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Original Research Article

Randomized, Placebo-Controlled Study to Investigate the Effects of Eplerenone in Patients with Heart Failure of Different Etiologies

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Abstract

Aim: To investigate the effects of eplerenone in patients with heart failure of different etiologies

Methodology: This is a type of randomized, placebo-controlled study. 500 patients with age more than 55 years old and diagnosed with heart failure were enrolled in this study visiting Department of General medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India. Patients were divided into two sub-groups, which are group A and group B. Group A included 250 patients who were randomly assigned to receive placebo in addition to recommended therapy. Group B included 250 patients to whom eplerenone (up to 50 mg daily) was prescribed with recommended therapy. The number of hospitalizations per person were recorded, separately, for all-cause and heart failure hospitalizations.th number of deaths of patients and their causes were also recorded and further analyzed.

Results: Out of 500 enrolled patients, 120 patients were died in total. Out of group A (placebo), total number of deaths reported were 68 (27.2%), out of which 44 (17.6%) deaths were due to cardiovascular reasons. Out of group B (eplerenone), total number of deaths reported were 53 (20.8%), out of which 32 (12.8%) deaths were due to cardiovascular reasons. Out of 500, 382 (76.4%) patients got admitted to hospitals for any cause during follow-up. The number of patients admitted for heart failure was 116 (23.2%).

Conclusion: In patients with heart failure, eplerenone added to recommended therapy is found to be associated with a reduction in the rate of death from a cardiovascular cause or hospitalization for heart failure as well as hospitalization from other causes also.

Keywords: Eplerenone, mineralocorticoid receptor antagonists, placebo.

Introduction

Eplerenone is in a class of medications called mineralocorticoid receptor antagonists. Mineralocorticoid receptor antagonist (MRA) therapy improves outcomes in patients with chronic systolic HF with mild symptoms (EMPHASIS-HF

trial), acute symptomatic systolic HF in post-myocardial infarction (EPHESUS trial) and in severe NYHA stage III–IV systolic HF (RALES trial). [1-3] Aldosterone blockade reduces the rate of death due to progressive heart failure and the rate of sudden death from cardiac causes, as well as the rate of hospitalizations for heart failure, among patients with severe heart failure due to systolic left ventricular dysfunction who are being treated with an angiotensin-converting–enzyme (ACE) inhibitor. [4] Aldosterone blockade also prevents ventricular remodeling and collagen formation in patients with left ventricular dysfunction after acute myocardial infarction [5] and affects a number of pathophysiological mechanisms that are thought to be important in the prognosis of patients with acute myocardial infarction. [6-9]

Strong data exist to support the use of angiotensin-converting enzyme inhibitor (ACE-I), angiotensin receptor blocker (ARB), beta-blockers (BBs), and mineralocorticoid receptor antagonists (MRAs) in patients with chronic HF. [10]. Eplerenone works by blocking the action of aldosterone, a natural substance in the body that raises blood pressure.

The three major consequences of heart failure are symptoms, hospital admission due to worsening heart failure, and premature death. [11, 12]. Not only are these hospital admissions very distressing for patients and their caregivers, but they are also the major driver of the enormous cost of heart failure to healthcare systems. [13].

Materials and Methods

This is a type of randomized, placebo-controlled study. 500 patients with age more than 55 years old and diagnosed with heart failure were enrolled in this study visiting Department of General medicine, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India.

Exclusion criteria:

Patients with history of stroke, cardiac surgery, or percutaneous coronary intervention within 30 days prior to randomization; or uncontrolled hypertension [systolic blood pressure (SBP) > 180 mmHg and/or a diastolic blood pressure >110 mmHg] or symptomatic hypotension, or an SBP < 85 mmHg; scheduled for cardiac transplantation; and any other pre-existing and ongoing significant co-morbid condition were not included in this study.

Patients were divided into two sub-groups, which are group A and group B.

Group A included 250 patients who were randomly assigned to receive placebo in addition to recommended therapy.

Group B included 250 patients to whom eplerenone (up to 50 mg daily) was prescribed with recommended therapy. All hospital admissions for suspected heart failure were adjudicated by a blinded end point committee. There was a subsequent median follow-up of 4.5 months on assigned double-blind treatment. The number of hospitalizations per person were recorded, separately, for all-cause and heart failure hospitalizations.th number of deaths of patients and their causes were also recorded and further analyzed.

Results

Out of 500 enrolled patients, 120 patients were died in total. Out of group A (placebo), total number of deaths reported were 68 (27.2%), out of which 44 (17.6%) deaths were due to cardiovascular reasons. Out of group B (eplerenone), total number of deaths reported were 53 (20.8%), out of which 32 (12.8%) deaths were due to cardiovascular reasons.

Out of 500, 382 (76.4%) patients got admitted to hospitals for any cause during follow-up. The number of patients admitted for heart failure was 116 (23.2%). This means that 30.2% of all hospital admissions were due to heart failure. Out of Group A, 82 patients were admitted more than one

time due to all causes while only 34 patients were admitted more than one time due to heart failure. But in group B, 44 patients were admitted more than one time due to all causes, while only 18 patients were admitted more than one time due to heart failure.

Table 1: Number of deaths and patients hospitalized due to all-cause and heart failure.

Parameters		Placebo	Eplerenone
Total number of patients		250 (100%)	250 (100%)
Number of deaths	All – cause deaths	68 (27.2%)	52 (20.8%)
	Number of deaths due to cardiovascular reasons	44 (17.6%)	32 (12.8%)
All- cause hospitalizations	Total admissions	214 (85.6%)	168 (67.2%)
	Patients with >1 admissions	82 (32.8%)	44 (17.6%)
Heart failure hospitalizations	Total no. of admissions	66 (26.4%)	50 (20.0%)
	Patients with >1 admissions	34 (13.6%)	18 (7.2%)

Discussion

Heart failure is a complex disease affecting about 5 million Americans, with 550,000 new cases diagnosed annually. [16] Although treatment strategies have improved morbidity and mortality rates over the past 20 years, the 5-year mortality rate is approximately 50%. [17, 18] Pharmacologic therapy is a major component in the management of heart failure and can include angiotensin converting-enzyme (ACE) inhibitors, angiotensin II-receptor blockers (ARBs), β-blockers, digoxin, diuretics, and aldosterone antagonists. Hydralazine and nitrates continue to be used in some patients with heart failure.

Eplerenone is a selective aldosterone antagonist. It is chemically derived from spironolactone by the addition of a 9α, 11α-epoxy Bridge and by substitution of the 17α-thioacetyl group of spironolactone with a carbomethoxy group. [19, 20] Eplerenone is well absorbed following oral administration, with a bioavailability of approximately 67% and reaching a peak plasma concentration in about 1.5 hours. [21, 22] Food does not affect its absorption. [19] Eplerenone is metabolized by the cytochrome P-450 (CYP) isoenzyme 3A4 to inactive metabolites. [22, 23] Eplerenone concentrations increase with the concomitant administration of the CYP 3A4 inhibitor ketoconazole, suggesting that dosage adjustments may be appropriate for patients receiving a potent CYP 3A4 inhibitor while taking eplerenone. [23] However, eplerenone does not inhibit CYP isoenzyme systems. [22] The metabolism of eplerenone may be altered in patients with advanced age, renal impairment, hepatic impairment, or heart failure.

From this study, it can be said that eplerenone not only reduces the risk of first admissions but decreases the likelihood of second and subsequent admissions for heart failure. 85.6 % of the patients with placebo got admitted to the hospitals, while only 67.2% of patients with eplerenone got admitted to the hospitals. 32.8% patients with placebo and 17.6% patients with eplerenone got admitted to hospitals more than once for all causes. 26.4% patients with placebo got admitted to hospitals due to heart failure while only 20% patients

having eplerenone got admitted because of heart failure. Out of them, 13.6% with placebo and 7.2 % with eplerenone got admitted more than once. These repeat events matter a great deal to patients (and their caregivers) and are an important contributor to the economic burden of heart failure, with most analyses showing that heart failure hospitalization accounts for 70% of the total cost of this condition to healthcare systems. [13, 24]

The second major trial to evaluate aldosterone antagonism on morbidity and mortality in heart failure was EPHESUS. [25] EPHESUS evaluated the efficacy and safety of eplerenone in 6642 patients with left ventricular dysfunction after an MI. Patients initially received eplerenone 25 mg daily or placebo 3–14 days after acute MI complicated by an LVEF of ≤40% and heart failure evidenced by chest radiograph showing pulmonary venous congestion, or the presence of a third heart sound. Cardiovascular death or hospitalization for a cardiovascular event occurred in 26.7% and 30.0% of patients in the treatment and placebo groups, respectively (relative risk, 0.87; 95% CI, 0.79–0.95) (p = 0.002). Pharmacoeconomic evaluations also have found eplerenone to be cost-effective when compared with placebo in the populations studied in the major aldosterone antagonist trials. [26, 27]

Although eplerenone is found as a life-saving agent in patients with severe heart failure, but careful monitoring is also critical in patients taking aldosterone antagonists to prevent potentially life-threatening hyperkalemia. Patients with renal disease, diabetes mellitus, advanced heart failure, or advanced age and those taking certain concurrent medications have the highest risk of developing hyperkalemia. Increased vigilance in monitoring for and patient education regarding hyperkalemic symptoms is necessary in these patients. If baseline CL_{cr} is less than 30 mL/min or baseline serum potassium concentration is greater than 5.5 mmol/L, aldosterone antagonist therapy should be withheld. Recent updates to heart failure guidelines suggest withholding aldosterone antagonist therapy in patients with a baseline serum potassium concentration exceeding 5.0 mmol/L. [28].

Conclusion

In patients with heart failure, eplerenone added to recommended therapy is found to be associated with a reduction in the rate of death from a cardiovascular cause or hospitalization for heart failure as well as hospitalization from other causes also. Early initiation of eplerenone after discharge from a heart failure hospitalization should be encouraged.

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