e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(9); 1425-1429

Original Research Article

Study of NT-Pro BNP Levels in Patients of Isolated Right Ventricular Systolic Dysfunction with Normal LV Function after Angiotensin Receptor Neprilysin Inhibitor

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Received: 15-08-2023 / Revised: 05-09-2023 / Accepted: 14-09-2023
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Conflict of interest: Nil

Abstract:

Background: Angiotensin Receptor Neprilysin Inhibitors (ARNI) have shown promising results in reducing NT-pro BNP levels in left-sided heart disease. However, their effects on isolated right ventricular systolic dysfunction with normal left ventricular function remain less defined.

Objective: This prospective study aimed to investigate the impact of ARNI therapy on NT-pro BNP levels in patients with isolated RV systolic dysfunction with normal left ventricular function.

Methods: A total of 50 patients with isolated RV systolic dysfunction with normal left ventricular function were enrolled in this study and divided into two groups: ARNI group (n=25) and Non-ARNI group (n=25).NT-pro BNP levels was evaluated at baseline and 4 weeks. Pulmonary function tests was also conducted to assess respiratory parameters at these specified time points.

Results: At baseline, there was no significant differences in NT-pro BNP levels and pulmonary function parameters between the two groups. After 4 weeks of treatment, the ARNI group showed a significantly greater decline in NT-pro BNP levels in the ARNI group ($p<0.001$) compared to Non-ARNI group while the change in airway resistance by PFT was equal in both groups

Conclusion: ARNI therapy in patients with isolated right ventricular systolic dysfunction resulted in a significantly greater decrease in plasma NT-pro BNP levels without difference in airway resistance. These findings suggest the potential benefits of ARNI therapy in right-sided heart failure and warrant further investigation in larger randomized trials.

Keywords: Angiotensin Receptor Neprilysin Inhibitor, right ventricular systolic dysfunction, NT-proBNP, pulmonary function, heart failure.

Introduction

Heart failure (HF) continues to be a critical global public health problem, affecting an estimated 45–67 million adults worldwide and leading to a myriad of challenges, including increased hospitalizations, reduced survival rates, and significantly diminished quality of life [1, 2]. Among the multifaceted presentations of HF, right-sided heart failure (RHF) stands as a notable concern, arising from diverse etiologies, The right-sided HF is rarely caused by a primarily cardiomyopathic process (<8% of cases)[3]. Rather, increased RV afterload secondary to left-sided HF (46%), intrinsic lung disease (17%), pulmonary thromboembolic disease (18%), and pulmonary arterial hypertension (11%) are the predominant causes of right HF. As such, most therapies for the latter syndrome focus on reducing RV afterload, preferentially by treating the underlying disease process. Progressive RV dysfunction in these disease states is associated with increased morbidity and mortality.

The management of RHF predominantly revolves around reducing RV afterload, with a particular emphasis on addressing the underlying disease process. The progression of RV dysfunction in these conditions is strongly associated with elevated morbidity and mortality rates, necessitating the development of novel therapeutic approaches to improve patient outcomes.

Among the strategies to enhance the levels of beneficial molecules in circulation, the inhibition of neprilysin holds promise. Neprilysin, a neutral endopeptidase present on the surface of various

cells and in the circulation, plays a crucial role in the metabolism of numerous counterregulatory vasoactive peptides, including the Natriuretic peptides. Inhibition of neprilysin is anticipated to lead to increased circulating and tissue levels of these peptides, thereby potentially providing therapeutic benefits in the management of HF.

Clinical trial results from various studies have revealed compelling evidence supporting the use of sacubitril-valsartan, an Angiotensin Receptor Neprilysin Inhibitor, as a first-line therapy for patients with left sided heart failure with reduced left ventricular ejection fraction. Sacubitril-valsartan can be initiated either in-hospital once the patient has stabilized or in the outpatient setting, (according to criteria outlined in the PIONEER-HF study) eliminating the need for prior ACEI or ARB therapy and simplifying the treatment approach[4].

Whether the initiation of sacubitril–valsartan therapy is effective in patients of RV systolic dysfunction with preserved LV function is unknown. Therefore our study was designed to prospectively investigate the efficacy of an Angiotensin Receptor Neprilysin Inhibitor in reducing NT pro BNP levels i.e markers of heart failure inthese patients. By contributing to our understanding of this emerging treatment modality, this research could pave the way for improved management strategies and better outcomes for patients with RHF.

Aims and Objectives

To assess the effect of Angiotensin Receptor Neprilysin Inhibitor (ARNI) on plasma NT pro BNP levels in patients of right ventricular systolic dysfunction with normal left ventricular function.

Material and Methods

Study Design

This study was conducted as a randomized prospective interventional study with the intention to treat. The study took place in both the outpatient and inpatient Department of Cardiology, Mathura Das Mathur Hospital, and the Department of TB and Chest Diseases, Kamla Nehru Chest Hospital which is affiliated with Dr. S.N. Medical College in Jodhpur. The study was conducted over a period of 6 months or until the desired sample size and follow-up is achieved. The sample size has 50 subjects.The study did not impose any financial burden on the patients, and there are no anticipated physical, social, or psychological discomforts or risks to the participants.

Sample Size

Sample size was calculated at alpha error 0.05 and study power 90% using the formula for hypothesis testing for two population mean -

$$n = \frac{2\times\left(Z_{1-\alpha/2}+Z_{1-\beta}\right)^2\times\sigma^2}{(\mu_1-\mu_2)^2}$$

Where,
n = Sample size

$\left(Z_{1-\alpha/2}\right)$ = Standard normal deviate for alpha error (taken as 1.96 for alpha error 0.05)

$(Z_{1-\beta})$ = Standard normal deviate for beta error (taken as 1.28 for 90% study power)

σ^2 = pooled variance of the two population where σ taken as 4.4 as per Eric et al.

$\mu_1 - \mu_2$= The difference in NT pro BNP levels between the two population taken as 4.4 as per Eric et al.

Sample size was calculated to be a minimum of 21 subjects in each group, which was rounded to 25 subjects in each group.

Study Procedures

Participant Recruitment:Patients diagnosed with Right ventricular systolic dysfunction with normal left ventricular function, as confirmed by 2D Echocardiography, were enrolled in the study after obtaining written informed consent. Consecutive sampling was utilized until the desired sample size is achieved. The enrolled patients were then randomly assigned to two equal groups using Block randomization through an online computer software random.org. Allocation concealment was maintained by a separate person using sealed opaque envelopes to ensure blinding. The first group (25 patients) will receive conventional treatment, while the second group (25 patients) will receive conventional treatment in addition to ARNI therapy.

All patients were counselled regarding the currently available treatment options, and they werealso informed about the potential benefits of the new drug (ARNI).After the counselling session,baseline data were collected, including demographic information, medical history, plasma NT-pro BNP level and baseline pulmonary function test. Participants were scheduled for follow-up visit at 4 week at the outpatient department. During that visit, clinical assessments was conducted, and any adverse events or complications related to the drug therapy was recorded. Plasma NT pro BNP levels andpulmonary function test were evaluated at baseline and at 4 weeks. All patients were started upon 50 mg twice daily dose of sacubitril-valsartan.

This study has received ethical approval from the institutional ethical and scientific committee. All participants included had provide informed consent before their inclusion in the study. Confidentiality of patient information were strictly maintained throughout the study.

Study Population

Inclusion Criteria

Patients diagnosed with Right Ventricular systolic dysfunction with Normal Left ventricular systolic function, as determined by transthoracic echocardiography parameters including TAPSE<17 mm, PASP, tricuspid annular velocity (S')<10 mm/s, and blood markers such as NT-pro BNP(>125 pg/ml), RV dimensions (basal and mid).

Exclusion Criteria

1. Patients with Left Ventricular Ejection Fraction (LVEF) less than 50%.
2. Patients with a known hypersensitivity to any component of the Angiotensin Receptor Neprilysin Inhibitor (ARNI) product.
3. Patients with a history of angioedema caused by an Angiotensin-Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB).
4. Diabetic patients receiving the renin inhibitor, aliskiren, are specifically contraindicated from using the valsartan component (and any ARB) due to an increased risk of hypotension, hyperkalaemia, and renal impairment.
5. Patients who have received an ACE inhibitor within the last 36 hours, as this could increase the risk of angioedema.

Statistical Analysis

Statistical analysis was performed using SPSS version 25 software. Continuous variables was presented as means ± standard deviations, while categorical variables was presented as frequencies with their corresponding 95% confidence intervals. Appropriate statistical tests was applied as needed to compare the two groups (conventional treatment group vs. conventional + ARNI therapy group). The unpaired Student's t-test was used for comparing continuous variables between the two groups and a two-sided p-value of less than 0.05 was considered statistically significant.

Results

The table presents the baseline characteristics of patients with isolated right ventricular systolic dysfunction, divided into two groups: the Case group (ARNI group, receiving Angiotensin Receptor Neprilysin Inhibitor therapy) and the Control group (non-ARNI group, receiving conventional treatment without ARNI therapy).

Table 1: Baseline characteristics of patient in both group

Variables	Case		Control		p value
	Mean	SD	Mean	SD	
Age	60.4	13.34	59.24	11.59	0.509
Female sex No. (%)	3 (12%)		4 (16%)		1.000
TAPSE	13.00	1.35	12.92	1.00	0.612
RVS'	7.12	0.60	7.16	0.55	0.858
PASP	54.76	8.94	51.32	6.60	0.267
RV Mid	39.68	3.44	40.36	3.46	0.285
RV basal	48.04	4.78	49.20	4.27	0.37
NT-pro-BNP	8811.68	2275.96	8740.56	1424.70	0.895
FEV1	1.16	0.13	1.11	0.07	0.076
FVC	2.13	0.12	2.11	0.19	0.534
FEV1/ FVC	54.68	4.13	53.32	3.56	0.218
Medical History					
Diabetes mellitus	2 (8)%		2 (8%)		0.09
Bronchial Asthma	3 (12%)		2 (8%)		0.564
Tuberculosis	12 (48%)		14 (56%)		0.786
Smoking	17 (68%)		15 (60%)		0.08

Both groups have comparable mean age, sex distribution, and plasma NT-pro-BNP levels at baseline.

FEV1 (Forced Expiratory Volume in 1 second) and other lung function parameters (FVC and FEV1/FVC) do not differ significantly between the groups at baseline.

Similarly, baseline renal functions were also similar between the two groups. Overall, the baseline characteristics of patients are similar between the ARNI and Non-ARNI groups, ensuring a balanced starting point for the study.

Effect of ARNI Therapy on plasma NT pro BNP levels

Table 2: Effect of ARNI Therapy on plasma NT pro BNP levels

		Case		Control		p value
		Mean	SD	Mean	SD	
NT-pro-BNP	Baseline	8811.68	2275.96	8740.56	1424.70	0.895
	4 weeks	5017.08	1245.42	6314.44	963.30	0.0001
FEV1	Baseline	1.164	0.13	1.111	0.07	0.076
	4 weeks	1.174	0.12	1.157	0.09	0.601
FVC	Baseline	2.133	0.12	2.109	0.19	0.534
	4 weeks	2.134	0.12	2.2	0.02	0.129
FEV1/ FVC	Baseline	54.68	4.13	53.32	3.56	0.218
	4 weeks	54.88	3.63	56.12	3.23	0.208

Effect on NT-proBNP

The table presents the effect of treatment on NT-proBNP levels in patients with isolated right ventricular systolic dysfunction, comparing the Case group (ARNI therapy) with the Control group (conventional treatment).

At baseline, there were no significant differences in NT-proBNP levels between the Case (8811.68 ± 2275.96) and Control (8740.56 ± 1424.70) groups (p-value = 0.895).

After 4 weeks of treatment, the Case group showed a significant decrease in NT-proBNP levels reaching 5017.08 ± 1245.42pg/ml compared to baseline, indicating an improvement in cardiac function (p-value = 0.0001).The Control group also showed a reduction in NT-proBNP levels reaching 6314.44 ± 963.30pg/ml after 4 weeks, but the changes in NT-pro BNP levels in the case group were more pronounced compared to the Control group, highlighting the beneficial effect of ARNI therapy in managing heart failure biomarkers.

None of the patients had any serious adverse reaction due to sacubitril / valsartan or any drug reaction leading to withdrawal of the drug

Discussion

The primary objective of this study was to comprehensively explore the impact of Angiotensin Receptor Neprilysin Inhibitor (ARNI) therapy on individuals presenting with isolated right ventricular systolic dysfunction with normal left ventricular function. Our investigation yielded noteworthy insights into the potential benefits of ARNI treatment in this specific patient population.

The initiation of sacubitril valsartan therapy led to a greater reduction in the NT-pro BNP concentration. The beneficial effect of sacubitril–valsartan on the concentration of NT-pro BNP, which is a biomarker of neurohormonal activation, hemodynamic stress, and subsequent cardiovascular events was seen while the changes in airway resistance by PFT was equal in both groups.

Previous studies have like PIONEER HF [4] and PARAMOUNT [9] trial revealed compelling evidence supporting the use of sacubitril-valsartan in reducing NT pro-BNP in patients with left sided heart failure. By corroborating these existing observations, our study provides a robust foundation for considering the use of ARNI therapy as a viable treatment option for patients with isolated right ventricular systolic dysfunction with normal left ventricular function.

Previous research studies were cited in the discussion to support the current findings. For instance, a study by Poglajen et al. (2020) reported significant enhancements in left and right ventricular function, along with reduced NT-pro BNP levels, with ARNI therapy in patients with heart failure with reduced ejection fraction[10].A study by Nagaya et al showed Biochemical markers like BNP/NT pro BNP seem to carry clinically relevant information regarding RV function and prognosis in patients with chronic PH and BNP/NT-proBNP can probably contribute to everyday clinical practice by improving and simplifying follow-up of patients with PAH[11].These studies provide additional evidence supporting the positive effects of ARNI therapy on cardiac function.

Furthermore, the study by Sharifi Kia et al. (2020) in a rat model of pulmonary hypertension demonstrated the beneficial effects of sacubitril/valsartan treatment on RV function, pressure, hypertrophy, and collagen reorientation [7]. In summary, the study demonstrates the potential of ARNI therapy in improving right ventricular function by reducing NT pro BNP levels in patients with isolated right ventricular systolic dysfunction and normal left ventricular function. However, more extensive research with larger patient cohorts and extended follow-up periods is necessary to establish ARNI therapy as a potential treatment option for right-sided heart failure. The study findings contribute valuable insights to the growing body of evidence concerning the role of ARNI therapy in RV function improvement, warranting further investigations in this field.

Conclusion

This study explored the effects of ARNI therapy on isolated right ventricular systolic dysfunction with normal left ventricular function. NT-pro BNP levels also decreased significantly after ARNI therapy while the change in pulmonary Function test was equal in both groups. The findings support the potential benefits of ARNI therapy in right-sided heart failure, but larger trials are needed to confirm its efficacy and safety. Overall, this study adds valuable insights to the growing evidence on ARNI therapy for heart failure treatment.

Limitation of study

Despite the encouraging findings, the study does have some limitations-

1. Small Sample Size: The study was conducted with a relatively small sample size, which may limit the generalizability of the findings.
2. Short Follow-up Duration: The follow-up period of 4 weeks may not capture potential longer-term effects of ARNI therapy.
3. Single centre: Conducting the study at a single centre may limit the applicability of the results to other healthcare settings.

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