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Antihypertensive Efficacy of Nebivolol and Low-Dose Spironolactone in Patients with Resistant Hypertension

Dirençli Hipertansif Hastalarda Nebivolol ve Düşük Doz Spironolaktonun Antihipertansif Etkinliği

ABSTRACT

Objective: Resistant hypertension is associated with increased mortality and morbidity. The optimal medical therapy is not fully elucidated in resistant hypertension. There are relatively few studies in the literature on the treatment of resistant hypertension. In this study, we compared the effectiveness of nebivolol 5 mg, a third generation beta-blocker, with spironolactone 25 mg in patients with resistant hypertension.

Methods: A total of 81 patients with resistant hypertension were included in the study. The spironolactone group was composed of 38 patients while the nebivolol group was composed of 43 patients. Resistant hypertension was defined as having office blood pressure ≥ 140/90 mmHg while the patients were under 3 or more antihypertensive agents treatment which included diuretic agents. Office and ambulatory blood pressure at basal and after 8 weeks of treatment were recorded.

Results: Office systolic blood pressure and diastolic blood pressure in 24-hour ambulatory blood pressure monitoring were significantly lower when compared to basal values in both nebivolol and spironolactone groups. The decrease in 24-hour mean systolic and diastolic blood pressure in nebivolol group was 14.9 ± 19.8 mmHg and 9.3 ± 12.7 mmHg compared to 19.5 ± 16.4 mmHg and 13.7 ± 10.8 mmHg in the spironolactone group, respectively. The decrease in 24-hour mean systolic and diastolic blood pressure was not significantly different between the nebivolol and spironolactone groups ($P=0.338$ and $P=0.153$).

Conclusion: Nebivolol is an effective treatment option for resistant hypertension and the antihypertensive effect of nebivolol is similar to low-dose spironolactone.

Keywords: Ambulatory blood pressure monitoring, nebivolol, resistant hypertension, spironolactone

ÖZET

Amaç: Dirençli hipertansiyon artmış mortalite ve morbiditede artış ile ilişkilidir. Dirençli hipertansiyonda optimal medikal tedavi tam olarak belirlenmemiştir. Literatürde dirençli hipertansiyon tedavisi ile ilgili az çalışma vardır. Bu çalışmada dirençli hipertansiyon hastalarında bir üçüncü kuşak beta bloker olan nebivolol 5mg'nin etkinliğini 25 mg spironolakton ile karşılaştırmayı amaçladık.

Yöntem: Çalışmaya dirençli hipertansiyonu olan toplam 81 hasta dahil edildi. Spironolakton grubu 38 hastadan, nebivolol grubu ise 43 hastadan oluştu. Dirençli hipertansiyon, hastaların biri diüretik olmak üzere üç veya daha fazla antihipertansif ilaç tedavisi alırken ofis kan basıncının ≥140/90 mmHg olması olarak tanımlandı. Bazal ve 8 haftalık tedaviden sonra ofis ve ambulatuar kan basınçları kaydedildi.

Bulgular: 24 saatlik ambulatuar basıncı takiplerinde sistolik kan basıncı ve diyastolik kan basıncı, hem nebivolol hem de spironolakton gruplarında bazal değerlerle karşılaştırıldığında anlamlı derecede düşüktü. 24 saatlik ortalama sistolik ve diyastolik kan basıncı düşüşü nebivolol grubunda sırasıyla 14,9 ± 19,8 mmHg ve 9,3 ± 12,7 mmHg, spironolakton grubunda 19,5 ± 16,4 mmHg ve 13,7 ± 10,8 mmHg idi. Nebivolol ve spironolakton gruplarının karşılaştırılmasında 24 saatlik ortalama sistolik ve diyastolik kan basıncındaki düşüş farkı anlamlı değildi ($P=0,338$ ve $P=0,153$).

Sonuç: Nebivolol dirençli hipertansiyonda etkili bir tedavi seçeneğidir ve nebivololün antihipertansif etkisi düşük doz spironolaktona benzerdir.

Anahtar Kelimeler: Ambulatuar kan basıncı izlemi, nebivolol, dirençli hipertansiyon, spironolakton

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

Hamdi Püşüroğlu[1]
Ender Özal[2]
Ahmet Yaşar Çizgici[3]
Yalçın Avcı[3]
Ali Rıza Demir[3]
İsmail Bıyık[4]

[1]*Department of Cardiology, Çam and Sakura Başakşehir Training and Research Hospital, Istanbul, Türkiye*
[2]*Bağcılar Training and Research Hospital, İstanbul, Türkiye*
[3]*Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital, İstanbul, Türkiye*
[4]*Departmant of Cardiology, Uşak University Training and Research Hospital, Uşak, Türkiye*

Corresponding author:
Ender Özal
✉ drender38@hotmail.com

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Resistant hypertension is defined as blood pressure (BP) that remains above target values in spite of the current use of 3 or more antihypertensive agents treatment which includes diuretic agents.[1] The prevalence of resistant hypertension among hypertensive patients is approximately 10%-15%.[2,3] It is known to be a risk factor for target organ damage, chronic renal diseases, and cardiovascular events.[2,4]

The most effective therapy for resistant hypertension is still a debate. Spironolactone, a mineralocorticoid receptor antagonist, was found to be an effective antihypertensive agent in some observational studies and recommended as first line antihypertensive drug for patients with resistant hypertension and estimated glomerular filtration rate ≥ 30 ml/min/1.73 m^2. It provides a reduction in both systolic and diastolic BPs that were more prominent in systolic BP.[5,6] Another placebo-controlled study investigating therapy in resistant hypertension reported that spironolactone reduced BP more than bisoprolol.[7]

Nebivolol has favorable effects on central BP, aortic stiffness, and endothelial dysfunction when compared to other beta-blockers (BBs). Nebivolol has vasodilator effects as it releases nitric oxide in addition to the other features it possesses as a BB. In a meta-analysis, nebivolol was found to be more effective at lowering BP than other antihypertensive agents.[8]

Despite being used to treat patients with hypertension, nebivolol has not yet been examined specifically in patients with resistant hypertension. In this study, we aimed to evaluate the effectiveness of nebivolol 5 mg, a vasodilating BB, by comparing it with spironolactone 25 mg in resistant hypertension.

Material and Methods

A total of 131 consecutive hypertensive patients between the ages of 27 and 78 who were admitted to our cardiology outpatient clinic and had office BP ≥ 140/90 mmHg while using 3 of the optimal therapy combinations of angiotensin-converting enzyme/angiotensin-receptor blocker or calcium channel blocker with diuretics were included in the study. Blood pressure was measured by a physician with an auscultatory sphygmomanometer after the patient was seated and had been relaxed for at least 5 minutes. Three BP measurements were recorded and BP was calculated as the average of the last 2 BP readings. A 24-hour ambulatory blood pressure monitoring (ABPM) was performed before and after the treatment. Medical history, physical examination findings, and anthropometric measurements of the patients were recorded by an experienced cardiologist. The patients were examined for secondary hypertension and sleep apnea syndrome. Renal Doppler ultrasound and other tests were performed in patients whose clinical and laboratory findings were suggestive of secondary hypertension. Patients diagnosed with resistant hypertension were excluded from the study if they were receiving nebivolol and spironolactone therapy. If they were using a BB other than nebivolol, they were included in the study, but in the spironolactone group. Other patients included in the study were randomly assigned to nebivolol and spironolactone groups.

An echocardiographic examination was performed on all patients. Patients with EF < 50% (n=3), diastolic dysfunction ≥ grade 3 (n=3), severe valvular disease (n=4). Glomerular filtration rate < 60 mL/min/1.73m^2 (n=13), missing follow-up data (n=5), and patients who were under nebivolol and spironolactone treatment (n=16) were excluded from the study. Six patients were excluded from the study due to secondary hypertension, of which 1 had Conn's syndrome, 2 had renal artery stenosis, 1 had coarctation of the aorta, and 2 had sleep apnea syndrome. Lastly, the patients were evaluated in terms of their compliance with antihypertensive treatment and diet and in terms of white coat hypertension. Patients who did not use their medications regularly and those who had high office BP but did not have high BP in ABPM were not included in the study (n=8).

At the end of the study, 38 patients were included in the spironolactone group and 43 patients were included in the nebivolol group (Figure 1).

Diabetes mellitus (DM) was defined according to the American Diabetes Association criteria (fasting serum glucose ≥ 126 mg/dL (7 mmol/L), or non-fasting glucose ≥ 200 mg/dL (11.1 mmol/L),

ABBREVIATIONS

A/C	Albumin/creatinine
ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin-convertingenzyme
ARB	Angiotensin-receptorblockers
BB	Beta-blockers
BMI	Body mass index
BP	Blood pressure
CCB	Calcium channel blockers
DBP	Diastolic blood pressure
DM	Diabetes mellitus
EGFR	Estimated glomerular filtration rate
HDL-C	High- density lipoprotein cholesterol
hs-CRP	High-sensitivity-creactive protei
HT	Hypertension
LDL-C	Low-density lipoprotein cholesterol
LVMI	Left ventricular mass index
SBP	Sytolic blood pressure
TG	Triglycerid
UACR	Urine albumine/creatinene ratio

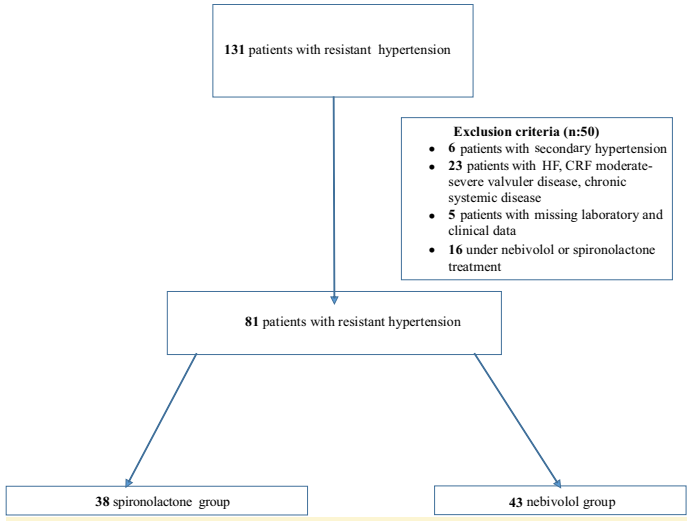

Figure 1. Selection of the study participants.

or active use of antidiabetic treatment).[9] Body mass index (BMI) was calculated as "weight in kilograms divided by the square of height in meters," and estimated glomerular filtration rate was calculated using the chronic kidney disease epidemiology collaboration formula.[10]

Urinary albumin was expressed in milligrams per gram (mg/g). Albuminuria was defined as an albumin/creatinine (A/C) ratio of 30 mg/g or higher, stratified in 2 groups of microalbuminuria and macroalbuminuria with an A/C ratio of 30-299 mg/g and 300 mg/g or higher, respectively.

Echocardiographic examinations were performed by an experienced cardiologist using the Vivid 7 system (General Electric Vivid 7 GE Vingmend Ultrasound AS, Horten, Norway). The left ventricular (LV) mass in grams was calculated from M-mode echocardiograms according to the formula described by Devereux et al.[11] The LV mass index in grams per square meter was calculated by dividing the LV mass by the body surface area.

Patients were questioned about the side effects and drug compliance. Office BP and ABPM were performed before and 8 weeks after the treatment. This study was approved by Ethics Committee of University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital (Approval No: 10678112-514.10-21, Date:03.09.2020) and informed consent was obtained from all patients.

Ambulatory Blood Pressure Monitoring

The ABPM was performed for 24 hours using an ambulatory BP monitor (Tonoport V, GE Healthcare). The monitor was programmed to measure BP every 20 minutes. Daytime and nighttime BPs were defined as from 07:00 AM to 11:00 PM and from 11:00 PM to 07:00 AM, respectively.

Blood Sampling

Standard laboratory parameters, including total leukocyte and neutrophil counts, hematocrit, glucose, creatinine levels, and lipid profiles were determined with standard methods. High-sensitivity-C-reactive protein was measured using a BN2 model nephelometer. Morning spot urine was collected at baseline for measurements of urine albumin/creatinine ratio.

Statistical Analysis

Statistical analysis of the study was performed using the Statistical Package for the Social Sciences (SPSS) software version 20 (SPSS Inc., Chicago, Ill, USA). Visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov) were used to determine the normality of the distribution of variables. Variables were expressed as mean ± standard deviations for normally distributed variables, medians and interquartile range for non-normally distributed and ordinal variables, and percentages for categorical variables. Statistical analysis of the numerical variables between the spironolactone group and the nebivolol group was performed with the unpaired Student's *t*-test or Mann–Whitney *U* test, and the analysis of categorical variables with the chi-square or Fisher exact test. Statistical analysis of the variables in the dependent groups was performed with the paired Student's *t*-test in dependent samples. The change in dependent groups according to the use of spironolactone or nebivolol was statistically compared among themselves with the analysis of variance test in 2-way repeated measurements. P value < 0.05 was considered as statistically significant.

If effect size f (standardized difference) is taken as 0.25 (correlation is taken as 0.80) and type 1 error is 0.05, type 2

Table 1. Characteristics of the Study Population

n=81	Spironolactone (n=38)	Nebivolol (n=43)	*P*
Age (years)	57.7 ± 11.6	58.3 ± 10.8	0.789
Sex (male)	17 (44.7%)	24 (55.8%)	**0.002**
BMI (kg/m²)	31.5 ± 5.4	32.2 ± 4.8	0.584
Smoking	9 (23.7%)	14 (32.6%)	0.377
Alcohol use	0 (0.0%)	5 (11.6%)	0.057
Diabetes mellitus	13 (34.2%)	12 (28.6%)	0.587
LMMI (g/m²)	111.6 ± 26.8	115.1 ± 31.5	0.645
UACR (mg/g)	0.38 (0.019-2.54)	0.22 (0.03-1.03)	0.753
Duration of HT (years)	15 (5-20)	6 (3-10)	**0.031**
Heart rate (beats/min)	74.0 ± 14.2	79.7 ± 14.1	0.155
Hemoglobin (mg/dL)	13.0 ± 1.4	14.0 ± 1.6	**0.005**
Hematocrit (%)	39.1 ± 4.4	41.0 ± 5.7	0.106
Platelet count (10^3 µL)	265 ± 72	276 ± 96	0.586
Leukocyte count (10^9cells/L)	7.66 ± 2.05	8.75 ± 3.03	0.072
Neutrophil count (10^9cells/L)	4.57 ± 1.42	5.27 ± 1.96	0.079
Creatinine (mg/dL)	0.87 ± 0.23	0.88 ± 0.23	0.845
Glucose (mg/dL)	102 (95-133)	107 (95-139)	0.771
Total cholesterol (mg/dL)	216 ± 47	189 ± 44	<0.05
HDL cholesterol (mg/dL)	45.8 ± 7.8	45.9 ± 13.8	0.978
LDL cholesterol (mg/dL)	143 ± 40	110 ± 31	**<0.001**
Triglycerides (mg/dL)	156 (116-217)	155 (113-220)	0.823
hs-CRP (mg/L)	3.5 (2.0-9.3)	3.9 (1.2-9.9)	0.846
ACE-ARB	38 (100.0%)	42 (100.0%)	1.0
CCB	38 (100%)	42 (100%)	1.0
BB without nebivolol	29 (%76.3)	0	**<0.001**
Doxazosin	6 (15.8%)	6 (14%)	0.816
Drug numbers	5 (4-5)	4 (4-4)	<0.05
Diuretic	38 (100%)	42 (100%)	1.0
Other antihypertensives	6 (15.8%)	1 (2.3%)	<0.05
Aspirin	7 (18.4%)	8 (21.7%)	0.459
Statin	8 (21.1%)	6 (20.0%)	0.915

ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; BB, beta blockers; CCB, calcium channel blockers; HDL, high-density lipoprotein; hs-CRP, high-sensitivity-C-reactive protein; HT, hypertension; LDL, low-density lipoprotein; LVMI, left ventricular mass index; UACR, urinary albumin/creatinine ratio.
P value was found with unpaired Student's *t*-test and Mann–Whitney U-test for numerical variables, and Chi-square or Fisher exact test for categorical variables. Values in bold indicate statistical significance (P < 0.05).

Table 2. Comparison of Blood Pressure Values Before and After Treatment Between Nebivolol and Spironolactone Groups

		Before	After	P†	P*
Office SBP (mm Hg)	Spironolactone	175.3 ± 24.7	152.4 ± 23.0	<0.001	0.931
	Nebivolol	165.0 ± 27.9	142.6 ± 23.9	<0.001	
Office DBP (mm Hg)	Spironolactone	96.4 ± 10.3	85.7 ± 10.7	<0.001	0.877
	Nebivolol	89 ± 15.2	78.9 ± 11.9	<0.001	
24-hour-SBP (mm Hg)	Spironolactone	166.9 ± 17.9	147.4 ± 23.3	<0.001	0.338
	Nebivolol	149.5 ± 20.1	134.6 ± 22.6	0.001	
24-hour-DBP (mm Hg)	Spironolactone	100.5 ± 15.9	86.7 ± 15.7	<0.001	0.153
	Nebivolol	92.1 ± 14.8	82.8 ± 17.2	<0.001	
Daytime-SBP (mm Hg)	Spironolactone	167.6 ± 18.9	150.4 ± 25.1	<0.001	0.199
	Nebivolol	148.3 ± 19.7	136.8 ± 22.2	<0.001	
Daytime-DBP (mm Hg)	Spironolactone	102.5 ± 17.3	90.0 ± 17.0	<0.001	0.083
	Nebivolol	92.1 ± 15.7	84.6 ± 18.4	<0.001	
Nighttime-SBP (mm Hg)	Spironolactone	162.0 ± 17.4	142.2 ± 25.1	0.001	0.156
	Nebivolol	144.1 ± 21.9	131.9 ± 21.6	<0.001	
Nighttime-DBP (mmHg)	Spironolactone	93.8 ± 14.3	80.6 ± 15.6	<0.001	0.219
	Nebivolol	88.0 ± 15.7	78.8 ± 15.2	<0.001	

DBP, diastolic blood pressure; SBP, systolic blood pressure.
†*P* value was found by paired Student's *t*-test in dependent samples. *P** value was found by analysis of variance test in two-way repeated measurements.

error is 0.80, and 2 measurements are taken, a total of 116 patients are required.

Results

The baseline characteristics and the laboratory findings of the study population were presented in Table 1. Total cholesterol and low-density lipoprotein cholesterol were statistically higher in the spironolactone group when compared to the nebivolol group ($P < 0.05$ and $P < 0.001$, respectively). The number of male patients was statistically higher in the nebivolol group ($P < 0.05$). The duration of hypertension and the total number of antihypertensive drugs were higher in the spironolactone group ($P < 0.05$, $P < 0.01$). The other baseline clinical characteristics and the laboratory findings were similar between the 2 groups (Table 1).

Office and ABPM values are shown in Table 2. After the treatment, there were statistically significant reductions in terms of office systolic and diastolic BP, ABPM 24-hour-systolic and diastolic BP, and morning and night systolic and diastolic BP in 2 groups (Table 2). The reductions in BP after the treatment for 2 groups are demonstrated in Table 3. The decrease in office systolic and diastolic, ABPM systolic, and diastolic BP was similar between the 2 groups (Table 3).

In the spironolactone group, ABPM 24-hour-SBP and DBP values were 166.9/100.5 mmHg before treatment, while 24-hour SBP and DBP pressures were 147.4/86.7 mmHg after treatment ($P < 0.001$, $P < 0.001$, Table 2, Figure 2). In the nebivolol group, ABPM 24-hour-SBP and DBP values decreased from 149.5/92.1 mmHg before treatment to 134.6/82.8 mmHg after treatment ($P < 0.05$, $P < 0.05$, Table 2, Figure 2). The amount of decrease in 24-hour systolic and diastolic BP values with treatment

Table 3. Comparison of the Decrease in Blood Pressure Values After Treatment Between 2 Groups

n=81	Spironolactone (n=38)	Nebivolol (n=43)	P†
Office SBP (%)	12 ± 14.3	12.4 ± 14.4	0.924
Office DBP (%)	10.4 ± 12	10.3 ± 14.1	0.956
24-hour-SBP (%)	11.7 ± 9.6	9.5 ± 12.1	0.449
24-hour-DBP (%)	13.4 ± 10.0	9.8 ± 12.4	0.223
Daytime-SBP (%)	10.4 ± 9.9	7.7 ± 9.8	0.316
Daytime-DBP (%)	12.0 ± 9.7	8.2 ± 11.1	0.178
Nighttime-SBP (%)	12.3 ± 11.6	7.9 ± 11.9	0.186
Nighttime-DBP (%)	13.8 ± 11.4	9.7 ± 12.4	0.215
Office SBP (mm Hg)	22.9 ± 27.4	22.4 ± 27.1	0.931
Office DBP (mm Hg)	10.6 ± 11.7	10.2 ± 32.3	0.827
24-hour-SBP (mm Hg)	19.5 ± 16.4	14.9 ± 19.8	0.338
24-hour-DBP (mm Hg)	13.7 ± 10.8	9.3 ± 12.7	0.153
Daytime-SBP (mm Hg)	17.2 ± 16.4	11.6 ± 15.3	0.199
Daytime-DBP (mm Hg)	12.5 ± 10.5	7.5 ± 10.6	0.083
Nighttime-SBP (mm Hg)	19.8 ± 19.5	12.3 ± 18.3	0.156
Nighttime-SBP (mm Hg)	13.2 ± 11.4	9.1 ± 12.1	0.219

DBP, diastolic blood pressure; SBP, systolic blood pressure.
†P value was found by unpaired Student's t-test. †P value was found by unpaired Student's t-test independent samples †P value was found by analysis of varience.

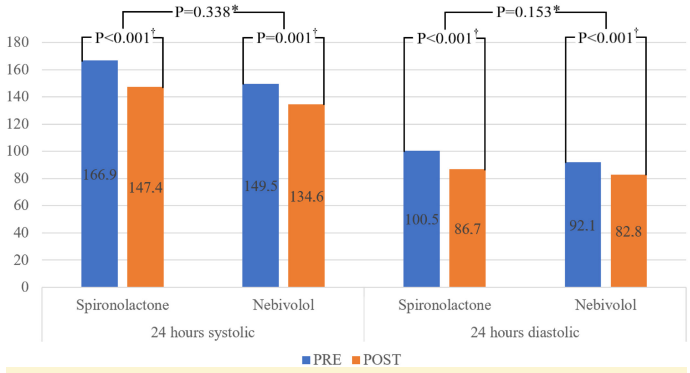

Figure 2. Twenty-four hour systolic and diastolic blood pressure values before and after the treatment in 2 groups.

was statistically similar in nebivolol and spironolactone groups ($P=0.338$, $P=0.153$, Table 2, Figure 2).

Discussion

In this study, it was shown that nebivolol was an effective antihypertensive agent for resistant hypertension. The antihypertensive effect of nebivolol on office and ambulatory systolic and diastolic BP was found to be similar to spironolactone.

The most effective therapy for resistant hypertension is not fully elucidated. Previous studies showed a significant decrease in office and ambulatory BP with spironolactone.[12-15] Current guidelines recommend spironolactone as the preferred agent in patients with resistant hypertension and eGFR ≥ 30 ml/min/1.73 m^2 and state that beta-blockers, alpha 1-blockers and centrally acting agents are other options. Herein, we found a higher decrease in the spironolactone group when compared to previous studies in both office and ambulatory systolic and diastolic BP. It could be explained by the higher basal office and ABPM BP values.

Nebivolol is a highly selective beta1 adrenergic receptor antagonist which has a vasodilator effect via nitric oxide secretion which differs from other BBs. A meta-analysis of 12 studies showed that nebivolol 5 mg had a better lowering effect on BP than other drug classes and other antihypertensive drugs combined. Another study revealed that nebivolol decreased heart rate and peripheral resistance more than atenolol.[8,15]

Bisoprolol, another BB, was found to be less effective in reducing home BP when compared with spironolactone in resistant hypertensive patients.[7] In a study by Sinnott et al,[16] although spironolactone treatment decreased mean systolic BP by 2 mmHg more within 12 weeks compared to BBs and alpha-blockers in resistant hypertensive patients, this difference disappeared in long-term follow-up. In a study by Desai et al,[17] there was no difference in the incidence of cardiovascular events in resistant hypertensive patients between the patients who were given spironolactone therapy and those who were given BB therapy.

In this study, nebivolol was found to provide a significant reduction in ABPM systolic and diastolic BP. Unlike the previous study,[7] decrease in BP was nonsignificantly higher in the spironolactone group when compared to the nebivolol group. Moreover, ABPM was used instead of home BP in our study, distinctive from previous studies.

Resistant hypertension is multifactorial. The most important clinical factors for resistant hypertension are obesity, excessive alcohol consumption and sodium and volume overload due to inappropriate aldosterone secretion.[18-20] The study evaluating the effect of spironolactone and bisoprolol in resistant hypertension presented that spironolactone decreased thoracic fluid index while bisoprolol had no effect on it. This could explain the effectiveness of spironolactone in patients using a high rate of BB in this study.

Inadequate reduction in night BP in hypertensive patients could be the result of increased sympathetic activity and volume load. High night BPs were found to be related to cardiovascular events and mortality.[21,22] In our study, we found that both spironolactone and nebivolol had lowering effects on night BP.

Resistant hypertension is related to obesity and DM.[23,24] This relation could be associated with aldosterone levels, mineralocorticoid receptor numbers, and activity in obese and diabetic patients.[25,26] In our study, we found a higher DM rate and BMI.

Limitations of the Study

Our study had some limitations. This was a single-center, not placebo-controlled study which had a relatively small patient volume and treatment duration is insufficient for such a comparison that may lead to bias. The main cause of non-placebo-controlled design was having patients with severely increased baseline office and ambulatory BP levels. Hence, the BP-reducing effect of placebo was not assessed in this setting. Moreover, the antihypertensive efficacy of nebivolol was compared with spironolactone, which has been previously tried and proven to be effective in resistant hypertensive patients.[6,7,14,19]

One of the most important limitations of the study is that it is a prospective observational study, not a prospective randomized controlled study. Therefore, the duration of hypertensive disease and the total number of drugs used were higher in the spironolactone group. Hence, resistant hypertension patients in the spironolactone group may represent a more severely hypertensive patients group than the patients in the nebivolol group, making it difficult to say that nebivolol 5 mg therapy is as effective as spironolactone 25 mg in the same patient group. Larger-scale prospective randomized studies are needed to explain this.

Drug levels in blood and urine were not assessed to investigate patients' compliance. However, patients were asked about adherence to treatment during each clinic visit. For these reasons, incompliance with the drug therapy was not excluded precisely in our study population.

A total of 116 patients were required for the study; however, we could not reach the number of 116 patients. Lastly, in the groups included in the study, the probability of receiving treatment can be matched with one of the propensity match methods, but it was not used, which was another limitation of the study.

Conclusion

As a result, we cannot say that nebivolol is not as effective as spironolactone due to the situation arising from the study design, but nebivolol was an effective antihypertensive agent in resistant hypertension that might be used as an alternative medical treatment. Moreover, the role of spironolactone in resistant hypertension was supported in our study.

Ethics Committee Approval: This study was approved by Ethics Committee of University of Health Sciences, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital (Approval No: 10678112-514.10-21, Date:03.09.2020).

Informed Consent: Verbal informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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