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The Effect Of Ranolazine Treatment Administered Before Coronary Artery Bypass Surgery On Perioperative Myocardial Damage In Patients With Stable Angina Pectoris

Stabil Angina Pektorisli Hastalarda Koroner Arter Baypas Cerrahisi Öncesi Ranolazin Tedavisinin Peroperatif Miyokard Hasarı Üzerine Etkisi

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ABSTRACT

Objective: Ranolazine is a piperazine derivative that has been approved as an antianginal agent. It is primarily used as a second-line antianginal agent in stable coronary artery disease. The study was designed considering that the active ingredient ranalozine, which has antiischemic effects through ischemic sodium channels, can reduce ischemia in the perioperative period and reduce the frequency of perioperative myocardial infarction.

Methods: The study included patients with stable angina pectoris who underwent coronary angiography between January 1, 2015 and June 30, 2016 at Koşuyolu Training and Research Hospital and who were diagnosed with multi-vessel disease or LMCA disease, and then for whom the joint council of Cardiology-Cardiovascular Surgery made a decision in favor of coronary artery bypass grafting.

Results: The mean age was 61.2 ± 8.6 years in the ranolazine group, while the mean age of the patients receiving standard therapy was 57.9 ± 8.8 years (p = 0.073).The EuroSCOREs of the patients before the operation which were used to predict intraoperative mortality were similar. Mean troponin value of Group 1 patients at 0 hour was 1.70 (1.13-2.77), while mean troponin value of the patients in Group 2 at 0 hour was 2.76(1.69-6.20) (p=0,01).

Conclusion: In the present study, the immediate postoperative troponin 0 value was found to be lower in the ranolazine group. There was no statistical difference in terms of troponin values measured at 12 and 24 hours. In this study, we showed that early myocardial damage was significantly reduced with ranolazine treatment.

Keywords: bypass, ranolazine, myocardial damage

ÖZ

Giriş: Stabil anjina pektoris(SAP), mortalite ve yaşam kalitesi üzerinde önemli etkisi olan kronik bir hastalıktır. Ranolazin, bir antianjinal olarak onaylanan bir piperazin türevidir. Öncelikle stabil koroner arter hastalığında ikinci basamak antianjinal olarak kullanılır. Ranolazin geç sodyum kanallarını (INa) bloke ederek etki eder ve sitosolik kalsiyumun yükselmesini önler. Çalışmamız ranalozinin, perioperatif dönemde iskemiyi azaltabileceği ve miyokard hasarını azaltabileceği düşünülerek tasarlanmıştır.

Yöntem: Çalışmaya 1ocak 2015 ile 30 haziran 2016 tarihleri arasında Kartal Koşuyolu Yüksek İhtisas Eğitim Araştırma Hastanesi Kardiyoloji Anabilim Dalında koroner anjiyografi (KAG) uygulanmış ve çok damar hastalığı veya LMCA hastalığı tespit edilip, daha sonra Kardiyoloji- Kalp Damar Cerrahisi ortak konseyinde CABG kararı verilen stabil angina pektorisli hastalar alındı. CABG dışında başka bir cerrahi prosedür (mitral kapak onarımı, mitral kapak değişimi aort kapak değişimi gibi) uygulanan hastalar çalışmadan dışlandı. Araştırma protokolü için hastanemiz etik kurulundan gereken izin alındı.

Bulgular: Ranolazin alan grupta ortalama yaş 61,2±8,6 iken standart tedavi alan hastaların ortalama yaşı 57,9±8,8 olarak saptandı. (p=0,073). Hastaların operasyon öncesi değerlendirilen ve işlem sırasındaki mortaliteyi öngörmek amacıyla kullanılan EuroSCORE' ları benzerdi. 1.Grup hastaların ortalama 0. Saat troponin değeri 1.70 (1.13-2.77) iken 2. Grup hastaların 0. Saat troponin değeri 2.76(1.69-6.20) (p=0,01).

Sonuç: Çalışmamızda postoperatif olarak hemen bakılan troponin 0 değeri ranolazin alan grupta daha düşük saptandı. 12. Ve
24. Saatte bakılan troponin değerleri bakımından istatistiksel fark saptanmadı. Çalışmamızda erken dönem miyokard hasarının ranolozın tedavisi ile anlamlı olarak azaldığını gösterdik.

Anahtar Kelimeler: baypas, ranolazin, miyokardiyal hasar

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INTRODUCTION

Stable angina pectoris (SAP) is a chronic disease that has a significant impact on mortality and quality of life. Angina pectoris is the most common clinical manifestation of ischemic heart disease. (1,2)

Ischemia-reperfusion injury is one of the most important problems in cardiac surgery and may cause postoperative malignant arrhythmia, perioperative myocardial infarction, and decreased cardiac output. Despite the scientific developments at the cellular level and the use of cardioprotective methods, it has not yet been possible to completely prevent reperfusion injury. (3)

The function of cardiac troponin in myocardial contraction is to regulate the calcium-related interaction of actin and myosin. Therefore, determination of cardiac troponin is a very important tool, for example in the diagnosis of acute myocardial infarction and myocardial cell necrosis. (4)

Ranolazine is a piperazine derivative that has been approved as an antianginal agent. It is primarily used as a second-line antianginal agent in stable coronary artery disease. Ranolazine acts by blocking the late sodium channels (INa) and prevents the elevation of cytosolic calcium. It reduces myocardial wall tension and improves coronary blood flow. (5)

The study was designed considering that the active ingredient ranalozine, which has antiischemic effects through ischemic sodium channels, can reduce ischemia in the perioperative period and reduce the frequency of perioperative myocardial damage. Which was evaluated previously and shown to reduce the frequency of perioperative myocardial damage after percutaneous coronary stent placement.

The aim of this study was to examine the postoperative effects of preoperative administration of ranolazine treatment on myocardial damage.

MATERIALS AND METHOD

The study included patients with stable angina pectoris who underwent coronary angiography (CAG) between January 1, 2015 and June 30, 2016 in the Department of Cardiology at Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital and who were diagnosed with multi-vessel disease or LMCA disease, and then for whom the joint council of Cardiology-Cardiovascular Surgery made a decision in favor of coronary artery bypass grafting (CABG). Patients who underwent a surgical procedure other than CABG (mitral valve repair, mitral valve replacement, aortic valve replacement, etc.) were excluded from the study. The necessary permission was obtained from the ethics committee of our hospital for the study protocol.

Age, gender, risk factors for coronary artery disease (hypertension, diabetes, hyperlipidemia, smoking, and family history) of all patients included in the study were recorded. Hypertension was defined as having been previously diagnosed and receiving antihypertensive treatment, diabetes as receiving oral anti-diabetic or insulin therapy, and dyslipidemia as receiving lipid-lowering treatment at presentation. Syntax scores, EuroSCORE II and LV ejection fraction (echocardiographic), body weight, and creatinine values of all patients were recorded.

Criteria for exclusion from the study:

Patients with a previous history of revascularization, patients with ejection fraction less than 40% (as it may cause high troponin), patients with preoperative renal failure (creatinine >1.3 mg/dl or creatinine clearance <80 ml/min), patients with long QTc on ECG (>440 ms in men) , (women >460 ms), patients with myocardial infarction (MI) or unstable angina pectoris (USAP) in the last 3 months, and patients with elevated troponin values for any reason were excluded from the study.

Patients who underwent coronary angiography (CAG) with a diagnosis of stable angina pectoris and for whom a decision was made in favor of

surgery were included in the study considering the exclusion criteria. Our study was designed retrospectively. Between 2015 and 2016, patients who were scheduled for CABG and who were using ranolazine were screened retrospectively. Troponin was measured at 0, 12, and 24 hours postoperatively. ECG monitoring was performed daily.

STATISTICAL ANALYSIS

Mean ± standard deviation and median (maximum-minimum) values were used for continuous variables, and percentage was used for categorical variables. Normal distribution was tested with one-sample Kolmogorov-Smirnov test. Unpaired t-test was used to test the difference in terms of the normally distributed continuous variables between the patient and control groups. In continuous variables that do not conform to the normal distribution, Mann–Whitney U test was used to test the difference between two groups. Pearson Chi-square test was used to test categorical variables.

A p-value of <0.05 was considered significant for all tests. Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used.

RESULTS

The mean age was 61.2 ± 8.6 years in the ranolazine group, while the mean age of the patients receiving standard therapy was 57.9 ± 8.8 years (p = 0.073).

While the rate of diabetic patients in group 1 was 52.8% and 38% in the second group (p = 0.077) While the rate of smoking patients in group 1 was 45.7% and 54% in group 2 (p = 0.239). The EuroSCOREs of the patients before the operation which were used to predict intraoperative mortality were similar.

The Syntax scores of the patients calculated by considering the morphological characteristics of all lesions on CAG were similar.

In group 1, the rate of single CABG was 5.7%, double CABG was 27.14%, triple CABG was 50%, quadruple CABG was 15.7%, and quintupleCABG was 1.42%;while in group 2, the rate of single CABG was 6%, double CABG was 28%, triple CABG was 42%, quadruple CABG was 24%, and quintuple CABG was 0%. (Table 1)

Table 1. Clinical and Demographic Characteristics of the Patients

	Group 1 N:70	Group 2 N:50	p
Age	61.2 ± 8.6	57.9 ± 8.8	0.073
Height	168.4 ± 7.0	169.8 ± 6.6	0.274
Body Weight	79.5 ± 11.0	80.2 ± 7.5	0.536
BMI	27.9 ± 3.3	27.7 ± 2.0	0.759
Ejection Fraction	58.5 ± 7.2	58.6 ± 7.8	0.714
DM n(%)	37 (52.8%)	19 (38%)	0.077
HT n(%)	46 (65.7%)	30 (60%)	0.326
HL n(%)	47 (67.1%)	30 (60%)	0.270
Smoking n(%)	32 (45.7%)	27 (54%)	0.239
Hemoglobin	13.54 ± 1.45	13.47 ± 2.3	0.639
Urea	37.19 ± 9.8	36,09 ± 8,0	0.727
Creatinine	0.82 ± 0.1	0.82 ± 0.1	1.0
TSH	1.69 ± 1.2	1.55 ± 0.9	0.933
Euroscore	1.19 ± 0.4	1.07 ± 0.3	0.051
Syntax Score	18.2 ± 2.7	18.9 ± 3.0	0.148
Number of grafts n(%)	1G 4 (5.7%)	2G 3 (6%)	0.239
	2G 19 (27.14%)	2G 14 (28%)	
	3G 35 (50%)	3G 21 (42%)	
	4G 11 (15.7%)	4G 12 (24%)	
	5G 1 (1.42%)	5G 0 (0%)	

Mean EF value of the patients in Group 1 was 58.5% (65-40), and mean EF was 58.6 (65-45) in Group 2 (p = 0.714). Perfusion time and aortic clamping times of both groups were similar (Table 2). In addition, the lowest temperature and the lowest pH value measured during the operation were also similar. (Table 2)

Mean troponin value of Group 1 patients at 0 hour was 2.52 ± 2.38, while mean troponin value of the patients in Group 2 at 0 hour was 7.95 ± 17.13 (p = 0.008).

The clinical and demographic characteristics of the patients in both groups are shown in Tables 1 and surgical features and troponin values are shown in Table 2.

Table 2. Table 2: Clinical and Demographic Characteristics of the Patients

	?	?	p
Perfusion time	84.94 ± 22.6	81.9 ± 19.7	0.657
Aortic clamping time	53.51 ± 14.7	56.16 ± 15.4	0.313
Temperature	30.3 ± 1.0	30.1 ± 0.6	0.688
Ph	7.33 ± 0.4	7.32 ± 0.6	0.157
Troponin value at 0 h	1.70 (1.13-2.77)	2.76(1.69-6.20)	0.01
Troponin value at 12 h	1.59(0.90-2.81)	1.76(1.08-3.28)	0.43
Troponin value at 24 h	0.71(0.49-1.44)	1.06(0.65-1.67)	0.12

DISCUSSION

In the present study, the immediate postoperative troponin 0 value was found to be lower in the ranolazine group. There was no statistical difference in terms of troponin values measured at 12 and 24 hours. In this study, we showed that early myocardial damage was significantly reduced with ranolazine treatment.

CABG is a basic and effective surgical method for coronary artery disease. [6] Ischemia reperfusion injury during and after CABG can lead to reversible and irreversible myocardial damage (7). Although various methods have been developed to reduce this adverse effect on the myocardial tissue, cardiac dysfunction is still common. (8)

Methods of myocardial preservation play a key role during CABG. (9)

Ranolazine acts by selective inhibition of late Na channels by decreasing intracellular calcium load and diastolic tension secondary to this (10). The most important feature of this drug is that it acts only on ischemic cells rather than normal myocytes at therapeutic doses. In addition, it does not have any effect on blood pressure and heart rate, which is also important.
The efficacy of ranolazine in chronic stable patients has been demonstrated in many randomized clinical trials. It was shown that the total exercise time and the time to angina onset significantly increased compared with placebo when ranolazine was given to the patients who participated in the MARISA study, (11).In the CARISA study, ranolazine significantly increased exercise time and time to anginal pain, regardless of the changes in blood pressure and heart rate and the treatment method used in the background, and decreased the weekly number of anginal attacks in patients with chronic stable angina (12). On the other hand, in the ERICA study, it was investigated whether addition of ranolazine to amlodipine treatment led to any additional benefits (13). Ranolazine was found to significantly reduce the prevalence of angina and nitrate consumption, and it was found to be equally effective in male and female patients, in patients who received and did not receive long-acting nitrates, and in those who were over or below 65 years of age.

It has been shown in multi-center randomized studies that ranolazine improves angina symptoms and exercise time in patients with known coronary artery disease. (14-16) The first study of ranolazine on periprocedural MI was conducted in 70 patients who underwent elective percutaneous coronary intervention (PCI) with the diagnosis of stable angina pectoris and ranolazine group has lower periprocedural MI than other group (17) It has been reported that the plerotropic-antianginal effect of ranolazine may improve endothelial dysfunction, decrease the inflammatory process, and decrease post-PCI microembolism by reducing alpha 1 activity in vascular tone.(18-19)

Post CABG miyocardial damage may be originated from insufficient protection of the myocardium during the period when the aorta is cross-clamped, incomplete surgical revascularization, vasospasm, atheromatous embolism from a previous bypass graft or aorta, air embolism, or thrombosis of a native artery or a new graft (20, 21)

In the present study, the efficacy of ranolazine was investigated in patients who underwent elective CABG with the diagnosis of SAP, based on a previous study showing the positive effects of ranolozine on post MI in the PCI group. in our study equal ischemia time and similar preoperative angiographic atherosclerosis grades between groups eliminated the difference in terms of ischemia-necrosis. The difference in early troponin values in the post period has shown that ranolazine is beneficial in terms of perioperative myocardial damage in the early period. This result may be originated by ranolazine late sodium channel blocking effect and the decreased intracellular calcium level by this mechanism ischemia and necrosis may be reduced. but this difference disappeared in the subsequent period after revascularization of ischemic myocardial tissue. Ivabradine which can be used as an antianginal drug showed positive results on myocardial damage in the post-CABG study and this effect was attributed to the decreased heart rate. (22) The fact that ranolazine does not affect heart rate and blood pressure may explain the absence of a decrease in troponin levels in the postoperative long term results . The early difference may be attributed to the effect of ranolazine on ischemic tissue. There is a need for larger randomized trials regarding this subject.

CONCLUSION

Our studydemonstratedthat ranolazin has protective effect in early period until revascularization for miyacardial damage , for patients who could not full revascularited by CABG ranolazine treatment should be keep in mind for protection of myocardial damage.

LIMITATIONS

The main limitations of the present study were that it was not single-centered and randomized, and the number of patients was low. In addition, involving different surgical teams was another limitation. Another limitation was that the newly developing wall motion abnormality and occlusion of native or graft artery were not demonstrated by an invasive or a non-invasive method for the diagnosis of post-operative MI. In addition, the CK-MB value was not analyzed in the laboratory of our hospital, which was also a limitation because of our study retrospective design.

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Conflict of Interest
The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration
Ethical approval was obtained from the Recep Tayyip Erdoğan University, Clinical Research Ethics Committee with date 14.04.2019 and number 2019-57, and Helsinki Declaration rules were followed to conduct this study.

Informed Consent
This is a retrospective study.

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