

THE EFFECT OF TRIMETAZIDINE ON IN-HOSPITAL MORTALITY IN PATIENTS WITH ACUTE CORONARY SYNDROME WITHOUT INTERVENTIONAL THERAPY

*İsmail Bıyık MD., *Aslan Özdemir MD., *Ahmet Salman MD., **Nezih Tayyar MD.

*Department of Cardiology, Usak State Hospital, **Department of Management, Statistics, Usak

Bu çalışma medikal tedavi ile tedavi edilen ST yükselmesi olmayan akut koroner sendrom (NSTEMI) hastalarında trimetazidinin hastane mortalitesine etkilerini araştırmak amacıyla planlandı.

2547 olgunun kaydında, hastalar kararsız angina pectoris (UAP) (grup-1) ve ST yükselmez miyokard infarktüsü (NSTEMI) (grup-2) olarak ayrıldı. Her iki grupta, hastaların heparin, asetil salisilik asit, klopidogrel, beta bloker ve nitratlardan oluşan standart tedavi ve trimetazidin ya da sadece standart tedavi alıp almamasına göre iki alt grup oluşturuldu. Tüm grupların hastane içi mortaliteleri karşılaştırıldı.

UAP geçiren 1221 hastada, standart tedaviye ek olarak trimetazidin alan 477 hastanın 2'si (grup-1a) ve almayan 744 hastanın 15'i (grup-1b) kardiyak nedenlerden kaybedildi. Hastane içi mortalite oranları sırasıyla % 0.4 ve % 2 bulundu ($p=0.003$). UAP hastalarında hastane içi mortalite oranı trimetazidin alan hastalarda daha düşüktü. NSTEMI

geçiren 1326 hastada, standart tedaviye ilave olarak trimetazidin alan 852 hastanın 27'si (grup-2a) ve almayan 474 hastanın 18'i kardiyak nedenlerden kaybedildi. Hastane içi mortalite oranları sırasıyla % 3.2 ve % 3.8 bulundu ($p>0.05$). Sonuçlar istatistiksel olarak anlamlı olmamasına rağmen NSTEMI hastalarında hastane içi mortalite oranları trimetazidine alan hastalarda daha düşüktü.

Bu analiz yalnızca medikal tedavi ile tedavi edilen NSTEMI hastalarında standart tedaviye eklenen trimetazidinin hastane içi mortalite yararı sağlayabileceğini ortaya koymaktadır. Ancak, bu sonuçların doğruluğunun kanıtlanması için daha geniş ölçekli, randomize klinik çalışmaların yapılması gereklidir.

Anahtar kelimeler: Trimetazidin, Mortalite, Akut koroner sendrom

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INTRODUCTION

Cardiovascular diseases have become the most common cause of death worldwide. It accounts for approximately 30 percent of all deaths. NSTEMI-ACS including UAP and NSTEMI remain leading causes of morbidity and mortality in the world wide. American Heart Association reports that 1.24 million people with NSTEMI-ACS have been admitted to hospitals per year¹. With improvements in the diagnosis and risk stratification of patients with acute coronary syndrome (ACS), therapeutic approaches to ACS have continued to evolve. The metabolic derangements caused by myocardial ischemia in ACS have been well characterized. Fatty acids are the main fuel for the healthy

heart, with a lesser contribution coming from the oxidation of glucose and lactate². Fatty acids are more energy-efficient fuel than glucose but glucose is more oxygen-efficient than fatty acids². Myocardial ischemia causes detrimental changes in energy metabolism of the heart and a switch from lactate uptake by the heart to lactate production and a dramatic disruption in cell homeostasis². Ischemic tissue continues to derive most of its energy from the oxidation of fatty acids despite a high rate of lactate production. This ischemia-induced disruption in cardiac metabolism can be reversed by reducing fatty acid beta-oxidation and increasing the combustion of glucose and lactate². Metabolically effective agents that inhibit fatty acid beta-oxidation such as trimetazidine have proven to be effective in the treatment of stable angina³⁻⁷. The available data suggest that combined therapy of trimetazidine and hemodynamic drugs is an effective anti-anginal treatment that reduces the risk of pain recurrence⁸⁻¹⁰. The recent studies also suggest that trimetazidine might be effec-

Corresponding Author: MD. İsmail BİYİK
İsmetpaşa Caddesi 75/1 Posta kodu: 64100
Usak/TURKEY
E-mail: ismailbiyikmd@yahoo.com
Tel.: +90 276 223 45 19 / 227 17 91
Fax: +90 276 223 84 75
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Table 1: The distribution of NSTEMI-ACS patients according to number of patients, mean age, gender and mean admission days

Groups Subgroups	UAP (Group-1)		NSTEMI (Group-2)	
	Grup-1a (TMZ)	Grup-1b	Grup-2a (TMZ)	Grup-2b
Patients (n)	477*	744*	852*	474*
Age (Mean±SD)	66±12*	63±12*	64±11	65±12
Male (n) (%)	258 (54)	435 (58)	564 (66)	294 (62)
Female (n) (%)	219 (46)	309 (42)	288 (34)	180 (38)
Admission Day (mean±SD)	3.25±1.6	3.35±1.7	3.8±1.6	3.9±1.7

*p<0.05: There was a significant difference between two groups.

tive in patients with acute myocardial infarction¹¹, ischemic cardiomyopathy^{12,13} and heart failure^{14,15}. However, there are no studies showing the effects of metabolic agents such as trimetazidine on short term mortality in patients with NSTEMI-ACS. Therefore, we hypothesized that trimetazidine added to standard medical therapy of NSTEMI-ACS per orally without loading dose may provide in-hospital mortality advantage in these patients. Thus, we aimed to investigate the effect of trimetazidine on short term cardiac mortality rates of patients with NSTEMI-ACS treated with medical approaches only.

METHODS

All patients admitted to coronary care unite (CCU) with the diagnosis of NSTEMI-ACS and providing the inclusion criteria of this study were included in the analysis. The diagnosis of UAP was made on the basis of the chest pain occurring at rest or minimal exertion and lasting over 20 minutes and not causing elevations in cardiac markers such as troponins or creatinin kinase MB fraction and ST segment elevations on electrocardiograms (group-1). Patients with the chest pain above mentioned and having elevations in troponins or creatinin kinase MB fraction and not showing ST segment elevations on electrocardiograms were considered as NSTEMI (group-2). The inclusion criteria of this study; patients admitted to CCU with diagnosis of UAP and NSTEMI and not treated with interventional therapy due to several causes, and taking standard therapy including heparin (heparin or enoxoparin), acetyl salicylic acid, clopidogrel, beta blocker, nitrates, and patients taking 20 mg trimetazidine three times in a day together with standard therapy were included in the analysis. The exclusion criteria of the study; patients treated with interventional approaches, patients taking incomplete standard medical therapy, and the patients of which the diagnosis of NSTEMI-ACS were not confirmed afterwards were excluded. The patients were divided in two subgroups of each group. The patients treated with standard therapy and also trimetazidine were included in group-1a and

2a. Group-1b and 2b were consisted of the patients treated with standard therapy only. In all patients, the route of trimetazidine administration was 20 mg three times in a day per orally and it was started together with other drugs at the same time after admission. Intravenous or oral loading dose was not used. In-hospital mortality rates of two subgroups in each group were compared retrospectively.

Statistical analysis: In-hospital mortality rates of groups were compared with independent samples proportion test. The chi-squared test was used for comparing male and female ratios. The mean age for each group were compared with independent samples t test. All statistical analyses were performed with SPSS version 15 software (SPSS Inc., Chicago, IL). A P-value of less than 0.05 was considered as significant.

RESULTS

In this analysis, 2547 patients with UAP and NSTEMI taking medical therapy alone were investigated. Demographic data of patients are shown in Table-1. In 1221 patients with UAP, 2 of 477 patients taking trimetazidine (group-1a) and 15 of 744 patients not taking (group-1b) were died of cardiac causes. In-hospital mortality rates were found 0.4 % and 2 %, respectively, (p =0.003) (Figure-1). The in-hospital mortality rates of patients with UAP treated with medical therapy only were lower in patients taking trimetazidine as an adjunct to standard therapy than not taking. The mean duration of hospitalization in patients with UAP was 3.3±1.7 day and there was no difference between two subgroups. There was no difference in the presence of diabetes, hypertension and the history of previous myocardial infarction between two subgroups in patients with UAP. However, there was significant age difference between two subgroups. The patients taking trimetazidine were significantly older than not taking in UAP group. In 1326 patients with NSTEMI, 27 of 852 patients taking trimetazidine (group-2a) and 18 of 474 patients not taking (group-2b) were died of cardiac causes. In-hospital mortality rates were found

Figure 1:The effect of trimetazidine on in-hospital mortality in patients with UAP

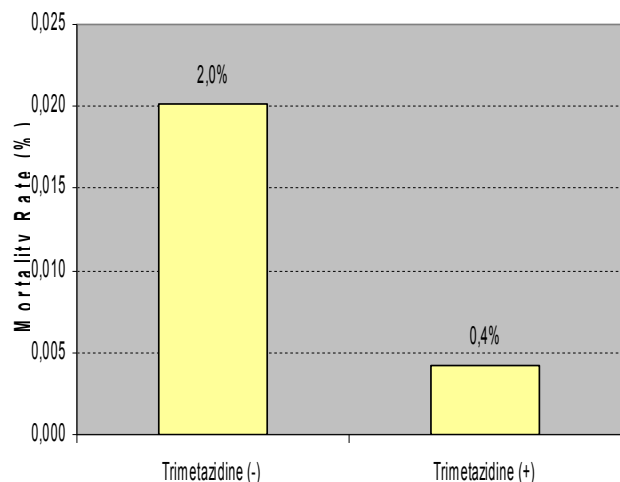
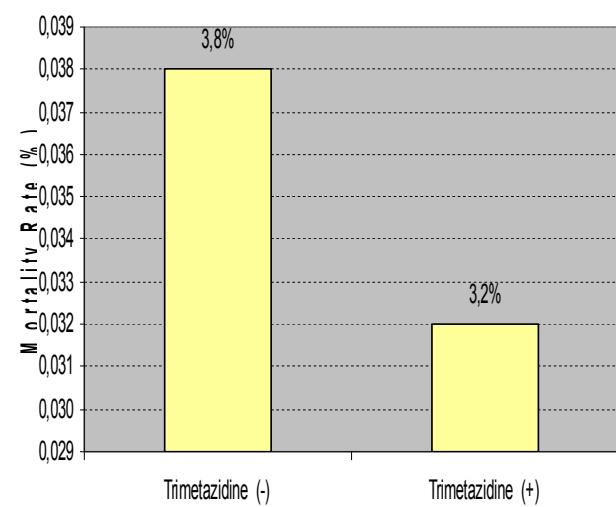


Figure 1:The effect of trimetazidine on in-hospital mortality in patients with NSTEMI



3.2 % and 3.8 %, respectively, ($p>0.05$) (Figure-2). Although, the results are not statistically significant, in-hospital mortality rates of patients with NSTEMI treated with medical therapy only were lower in patients taking trimetazidine as an adjunct to standard therapy than not taking. The mean duration of hospitalization in patients with NSTEMI was 3.8 ± 1.6 day and there was no difference between two subgroups. There was no difference in the presence of diabetes, hypertension and the history of previous myocardial infarction between two subgroups of patients with NSTEMI.

DISCUSSION

These data analyzed the effects of trimetazidine on in-hospital mortality rates of patients with NSTEMI treated with medical treatment strategies only. Our findings reveal that the addition of trimetazidine 20 mg three times in a day per orally without loading dose to standard medical therapy of NSTEMI reduces in-hospital mortality rates of the patients with UAP or NSTEMI, although, results in NSTEMI group are not statistically significant.

The term "metabolic treatment" has been used to describe the use of drugs which improve the function of a single cardiomyocyte¹⁴. Trimetazidine is a piperazine derivate (1-[2, 3, 4-trimethoxy-benzyl]-piperazine) anti-anginal agent that acts metabolically. The main mechanisms of actions of trimetazidine are selectively inhibition of the activity of 3-ketoacyl coenzyme A thiolase which is the last enzyme of the long chain fatty acid beta-oxidation path and an increase in pyruvate dehydrogenase activity which

enables the restoration of the coupling glycolysis and glucose oxidation impaired in ischemic circumstances^{15,17}. Thus, trimetazidine optimizes the demand of oxygen in the mitochondria and prevents a decrease in adenosine three-phosphate (ATP) levels¹⁸ and reduces intracellular acidosis, calcium ion accumulation, hydrogen ion production^{15,19}. Cytoprotective properties of trimetazidine in ischemia-reperfusion injury have been demonstrated numerous experimental studies of ischemia and reperfusion models. Allibardi et al.²⁰ suggested that trimetazidine improves cardiac metabolism in rat hearts in ischemia and reperfusion. Williams et al.²¹ reported that trimetazidine inhibits neutrophil accumulation after myocardial ischemia and reperfusion in rabbit hearts. It has also been reported that trimetazidine limits cytolysis²², apoptosis^{23,24} and membrane damage induced by free radicals²⁵, and reduces mitochondrial sodium and calcium accumulation²⁶ and decreases intracellular acidosis²⁷, and saves mitochondrial function and energy metabolism by decreasing depletion of purines and adenine nucleotides²⁸. Most importantly, the inhibition of mitochondrial long chain 3-ketoacyl coenzyme A thiolase resulting in a change of cardiac energy metabolism from fatty acid oxidation to glucose oxidation may be major mechanism responsible for its cardioprotective effects¹⁷. Moreover, trimetazidine inhibits intra-coronary platelet aggregation on arterial platelet thrombosis superimposed on a ruptured coronary plaque²⁹. All of the above mentioned experimental data explain and support the mortality advantage of trimetazidine added to standard

medical therapy in patients with NSTEMI-ACS in our study.

In several clinical trials, anti-ischemic effects of trimetazidine have been pointed out in patients with stable angina pectoris³⁰⁻³⁵. In contrast, the use of trimetazidine in acute coronary syndrome treatment remains unclear. The European Myocardial Infarction Project-Free Radicals (EMIP-FR) trial in which 19725 patients with acute myocardial infarction were randomized is the largest study investigating the mortality benefit of trimetazidine in acute myocardial infarction patients³⁶. This study reported that trimetazidine does not reduce the mortality in patients taking thrombolytic therapy but it might have some beneficial effects for non-thrombolysed patients³⁶.

Recent years, several clinical trials reported that trimetazidine has many beneficial effects in patients with acute coronary syndrome. Papadopoulos et al. reported that trimetazidine given per orally as adjunct to thrombolytic therapy reduces reperfusion arrhythmias in patients with acute myocardial infarction³⁷. Di Pasquale et al.³⁸ pointed out that trimetazidine added to thrombolytic therapy in patients with anterior wall myocardial infarction lowers the incidence of reperfusion arrhythmias and limits reperfusion damage and infarct size. Ozdemir et al.³⁹ suggested that trimetazidine decreases late potentials after acute myocardial infarction. Ulgen et al.⁴⁰ showed that trimetazidine added to conventional therapy including thrombolytic, beta blocker, heparin, nitrates and aspirin changes the sympatho-vagal balance in favor of vagal activity by increasing parasympathetic activity in acute myocardial infarction. Kountouris et al.⁴¹ suggested that trimetazidine as adjunctive treatment decreases QT dispersion in patients with first acute myocardial infarction. Steg et al.⁴² reported that trimetazidine given as an adjunct to primary angioplasty in patients with acute myocardial infarction led to earlier ST-segment resolution.

Anti-inflammatory effects of trimetazidine have been reported by Kuralay et al.⁴³. They concluded that pre-procedural administration of trimetazidine reduces the levels of tumor necrosis factor alpha, C-reactive protein, nitric oxide products after percutaneous transluminal coronary angioplasty. It has been also reported that trimetazidine reduced in hospital mortality and recurrent myocardial infarctions in patients with acute myocardial infarction and diabetes mellitus type 2⁴⁴. Trimetazidine on the background of standard therapy reduces left ventricular volumes and improves left ventricular systolic and diastolic functions in patients with acute myocardial

infarction⁴⁵. It has also been reported that pre-procedural oral trimetazidine administration significantly reduces acute myocardial injury and improves left ventricular function after percutaneous coronary intervention in patients with acute coronary syndrome^{46,47}.

There are limited reports investigating the effects of trimetazidine on mortality and morbidity in patients with NSTEMI-ACS. Qui et al.⁴⁸ reported that trimetazidine added to standard therapy of senile UAP in 120 patients had reduced the incidence of arrhythmia, the rate of acute myocardial infarction and also the prevalence of sudden death. Romanov et al.⁴⁹ reported that there is a significant rise in functional activity of neutrophils and monocytes in UAP and trimetazidine reduces this activation. Willough et al.⁵⁰ suggested that trimetazidine exerts clinically relevant, significant anti-aggregatory effect in normal subjects and patients with angina pectoris. These studies may support our results and explain in-hospital mortality benefit of trimetazidine in patients with NSTEMI-ACS.

However, our study has some important limitations. These are the relatively small sample size of study population, that the data are non-randomized and retrospective, that there was no homogeneity between subgroups and that there was no long term follow up data since the most of the patients underwent interventional therapies such as percutaneous coronary intervention or bypass surgery in post-discharge period. Also, it is possible that the patients without true UAP might not have been clearly excluded from the analysis, so this might have resulted in high mortality benefit in favor of trimetazidine in UAP group. Moreover, we were not able to collect many patients to calculate mortality difference in the long term follow up since the treatment accordance of non-selected and non-randomized patients was very low in long term period and frequent changes in treatment modalities by physicians' or patients' preference were very high in real-world clinical practice.

CONCLUSIONS

Despite the limitations, this study reveals that trimetazidine added to standard medical therapy in patients with NSTEMI-ACS treated with medical approaches only may provide important in-hospital mortality benefit. However, to verify these results, large scale, randomized clinical trials are needed.

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