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ORIGINAL ARTICLE

Evaluation of Sleep Quality with Use of Angiotensin Receptor Neprilysin Inhibitor in Patients with Reduced Ejection Fraction Heart Failure

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ABSTRACT

Background and Aim: It is known that chronic heart failure reduces sleep quality by causing sleep problems. In recent years, it has been observed that sacubitril-valsartan, which is an angiotensin receptor neprilysin inhibitor, reduces mortality and hospitalization in patients with heart failure. The aim of our study is to examine whether sacubitril-valsartan affects sleep quality in patients with reduced ejection fraction heart failure apart from these benefits.

Material and Method: In our study, 44 patients with a history of heart failure with reduced ejection fraction applied to our cardiology outpatient clinic of Gazi Yaşargil Training and Research Hospital were included. Demographic, clinical, laboratory, electrocardiographic, and echocardiographic parameters of these patients were examined. Sacubitril-valsartan treatment was initiated in all patients. Dose titration was performed in patients who could tolerate the treatment. Pittsburgh sleep quality index questionnaire was performed in all patients before treatment and at the end of the second month.

Result: The median age of the study population was 61.5 (47.2 - 70.7, IQR) years and 30 (68.2 %) of them were male. There were 30 (72.7 %) ischemic heart failure patients and 14 (27.3 %) non-ischemic heart failure patients. There was a significant decrease in the number of patients with poor sleep quality after angiotensin receptor neprilysin inhibitor treatment compared to baseline [36 (81.8 %) vs 30 (68.2 %), p= 0.031]. In addition, there was a significant decrease in the total Pittsburgh sleep quality index score of patients compared to the baseline [9.0 (7.0 - 12.0) vs 7.0 (5.0 - 9.0), $p < 0.001$].

Conclusion: In our study, we observed that sacubitril-valsartan treatment improves sleep quality in patients with reduced ejection fraction heart failure.

Keywords: Sacubitril-valsartan, heart failure, sleep quality

INTRODUCTION

Heart failure (HF), which a chronic and progressive disease, is a rapidly increasing and important health problem characterized by a low quality of life, with high mortality and morbidity rates [1-3]. The prevalence of HF is approximately 1-2% of the adult population in developed countries, rising to ≥ 10 % among people > 70 years of age. A recent study in our country observed that the prevalence of HF is 2.9 %, affecting 1.5 million people along with 3 million people under contiguous risk in the soon [2-4]. In HF patients, sleep quality decreases and sleep problems occur in these patients due to symptoms such as shortness of breath, weakness and fatigue, and limited functional capacity. The prevalence of subjective sleep problems reported in HF patients in the literature is between 60 - 95 % [5-8]. In addition, sleep disorders such as difficulty in initiating and maintaining sleep, insomnia, sleep apnea syndrome, excessive daytime sleepiness have been observed frequently in individuals with HF [9-12]. All these adverse outcomes emphasize the need for a better understanding of the sleep problems experienced by patients with HF.

Sacubitril-valsartan is an angiotensin receptor neprilysin inhibitor (ARNI) combination. In the results of the PARADIGM-HF study, there were significant changes in the medical treatment of heart failure with reduced ejection fraction (HFrEF), and ARNI has been used in clinical practice. The beneficial effects of ARNI with the PARADIGM-HF study are as follows; decrease in symptoms, improvement in New York Heart Association- Functional Capacity (NYHA-FC), increase in the quality of life, improvement in physical examination findings, decrease in N-terminal pro-B type natriuretic peptide/troponin levels, decrease in the need for diuretics and/or additional therapy, decrease in systolic pulmonary artery pressure in echocardiography, increase in EF, decrease in ventricular volumes, improvement in global longitudinal strain, reduction in the need for hospitalization and mortality [13].

Although ARNI has beneficial results shown in HFrEF patients, there are no data in the literature on its effect on sleep in these patients. The aim of our study is to investigate the effect of ARNI on sleep quality before and after treatment in patients with HFrEF.

MATERIALS AND METHODS

In our study, 51 patients with a history of HFrEF (EF ≤ 40 %) who applied to our cardiology outpatient clinic of Gazi Yaşargil Training and Research Hospital were examined between 1 July and 31 October 2019. All of the patients were NYHA - FC Class II and III patients. Patients with symptomatic hypotension, creatinine > 2.5 mg/dL, glomerular filtration rate < 30 ml/min, and potassium > 6 meq / L were excluded from the study. In addition, patients who were treated with continuous positive airway pressure and had cognitive dysfunction were excluded from the study. After the exclusion criteria, 46 patients were included in the study. Demographic, clinical, laboratory, electrocardiography, and echocardiographic parameters of these patients were examined. Sacubitril-valsartan treatment was initiated in each patient. Patients who used angiotensin converting enzyme inhibitors (ACEI) before treatment were started 36 hours after the last dose, and patients who received angiotensin receptor blockers (ARB) were started directly. Dose titration was performed 2-4 weeks later in patients who could tolerate the treatment. During the ARNI treatment, there was no change in the HF treatments of the patients, except for ACEI and ARB. While the study was ongoing, two patients who could not tolerate the drug were excluded from the study. Blood pressure measurements, routine laboratory parameters, electrocardiographic and echocardiographic parameters of all patients were enrolled before and after the treatment. The sleep quality of all patients was assessed by using the Pittsburgh Sleep Quality Index (PSQI) questionnaire before and after treatment. The ethics committee approval required for our study was obtained from the Ethics Committee commission of our hospital.

Sleep Quality Index

All patients were asked to complete a self-report questionnaire (Turkish version of Pittsburgh Sleep Quality Index; PSQI) before and 2 months after ARNI treatment. PSQI consists of a 19-items scale and measures 7 components of sleep quality: Subjective sleep quality, sleep delay, sleep duration, habitual sleep efficiency, sleep disturbances, sleep drug use, and daytime dysfunction. The PSQI

score corresponds to the total of individual scores consisting of 7 components. A PSQI score ≥ of 6 points is considered to be indicative of poor sleep quality. The test has a high diagnostic specificity for detecting clinical sleep disturbance. The reliability and the validity of the Turkish version of this index have been confirmed by Ağargün et al [14].

Statistics

The analysis of the data was carried out using SPSS (Statistical Package for Social Science for Windows)-24 packaged software. The histogram and Shapiro-Wilks test were used to verify the normal distribution of data. The continuous variables were presented as a median interquartile range (IQR) (25-75 %) owing to their non-normal distribution. The categorical variables were expressed as percentages. Wilcoxon tests were used for continuous variables. Mc Nemar test was used to compare categorical variables. The statistical significance level of the obtained data was interpreted with the "p" value. Values of $p < 0.05$ were considered to be statistically significant.

RESULTS

Forty-four patients were included in the study. The median age of the study population was 61.5 (47.2 - 70.7, IQR) and 68.2 % (n=30) of patients were male. There were 30 (72.7 %) ischemic HF patients and 14 (27.3 %) non-ischemic HF patients. Clinical, demographic characteristics and medications of all patients were given in Table 1. Systolic blood pressure ($p < 0.001$), diastolic blood pressure ($p < 0.001$), alanine transaminase ($p= 0.011$) were significantly lower after ARNI treatment compared to baseline. Clinical, laboratory and echocardiographic parameters of all patients before and after treatment were given in Table 2.

At the end of two months, there was a significant decrease in the total PSQI score of the patients compared to the baseline [9.0 (7.0 - 12.0) vs 7.0 (5.0 - 9.0), $p < 0.001$]. The initial and after treatment scores of the total PSQI score, which consists of a total of 7 components, are given in Figure 1.

After ARNI treatment, there was a significant increase in the number of patients with good subjective sleep quality (26 vs 12, $p < 0.001$) and sleep latency less than once a week (30 vs 19, $p= 0.003$). In addition, there was a significant decrease in the number of patients with sleep latency 1-2 times a week (21 vs 10, $p= 0.013$). The rate of patients with a poor PSQI score before treatment decreased compared to after treatment (81.8 % vs 68.2 %), and this was statistically significant ($p=0.031$). The frequency distribution of dimensions of the sleep quality is given in Table 3.

Table 1. Clinical, demographic features, and medications of all patients.

	n	%
Gender		
Female	14	31.8
Male	30	68.2
Hypertension	18	40.9
Diabetes mellitus	17	38.6
Coronary artery disease	32	72.7
Hyperlipidemia	19	43.1
Familial history	6	13.6
New York Heart Association Functional Capacity		
II	20	45.4
III	24	54.6
IV	-	-
Cardiac resynchronization therapy/ pacemaker	10	22.7
Smoking	23	52.2
Asetilsalisilic acid	32	72.7
Clopidogrel/ticagrelor	13	29.5
Beta blocker	43	97.7
Ivabradine	14	31.8
Angiotensin converting enzyme inhibitors	31	70.5
Angiotensin receptor blockers	10	22.7
Mineralocorticoid receptor antagonists	25	56.8
Hydrochlorotiazid-indapamide	16	36.3
Loop diuretic	31	70.5

DISCUSSION

HF patients are known to have sleep problems and poor quality sleep. To the best of our knowledge, this study is the first to evaluate sleep quality in patients with chronic systolic HF who were given ARNI treatment. As a result of our study, we can say that with ARNI treatment, the sleep quality of HFrEF patients increased, and these patients sleep better.

Table 2. Comparison of clinical, laboratory, and echocardiographic parameters of all patients before and after treatment.

	Before ARNI treatment	After ARNI treatment	p value
Systolic blood pressure, mm/Hg	120 (110 - 130)	115 (110 - 125)	<0.001
Diastolic blood pressure, mm/Hg	75 (70 - 80)	70 (65 - 75)	<0.001
Heart rate, beat/min	66 (64 - 70)	65 (64 - 70)	0.184
Ejection fraction, %	26.5 (20.0 - 34.7)	30.0 (25.0 - 39.0)	<0.001
Left ventricle diastolic parameter, mm	6.00 (5.62 - 6.77)	5.85 (5.60 - 6.50)	<0.001
Left ventricle systolic parameter, mm	4.90 (4.50 - 5.50)	4.80 (4.40 - 5.40)	<0.001
Urea, mg/dL	37 (30 - 48)	39 (30 - 54)	0.700
Creatinine, mg/dL	1.03 (0.84 - 1.17)	1.02 (0.82 - 1.16)	0.906
Aspartat transaminase, IU/L	22 (16 - 28)	20 (15 - 23)	0.155
Alanine transaminase, IU/L	19 (16 - 30)	19 (15 - 26)	0.011
Sodium, meq/L	138.5 (136.0 - 140.7)	139.0 (137.2-141.7)	0.206
Potassium, meq/L	4.3 (4.1 - 4.6)	4.4 (4.0 - 4.8)	0.653
Calcium, meq/L	9.2 (8.8 - 9.8)	9.1 (8.9 - 9.6)	0.103
White blood cell, 10^9/ L	8.46 (7.06 - 10.31)	8.40 (7.14 - 10.22)	0.824
NLR	2.52 (1.79 - 3.53)	2.62 (2.03 - 3.33)	0.889
Hemoglobin, gr/dL	14.3 (12.1 - 15.2)	14.0 (13.1 - 15.1)	0.262
Platelet, 10^9/ L	239 (187 - 277)	236 (195 - 279)	0.806

Data are expressed as median interquartile range. NLR: Neutrophil/lymphocyte ratio

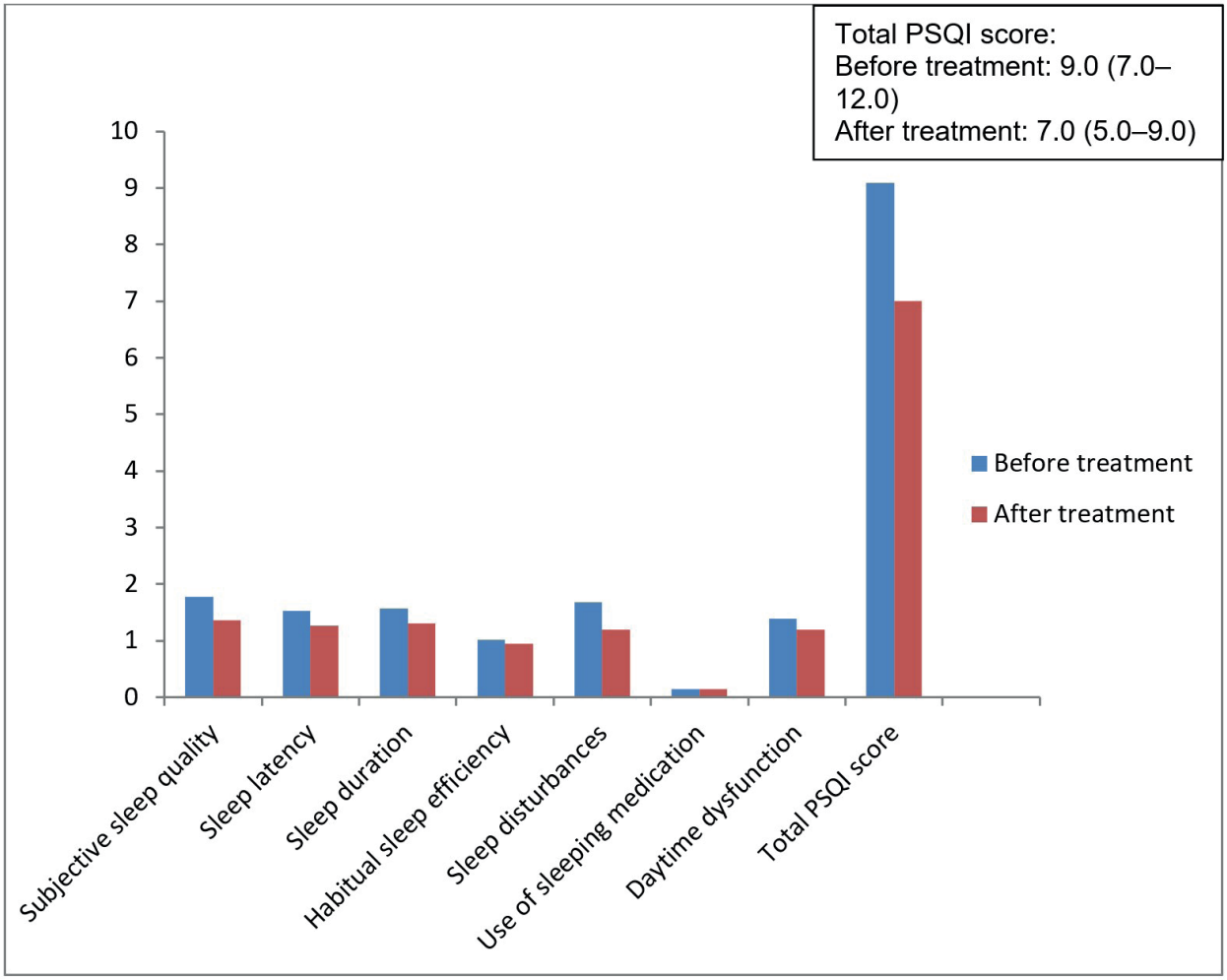

Figure 1. Comparison of the total PSQI score consisting of seven components before and after treatment.

Table 3. Frequency distribution of dimensions of sleep quality.

	Before ARNI treatment	After ARNI treatment	p value
Subjective sleep quality			
Very good, n (%)	3(6.8)	3(6.8)	-
Good, n (%)	12(27.2)	26(59.1)	<0.001
Bad, n (%)	21(47.7)	11(25.0)	0.078
Very bad, n (%)	8(18.2)	3(6.8)	0.125
Sleep latency			
Never, n (%)	2(4.5)	2(4.5)	-
< once/week, n (%)	19(43.2)	30(68.2)	0.003
1-2 times/week, n (%)	21(47.7)	10(22.7)	0.013
≥ 3 times/week, n (%)	2(4.5)	2(4.5)	-
Sleep duration			
> 7 hours, n (%)	4(9.1)	8(18.2)	0.125
6-7 hours, n (%)	18(40.1)	22(50.0)	0.388
5-6 hours, n (%)	15(34.1)	9(20.5)	0.109
< 5 hours, n (%)	7(15.9)	5(11.3)	0.500
Habitual sleep efficiency			
> 85%, n (%)	7(15.9)	9(20.5)	0.500
75-84%, n (%)	29(65.9)	29(65.9)	-
65-74%, n (%)	8(18.2)	6(13.6)	0.502
< 64%, n (%)	0(0)	0(0)	
Use of sleeping medication			
Never, n (%)	41(93.2)	41(93.2)	-
< once/week, n (%)	1(2.3)	1(2.3)	-
1-2 times/week, n (%)	2(4.5)	2(4.5)	-
≥ 3 times/week, n (%)	0(0)	0(0)	-
Total PSQI score ≥ 6, n (%)	36(81.8)	30(68.2)	0.031

HF continues to be a global health problem. It is known that HF patients have negative physical symptoms and findings as well as psychological and sleep problems. Patients with HF have poor sleep quality and this condition is associated with poor quality of life and health status. In a study comparing the sleep characteristics of patients with and without HF, it was found that patients with HF had lower sleep quality and more daytime sleepiness [15]. In another study, 31.3 % of HF patients were reported to show symptoms of chronic insomnia and paroxysmal nocturnal dyspnea, and NYHA classification status was associated with insomnia [16]. In a study conducted to determine the relationship between the course of sleep problems and re-hospitalization in HF patients for one year, it was determined that one-third of HF patients had sleep problems one year after discharge from the hospital. In addition, it was observed that the risk of re-hospitalization of patients who continued to have sleep problems had twice as high. In the studies, it has been reported that sleep problems in patients with HF are related to the disease and treatment, and apart from these, factors such as demographic characteristics, advanced age, gender, comorbid conditions, sedentary life, and the emotional state contribute to sleep disorders [5-7]. Also, changes in sleep patterns seen in patients with HF can negatively affect the prognosis of the disease [17].

In a study by Lee et al., HF patients with PSQI > 5 (HFrEF and HFpEF) were defined as poor sleepers and followed up for one year. 63 % of these patients reported poor sleep quality. It was found that those with poor sleepers had 2.5 times less cardiac event-free survival (95% CI, 1.164 - 5.556) than good sleepers [18]. In a study by Türoff et al., HF patients with EF 45% and below NYHA- FC Class II and above were examined. The presence of whether a breathing disorder during sleep was evaluated by polysomnography. Less restorative sleep may

cause changes in sympathovagal balance and impairment in the reset of important reflexes. This may contribute to poor cardiovascular outcomes in patients with HFrEF [19]. Wang TJ et al., investigated factors affecting sleep quality in patients with HF. The mean PSQI of these patients was 10.78 ± 4.78 and 81 % of the patients had low sleep quality. The most common cause of sleep interruption was urination. Gender, perceived health, depressive mood, and number of comorbidities were seen as factors related to sleep quality [20]. In our study, the total PSQI score of baseline was higher than after treatment. Also, patients with poor sleep quality after treatment were less than baseline.

In the AWAKE-HF study, sacubitril/valsartan and enalapril were compared. In this study, physical activity and sleep were evaluated using actigraphy, which a wearable biosensor. Actigraphy is a non-invasive method that can be evaluated objectively and accurately for 24 hours. No difference in activity or sleep was observed between sacubitril/valsartan and enalapril. However, with sacubitril/valsartan therapy for 16 weeks, it was seen with a statistically significant improvement in health-related quality of life compared to onset [21]. In the PROVE-HF study, significant improvements were observed in left ventricular ejection fraction (LVEF) after ARNI treatment. At 12 months, the LVEF median increased from 28.2 % to 37.8 % [difference, 9.4% (95% CI, 8.8 % - 9.9 %)]. A significant 5.2 % increase in LVEF was also seen as early as 6 months (5.2 %, 95 % CI, 4.8 % to 5.6 %). An absolute LVEF increase of over 13 % was observed in 25 % of patients. Overall, the results of the PROVE-HF study show significant improvements in cardiac structure and function measurements at six months and one year in patients with HFrEF [22]. In our study, there was a significant increase in LVEF after ARNI treatment compared to baseline [30.0 (25.0 - 39.0) vs 26.5 (20.0 - 34.7), $p < 0.001$]. LVEF increased 13.2 % after treatment. In addition, a significant reduction was observed in LV diastolic and systolic diameters after treatment.

In our study, symptomatic hypotension was observed in only three patients during ARNI treatment. These patients who were given the form 49/51 mg were switched to a lower dose (24/26). Two patients who could not tolerate drugs were stopped treatment. In other patients, there were no problems that would stop treatment. In our study, the frequency of responding to the question " I can not breathe comfortably" in item d of the 5th question of the PSQI index decreased after the treatment compared to the baseline. We can comment on this as a decrease in the frequency of paroxysmal nocturnal dyspnea. As a result of our study, ARNI treatment reduces the total PSQI scores in patients with HFrEF. Thus, we can say that the patients had a better quality of sleep after the ARNI treatment.

CONCLUSION

Sleep problems in chronic HF patients are one of the unfavorable clinical conditions. In conclusion, sleep quality increases with ARNI treatment in patients with HFrEF. Patients can sleep more comfortably with this treatment.

Limitations

Although our study is a prospective study, it has some limitations. The first and most important of these is the small study population. Studies with more patients can give more consistent results regarding the sleep quality of ARNI in the treatment of HF. Second, this drug is still not included in the refund coverage of the Ministry of Health in our country. This expensive drug was only can give for a few months in most of the study population. This may be perceived as a tendency to select patients in the study population. Third, due to the illiteracy of some patients, the assistance of the relatives of the sleep questionnaire was conducted by asking questions to the patient. It can not be ruled out that this issue can create bias. Fourth, we only did a sleep assessment with PSQI. Studies with more quantitative methods such as polysomnography or actigraphy may give a better idea to clinicians.

Author contribution

FI originated the idea of the research. FI designed the study. BA, MO, and ET collected data. FI and BA analyzed the data. FI wrote the paper. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ethical Committee (Protocol No: 319, 04/07/2019).

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Conflict of interest

The authors declare that there is no conflict of interest.

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