Renal Protective Effect of Nebivolol vs. Metoprolol in Diabetic Patients Undergoing Coronary Artery Bypass Surgery

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ABSTRACT

Introduction: This study aimed to determine whether pre-treatment with nebivolol provides better protection against postoperative renal injury than metoprolol in patients undergoing coronary artery bypass grafting.

Patients and Methods: Sixty diabetic patients were divided into two groups as those receiving either nebivolol (Group I, n= 30) or metoprolol (Group II, n= 30) treatment. The patients in Group I were initiated on nebivolol 5 mg/day and those in Group II were initiated on metoprolol 50 mg/day. Postoperative renal functions were assessed by serial measurements of serum neutrophil gelatinase associated lipocalin (NGAL) and serum creatinine levels. P< 0.05 was considered as the level of statistical significance.

Results: Demographic, preoperative clinical parameters and operative variables were similar between the two groups. The number of patients with two-hour NGAL positivity was not different between the two groups (7 [26.9%] vs. 7 [25.9%] p= 0.93). Only 1 patient from each group had higher creatinine values than the reference limit at 24 hours; whereas, 72-hour creatinine positivity was observed in 7 patients from each group. All patients achieved improvement with renal replacement therapy and hemodialysis requirement did not occur.

Conclusion: Any difference between the use of metoprolol and nebivolol was not found in terms of better protection against early renal impairment in diabetic patients who underwent coronary artery bypass grafting.

Key Words: Nebivolol; metoprolol; coronary artery bypass surgery; renal injury; NGAL

Koroner Arter Bypass Cerrahisi Uygulanan Diabetik Hastalarda Nebivolol ve Metoprololün Böbrek Koruyucu Etkilerinin Karşılaştırılması

ÖZET

Giriş: Çalışmanın amacı koroner arter baypas cerrahisi uygulanan hastalarda nebivololün postoperatif böbrek hasarına karşı metoprolole göre daha iyi koruma sağlayıp sağlamadığını belirlemektir.

Hastalar ve Yöntem: Altmış diyabetik hasta nebivolol (Grup I, n= 30) veya metoprolol (Grup II, n= 30) kullanımına göre iki gruba ayrıldı. Grup I'deki hastalar 5 mg/gün nebivolol, Grup II'deki hastalar ise 50 mg/gün metoprolol kullanan hastalardan seçildi. Postoperatif böbrek fonksiyonları serum nötrofil jelatinaz ile ilişkili lipokalin (NGAL) ve serum kreatinin düzeylerinin seri ölçümleriyle değerlendirildi. p< 0.05 değeri istatistiksel anlamlı kabul edildi.

Bulgular: İki grup arasında demografik, preoperatif klinik parametreler ve operatif değişkenler benzerdi. Postoperatif iki saatlik NGAL pozitifliği olan hasta sayısı iki grup arasında fark saptanmadı (7 [% 26.9] ve 7 [% 25.9] p= 0.93). Her gruptan sadece 1 hastada 24. saatte referans sınırdan daha yüksek kreatinin değerleri varken, her gruptan 7 hastada 72 saatlik kreatinin pozitifliği gözlendi. Tüm hastalar renal replasman tedavisi ile düzeldi ve hemodiyaliz gereksinimi olmadı.

Sonuç: Koroner arter baypas cerrahisi uygulanan diyabetik hastalarda nebivolol ile metoprolol kullanımı arasında erken böbrek hasarına karşı koruyucu etki açısından fark saptanmadı.

Anahtar Kelimeler: Nebivolol; metoprolol; koroner arter baypas cerrahisi; böbrek hasarı; NGAL

INTRODUCTION

Newly developed acute renal failure (ARF) during the early postoperative course of open heart surgery is an important cause of significant mortality and morbidity[1]. ARF has been defined as a 50% increase of serum creatinine over the baseline level or a 25% decline of baseline glomerular filtration rate (GFR)[2]. The incidence has been reported to be as high as 30% following open heart surgery, and 1 to 5% of the patients require hemodialysis

despite being appropriately treated[3,4]. Hemodialysis require-ment after cardiac surgery has been shown to be an important marker of early mortality, and Chertow et al. have reported a mortality rate as high as 63.7% in patients requiring hemodi-alysis; whereas it was 4.3% in those who also developed ARF but improved without hemodialysis[3].

In recent years, nebivolol, a third generation highly selec-tive β-1 receptor antagonist, has been shown to reduce renal tubular damage in certain circumstances[5]. Besides its known antihypertensive and cardioprotective properties, it has also been reported that nebivolol has antioxidant and endothe-lial protective effects and is also preventive against renal fi-brosis[6,7]. These properties are postulated to be related with increased release of nitric oxide (NO) from vascular endothe-lium. Activated NO causes an increase in the renal blood flow and a subsequent increase in GFR occurs[8].

In this study, we sought to determine whether renal func-tional parameters showed difference in the early postopera-tive period between diabetic patients who were either initiated on nebivolol or metoprolol treatment before coronary artery bypass surgery. Baseline renal functions were normal in all patients by means of standard laboratory measures, and renal damage monitoring was made by serial measurements of se-rum neutrophil gelatinase associated lipocalin (NGAL) and serum creatinine. NGAL is a relatively small (25 kDa) protein released from the activated neutrophils in renal proximal tu-bular epithelium, and yet it is known as the earliest positive test in acute kidney injury. NGAL positivity can be measured in blood and urine samples within two hours of renal damage, even when the insult is minimal[9]. Serum creatinine is a useful indicator of renal function in patients with advanced stage re-nal failure; whereas it is less valuable in the diagnosis of acute conditions. It has been reported that serum creatinine starts to rise after 48 to 72 hours of the onset of renal damage and that the GFR may reduce by 50% until it becomes detectable in blood[10].

PATIENTS and METHODS

The study was approved by the local ethics committee (AIBU 2011/87). Prospectively included patients gave in-formed consent for inclusion. The study was carried out in a blinded fashion, and data were collected prospectively between February 2010 and May 2013. Sixty diabetic patients who were scheduled for elective CABG procedure were included into the study according to the pre-accepted criteria. In order to control any bias, patients with a certain preoperative condition related to postoperative renal impairment were excluded from the study (i.e. uncontrolled hypertension, renovascular hyper-tension, polycystic renal disease, urinary obstruction or infec-tion and other diagnosed systemic diseases). Patients with a clear indication of a combined valve or aortic root procedure or emergency operation and those with serum creatinine > 2 mg/dl, ejection fraction (EF) < 35% and history of previous cardiac operation was also excluded from the randomization with the intention to constitute an isolated population.

Patients were divided into two groups as those receiving either nebivolol (Group I, n= 30) or metoprolol (Group II, n= 30) treatment.

Anesthesia and Operation

All patients in the study underwent elective operation, and all operations were performed by the same surgical team with the participation of the same two experienced surgeons. Gen-eral anesthesia was provided in standardized protocol. Patients were premedicated orally with diazepam 5 mg in the night be-fore the operation, and anesthesia was induced by thiopental (3 to 4 mg/kg) and fentanyl (2 to 6 g/kg). Tracheal intubation was achieved with pancuronium 0.1 mg/kg. Invasive monitor-ing was carried out with 20-gauge radial artery catheter. An 8 Fr catheter was inserted through the internal jugular vein, and an indwelling bladder catheter was used for urine collection. Intravenous cefazolin 1 g was used for surgical prophylaxis. Midline sternotomy incision and pericardiotomy were made. Before the institution of CPB, systemic heparin (300 IU/kg) was administered, and activated coagulation time (ACT) was maintained up to 480 seconds. CPB was provided using a Stockert roller pump with an open reservoir. The priming of the circuit was made with 1000 ml Ringer's lactate and 50 mg heparin. The flow was maintained at 2.4 l/min/m^2 with a mean arterial pressure maintained within 60 to 90 mmHg. Naso-pharyngeal temperature was lowered down to 32°C. Myocar-dial protection was achieved with intermittent doses (every 20 min) of antegrade normothermic blood cardioplegia combined with retrograde infusion.

Sample Taking and Assessment

Postoperative renal functions were assessed by serial meas-urements of serum NGAL and serum creatinine levels. In the postoperative period, blood samples were taken at 2 and 24 hours for NGAL measurement and at 24 and 72 hours for creatinine measurement. Serum NGAL was measured using Triage® meter (Alere Inc., San Diego, CA, USA). Negative outcomes for renal function were defined as serum creatinine being higher than 1.2 mg/dl and serum NGAL being higher than 150 ng/dl and denoted as acute renal injury (ARI)[11].

Statistical Analysis

All statistical analyses were performed using SPSS (SPSS version 16.0 Inc. Chicago, IL. USA) packaged software. Visual

histograms and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) were used for the determination of normal distribution. Continuous parameters were represented as mean ± standard deviations or median and maximum – minimum values. Categorical data were represented as number (percentages), and proportions were compared using chi-square test or Fisher's exact test. Comparison of means between the two groups was done using t-tc. P< 0.05 was considered as the level of statistical significance.

RESULTS

4 patients in Group I and 3 patients in Group II were excluded from the data analysis because of the concerns regarding the complications they developed might be related with postoperative renal dysfunction (high volume transfusion of blood products in 3 patients, prolongation of mechanical ventilation [> 48 hours] in 5 patients and long intensive care stay [> 3 days] in 6 patients). 26 patients in Group I and 27 patients in Group II were included into the data analysis. Demographic data and preoperative clinical parameters were similar between the two groups (Table 1). Operative parameters were also similar between the two groups suggesting that all patients seem to have been exposed to the same operative conditions (Table 2).

Number of patients with two-hour NGAL positivity was not different between the two groups; 7 patients (26.9%) from Group I and 7 patients (25.9%) from Group II had higher values than the reference limit (i.e. 150 ng/dl) (p= 0.93). Only 1 patient from each group (3.8% vs. 3.7, for Group I and II, respectively, p= 1.0) had higher creatinine values than the reference limit at 24 hours (i.e. 1.2 mg/dl); whereas 72-hour creatinine positivity was observed in 7 patients from each group (26.9% vs. 25.9%, for Group I and II, respectively, p= 0.93). The patients with either 24-hour or 72-hour creatinine positivity were the same patients who had already had two-hour NGAL positivity. None of the patients with creatinine positivity had been free of NGAL positivity within 72 hours, and this finding was statistically significant (p< 0.001). Within 24 hours, acute renal injury was significantly more prevalent when the diagnosis was made upon serum NGAL measurement (14 patients, 26.4%) compared to that made upon serum creatinine (2 patients, 3.8%, p< 0.001) (Table 3). All patients had serum NGAL levels below the reference limit in the 24-hour measurement. Patients achieved improvement with renal replacement therapy, and hemodialysis requirement did not occur.

Table 1. Baseline characteristics

Variable	Nebivolol group (n= 30)	Metoprolol group (n= 30)	p
Age	65.2 ± 7.4	62.1 ± 6.8	0.11
Male	15 (50%)	18 (60%)	0.50
Fasting blood glucose (mg/dl)	203 ± 38.7	196.5 ± 41.2	0.22
Hemoglobine A1c (%)	6.9 ± 1.7	6.2 ± 1.2	0.15
History of diabetes (years)	12.7 ± 7.1	15.9 ± 5.2	0.18
Ejection fraction (%)	50.4 ± 10.3 (40-65)	55.2 ± 10.1 (40-65)	0.25
Creatinine (mg/dl)	0.91 ± 0.1	0.83 ± 0.2	0.46
Body mass index (kg/m^2)	27.1 ± 2.4	25.9 ± 4.6	0.65

Table 2. Operative and postoperative parameters

Variable	Nebivolol group (n= 26)	Metoprolol group (n= 27)	p
Time of cross clamping (min)	50.8 ± 13.7	53.1 ± 12.1	0.33
Time of CPB (min)	77.8 ± 16.5	82.8 ± 14.7	0.29
Number of bypass vessels	2.8 ± 1.8	3.1 ± 1.1	0.65
ICU stay (days)	2.2 ± 1.1	2.6 ± 1.8	0.47
Hospital stay (days)	8.1 ± 3.4	7.6 ± 3.7	0.61

CPB: Cardiopulmonary bypass, ICU: Intensive care unit.

Table 3. Number of patients with blood NGAL and serum creatinine positivity within different time points

Variable	Nebivolol group (n= 26)	Metoprolol group (n= 27)	p
Patients with 2-hour NGAL positivity	7 (%26.9)	7 (%25.9)	0.93
Patients with 2-hour NGAL positivity	0 (0)	0 (0)	1.00
Patients with 24-hour creatinine positivity	1 (%3.8)	1 (%3.7)	1.00
Patients with 72-hour creatinine positivity	7 (%26.9)	7 (%25.9)	0.93

DISCUSSION

We sought to determine whether treatment with either nebivolol or metoprolol is beneficial in the prevention of postoperative acute renal injury, which is known to be the most important risk factor for occurrence of mortality after coronary artery bypass surgery[12]. Risk factors for the development of acute renal injury after open heart surgery have been reported as follows: diabetes, low glomerular filtration rate (< 60 ml/min per body surface in m^2), low ejection fraction (< 35%), emergency operation, cardiogenic shock, recent myocardial infarction, advanced age, preoperative use of diuretics, inotropes, nephrotoxic drugs, longer times of cardiopulmonary bypass and cross clamping, massive transfusion of blood products, renal hypoperfusion, reperfusion injury, hemodilution, inflammatory response, prolonged intensive care and hospital stay and history of recent percutaneous coronary intervention[13,14]. In this study, pre-accepted criteria for patient selection were constructed as certain bias must be overcome by excluding patients who had known risk factors other than diabetes. Also, patients who developed one or more of the above-mentioned operative morbidities were further excluded from the comparative analysis to accurately prove or disprove the hypothetical benefit of either drug on study outcomes.

This study mainly focused on patients with previously known diabetes. Increasing incidence of both diabetes and renal failure has been attributed to the increase in the elderly population[15]. More than a 20% of the patients undergoing CABG are diabetic[16]. Although mortality disadvantage of CABG patients who have diabetes has substantially reduced to some degree, that disadvantage has been shown not to be not totally eliminated[17]. Nevertheless, diabetes is suggested to be associated with an increased risk of acute renal failure without causing an increased risk of mortality[18]. Rakajuna et al.[19] have reported that diabetes constitutes a significant risk factor for development of postoperative renal and neurological complications; whereas it is not associated with an increased risk of infection. In a study reported by Calafiore et al.[20], close monitoring of blood sugar level and dietary regulation has achieved similar in-hospital and 5-year mortality between diabetic and non-diabetic patients in whom they used arterial grafts. Kubal et al.[21] have suggested that insulin dependent diabetes mellitus do not increase the risk of in-hospital mortality; whereas it has been found to be associated with an increased risk of renal complications, sternal infections and 5-year mortality.

Since certain conditions, such as prolonged ventilation or bleeding and also fluid balance during the intensive care stay may act as confounding factors until the time serum creatinine begins to rise, an effective measurement of renal functions in the early postoperative period was the most important matter that should be overcome to establish any potential benefit of nebivolol over metoprolol for the prevention of adverse renal outcome in this study. Among a variety of emerging options including cystatin C, interleukin 18, kidney injury molecule 1, n-acetyl-β-(D) glycosaminidase, hepcidin, α-1 microglobulin and neutrophil gelatinase associated lipocalin (NGAL)[22], the latter has reported to be the earliest positive test with a 98% sensitivity and 100% specifity in diagnosis of acute renal injury[23]. Recent reports support that NGAL potentially stands out as a useful tool in both prevention of delayed diagnosis and predicting clinical outcomes in the setting of cardiothoracic surgery[24,25]. Moreover, it has been demonstrated that sensitivity and specifity of plasma NGAL at 4 hours after CPB is optimal for the prediction of acute kidney injury[26]. In our study, NGAL increase was over the pre-accepted limit of normality in equal number of patients from each group that had comparable perioperative properties to each other.

B-receptor antagonists, which are among the most commonly used drugs in the treatment of cardiovascular diseases, have been shown to reduce blood levels of renin, angiotensin-II and aldosterone via blockage of β1 receptors[27]. Renal protective effect of nebivolol has been attributed to its ability to cause an increased release of NO, the main endothelial vasodilator, from the vascular wall[28]. Increased release of NO has been detected in cells exposed to high levels of oxidative damage[29]. Increased NO level enhances renal blood flow, raises blood pressure and improves glomerular filtration rate. As a result, improvement in renal medullary congestion, renal oxidative damage and micro proteinuria ensues[30]. Another advantage of nebivolol over metoprolol is that the former has been shown to reduce the expression of proinflammatory genes in endothelial cells and vascular smooth muscle cells in an experimental setting[31].

Some authors have advocated that effective blood sugar and hypertension regulation is the most effective way of preventing or attenuating the development of nephropathy in diabetic patients, whereas they have not found any difference in renal outcomes between patients who either use or do not use ACE inhibitors, β blockers and calcium channel blockers[32-34]. Ito et al.[35] have reported that renal functions are better preserved in hypertensive patients treated with β-blockers. Kalinowski et al.[36] have demonstrated that all types of β-receptor antagonists enhance NO release. However, prevention of renal injury by the usage of certain drugs that have known properties on arterial system has not been adequately studied within the context of cardiac surgery. In a similar manner to our study but in a clinical trial setting, Prowle et al.[37] have shown that a 4-day pre-treatment atorvastatin is not associated with lower urinary NGAL measurements postoperatively, as well. Thus, the fact that postoperative renal damage could be attenuated by pre-operative administration of an already known medication still awaits confirmation and deserves further investigation.

CONCLUSION

Two-hour blood NGAL measurements well predicted 72-hour creatinine increase in patients undergoing CABG. Treatment with nebivolol was found not associated with lower NGAL levels when compared to metoprolol in the early postoperative period. Usage of NGAL measurements for the assessment of renal functions may have ensured good postoperative renal outcomes because none of the patients with elevated 72-hour serum creatinine eventually required hemodialysis owing to early institution of renal replacement therapy.

Limitations

The limitations of the study were the small number of patients and the lack of late evaluation.

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