ST-YÜKSELMELİ MİYOKARD ENFARKTÜSÜ (STYME) HASTALARINDA HASTANE İÇİ MAJÖR KARDİYAK OLAYLARIN ÖNGÖRDÜRÜCÜSÜ: SERUM POTASYUM DÜZEYLERİNDEKİ DEĞİŞKENLİK ORANI

Variability Rate of Serum Potassium Levels Predicts In-hospital Major Adverse Cardiac Events in Patients with ST-Elevation Myocardial Infarction (STEMI)

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ÖZET

Amaç: Potasyumun (K+) kardiyovasküler hastalıklardaki kritik rolü ve olumsuz kardiyak olayları önlemede normokalemik durumu devam ettirmenin önemi her geçen gün daha iyi anlaşılmaktadır. Çalışmamızda, normal sınırlar içerisinde olmasına rağmen, serum potasyum düzeylerindeki değişkenlik oranı ile ST-yükselmeli miyokard enfarktüsü (STyME) hastalarında izlenen hastane içi majör kardiyak olaylar (MACE) arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntemler: 2013 – 2015 yılları arasında tersiyer merkezimize STyME tanısı ile başvuran toplam 419 hasta retrospektif olarak dizayn edilen çalışmamıza dahil edildi. Hastaneye başvuru anında veya hastane içi takipleri sırasında normal değerlerin dışında K+ düzeyi saptanan hastalar çalışmaya alınmaz iken, hastane yatışı boyunca en az 5 (beş) ardışık K+ değeri mevcut olan hastalar çalışmaya dahil edildi.

Bulgular: Çok değişkenli regresyon analizinde, çalışma populasyonundaki serum K+ düzeylerinin değişkenlik oranı (OR: 7.84, 95%CI: 1.18-51.81, p=0.03) hastane içi olumsuz kardiyak olayların (MACE) bağımsız öngördürücüsü olarak saptandı. Serum K+ düzeylerinin değişkenlik oranı ≥ 0.57 (optimal kestirim değeri) olması halinde, hastane içi olumsuz olayları % 46.2 duyarlılık ve % 84.9 özgüllükle öngörmekteydi. [area under curve (AUC) 0.66, p=0.001].

Sonuç: Çalışmamızın sonuçları, normal sınırlar içinde olsa dahi değişkenlik gösteren K+ düzeylerinin STyME hastalarında hastane içi olumsuz olayların bağımsız bir öngördürücüsü olabileceğini göstermiştir. Bu nedenle, artmış oranda K+ düzeyi değişkenliği gösteren hastaların daha yakından takibi olumsuz kardiyak olayları en aza indirmek açısından büyük önem arz etmektedir.

Anahtar kelimeler: *Potasyum; ST-yükselmeli miyokard enfarktüsü; Majör olumsuz kardiyak olaylar*

ABSTRACT

Objective: The critical role of potassium (K+) in cardiovascular disease and, maintaining a normokalemic state are increasingly being recognized to preclude adverse cardiac events. The main objective of our study was to evaluate whether there is an association between the variability of serum potassium levels, even within the normal range, and in-hospital major adverse cardiovascular events (MACE) in patients with ST-elevation myocardial infarction (STEMI).

Materials and Method: A total of 419 patients who were admitted to our tertiary heart center with a diagnosis of STEMI from May 2013 to May 2015 were included in this retrospective study. The patients who have any serum K+ levels beyond the normal range on admission and during the in-hospital follow-up interval were excluded. The patients who had at least five consecutive serum K+ measurements during the in-hospital stay were included in the study.

Results: In multivariable logistic regression analysis, the variability of serum K+ levels (OR: 7.84, 95%CI: 1.18-51.81, p=0.03) was found to be independently associated with MACE in the study population. The optimal cut-off value of the variability of serum K+ levels was ≥ 0.57 with a sensitivity of 46.2% and a specificity of 84.9% [area under curve (AUC) 0.66, p=0.001].

Conclusion: Our findings provide evidence that variability of serum K+ levels even within the normal range may be an independent predictor of MACE in STEMI patients. Therefore, close follow up of the patients with a high variability of serum K+ levels has utmost importance in order to minimize the risk of MACE.

Keywords: *Potassium; ST-elevation myocardial infarction; Major adverse cardiovascular events*

INTRODUCTION

In the human body, extracellular level of potassium (K+) is mainly regulated by renal excretion in addition to the shift between intracellular and extracellular spaces (1). Particularly, these shifts can alter the electrophysiological features of resting membrane potential in myocardial cells and thus, effect the generation and conduction of impulses in the heart (1). After it had been demonstrated that the lower serum K+ levels are associated with decreased threshold for fibrillation in an animal model (2), several observational studies pointed out the association between increased risk of arrhythmias and hypokalemia in patients with acute myocardial infarction (AMI) (3,4). Hence, serum K+ levels of > 4 mEq/L or even > 4.5 mEq/L was recommended as an optimum target by practical guidelines for the management of ST-elevation myocardial infarction (STEMI) (5). However, recent observational studies consistently report that both reduced and increased levels of K+, even within the normal range, are associated with negative outcomes and increased mortality in patients with AMI (6-8). Moreover, Shiyovich et al. have found that fluctuations which lead K+ levels beyond upper and lower limits were associated with increased risk of in-hospital mortality in AMI patients (9).

AMI, particularly STEMI, influences serum K+ levels by the stimulation of sympathetic nervous system discharge, which subsequently leads beta-adrenergic receptor stimulation that facilitates K+ shift into cells in the first hours (10). Sekiyama et al. showed that such an early transient hypokalemic dip is associated with the severity of ischemia and higher incidence of myocardial infarction (11). Nevertheless, such an early hypokalemic decline was not found in AMI patients who were treated with beta-blockers (12). Not only beta-blockers but also aldosterone blockers, and diuretics can effect serum K+ levels and influence the rate of K+ level changes. In a nutshell, although the pathophysiological mechanisms behind the association between decreased or increased K+ levels and cardiovascular adverse events in patients with AMI are not totally understood, it is evident that even fluctuations, which carry K+ levels to the upper or lower limits, are closely related with adverse cardiac events in AMI patients (9).

As it may be called a further step with regard to this type of a study, we speculated that the variability of consecutive serum K+ measurements in normal range (defined as 3.5 mEq/L-5.5 mEq/L) with using a standard deviation method may be associated with in-hospital major adverse cardiac events (MACE) in STEMI patients. Hence, in the present study, our objective was to find out whether any association exists between serum K+ variability rates and in-hospital MACE in patients with STEMI.

MATERIAL and METHODS

Data collection

A total of 419 patients who were admitted to Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, from May 2013 to May 2015, with a diagnosis of STEMI were included in this retrospective study. Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital is a tertiary referral heart center with a high-volume of percutaneous coronary intervention (PCI) (around 2500 PCI per year). The patients who underwent a thrombolytic treatment, were pregnant, were on chronic renal replacement therapy (any type of dialysis), had an acute or chronic infection, needed mechanical ventilation, and those who referred to emergency or urgent coronary artery bypass graft surgery were excluded from the study. In addition, patients with incomplete data in the hospital records were excluded. All the data including demographic, clinical as well as the laboratory measurements were obtained from the hospital's medical records. In the current study, the patients who had at least five consecutive serum K+ measurements during the in-hospital stay were included in the study. The patients who had any serum K+ level beyond 3.5–5.5 mEq/L on admission and during the in-hospital follow-up were excluded in order to preclude potential variability bias. In all patients, serum K+ levels were measured within the first two hours of index hospitalization. Also, the patients who died due to non-cardiovascular causes were not included in the study. According to current guidelines, all patients received the standard medical therapy such as beta-blocker, acetylsalicylic acid, clopidogrel or ticagrelor or prasugrel, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB).

The study was approved by the local ethics committee, and it was performed according to the principles of the Declaration of Helsinki.

Echocardiography and laboratory analysis

Routine complete blood cell count was performed on a blood sample obtained on admission. The creatine kinase myocardial band (CK-MB) measurements were repeated at six hours until the peak values were achieved. Serum K+ level was measured by the ion-selective electrodes indirect method using Roche Cobas 6000 Biochemistry Auto-Analyzer (Indianapolis, USA). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. The left ventricular ejection fraction was measured using the modified Simpson method.

Definitions and in-hospital follow-up

The variability of serum K+ levels was defined as the standard deviation of the consecutive K+ measurements in every patient. In the study, MACE was accepted as the combination of cardiac mortality, advanced atria-ventricular (AV) block, and malignant ventricular arrhythmias (13). All clinical events were evaluated by a trained study coordinator who reviewed the patients' electronic hospital records. Ventricular arrhythmias consisted of sustained ventricular tachycardia (VT) that was defined as a regular and fast heart rate that arises from improper activity in the ventricle of the heart that exceeds 30 seconds in duration and ventricular fibrillation (VF) that is a vibration of the heart instead of pumping due to disorganized electrical activity in the ventricles (14). Advanced AV block was accepted as two or more consecutive P-waves were blocked (15). STEMI diagnosis was accepted based on the following criteria; (I) typical chest pain lasting for > 30 minutes and (II) ST-segment elevation in at least 2 contiguous leads with the following cut-off points: at least 0.2 mV in men or at least 0.15 mV in women in leads V2–V3 and/or at least 0.1 mV in the other leads (III) definite/probable a new left bundle branch block (16).

Statistical analyses

All data were presented as a mean ± SD for parametric or a median [interquartile range] for non-parametric variables and as percentages (%) for categorical variables. Continuous variables were checked for the normal distribution assumption using Kolmogorov-Smirnov statistics. Differences between MACE (+) and MACE (-) subjects were evaluated using the Kolmogorov-Smirnov test or the Student-t test when appropriate. Categorical variables were tested by Pearson's $\chi 2$ test and Fisher's Exact Test. Univariable and multivariable logistic regression analysis were performed to investigate the predictors of MACE in the study population. Forward stepwise multivariate regression models using parameters with $p<0.10$ were created to identify the independent predictors of MACE. Receiver operating curves (ROC) were generated to define the cut-off values for the variability of K+ levels. P-values were two-sided, and values $p<0.05$ were considered statistically significant. All statistical studies were carried out using Statistical Package for Social Sciences software (SPSS 16.0 for Windows, SPSS Inc., Chicago, Illinois).

RESULTS

In the present study, the sample size consisted of 419 patients who had a diagnosis of STEMI. Baseline characteristics and laboratory findings of all patients were depicted in Table 1. The mean age of the subjects was 57.1±12.6 years, and the majority of the patients were male gender (84%). MACE was observed in 39 (9.3%) out of 419 patients in our cohort. The study population was divided into two groups; the patients who had a MACE and those who did not. The frequency of hypertension and smoking reach statistical significance between the groups ($p<0.05$, for all), while the frequency of diabetes mellitus, hyperlipidemia, and a prior history of myocardial infarction was not different between the groups ($p>0.05$, for all). On admission, the patients who had a MACE had higher Killip class examination, anterior myocardial infarction and lower systolic blood pressure and decreased left ventricular ejection fraction when compared to those who did not suffer from MACE. In terms of laboratory findings, peak CK-MB and serum K+ levels at admission were significantly different between the groups ($p<0.05$, for all). Comparison of other laboratory findings was similar between both the groups ($p>0.05$, for all).

Table 1: Baseline characteristic and laboratory findings of all patients with P value.

	MACE (+), n=39	MACE (–), n=380	P value
Age, years	63 ± 13.9	56.4 ± 12.3	**<0.01**
Male gender, n (%)	31 (79.5)	320 (84)	0.44
History			
Diabetes mellitus, n (%)	11 (28.2)	71 (18.7)	0.15
Hypertension, n (%)	24 (61.5)	151 (39.7)	**0.01**
Hyperlipidemia, n (%)	6 (15.4)	53 (13.9)	0.80
Smoking, n (%)	20 (51.3)	272 (71.6)	**0.01**
Prior MI, n (%)	8 (20.5)	63 (16.6)	0.11
At admission			
Systolic blood pressure, mmHg	104.8 ± 33.6	122.4 ± 19.7	**< 0.01**
Heart rate, rate/min	81.7 ± 25.2	79.7 ± 16.4	0.48
Killip class 2-4, n (%)	37 (94.9%)	98 (25.8%)	**< 0.01**
Ejection fraction, %	38.3 ± 12	45.6 ± 8.7	**0.01**
Anterior myocardial infraction, n (%)	10 (25)	206 (54)	<0.01
Duration of chest pain, h	4.2 ± 2.1	3.6 ± 2.8	0.21
Door to balloon time, min	32.3 ± 11.1	31.1 ± 9.8	0.46
Laboratory findings			
Peak CK-MB, ng/mL	300 [272]	136 [161.2]	**< 0.01**
Glucose, mg/dL	148.1 ± 39.2	157.6 ± 73.5	0.42
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.3	0.92
eGFR, mL/min/1.73m2	78±13	81±15	0.86
Hematocrit, %	39.4 ± 3.7	40.6 ± 5.0	0.13
Platelet count, x103/mm3	239.5 ± 77.1	254 ± 76.8	0.24
White blood cell count, x103/mm3	12.1 ± 3.8	12.1 ± 3.4	0.90
Potassium, mEq/L (admission)	4.39 ± 0.71	4.16 ± 0.52	**0.01**
During hospital stay			
Variability of potassium (K+) levels	0.51 ± 0.26	0.37 ± 0.19	**<0.01**
Total number of potassium (K+) checks	242	2224	-
Number of potassium (K+) checks per patient	6.2 ± 0.7	5.8 ± 0.5	0.76

Abbreviations: MACE; major adverse cardiovascular events, MI; myocardial infarction, CK-MB; creatine kinase-myocardial band, eGFR; estimated glomerular filtration rate.

Table 2: Multivariate logistic regression analysis for prediction of in-hospital MACE.

	OR (95% CI)	P value
Peak CK-MB	1.003 (1.001-1.005)	0.01
Smoking	0.37 (0.147-0.949)	0.03
Systolic blood pressure	0.97 (0.961-0.949)	0.01
Killip class 2-4 on admission	39.44 (8.77-177.35)	< 0.01
Ejection fraction	0.95 (0.919-0.997)	0.03
Variability of serum K+ levels	7.84 (1.18-51.810)	0.03

Abbreviations: MACE; major adverse cardiovascular events, CK-MB; creatine kinase myocardial band, K+; potassium.

During the hospital course, the number of serum K+ checks per patient was similar between the groups; however, the variability of serum K+ levels was significantly different in patients who had a MACE compared to those who did not (p<0.05). Both groups were not different in terms of standard medical treatment. In univariable regression analysis; age, K+ at admission, hypertension, smoking, peak CK-MB levels, Killip 2-4 class examination, systolic blood pressure, left ventricular ejection fraction, and the variability of serum K+ levels were found to be correlated with MACE. After applying these parameters to the multivariable logistic regression analysis; only peak CK-MB levels (OR: 1.003, 95%CI: 1.001-1.005, p=0.01), systolic blood pressure (OR: 0.97, 95 %CI: 0.961-0.996, p=0.01), smoking (OR: 0.37, 95%CI: (0.147-0.949, p=0.03), Killip 2-4 class examination (OR: 39.44, 95% CI: 8.77–77.35, p< 0.01), left ventricular ejection fraction (OR:0.95, 95%CI: 0.919–0.997, p=0.03), and the variability of serum K+ levels (OR:7.84, 95%CI: 1.18-51.81, p=0.03) were found to be independently associated with MACE in the study population (Table 2). In ROC analysis, the variability of serum K+ level of 0.57 predicted MACE with a sensitivity of 46.2% and a specificity of 84.9% [area under curve (AUC) 0.66, p=0.001] (Figure 1).

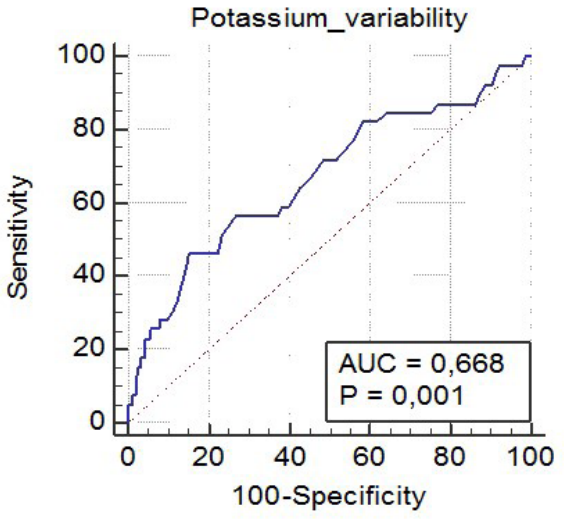

Figure 1. ROC curve analysis of the association between the variability of serum K+ levels and in-hospital MACE in STEMI patients. Abbreviations: ROC: Receiver operating characteristic. AUC: Area under the curve.

DISCUSSION

The main finding of the current study can be summarized as; the variability of serum K+ levels, even within the normal range (defined as 3.5 mEq/L-5.5 mEq/L), was found to be associated with an increased risk of MACE in STEMI patients. As a result, this finding provides and supports the evidence that close follow-up of serum K+ levels has utmost importance in STEMI patients during the in-hospital course.

In the human body, maintaining the proper distribution of K+ across the cell membrane plays a crucial role in the myocardial cells for the generation and conduction of impulses in the heart (1). In the acute phase of STEMI, there is an activation of the sympathetic nervous system secondary to acute myocardial ischemia, which results in the increase of catecholamines levels such as noradrenaline and adrenaline (17). These elevated levels of catecholamines stimulate the myocardial cell membrane ion pump, namely Na-K-ATPase pump, via Beta1-adrenergic receptor resulting in the distribution of K+ more intra-cellularly and less extra-cellularly, thus, causing redistributional hypokalemia (17). Consequently, the ischemic myocardium becomes more hyperpolarized and the electrical inhomogeneity, which increases susceptibility to ventricular arrhythmia, occurs. Besides these mechanisms, acute myocardial injury can lead to decreased cardiac output, thus causing constriction of the renal artery and renal medullary hypoxia, all of which may induce the development of hyperkalemia (18). Accordingly, several studies reported that admission serum K+ levels, either profoundly low or extremely high, were shown as an independent predictor of in-hospital mortality, particularly secondary to ventricular arrhythmia in STEMI patients (8-10). In our study, in order to exclude these factors, our sample size consisted of the patients whose serum K+ levels were within the normal range during the index hospitalization.

The prognostic value of normal range serum K+ levels has been investigated in previous studies. In a recent study, which included 1924 AMI patients (half of the study population was diagnosed as STEMI), Choi et al. found that there was no association between the mean serum K+ levels and the development of

ventricular arrhythmias (19). A consistent finding was found in our study as the mean serum K+ level was not an independent predictor of MACE in the multivariable logistic regression analysis. Moreover, Shlomai et al. demonstrated that the patients with 'normal-very high' serum K+ levels (which was defined as 4.45 mEq/L-5.2 mEq/L) displayed increased frequency of in-hospital and short-term mortality when compared to those with 'low-normal' serum K+ levels (which was defined as 3.5 mEq/L-3.9 mEq/L) (20). Furthermore, two retrospective studies revealed that admission K+ level of 4.3, even within the normal range, might be an independent predictor of recurrent target vessel revascularization and the infarct size in patients with AMI (21, 22).

Even though profoundly low or extremely high serum K+ levels are associated with deleterious prognosis in patients with AMI, the data regarding the association between the variability of serum K+ levels within the normal range and in-hospital adverse outcomes among STEMI patients is scarce. In a retrospective study, which consisted of a heterogeneous group of AMI patients (nearly half of these patients were diagnosed as STEMI), Shiyovich et al. reported that the first serum K+ levels in the extreme categories and increased serum K+ fluctuations were found to be more common in patients with AMI who died in hospital rather than survivors (9). However, in this study, the authors did not exclude the patients whose serum K+ levels beyond out of normal range on admission and during the in-hospital follow-up. The main focus of our study was to assess whether the variability of serum K+ levels, even within the normal range, is associated with in-hospital adverse cardiovascular outcomes in STEMI patients. Our findings demonstrated that variability of serum K+ levels is related to a higher risk of MACE in STEMI patients. In addition, these findings provide evidence that variability of serum K+ levels, rather than mean values, may be more valuable in terms of prognosis. We thought that the variability of serum K+ levels might be a marker of severity because we noted a higher rate of Killip class examinations, lower systolic blood pressure and left ventricular ejection fraction in patients with a higher variability of serum K+ levels. Hence, the increased rate of MACE in patients with a higher variability of serum K+ levels might be confounded by the aforementioned factors. However, after adjustments of these factors, the variability of serum K+ levels remained an independent predictor of MACE in our study. According to the present study results, the close monitoring of variability of serum K+ levels, even within the normal range, may be necessary in STEMI patients during the hospital course.

Limitations of the study

Our study had some limitations. Firstly, it was a single-center, retrospective, and observational study; however, consecutive patients were enrolled in the study. Secondly, our sample size was relatively small. Thirdly, even though the patients with at least 5 serum K+ measurements were included in the study, the timing of the tests was not uniform. Fourthly, we might not able to exclude some unmeasurable confounders of MACE in spite of using a multivariable logistic regression analysis. Fifth, the data regarding the association of serum K+ levels and the timing of the development of ventricular arrhythmia was not able to be correctly identified in all patients. Finally, our study findings warrant further multi-center, prospective, and large studies in order to elucidate the exact role of variability of serum K+ levels in STEMI patients and to apply these findings to daily clinical practice.

CONCLUSION

In the present study, we observed that variability of serum K+ levels may be an independent predictor of MACE in STEMI patients. Hence, the patients with a high variability of serum K+ levels should be more closely followed up due to an increased risk of mortality among these patients. However, as this was a retrospective and single-center study, definitive conclusions cannot be drawn about the value of variability of serum K+ levels based on the present findings. Thus, further prospective, multicenter, and larger studies are needed to confirm our findings.

Declaration of conflict of interest

All authors declare that they do not have conflict of interest.

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