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Research article

EPLERENONE IN THE MANAGEMENT OF CARDIOVASCULAR DISEASES: AN OBSERVATIONAL STUDY

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ABSTRACT

Back ground information: The aim of the study is to identify the effectiveness of EPLERENONE in the treatment of cardio vascular diseases. **Materials and methods:** 60 patients were included in our study. Those patients who meet the study criteria will be enrolled in to the study. Relevant data such as demographics details, risk factors, past medical history, drug name, dose, route, frequency, duration of therapy, total pills per day was collected from profile form of the patient and by patient interview. Complete follow up should be done within 6 months by interviewing during their review or by phone calls. **Statistical consideration:** All the raw data was collected , entered in excel sheet 2007 in windows 7 version, the statistical analysis was done in SPSS 16.0 software by an appropriate statistical methods using One-sample T test for knowing the significant p-value <0.005(confidence interval 95%). **Results:** Among 60 patients, 60% of patients are with IHD, 73.30% patients are with HTN, 23.30% are with DCMP, and 3.30% are with cardiac arrhythmias. The study shows that there is a significance decrease in Systolic BP when compared with before treatment i.e. 20.16±6.344mmHg and a significance decrease in Diastolic BP when compared with before treatment i.e. 9.00±4.002 mmHg. During therapy the heart rate was improved to 87.40±14.346 which is found to be statistically significant ($p<0.05$). After 2 months of treatment the dysfunctions are left with only 10% of systolic, 16.6% of diastolic & 10% of both dysfunctions. The patient with severe, moderate and mild EF was improved by the treatment. **Conclusion:** In our study we observed that eplerenone was safe and effective in treating patients with both acute and chronic cardiovascular diseases. The patient clinical and functional status was improved by his clinical manifestations, 6MWT, Echo and ECG changes and also improved ejection fraction by avoiding further exacerbation of condition, without occurrence of adverse effects. The monotherapy of eplerenone is as effective as polytherapy and the improvement of medication adherence was due to the patient counselling.

Key Words: -IHD, HTN, DCMP, 6MWT, ECG, ECHO.

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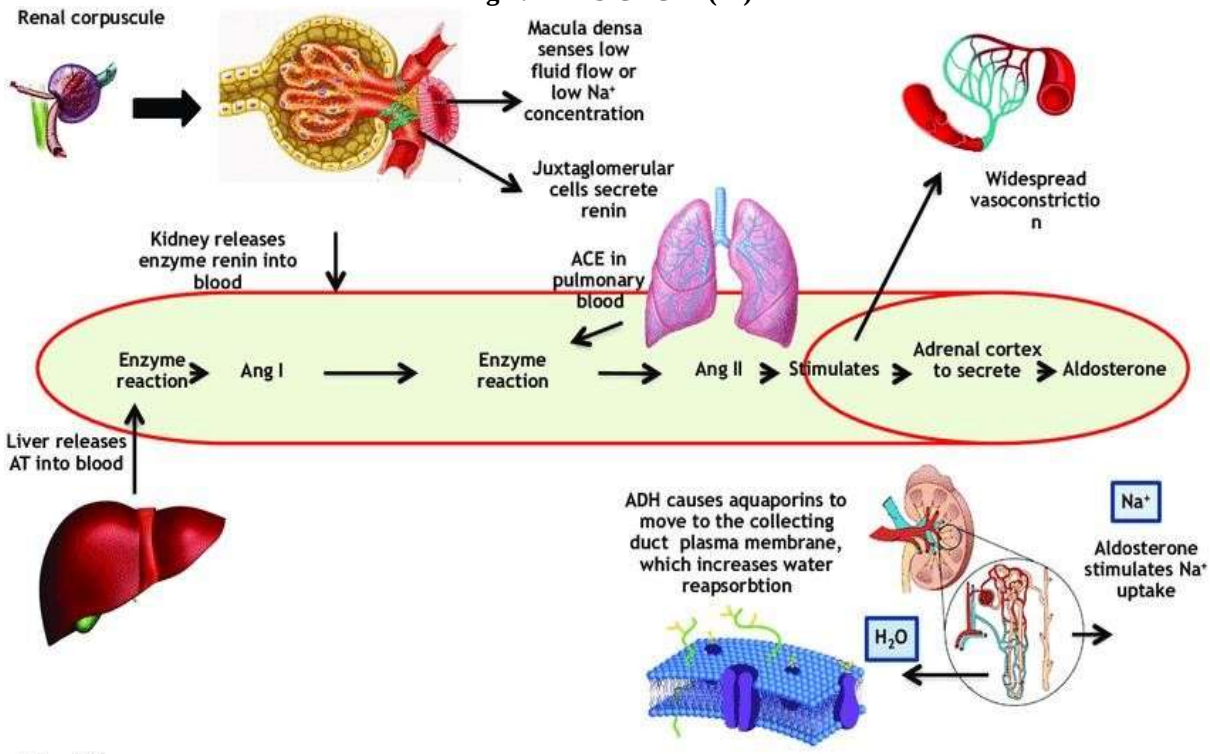
INTRODUCTION

In September 2002, eplerenone (Inspra; Pharmacia), the first selective aldosterone receptor antagonist, was approved by the FDA for the treatment of hypertension(EllenD, *et al*, 2003 & Xavier Jeunemaitre MD *et al*, 1987).Eplerenone (Inspra) is the second aldosterone antagonist available in the USA(Susan M Garthwaite, *et al*, 2004). It received Food and Drug Administration approval on September 27, 2002, and October 7, 2003, for the treatment of hypertension and heart failure, respectively(William B, *et al*, 2003 & Romain Eschalier, *et al*, 2013 & Tam TSC, *et al*, 2017).Eplerenone (epoxymexrenone) is a 9α, 11α-epoxy-

derivative ofmexrenone, an aldosterone antagonist that is structurally related to spiranolactone(Keating GM, ety al, 2004). Eplerenoneis only available agent in the aldosterone antagonist class, is much more specific thanspiranolactone in its blockade of aldosterone receptors and will be an excellent alternative to spiranolactone for patients with lv dysfunction, heart failure, hypertension(Christophe Leroyer, *et al*, 2017 & Chris Stenton, 2008 & Fletcher CM. *et al*, 1952).

Fig 1: RAAS CYCLE(11)



Abbreviations:
Ang I-angiotensin I; Ang II-angiotensin II; AT-angiotensinogen; ADH-antidiuretic hormone (vasopressin)

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(Alderman MH, *et al*, 1991). Until recently, the only approved aldosterone antagonist for the treatment of hypertension and heart failure was spironolactone(Coleman CI, *et al*, 2002). Spironolactone, although effective for these conditions, has progestational and antiandrogenic adverse effects due to its nonspecific binding to various steroid Receptors(Nishizaka MK, *et al*, 2003 & Jeunemaitre X, *et al*, 1987).Relative risk reduction from blood pressure reduction is similar across populations with varying absolute risk, so the absolute benefit is greater in patients who are at higher risk independent of their hypertension (for example, patients with diabetes or hyperlipidemia), and such patients would be expected to benefit from more aggressive treatment to a lower blood pressure goal(Weber KT., 1999 & Oh JK, Appleton CP, *et al*, 1997). Some antihypertensive drugs have smaller blood pressure effects (as monotherapy) in black patients, and many antihypertensive drugs have additional approved indications and effects (e.g., on angina, heart failure, or diabetic kidney disease)(Klein H, *et al*, 1999). These considerations may guide selection of therapy. INSPRA may be used alone or in combination with other antihypertensive agents.

AIM:

To determine the role of EPLERENONE in the management of cardio vascular diseases.

OBJECTIVES OF THE STUDY:

1. To determine effectiveness of Eplerenone.
2. To determine the improvement in clinical and functional outcomes (ECHO&ECG) in cardiovascular disease.

MATERIALS & METHODS:

STUDY SITE:

The study will be done in both inpatient and outpatient wards of cardiology department in sri Krishna institute of medical sciences (SKIMS), located beside manipuram flyover, near RTC Bus stand, Thammarangareddy nagar, Guntur, Andhra Pradesh-522001.

STUDY DESIGN: It is a prospective observational study.

STUDY PERIOD: The study will be carried out for a period of six months i.e. from October 1, 2018 to March 31, 2019 at Sri Krishna Institute Of Medical Sciences, Guntur.

STUDY CRITERIA:

Inclusion criteria:

i. Patient with age group greater than 20 years.
ii. Patient of either gender. iii.Patients who undergone investigations of both 2D/3D Echo& ECG.
iii. iv. Patients with Hypertension, Heart failure, Myocardial infarction were included. v. Patients both diabetic and non-diabetic were included.

Exclusion criteria:

Patients with age group less than 20 years.

i. Patients with other co-morbid conditions (hepatic& renal).
ii. Patients with other heart diseases were excluded.
iii. Patients with who are pregnant & lactating mothers were excluded.
iv. Patients who undergone investigations of only Echo or only ECG.

MATERIALS AND METHODS:

- Patients who are admitted into inpatient and outpatient wards in the cardiology department of Sri Krishna Institute of medical sciences and who meet the study criteria are enrolled for the study.
- Relevant data such as demographic details ,disease history, diagnosis, drug name dose, route, frequency, duration of therapy, total pills per day, laboratory data, allergy status will be collected from medical records of the patient and by patient interview where ever required are collected and documented.
- Changes to drug therapy, if any will be noted on daily basis and documented A suitable data collection form is designed for use in the study. Monitor the patient about the clinical events for 30 days.

SOURCES OF DATA:

All the relevant and necessary data will be collected from

1. Treatment charts
2. ECHO & ECG reports, Blood pressure reports, Serum potassium levels, Serum creatinine levels and 6 minute walk test.
3. Interviewing the patient and patient care takers.
4. Interviewing nurse, Physician.
5. Any other relevant sources.

FOLLOW UP:

- Before and after the treatment check the patient clinical condition, blood pressure, ECHO and ECG parameters.
- Advise the patients regarding their medication regimen and importance of medication adherence.
- Follow up done for 10 days, 1 month and 2 months period.

STATISTICAL ANALYSIS:

All the raw data was collected, entered in Excel sheet 2007 in windows 7 version, the statistical analysis was done in SPSS 16.0 Software by an appropriate statistical methods like one sample T-test for knowing the significant p-value <0.005(confidence interval 95%).

RESULTS:

- Over a period of 6 months study, data of 60 patients with cardiovascular diseases have collected. Patient inclusion criteria were assessed based on symptoms, ECG, Echo and TMT and 6 Minute walk test..
- Initially 71 patients were included in study, out which 11 patients were excluded.
- Because of no proper follow up and patients disinterest towards study.
- Based on the age, patients are grouped as following:
- Age of patients observed as follows, 33.3% of patients were between the age of 61-70 years, followed by 26.6% of patients were between the age of 51-60 years, 23.3% of patients were between the age of 41-50 years, 13.3% patients were between 71-80 years of age and 3.3% patients were between 31-40 years of age.

Figure 1: Age distribution of the patients from the study:

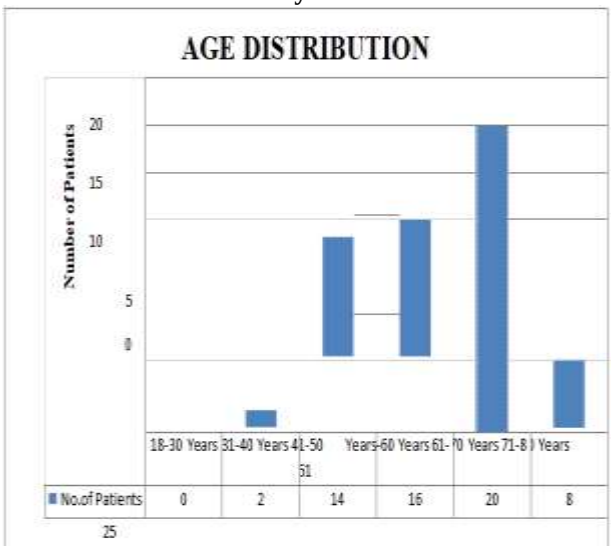
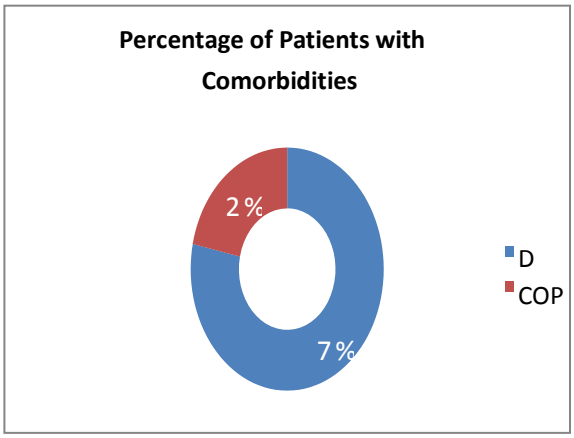
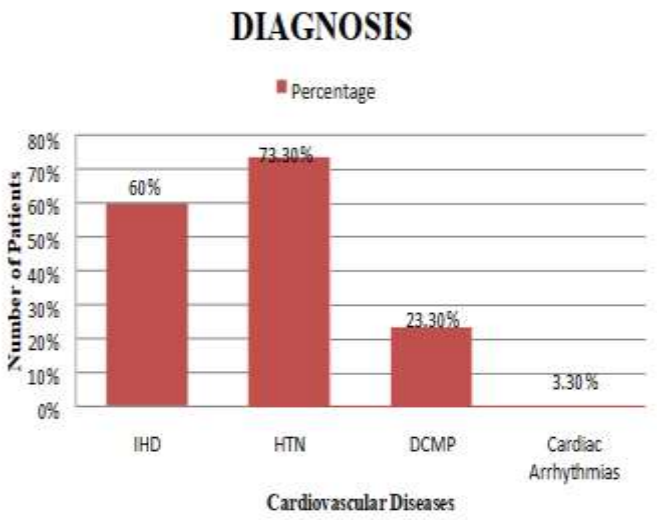


Figure 2. Co-morbidities



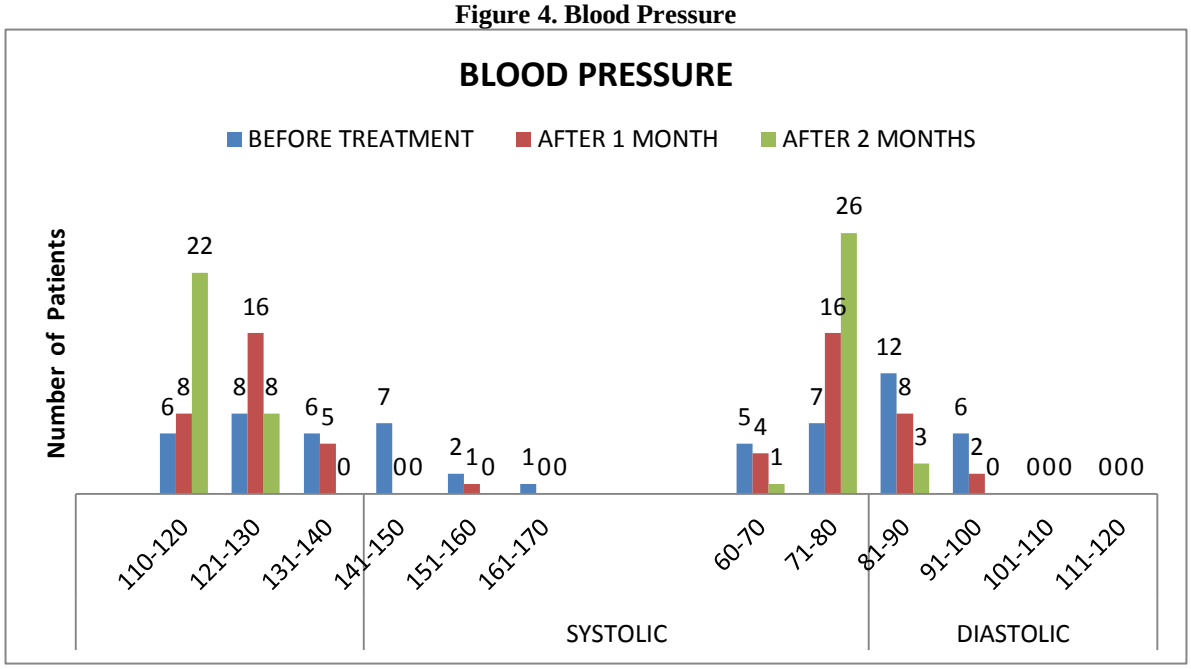
- 60% of patients were reported with having DM and 16.6% patients were reported having co morbidity of COPD.

Figure 3: Diagnosis



Over a 6 months period of study, 60 patients data have observed, of which 60% patients were with Ischemic Heart Disease (IHD), 73.30% patients were with Hypertension (HTN), 23.30% patients were with Dilated cardiomyopathy (DCMP), 3.30% patients were with Cardiac Arrhythmias.

Figure 4. Blood Pressure

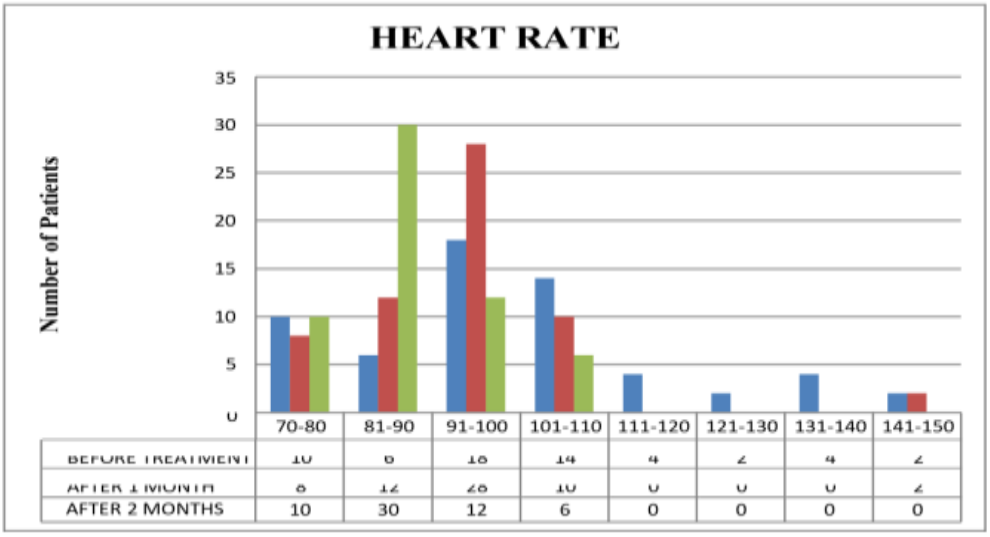


The pre and post treatment systolic BP of 60 patients included in the study, the mean of the pre treatment Systolic BP was 141.83±11.273mmHg and the mean of Systolic BP after 1 month treatment was 129.50±9.987mmHg. This shows that there was a significant decrease in Systolic BP i.e., 12.33±1.286mmHg in 1 month treatment of EPLERENONE 25mg, and the mean of the Systolic BP after 2 months treatment was 121.67±4.929mmHg. This shows that there was a significant decrease in Systolic BP when compared with pre treatment i.e., 20.16±6.344mmHg. There was a significant difference in reduction of BP having p-value <0.05(95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

The pre and post treatment diastolic BP of 60 patients included in the study. The mean of pre treatment Diastolic BP was 89.17±8.693 mmHg and the mean of Diastolic BP after 1 month treatment was 83.83±7.386 mmHg. This shows that there

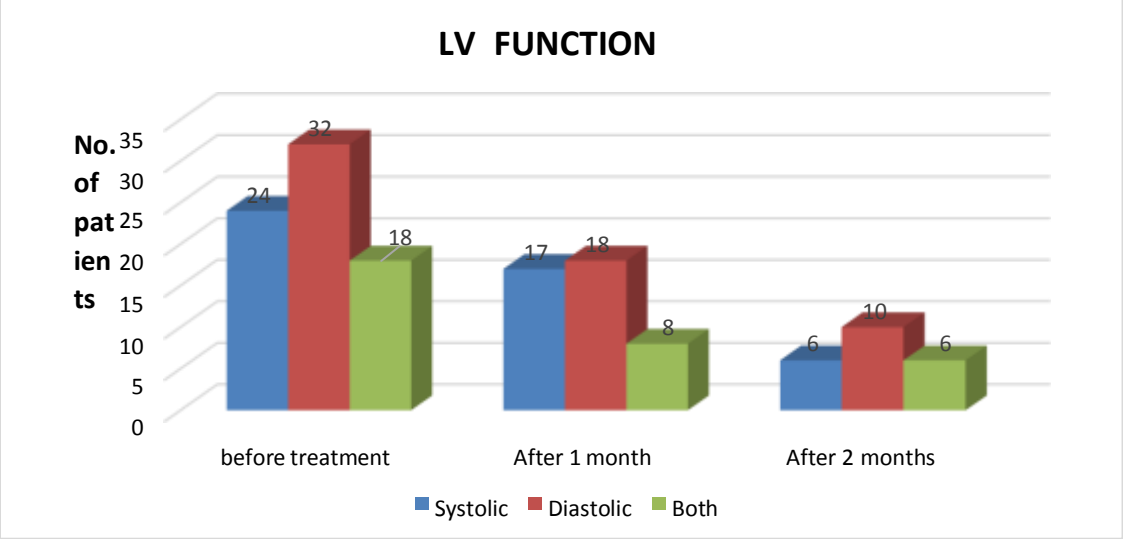
was a significant decrease in Diastolic BP i.e., 5.34±1.307 mmHg in 1 month treatment of EPLERENONE 25mg , and the mean of the Diastolic BP after 2 months treatment was 80.17±4.691 mmHg. This shows that there was a significant decrease in Diastolic BP when compared with pre treatmenti.e 9.00±4.002 mmHg. There was a significant difference in reduction of BP having p-value <0.05(95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

Figure 5 : Heart Rate



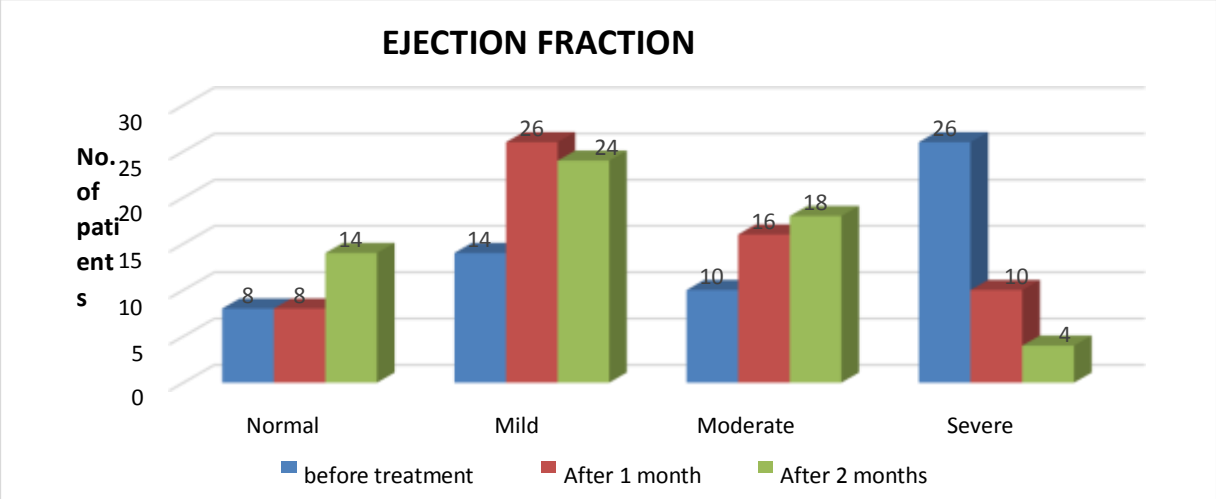
Heart Rate was used as another outcome to measure the functional capacity of patients with cardiovascular diseases. Among 60 patients who are included in study the mean baseline was 100.30±19.120. It was improved to 93.17±13.115 after a month therapy of Eplerenone 25mg and after 2 months of therapy it was found to 87.40±14.346. which is found to be statistically significant. ($p<0.05$).

Figure 6: LV Function



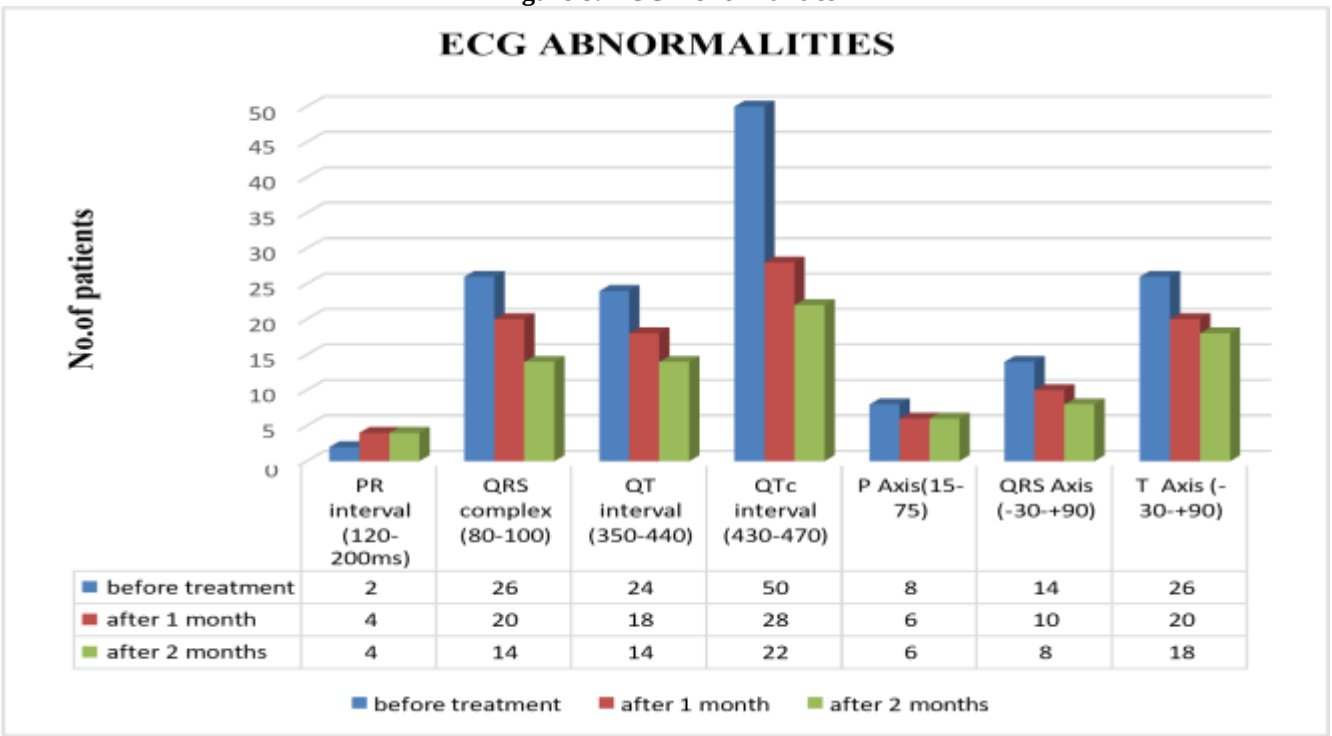
The data of LV function (ECHO). 53.3% of patients were having Diastolic dysfunction, 40% of patients were having Systolic dysfunction & 30% of the patients were having both systolic and diastolic dysfunction at base line data. After a month of treatment with EPLERENONE 25 mg, 23.3 % of patients were having systolic dysfunction, 30% of patients were having diastolic dysfunction & 13.3% were having both Systolic & Diastolic dysfunctions. After 2 months of treatment the dysfunctions were declined to 10% of systolic, 16.6% of diastolic & 10% of both dysfunctions. Above numbers shows that dysfunctions were gradually improved with treatment follow up and is found to be statistically significant.

Figure 7. Ejection fraction



Ejection fraction (EF) is an important measurement in determining heart function and in diagnosing the heart failure. From baseline data, most of the patients were having severe EF (<30). 43.33 % of patients were having severe EF , 16.6 % of patients were having moderate EF (30-44) , 23.33% of patients were having mild EF (45-54) & 13.33% of patients are having normal EF (≥55%) and it was improved after 2months of EPLERENONE 25mg and is found to be statistically significant.

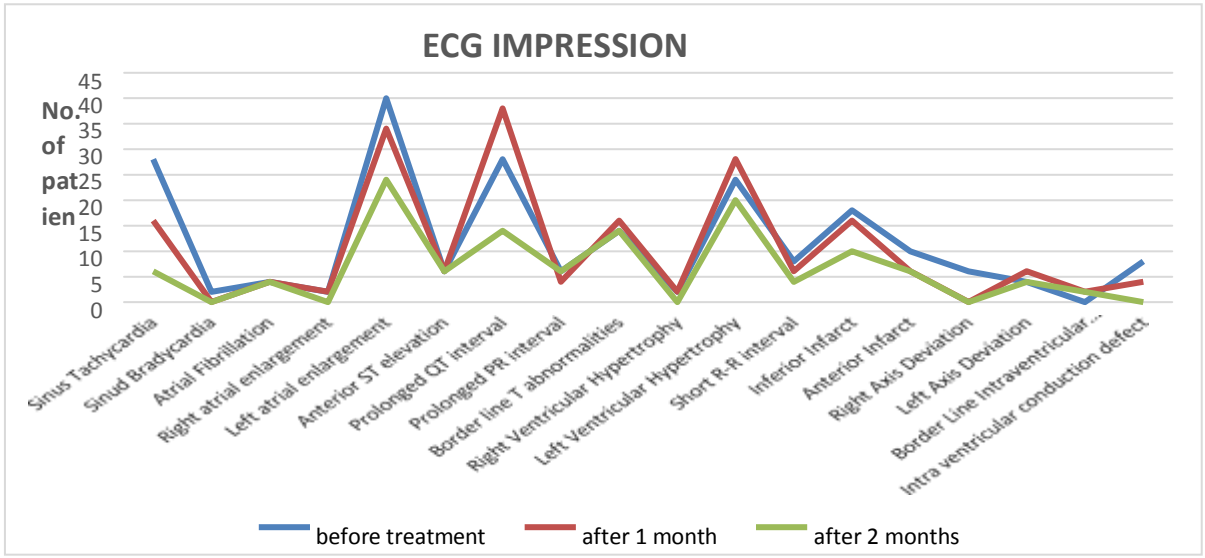
Figure 8: ECG Abnormalities



	PR interval (120-200ms)	QRS complex (80-100)	QT interval (350-440)	QTc interval (430-470)	P Axis(15-75)	QRS Axis (-30-+90)	T Axis (-30-+90)
before treatment	2	26	24	50	8	14	26
after 1 month	4	20	18	28	6	10	20
after 2 months	4	14	14	22	6	8	18

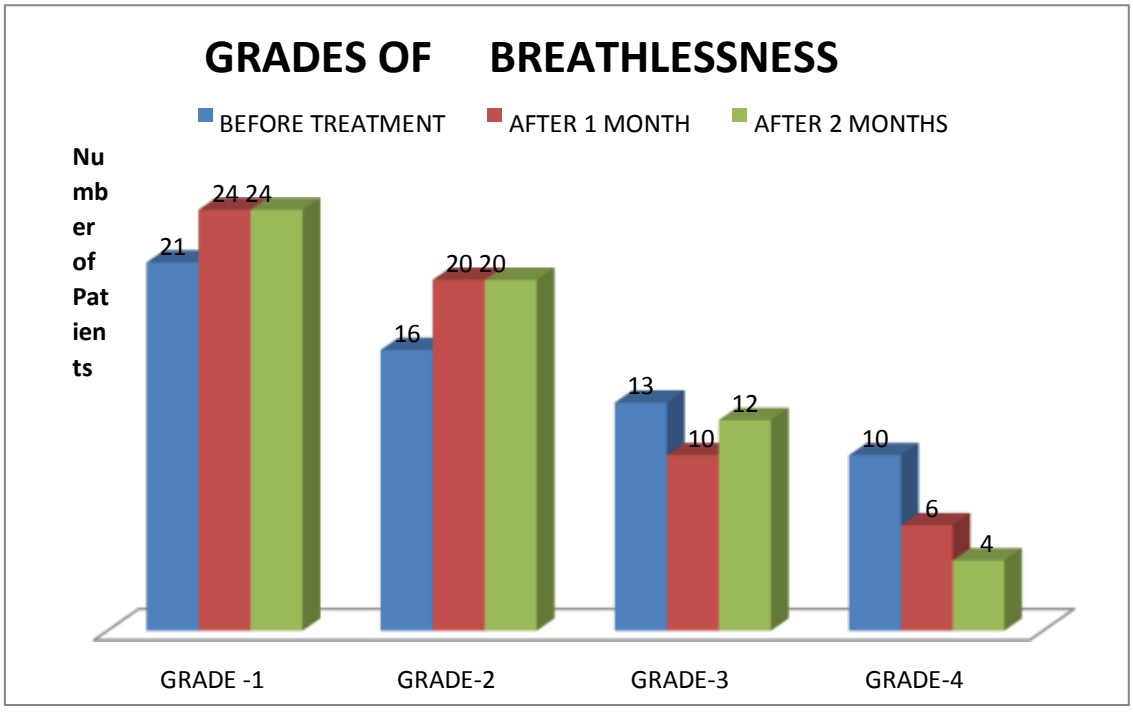
Table shows the data of ECG abnormalities. Pre treatment mean difference of baseline data is 10.714. After a month of treatment with EPLERENONE 25mg was 7.571 & after 2 months of treatment was 5.667. fig shows that ECG abnormalities were gradually improved on 3 months follow up and is found to be statistically significant.

Figure 9: ECG Impressions



The data of ECG impression, Pre treatment most of the patients had impression of left Atrial enlargement and mean difference is 5.833. After 1 month of treatment with EPLERENONE 25 MG was 5.278, after 2 months of treatment is 3.333 and was found to be statistically significance.

Figure 10: Grades of Breathlessness



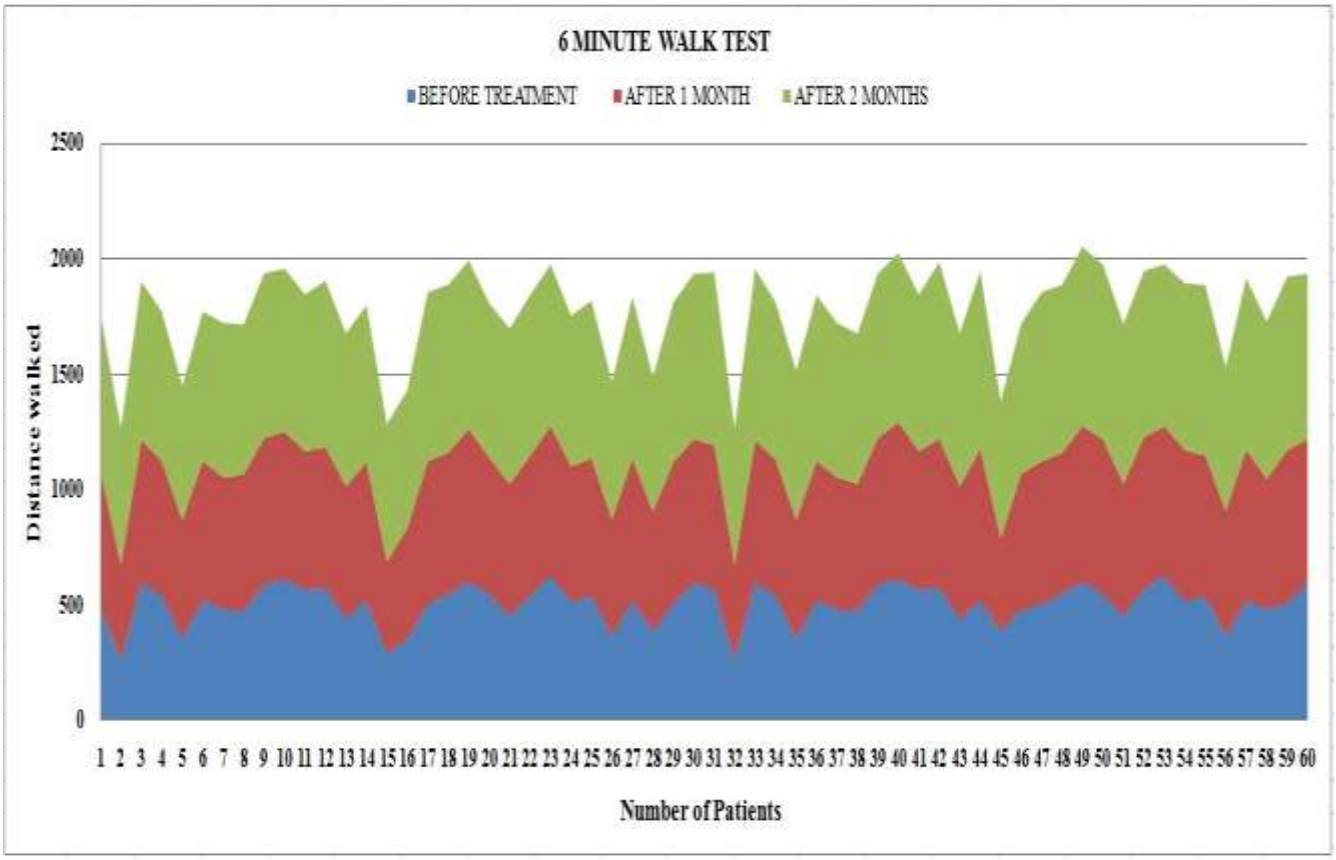
The graphical representation of outcome shows that 35% of patients were with Grade 1 SOB, 26.6% patients were with Grade 2 SOB, 21.6% patients were with Grade 3 SOB, 16.6 patients were with Grade 4 SOB reactions. By the end of the 3 months follow up the severity of SOB was reduced by 40% in patients with Grade 1, 33.3% in patients with Grade 2, 20% in patients with Grade 3, 6.6% in patients with Grade 4. There is a significant improvement in the breathlessness/SOB with p-value <0.05(95% confidence interval). By conventional criteria this difference is considered to be statistically significant.

Table 2: 6 Minute Walk Test :*One -Sample Statistics*

	N	Mean	Std. Deviation	Std. Error Mean
BEFORE_TREATMENT	60	497.47	94.824	12.242
AFTER_1_MONTH	60	580.33	61.935	7.996
AFTER_2_MONTHS	60	670.93	46.691	6.028

6MWT is used as another outcome measure to determine the functional capacity. Pre treatment mean baseline in 60 patients was 497.47±94.824. It was improved to 580.33±61.935 after a month of Eplerenone 25mg and 670.93±46.691 after 2 months of therapy. which is found to be statistically significant. ($p<0.05$).

Figure 11: 6 Minute Walk Test



DISCUSSION:

- This study is to determine the effectiveness of eplerenone in the management of cardiovascular diseases.
- This study was carried out with 60 patients, who were diagnosed with cardiovascular diseases based on the criteria (symptoms, ECG, Echo, and TMT).
- Initially 71 patients were included in our study, 11 patients were excluded from our study. Among 11 patients, 4 patients were not interested to participate in the study & 7 patients have no proper follow up.
- In the taken sample size and subjects, the prevalence of cardiac disorders was greater in male subjects than in female subjects that is 80% in males and 20% in females.
- New York Heart Association (NYHA) Functional classification[20-22] which is used to estimate the grades of degree of breathlessness related to respective activities.
- In grade-1 (Mild) No limitation on physical activity. Ordinary physical activity doesn't cause undue fatigue, palpitations, dyspnoea.

- In grade-2 (MILD) Slight limitation of physical activity. Comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnoea.
- In grade-3 (Moderate) Marked limitation of physical activity. Comfortable at rest but, less than ordinary activity causes fatigue, palpitations, dyspnoea.
- In grade-4 (Severe) Unable to carry out any physical activity without dyscomfort. Dyspnoea present at rest, if any physical activity is undertaken the discomfort increases.
- 35% patients are with Grade 1 SOB, 26.6% patients are with Grade 2 SOB, 21.6% patients are with Grade 3 SOB, 16.6% patients are with Grade 4 SOB reactions. By the end of the 3 months follow up the severity of SOB was reduced and 40% are with Grade 1, 33.3% are with Grade 2, 20% are with Grade 3, 6.6% are with Grade 4 SOB reactions. This shows that significant improvement in the breathlessness during the 3 month follow up period.
- In a study by Jane A. Cannon[23] found that even moderate prolongation of QRS duration and right BBB/IVCD were associated with a high risk of adverse outcomes in HF-REF.
  Eplerenone was similarly effective, irrespective of QRS duration/morphology.
- In our study we observed that ECG abnormalities where the mean difference of base line data is 10.714, after one month of treatment with eplerenone is 7.571 and after 2 months of treatment is 5.667.The ECG abnormalities are gradually improved on 3 months follow up.
- In our study the ECG impression states that most of the patients had impression of left atrial enlargement.
- In our study we used 6-minuite walk test. The 6-minute walk test (6MWT) is an easy to perform and practical test that has been used in the assessment of patients with a variety of cardiopulmonary diseases including pulmonary arterial hypertension (PAH). It
  simply measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes.[48,49]
- It is also an outcome measure to determine the functional capacity in our study the test results were improved to 580.33±61.935 after first review the mean base line result was 497.47±94.824.After second review the results were improved to 670.93±46.694.
- In our study we observed that 33.3% patients were highly adhered to their regimen and 41.6% patients were poorly adhered in their 1st visit. By the 3rd visit 38% patients were highly adhered to their medications and poor adherence were lower to 20%. This change has occurred due to the proper patient counselling by clinical pharmacist whichwe need to appreciate. This enhancement in the medication adherence also lead to the improvement of these outcome measures.

CONCLUSION:

In our study we observed that eplerenone was safe and effective in treating patients with both acute and chronic cardiovascular diseases. The patient clinical and functional status was improved by his clinical manifestations, 6MWT, Echo and ECG changes and also improved ejection fraction by avoiding further exacerbation of condition, without occurrence of adverse effects. The monotherapy of eplerenone is as effective as polytherapy and the improvement of medication adherence was due to the patient counselling. Finally it can be concluded that latest therapy possesses significant beneficial effects in cardiovascular diseases and is fairly safe and well tolerated.

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