Effect of nebivolol on endothelial dysfunction in patients with Behçet's disease; a prospective single-arm controlled study

Behçet hastalığında nebivololün endotel disfonksiyonuna etkisi; prospektif, tek grup kontrollü çalışma

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Abstract

Objective: Behçet's disease (BD) is a systemic vasculitis, capable of involving all types of vessels. Endothelial dysfunction (ED) has been previously documented in BD. Previous studies showed that nebivolol might improve endothelial functions in endothelial dysfunction. The aim of our study is to assess the effects of nebivolol on endothelial dysfunction in patients with Behçet's disease.

Methods: This study was designed as prospective single-arm controlled study. We prospectively studied 35 Behçet's patients who were diagnosed according to the International Study Group criteria. Patients received 5 mg nebivolol per day for 3 months. Endothelial dysfunction was evaluated by brachial artery flow-mediated dilatation (FMD) method using high-resolution vascular ultrasound device at baseline and after for 3-month therapy. The paired samples t test, Wilcoxon test, Pearson, Spearman correlation analyses were used for statistical analysis.

Results: A significant improvement was observed in FMD after therapy period (4.23±1.19 vs 7.95±2.21%, p<0.001). The correlation analysis showed a negative correlation between post-treatment high-sensitive C-reactive protein and FMD (r=-0.435, p=0.009). No adverse effects were observed in treatment period.

Conclusion: Nebivolol improved endothelial dysfunction in Behçet's patients. However, further comprehensive studies are needed to determine the long-term effects of nebivolol. *(Anadolu Kardiyol Derg 2013; 13: 115-20)*

Key words: Behçet's disease, endothelial dysfunction, nebivolol

ÖZET

Amaç: Behçet Hastalığı (BH) tüm damarları tutabilen sistemik bir vaskülittir. BH'da endotel disfonksiyonu geliştiği gösterilmiştir. Daha önce yapılan çalışmalarda nebivololün endotel disfonksiyonunda endotel fonksiyonlarını iyileştirdiği gösterilmiştir. Çalışmamızın amacı BH'da nebivololün endotel disfonksiyonu üzerine etkisini araştırmaktır.

Yöntemler: Bu araştırma prospektif, tek grup kontrollü çalışma olarak tasarlandı. Çalışmaya Uluslararası Çalışma Grubu kriterlerine uyan 35 BH alındı. Hastalara 3 ay süreyle 5 mg/gün nebivolol verildi. Endotel disfonksiyonu, çalışmanın başlangıcında ve 3 ay tedavi sonrası yüksek çözünürlüklü vasküler ultrason cihazı kullanılarak brakiyal arter akım aracılı dilatasyon metodu ile değerlendirildi. Paired samples t test, Wilcoxon test, Pearson, Spearmann korelasyon analizleri istatistiksel değerlendirme için kullanıldı.

Bulgular: Tedavi sonrasında akım aracılı dilatasyonda belirgin iyileşme izlendi (4.23±1.19 vs 7.95±2.21%, p<0.001). Korelasyon analizinde, tedavi sonrası yüksek-duyarlıklı C-reaktif protein ile akım aracılı dilatasyon değerleri arasında negatif korelasyon izlendi (r=-0.435, p=0.009). Tedavi süresinde herhangi bir yan etki izlenmedi.

Sonuç: Nebivolol Behçet hastalarında endotel disfonksiyonunu iyileştirdi. Ancak nebivololün uzun dönem etkilerini saptayabilmek için daha kapsamlı çalışmalara ihtiyaç vardır. *(Anadolu Kardiyol Derg 2013; 13: 115-20)*

Anahtar kelimeler: Behçet hastalığı, endotel disfonksiyonu, nebivolol

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Introduction

Behçet's disease (BD), a multisystem inflammatory disease characterized mainly by recurrent attacks of oral aphthous ulcers, genital ulcers, uveitis, skin lesions and arthritis, is recognized as an unclassified vasculitis with a tendency towards thrombotic events (1). Vascular involvement affects both veins and arteries of all sizes in up to 40% of the patients, and it is more frequent and has a more severe course in young males (2). Venous side has been affected predominantly in BD, most commonly as superficial thrombophlebitis and deep-vein thrombosis of the lower extremities. Arterial involvement is seen less frequently and causes true and/or false aneurysms as well as rare thrombotic occlusions (3).

The exact etiopathogenesis of BD remains to be elucidated. Like most of the vasculitic pathologies, the endothelial damage and dysfunction are apparently associated with the etiopathogenesis of BD. Due to vasculitis and inflammatory response, impairment of endothelial function occurs or is accompanied by endothelial damage. In the active stage of the disease, a high systemic inflammatory activity is observed in the circulation or the vascular tissue (4-6).

It was demonstrated that endothelial dysfunction documented by brachial artery flow-mediated dilatation (FMD) is a feature of BD (3). Recently, Güllü et al. (7) confirmed the coronary microvascular dysfunction by coronary flow reserve method in BD without a previous vascular involvement. Histopathologic sectional preparations have demonstrated panvasculitic invasion by activated leucocytes that produce free-oxygen radicals that affect whole body endothelium (8, 9). Chambers et al. (10) formerly reported the relation between oxidative stress and vascular injury in patients with BD. Supporting this document, serum nitric oxide (NO) concentrations as an indicator of endothelial function has been found to be decreased (11). Plasma levels of prostacyclin have been reported to be reduced in BD, and it has been suggested that this contributes to endothelial dysfunction in this disease (12).

Nebivolol is a selective beta-adrenergic blocker with vasodilatory property. This vasodilatory action depends on its potentiating effect on the bioactivity and levels of nitric oxide (13, 14). An apparent effect of conventional beta-blockers on endothelial dysfunction has not been demonstrated (15). There is no study in the literature that investigated how nebivolol affects endothelial dysfunction in patients diagnosed with BD.

In the present study, we analyzed the effect of nebivolol on endothelium dysfunction in patients with BD.

Methods

Study design

This study was designed as a prospective single-arm controlled (patients are served as self -controls) study.

Study population

A total of 35 consecutive patients who were examined at the dermatology polyclinic of Erciyes University Faculty of Medicine between January 2008 and August 2008 and fulfilled the International Study Group's criteria for BD, were recruited prospectively (16). The inclusion criteria were ultrasonographically documented endothelial dysfunction and a stable condition. Each subject was screened by a complete history, physical examination, ultrasonographic investigation, and laboratory analysis. Exclusion criteria were as follows: (1) impaired cardiopulmonary function, defined as the occurrence of respiratory failure, pulmonary infection or congestive heart failure; (2) coronary artery disease, defined as having a typical angina pectoris, history of a prior myocardial infarction, presence of a positive stress test or positive coronary angiographic findings; (3) valvular disease, atrial fibrillation, atrioventricular block or congenital heart disease; (4) hypertension, diabetes, dyslipidemia (LDL cholesterol >160 mg/dL, total cholesterol >240 mg/dL, triglyceride >200 mg/dL), using antihypertensive, antidiabetic and lipid-lowering treatments; (5) chronic alcoholism and smoking; (6) malignancy, hyperthyroidism and hypothyroidism; (7) use of any vasoactive drug; (8) renal and liver insufficiency; (9) vitamin B12 or folic acid deficiency; and (10) active phase of Behçet's disease clinically.

Study protocol

Patients were given 5 mg/day nebivolol. Pre-treatment endothelial functions were evaluated and tests for endothelial function were repeated after three months of therapy with discontinuation of nebivolol 12 hours before the tests. The patients were observed for any adverse effects. Written informed consent was obtained from each subject, and institutional ethic committee approved the study protocol.

Endothelial function testing

To investigate the effect of the nebivolol on endothelium dysfunction, brachial artery endothelium-dependent FMD and the nitrate-mediated endothelium-independent dilatation (NMD) were examined at baseline and at 3 months after administration of the drug. Images were recorded on hard disk drive of echocardiography machine. Two qualified echocardiographers examined the recordings. Standard flow-mediated, endothelium-dependent vasodilatation was assessed as follows. All subjects were studied at rest in a supine position. All measurements were performed in a quiet and temperature controlled room (25°C). Patients fasted for at least 12 hours before measurements. A high-resolution ultrasound system (GE Vingmed Ultrasound, Vivid 7 Dimension, Horten, Norway) was used. The diameter of the brachial artery was measured from two-dimensional ultrasound images using a 7.5-MHz linear array transducer. Subjects had to rest for at least 10 minutes before the first scan was recorded. A pneumatic cuff was positioned just below the elbow. The brachial artery was scanned in longitudinal sec-

tions 2-10 cm above the elbow. Diameter measurements were performed according to the guidelines for measuring FMD (17). After measurement of baseline diameter and baseline flow, a pneumatic cuff was inflated on the forearm at least 50 mm Hg above systolic pressure for 5 minutes. Post-ischemic flow measurements were performed 15 seconds after cuff deflation; diameter measurements were performed 45-60 seconds after cuff deflation. After an additional 10 minutes (to allow vessel recovery), NMD was assessed 5 minutes after sublingual administration of 5 mg isosorbide dinitrate. Vessel diameters were analyzed with the use of electronic calipers on frozen images over a length of the artery of 1 cm. Three measurements were taken at each scan for three cardiac cycles at the end of the diastole (incident with the R wave on the ECG), and the mean was then calculated. Endothelium-dependent and independent dilations were expressed as the percentage change in the brachial artery diameter from baseline to following reactive hyperemia and to following sublingual nitrate administration. FMD was calculated as: (reactive hyperemia diameter-baseline diameter)/baseline diameters × 100%.

The intraobserver coefficient of variation (CV) for FMD measurements was 4.2%. A median FMD value of 7% was used as the cutoff value, and endothelial dysfunction was defined as FMD <7% (18).

Laboratory methods

Blood samples were taken for renal and liver function tests', high-sensitive C-reactive protein (hs-CRP) (Dade-Behring, Deerfield, IL, USA) and erythrocyte sedimentation rate (ESR) after an 12 hours overnight fasting.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA). Deviation from normality was evaluated by Kolmogorov-Smirnov test. Data were expressed as the mean value±SD. To assess the effects of nebivolol, we used paired samples t test for the continuous variables with normal distribution, while the Wilcoxon test was employed for the continuous variables outside the normal distribution. Pearson or Spearman correlation analysis were used to analyze the correlation. All probability values were two-tailed, and a value <0.05 was considered statistically significant.

Results

Demographic and clinical results

Twenty (57%) of the enrolled patients were female and 15 (43%) were male. Mean age was 38±10.8. The mean disease duration of BD was 8.3±5.7 years. Body mass index was 26.8±4.9 kg/m^2. Pre-treatment values of patients were as follows: left ventricular ejection fraction (LVEF) 63±3.8%, heart rate (HR) 78.4±9.6 beats/min, systolic blood pressure (SBP) 123.4±11.9 mmHg and diastolic blood pressure (DBP) 79.8±9.5 mmHg. After three months of therapy LVEF was found to be 63.4±3.7%, HR 71.4±8.7 beats/min, SBP 121.2±11.0 mmHg and DBP 75.5±9.9 mmHg. Before medical treatment, mean hs-CRP level of patients was 6.02±6.10 mg/L (median: 3.84 mg/L, minimum: 3.02 mg/L, maximum: 34.70 mg/L). Following three months of treatment with nebivolol, mean hs-CRP level was 5.48±4.73 mg/L (median: 3.24 mg/L, minimum: 3.02 mg/L, maximum: 23.60 mg/L). Reduction in post-treatment hs-CRP level was not statistically significant compared to pre-treatment level (p>0.05). Mean sedimentation rate of patients before nebivolol treatment was 21.08±13.04 mm/hr. Repeated measurements of sedimentation after treatment revealed a mean value of 18.14±10.07 mm/hr. Change in the mean sedimentation rates following nebivolol treatment was not statistically significant (p>0.05).

Effects of nebivolol on brachial artery lumen diameters, FMD and NMD

Pre-treatment values of brachial artery basal lumen diameter, brachial artery lumen diameter after nitrate administration and post-flow brachial artery lumen diameter measured before nebivolol treatment have increased at the end of three months of therapy and this increase was found to be statistically significant (Table 1).

Estimated FMD percentages of patients revealed an increase in FMDs after nebivolol treatment compared to pre-treatment and this increase was statistically significant (p<0.001) (Table 1) (Fig.1). Similarly, post-treatment NMD value was found to be higher than NMD value measured before nebivolol treatment and the difference was statistically significant (p<0.001) (Table 1) (Fig. 2).

The correlation analysis showed a negative correlation between post-treatment hs-CRP and FMD and NMD levels (r=-0.435, p=0.009 and r=-0.493, p=0.003 respectively) (Fig. 3).

Discussion

This study aimed to assess the effects of nebivolol on endothelial dysfunction in patients with BD. A significant improve-

Table 1. Brachial artery lumen diameters, FMD (flow-mediated dilatation) and NMD (nitrate-mediated endothelium-independent dilatation) values before and after nebivolol treatment

Variables	Before treatment	After treatment	*p
Brachial artery basal lumen diameter, mm	3.10±0.61	3.16 ± 0.52	<0.05
Post-flow brachial artery lumen diameter, mm	3.23±0.65	3.41±0.54	<0.001
Brachial artery lumen diameter after nitrate administration, mm	3.30±0.65	3.48±0.57	<0.001
FMD, %	4.23±1.19	7.95±2.21	<0.001
NMD, %	6.52±1.69	10.16±2.31	<0.001

Data are presented as mean±SD
*Paired samples t test
FMD - flow-mediated dilatation, NMD - nitrate-mediated endothelium-independent dilatation

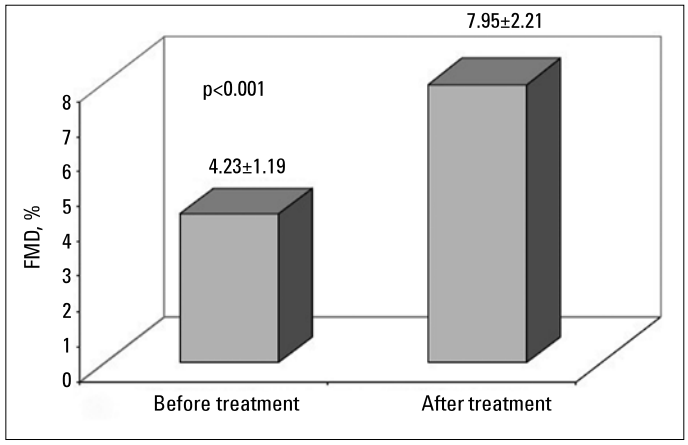

Figure 1. FMD (flow-mediated dilatation) values before and after nebivolol treatment

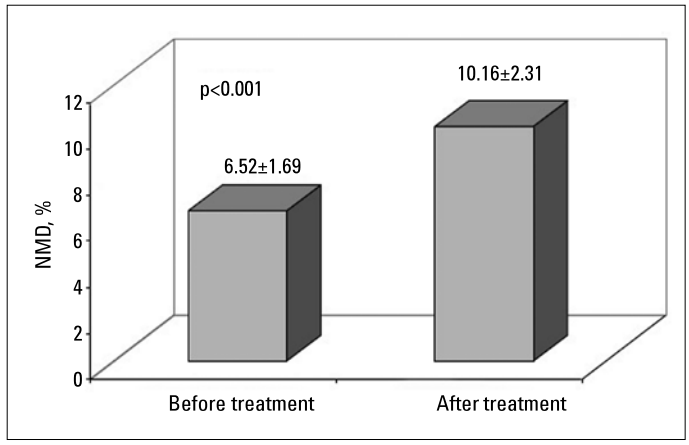

Figure 2. NMD (nitrate-mediated endothelium-independent dilatation) values before and after nebivolol treatment

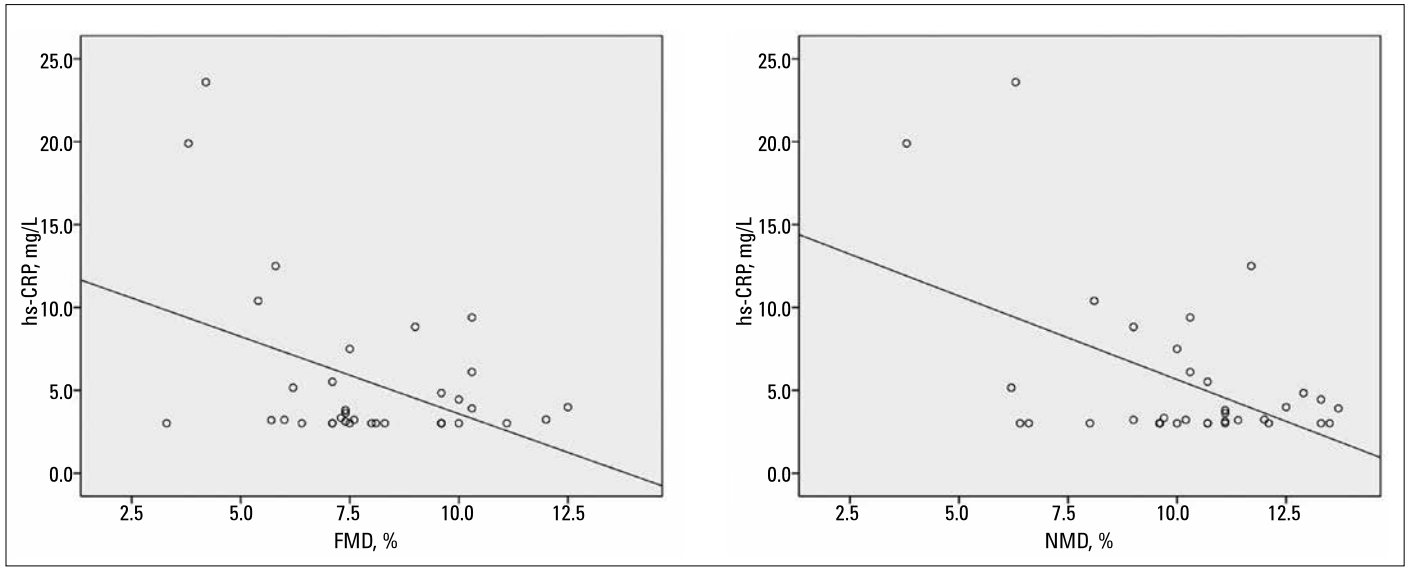

Figure 3. Correlation between high-sensitive C-reactive protein and flow-mediated dilatation, nitrate-mediated endothelium-independent dilatation

ment was observed in FMD and NMD after therapy period. Our study showed that nebivolol improved endothelial dysfunction in Behçet's patients.

Endothelial dysfunction is an indicator for vascular involvement in any disease affecting the vascular structure. Although the triggering factor is still unclear, endothelial dysfunction is one of the suspected underlying mechanisms in BD. In present study, we hypothesized that nebivolol therapy may improve endothelial dysfunction in patients with BD. The specific effect of nebivolol on endothelium-dependent vasodilatation has not been previously studied in patients with BD. In our study, the effect of nebivolol on endothelial functions was assessed in patients with BD showing endothelial dysfunction by using FMD. We have observed significant improvement in FMD with nebivolol therapy for 3-month period. These results may be a guide to therapeutic approach for patients with BD.

Numerous observations suggest that nebivolol therapy could be a useful treatment for endothelial dysfunction, and it could also improve endothelial dysfunction (13, 19-23). Previous studies have investigated the effect of beta-blockers on the endothelial functions and showed that only carvedilol and nebivolol had an improving effect on the endothelial functions (24-31). Although some studies have investigated the effect of beta-blockers on the endothelial function, there is not any study that explored the specific effect of beta-blockers on the endothelium-dependent vasodilatation in patients with BD. One of the main findings of the present study is that short-term treatment with nebivolol improves impaired endothelial vasodilator function. Several case-control studies have observed an association between vascular involvement and decreased brachial FMD and increased arterial stiffness in patients with BD (10, 32-34). Reduced NO production is the one of the possible mechanisms for endothelial dysfunction in BD (11), and the decreased NO production may play a critical role in the impairment of FMD. Because FMD is endothelium-dependent and mediated largely by the release of endothelial NO (35), most possible mechanism for present results is increased NO effect via increasing NO availability or by enhancing NO releasing.

Nebivolol is an antihypertensive agent with a dual mechanism of action showing both a vasodilatory effect through modulation of NO release and an antagonistic effect on β1-adrenoreceptors (13). In our study, a statistically significant increase was found in FMD and NMD following treatment with nebivolol compared to pretreatment. As a result, we can suggest that nebivolol reorganizes degenerated endothelium by increasing NO levels in patients with BD. A statistically significant increase was achieved in the brachial artery basal lumen diameter, brachial artery lumen diameter after nitrate administration and post-flow brachial artery lumen diameter measured after nebivolol treatment compared to pretreatment. This increase in lumen diameter was thought to result from the vasodilatory action of nebivolol.

When endothelium-independent NMD values were analyzed; a significant increase was seen following 3-month nebivolol treatment compared to pretreatment values. Previous studies showed that ACE inhibitors may improve NMD in BD (36). Improvement in NMD may due to decreasing oxidative stress, increase nitrite oxide level, and neurohumoral changes. Further studies are needed to clearly explain underlying mechanism.

C-reactive protein (CRP) decreases NO release by showing effects on the enzyme nitric oxide synthesis. Studies have demonstrated that CRP leads to endothelial dysfunction and hs-CRP is one of the strong independent predictors for cardiovascular events (37, 38). Increased hs-CRP levels have been shown in BD (34). In their study, Çalışkan et al. (39) showed that there was an association between hs-CRP and FMD levels in patients with BD, that hs-CRP levels increased during the active phase of the disease and endothelial functions correlatively deteriorated, as evaluated by FMD. Hamit et al. (36) have seen a significant decrease in hs-CRP levels in their study following 3 months of lisinopril therapy; however, they did not describe with what mechanism lisinopril has reduced hs-CRP and thought that other therapies that patients have received during the active phase probably have produced the reduction in hs-CRP levels. In that study, the correlation between FMD and hs-CRP was not assessed. Additionally, no information was available regarding whether the patients were in the active phase or inactive phase. In our study, a decrease in hs-CRP values was observed with nebivolol therapy but the hs-CRP reduction did not reach a statistically significant level. The correlation analysis showed an association between hs-CRP values and FMD, NMD. The lack of a statistically significant reduction in hs-CRP values was thought to have resulted from the low number of study patients and the enrollment of patients during the clinically inactive phase by their Behçet's Disease Activity Index. In addition, it was considered that, with increased number of patients and enrollment of patients during the active phase of the disease would produce a statistically significant decrease in the hs-CRP values.

Study limitations

Our study has some limitations. One of the major limitations is that this is a single arm study without placebo group. A limitation is the small sample size. Another limitation is that in our study, levels of NO and asymmetrical dimethylarginine (an endogenous inhibitor of nitric oxide synthase) have not been measured in patients before and after treatment.

Conclusion

Endothelial dysfunction is an important and frequent feature of BD. We demonstrated that endothelial dysfunction can be improved by nebivolol treatment in patients with BD. Prospective long-term trials assessing the effects of nebivolol treatment of cardiovascular mortality will reveal whether such protective effects may translate into the clinic and improve the prognosis of BD patients.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

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