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Original Research Article

Effect of angiotensin receptor neprilysin inhibitor in patients of heart failure with reduced ejection fraction with reduced ejection fraction with cardiorenal syndrome type-1

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ABSTRACT

Background: Heart failure is recognized as one of the most common indications for hospitalization. The dysfunction of either the heart or the kidneys affect the functioning of each other and thus play an important role in the quality of life.
Methods: This study is a Prospective interventional Cohort study over a period of 18 months in 125 patients. The patients were divided into two broad treatment groups. The primary end point of the study was to quantify the response of ARNI for renal recovery in patients of cardio-renal syndrome and improvement in cardiovascular parameters by measuring the change in urine output, estimated glomerular filtration rate, serum creatinine, change in weight of the patients, control of blood pressure and change in left ventricular ejection fraction. The secondary end-points were evaluated during the 60 days follow up period post admissions.
Results: Cardio-renal syndrome was seen in 39% of the patients. On screening e-GFR was 91±14 and 49±8 for group 1and 2 respectively, the median age, UACR was 59 years ,1.0 mg/mmol respectively for both the groups and 19% had micro albuminuria. ACEIs had more reports of hyperkalemia (8/32, 25%), and greater deterioration of renal parameters (10/32, 34%) needing discontinuation of the drug in some patients. Patients also developed cough (6/32, 20%) needing replacement with ARBs. ARNI group developed more hypotension (6/31, 20%). In all cardiovascular and renal end points except UACR, ARNI showed better recovery profile in CRS-1patients including diabetics.
Conclusions: This study showed beneficial effects of ARNI in heart failure patients with cardio-renal syndrome.

Keywords: Heart failure, ARNI, Cardiorenal syndrome, Reduced ejection fraction, ACEI

INTRODUCTION

Heart failure is recognized as one of the most common indications for hospitalization in the Cardiology Unit. The heart is responsible for perfusion of all vital organs including the kidneys. The dysfunction of either the heart or the kidneys affect the functioning of each other. Cardiorenal syndrome (CRS) refers to the clinical and metabolic consequences of acute and chronic heart failure on the kidneys.[1] The underlying pathophysiology of CRS has been poorly understood and is believed to be multifactorial.[2] Worsening renal function is defined as an increase in serum creatinine > 0.3mg/dl from baseline and occurs in 20-30% of patients with acute decompensated heart failure and is associated with greater length of hospital stay, hospital readmission and death.[3] Till now angiotensin converting enzyme inhibitors (ACEI) have been seen as a protective drug in the above case scenarios. Effect of angiotensin converting neprilysin inhibitor (ARNI) on cardiorenal syndrome has

not been studied though we have literature on chronic kidney disease. Major clinical trials have established ACEIs as the standard-of-care for renin angiotensin system blockade and it has been recommended by standard guidelines for treatment in patients with left ventricular (LV) systolic dysfunction with or without heart failure.[4] Ramipril is one of the most commonly used ACEIs and is selected as an active comparator.[5] (Sacubitril/Valsartan) is a combination of neprilysin inhibitor and angiotensin II type 1 receptor blocker, providing concomitant neprilysin inhibition and angiotensin type 1 blockade.[6] Upon oral administration there is a systemic exposure of Sacubitril and Valsartan. Sacubitril is then further metabolized by esterases to their active metabolite thereby enhancing the biological properties. With these already proven beneficial effects from the previous studies we decided to move a step ahead to see whether these beneficial effects can be extended to patients of Cardio-renal syndrome.

Objectives

The primary end point of the study is to quantify the response of ARNI for renal recovery in patients of cardio-renal syndrome by measuring the change in urine output, serum creatinine and change in weight of the patients admitted for acute decompensated heart failure. The secondary end points are to measure the length of hospitalization, number of re-admissions and the unscheduled visits to the cardiology unit or the Emergency Unit during the 60 days follow up period.

METHODS

This study was conducted in the department of cardiology and general medicine Shadan institute of medical sciences, Hyderabad over a period of 18 months after taking due permission from the institutional ethics committee. Around 125 patients were enrolled after fulfilling the inclusion and exclusion criteria. Diagnosis was based on proper guidelines for heart failure. The study was a prospective interventional cohort study but the data was analyzed retrospectively (observational analysis). Left ventricular systolic function was assessed prospectively by echocardiography along with New York heart association (NYHA) functional class at baseline retrospectively. Complete information of individual patients was recorded in a proforma from the time of problem inception to till the end of study period. Prescription data of cardiovascular drugs was collected along with the status of the symptoms. We defined the cardio-renal syndrome as heart failure with serum creatinine >1.5 mg/dl in males and >1.4 mg/dl in females with e-GRF <90 ml/min/1.73 m2.

Inclusion criteria

Inclusion criteria for current studies were; age >18 years of either sex, admitted to the hospital with a primary diagnosis of decompensated heart failure (stage III/IV), onset of cardio-renal syndrome after or before hospitalization (48hrs from time of admission in-spite of standard therapy), persistent volume overload and NT-Brain natriuretic-peptide (BNP >400 pg/ml).

Exclusion criteria

Exclusion criteria for current studies were; intravascular volume depletion, acute coronary syndrome within 4 weeks, indication for hemodialysis, systolic blood pressure <90 mmHg or mean arterial pressure <60 mmHg at the time of enrollment, patients with renal artery stenosis or alternate diagnosis for worsening of renal function, clinical instability likely to require additional intravenous drugs, the use of iodinated radio-contrast material in the past 72 hours and patients who underwent cardiac resynchronization therapy or having any rhythm disorder.

Parameters in relation to heart failure will be left ventricular internal diameter in diastole (LVIDD), left ventricular internal diameter in systole (LVIDS), left ventricular ejection fraction (LVEF). All the patients will be grouped under two categories ACEIs group 1: patients admitted with decompensated heart failure with/without cardio-renal syndrome undergoing treatment with standard therapy plus Ramipril 1.25 mg twice daily adjusted on creatinine clearance and titrated to a maximum tolerated dose of 5 mg twice daily. ARNI group 2: Patients admitted with decompensated heart failure with/without cardio-renal syndrome undergoing treatment with standard therapy plus Sacubitril (Vymeda) 25 mg twice daily and titrated to a maximum tolerated dose of 200 mg twice daily. In both the groups the patients without a cardiorenal syndrome served as controls for the treatment groups. The primary end point of the study is to quantify the response of ARNI for renal recovery in patients of cardio-renal syndrome by measuring the change in urine output at the end of every 24 hours till discharge, serum creatinine & change in weight of the patients. The secondary end-points are to measure the length of hospitalization, overall mortality, number of readmissions and the unscheduled visits to the cardiology unit or the Emergency Unit during the 60 days follow up period. The change in the LV systolic function expressed as LVEF between baseline and the 3-month follow up and change in NYHA functional class between baseline and 3-month follow up in patients of both the groups will also be noted. Overall mortality in each group, number of hospital admissions, number of parenteral drugs used or required and episodes of exacerbation of symptoms will be recorded separately.

Statistical analysis

Continuous variables will be expressed as mean (SD). For each parameter the analysis of result will be done by means of unpaired Student t test or Wilcoxon rank sum test as appropriate based on the differences between the groups. Paired t test will be performed for data within the

groups. Categorical variables will be presented as percent values and compared by Chi-square test. Analyses will be performed using SPSS version 23.

RESULTS

The base line characteristics of the entire study population is as shown in (Table 1). Cardio-renal syndrome was seen in 39% of the patients before or within 72 hours of the enrollment date of the study. At screening the e-GFR was 91±14 for Group 1 and 49±8 for group 2, the median UACR was 1.0 mg/mmol for both the groups and 19% had micro or macro albuminuria.

Table 1: Baseline characteristics of the patients enrolled in the study 72 hours after their first OPD visit.

Parameters	Without CRS*-1 eGFR ≥90 ml/min/1.73m2	With CRS*-1
N	58	63
Age (years)	60±12	69±11
Males (N)	44	41
SBP (mmHg)	126±17	128±17
DBP (mmHg)	80±10	78±11
HR (count/min)	76±12	78±12
Weight (kg)	78±20	80±18
Creatinine (mg/dl)	1.1(0.85-1.2)	1.6 (1.46-1.94)
eGFR (ml/min/1.73m2)	91±14	49±8
UACR (ratio)**	1.0 (0.5 -1.7)	1.7 (0.5-3.1)
LVEF (%)	29±6	30 ±6
NT ProBNP (pg/ml)	490 (403-963)	943 (920-2160)

*CRS- Cardio-renal syndrome; **UACR- Urinary albumin/ creatine ratio

Treatment

ACEIs and ARNI were started if BP >120/80 mmHg off the diuretic infusion and with no feature of fluid overload. The treatment protocol is shown in (Figure 1).

Primary end points

During the course of treatment & study period it was observed that patients with HF with CRS-1 when started on ACEIs had more reports of hyperkalemia (8/32, 25%), and greater deterioration of renal parameters (10/32, 34%) needing discontinuation of the drug. Patients also developed cough (6/32, 20%) needing replacement with ARBs. Patients with HF with CRS-1 who were started on ARNI developed more hypotension (6/31, 20%) with 2 patients requiring discontinuation of the drug. No hyperkalemia was observed in any of the patients on ARNI. Only (3/31,10%) patients developed deterioration of renal function. Blood pressure improved over the next 14 days in (9/31, 30%) of patients. There was improvement in urine output post the diuretic infusion in patients who were on ARNI than in the patients on ACEIs and this was a consistent finding in at least one hospitalization over a duration of 18 months in all the 31 patients of ARNI group and in 8 patients with >1 readmissions (ARNI group) over the 18 months durations. Consistent appreciable weight loss was seen in both the treatment groups (-1.6±2.3 kg) in ACEIs group Vs (-0.8±1.8 kg) in the ARNI group.

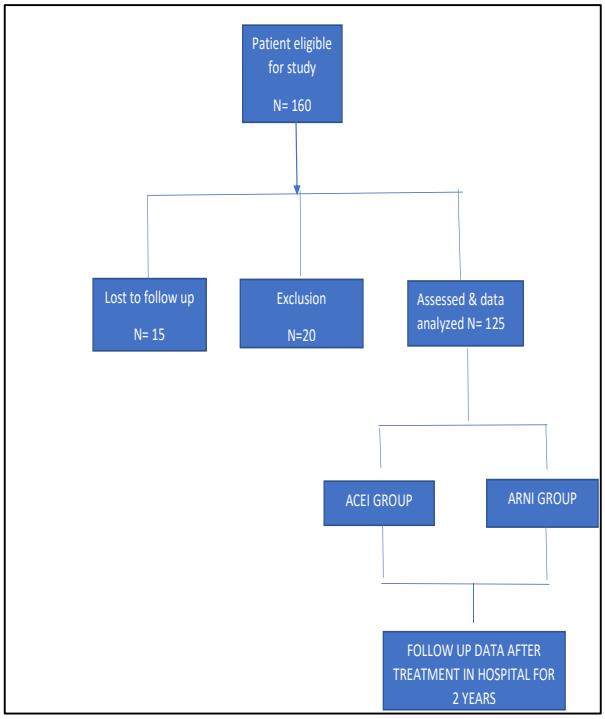

Figure 1: Flow chart depicting the study design.

Serum creatinine

In the non-CRS -1 patients of both the groups, serum creatinine levels dropped from 1.1(0.85-1.2) mg/dl to 0.97(0.84-1.08) mg/dl while in the CRS-1 patients we observed a greater improvement (lowering of values) in the ARNI group compared with the ACEIs group.

e-GFR

In the non-CRS-1 patients of both the groups, e-GFR levels were raised by 91±14 to 94±16 while in the CRS-1 patients we observed a greater improvement (median raised values) in the ARNI group compared with the ACEIs group.

UACR

UACR remained relatively unchanged in the ARNI group but decreased in the ACEIs group.

Secondary end points

Readmissions for HF at 60 days was 11% in the ARNI group and 22 % in the ACEIs group (Odds ratio 0.68, 95% CI -0.45 to 0.78, p=0.01). At the end of the study period hospital mortality was 4% (2/63 patients) out of which both belonged to ACEIs group and none from the ARNI group.

Table 2: Study parameters in the two treatment groups with CRS-1 after 18 months of study period.

Parameters	ACEI* group (N=32)	ARNI** group (N=31)
Weight loss (kg)	-0.8±1.8	-1.6±2.3
Serum creatinine (mg/dl)	1.03 (0.9-1.2)	0.92 (0.8-1.3)
eGFR (ml/min/1.73m2)	81 (68-87)	84 (66-91)
UACR	1.3 (0.5-2)	1.5 (0.5-2.3)
Hyperkalemia (N)	8	Nil
LVEF (%)	35±4	37±2
NT-ProBNP (pg/ml)	324 (278-819)	353 (259-620)

*ACEI: Angiotensin converting enzyme inhibitors; **ARNI: Angiotensin receptor/neprilysin inhibitor

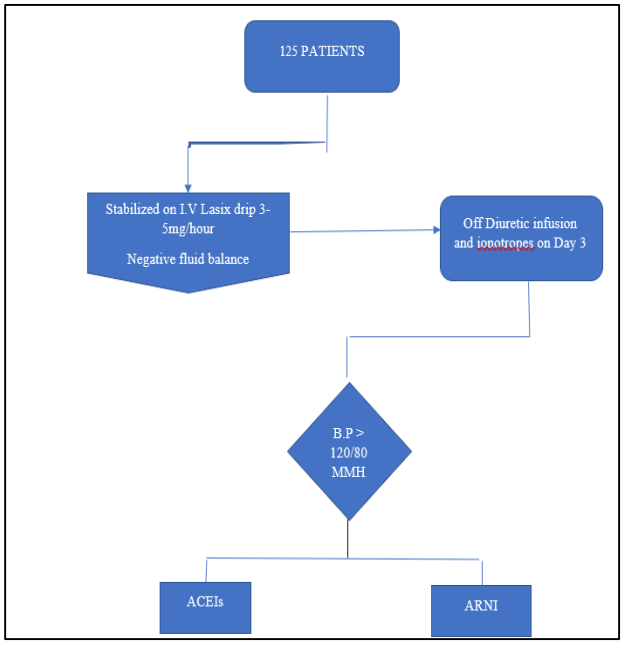

Figure 2: Treatment protocol.

After 10 months of treatment decrease in SBP & DBP in ACEIs group was smaller compared to ARNI group (p<0.01). Out of the 63 patients (CRS-1) whose data was evaluated, 25 of them had NT-PROBNP above 1000 pg/ml. NT-PROBNP fell to below 1000 pg/ml in all the patients of ARNI group and in 75% of patients of ACEIs group. LVEF improved in 14/31 patients of the ARNI group (mean increase by 5%) and in 9 patients of the ACEIs group (mean increase of 3.8%).

Subgroup analysis

In- addition we tried to analyze the findings in the non-diabetic and the diabetic patients as diabetes is a common syndrome which can co-exist in our study population. We observed that the diabetic patients with CRS-1improved at par with the non- diabetic patients without deterioration in the ARNI group whereas in the ACEIs patients the diabetic patients showed signs of renal impairment and blood glucose levels (Hb1AC).

Table 3: Subgroup analysis: diabetic patients (n=29).

Parameters	Baseline values (N=29)	ACEI group (N=15)	ARNI group (N=14)
Serum creatinine (mg/dl)	1.8±0.3	1.34±0.2	1.30±0.08
eGFR (ml/min/1.73m2)	81±5	98±5.1	95±2.3
UACR	1.6±0.2	1.8	1.5
LVEF (%)	31±2	32±3	35±2
NT-ProBNP (pg/ml)	874±181	810±157	482±92
Hb1AC at 90 days (%)	7.8	7.2	6.5

DISCUSSION

The adverse health influence of renal dysfunction has been a matter of medical concern for long. The pathophysiology of CVD and renal dysfunction is both complex and these overlap with each other sharing features of systemic inflammation, oxidative stress, arterial stiffening and endothelial dysfunction.[7] Given the mutual connection between CVD and renal dysfunction, therapies that target either of the two diseases may potentially benefit the other at the same time. A lot of information and literature has been documented in regard to ARNI with respect to its beneficial effects in CVD and CKD.[8] Our study is unique as it evaluated the beneficial effects of ARNI in Cardio-renal syndrome-1 where the renal impairment is an outcome of the cardio-vascular dysfunction compared to CKD which could be an independent disease entity. Hyperkalemia is one of the complications encountered with the ACEIs group because of decreased aldosterone and retention of potassium. This complication was less in the ARNI group as it is spared because of its additional vasodilatory and diuretic effect. Hypotension was more observed in ARNI group because of the dual inhibition.[9] We found that Sacubitril/valsartan, compared with enalapril slowed the rate of decrease in the eGFR and had favorable effects in cardiovascular and renal outcomes in HFrEF patients with and without CRS-1. These renal and CV benefits were observed even though ARNI did not show any reduction in the UACR

levels compared with enalapril. This may be more because of medication causing micro-albuminuria or it could be because of prolonged diabetes in some patients. Our finding is consistent with the other studies where the decrease in eGFR from baseline to 36 weeks was less in patients with ARNI than with an ACEIs.[10] Similarly in older studies with omapatrilat, the incidence of renal adverse events was lower than those receiving enalapril.[11,12] Improvement in urine output was seen best in the ARNI group post the diuretic infusion and reduction in the oral dose of furosemide was observed. This is probably because ARNI is not only associated with an increase in ANP and natriuresis but also a decrease in intraglomerular pressure.[13,14] The weight loss seen in the ARNI group patients could also be explained because of the above reasons. The mechanism of reactive preservation of eGFR with ARNI is not clear. There is a positive shift in hemodynamics with increased natriuretic peptides with ARNI with greater glomerular endothelial permeability.[5] So, the above study results re-established the proven concepts of the beneficial effects of ARNI in a subset of patients having cardio-renal syndrome. The overall decrease in rate of hospitalizations and mortality can be explained with the above favorable positive CV and renal hemodynamics. The improvement in the systolic and diastolic blood pressure maintenance can be attributed to the dual inhibitory nature of ARNI which also explains the rapid fall in the NT-PROBNP levels in the ARNI group specially in those patients where the levels were >1000 pg/ml which well explains the reduction the ventricular wall pressures due to the inhibition of degradation of natriuretic peptides caused by Sacubitril.

CONCLUSION

ARNI has shown protection against renal impairments and its usage led to improved cardiovascular outcomes as it lowers the risk of renal dysfunction by improving the e-GFR relatively. Renal dysfunction with marked heart failure constitutes a major clinical setting (CRS). With a very little scientific data on treatment for the combination of the above pathologies, the potential benefits of Sacubitril seen in our study could add to the scientific knowledge to reduce the morbidity and mortality in high-risk patients.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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