Nebivolol compared with metoprolol for erectile function in males undergoing coronary artery bypass graft

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ABSTRACT

Objective: The aim of this study was to evaluate erectile function in males undergoing coronary artery bypass graft (CABG) while on two different adrenoceptor beta-blocker regimens, namely nebivolol and metoprolol. We hypothesize that the negative effects of cardiopulmonary bypass on erectile function may be possibly attenuated by preferring a vasodilating selective β_1-blocker, nebivolol, to metoprolol as an anti-ischemic and antiarrhythmic agent in males undergoing CABG.

Methods: This randomized, double-blind, prospective clinical study was conducted in patients scheduled for CABG surgery between February 2012 and June 2014. A total of 60 consecutive patients who met inclusion criteria were randomized and divided into the following two groups: N group, which received 5 mg of nebivolol orally for 2 weeks before surgery plus 12 weeks after surgery or M group, which received 50 mg of metoprolol orally for the same period. All patients were evaluated by the erectile function domain of the International Index of Erectile Function-5 (IIEF-5) at the time of admission (before starting the beta-blocker) and 3 months after surgery.

Results: In the metoprolol group, the mean IIEF-5 score decreased significantly from a baseline of 15.2±5.8 to 12.9±5.8 ($p<0.001$), but in the nebivolol group, this difference was not significant (from a baseline 12.9±5.5 to 12.4±5.5, $p=0.053$). In all patients, the mean IIEF-5 score decreased significantly from a baseline of 14.0±5.7 to 12.6±5.6 ($p<0.001$).

Conclusion: Although erectile function in males undergoing CABG surgery decreases when metoprolol is used, nebivolol exerts protective effects on erectile function against the disruptive effects of cardiopulmonary bypass in patients undergoing CABG.

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Key words: coronary artery bypass grafting, erectile function, metoprolol, nebivolol

Introduction

Coronary artery bypass grafting (CABG) is the most commonly applied procedure in cardiovascular surgery. However, the procedure itself is also associated with significant morbidity and mortality. CABG with the use of cardiopulmonary bypass (CPB) may cause endothelial dysfunction by reducing the synthesis and release of plasma nitric oxide (NO) (1). Endothelial dysfunction is a major cause of erectile dysfunction (ED) (2).

Myocardial revascularization is used to increase supply part of "the supply/demand ratio" in myocardial ischemia. On the other hand, decreasing the demand part of "the supply/demand ratio" is also very important. Beta-blockers are drugs used as anti-ischemic, antihypertensive, and antiarrhythmic agents to reduce extra unnecessary energy consumption. When choosing the beta-blocker in patients undergoing CABG, its side effects must be considered together with the side effects of CPB. One of the unintended consequences of CPB, erectile dysfunction, can be defined as the inability to achieve or maintain penile erection required for sexual intercourse (3). Vascular, neurogenic, structural, hormonal, psychogenic, and drug-related pathophysiological mechanisms are suspected to be associated with ED (4).

Nebivolol, which is a highly selective β_1-blocker, has been shown to cause vasodilation by inducing NO production (5). This effect is possibly due to the β_3-adrenoceptor mediated stimulation of endothelial NO-synthase (eNOS) via Ser1177 phosphorylation and activation of the enzyme (6). eNOS is located in the smooth muscle cells of the corpus cavernosum tissue, in con-

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trast to vascular smooth muscle cells (7). NO has a crucial role in erectile function by mediating trabecular muscle relaxation of the corpus cavernosum (8). Different beta-blockers, including metoprolol and nebivolol that have been used in the treatment of hypertension, have been studied with respect to their effects on erectile function, and it was demonstrated that nebivolol has significant beneficial effects (9). Even in normotensive patients, beta-blockers are the major drugs used as medication in ischemic heart disease. However, in the literature, no study was designed to investigate their relations with erectile function in patients undergoing CABG. The present study was designed to evaluate the relations of two widely used adrenoceptor beta-blockers, namely nebivolol (a third-generation beta-blocker with high β_1-adrenoceptor selectivity and endothelial NO-dependent vasodilator effects) and metoprolol (a second-generation beta-blocker), with erectile function in males undergoing CABG.

Methods

This randomized, double-blind, prospective clinical study was performed after approval of the local Ethics Committee of the University, Faculty of Medicine. Written informed consent was obtained from all patients. The study was conducted in 83 male patients who had coronary artery disease and were scheduled for coronary artery bypass surgery. Patients were evaluated between February 2012 and June 2014 in cardiovascular surgery and urology clinics of the University. The inclusion criteria included all male patients between 30 and 80 years of age, NYHA Class II-IV but with an ejection fraction >30%, and coronary artery disease confirmed by angiographic study. This study was planned to be performed in at least 60 male patients applying to our clinic just after diagnosis of coronary artery disease and who were referred to CABG. In this way, we aimed to enroll patients before starting any beta-blocker use, including nebivolol. We did not include patients taking any beta-blocker before admission for CABG. Each randomly assigned patient was started on oral nebivolol (5 mg/day; group N, n=30) or oral metoprolol succinate (50 mg/day; group M, n=30) at least 15 days before surgery, and these regimens were continued postoperatively. Randomization assignment of patients to the groups was performed by opening an envelope. Some clinical features of patients may be possibly related to impaired response to flow mediated dilatation (FMD). Patients having such clinical features were excluded from the study. These features are as follows: congestive heart failure associated with elevated sympathetic activation, diabetes mellitus, renal or hepatic dysfunction [blood creatinine>1.5 mg/dL and blood aspartate aminotransferase (AST) and blood alanine aminotransferase (ALT) levels higher than two fold of normal values] (10). All patients were evaluated by an urologist, and patients with prostatitis, elevated prostate specific antigen (PSA) levels, and abnormal digital rectal examination findings were excluded from the study. Additionally, active inflammatory disease, history of myocardial infarction in the past 6 months, reoperations, CABG surgery associated with valvular replacement or any other procedure, an ejection fraction less than 30%, peripheral vascular disease, history of cerebrovascular disease, emergent coronary revascularization, and circulatory support with intra-aortic balloon pump before surgery were also excluded from the study. All medications used in the preoperative or postoperative period were recorded.

After exclusion of 23 patients because of their refusal to participate, the remaining 60 patients were evaluated with the erectile function domain of the International Index of Erectile Function-5 (IIEF-5), which was translated and validated in Turkish, by the same examiner who was blinded to treatment groups (11). Patients were stratified at baseline (at the time of admission and before starting the beta-blocker), and 3 months after surgery, erectile function was re-evaluated according to the same preoperative measures. Patients were categorized based on their scores as follows: 22-25 (no ED), 17-21 (mild ED), 12-16 (mild-moderate ED), 8-11 (moderate ED), and 5-7 (severe ED) (12). All included patients in the study were married or had a regular partner.

All patients were given exactly the same anesthesia protocol. They were premedicated with midazolam. A balanced anesthetic technique (fentanyl, etomidate, esmeron, and inhalational sevofluorane) was applied. Median sternotomy was performed. All patients underwent conventional CABG under CPB by the same surgical team (13).

Statistical analyses

SPSS software version 15.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. Visual (histogram and probability graphs) and analytical (Kolmogorov–Smirnov test) methods were used to determine conformance of variables to normal distribution. The Student's t-test was used to compare two groups for normally distributed parameters. Age, preoperative IIEF-5 scores, postoperative IIEF-5 scores, total cholesterol levels, and triglyceride levels were not normally distributed, and we used the Mann-Whitney U test and Wilcoxon tests to analyze them. For the frequency distributions of nitroglycerine, ACE inhibitors, Ca channel blockers, lipid-lowering statin use, hypertension and smoking, the Pearson chi-square test was used. Statistical significance was set at $p<0.05$.

Results

Demographic characteristics and perioperative clinical data of the groups are shown in Table 1. Patient characteristics were similar in both groups ($p>0.05$).

In the metoprolol group, the mean IIEF-5 score decreased significantly from a baseline of 15.2±5.8 to 12.9±5.8 ($p<0.001$); however, in the nebivolol group, this difference was not statistically significant (from 12.9±5.5 to 12.4±5.5 and $p=0.053$) (Table 2). In all patients, we found that the mean IIEF-5 score decreased significantly from a baseline of 14.0±5.7 to 12.6±5.6 ($p<0.001$). It

Table 1. Demographic characteristics and perioperative clinical data of patients

Variables	Group N (n=30)	Group M (n=30)	*P*
Age, years	60.6±10.6	58.8±11.6	0.61
BMI, kg/m^2	24.0±7.2	22.1±8.1	0.32
EF, %	48.7±9.0	51.6±9.4	0.24
Nitroglycerine, n (%)	12 (40)	7 (23.3)	0.27
ACE inhibitor, n (%)	12 (40)	11 (36.6)	1.0
Calcium channel blocker, n (%)	5 (16.6)	6 (20)	1.0
Antihyperlipidemic, n (%)	13 (43.3)	14 (46.6)	1.0
Hypertension, n (%)	12 (40)	14 (46.6)	0.79
Smoking, n (%)	11 (36.6)	15 (50)	0.43
Total cholesterol, mg/dL	199.5±43.7	200.1±49.6	0.91
LDL cholesterol, mg/dL	99.8±23.1	104.8±20.8	0.24
CPB time, min	87.0±21.2	76.9±45.8	0.10
Cross-clamp time, min	48.1±14.6	44.3±16.2	0.34
MAP during CPB, mm Hg	54.0±6.1	53.7±6.1	0.85
Mechanical ventilation time, h	6.6±2.5	6.2±2.8	0.53
Blood product transfusions, unit	3.6±1.5	3.0±1.6	0.17
ICU stay, day	1.9±0.6	1.9±0.8	0.79
Hospital stay, day	7.4±1.1	7.4±1.3	0.82
Postoperative MI, n (%)	2 (6)	0 (0)	0.49
Dysrhythmia, n (%)	4 (13.3)	6 (20)	0.48
Preoperative IIEF-5 score	12.9±5.5	15.2±5.8	0.12

Data are expressed as mean±standard deviation or n (%). ACE - angiotensin-converting enzyme; BMI - body mass index; CPB - cardiopulmonary bypass; EF - ejection fraction; IIEF - International Index of Erectile Function; ICU - intensive care unit; LDL - low density lipoprotein; MAP-mean arterial pressure; MI - myocardial infarction
Student's t-test, Pearson chi-square test, Mann-Whitney U test were used

Table 2. Comparison of preoperative and postoperative IIEF-5 scores in all patients and groups

	Preoperative IIEF-5	Postoperative IIEF-5	*P*
All patients, n=60	14.0±5.7	12.6±5.6	<0.001
Group N, n=30	12.9±5.5	12.4±5.5	0.053
Group M, n=30	15.2±5.8	12.9±5.8	<0.001

Data are expressed as mean±standard deviation. IIEF - International Index of Erectile Function
Wilcoxon test was used

Table 3. Comparison of two groups on the basis of IIEF-5 score subgroups

	Group N (n=30) n (%)	Group M (n=30) n (%)	All patients (n=60) n (%)
IIEF-5 scores before surgery			
Normal	3 (10)	8 (26.7)	11 (18.3)
Mild ED	4 (13.3)	2 (6.7)	6 (10)
Mild-moderate ED	8 (26.7)	11 (36.6)	19 (31.7)
Moderate ED	11 (36.7)	7 (23.3)	18 (30)
Severe ED	4 (13.3)	2 (6.7)	6 (10)
IIEF-5 scores after surgery			
Normal	3 (10)	3 (10)	6 (10)
Mild ED	5 (16.7)	6 (20)	11 (18.3)
Mild-moderate ED	5 (16.7)	3 (10)	8 (13.3)
Moderate ED	11 (36.6)	12 (40)	23 (38.4)
Severe ED	6 (20)	6 (20)	12 (20)

Data are expressed as n (%). ED - erectile dysfunction. Mild ED score: 17-21. Mild-Moderate ED score: 12-16. Moderate ED score: 8-11. Severe ED score: 5-7
Pearson chi-square test was used

was clear that the decline in the metoprolol group was effective in this change.

Based on the preoperative IIEF-5 scores, ED was present in 49 (81.7%) of the 60 patients selected for the study (Table 3). Before surgery, ED of any degree was found in 27 of 30 patients in the nebivolol group. After a 14-week period of nebivolol administration (2 weeks before CABG plus 12 weeks after CABG), the total number of patients having ED was the same as before CABG, but the distribution of patients to subgroups was different (Table 3). All the four patients with severe ED remained the same without any change. Of the eleven patients with moderate ED, nine experienced no change, and two experienced deterioration to severe ED. Of the eight patients with mild-moderate ED, five remained in the same class, two experienced deterioration to moderate ED, and one experienced improvement to mild ED. All the four patients with mild ED remained in the same class, and all the three patients with normal erectile function remained unaltered. In the metoprolol group, ED of any degree was found in 22 (73.3%) of 30 patients at the time of admission. After metoprolol administration for the same period as that of nebivolol administration, the total number of patients having ED increased from 22 to 27, and also, their distribution to subgroups changed (Table 3). Each of the two patients with severe ED remained the same without any change. Of the seven patients with moderate ED, three experienced no change, and four experienced deterioration to severe ED. Of the eleven patients with mild-moderate ED, two remained in the same class, and nine experienced deterioration to moderate ED. One of the two patients with mild ED remained in the same class, and the other patient experienced deterioration to mild-moderate ED. Of the eight patients with normal erectile function, three remained unaltered, and five experienced deterioration to mild ED.

Discussion

The results of this prospective clinical study showed that the vasodilating selective β_1-blocker nebivolol, unlike the selective β_1-blocker metoprolol, had a protective effect on

the sexual activity of men undergoing coronary artery bypass surgery with CPB. Screening postoperative clinical data related to myocardial ischemia, such as postoperative myocardial infarction or dysrhythmia, also showed that metoprolol and nebivolol had similar anti-ischemic activity in these patients, suggesting that the differences between the two agents with regard to sexual activity were independent of their anti-ischemic effects.

In the literature, there are few published studies related to the effects of CABG surgery on erectile function. In a study designed by Heaton et al. (14), it was suggested that CABG with the use CPB could have a significant effect on sexual function because of the use of a CPB circuit device. Gueglio et al. (15) concluded that the most important predictive factor was the preoperative condition in their study investigating predictive factors for erectile function after CABG. In a different study, Hızlı et al. (16) suggested that the best predictor of postoperative erectile function in patients undergoing CABG was preoperative erectile function. Mohamed et al. (17) investigated the impact of CABG surgery in a study design including subjective (IIEF-5 score) and objective (penile duplex ultrasonography) findings related to erectile function. In their study, patients were operated with or without the use of CPB to differentiate the effects of CPB on erectile function. Although they could not find any significant change in the duplex ultrasound data (peak systolic, end-diastolic velocities, and resistance index) after surgery between groups, significantly lower IIEF-5 scores were attributed in patients operated with the use of CPB (17). According to this study, it can be considered that CPB has some detrimental effects on erectile function following CABG, but it is not clear how it affects penile tissue without any change in the vascular bed. In contrast, Cangüven et al. (18) investigated plasma NO levels after on- or off-pump CABG. They demonstrated that in on- and off-pump CABG surgeries, the IIEF-5 score and plasma NO levels did not reveal any significant difference in the early postoperative period. Beghetti et al. (1) proposed that the destructive effects of CPB leading to endothelial dysfunction depend on the synthesis and release of plasma NO, which has an increased risk in postoperative complications, including erectile dysfunction. In our study, all patients were operated with the use of CPB, that's why we analysed all of our patients as a total, so, the decrease in IIEF-5 score could be attributed to the use of CPB, consistent with the literature.

Beta-blockers are one of the most commonly used drugs in the treatment of ischemic heart disease (19). In the literature, the cardioprotective action of beta-blockers in patients with ischemic heart disease undergoing major vascular surgery has been proven (20). Sharma et al. (21) showed the cardioprotective effect of prior beta-blocker therapy in limiting CK-MB release and resulting in lower mortality rates after percutaneous coronary interventions. With respect to beta-blocker use in patients undergoing CABG, Weightman et al. (22) demonstrated beneficial effects on in-hospital mortality in patients on preoperative beta-blockers. In an observational, large multi-center study, it was shown that peroperative beta-blockers enhanced operative survival in all patients who underwent CABG, except in those with impaired left ventricular function (<30%). It was also demonstrated that stroke, renal failure, and respiratory problems were seen at lower rates (23).

Complications related to the use of beta-blockers are now being reconsidered in light of the development of more cardiac selective medications and increasing evidence of the long-term benefit of these drugs (24). The β_1-adrenoceptor selectivity and vasoactive effects of three different generations (first-third generations) of beta-blockers are different. Nebivolol, a third-generation beta-blocker, has a vasodilating effect that is attributed to the generation of endothelial NO, in addition to β_1-adrenoceptor selectivity (25). Nebivolol and metoprolol used in the treatment of hypertension have been compared in many studies with respect to erectile function. Birixius et al. (26) showed that IIEF-5 scores in hypertensive men treated with nebivolol did not decrease even with respect to secondary sexual activity, and other IIEF subscores improved compared with metoprolol. Doumas et al. (27) demonstrated similar findings with nebivolol when compared with atenolol and other beta-blockers.

A potent vasodilator, NO, that is released from nerve endings initiates penile erection. Shear stress, resulting in increased blood flow, causes more production of NO (28). The stimulus caused by increasing shear stress over the endothelium induces NO release. eNOS activation in the endothelium has been shown to be induced by shear stress over the brachial artery, and it has also been reported that eNOS activity causes changes in circulating NO by up to 72-90% (29). The ability of nebivolol to increase NO may have a protective effect on erectile function in males (30). In an experimental study comparing nebivolol and metoprolol, activation of endothelial NO synthase (eNOS) and induction of NO release by nebivolol in the rat corpus cavernosum have also been shown, but not with metoprolol (31). Moreover, nebivolol has the ability to enhance NO/cGMP signaling and improve endothelial and erectile function in men. Therefore, nebivolol indicated for ischemic heart disease or hypertensive men might provide additional benefits over other beta-blockers (32). These results support our study indicating that nebivolol does not aggravate ED or that at least it protects erectile function against the negative effects of CPB (33).

In addition to endothelial-induced activation, the corpus cavernosum is affected by the fact that nebivolol increases eNOS activation in smooth muscle cells. This interaction is particular to nebivolol but not metoprolol. Our results support the suggestion that for the maintenance of penile erection, eNOS activation in smooth muscle cells of the corpus cavernosum is essential. The results of our study are compatible with clinical findings that nebivolol does not cause erectile dysfunction in CABG patients when chosen as an anti-ischemic and antiarrhythmic agent.

Study limitations

We planned a study of a continuous response variable from independent control and experimental subjects with one control(s) per experimental subject. In a previous study, the response within each subject group was normally distributed with a standard deviation of 5. If the true difference in the experimental and control means is 3.75, we will need to study 29 experimental subjects and 29 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

The limitations of our study are the relatively small number of patients and the lack of long-term follow-up data. Another limitation is that the information regarding cardiac rehabilitation might be provided. Preoperative IIEF-5 scores of two groups were not similar. Although that might be seen as a limitation of our study, the difference between them was not statistically significant. A better study design for simultaneous evaluation of plasma NO levels is warranted in further studies.

Conclusion

Although erectile function decreases in males using the β_1-blocker metoprolol, nebivolol exerts protective effects on erectile function against the disruptive effects of CPB in patients undergoing CABG. However, further larger, prospective, randomized, placebo-controlled, double-blind studies are needed to confirm our results and to verify the beneficial effect of nebivolol on erectile function.

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