Comparison of antihypertensive efficacy of carvedilol and nebivolol in mild-to-moderate primary hypertension: a randomized trial

Hafif-orta birincil hipertansiyonda karvedilol ve nebivolol'ün antihipertansif etkinliğinin karşılaştırılması: Bir randomize çalışma

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ABSTRACT

Objective: The aim of the present study is to compare the antihypertensive effects of carvedilol and nebivolol in mild to moderate hypertensive patients.
Methods: It is a prospective; placebo-controlled, cross-over, double-blind, randomized, single-center clinical trial. Patients (n=20) who were first diagnosed with mild to moderate systemic hypertension according to mean ambulatory blood pressure measurements > 130/85 mmHg and no previous antihypertensive therapy were prospectively enrolled into the study. After 10 days of placebo run-in period, they were randomized within the same group as cross-over design to one month carvedilol 25 mg and one month nebivolol 5 mg regimen given once daily in the morning. The primary outcome variables were systolic and diastolic blood pressures determined by 24-hour ambulatory blood pressure measurements. Mutlivariate analysis of variance for repeated measurements with 3x2 factorial design was used for statistical analysis of results.
Results: The study group consisted of 6 women and 14 men whose mean age was 42.9±12.8 years (range 19-63 years). Mean heart rate was significantly decreased after commencing both carvedilol (70.2±5.2 bpm) and nebivolol (64.9±3.9 bpm) treatments compared to placebo (78.8±5.2 bpm) ($p<0.05$). Both carvedilol (133.8±9/86.6±8.6 mmHg) and nebivolol (134±8.7/85.6±7.4 mmHg) significantly decreased mean systolic and diastolic blood pressures compared to placebo (143.9±8.9/94.4±9.2 mmHg), respectively ($p<0.05$). However, there was no significant difference in decreasing either systolic or diastolic blood pressure between nebivolol and carvedilol therapies ($p>0.05$). No side effects were recorded during both carvedilol and nebivolol treatments.
Conclusion: Although both carvedilol and nebivolol effectively decreased blood pressure compared to placebo, they showed similar efficacy for lowering blood pressure. *(Anadolu Kardiyol Derg 2011; 11: 310-3)*
Key words: Hypertension, nebivolol, carvedilol, beta-blocker

ÖZET

Amaç: Karvedilol ve nebivolol'ün hafif-orta hipertansif hastalarda etkinliğini karşılaştırmaktır.
Yöntemler: Plasebo kontrollü, prospektif, çapraz-geçişli ve çift-kör randomize olarak tek merkezde gerçekleştirilen çalışmada, ilk kez hipertansiyon tanısı almış 20 hipertansif hasta 24 saatlik ambulatuvar kan basıncı yöntemiyle takip edilmişlerdir. On günlük plasebo sonrası hastalar 5 mg nebivolol ve 25 mg karvedilol tedavilerine randomize edildiler. Primer sonlanım değişkenleri 24-saat ambulatuvar kan basıncı ile ölçülen sistolik ve diyastolik kan basınçları idi. Bulguların istatistiksel analizinde 3x2 faktoriyel dizaynlı tekrarlayan ölçümler için çoklu varyans analizi kullanıldı.
Bulgular: Yaşları 43±13 olan 6 kadın, toplam 20 hasta çalışmaya alındı. Ortalama sistolik ve diyastolik kan basınçları karvedilol (133.8±9/86.6±8.6 mmHg), nebivolol (134±8.7/85.6±7.4 mmHg) tedavilerinde plaseboya göre anlamlı azaldı (143.9±8.9/94.4±9.2 mmHg, $p<0.05$). Ancak, her iki ilaç kan basıncını azaltmada birbirine üstünlük sağlayamadı ($p>0.05$). Hem karvedilol, hem nebivolol tedavileri sırasında hiçbir yan etki gözlemlenmedi.
Sonuç: Plaseboya göre anlamlı düzeyde kan basıncını azaltmalarına karşın karvedilol ve nebivolol'ün birbirine üstünlüğü saptanamadı.
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Anahtar kelimeler: Hipertansiyon, karvedilol, nebivolol, beta bloker

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Introduction

Carvedilol is a third-generation, vasodilating non-cardioselective beta-blocker (BB) which lacks intrinsic sympathomimetic activity. It has blocking effects at vascular α1-receptors, antioxidant, and calcium antagonist properties (1). In contrast, nebivolol is a new beta-1-selective adrenergic receptor antagonist with nitric oxide (NO)-mediated vasodilatory properties. A novel aspect of the pharmacology of nebivolol is its ability to augment endothelium-dependent vasodilation through the L-arginine/NO pathway (2). Nebivolol has been shown to cause endothelium-dependent vasodilation in both normotensive and hypertensive subjects (3, 4). Several head-to-head studies have convincingly shown that non-selective agents, such as atenolol, have a negative effect on myocardial contractility, vascular resistance and carbohydrate and lipid metabolism (5, 6), while newer agents with vasodilating properties, such as carvedilol and nebivolol, have a hemodynamic and metabolic profile that is much better than that of older compounds (7, 8). However, antihypertensive effect of carvedilol and nebivolol compared to each other has not been tested before and therefore it is yet unknown, which one of them is more effective than the other in terms of lowering blood pressure.

Hence, we aimed to conduct a placebo controlled clinical study to compare the antihypertensive effects of both carvedilol and nebivolol in mild to moderate hypertensive patients.

Methods

Patients

Patients who were first diagnosed with mild to moderate systemic hypertension and no previous antihypertensive therapy were prospectively evaluated at the outpatient clinic. Patients underwent physical examination, laboratory tests, electrocardiography, chest X-ray, transthoracic echocardiography and ophthalmological examination. Patients who had one of the following conditions such as target organ damage (left ventricular hypertrophy, retinopathy, renal dysfunction, cerebrovascular events) secondary hypertension, diabetes mellitus, coronary artery disease, heart failure, electrolyte disturbance, systemic disease, previous antihypertensive or any other drug use, liver failure, pregnancy were excluded. Eligible patients who were recommended to apply life style modification received 10 days placebo run-in after which they underwent 24 hour ambulatory blood pressure monitoring. All patients having mean systolic blood pressure >130 mmHg and/or mean diastolic BP >85 mmHg after placebo were prospectively included into the study. Study patients who fulfilled inclusion criteria were 14 men and 6 women.

All patients gave written informed consent to participate in the study. The study protocol was approved by the local Institutional Ethics Committee.

Study design and protocol

The present study is a prospective; placebo-controlled, cross-over, double-blind, randomized, single-center clinical trial. Study patients (n=20) were randomized within the same group using cross-over method to one month treatment with each of carvedilol 25 mg and nebivolol 5 mg given once daily in the morning. Hence, each group comprised same patients (n=20) at different drug dose and regimen. At the end of that month 24-hour ambulatory blood pressure monitoring was performed and the study drug was stopped. Without giving a washout period the other study drug was commenced and continued for the next month. At the end of the next month 24-hour ambulatory blood pressure monitoring was repeated.

Ambulatory blood pressure measurement

All patients underwent 24-hour ambulatory blood pressure monitorization which was performed by using an oscillometric device (Tonoport 5, GE medical Systems, Germany) and blood pressures were measured every 30 minutes. Nighttime comprised the time interval between 10:00 pm and 06:00 am. The primary outcome variables were daytime and nighttime systolic and diastolic blood pressures.

Statistical analysis

Statistical analysis was performed by using Statistica AXA 7.1 version (StatSoft Inc., USA; Serial number: AXA507C775506FAN3). Data are presented as mean±SD. Homogenous distribution was tested by using Kolmogorov-Smirnov test. Analysis of variance for repeated measurement (MANOVA) 3x2 factorial design test was used for comparison of more than two measurements within the same group. Statistical differences for comparative variables were further defined as F for interaction and p for interaction values. A $p<0.05$ was considered significant.

Results

The study group consisted of 6 women and 14 men whose mean age was 42.9±12.8 years (range 19-63 years). Their mean body mass index was 28±5 kg/m^2 (Table 1).

Pulse pressure, systolic, diastolic blood pressure changes as well as day and night time comparison of both drug regimens compared to placebo are shown in Table 2. Mean heart rate was significantly decreased ($p<0.05$) after commencing both carvedilol and nebivolol compared to placebo.

Both carvedilol and nebivolol significantly decreased ($p<0.05$) mean systolic and diastolic blood pressures compared to placebo. However, there was no significant difference in decreasing ($p>0.05$) either systolic or diastolic blood pressure between nebivolol and carvedilol therapies. Hence, both drugs seemed to be similar or at least not superior to each other in efficacy of lowering blood pressure.

All patients completed the study period and tolerated the study medications without any apparent side effect.

Discussion

Our study demonstrated that although both carvedilol and nebivolol effectively reduced blood pressure compared to placebo, their effects of lowering blood pressure are not significantly different from each other.

Third generation beta-blockers such as carvedilol and nebivolol with their favorable therapeutic profiles constitute a new spectrum in the treatment of hypertension as opposed to old fashioned drugs such as atenolol whose effectiveness has been questioned by recent clinical trials in prevention of stroke. The most common dose of nebivolol used in hypertension is 5 mg/day. Once-daily dosing of nebivolol is sufficient based on the relatively long half-life and high trough-to-peak ratio (84-90%) of the drug (9). A clinical study conducted in patients with mild to moderate hypertension revealed that daily 5 mg nebivolol and 5 mg bisoprolol treatments had similar efficacy in lowering diastolic blood pressure (nebivolol -15.7 +/- 6.4 mm Hg vs. bisoprolol -16.0 +/- 6.8 mm Hg) and a high proportion of responders was noted in both groups (nebivolol 92.0% vs. bisoprolol 89.6%) (10). Another randomized, placebo controlled clinical trial compared nebivolol 5 mg with atenolol 50 mg each given daily in patients with mild to moderate hypertension. Both medications were significantly effective in reducing blood pressure compared to placebo. However, responder rates were equal in each treatment groups (nebivolol 59% vs atenolol 59%) (11). In experiments in vitro and in trials in patients with diabetes and hypertension, carvedilol increased endothelial vasodilation and reduced inflammation and platelet aggregation (12). In the Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial, carvedilol was associated with better maintenance of glycemic control in diabetic hypertensive patients than was metoprolol. Insulin sensitivity improved with carvedilol but not with metoprolol, and fewer patients on carvedilol progressed to microalbuminuria (13). Although both beta-blockers used in the present study have additional vasodilating properties mediated through different pathways, according to our

Table 1. Basal clinical characteristics of study patients

Patient, n	20
Age, years	42.9±12.8
Male, n (%)	14 (70)
Body mass index, kg/m^2	28±5
Systolic blood pressure, mmHg	141±7.5
Diastolic blood pressure, mmHg	92.4±7.7
Pulse pressure, mmHg	46.7±7.7
Heart rate, beats/min	75.0±5.5
Systolic blood pressure, day, mmHg	144±9
Diastolic blood pressure, day, mmHg	95.8±9.0
Systolic blood pressure, night, mmHg	133±9.6
Diastolic blood pressure, night, mmHg	83.9±8.5
Data are presented as mean±SD and number (percentage)	

Table 2. Comparison of mean ambulatory systolic blood pressure, diastolic blood pressure, pulse pressure and heart rate after placebo, carvedilol and nebivolol therapies

Variables	Placebo (P)	Carvedilol (C)	*pP vs C	Placebo (P)	Nebivolol(N)	*pP vs N	*F and p
SBP, mmHg	143.9±8.9	133.8±9.1	<0.05	143.9±8.9	134±8.7	<0.05	F=51.9 p<0.0001
DBP, mmHg	94.4±9.2	86.6±8.6	<0.05	94.4±9.2	85.6±7.4	<0.05	F=33.5 p<0.0001
PP, mmHg	47.4±7.2	45.2±7.9	NS	47.4±7.2	45.2±6.9	>0.05	p>0.05
Day SBP, mmHg	146.3±10.4	136.4±9.6	<0.05	146.3±10.4	137.5±8.0	<0.05	F=29 p<0.0001
Day DBP, mmHg	97.4±10.0	90±10	<0.05	97.4±10.0	89.0±7.2	<0.05	F=21.1 p<0.0001
Day PP, mmHg	48.7±6.0	46.2±7.8	NS	48.7±6.0	48.3±5.0	>0.05	p>0.05
Night SBP, mmHg	139.7±11.0	128±10	<0.05	139.7±11.0	129.7±11.6	<0.05	F=23 p<0.0001
Night DBP, mmHg	88.7±9.0	80±8	<0.05	88.7±9.0	80±9	<0.05	F=33.5 p<0.0001
Night PP, mmHg	51±9	49±9	NS	51±9	51±11	>0.05	p>0.05
HR, bpm	78.8±5.2	70.2±5.2	<0.05	78.8±5.2	65±4	<0.05	F=115 p<0.0001

Data are presented as mean±SD

*MANOVA test

**"F and p values for interaction of carvedilol and nebivolol groups are nonsignificant"

BPM - beats per minute, DBP - diastolic blood pressure, HR - heart rate, PP - pulse pressure, SBP - systolic blood pressure

study results it seems that NO mediated vasodilation is not superior as opposed to peripheral α1-receptor blockage mediated vasodilation in terms of antihypertensive efficacy. However, due to their potential metabolic and side effect profiles new generation BB should still be considered as important alternatives compared to old generation BB in patients with hypertension who definitely need additional beta-blockers in their antihypertensive regimen for any condition such as coronary artery disease.

Study limitations

One limitation of our study may be the considerable small size of study population. However, small number patient groups are generally considered appropriate for cross-over designed and self-controlled studies. We believe that possible carry-over effect was not of considerable size enough in the present study because blood pressure measurement was performed at the end of each treatment period, namely one month later after the previous drug had been discontinued. In addition, washout period for each study drug generally requires 5 times of its elimination half-life.

Conclusion

According to our study results, treatment with carvedilol did not show any superiority compared to nebivolol in terms of antihypertensive efficacy although both drugs were significantly effective in lowering blood pressure compared to placebo.

Conflict of interest: None declared.

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