sociodemographic profile, clinical and laboratory status was evaluated which included blood pressure measurements, lipid profile, kidney function tests, and other vitals. Assessment of parameters was done after 8 weeks of treatment.

**Results:** Systolic blood pressure, diastolic blood pressure and CK levels showed a significant change over the study duration, with Eplerenone producing a better result than Spironolactone ( $p < 0.05$ ). Remaining parameters showed a non-significant difference.

**Conclusion:** Eplerenone group proved to be associated with a better outcome in hypertension and cardiovascular parameters; however, due to limitations in sample selection, more research is warranted.

**Keywords:** Eplerenone, Spironolactone, Congestive heart failure, Hypertension

## Introduction

Congestive heart failure (CHF) is a clinical condition characterized by lack of perfuse systematic circulation due to the heart's damaged pumping capabilities.<sup>1,2</sup> CHF affects nearly 5 million people each year, in which at least 500,000 are newly diagnosed cases.<sup>3</sup> CHF is traditionally viewed as a chronic condition that is the result of silent killers such as hypertension and unmanaged diabetes. However,

more recently, clinical research has focused on CHF cases that occur suddenly.<sup>1</sup> CHF has always been a keen area of research due to its high rate of mortality and morbidity as well as being the leading cause of hospitalization in the elderly.<sup>4</sup>

Unfortunately, most forms of heart failure (those due to damaged heart muscle) have no known cure. The treatments available aim to improve the patient's quality of

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life as well as length of survival.<sup>1</sup> These treatments comprise drug therapy and, more importantly, lifestyle changes by the patient. The recommended changes consist of: quitting smoking (if applicable), losing weight (if necessary), abstaining from alcoholic beverages, reducing salt and fat intake, and regular physical activity.

In addition to this, a doctor through follow-up appointments must closely monitor the patient. Furthermore, a majority of heart failure patients have to take medications to help the heart in its ability to pump. The common medications are ACE (angiotensin converting enzyme) inhibitors, diuretics, digitalis glycosides, aldosterone antagonists, angiotensin receptor blockers (ARBs), and beta-blockers. Some patients who suffer from the more severe forms of CHF require the implantation of devices such as IABPs (intra-aortic balloon pumps) or LV ADs (left ventricular assist devices) to assist with their management.

Eplerenone (Inspra) is the second aldosterone antagonist commonly available in the US. It received Food and Drug Administration (FDA) approval in 2002 and 2003, for the treatment of hypertension and heart failure, respectively. Eplerenone blocks the mineral corticoid receptors in the kidney, heart, blood vessels and brain more selectively than Spironolactone (another aldosterone antagonist; it has progestational and anti-androgenic adverse effects due to its nonspecific binding to various steroid receptors.<sup>5</sup>

Adverse reactions of Eplerenone are gastrointestinal intolerance, dizziness, hypercalemia and hypertriglyceridemia.<sup>6</sup> Breast discomfort and enlargement or other anti-androgen effects are seen in men, treated with Spironolactone but are infrequent with Eplerenone.<sup>7</sup> Although its use is common in the US and other developed parts of the world, its effectiveness in Indian scenario is debatable. Hence, the intention of this study is to study the effect of Eplerenone (Inspra): second Aldosterone antagonist in patients of CHF visiting a tertiary care hospital in North India.

## Methodology

The present cross-sectional observational study was done in a tertiary care hospital in North India from July 2015 to June 2017 among 100 adult patients (>20 years of age), diagnosed with chronic CHF unknown of their blood pressure status. Selected patients essentially had poor left ventricle function (ejection fraction <40%) of any cause. Patients with congenital heart malformations, other chronic comorbidity such as uncontrolled diabetes mellitus, patients with life expectancy less than 1 year, patients who had a myocardial infarction less than 4 weeks prior to enrollment in the study, overt renal disease, cancer or suspicion of malignancy, pregnant patients and patients with hypertensive emergency were excluded.

Ethical approval was taken from the Institutional Ethical Committee after explaining the aims and objectives of the study. A written informed consent was obtained from each patient for the study. The involvement of the subjects was voluntary and deliberate.

All patients underwent a clinical and laboratory evaluation. The demographic data were obtained from a questionnaire survey. Following variables were assessed: gender, age (years), ethnicity, occupation, education, income, socioeconomic status (calculated with combination of occupation, income and education in accordance with modified Kuppaswamy scale, 2016).<sup>8</sup> Other parameters evaluated were: body mass index (BMI), pulse, blood pressure (BP), weight and temperature in Fahrenheit scale. Data on comorbidities such as dyslipidemia, cancer, and diabetes were also noted.

Blood samples were obtained during the time of patient reporting for serum electrolytes. Estimation of hemoglobin by hematocrit, serum creatinine, BUN, uric acid, RBS, enzymes and serum lipid profile was also done by the principle of colorimetry using spectrophotometer.

## Study Groups

Patients already undergoing treatment from physicians in the hospital were equally randomized in two treatment groups: Eplerenone group and Spironolactone group of 50 subjects each. Patient compliance was noted and patients were asked to keep a record of medications taken. Biochemical and BP evaluation was performed at follow-up visits and compared at the end of 8-week period. Loss to follow-up and non-compliance was insignificant.

## Study Factors

- Vitals of the individual: pulse, weight, temperature
- Lipid profile: total cholesterol, LDL and triglyceride levels
- Serum creatinine and blood urea nitrogen (BUN) levels
- Serum electrolytes (Na, K)
- Systolic and diastolic blood pressure
- ECG and echocardiogram findings; noted as normal/ abnormal

## Statistical Analysis

Statistical analysis was performed using SPSS v17.0. Differences between parametric groups were compared by the Student-t test; correlation was done by Pearson's correlational analysis. Non-parametric variables were evaluated using chi-square test for statistical comparisons.

## Results

Majority of study participants were in the 31–50 year age group, with a mean of 51.3±9.7 years and range 44–72

years. Majority were males (87%) and 13% females. Most of the study participants were married (89%), 9% were unmarried and 2% divorced/separated. More than three-fourths of subjects (79%) belonged to middle class, followed by 14% in lower-middle class, 5% in upper-middle and 2% in upper class (Table 1).

**Table 1. Sociodemographic Characteristics**

Sociodemographic Characteristics		Frequency	Percent (%)	p-value
Age group (years)	31–40	8	8	0.127
	41–50	26	26	
	51–60	45	45	
	>60	21	21	
Gender	Males	87	87.0	0.884
	Females	13	13.0	
Marital status	Married	89	89	0.291
	Unmarried	9	9	
	Divorced/Separated	2	2	
Socio-economic status	Lower-middle	14	14	0.929
	Middle	79	79	
	Upper-middle	5	5	
	Upper	2	2	

The mean pulse rate of study participants was  $77.2 \pm 8.74$  (range 64–94). The mean weight of study participants was  $88.9 \pm 10.2$  kg (range 75–111 kg). Mean body temperature of study participants was  $97.8 \pm 0.9$  (range 96–100). Systolic BP had a mean value of  $132.8 \pm 9.4$ ; mean diastolic BP was  $92.4 \pm 4.3$ . Tables 2 and 3 show descriptive statistics of baseline levels of study parameters.

**Table 2. Descriptive Statistics of Study Parameters**

	Blood Pressure		KFT		CK
	Systolic	Diastolic	Blood Urea	Serum Creat	
N	100	100	100	100	100
Mean	132.8	92.43	45.33	2.283	195.74
SE	.0572	.1695	1.236	.0548	2.163
Median	133	94	43.50	2.300	192.00
SD	9.43	4.35	13.537	.6002	23.697
Minimum	122	74	25	1.0	159
Maximum	156	104	81	3.2	241
Percentiles	25	132	80	32.00	182.00
	50	138	88	43.50	192.00
	75	152	102	51.00	211.00

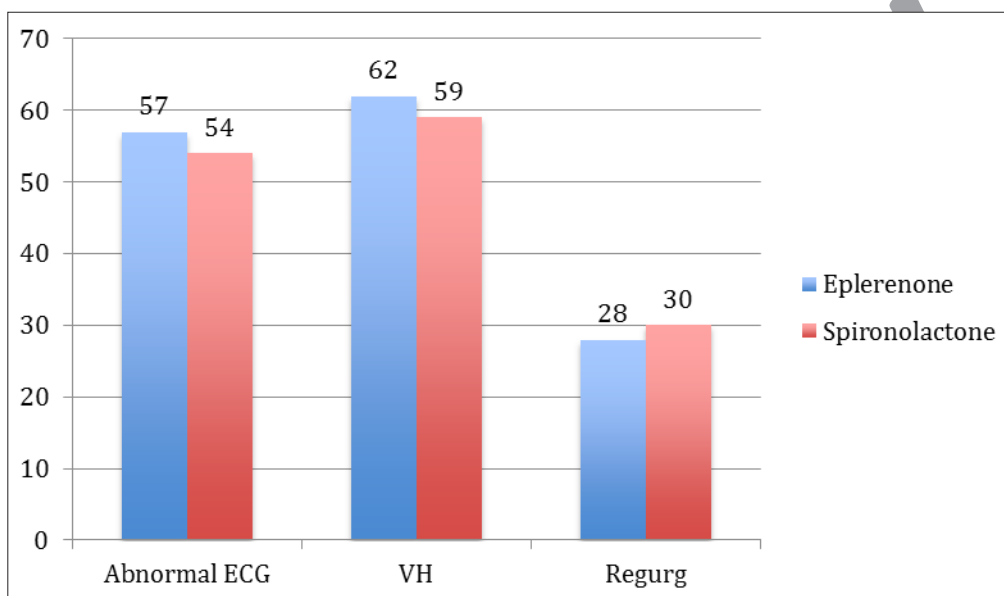
**Table 3. Descriptive Statistics of Study Parameters**

	Total Cholesterol	HDL	LDL	Triglyceride	SGOT	SGPT	LDH	Alk Phosp	
N	120	120	120	120	120	120	120	119	
Mean	246.08	41.19	138.69	199.38	35.918	57.74	242.31	126.00	
SE	3.582	.290	2.779	2.595	.6178	1.059	2.979	1.872	
Median	251.00	41.00	130.00	200.00	38.300	61.00	231.00	128.00	
SD	39.242	3.176	30.437	28.423	6.7677	11.605	32.629	20.426	
Minimum	185	37	95	159	22.7	34	185	95	
Maximum	308	47	195	249	47.0	73	293	166	
Percentiles	25	208.00	39.00	108.00	171.00	29.100	50.00	217.00	106.00
	50	251.00	41.00	130.00	200.00	38.300	61.00	231.00	128.00
	75	280.00	44.00	169.50	223.00	40.100	69.00	275.00	139.00

Table 4 shows the baseline statistics among study participants in terms of ECG, Echo findings and serum electrolytes in both the treatment groups using unpaired-t test. At the baseline, the mean abnormal ECG was 57% and 54% in Eplerenone and Spironolactone group, respectively. Similarly, 62% of the subjects had ventricular hypertrophy in Eplerenone group and 59% in Spironolactone group. Regurgitation was seen in 28% subjects in Eplerenone group and 30% in Spironolactone group. The mean baseline ejection fraction was 36% (2.2 SD) in Eplerenone group and 34% (4.1 SD) in Spironolactone group (Fig. 1). None of the baseline characteristics was statistically different among study groups.

**Table 4. Estimates of Baseline Study Parameters among Two Treatment Groups**

Baseline	ECG		Ejec Frac		Ventricular Hypertrophy		Regurgitation		Serum Na		Serum K	
	Normal	Abnormal	Mean	SD	Yes	No	Yes	No	Mean	SD	Mean	SD
Eplerenone	43%	57%	36%	2.2	62%	38%	28%	72%	137.2	4.1	4.8	0.5
Spironolactone	46%	54%	34%	4.1	59%	41%	30%	70%	139.1	5.8	5.1	0.8
p-value	0.463		0.984		0.743		0.672		0.712		0.135	



**Figure 1. Baseline Study Parameters among Sample Population**

Table 5 shows the 8-week estimates among study participants in terms of ECG, Echo findings and serum electrolytes in both the treatment groups using unpaired-t test. The mean abnormal ECG prevalence was 51% in Eplerenone group and 49% in Spironolactone group. Nearly 41% of subjects had ventricular hypertrophy in Eplerenone group and 45% in Spironolactone group.

Both these parameters were significantly different among study groups. Regurgitation was seen in 22% of subjects in Eplerenone group and 28% in Spironolactone group, not statistically significant. The mean baseline ejection fraction was 54% (3.1 SD) in Eplerenone group and 52% (2.7 SD) in Spironolactone group, statistically significant (Fig. 2).

**Table 5. Estimates of 8-week Study Parameters among Two Treatment Groups**

Baseline	ECG		Ejec Frac		Ventricular Hypertrophy		Regurgitation		Serum Na		Serum K	
	Normal	Abnormal	Mean	SD	Yes	No	Yes	No	Mean	SD	Mean	SD
Eplerenone	49%	51%	54%	3.1	41%	59%	22%	78%	155.7	3.7	3.5	0.3
Spironolactone	51%	49%	52%	2.7	45%	55%	28%	72%	152.3	4.1	4.1	0.5
p-value	0.003*		0.041*		0.039*		0.371		0.002*		0.015*	

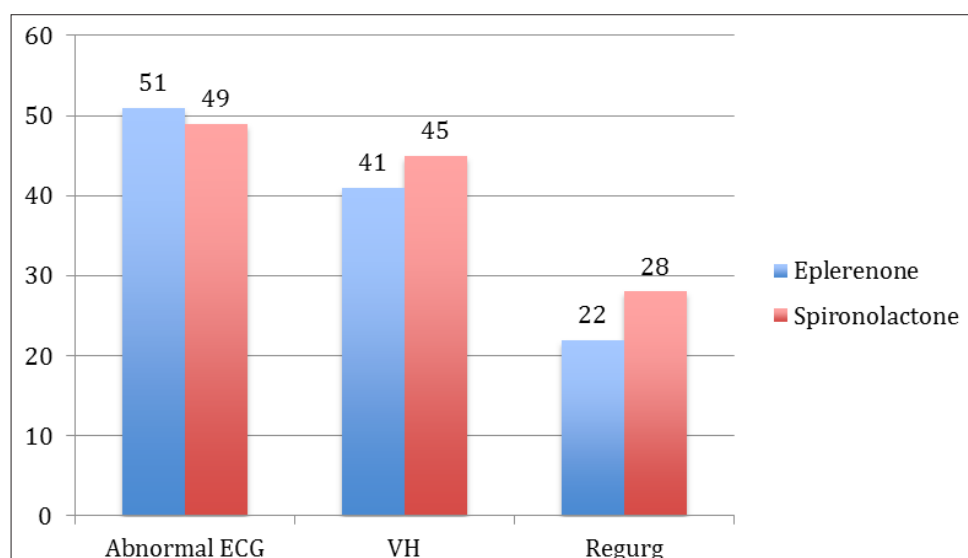


Figure 2. Eight-week Study Parameters among Sample Population

Table 6 shows the change in study parameters among treatment groups. Systolic blood pressure, diastolic blood pressure and CK levels showed a significant change over the study duration, with Eplerenone producing a better result than Spironolactone. Remaining other parameters showed a non-significant difference.

Table 6. Comparison of Change in Study Parameters among Treatment Groups

	Eplerenone		Spironolactone		p-value
	Mean	SD	Mean	SD	
Systolic BP	132.8	9.43	133.1	9.3	0.031*
Diastolic BP	92.43	4.35	92.73	4.22	0.048*
Blood Urea	45.33	13.537	45.63	13.407	0.345
Serum Creatinine	2.283	0.6002	2.583	0.4702	0.564
CK	195.74	23.697	196.04	23.567	0.018*
Total Cholesterol	246.08	39.242	248.18	38.542	0.364
HDL	41.19	3.176	43.29	2.476	0.678
LDL	138.69	30.437	140.79	29.737	0.543
Triglyceride	199.38	28.423	201.48	27.723	0.788
SGOT	35.918	6.7677	38.018	6.0677	0.867
SGPT	57.74	11.605	59.84	10.905	0.962
LDH	242.31	32.629	244.41	31.929	0.138
Alkaline Phosphatase	126	20.426	128.1	19.726	0.978

## Discussion

Aldosterone, a hormone of the renin-angiotensin-aldosterone system, has been linked to hypertension, cardiac hypertrophy, and cardiac and vascular fibrosis. Despite treatment with an angiotensin-converting enzyme inhibitor or angiotensin-II receptor blocker, suppression of aldosterone is incomplete due to non-angiotensin-II regulators of aldosterone production, such as serum potassium. Until recently, the only approved aldosterone antagonist for the treatment of hypertension and heart failure was Spironolactone.<sup>9</sup> Eplerenone selectively binds to the mineralocorticoid receptor, thereby blocking the binding of aldosterone and thus inhibiting sodium reabsorption and other deleterious aldosterone-mediated mechanisms.<sup>10</sup>

Most published clinical trials evaluated the efficacy of Eplerenone for the treatment of hypertension. No clinical trials directly compared Eplerenone and Spironolactone for heart failure.<sup>10</sup> With this background, the present observational study was attempted to study the efficacy of Eplerenone in treatment of heart failure and compare it with Spironolactone. Comparison of reduction in blood pressure with two treatments showed relative reduction to be significantly higher with Eplerenone than Spironolactone in the current study. Similar results have been obtained in a 12-week multicenter, double blind, randomized, placebo-controlled, parallel-arm, and intention-to-treat trial.<sup>11</sup> EPHEUS Trial on heart failure also presented with similar findings.<sup>12</sup>



Clearly, patients with chronic severe HFREF (NYHA class III–IV) and patients with HFREF early post-MI should receive mineralocorticoid receptor antagonists (MRAs) in addition to standard therapy including an ACEI or ARB and a  $\beta$ -blocker if there is no contraindication to their use such as a serum potassium  $>5.0$  meq/L or an estimated glomerular filtration rate (eGFR)  $<30$  mL/min/1.73 m<sup>2</sup>.<sup>13</sup> Other parameters like ECG findings improved significantly with treatment with Eplerenone in the current study. The pharmacologic effects of Eplerenone (a selective aldosterone antagonist) have not been studied as extensively as those of Spironolactone, particularly in humans.

In rats given exogenous angiotensin-II and dietary sodium chloride, Eplerenone reduced myocardial hypertrophy, expression of markers of coronary inflammation, and myocardial necrosis.<sup>14</sup> The LV ejection fraction (LVEF) also improved significantly from 36% to 54% with Eplerenone at 8 weeks of treatment. The LVEF increased in patients enrolled in EPHEUS from 33% at baseline.<sup>12</sup> The possible explanation could be revascularization and recovery from the acute event. These findings have important consideration for choosing MRA in treatment of chronic HF with a reduced left-ventricular ejection fraction (HFREF) and in patients with HFREF early postmyocardial infarction (post MI).

Current guidelines in general do not distinguish between the uses of these two agents. Spironolactone however has a known side effect profile including breast pain and gynecomastia in males and menstrual irregularities in premenstrual females due to its relative non-specificity for the mineralocorticoid receptor and its effects on androgen and progesterone receptors. Eplerenone, due to its relatively higher specificity for the mineralocorticoid receptor, is devoid of these side effects and therefore better tolerated, at least in males.<sup>13</sup> Hyperkalemia appeared to be an issue when Spironolactone became routine practice for treatment of HF. After the RALES study, Spironolactone tended to be confined to the sickest New York Heart Association class-III and IV heart failure, with careful monitoring.<sup>15</sup>

The present research also showed greater potassium balance with Eplerenone. This is contrary to the findings of EPHEUS trial wherein serum concentrations of potassium and creatinine increased in both groups, and the increases were greater in patients who received Eplerenone. Serious hyperkalemia was more frequent in the Eplerenone-treated patients (5.5%) than in those treated with placebo (3.9%) ( $P=0.002$ ).<sup>12</sup> Even a study by Pitt et al. in 2003 demonstrated hyperkalemia to be a major side effect with the drug.<sup>16</sup> However, direct comparison with Spironolactone is warranted in future research for comparison.

No significant improvement was observed with respect to lipid profile of the patients on treatment with the two

drugs in our research. This is corroborating with the fact that Eplerenone has major adverse effect in the form of hypertriglyceridemia as reported in studies by Craft et al.<sup>9</sup> A study by Goodfriend et al. showed a negative correlation between aldosterone and cardio-protective high-density lipoprotein (HDL) levels, suggesting that these effects are, at least in part, mediated through increased MR activation.<sup>17</sup> However, in summary, the available data remains controversial and there is still no conclusive evidence that establishes aldosterone and MR activation as critical factors in lipid or glucose homeostasis. Different MR blockers, e.g., Spironolactone versus Eplerenone, have different pharmacokinetic profiles.

Therefore, the effect of MR blockade on metabolic parameters may vary by the MR antagonist applied. For example, Eplerenone has been shown to improve insulin resistance in animal models of obesity. Similarly, in a mouse model of diet-induced diabetes mellitus MR blockade by Spironolactone induced improvements in glucose and lipid metabolism.<sup>18,19</sup> The present study did not show any significant improvement in kidney function tests with two drugs; however, the decline was more seen with Spironolactone. Similar findings have been reported elsewhere also.<sup>20</sup> Blockade of the MR has been demonstrated to have a general reno-protective effect in patients with diabetes mellitus and with chronic kidney disease. Evidence suggests Spironolactone to be more effective in stabilizing renal function tests in comparison to other MRAs.

### Limitations of the Study

- The study was restricted to observational design, which has its own limitations. Compliance was an issue which, however, stringently followed, will probably encounter a trace of error, leading to bias in outcome.
- A research group of 100 individuals may not be diagnostically sufficient for concluding such evidences. A larger sample size with preferably a cohort-based periodical evaluation would be more helpful.
- Other parameters, particularly related to cardiovascular abnormalities, would also have been helpful in judging the status of the chronic comorbidity.

### Conclusion

Comparison of reduction in blood pressure with two treatments showed relative reduction to be significantly higher with Eplerenone than Spironolactone in the current study. Other parameters like ECG findings improved significantly with treatment with Eplerenone in the current study. No significant improvement was observed with respect to lipid profile of the patients on treatment with the two drugs in our research. The present study did not show any significant improvement in kidney function tests

with two drugs; however, the decline was more seen with Spironolactone.

**Conflict of Interest:** None

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