Comparison of the effects of metoprolol or carvedilol on serum gamma-glutamyltransferase and uric acid levels among patients with acute coronary syndrome without ST segment elevation

Lütfü Aşkın, Şule Karakelleoğlu, Hüsnü Değirmenci, Selami Demirelli[1], Ziya Şimşek, Muhammed Hakan Taş, Selim Topçu, Zakir Lazoğlu

Department of Cardiology, Faculty of Medicine, Atatürk University; Erzurum-*Turkey*
[1]Department of Cardiology, Erzurum Education and Research Hospital; Erzurum-*Turkey*

Abstract

Objective: Serum gamma-glutamyltransferase (GGT) and uric acid levels measured in patients with acute coronary syndrome without ST segment elevation (NSTEMI) are important in diagnosis and in predicting the prognosis of the disease. There is a limited number of clinical studies investigating the effects of beta-blockers on GGT and uric acid levels in these patients. In our study, we aimed to investigate the effects of beta-blocker therapy on GGT and uric acid levels.

Methods: We conducted a randomized, prospective clinical study. Hundred patients with NSTEMI were included in this study, and they were divided into two groups. Fifty patients were administered metoprolol succinate treatment (1 x 50 mg), whereas the remaining 50 patients were administered carvedilol treatment (2 x 12.5 mg). Thereafter, all of the patients underwent coronary angiography. Blood samples were taken at the time of admission, at the 1st month, and 3rd month to detect GGT and uric acid levels.

Results: There was no statistically significant difference among the metoprolol or carvedilol groups in terms of the GGT levels measured at the baseline, 1st month, and 3rd month (p=0.904 and p=0.573, respectively). In addition, there was no statistically significant difference among the metoprolol or carvedilol groups in terms of uric acid levels measured at the baseline, 1st month, and 3rd month (p=0.601 and p=0.601, respectively).

Conclusion: We found that GGT and uric acid levels did not show any change compared to the baseline values, with metoprolol and carvedilol treatment initiated in the early period in patients with NSTEMI. *(Anatol J Cardiol 2016; 16: 16-22)*

Keywords: acute coronary syndrome, carvedilol, gamma-glutamyltransferase, metoprolol, uric acid

Introduction

NSTEMI is a life threatening outcome of atherosclerosis. Generally, ruptured atherosclerotic plaque alone or together with vasoconstriction causes a sudden and critical reduction in coronary blood flow, thereby triggering acute thrombosis. A marked reduction in mortality is observed with the use of beta-blockers in patients with acute coronary syndrome (1). Beta-blockers, which are used as the cornerstone in treatment of cardiovascular diseases and reduces oxygen consumption of the myocardium, have been shown to be beneficial as antianginals before acute coronary syndrome in large scale studies including "GRACE and CANRACE" (2). In many studies conducted in recent years, it has been shown that serum gamma-glutamyltransferase (GGT) and uric acid levels are important in the diagnosis and in predicting the prognosis in patients with stable coronary disease and NSTEMI. A relation between coronary plaque load and serum GGT levels has been shown in patients with stable angina and NSTEMI (3, 4). GGT is an important plasma membrane enzyme and is also important in glutathione homeostasis (5). Uric acid causes cardiovascular diseases by damaging vascular smooth muscle cells with aminocarbonyl radicals which have proinflammatory and antioxidant properties (6). Coronary calcification may develop with increased uric acid levels. Some cohort studies have associated serum uric acid levels with impaired fasting glucose and type 2 diabetes and shown that serum uric acid constitutes an increased risk for cardiovascular diseases because of uncontrolled blood glucose

Address for Correspondence: Dr. Lütfü Aşkın, Atatürk Üniversitesi Tıp Fakütesi, Kardiyoloji Anabilim Dalı, Erzurum-*Türkiye*
Phone: +90 534 514 46 03 Fax: +90 442 232 50 25 E-mail: lutfuaskin23@gmail.com

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levels (7). According to the results of NHANES 3 study, it was shown that serum uric acid levels have a marked predictive value in all-cause mortality in diabetic patients. In another 10-year, large-scale study which included 1268 diabetes patients, no relation between basal uric acid levels and all-cause mortality could be shown (8, 9).

Although there are many studies related to serum GGT and uric acid levels for which diagnostic and prognostic efficiency have been shown in the literature, there are few studies targeting the reduction of their levels in patients with acute coronary syndrome. The effects of a new generation beta-blocker carvedilol or the well-known cardioselective beta-blocker metoprolol, which are used as the cornerstones in treatment of cardiovascular diseases, have not been studied till date. In this study, we aimed to evaluate the effects of metoprolol and carvedilol on serum GGT and uric acid levels in patients with NSTEMI.

Methods

The study was conducted with 100 patients who were admitted to cardiology outpatient and emergency units and were diagnosed with NSTEMI between January 2013 and June 2013. The patients were informed of the study and their informed consents were obtained. Approval of the "Ethical Committee" of our hospital was obtained. The study was conducted in line with the "Declaration of Helsinki."

Study population

A total of 100 patients diagnosed with NSTEMI were included in the study. Our inclusion criteria were diagnosed NSTEMI and indications for beta-blocker therapy. Patients were divided into two groups at the hospital admission. Fifty patients were administered metoprolol succinate treatment (1 x 50 mg/day), whereas the remaining 50 patients were administered carvedilol treatment (2 x 12.5 mg/day). There were 36 male and 14 female patients in the metoprolol group, whereas 41 male and 9 female patients were present in the carvedilol group.

Thereafter, all of the patients underwent coronary angiography in the first 24 h. Blood samples were taken at the time of admission, in the 1st month, and 3rd month to detect GGT and uric acid levels. Patients who consumed alcohol, those with liver diseases with primary and secondary causes, those who received beta-blocker treatment previously, those with chronic renal failure and other renal pathologies, those who did not come to hospitals for routine tests and treatment after hospital discharge, those previously known to have high uric acid levels, those with bradycardia, those with intolerability to beta-blockers, those with gout disease, those with obesity (BMI ≥30 kg/m^2), and those receiving diuretics were excluded from the study. Only those who were diagnosed with NSTEMI and who underwent coronary angiography were included in the study.

Study design

It was a randomized, prospective clinical study. Metoprolol succinate was initiated with a dose of 1 x 50 mg/day, whereas carvedilol was initiated with a dose of 2 x 12.5 mg/day. Medical treatment was standardized with an aimed heart rate of 50-60 beats/min. All of the patients underwent coronary angiography in the first 24 h after the medical treatment was started. Blood samples were taken at the time of admission, at the 1st month, and 3rd month to detect GGT and uric acid levels. Visits for medical check-ups were made in the 1st and 3rd months.

Echocardiographic assessment

Transthoracic echocardiography recordings of the cases were performed with GE Vivid 7 Dimension with a frequency of 2.5 MHz electronic transducer. Echocardiographic recordings were performed with the patient on the left side supine position at the end of the expiration. The values were obtained to include three subsequent cycles in those with sinus rhythms and five subsequent cycles in those with atrial fibrillation during expiration. In the images of parasternal long-axis, ejection fraction measurement was performed with M-mode.

Biochemical and haematological assessment

Blood samples were taken from the patients diagnosed with NSTEMI to measure serum GGT and uric acid levels. In addition, blood samples were taken for routine biochemical parameters, sedimentation, C-reactive protein, and full blood counts. After the blood samples were centrifuged, they were analyzed in the serum analyser with turbidimetric method. Thus, GGT and uric acid levels were obtained. Baseline values for GGT were <55 unit/L among the male patients and <38 unit/L among the female patients. Baseline values for uric acid were 3.5-7.2 mg/dL among the male patients and 2.6-6 mg/dL among the female patients.

Statistical analyses

Numeric variables were presented as mean±standard deviations or medians (interquantile range) because appropriate and categorical variables were presented in percentages. The Kolmogorov-Smirnov test was used to test the distribution of the numeric variables. The difference among the variables that followed a normal distribution was calculated by the Student's t-test, whereas the difference among the variables that did not follow a normal distribution was calculated by the Mann-Whitney U test. The difference in the categorical variables between the groups was analyzed by the chi-square test or Fisher's exact test. The level of statistical significance was set at 0.05. Serum GGT and uric acid levels were investigated as a repeated measure between levels (baseline, 1st, and 3rd months). Serum GGT levels were abnormally distributed; therefore, we used the repeated measure analysis of variance test with Bonferroni correction. Serum uric acid levels were normally distributed; therefore, we used the Friedman test. SPSS 20.0

Table 1. Baseline clinical, echocardiographic, laboratory, and angiographic characteristics of the study population

Variables	Metoprolol (n=50)	Carvedilol (n=50)	*P***
Age, years	60±13	67±10	0.091
Gender Male/Female, n, %	36(73)/14(27)	41(82)/9(18)	0.475
Diabetes, n, %	4 (8)	4 (8)	1.000
CVD, n, %	2 (4)	2 (4)	1.000
Hypertension, n, %	15 (30)	21 (42)	0.359
COPD, n, %	12 (4)	6 (12)	0.295
Baseline ritm, nsr, n, %	45 (90)	47 (94)	0.550
Smoking, n, %	26 (52)	32 (64)	0.369
Decision, n,%			
Medical	17 (34)	10 (20)	0.288
PTCA	30 (60)	30 (60)	
CABG	13 (4)	10 (20)	
Angiography, CAD, n,%			
One vessel	19 (38)	28 (56)	0.088
Two vessel	15 (30)	8 (16)	
Three vessel	6 (12)	14 (28)	
LDL, mg/dL	123±29	121±40	0.796
HDL, mg/dL	42±13	42±12	0.902
Total cholesterol, mg/dL	186±32	193±52	0.578
TG, mg/dL	181±89	193±52	0.529
Glucose, mg/dL	156±174	124±43	0.403
Creatinine, mg/dL	0.8±0.2	0.9±0.3	0.637
Hemoglobin, g/dL	14±1	14±2	0.233
WBC, $10^3 \times \mu L$	9.347±3.444	8956±3059	0.686
Platelet, $10^3 \times \mu L$	233652±51759	344565±408320	0.203
Sedimentation, %	21±26	24±21	0.684
CRP, mg/dL	7±12	6±6	0.751
LV-EF, %	55±7	59±23	0.374
Systolic blood pressure, mm Hg	119±14	120±14	0.757
Diastolic blood pressure, mm Hg	72±10	75±9	0.253
Heart rate, beats/min	74±12	79±12	0.146
Drug story, %			
Calcium channel blocker, n, %	8 (16)	4 (8)	0.381
ACEI/ARB, n, %	11 (22)	11 (22)	1.000
Acetyl salicylic asid, n, %	6 (12)	10 (20)	0.437
Diuretics, n, %	0	2 (4)	0.312
Statins, n, %	4 (8%)	6 (12)	0.636

**Student t, Mann-Whitney U, chi-square test obstructive pulmonary disease; ACE/ARB - angiotensin-converting enzyme inhibitors /angiotensin receptor blockers; CABG - coronary artery bypass; CAD - coronary artery disease; COPD - chronic CRP - C-reactive protein; CVD - cerebrovascular diseases; HDL - high density lipoprotein; LDL - low density lipoprotein; LV-EF - left ventricular ejection fraction; nsr-normal sinus rhythm; PTCA - perkutan transluminal coronary angioplasty; TG - triglyceride; WBC - white blood cell

(SPSS Inc., Chicago, Illinois, USA) package software was used for the statistical analyses.

Results

The study was completed with a total of 100 patients; 23 of them were female and 77 of them were male. Table 1 shows baseline demographic, clinical, echocardiographic, and angiographic characteristics of the participant patients. Mean age in the metoprolol group was 60±13 years, whereas mean age in the carvedilol group was 67±10 years; there was no statistically significant difference between the two groups (p>0.05). The groups were similar in terms of gender, and there was no statistically significant difference between the groups in terms of demographic, clinical, echocardiographic, and angiographic characteristics. It was observed that two patients from each of the metoprolol and carvedilol groups were diabetic; one patient from each of the metoprolol and carvedilol groups had cerebrovascular events; and seven patients in the metoprolol group and 10 patients in the carvedilol group were hypertensive. It was noted that one patient in the metoprolol group had stable Chronic Obstructive Pulmonary Disease (COPD), whereas three patients in the carvedilol group had stable COPD. No statistically significant difference existed between the groups with respect to these diseases (p>0.05).

With respect to serum GGT and uric acid levels, none of the groups demonstrated any statistically significant difference at the time of hospital admission. The serum GGT levels in the metoprolol and carvedilol groups were 33.7±21.9 mg/dL and 49.8±84.8 mg/dL, respectively. The serum uric acid levels in the metoprolol and: carvedilol groups were 6.0±1.0 mg/dL and 5.0±1.0 mg/dL, respectively (p>0.05). The serum GGT levels in the first month are listed as follows: metoprolol group, 32.0±17 mg/dL; carvedilol group, 40.0±23.0 mg/dL; p>0.05, whereas the levels in the third month are listed as follows: metoprolol group, 31.0±16.0 mg/dL; carvedilol group, 41.0±52.0 mg/dL; p>0.05. Serum uric acid levels in the first month are listed as follows: metoprolol group, 6.0±1.0 mg/dL; carvedilol group, 5.0±1.0 mg/dL; p>0.05, whereas the levels in the third month are listed as follows: metoprolol group, 5.0±1.0 mg/dL; carvedilol group, 5.0±1.0 mg/dL; p>0.05 (Table 2). No statistically significant intragroup difference was found in the groups (p>0.05) (Table 3, 4). No statistically significant difference was observed when intergroup and intragroup differences were assessed in terms of GGT and uric acid levels (Fig. 1, 2). There was no difference between the patient groups included in the study in terms of association of conventional risk factors, and no significant change was found in serum GGT and uric acid levels in subgroup analyses performed in patients who had undergone percutaneous coronary intervention or CABG operation similar to the patients who received medical treatment (p: 0.288). There was no change in serum GGT and uric acid similar to the patients who received medical treatments (p: 0.288).

Table 2. Changes in GGT and UA values between metoprolol and carvedilol groups during the follow-up

Variables	Metoprolol (n=50)	Carvedilol (n=50)	*P*
Baseline GGT, mg/dL	28 (16-51)	24 (19-38)	0.382
Baseline UA, mg/dL	6±1	5±1	0.157
1st month GGT, mg/dL	32±17	40±50	0.432
1st month UA, mg/dL	6±1	5±1	0.222
3rd month GGT, mg/dL	31±16	41±52	0.407
3rd month UA, mg/dL	5±1	5±1	0.170
Δ $GGT_{baseline\text{-}1^{st}\ month}$	1±12	8±36	0.371
Δ $UA_{baseline\text{-}1^{st}\ month}$	0.017±0.43	0.08±0.55	0.399
Δ $GGT_{baseline\text{-}3^{rd}\ month}$	1±11	8±34	0.500
Δ $UA_{baseline\text{-}3^{rd}\ month}$	0.11±0.71	0.03±0.57	0.685

GGT - gamma-glutamyltransferase; UA - uric acid
Student t-test, Mann-Whitney U test

Table 3. The follow-up values of GGT and UA in the metoprolol group

Variables	Baseline	1st month	3rd month	*P*
GGT, mg/dL	33.7±21.9	32±17	31±16	0.904*
UA, mg/dL	6±1	6±1	5±1	0.601**

*Friedman analysis, **Repeated measure one-way ANOVA
GGT - gamma-glutamyltransferase; UA - uric acid

Table 4. The follow-up values of GGT and UA in the carvedilol group

Variables	Baseline	1st month	3rd month	*P*
GGT, mg/dL	49.8±84.8	40±50	41±52	0.573*
UA, mg/dL	5±1	5±1	5±1	0.601**

Friedman analysis, **Repeated measure one-way ANOVA
GGT - gamma glutamyltransferase; UA - uric acid

Discussion

We investigated the effects of beta-blockers metoprolol and carvedilol on serum GGT and uric acid levels in this study.

GGT is an important plasma membrane enzyme and is important in glutathione homeostasis. It has been found that GGT plays a role in the pathogenesis of cardiovascular diseases, particularly in the pathogenesis of coronary artery diseases; thus, it has been proposed that increased GGT levels may be a predictor of the prognosis in cardiovascular diseases (5, 10-16). Many studies have shown a relation between serum GGT levels and CAD; GGT has also been associated with major cardiac events in acute coronary syndromes (17-24).

Onat et al. (25) reported that increased serum GGT levels were an independent indicator for the risk of DM, HT, metabolic syndrome, and CAD. In addition, increased GGT levels accompanying metabolic disorders, including hyperlipidaemia and insulin resistance, contribute to the progress of atherosclerosis in patients with ACS (20). In one study, it was reported that plasma GGT was strongly determined the presence of Acylation

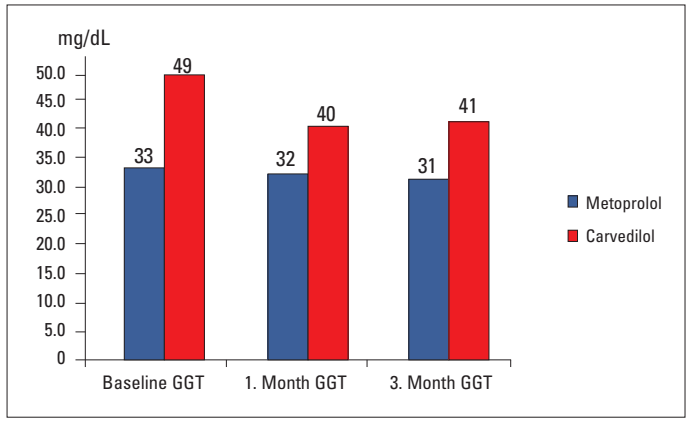

Figure 1. The baseline, 1st, and 3rd month follow-up values of GGT between the metoprolol and carvedilol groups

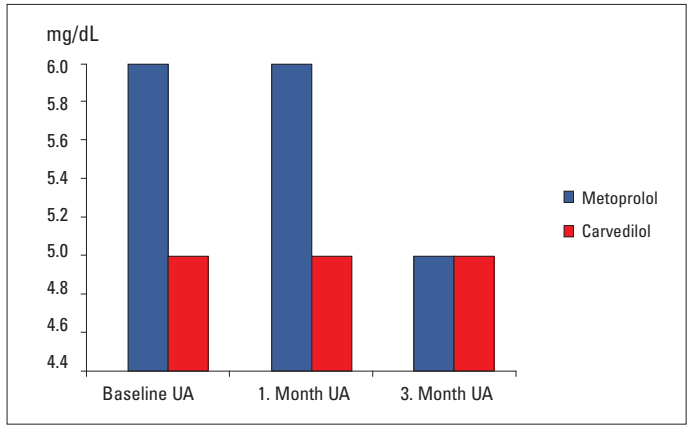

Figure 2. The baseline, 1st, and 3rd month follow-up values of UA between the metoprolol and carvedilol groups

Stimulating Protein (ASP). In patients with ACS, strong association of ASP and GGT showed that ASP, which has a strong lipid storing effect, may contribute to the vicious cycle of hepatic lipogenic stimulation and GGT release, which increases atherosclerosis independence of insulin resistance (26).

İn a clinical study conducted by Mao et al. (27), a positive correlation was found between coronary lesion complexity and GGT, Hs CRP, hypertension, and smoking. In some similar studies, an independent correlation was shown between serum GGT levels and coronary lesion complexity and long-term outcome in patients with stable coronary artery disease (3, 24, 28).

In another study performed by Baktır et al. (29), the relation between GGT activity and coronary atherosclerotic load was investigated in patients with STEMI and a high SYNTAX score, and no significant correlation was found between high SYNTAX score, major cardiovascular events and GGT activity. The SYNTAX score is a known useful angiographic scoring system which gives important information regarding the complexity and extensiveness of coronary lesions (24, 29).

Studies conducted with patients with stable coronary artery disease with chronic total occlusion have shown that increased GGT levels accompanied poor coronary collateral development (17, 30, 31). It has been proposed that GGT may be used in the

grading of coronary collateral circulation and may be a better marker compared to the other inflammatory and oxidative stress markers (17, 30, 31).

In contrast to previous studies, the study of Şarlı et al. (32), which was conducted with patients who had coronary artery ectasia, found no correlation between GGT, uric acid levels and mean platelet volume. However, it is known that coronary artery ectasia is attributed to atherosclerosis in many patients. GGT levels have also been shown as an independent marker of cardiovascular mortality and transplantation in patients with acute and chronic heart failure (15, 33).

Detailed examination of the role of GGT in the mechanism of cardiac diseases, including hypertension, CAD, cardiac syndrome X, and heart failure, would shed light on the development of new protective strategies and treatment methods.

In our study, baseline GGT levels were measured in patients presented with myocardial infarction without ST elevation, and they were randomly divided into two different groups. Metoprolol was administered in the first group which included 50 patients, and carvedilol was administered in the second group which also included 50 patients. The patients were followed up for 3 months. No significant change was found in GGT levels with treatment in both groups in the blood samples obtained in the 1st and 3rd months. Revascularization was performed in the majority of the patients (PCI or CABG surgery), and some patients were followed up with medical treatment. No significant difference was found in the subgroup analyses performed in patients who underwent revascularization. However, these results may show differences with more comprehensive studies and studies with longer follow-up periods.

Uric acid causes cardiovascular diseases by damaging vascular smooth muscle cells with aminocarbonyl radicals which have proinflammatory and antioxidant properties (6). Many studies in the literature have documented the relation between and the association of serum uric acid levels with cardiovascular diseases. However, it is still controversial whether uric acid is an independent risk factor for cardiovascular disease and mortality.

In a study performed by Kivity et al. (34) with healthy individuals, a correlation between serum uric acid levels and the risk of cardiovascular disease was observed in a similar manner, and this was reported to be particularly prominent in the female population.

In a study performed in China, 8,510 participants who were middle-aged and older (≥40 years) were examined; it was observed that increased serum uric acid levels accompanied cardiovascular diseases that were independent of conventional cardiovascular disease risk factors and metabolic syndrome (35). This study draws attention to the finding that the risk of cardiovascular diseases increases in patients with hyperuricemia.

In a few studies, the relationship between serum uric acid and coronary collateral development has been researched in patients with coronary artery disease. Researchers suggested that serum uric acid levels are useful biomarker for determining the severity of coronary artery disease in patients with NSTEMI (36-41).

Several large, long-term trials involving ≥35,000 survivors of myocardial infarction have demonstrated that the use of beta-blockers in patients recovering from an episode of AMI improves survival by 20%-25% through a reduction of cardiac mortality, sudden cardiac death, and reinfarction. Positive results have been found in trials comparing propranolol, metoprolol, timolol, acebutolol, and carvedilol with a placebo; conversely, no benefit was demonstrated in trials with alprenolol, atenolol, oxprenolol, or xamoterol. Pooled data from 2,894 patients with acute coronary syndromes included in five randomised, controlled trials of abciximab during coronary intervention showed a reduction of 30-day and 60-day mortality associated with the use of beta-blockers (42-44). In our study, we assumed GGT and uric acid levels, which are considered as cardiovascular risk factors, to be decreased with beta-blocker therapy, thereby having a positive impact on prognosis. Some investigators reported that serum uric acid level could not be a coronary risk factor by itself and it may be a risk factor only if it was associated with the presence of HT, metabolic disorders including diabetes, lifestyle, alcohol consumption, excessive meat consumption, hypoadiponectinemia, and hypertriglyceridemia (7, 41, 45, 46). In our study, it was found that serum uric acid levels did not show significant difference after a 3-months beta-blocker treatment period (carvedilol or metaprolol) compared to the baseline values (before treatment) in patients diagnosed with NSTEMI. There was no difference between the patient groups included in this study in terms of association of conventional risk factors, and no significant difference was found in uric acid levels in patients who underwent percutaneous coronary intervention or CABG operation in the subgroup analyses performed similar to the patients who received medical treatment.

Study limitations

The present study has some limitations, This study was based on a limited number of observations made in a small population of patients and a brief follow-up period. The patients are particularly hard to find in the general population. The fact that we had too many exclusion criteria also resulted in a limited number of subjects. Future studies are required for these findings to be applied for clinical practice.

Conclusion

In the study, it was found that beta-blockers carvedilol or metoprolol, the primary anti-ischemic treatment among the patients with NSTEMI, did not affect GGT levels and uric acid levels in the 1st and 3rd months as compared to the baseline values. Our study should be supported with studies with larger samples and long term follow-up periods to generalize our findings/results for clinical practice.

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