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Original Research Article

Chronotherapy in dipper and nondipper hypertension patients, researching sodium in 24 hours urine and serum urotensin II levels

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ABSTRACT

Background: The aim of this research was to study the chronotherapy in patients with differentiated dipper and nondipper hypertension, researching the differences between sodium in 24 hours urine and serum urotensin II.
Methods: About 32 nondipper and 29 dipper hypertension patients who have study admission criteria, sodium levels in 24 hours urine, serum urotensin II levels and routine biochemical laboratory tests of were studied. The statistical relationship between the results was analyzed.
Results: In the patient group we examined, nondipper patients were found older and predominantly seen in the female patient population. We determined that the dipper patients differed significantly in family history from nondipper patients. Although it is not statistical significance, we observed accordance of treatment who nondipper patients was worse, we have found that serum urotensin II levels can be used at this distinction.
Conclusions: It is important to distinguish nondipper and dipper hypertension in terms of the prognosis of hypertension and the efficacy of the treatment. For this reason, we want to underline that nondipper patients are older and predominantly seen in the female patient population. Although left ventricular mass index is important in the course and outcome of hypertension, we determined that is was not useful in distinguishing dipper-nondipper hypertension. We think that serum urotensin II levels will be useful in determining the efficacy of the treatment used, the prognosis of hypertension and the differentiation of nondipper-dipper hypertension.

Keywords: Dipper, Hypertension, Nondipper, Serum urotensin II

INTRODUCTION

Primary hypertension (HT) is a highly prevalent health problem with high morbidity and mortality. With the lack of physical exercise induced by contemporary living, hereditary factors, obesity, and the rising habit of dietary patterns containing salt much beyond physiological demand, HT has become a worldwide epidemic.[1-4]

Blood pressure (BP) drops to its lowest levels in the early hours of sleep and begins to rise again in the morning. If the rate of decrease in systolic blood pressure at night is greater than 10%, it is referred to as dipper hypertension; if it is less, it is referred to as nondipper hypertension.

The aim of this classification in hypertension patients is to show that cardiovascular morbidity and mortality are different between the two groups against nondippers.

Hypertension induces atherosclerosis as a result of the inflammatory process created in the arterial wall, causing disruption of a wide number of organs such as the heart,

brain, kidneys, and eyes. Genetic, experimental, epidemiological, interventional, and therapeutic studies have revealed that as dietary sodium intake increases, BP rises, the amount of sodium removed by the kidney decreases, and sodium intake in excess of physiological need is one of the major factors contributing to the development of HT. It has been proposed that severe sodium restriction increases sympathetic activity, plasma renin activity, and angiotensin II levels, and may contribute to an increase in cardiovascular mortality.[5-7]

Urotensin-II has been proven to cause hypertrophy in coronary vasoconstriction, reflex tachycardia, fibrosis and cardiomyositis of the heart.[8] A positive relationship between serum U-II levels and blood pressure was identified in a brief pilot investigation of hypertensive and normotensive patients. In another study, plasma U-II levels were observed to be greater in hypertension patients than in normotensive patients.[8,9]

In our study, we studied chronotherapy, the difference in 24-hour urine sodium excretion between dipper and nondipper HT, and the change in serum urotensin II levels in individuals with dipper and nondipper HT.

METHODS

A total 60 HT patients (32 Nondipper and 29 Dipper), who were diagnosed at the Internal Medicine Clinics of Abant İzzet Baysal University Medicine Faculty between June 2015 and January 2016, were enrolled in this case control study. hypertension patients aged 18-70 years were monitored with ambulatory blood pressure and blood pressure. Patients were evaluated in two groups. 1. Group: Patients with nondipper hypertension (n:32) 2. Group: Patients with dipper hypertension (n:29). The study included 61 patients who had undergone ECHO for target organ damage, chronic renal failure, heart failure, liver failure, or diabetes and had signed a consent form.

Exclusion criteria

Secondary hypertension-causing disorders (such as pheochromostoma, renal parenchymal diseases, aortic coarctation, renovascular hypertension, and preeclampsia), diagnosis of coronary artery disease, chronic renal failure (MDRD), diabetes mellitus, systolic heart failure (ejection fraction <50%), cardiomyopathies, and amputations Cerebrovascular disease, significant valvular heart disease, and liver failure.

According to the change in ambulatory blood pressure monitoring, a 10% or more decrease in blood pressure at night was considered dipper hypertension, whereas less than 10% or no decrease was considered nondipper hypertension.[10-11] It was planned to evaluate the difference between serum urotensin II levels and the difference in sodium excretion in 24-hour urine in patients divided into dipper and nondipper hypertension groups.

Patients were evaluated in the outpatient clinics for internal medicine and nephrology. First, demographic information was collected from patients who met the study requirements and completed the consent form. Height, weight and blood pressure were measured. The study included patients who had their ambulatory blood pressure measured. After fasting for eight hours, a venous blood sample was collected in the morning, along with 24-hour blood pressure measurements. The levels of plasma glucose, creatinine, and alanine aminotransferase (ALT) were all measured. A complete blood count was taken. 24-hour urine was tested for sodium.

Blood samples were obtained from the patient and placed in tubes that did not contain anticoagulants. After soaking at room temperature for at least 30 minutes and up to 2 hours, it was centrifuged at 3000 xg for 10 minutes. The serum samples were collected and stored in ependorf tubes at -80 °C until the biochemical parameters were established. Human Urotensin II ELISA Kit 27 (Catalog Number:CSB E12057H, Lot No:U27222411; Cusabio Biotech Co., Ltd, Wuhan, China) was used to measure serum urotensin II levels. Test results were calculated using calibration curve using 20,10,5,2.5,1.25,0.625,0.312 ng/ml standards. The measurements were taken at 450 nm wavelength. The measurement range of the test was 0.312-20 ng/ml, intraday reproducibility <8%, inter-day repeatability <8%, <10% analytical sensitivity between days and 0.078 ng/ml. The results were presented in ng/ml using a conventional graph.

Mindray MW-12A (Shenzhen, China) was used as the microrecord washer for ELISA measurements. Biotek Elx800 (Vermont USA) was used as ELISA reader.

After the patients had their first urination in the morning, they accumulated all of their urine in the hollow bottle for 24 hours and took the first urine after waking up the next day in the bottle, and the sodium level in the urine was analyzed for 24 hours. The sodium content of the obtained urine sample was determined using the indirect ion selective electrode (ISE) method in the Architect c8000 (Abbott IL, USA). The sodium value in 24-hour urine was calculated using the formula (24-hour urine volume) x (urine sodium value measured in the device)/1000.

The study was approved by Abant İzzet Baysal University Medicine Faculty Ethical Committee and was performed in accordance with the Helsinki Declaration (20.01.2015-71522473-050.01.04/531).

The study's statistical analyses will be carried out using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). Numerical variables with normal distributions are expressed as mean standard deviation, those without a normal distribution as median (minimum-maximum range), and ratios as n (%). The Chi-square or Fisher exact chi-square test will be used to

compare ratios, the Mann-Whitney U test will be used to compare two independent groups that are not normally distributed, and the t test will be used to compare independent groups that are normally distributed. Spearman correlation analysis was used to examine the link between the left ventricular mass index and other laboratory values. The statistical significance level will be taken as $p<0.05$.

RESULTS

The study analyzed the findings of 61 patients, 32 nondippers (52.5%) and 29 dippers (47.5%). The average age of nondipper patients was 53.7±10.4 years, while dipper patients were 47.8±12.9 years. The difference in mean age between the two groups was not statistically significant (p=0.054).

Nondipper patients included 22 females (68.8%), 10 males (31.3%), 11 females (37.9%), and 18 males (62.1%). Gender differences between the two groups were statistically significant. (p=0.016). Nondipper patients had a mean body mass index (BMI) of 30.7±4.1 kg/m², while patients had a mean BMI of 29.7±6.0 kg/m². BMI differences across the two groups were not statistically significant (p=0.43).

Nondipper patients had a median HT duration of 5 (min.1-max.31) years, while dipper patients had a median HT duration of 3 (min.1-max.28) years. There was no statistically significant difference in HT duration between the two groups (p=0.13). It was discovered that 18 nondipper patients used HT drugs in the morning (56.3%), 2 in the evening (6.3%), 11 in the morning-evening (34.4%), 1 in the morning-noon-evening (3.1%), 15 in the morning (51.7%), 10 in the morning-evening (34.5%), and 4 in the morning-noon-evening (13.8%). The difference in the meal during which the two groups used HT medications was not statistically significant (p=0.26). While 9 (28.1%) of nondipper patients were adhering to the treatment, 23 (71.9%) were not adhering to the treatment, while 13 (44.8%) of nondipper patients were adhering to the treatment and 16 (55.2%) were not adhering to the treatment. The difference in treatment adherence between groups was not statistically significant (p=0.17).

When the nondipper patients' family histories were checked, 14 (43.8%) had no family history, 14 (43.8%) had no family history in the mother, 2 (6.3%) had a family history in both the mother and the father, and 2 (6.3%) had a family history in both the mother and the father. Eight (27.5%) of the patients with Dipper had no family history, eight (27.5%) had a family history in the mother, five (17.2%), eight (27.5%) in the father, and eight (27.5%) in the other patients. There was a statistically significant difference in family history between the two groups (p=0.045).

Nondipper patients had a median fasting blood glucose (ACS) value of 93 (min.70-max.100) mg/dl, while dipper patients had a median ACS value of 94 (min.76-max.101) mg/dl. The difference in ACS median values between the two groups was not statistically significant (p=0.29). Creatinine clearance of nondipper patients was calculated by MDRD formula and the mean creatinine clearance of patients was calculated as 89±20.7 ml/min and creatinine clearance of dipper patients was calculated as 99.1±17.8 ml/min. There was no statistically significant difference in creatinine clearance between the two groups (p=0.066). In nondipper patients, the median ALT value was 17 I/l (min.10-max.40), while in dipper patients, the median ALT value was 20 I/l (min.8-max.42). The ALT value difference between the two groups was not statistically significant (p=0.5) (Table 1).

Table 1: Clinical and laboratory findings.

		Nondipper (%)	Dipper (%)	P value
Number of patients		32;52.5	29;47.5	
Age (years)		53.7±10.4	47.8±12.9	0.054
Gender	Male	22;68.8	11;37.9	0.016
	Female	10;31.3	18;62.1	
Body mass index (height/m²)		30.7±4.1	29.7±6.0	0.43
HT duration (years)		5 (1-31)	3 (1-28)	0.13
HT hour	Sabah	18;56.3	15;51.7	0.26
	Evening	2;6.3	0	
	Morning-evening	11;34.4	10;34.5	
	Morning-noon-evening	1 (3.1)	4;13.8	
Salt-free diet	Adapts	9 (28.1)	13;44.8	0.17
	Doesn't adapt	23;71.9	16;55.2	
Family history	No	14;43.8	8 (27.6)	0.045
	Mother	14;43.8	8 (27.6)	
	Father	2;6.3	5;17.2	
	Mother-father	2;6.3	8 (27.6)	
Fasting blood glucose (mg/dl)		93 (min.70-max.100)	94 (min.76-max.101)	0.29

Continued.

	Nondipper (%)	Dipper (%)	P value
Creatinine clearance (MDRD) (ml/min)	89.8±20.7	99.1±17.8	0.066
ALT (İ/L)	17 (min.10-max.40)	20 (min.8-max.42)	0.5

In nondipper patients, the median U-II level was 0.47 ng/ml (min.0.13-max.11.56), while in dipper patients, the median U-II level was 0.34 ng/ml (min.0.23-max.2.03). The difference in U-II levels between the two groups was statistically significant (p=0.01) (Table 2).

Table 2: Serum urotensin-II levels.

	Nondipper	Dipper	P value
Urotensin-II (ng/ml)	0.47 (min.0.13-max.11.56)	0.34 (min.0.23-max.2.03)	0.01

Nondipper patients had a median 24-hour urine volume value of 1310 ml (min.800-max.4000), while dipper patients had a median 24-hour urine volume value of 2100 ml (min.800-max.4700). The 24-hour urine volume difference between the two groups was not statistically significant (p=0.11). The median value of 24-hour urine sodium was 179 mmol/day (min.81-max.440) in nondipper patients and 213 mmol/day (min.43-max.400) in dipper patients was 24-hour urine sodium (min.43-max.400). The 24-hour urine sodium difference between the two groups was not statistically significant (p=0.33) (Table 3).

Table 3: 24-hour urine volume and sodium.

	Nondipper	Dipper	P value
Urine sodium (mmol/day)	179 (min.81-max.440)	213 (min.43-max.400)	0.33
Urine volume (ml)	1310 (min.800-max.4000)	2100 (min.800-max.4700)	0.11

It was determined that 8 (25%) of nondipper patients were using ACEI, 12 (37.5%) were using ARB, 18 (56.3%) were using thiazide, 1 (3.1%) was using spironolactone, 13 (40.6%) were using beta blockers, 12 (37.5%) were using calcium channel blockers, 2 (6.3%) were using alpha blockers, 9 (31%) were using ACEI, 9 (31%) were using ARB, 17 (58.6%) were using thiazid, 2 (6.2%) were spironolactone, 10 (37.7%) were beta blockers, 18 (62.1%) were calcium channel blockers, and 2 (6.9%) were alpha-blockers. (Table 4).

Nondipper patients had 11 (34.4%) single pharmaceuticals, 11 (34.4%) dual medications, 7 (21.9%) three drugs, and 3 (9.4%) four drugs. There was a single drug use in 10 (34.5%) of dipper patients, two drugs in 7 (24.1%), three drugs in 7 (24.1%), three drugs in 3 (10.3%), four drugs in 2 (6.9%) and five drugs (Table 5).

Table 4: Hypertension medication.

Hypertension medication	Nondipper patient number N (%)	Number of patients in dipper N (%)	P value
ACE	8;25	9;31	0.6
ARB	12 (37.5)	9;31	0.6
Tiazid	18;56.3	17;58.6	0.85
Spironolactone	1 (3.1)	2;6.2	0.5
Beta-blocker	13;40.6	10;37.7	0.62
Calcium channel blocker	12 (37.5)	18;62.1	0.055
Alfa-blocker	2;6.3	2;6.9	0.92

Table 5: Number of medications.

Medication used number	No. of nondipper patients N (%)	No. of patients in dipper N (%)	P value
Single medication	11;34.4	10;34.5	0.59
Two medications	11;34.4	7 (24.1)	
Three medications	7 (21.9)	7 (24.1)	
Four medications	3;19.4	3;10.3	
Five medications	0 (0)	2;6.9	

DISCUSSION

Although studies on hypertension have solved many concerns concerning etiology, classification, and treatment, the question of what role personal differences between risk levels of different persons with near BP values play, independent of other factors, has yet to be answered.[4] With the definition of dipper HT and nondipper HT by O'Brien et al the role of personal variables as risk factors for hypertension has begun to be called into doubt.[12] Many studies have found that BP decreases during nighttime sleep and shows diurnal variability.[13,14] According to Verdecchia et al the prevalence of nondipper hypertension among hypertensive patients was between 10 and 40%.[15] In one study, 253 hypertension patients had their blood pressure measured ambulatorily, and it was revealed that 161 were dippers and 92 were nondippers.[14] In the essential hypertension population studied, 32 patients (52.5%) were nondippers and 29 cases (47.5%) were dippers. In comparison to our study, we discovered that the prevalence of nondipper hypertension was lower in studies conducted abroad. This discovery prompted us to reassess the treatment we provide to our country's critical hypertension population. Furthermore, no specific study

has been undertaken in our nation to establish the frequency of dipper HT and nondipper HT in hypertensive patients.

While the majority of studies examining the relationship between dipper HT and nondipper HT and body mass index in patients with hypertension found no difference in BMI between the two groups, there was no difference in BMI between the patient groups in our study.[15-17] Nondipper patients had a median HT duration of 5 (min.1-max.31) years, while dipper patients had a median HT duration of 3 (min.1-max.28) years. In terms of HT duration, there was no statistically significant difference between the two groups. However, when we look at it broadly, nondipper HT patients have a greater BMI and a longer HT duration.

While there is a strong link between nondipper and cardiovascular issues, the next step is to show that when nondipper HT is converted to dipper HT, these complications are minimized. A study of 215 patients indicated that using 80 mg telmisartan at night converted nondippers into dippers.[18] A similar study of 148 patients compared valsartan (160mg/day) monotherapy taken in the morning or at night before bedtime. After 3 months of therapy before going to bed, 75% of the patients became dipper, and proteinuria was reported to reduce.[19] Ramipril administered at night was demonstrated to minimize the incidence of CVD by regulating blood pressure at night in the Heart Outcomes Prevention Evaluation (HOPE) research.[20] Although there was no statistical difference in the number of drugs used by nondipper and dipper HT patients and the time period (morning-evening) in which they used the drug in our study, studies demonstrated that nondipper HT patients receiving antihypertensive treatment at night had fewer complications and that nondipper HT turned into dipper HT.

In terms of the contribution of history in the differentiation of nondipper-dipper HT, we investigated family history and adherence to therapy as secondary observations in our study. Despite the lack of statistical significance in this study, we found that nondipper HT patients had lower adherence to medication. Perhaps if our sample size was larger, we could achieve statistically significant results in terms of treatment non-compliance. We also discovered that a positive family history of dipping HT was statistically significant.

The Salt Consumption and Blood Pressure Study in the Turkish Community (SALTurk), funded by the Turkish Society of Hypertension and Kidney Diseases, explored the relationship between salt consumption and blood pressure in our country for the first time.[21] Our people tend to have the greatest sodium intake rate in the world, comparable to societies that use excessive salt, such as China, India, and European Union countries.[22,23] The International research of macro and micronutrients and blood pressure, “International study of macro and micro-nutrients and blood pressure” (INTERMAP) and the Norfolk cohort of the European prospective investigation into cancer, “The Norfolk cohort of the European prospective investigation into cancer” (EPIC-Norfolk) studies both found that higher dietary salt intake was important in influencing population BP levels.[24,25] To investigate the link between dietary sodium intake and blood pressure, we employed 24-hour urine sodium excretion, which is considered a good predictor of daily sodium intake. When the data from the dipper and nondipper groups were analyzed in our study, it was discovered that the dipper group consumed 213 mmol of sodium per day, while the nondipper HT group consumed 179 mmol. In our study, there was no statistically significant difference in sodium excretion between the two groups, and we suspected that this was due to nondipper patients paying more attention to salt consumption in the foreground.

Human urotensin II is the most potent vasoconstrictor peptide identified to date, and blood levels have been shown to rise in nondipper hypertension patients.[26] Previous research has demonstrated that urotensin II increases the creation of atherosclerotic plaques, macrophage foam cells, and vascular smooth muscle cell proliferation. Urotensin II expression is elevated in atherosclerotic lesions of the coronary artery, carotid artery, and aorta.[27-29]

The primary goal of our study was to see if there was a significant difference in urotensin II levels between the two groups. Urotensin II levels in the nondipper hypertension group were found to be higher. Although ambulatory BP measurement is now utilized to diagnose nondipper HT, urotensin II level measurement may be employed in the future to diagnose nondipper HT. The level of urotensin II allows for information on both the diagnosis of nondipper HT and the course and consequences of HT. If the level of urotensin II is high in a hypertension patient for whom we cannot perform outpatient blood pressure monitoring, we believe that the hypertension control is not good until that day, it will not be prognostically good, and the treatment should be closely monitored.

This study has few limitations. A larger cohort with comparison of nondipper to dipper hypertension is required for further validation.

CONCLUSION

In this study, we looked at how serum urotensin II levels changed in individuals with dipper and nondipper hypertension, as well as its value as a mediator and a prognostic predictor. Serum urotensin II levels were observed to be considerably greater in patients with nondipper hypertension. Based on this finding, hypertension patients with high serum urotensin II levels are more likely to be nondippers, with a worse prognosis.

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