THE EFFECTS OF SACUBITRIL/VALSARTAN ON CLINICAL AND ECHOCARDIOGRAPHIC PARAMETERS IN PATIENTS WITH HEART FAILURE

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ABSTRACT

Objective: To evaluate the effects of Sacubitril/Valsartan on clinical and echocardiographic parameters in patients with heart failure with reduced ejection fraction who were previously being treated with ACE inhibitors.

Study Design: Prospective cross-sectional study.

Place and Duration of Study: Combined Military Hospital Bahawalpur, from Sep 2020 to Mar 2021.

Methodology: A hundred patients with heart failure with reduced ejection fraction (HFrEF) previously treated with ACE inhibitors for at least 24 weeks were enrolled for the study. Fifty patients were then switched from treatment with ACE inhibitors to sacubitril/valsartan and defined as the A to S/V group and treated to observe changes in NYHA class and left ventricular ejection fraction up to 6 months. In the same period, the rest of the 50 patients were continued with ACE inhibitor treatment defined as the A to A group, the dose of ACE Inhibitor was maintained at the same level. NYHA class and echo-cardiography was performed in outdoor clinics at enrolment (baseline) and after 6 months of Sacubitril/Valsartan treatment. NYHA class and echocardiographic parameter were recorded and analyzed after 6 months.

Results: There was no statistically significant difference in the age, gender, HR, Systolic BP, Diastolic BP, NYHA class and LVEF between the two groups at enrollment. In A to A group there was no significant change in LVEF and NYHA class after 6 month of observation and continued treatment with ACE inhibitors. A significant improvement was found in the baseline LVEF (%) (30.2 ± 2.62) to (32 ± 2.43) *p*-value (<0.001) in A to S/V group. At the end of the study, LVEF showed improvement in echocardiography in patients treated with sacubitril/valsartan compared to ACE Inhibitor treatment. Clinical improvement was observed in 16 (32%) patients who moved to NYHA class-II from NYHA class-III.

Conclusion: Sacubitril/Valsartan in comparison to ACE Inhibitor treatment had a statistically significant clinical improvement in NYHA class II/III and LVEF on echocardiography at 6 months.

Keywords: Echocardiography, Heart failure, Left ventricular ejection fraction, NYHA class.

INTRODUCTION

In recent years, there has been an appreciable reduction in cardiovascular mortality due to innovation and excellence in the management of the cardiovascular disease. This encouraging factor has also increased the number of heart failure and also exceptionally increased the economic burden on the management of heart failure cases. Heart failure is mainly the disease of the elderly and frequently requires indoor management. Even in developed countries like the USA, heart failure leads to over a million admissions in a year[1]. Reduced ejection fraction is present in >50% of symptomatic heart failure patients. It is estimated by the year 2030 in USA prevalence of heart failure is expected to increase by 46% with a huge drain on medical resources[2,3]. Inspite of these alarming statistics, fortunately, we have ascended a long way in the management of heart failure in the last couple of years and currently, there are many therapies available that have provided significant relief in symptoms and also improved the survival of these patients. To make the matter more grievously complex the incidence of heart failure is increasing likely due to increases life expectancy and better management of acute cardiac events[4,5]. These improved management strategies were a result of a better understanding of the pathophysiology of heart failure and then targeting the resulting factors with a combination of medications. With this better understanding, it was revealed that a number of patients could have a better prognosis and improvement in symptoms if angiotensin II receptor blockers (ARBs) or angiotensin receptor neprilysin inhibitors (ARNIs), and Beta-Blockers were used in time[6]. If the patient remains symptomatic it is recommended to augment the above regimen with a mineralocorticoid-receptor antagonist[7,8].

ARNIs are a relatively newer class of drugs and are combined with an ARB for blocking both the angiotensin II receptor pathway and inhibition of the neprilysin enzyme[9]. The American College of Cardio-

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logy/American Heart Association task force on clinical practice guidelines, the heart failure society of America and The European Society of Cardiology recommend ARNIs as a substitute of ACE-I in patients with heart failure with reduced ejection fraction (EF <35%) who remain symptomatic despite optimal medical therapy with an ACE-I, mineralocorticoid-receptor antagonist and a beta-blocker[8,10].

The effect of the combination of sacubitril/valsartan has never been evaluated on clinical and echocardiographic parameters in patients with heart failure in our population and this potentially rewarding combination requires to be evaluated in our population. With this view in perspective, we proceeded to perform this study aiming at evaluating the role of this combination in our patients with heart failure.

METHODOLOGY

Combined Military Hospital Bahawalpur is a 400-bedded hospital with a well established cardiac care unit and equipped outpatient department for the provision of cardiac care facility to the dependent population. This study was a prospective, comparative cross-sectional study, formulated to evaluate the effects of Sacubitril/Valsartan on clinical and Echocardiographic parameters in patients with heart failure with reduced ejection fraction. A total of 100 patients with symptomatic heart failure defined as New York Heart Association (NYHA) class II-III, left ventricular ejection fraction (LVEF) below 40% measured by echocardiography who were previously treated with ACE inhibitor enalapril or lisinopril for at least 24 weeks with systolic blood pressure ≥100 mmHg and serum potassium (K+) level <5.4 mEq/L were enrolled for the study. Fifty patients were then randomly switched from ACE Inhibitors to Sacubitril/Valsartan and defined as the A to S/V group. They were treated to observe changes in NYHA class and left ventricular ejection fraction up from Sep 2020 to Mar 2021. In the same period, the rest of the 50 patients were continued with ACE Inhibitor treatment defined as the A to A group and the dose of ACE Inhibitor was titrated as per the clinical condition. NYHA class assessment and Echocardiography was performed in outdoor clinics at enrolment (baseline), and after 6 months in both groups. Left ventricular ejection fraction was measured by the standard biplane method of disks (modified Simpson's rule) utilizing Philips Epiq 7 echocardiography equipment. NYHA class and Echocardiographic parameter were analyzed.

We excluded patients who had myocardial revascularization in the previous 6 months, concomitant implantation of cardiac resynchronization therapy (CRT), presence of congenital heart disease, severe liver insufficiency (child-pugh C) or history of angio-edema.

At enrollment, all patients were clinically assessed, with a record of medical history, physical exam, weight, blood pressure, NYHA class, 12 lead electrocardiogram (ECG), and renal function test including serum potassium, were obtained to undertake sacubitril/valsartan dose up-titration. A dose of sacubitril/valsartan was prescribed according to established recommendations. The recommended starting dose was 49/51 mg twice daily. Patients were switched from an ACE-I after a 36 hour washout period. A standard 2-dimensional and doppler transthoracic echocardiogram was performed at baseline assessment and after 6 months in all patients.

Data were expressed as means ± standard deviation for continuous variables and as frequencies for categorical variables using SPSS-25. A *p*-value <0.05 was considered statistically significant. All statistical analysis was carried out in an unbiased and professional environment. No financial or administra-tive services from any pharmaceutical source were utilized for investigations, data collection or their interpretation to obtain reliable and efficient results. Similarly, strict privacy and confidentiality was ensured at all levels until the completion of the results.

RESULTS

A total of 100 patients were prospectively enrolled and divided equally into (A to A) and (A to S/V) groups randomly with follow up to 6 months. In group (A to A) the mean age was 64 ± 8 years. Out of 72% were males with comorbid hypertension in 32% and DM in 30%.

In group (A to S/V) the mean age was 62 ± 6 years, 68% were males with HTN in 28% and DM in 34%. There was no statistically significant difference in the baseline HR, systolic BP, diastolic BP, NYHA class and LVEF in two groups. Baseline characteristics of patients were presented in table-III.

In the (A to A) group there is no significant change in LVEF and NYHA class after 6 month of observation fig-1 and table-III.

A significant improvement was found in the baseline LVEF (%) (30.2 ± 2.62) to (32 ± 2.43) *p*-value <0.001 in (A to S/V) group fig-2. At the end of the study, LVEF showed improvement on Echocardiography in patients with Sacubitril/Valsartan treatment

than with ACE Inhibitor treatment table-II. Clinical improvement was observed in 16 (32%) patients who moved to NYHA class ll from NYHA class lll.

Table-I: Baseline LVEF percentage values and values after 6 months in study group A to A (*p*-value 0.145)

A to A Group	n	Mean	SD	SE Mean
Baseline LVEF % Values	50	30.76	3.24	0.45
After 6 Month LVEF % Values	50	30.46	3.13	0.44

SD: Standard Deviation, SE Mean: Standard Error Mean.

Table-II: Baseline LVEF percentage values and values after 6 months in study group A to S/V (*p*-value <0.001)

A to S/V Group	n	Mean	SD	SE Mean
Baseline LVEF % values	50	30.4	2.62	0.37
After 6 month LVEF % values	50	32	2.43	0.34

SD: Standard Deviation, Se Mean: Standard Error Mean.

Table-III: Baseline characteristics of A to A and A to S/V therapy groups (n=100).

Variables	A to A group (n=50)	A to S/V group (n=50)
Age (years)	64 ± 8 (48-73)	62 ± 6 (55-75)
Gender (males), n (%)	38 (72%)	34 (68%)
BMI (kg/m²)	23.2 ± 2.9	24.5 ± 2.6
Heart rate (bpm)	75 ± 8.0	70 ± 6.7
Systolic BP (mm of Hg)	117 ± 6.6	118 ± 7.5
Diastolic BP (mm of Hg)	74 ± 5.5	72 ± 4.0
Hypertension, n (%)	16 (32%)	14 (28%)
Diabetes mellitus, n (%)	15 (30%)	17 (34%)
Serum creatinine (mg/dl)	0.86 ± 0.12	1.1 ± 0.21
Serum Potassium (mmmol/L)	4.36 ± 0.37	4.4 ± 0.38
NYHA class ll at Baseline, n (%)	23 (46%)	18 (36%)
NYHA class ll at 6 months, n (%)	26 (52%)	34 (68%)
NYHA class lll at Baseline, n (%)	27 (54%)	32 (64%)
NYHA class lll at 6 month, n (%)	24 (48%)	16 (32%)

No serious adverse effects were observed in both groups. Continuous normally distributed variables are expressed as mean ± SD. Categorical variables are n(%). BMI, body mass index; NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction.

DISCUSSION

Cardiovascular disease is storming the globe as a new epidemic with lethal results and a huge economic drain. Every year >20 million people have an acute cardiac or cerebral event but survive though at a cost of substantially expensive continuous clinical care. Improvement in early diagnosis, management and prevention has resulted in a significant decline in mortality. This decline in mortality has naturally increased the number of heart failure patients. It is roughly estimated that the prevalence of congestive heart failure in Pakistan is 2.8 million patients, unfortunately, though there is no prior published demographic data of this patient population in our country.

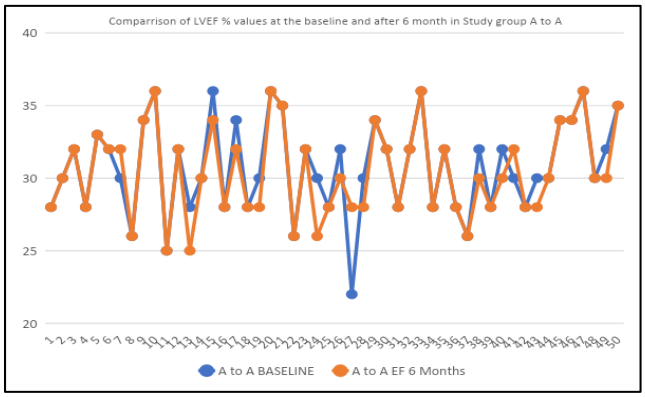

Figure-1: Comparison of LVEF % at baseline and after 6 month in study group A to A.

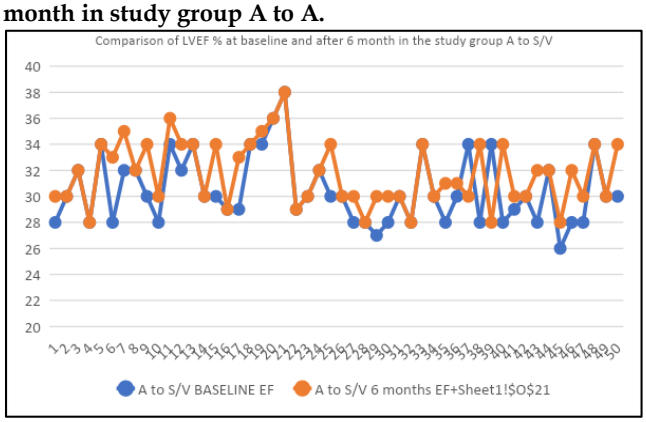

Figure-2: Comparison of LVEF % at baseline and after 6 month in study group A to S/V.

Heart failure occurs when the weakened heart muscle fails to pump an adequate amount of blood to other parts of the body. These patients are at a high risk of death and require frequent hospitalizations due to pulmonary or generalized oedema, cardiac arrhythmias and other complications. The renin-angiotensin-aldosterone system (RAAS) activation and over adaptation is the main event followed by vasoconstriction, hypertension, build-up of aldosterone levels, aggressive sympathetic tone, and finally, cardiac remodelling, which in concert has a detrimental effect on the health [11,12]. Hand in hand with the RAAS system natriuretic

peptide system is also activated resulting in elevated levels of BNP. This is an automatic compensatory response resulting in vasodilation, natriuresis and diuresis, reduced blood pressure, reduces aldosterone levels and lower sympathetic tone. This cascade though initially beneficial leads to a positive feedback loop leading to progression of heart failure due to deteriorating ejection failure and culminating into death[13]. Followed by an aggravated natriuretic peptide system and a favourable response against the harmful aldosterone and sympathetic storm. Natriuretic peptic is broken down by Neprilysin which also breaks down the bradykinin and angiotensin II. ACE Inhibitors and ARBs were the primary medications used in the routine care of patients with heart failure based on an exponential amount of clinical trial data and evidence-based results.

Several studies in the last few years have highlighted the role of sacubitril/valsartan in patients with varying severity of heart failure[14,15]. Based on these promising results many studies were formulated. Sacubitril/valsartan evaluation in the patients of heart failure the famous landmark trial PARADIGM-HF, followed by series of studies, like TITRATION trial, on the role of dose adjustment of sacubitril/valsartan in heart failure patients[16], the PIONEER and TRANSITION studies, which address the question of initiating sacubitril/valsartan in the acute HF scenario. This was soon augmented by PRIME study, PROVE-HF and EVALUATE-HF studies, exploring the subject of reverse remodelling effect of sacubitril/valsartan[17,18]. Sacubitril/valsartan is a combination where Sacubitril is a prodrug that finally inhibits neprilysin followed by a reduction in the breakdown of natriuretic peptides thus prolonging their action. Valsartan on the other hand is an angiotensin receptor blocker resulting in blocking the RAAS system[19]. The combination is required as inhibiting neprilysin alone will lead to the accumulation of angiotensin II circumventing the benefits. When combined with an ARB excess angiotensin II is blocked. Similarly combining neprilysin inhibition with ACEI will result in high levels of bradykinin followed by angioedema and cough.

To date, PARAGON-HF is the largest clinical trial in heart failure due to reduced ejection fraction. The double-blind, randomized, active-controlled parallel-group, phase three, two-arm trial compared Sacubitril /valsartan long-term effectiveness and safety to valsartan in 4,822 heart failure patients. The trial showed a 13% relative decrease in the primary composite endpoint of cardiovascular death and total (first and recurrent) cardiac failure hospitalizations but missed statistical significance. It was the biggest heart failure study ever conducted and was completed before schedule as the drug showed significant results in reducing the cardiovascular death risk.

PARADIGM-HF enrolled 8,442 patients with HFrEF and NYHA Class II-IV heart failure. The study compared Sacubitril/valsartan with another ACE inhibitor, Enalapril, and was designed to find out whether it is superior to Enalapril in decreasing cardiovascular mortality by at least 15%[20].

Our findings were in line with the previous studies and revealed that a significant improvement in NYHA class and Ejection fraction on Echocardiography was found from the baseline NYHA class and Ejection Fraction (p=0.001) in the A to S/V group. At the end of the study, there was clinical improvement in NYHA class and Ejection fraction with Sacubitril/Val sartan treatment than with ACE inhibitors treatment in A to S/V group. These findings were though in a small set of the population but stand out as a preliminary study that can act as a pilot study for further major multicenter trials to explore the potential of this nova combination in our population.

LIMITATIONS OF STUDY

This study was limited by the relatively short observation period and small sample size. Further large scale multicenter trials are required to assess the outcomes of long term clinical improvement in NYHA class and LVEF with Sacubitril/Valsartan treatment.

CONCLUSION

Sacubitril/Valsartan in comparison to ACE Inhibitor treatment had more clinical improvement in NYHA class and Left ventricular ejection fraction on Echocardiographic parameter in patients with heart failure with reduced ejection fraction.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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