

Clinical Research

Red Blood Cell Distribution Width, Mean Platelet Volume and Neutrophil/Lymphocyte Ratio in 'Non-Dippers' Versus 'Dippers'

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ABSTRACT

Objective: The aim of this study is to compare red blood cell distribution width (RDW), mean platelet volume (MPV) and neutrophil/lymphocyte ratio (NLR) in dipper and non-dipper hypertensive patients.

Material and Method: A total of one hundred and sixteen patients were included in our study. Twenty-four-hour ambulatory blood pressure monitoring (ABPM) were performed for each patient. There after patients were divided into two groups: 54 dipper hypertensives (mean age; 54.7 ± 13.6) and 62 non-dipper hypertensives (mean age; 59.7±12.6). Complete blood count and biochemistry were performed in all subjects.

Results: Daytime systolic and diastolic blood pressure (BP) measurements were similar between dippers and non-dippers, but night-time measurements were significantly different (night-time systolic BP: 127.7±12.7 vs 116±11.4 mmHg, p<0.0001; night-time diastolic BP: 78.6±9.0 vs 72.4±8.5 mmHg, p<0.0001). Non-dippers had significantly higher RDW levels than dippers (14.5±1.3 vs 13.8±1.2 p =0.005). Non-dipper patients demonstrated higher levels of MPV and NLR compared with dippers (9.5±1.1 vs 8.9±1.0 fL p=0.05 and 2.7±1.1 vs 2.1±0.7 p<0.001). There was significant negative correlation between percentage decline of systolic and diastolic BP from day to night and RDW (r = - 0.2 p <0.025 and r = - 0.3 p <0.003 respectively), MPV night (r=-0.2 p<0.025 and r=-0.2 and p<0.03 respectively) and NLR (r=-0.21, p<0.02 and r=-0.2and p<0.04 respectively).

Conclusion: Our results suggest that RDW, MPV and NLR levels, which are indicators of platelet activation and inflammatory response are significantly higher in non-dipper hypertensive patients compared to dipper hyperensives.

Key Words: Red blood cell distribution width, Mean platelet volume, Neutrophil/lymphocyte ratio, non-dipper.

ÖZET

“Dipper” ve “Non-dipper” Hipertansif Hastalarda Eritrosit Dağılım Genişliği, Ortalama Trombosit Hacmi ve Nötrofil/Lenfosit Oranı

Amaç: Çalışmamızın amacı dipper ve non-dipper hipertansif hastalarda eritrosit dağılım genişliği (EDG), ortalama trombosit hacmi (OTH) ve nötrofil/lenfosit oranını (NLO) karşılaştırmaktır.

Gereç Yöntem: Çalışmaya kardiyoloji polikliniğinde takibi yapılan 116 hipertansif hasta dahil edildi. 24 saatlik ambulatuvar kan basıncı (KB) monitörizasyonuna göre hastalar dipper ve non-dipper olmak üzere iki gruba ayrıldı. Tüm hastalara biyokimyasal testler ve tam kan sayımı yapıldı.

Bulgular: Hastaların 54’ü dipper (ortalama yaş; 54.7 ± 13.6), 62’si non-dipper (ortalama yaş; 59.7±12.6) gruptaydı. Her iki grubun gündüz KB ölçümleri arasında anlamlı fark yoktu. Dipper KB profili olan hastaların non-dipper olanlara göre gece ortalama sistolik (116±11.4 ve 127.7±12.7 mmHg p<0.0001) ve diastolik KB (72.4±8.5 ve 78.6±9.0 mmHg) p<0.0001 daha düşük saptandı. Non-dipper hasta grubunun EDG (14.5±1.3 ve 13.8±1.2 p =0.005), OTH (9.5±1.1 ve 8.9±1.0 fL p=0.005) ve NLO (2.7±1.1 ve 2.1±0.7 p<0.001) anlamlı olarak yüksekti. Sistolik ve diastolik KB gece gündüz farkı yüzdesi ile EDG arasında (sırası ile; r = - 0.2 p <0.025 ve r = - 0.3 p <0.003), OTH arasında (sırası ile r=-0.2 p<0.025 ve r=-0.2 ve p<0.03) ve NLO arasında (sırası ile; r=-0.2 p<0.02 ve r=-0.2 and p<0.04) negatif korelasyon saptandı

Sonuç: Sonuçlarımız non-dipper hipertansif hastalarda enflamatuvar cevap ve trombosit aktivasyonunun bir göstergesi olan EDG, OTH ve NLO düzeylerinin dipper hipertansif hastalara göre daha yüksek olduğunu göstermektedir.

Anahtar Kelimeler: Eritrosit dağılım genişliği, ortalama trombosit hacmi, nötrofil lenfosit oranı, non-dipper.

High blood pressure (BP) levels are among the most important risk factors for cardiovascular disease. BP generally varies according to a circadian rhythm characterized by a reduction during sleep and an increase during wakefulness. The same circadian fluctuation is observed in normotensive subjects and in

both treated and untreated hypertensive patients (1). The average systolic BP (SBP) and diastolic BP (DBP) difference between day and night is 10-20% and this is referred to as dipping pattern. In some subjects, whether they have normo- or hypertension the normal nocturnal fall in BP <10%, which is referred to as non-

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Received/ Geliş Tarihi: 02.07.2014

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Accepted/Kabul Tarihi:29.10.2015

dipping pattern (2). Non-dipper subjects Have worse Cardiovascular outcomes than dippers. Many studies suggest that patients who do not show an appropriate nocturnal dip in BP can suffer from a variety of disorders associated with increased rates of cardiovascular morbidity and mortality (3,4).

Patients with non-dipping hypertension tend to have increased platelet activation and inflammatory response. Increased platelet activation and inflammatory response could also contribute to increase the atherosclerotic risk in non-dipper patients compared to dippers (5,6).

The aim of this study was to explore the association between red blood cell distribution width (RDW), mean platelet volume (MPV) and neutrophil/lymphocyte ratio (NLR) in patients with dipper versus non-dipper hypertension.

MATERIAL AND METHOD

Between June 2012 and January 2014 we prospectively studied 116 hypertensive patients aged over 18 years. Istanbul University Institute of Cardiology Ethics Committee approved the study protocol and each subject were informed consent prior to enrollment. The patients' age, sex, history of hypertension and medication use were recorded. In all subjects special laboratory studies for secondary causes of hypertension were performed when considered appropriate on clinical grounds. Patients with secondary hypertension, congestive heart failure, cardiac valve diseases, conditions preventing technically adequate ABPM and major and potential confounding factors, such as active infection, inflammatory disease, malignancy, thyroid function disorders, renal or hepatic dysfunction, that might affect the NLR excluded from the study. Twenty-four-hour ABPM was carried out on the non-dominant arm using a PhysioQuant device (Envitec Germany). The device was set to obtain BP readings at 15 min intervals during the day (07:00–23:00 h) and at 20 min intervals during the night (23:00–07:00 h). Of the 116 study participants 54 showed a fall in SBP/DBP > 10% during night time sleep and were categorized as dippers, while the remaining 62 showed a fall ≤ 10% and were categorized as non-dippers.

The blood samples were drawn from patients after an over night fasting of more than 12 h. The RDW, hemoglobin level, white blood cell count and mean platelet volume were determined using a ADVIA 2120 system (Siemens, USA).

Statistical Analysis

Continuous variables were expressed as mean±SD. Categorical variables were expressed as percentages. To compare parametric continuous variables, Student's t-test was used; to compare categorical variables, the Chi-square was used. The correlations between the observed variables were

examined by Pearson's correlation test. The receiver-operating characteristic (ROC) curve was used to determine the cutoff value of red cell distribution width in non-dipper hypertensive patients. All variables showing significance values less than 0.05. All statistical studies were carried out using the SPSS program (version 15.0; SPSS Inc. Chicago, Illinois, USA).

RESULTS

The clinical and demographic data of the study population is shown in (Table 1). On the basis of the profile of diurnal changes of BP, 62 subjects were classified as non-dipper hypertensive, 54 subjects were classified as dipper hypertensive. Age was found to be significantly higher in non-dipper hypertensive group. There were no significant differences in gender, smoking habit, hyperlipidemia, diabetes mellitus, hemoglobin level, ischemic heart disease, and cerebrovascular disease between dippers and non-dippers. Left ventricular ejection fraction was normal in both groups. Patients had been treated with the following antihypertensive agents: β-blocker, diuretic, calcium channel blocker, angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. There were no difference in medication use between two groups.

Table 1. Clinical Characteristics of the patients.

	Non-dippers (n=62) n (%)	Dippers(n=54) n (%)	P value
Age (Years)	59.7±12.6	54.7±13.6	0.04 [†]
Male	29 (46.8%)	26 (48.1%)	0.88*
Female	33 (53.2%)	28 (51.9%)	
Current smoker	17 (27.4%)	16 (29.6%)	0.79*
EF	59.5±4.8	60.2±6.3	0.49
HL	13 (21%)	6 (11.1%)	0.15*
DM	12 (19.4%)	14 (25.9%)	0.40*
Stroke	1 (1.6%)	0 (0)	0.35*
CAD	4 (6.5%)	2 (3.7%)	0.50*
Medical treatment			
Beta blocker	21 (34.4%)	15 (27.8%)	0.44*
Ca-channel blocker	9 (14.5%)	12 (22.2%)	0.28*
ARB	12 (19.4%)	17 (31.5%)	0.13*
ACE-I	32 (51.6%)	19 (35.2%)	0.07*
Diuretic	9 (14.5%)	11 (20.4%)	0.40*

EF: Ejection fraction, HL: Hyperlipidemia, DM: Diabetes mellitus, CAD: Coronary artery disease, ARB: Angiotensin receptor blocker, ACE-I: ACE inhibitor.

There were no difference in SBP and DBP between the dippers and the non-dippers during the day. However, SBP and DBP were significantly higher among the non-dippers at night (Table 2). The percentage decline of systolic and diastolic BP from day to night in dipper and nond-dipper patients were 15.18%, 15.13% and 3.71%, 4.17%, respectively. Table 3 summarizes biochemical variables in dippers

and non-dippers. RDW values in non-dippers were statistically higher compared to those in dippers. RDW was negatively correlated with the percentage decline of systolic and diastolic BP from day to night ($r = -0.2$, $p < 0.025$ and $r = -0.3$, $p < 0.003$, respectively). ROC curve analysis showed that RDW had a sensitivity of 61.3% and specificity of 57.4% for non-dipper hypertensive patients when the cut-off value of RDW was 13.85% ($p < 0.003$) (Figure 1). MPV and NLR were also significantly higher in non-dipper hypertensive group. There was significant negative correlation between MPV and percentage decline of systolic and diastolic BP from day to night ($r = -0.2$, $p < 0.025$ and $r = -0.2$ and $p < 0.03$ respectively). NLR was negatively correlated with the percentage decline of systolic and diastolic BP from day to night ($r = -0.21$, $p < 0.02$ and $r = -0.12$ and $p > 0.04$ respectively).

Table 2. Systolic and diastolic BP of the patients during day and night.

	Non-dippers mean \pm SD	Dippers mean \pm SD	P value
Day systolic BP (mmHg)	130.1 \pm 10.8	131.8 \pm 13.5	0.46
Day diastolic BP (mmHg)	83.3 \pm 9.4	85.5 \pm 9.3	0.20
Night systolic BP (mmHg)	127.7 \pm 12.7	116.6 \pm 11.4	0.0001
Night diastolic BP (mmHg)	78.6 \pm 9.01	72.4 \pm 8.5	0.0001

$p < 0.05$ was significant; Student's *t*-test, BP: Blood pressure.

Table 3. Biochemical variables of the patients.

	Non-dippers	Dippers	p
Hemoglobin (g/L)	13.5 \pm 1.9	14.0 \pm 1.6	0.10
RDW (%)	14.46 \pm 1.29	13.79 \pm 1.19	0.005
MPV (fL)	9.49 \pm 1.08	8.93 \pm 0.97	0.005
Neutrophil (10e3/ μ L)	4.88 \pm 1.35	4.27 \pm 1.25	0.01
Lymphocyte(10e3/ μ L)	1.92 \pm 0.51	2.11 \pm 0.59	0.06
NLR	2.70 \pm 1.07	2.12 \pm 0.67	0.001

$p < 0.05$ was significant, : Student's *t*-test

RDW: Red blood cell distribution width, MPV: Mean platelet volume, NLR: Neutrophil/lymphocyte ratio.

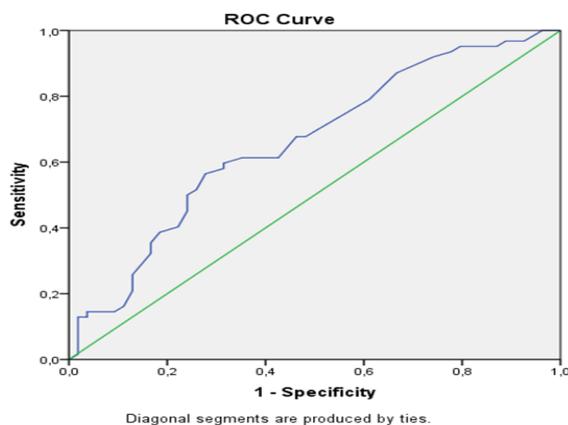


Figure 1. Identification of a cut off value for red cell distribution width in non-dipper hypertensive patients by a receiver operating characteristic curve analysis.

DISCUSSION

Hypertension, especially non-dipper hypertension is a risk factor for adverse cardiovascular events. Lack of nocturnal BP fall (nondipping) is more closely associated with target organ damage and worsened cardiovascular outcomes (7,8). In a meta analysis including data of 3468 patients from four prospective studies, the dipping pattern and the night-day BP ratio significantly and independently predicted mortality and cardiovascular disease (9). The present study carried out in a treated dipper and non-dipper essential hypertensive patients showed that inflammatory activity and platelet activation were higher in non-dipper hypertensives. There was strong and independent association of RDW level with risk of all-cause and cardiovascular (CV) mortality in patients with cardiovascular disease (CVD) (10) and in the general population (11). High RDW indicate the presence of anisocytosis which is related to impairment of erythropoiesis and degradation of erythrocytes, reflecting chronic inflammation and increased level of oxidative stress (12). However the underlying biological mechanism remains unclear. RDW is recognized as a global marker of chronic inflammation and oxidative stress (13). The relation of RDW to hypertension has been investigated in several studies. Tanindi et al reported that RDW is higher in prehypertensive and hypertensive patients compared with healthy controls. They found a positive correlation between RDW and both systolic and diastolic blood pressures (14). Gunebakmaz et al reported not only higher RDW levels in hypertensive patients compared to controls but also elevated RDW levels in the non-dippers compared to dippers (15). Another study showed that RDW is significantly increased in patients with non-dipper hypertension compared with the dipper Hypertension and inflammatory activity was closely related to RDW in non-dipper hypertensives (16). We showed that the sensitivity and specificity of RDW with a cut-off value of 13.85 for nondipper hypertensive patients was 61.3 % and 57.4 %, respectively.

Platelets are known to have a major effect on the formation of atherosclerotic plaques and therefore play an essential role in the pathogenesis of atherothrombosis. Mean platelet volume (MPV), a determinant of platelet function, is a newly emerging risk factor for atherothrombosis. Several studies indicate that high MPV levels and high platelet reactivity are associated with overall vascular mortality, including myocardial infarction (17-21). MPV has been reported to increase in HT. MPV was found to be higher in patients with hypertension (22). MPV, has a positive correlation with blood pressure and is elevated in non-dippers compared with dipper hypertensives (23). Non-dipper hypertensives have increased platelet activation (6,24).

NLR, is a cost-effective, easily applicable, and reproducible inflammatory marker used in our clinical practice. The relationship between neutrophil count, cardiovascular risk and development of HT is known (25,26). We have found that non-dipper hypertensive patients have significantly higher NLR values compared to dipper hypertensives. This result indicates that non-dipper hypertensive patients tend to have increased inflammatory status. Non-dipper hypertensive patients have reduced availability of endothelium-dependent vasodilation, mediated by a decrease in nitric oxide release (5). Inflammation modifies endothelial function and an inability of the endothelium to produce nitric oxide and prostacyclin can result in the depletion of vasodilator, antithrombotic and anti-atherogenic properties of the vascular endothelium. In addition, stimulated leukocytes alter rheological properties with an increased capacity to adhere to vascular endothelium and may result in capillary leukocytosis and subsequent increased vascular resistance (27). All these changes determine a worse long-term prognosis of those hypertensives with absence of nocturnal dip in BP.

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