The role of nebivolol in the prevention of contrast-induced nephropathy in patients with renal dysfunction

Renal disfonksiyonlu hastalarda kontrast nefropatisinin önlenmesinde nebivololün rolü

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ABSTRACT

Objective: This prospective study was designed to evaluate the potential protective effect of nebivolol compared with metoprolol on the development of contrast-induced nephropathy (CIN) following coronary angiography in patients with renal dysfunction.
Methods: Ninety patients with stable coronary angina pectoris with renal insufficiency (creatinine value ≥ 1.2 mg/dl) were included for this prospective study. Patients were divided into two groups. Patients in group 1 (n=55) received oral administration of nebivolol 5 mg/daily for coronary artery disease and/or hypertension. Group 2 consisted of 35 patients who received metoprolol 50 mg/daily for the same indications. All patients were hydrated with 0.9% NaCl at a rate of 1 mL/kg/hr for 12 hours before and 24 hours after the procedure. Patients were also given N-acetylcysteine (NAC) 600 mg twice a day, beginning 24 hours before and continuing 48 hours after the procedure. All patients underwent routine coronary angiography. Serum creatinine was assessed just before, immediately after and 48 hours after the procedure. CIN was defined as an increase in serum creatinine concentration of ≥25% within 48 hours after the procedure compared to the patient's baseline value. Tests for significance between groups were conducted using the independent sample t-test for continuous variables and Chi-square test for categorical variables.
Results: Baseline serum creatinine levels were statistically comparable in two groups. Following angiography, serum creatinine levels increased in both groups. Post-angiographic creatinine levels were not statistically different in the nebivolol and the metoprolol groups. Contrast induced nephropathy developed in 13 patients (24%) of the nebivolol group and in 12 patients (33%) of the metoprolol group. The incidence of CIN was statistically significantly lower in the nebivolol group comparing with the metoprolol group (p=0.03).
Conclusion: The use of oral nebivolol for one week at a dose of 5 mg per day may decrease the incidence of contrast-induced nephropathy in patients who underwent coronary angiography with renal dysfunction. The small numbers of this study do not allow to draw final conclusion on the use of nebivolol in the prevention of CIN. Therefore, larger studies may be necessary to address the definite role of nebivolol in this setting. *(Anadolu Kardiyol Derg 2011; 11: 613-7)*
Key words: Contrast-induced nephropathy, beta-blocker, nebivolol, renal dysfunction

ÖZET

Amaç: Bu prospektif çalışma renal disfonksiyonlu olgularda koroner anjiyografiyi takiben kontrast nefropati gelişimi üzerine nebivolol'ün potansiyel koruyucu etkisini metoprolol ile karşılaştırmak amacı ile gerçekleştirilmiştir.
Yöntemler: Kreatinin seviyeleri 1.2 mg/dl ve üzerinde olan stabil koroner anjina pektoris'li 90 olgu bu prospektif çalışmaya alındı. Hastalar 2 gruba ayrıldı. Birinci gruptaki 55 olgu koroner arter hastalığı ve/veya hipertansiyon endikasyonu ile 5 mg/gün dozda oral nebivolol aldı. İkinci gruptaki 35 olgu ise benzer endikasyonlarla 50 mg/gün dozda metoprolol aldı. Renal koruma amacı ile hastalar %0.9 NaCl ile (1 mL/kg/saat) işlem öncesi 12 saat ve işlem sonrası 24 saat hidrate edildiler. Hastalara ayrıca işlemden 24 saat önce başlamak ve işlem sonrası 48 saat devam etmek üzere 600 mg N-acetylcysteine (NAC) günde 2 doz halinde verildi. Hastalar daha sonra rutin koroner anjiyografiye alındılar. Serum kreatinini işlemden hemen önce, işlemden sonra ve 48. saatte ölçüldü. Kontrast nefropatisi işlemden sonraki 48 saat içerisinde serum kreatinin değerinde bazal ölçüme göre %25 ve daha fazla artış olarak tanımlandı. Çalışma sonunda gruplar arasında sürekli değişkenlerin karşılaştırması için bağımsız örneklem t-testi, kategorik verilerin karşılaştırılmasında ise Ki-kare testi kullanıldı.
Bulgular: Anjiyografi öncesi her iki grupta da serum kreatinin seviyeleri benzerdi. Anjiyografi sonrası serum kreatinin seviyeleri her iki grupta da artış gösterdi. Anjiyografi sonrası kreatinin seviyeleri bakımından nebivolol ve metoprolol grupları arasında istatistik olarak anlamlı bir fark yoktu.

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Kontrast nefropatisi nebivolol grubunda 13 hastada (%24) metoprolol grubunda ise 12 hastada (%33) gelişti. Kontrast nefropatisi gelişme sıklığı metoprolol grubu ile kıyaslandığında nebivolol grubunda istatistik olarak anlamlı derecede daha düşük bulundu (p=0.03).
Sonuç: Renal disfonksiyonlu hastalarda kontrast nefropatisi insidansı anjiyografi işleminden bir hafta önce başlanılan 5 mg/gün dozda oral nebivolol tedavisi ile azaltılabilir. Bu çalışmadaki hasta sayısının azlığı kesin karara varılmasını güçleştirmektedir. Bu konuda daha geniş çalışmaya ihtiyaç vardır. *(Anadolu Kardiyol Derg 2011; 11: 613-7)*
Anahtar kelimeler: Kontrast nefropatisi, beta-bloker, nebivolol, renal disfonksiyon

Introduction

Contrast-induced nephropathy (CIN) is a recognized complication of coronary angiography and is associated with prolonged hospitalization and adverse clinical outcomes (1-3). The proposed pathophysiologic mechanisms of CIN are outer-medullary hypoxia due to decreased renal blood flow secondary to renal artery vasoconstriction, tubular obstruction and direct tubular toxicity (4). Moreover, the decrease production of nitric oxide (NO) and the increase of oxidative stress may play an important role in the pathogenesis of CIN (5, 6).

There is still no universally accepted method for prevention of CIN, except for extracellular volume expansion. CIN is the third leading cause of hospital-acquired acute renal failure (7). In a previous study, nebivolol has improved renal function in patients who underwent angioplasty due to renal artery stenosis (8). An experimental study in rats has also shown preventive effect of nebivolol on contrast-induced nephropathy previously (9). Nebivolol is a β_1-adrenergic receptor antagonist with vasodilator and antioxidant properties (10).

Based on this pilot studies on nebivolol and CIN, we hypothesized that nebivolol may also protect the kidney in human against CIN through its antioxidant and NO-mediated vasodilator actions. By examining the differences among members of the beta- blocker classes, it may be possible to determine whether renal protection is a class effect of beta-blockers or whether this effect is indeed specific to nebivolol and these agents should be evaluated on a case-by-case basis.

We designed this study to compare nebivolol and metoprolol for their effects on creatinine levels and CIN incidence. This prospective study evaluates the potential protective role of the pretreatment with nebivolol, compared to metoprolol, in the prevention of CIN in consecutive patients with renal insufficiency undergoing coronary angiography. Third-generation vasodilator beta-blocker nebivolol was compared with metoprolol in this study, considering the fact that metoprolol is one of the most widely-used member of second generation beta-blocker family.

Methods

Study design and population

Between June 2008 and July 2009, consecutive patients who referred to the 1st cardiology department of our Atatürk Training and Research Hospital for coronary angiography were screened for this prospective cohort study. Ninety patients with stable coronary angina with a creatinine level ≥1.2 mg/dl were included for this study (11). Patients with any contraindication to beta-blocker treatment were excluded. Other exclusion criteria were: hypotension, low ejection fraction (EF≤45), heart failure (NYHA class III and IV), maintenance dialysis, a history of myocardial infarction, allergy to contrast media, pregnancy and recently exposure to any nephrotoxic medication.

Patients were divided into two groups. Patients were appointed non-randomly to Group 1 and 2 with physician discretion. Patients who previously used one of these medications were also given the same molecule. Patients in Group 1 (n=55) received oral nebivolol 5 mg, starting one week before the angiography and continuing at least 48 hours thereafter for coronary artery disease and/or hypertension. Group 2 consisted of 35 patients who received another beta-blocker with the same indications (metoprolol 50 mg, n=35).

The study was approved by the Ethics Committee of our institute, and written informed consent was obtained from all patients.

Study protocol

Patients underwent routine coronary angiography.

Serum creatinine was assessed before, immediately after and, 48-hours after the procedure. A variety of definitions of CIN are described in literature, but the one most commonly used is the acute deterioration in renal function after intravenous radiographic contrast agent exposure with no other identifiable cause (12). For research purposes CIN was defined as an increase in serum creatinine concentration of ≥25% within 48 hours after the procedure compared to the patient's baseline value (13). Glomerular filtration rate was calculated with MDRD formula.

Coronary angiography

All patients underwent the angiographic procedure using same nonionic contrast media Ioxaglate (Hexabrix, Guerbet, France). The volume of contrast agent used during coronary angiograph recorded. Patients' age, body mass index, hematocrit value, and routine biochemistry were assessed before the procedure. All patients were hydrated with 0.9% NaCl at a rate of 1 mL/kg/hr for 12 hours before and 24 hours after the procedure. Patients were also given N-acetylcysteine (NAC) 600 mg twice a day, beginning 24 hours before and continuing 48 hours after the procedure.

Statistical analysis

Data were analyzed using SPSS for Windows, version 13 (SPSS, Inc, Chicago, IL). Continuous data are expressed as mean±SD and also as median (minimum-maximum). Categorical data are expressed as percentage of the total. Test for significance between groups were conducted using the independent sample t-test for continuous variables and Chi-square test for categorical variables.

Results

The baseline characteristics of patients in both groups are shown in Table 1. The two groups were matching in the principal baseline characteristics, with the exception of hypertension prevalence. Hypertension prevalence was significantly higher in Group 1 (100% vs 71% in Group 1 and 2 respectively). The mean volume of contrast agent used during angiography were also similar in both groups (87.5±15.3 ml and 83.4±13.9 ml respectively in Group 1 and 2, p=0.8). There was no significant difference in the mean left ventricular EF between the 2 groups (53.3±4.1% vs 52.9±3.8%, p=0.6). Concomitant medications were found comparable in both groups (Table 2). Mortality or life-threatening arrhythmia did not develop in any patient as an angiographic complication. One patient in the nebivolol group received two units of erythrocyte suspension due to retroperitoneal bleeding and hypotension.

Baseline serum creatinine levels were statistically similar in two groups (Table 3). Following angiography, serum creatinine levels increased in two groups. Post-angiographic creatinine levels were not statistically different in the nebivolol and the metoprolol groups (Table 3).

Contrast induced nephropathy developed in 13 patients (24%) of the nebivolol group and in 12 patients (33%) of the metoprolol group (Fig. 1). The incidence of CIN was statistically significantly lower in the nebivolol group compare with the metoprolol group (p=0.039).

Table 1. Baseline clinical and biochemical characteristics of patients with and without nebivolol pretreatment

Variables	Nebivolol group (n=55)	Metoprolol group (n=35)	p*
Age, years	62 (45-86) 59±10	63 (42-80) 60±13	0.7
Female gender, n (%)	22 (40)	13 (37)	0.8
Hypertension, n (%)	55 (100)	25 (71)	<0.001
Diabetes mellitus, n (%)	35 (63)	18 (51)	0.2
Hyperlipidemia, n (%)	20 (36)	13 (37)	0.9
Hyperuricemia, n (%)	10 (18)	5 (15)	0.4
BMI kg/m^2, n (%)	27 (20-46) 26±4	28 (19-40) 25±3	0.1
GFR, ml/min	44.75±9.17	43.27±10.17	0.8
Smoking, n (%)	37 (67)	25 (71)	0.7

Data are expressed as median (minimum-maximum), mean±SD and number (percentage)
*Chi-square test and independent samples t-test
BMI-body mass index, GFR-glomerular filtration rate, ns-not significant
Definitions: hyperlipidemia- Total cholesterol >240 mg/dl, hyperuricemia- uric acid ≥7mg/dl, smoking: ≥1 pack year cigarette consumption

Table 2. Concomitant treatment regimes in both groups

Medications	Nebivolol group (n=55)	Metoprolol group (n=35)	p*
Clopidogrel, n (%)	3 (6)	2 (6)	0.8
ASA, n (%)	33 (60)	24 (67)	0.7
Statin, n (%)	21 (38)	14 (40)	0.9
ACEI, n (%)	14 (25)	10 (29)	0.6
ARB, n (%)	11 (20)	6 (18)	0.9
Insulin, n (%)	9 (16)	4 (13)	0.8
Metformine, n (%)	3 (6)	2 (6)	0.8

Data are expressed as number (percentages)
*Chi-square test
ACEI - angiotensin converting enzyme inhibitor, ARB - angiotensin receptor blocker, ASA - acetyl salicylic acid, ns-not significant

Discussion

The results of this study show that in patients with renal insufficiency undergoing coronary angiography, the prophylactic administration of nebivolol, compare to metoprolol, may be more effective in prevention of CIN development. CIN is a well-known complication after contrast administration and it is associated with increased hospitalization and mortality (1-3). Pathogenesis of CIN is not well understood. Clinical and experimental data suggest CIN is due to renal ischemia and/or direct renal injury mediated by reactive oxygen species (14). Several injury pathways have been proposed. Radio-contrast agents may induce renal vasoconstriction by creating an imbalance between vasoconstrictive and vasodilatory factors (15). The end-result is ischemic tubular injury and necrosis. Secondly, contrast agents may precipitate in tubular lumen and form obstructive casts (16). Tissue injury may also develop due to oxidative stress. Renal damage may also results from direct contrast-induced cytotoxicity or contrast-induced elevations in tissue osmolality (17). In addition, alterations in the metabolism of prostaglandin, nitric oxide, endothelin and adenosine may also play a role in the pathogenesis.

There are some risk factors for the development of CIN. Pre-existing renal impairment is the most important risk factor. Our study included patients with creatinine level ≥1.2 mg/dl. There were no significant differences between groups in terms of baseline serum creatinine concentration and glomerular filtration rate. Diabetes mellitus, hyperuricemia, metabolic syndrome and treatment with ACE inhibitors seem to have major impact on CIN development (18-21). Diabetes mellitus and hyperuricemia prevalence was not statistically different between both groups. Body mass index and percentage of patients who received ACE

Table 3. Basal and post-procedural creatinine values of patients in both groups

Variables	Nebivolol group (n=55)	Metoprolol group (n=35)	p*
Creatinine before CA, mg/dl	1.6 (1.3-2.2) 1.5±0.1	1.8 (1.3-2.6) 1.6±0.2	0.06
Creatinine after CA, mg/dl	1.8 (1.2-2.8) 1.7±0.3	2.0 (1.4-3.4) 1.9±0.4	0.08

Data are expressed as median (minimum-maximum) and mean±SD
*Independent samples t-test
CA - coronary angiography, NS - not significant

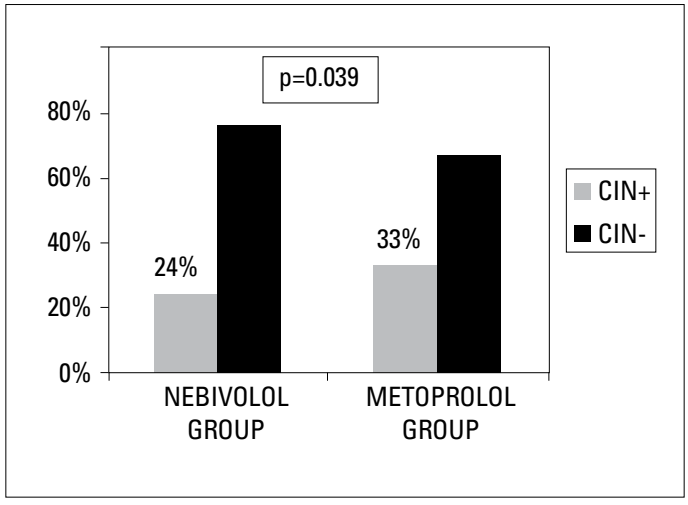

Figure 1. Prevalence of contrast-induced nephropathy (CIN+) in both groups

inhibitors were also comparable in both groups. Clinical studies and meta-analyses have shown that the use of low-osmolar contrast agents reduces the risk of CIN (22). Although iso-osmolar contrast agents have better risk profile for CIN development, their cost limits the use of these agents. Accordingly during this study, in a high-risk patient population with pre-existing renal impairment, low-osmolar contrast agent ioxaglate was used for coronary angiography. Doses of contrast agent and volume of intravenous fluid were also similar in both groups. So that beneficial effect of nebivolol cannot be attributed (or) ascribed to the better hydration or lower contrast agent doses in this group.

Various prophylactic measures including vasodilator therapy, dopamine, theophylline, atrial natriuretic peptide have been tested with controversial results. Hydration remains the standard measure to prevent CIN in patients with increased risk (23).

Nebivolol is a new generation beta-blocker with vasodilator and antioxidant properties. Nebivolol increases renal NO excretion, renal plasma flow, and glomerular filtration rate (24). This molecule also suppresses renin-angiotensin-aldosterone system, and reduces endothelin-1 levels (25, 26). All these beneficial effects of nebivolol are related with the pathogenesis of CIN. These properties of nebivolol may exert a protective effect against CIN through its antioxidant and NO-mediated vasodilator action. In a previous experimental study, pretreatment with nebivolol has attenuated the decrease of creatinine clearance following contrast agent administration in rats (9). The physiopathological mechanism of nebivolol renal protection are: the decrease of medullar congestion, protein casts, and tubular necrosis which occurred secondary to contrast media, the reduction of systemic and renal oxidative stress, the improvement of microproteinuria and protein casts which occurred secondary to contrast media and dehydration, the increase of kidney nitrite level which attenuated secondary to contrast media.

In the current study, we compared renal protective effect of nebivolol with metoprolol in patients undergoing coronary angiography. Patients with coronary artery disease may undergo coronary angiography emergently or electively. In the selection of beta-blocker molecule for coronary artery disease, this possibility should be considered. Choice of nebivolol in this patient population may have an additional beneficial effect by decreasing the risk of CIN development.

In summary, the incidence of CIN may be decreased in patients with impaired renal function with the use of oral nebivolol administration one week before angiography, in addition to low-osmolar nonionic contrast agents and administration of intravenous saline.

Study limitations

In this study nebivolol pretreatment began one week before coronary angiography. Current study evaluated only acute or subacute effects of these beta-blockers on CIN development. Conclusions do not necessarily apply to long-term administration of beta-blockers. Longer use of nebivolol may increase beneficial effect of this molecule on CIN development. This study included only patients with renal dysfunction. So that conclusions also do not necessarily apply to patients with normal renal function. We could not have the opportunity of studying oxidative stress markers and other markers of nitric oxide bioavailability. Therefore current study does not extend our understanding of beneficial pathophysiologic mechanisms of nebivolol pretreatment. Non-randomized study design is a major limitation. The small numbers of this prospective cohort study do not allow drawing final conclusion on the use of nebivolol in the prevention of CIN. Larger prospective randomized studies are necessary to address the definite role of nebivolol in this setting. Lastly, prior to the study, metoprolol group had slightly higher creatinine levels (statistically not significant) than Nebivolol group. This variable was not controlled in the analysis for that reason. This may be a confounding variable and may need to be controlled in the analysis.

Conclusion

In summary, according to the results of this study, incidence of CIN may be decreased in patients with impaired renal func-

tion with the use of oral nebivolol administration starting one week before angiography. The small numbers of this study do not allow to draw final conclusion on the use of nebivolol in the prevention of CIN. Therefore, larger studies may be necessary to address the definite role of nebivolol in this setting.

Conflict of interest: None declared.

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