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Original Article

The Comparison of the Effects of Nebivolol and Metoprolol on Erectile Dysfunction in the Cases with Coronary Artery Bypass Surgery

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Purpose: Beta-blocker use is common in the cases with coronary artery bypass surgery. According to the literature, beta-blockers have positive effects but may cause erectile dysfunction (ED). The most commonly used beta-blockers in ischemic cardiac disease are nebivolol and metoprolol. In our clinic, we aimed to compare the effects of nebivolol and metoprolol succinate on ED in the sexually active cases with coronary artery bypass surgery.
Methods: In our clinic, a total of 119 patients with coronary artery bypass surgery were included in the study. International Index of Erectile Function (IIEF-5) Test was used to evaluate whether the patients had ED and to grade the cases.
Results: No significant difference was found in terms of anti-ischemic efficacy between metoprolol succinate and nebivolol in the postoperative period; however, the incidence of any grade ED was %85.96 in Group 1, %83.87 in Group 2. This difference was considered as statistically significant (p = 0.036).
Conclusion: Beta-blocker use increases the risk of ED in cases with ischemic cardiac disease. We suggest that the complaints of ED could be less frequent with nebivolol use in sexually active cases with ischemic cardiac disease.

Keywords: coronary artery bypass surgery, beta-blocker, erectile dysfunction

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve or maintain an erectile function sufficient for satisfactory sexual performance.[1)] Today, it is reported that the most common etiology for ED is organic disorders accompanying with vascular diseases and several studies suggest that there is a strong relationship between cardiovascular risk factors and ED.[2,3)] Ischemic cardiac diseases are common health problems for elderly population and despite the new treatment methods, coronary artery bypass graft (CABG) operations are still commonly performed.

In the cases with CABG operation and ischemic cardiac disease, beta-blocker agents are the preferred treatment methods and besides, they are recommended for the patients with hypertension, cardiac failure, and atrial fibrillation.[4,5)] It is reported that these agents indicated as class I use in CABG operations cause ED.[6,7)] It is observed that the third-generation beta-blocker agent nebivolol which has a high β_1-adrenoceptor selectivity leads directly to arterial and venous vasodilatation by nitric oxide (NO) system activation.[6,8,9)] Given this feature of nebivolol, in contrast to other beta-blocker agents, it may increase NO release and improve erection or may not cause impotence.

This study aims to investigate ED in male patients who used nebivolol (third-generation beta-blocker) and metoprolol (second-generation beta-blocker) following CABG operation.

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Materials and Methods

This prospective randomized study was started between February 2014 and December 2015 following the approval by University Ethics Committee, "Ministry of Health, Head Office, The Department of Pharmaceutics and Pharmacy" when the informed consents were obtained. Inclusion criteria were as follows: the patients with isolated coronary bypass operation, use of metoprolol succinate (50 mg/day) and nebivolol (5 mg/day) in the preoperative and postoperative period at least for 3 months, and being under 65-year-old male patient having regular sexual partner. The metoprolol group was classified as group 1 and nebivolol group was classified as group 2. The blood samples were investigated for free T3 (FT3), free T4 (FT4), thyroid stimulant hormone (TSH), prolactine, follicle stimulant hormone (FSH), luteinizing hormone (LH), testosterone levels at postoperative 6 months. The patients with hormonal ED were excluded.

Given the sociocultural properties of the patients, a reliable place was prepared for the patients and a blinded urologist interrogated the detailed history and sexual functions of the patients. During the interrogation, no information about the studied medicine was given to the patients to avoid any negative effects. "International Index of Erectile Function Test" (IIEF-5) was used to determine whether the cases had ED. (IIEF-5 test contains the following questions: 1) How do you rate your confidence of geting and maintaining an erection? 2) When you have erections with sexual stimulation, how often are your erections hard enough for penetration? 3) During sexual intercourse, how often are you able to maintain your erection after you have penetrated (entered) your partner? 4) During sexual intercourse, how difficult is it to maintain your erection to completion of intercourse? and 5) When you attempt sexual intercourse, how often is it satisfactory for you?)

IIEF-5 below 21 was considered as ED. According to the classification by IIEF-5 test, scores above 21 was considered as normal, whereas the scores 17–21 were mild, 12–16 were mild-moderate, 8–11 were moderate, and 5–7 were severe.

IIEF-5 score test was used after the operation but before coronary artery bypass surgery, during the ED investigation, the cases were excluded if they had ED. The other exclusion criteria were as follows: previous genitourinary or prostate surgery that might affect sexual activity, neurological disease, major depression, hypothalamo-hypophyseal axis hormone abnormality, thyroid disease, peripheral artery disease (Ankle brachial index: <0.9), renal failure (creatinine: >1.5 mg/dL), and diabetes.

The patients in both groups had undergone operation under cardiopulmonary bypass following sternotomy. Anesthesia induction and maintenance were similar in both groups.

Statistical analysis

The statistical analyses were done with the SPSS for Windows version 19.0 software program (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to evaluate the distribution pattern of the continuous variables, whereas the Mann–Whitney U test was used to compare the groups. A chi-square test was also used to compare the categorical variables. A p value of 0.05 was considered to be statistically significant.

Results

In all, 119 patients (median age: 55.02 ± 7.55; min: 38, max: 65) who used beta-blockers at least for 3 months in the postoperative period were included in the study. Total of 57 patients in Group 1 (median age: 55.11 ± 6.80; min: 38, max: 65) and 62 patients in Group 2 (median age: 54.94 ± 8.20; min: 40, max: 65) were evaluated. No statistically significant difference in the preoperative hypertension, hyperlipidemia, antihypertensive drug, renal function, demographical, and operative data was found. No significant difference in the postoperative intensive care and hospitalization duration and antiischemic (postoperative myocardial infarction [MI], arrhythmia) effects was observed (**Table 1**).

The incidence of any level of ED was %85.96 in Group 1 and %83.87 in Group 2. The incidence of severe ED was %7.01 in Group 1 and %1.61 in Group 2. Eight patients (14.03%) in Group 1 and 10 (16.10%) patients in Group 2 did not have ED (**Table 2**). When IIEF-5 scores were compared, they were 13.79 ± 6.00 in Group 1 and 16.02 ± 5.50 in Group 2. This difference was considered as statistically significant (p = 0.036).

Discussion

This study investigated the effect of nebivolol, which is one of the third-generation beta-blocker agents with high-β1-adrenoceptor selectivity and metoprolol with high-β1-adrenoceptor selectivity, on ED in patients undergoing CABG.

Table 1 Preoperative characteristics, operative, and postoperative data of patients

	Metoprolol (n:57) Group 1	Nebivolol (n:62) Group 2	p value
Age	55.11 ± 6.80	54.94 ± 8.20	0.879
BMI	27.85 ± 3.76	27.71 ± 3.48	0.404
Number of grafts	2.98 ± 0.76	3.03 ± 0.94	0.716
EF	53.35 ± 8.46	52.39 ± 7.09	0.334
CCT (min)	50.39 ± 26.28	47.26 ± 19.74	0.819
TBT (min)	82.95 ± 30.30	79.95 ± 27.43	0.840
ICU stay (day)	2.46 ± 1.07	2.21 ± 0.41	0.372
Hospital stay (day)	6.16 ± 1.38	5.55 ± 0.893	0.317
Atrial fibrilation, n (%)	12 (21%)	14 (22.5%)	0.460
Postoperative MI, n (%)	1 (1.7%)	0 (0%)	0.357
FSH	8.49 ± 10.01	7.18 ± 7.14	0.890
LH	6.43 ± 4.24	6.17 ± 3.45	0.977
Prolactin	12.21 ± 7.63	13.58 ± 7.98	0.422
Total testesteron	407.13 ± 139.88	456.80 ± 196.10	0.380
IIEF-5 score	13.79 ± 6.00	16.02 ± 5.50	0.036

ICU: intensive care unit; FSH: follicle stimulant hormone; LH: luteinizing hormone; IIEF: International Index of Erectile Function; BMI: body mass index; EF: Ejection Fracttion; CCT: Cross-clamp time; TBT: total bypass time

Table 2 Distribution of ED in comparison with nebivolol and metoprolol

	Metoprolol (n = 57) Group 1	Nebivolol (n = 62) Group 2	All patients (n = 119)
IIEF-5 results			
Normal (<17)	8 (14.03%)	10 (16.10%)	18 (15.12%)
Mild ED (17–21)	16 (28.07%)	27 (43.54%)	43 (36.13%)
Mild-moderate ED (12–16)	19 (33.33%)	15 (24.19%)	34 (28.57%)
Moderate ED (8–11)	10 (17.54%)	9 (14.51%)	19 (15.96%)
Severe ED (5–7)	4 (7.01%)	1 (1.61%)	5 (4.20%)
IIEF-5 mean ± SD	13.79 ± 6.00	16.02 ± 5.50	

ED: erectile dysfunction; IIEF: International Index of Erectile Function; SD: standard deviation

Although ED was detected to be significantly lower in the cases on nebivolol compared to the patients using metoprolol, there was no significant difference in terms of postoperative anti-ischemic effects. Beta-blocker agents are particularly preferred in the treatment of hypertension and cardiovascular diseases due to their antihypertensive, antiarrhythmic, and anti-ischemic properties. For this reason, the use of beta-blockers after CABG surgery is common and one of the important side effects is the impact on one's sexual life.[6,7,10]

Age, smoking, diabetes, hypertension, and hyperlipidemia are the risk factors for ED ischemic heart disease.[11]

Antihypertensive, statin, diuretics, and antidiabetic drugs are used for the treatment of these diseases and also there are studies showing that these drugs can also be the cause of ED.[12] In our study, there were no significant differences in preoperative comorbidities and drugs usage as well. In addition to these risk factors, atherosclerosis is the main cause of vascular ED. Atherosclerotic lesions in patients with ED prevent tumescence by inhibiting blood flow to corpus cavernosum and impair erection.[13] Contractions over 50% in internal pudendal, common penile, and cavernous artery lumen may cause ED.[14] Solomon et al. revealed in their study that 65% of 132 male patients angiographically detected coronary artery disease was present with ED and they found a significant correlation between cardiovascular risk factors and erectile function scores.[15]

This study shows that ED is a commonly encountered condition in patients who have undergone CABG surgery. Penile erection is a complex neurovascular phenomenon which is coordinated with corpus cavernosum smooth muscle relaxation and which involves increased arterial inflow and restricted venous return. NO key has been recently shown to play a role in penile erection.

Caused by autonomic innervation of the penis, NO acts as a local neurotransmitter of noncholinergic nonadrenergic nerves.[16] NO leads to increased intracellular cyclic guanosine monophosphate (cGMP) accumulation, which causes corporeal smooth muscle relaxation. The role of NO in the physiology of male sexual function has been shown as the primary modulator of penile erection. So, drugs resulting in NO release may improve erectile function. Nebivolol is one of the third-generation beta-blocking agents developed in recent years and exhibits high β1-adrenoceptor selectivity.

Nebivolol is called dl-nebivolol since it is a racemic mixture of d- and l-enantiomers.[17]

Although d-nebivolol enantiomer presents high-β1 adrenoreceptor selectivity, l-nebivolol isomer is more commonly responsible for vasodilation effect. Both in animal models and in clinical studies, it was found that nebivolol displays a vasodilatory effect by means of endothelium-derived NO.[18,19]

Although Gao et al. achieved NO-dependent vasodilatation response via nebivolol in isolated dog coronary arteries in their study, they could not see this response with beta-blocking agents such as alprenolol, nadolol, carvedilol, propranolol, and dilavelol.

In another study, Broeders et al. studied the plasma of the mice they injected with nebivolol and metoprolol. Although there was a two-fold increase in plasma NO levels in the group injected with nebivolol, they could not see this increase in the group injected with metoprolol.

They interpreted this as the capacity of metabolized nebivolol to increase NO release.[20]

Similarly, we could not detect a significantly higher the rate of ED in the group using metoprolol compared to the one using nebivolol in our study.

This low value of IIEF-5 of the group using nebivolol compared with the one using metoprolol can be explained by the fact that nebivolol contributes to erection by NO release. NO, released through the mechanisms we mentioned earlier, and increasing cyclic guanosine monophosphate (cGMP) act as main neurotransmitters of penile erection. Similar results were obtained by Brixius et al. in a comparison of metoprolol and nebivolol in hypertensive patients.

Although there was not any observed decline in IIEF-5 score in the metoprolol group, a significant decrease in the nebivolol group was detected.[6] In another study by Doumos et al. on hypertensive patients, 44 patients using various beta-blockers were involved in the study, ED was detected in 65% of these patients at various levels.

During the follow-up of the study, patients' treatment was replaced with nebivolol and it was reported that a statistically significant improvement was observed in erectile functions of 69% of the patients with ED.[20]

In other studies comparing another beta-1-selective blocker atenolol and nebivolol, it was also observed that nebivolol had a significantly lower International Index of Erectile Function (IIEF) score in terms of ED.[19,22,23]

Conclusion

With their antihypertensive, antiarrhythmic, and anti-ischemic effects, beta-blockers, one of the widely used agents in the cases performed CABG, have adverse effects on ED.

These negative impacts should not be ignored in CABG planned sexually active male patients and we are of the opinion that nebivolol should be used more frequently than other beta-blocking agents in this group of patients.

Study limitation

This can be considered as the fact that levels of NO plasma were not measured at the time when both groups were surveyed simultaneously with the study and some patients could not be objective in the survey due to socio-cultural reasons.

Disclosure Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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