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Prognostic Impact of Hyperosmolarity in Patients Undergoing Primary Angioplasty for ST-Segment Elevation Myocardial Infarction

ST-Yükselmeli Miyokard İnfarktüsü için Primer Anjiyoplasti Uygulanan Hastalarda Hiperosmolaritenin Prognoza Etkisi

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Özet

Amaç: Hiperosmolarite yüksek mortalite ile ilişkilidir, fakat kestirim değeri ile ilgili çok az şey bilinmektedir. Primer perkütan koroner girişim uygulanan ST-yükselmeli miyokart infarktüsü (STYMI) hastalarında hiperosmolarite ve uzun dönem sonuçlar arasındaki ilişki bilinmemektedir.

Yöntem: Ardışık olarak alınan, primer perkütan girişim planlanan STYMI tanılı 2.503 hasta retrospektif olarak değerlendirildi. Hiperosmolarite için kestirim değeri ROC eğrisi ile elde edildi. Osmolarite eşiği kestirim değerinin üzerindeyse "yüksek grup", altındaysa "düşük grup" olarak sınıflandırıldı.

Bulgular: : Düşük grupta 1.669 hasta (ort. yaş 55.3±11.6), yüksek grupta 834 hasta vardı (ort.yaş 59.1± 12.1). Serum osmolarite seviyeleri yüksek grupta 295,9 ± 6,01 mosm/l, düşük grupta 281,6 ± 6,8 mosm (p

Yüksek grupta hastane içi ve uzun dönem mortalite anlamlı olarak daha yüksekti (62, 2.4% vs 1.5%, P < 0.001,sırasıyla). Ortalama takip süresi 23 (1-54) aydı. Uzun dönem takipte çok değişkenli analiz; büyük olumsuz kardiyak olayları, yüksek hiperosmolarite grubunda bağımsız olarak öngördü (olasılık oranı 1.72, 95% güven aralığı 1.07 to 2.77, p 0.02).

Sonuç: Uzun dönem takipte, primer perkütan koroner girişim uygulanan ST-yükselmeli miyokart infarktüslü (STYMI) hastalarda hiperosmolarite; sodyum, kan şekeri ve kan üre azotu (BUN)' dan bağımsız olarak, büyük olumsuz kardiyak olayları bağımsız olarak öngördürdü.

Anahtar Kelimeler: ST-yükselmeli miyokart infarktüsü, primer anjioplasti, hiperosmolarite.

Abstract

Objective: Hyperosmolarity (hyp) is associated with high mortality rates, yet little is known about its predictive value. The relation between hyperosmolarity and long-term outcomes in patients with ST-segment elevation myocardial infarction who undergo primary percutaneous coronary intervention is not known.

Method: A total of 2.503 consecutive patients with STEMI undergoing primary angioplasty were retrospectively evaluated. Cutoff value for hyperosmolarity was calculated with receiver–operating characteristic (ROC) curves. If osmolarity was above the threshold, patients were classified as ''high group''. If osmolarity was under the threshold, patients were classified as ''low group''.

Results: There were 1.669 patients in the low-group (mean age 55.3±11.6 years) and 834 patients in the high-group (mean age 59.1± 12.1 years). Serum osmolarity levels were 295,9 ± 6,01 mosm/l in the high-group and 281,6 ± 6,8 mosm/l in the low-group (p < 0.001, respectively). The mean follow-up time was 23 (1-54) months. In a multivariate analyses, high-hyp group was an independent predictor of major adverse cardiac events during the long-term follow-up (odds ratio 1.72, 95% confidence interval 1.07 to 2.77, p 0.02).

Conclusion: In conclusion, independently of sodium, glucose and BUN, hyperosmolarity is an independent predictor of long-term major adverse cardiac outcomes in patients with ST-segment elevation myocardial infarction who undergo primary percutaneous coronary intervention.

Keywords: ST-segment elevation myocardial infarction, primary angioplasty, hyperosmolarity.

Introduction

Hyperosmolarity (hyp) and hypernatremia are prognostic factors in patients admitted to Intensive Care Units (1–3). Hyperosmolar circumstances are a known concern in geriatric institutionalized patients (4). Whether diabetic or not, hyperosmolar states in older patients are generally associated with a high mortality rate during hospitalization, within the range of 30 to 41% (5-7) and involving high costs (8). A well-balanced state of hydration is an integral issue in vitally ill patients and serum osmolarity can be used to estimate it directly (9). The degree of hypo- or hyper-natremia has been reported to be a risk factor for death (7,8,10). Numerous studies showed that in patients presenting with acute myocardial infarction, elevated plasma glucose at admission is associated with increased mortality (11-13).

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Table 1. Baseline characteristics of study patients

Variables	Low group (N=1669)	High group (N=834)	p value
Age (years) (SD)	55,3±11,6	59,1±12,1	<0,001
Men n (%)	1425 (56,9)	651 (26)	<0,001
Diabetes mellitus n (%)	306 (12,2)	315 (12,5)	<0,001
Hypertension n (%)	612 (24,4)	370 (14,7)	<0,001
Current smoker n (%)	1006 (40,1)	442 (17,6)	<0,001
Anterior myocardial İnfarction n (%)	849 (33,9)	379 (15,1)	0,01
Admission cardiogenic Shock n (%)	27 (1)	44 (1,7)	<0,001
Door-to-balloon time (hours) (SD)	3,24±2,4	3,34±2,44	0,42

SD, standard deviation. Data are expressed as mean ± SD for normally distributed data and as number (percentage) for categorical variables.

Additionally, the relationship between impaired renal function and worse clinical result is well established (14,15). Crucially, elevated blood urea nitrogen (BUN) is tremendously predictive of mortality, myocardial infarction, and stroke, independently of serum creatinine, estimated glomerular filtration rate (GFR), and other biomarkers (16). On account of this, the combination of plasma sodium, glucose and BUN into a single marker may yield a higher predictive accuracy as well as feasible application in clinical practice in patients with ST-segment elevation myocardial infarction who undergo primary percutaneous coronary intervention. Although there is an association between hyp and cardiovascular disease (17), the underlying pathophysiology remains unclear. Additionally, there is no study evaluating the prognostic impact of hyp in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (p-PCI) in the literature. The aim of the present study was to assess, in a great population, it was hypothesized that hyp would be related with enhanced risk of in-hospital and long-term adverse outcomes after p-PCI for STEMI.

Materials and Methods

After obtaining approval from the local ethics committee, we retrospectively assessed 2.825 consecutive patients with STEMI who were admitted to the emergency department of our hospital and underwent p-PCI procedures in our catheter laboratory between October 2003 and March 2009. All patients gave their written informed consent. Patients were enrolled in the study if they fulfilled the following criteria: (i) if they presented within 12 h (18 h for cardiogenic shock) from the onset of symptoms (typical chest pain lasting for >30min), (ii) if there was ST-segment elevation of at least 2mm in at least two contiguous electrocardiography (ECG) leads or new onset of complete left bundle-branch block, (iii) patients with p-PCI (angioplasty and/or stent deployment). Patients with active infection, autoimmune diseases, hematologic proliferative disease, and neoplasia were excluded .Three hundred twenty-two patients were excluded because of no indication for PCI (n=96), coronary bypass surgery was not suitable for PCI (n=85), missing or unavailable hyp value (n=133), and dialysis history (n=8). Therefore, the final study population consisted of 2.503 patients. Patients were divided into low and high groups depend on admission hyp values A high hyp group (n = 834) was defined as a value in the high tertile (≥ 289.83 mosm/l), and a low hyp group (n = 1669) was set as a value in the low tertile (< 289.83 mosm/l). All pPCI procedures were performed by experienced interventional cardiologists who were unaware of the patient's clinical information. Cardiovascular risk factors (smoking, hypercholesterolemia (HL), hypertension (HT), and diabetes mellitus (DM), the patients' demographic information and cardiovascular history, were taken from the

medical records. DM was defined as a previous diagnosis, use of antidiabetic medicines, or a fasting venous blood glucose level ≥126 mg/dL on 2 occasions in previously untreated patients. HT was defined as previous use of antihypertensive medication, a systolic pressure >140 mm Hg, or a diastolic pressure >90 mm Hg on at least 2 separate measurements. HL was defined as total cholesterol of >200 mg/dL. Anemia was defined as a baseline hemoglobin <13 mg/dL in men and <12 mg/dL in women (18). Angina-to-reperfusion time and door-to-balloon time were also obtained during hospital stay. Electrocardiography was performed and complete blood counts and other serum values (Na+, urea and glucose etc.) were determined on admission before catheterization procedures. Osmolarity is an estimation of the osmolar concentration of plasma and is proportional to the number of particles per liter of solution; it is expressed as mosm/l (19). This is what is used when a calculated value is derived. It is derived from the measured Na+, urea and glucose concentrations. The following equations can be used to calculate osmolarity: ''2 [Na+]+ Glucose÷18+Bun÷2.8''. The reference values for plasma osmolarity were between 275 and 295 mosm/l (19). Osmolality is a measure of the moles (or osmoles) of solute per kilogram of solvent expressed as (mol/kg, molal , or m) (19). At 48 to 72 hours after revascularization, transthoracic echocardiography was performed using Vivid S5 probe 3S-RS (GE Healthcare) with a 1.7/3.4 MHz phased-array transducer, recordings were received with patients positioned in the left lateral decubitus position and the left ventricular ejection fraction (LVEF) was measured using the biplane Simpson method (20). All patients took chewable aspirin 300 mg (unless contraindicated) and a 300-mg loading dose of clopidogrel before they underwent coronary angiography. The infarct related artery (IRA) was then graded according to the Thrombolysis In Myocardial Infarction (TIMI) classification (21). Heparin (10,000 U) was administered once the coronary anatomy had been ascertained. P-PCI was performed only in the infarct artery. Successful primary PCI was defined as a residual stenosis <50% and TIMI grade 3 flow after the procedure. The use of glycoprotein IIb/IIIa inhibitors was left to the discretion of the operator. Follow-up data were obtained from hospital records or by interviewing (in person or by telephone) patients, family members, or primary care physicians. Cardiogenic shock was identified as explicit and persistent (>30 minutes) hypotension with systolic arterial pressure <80 mm Hg and signs of hypoperfusion owing to left ventricular dysfunction, right ventricular infarction, or mechanical complications. Advanced heart failure was defined as New York Heart Association functional classification ≥III. Multivessel disease was defined as stenosis >50% in >1 of the major coronary arteries. Acute stent thrombosis was defined as an abrupt onset of cardiac symptoms (i.e., acute coronary syndromes), elevations in biomarker levels, or electrocardiographic evidence of myocardial injury after stent deployment in the first 24 hours and angiographic evidence of a flow-limiting thrombus near a previously placed stent.

Table 2. Laboratory Findings of Patients.

Variables	Low group (N=1669)	High group (N=834)	P value
Creatinine concentration at admission (mg/dl)	0,94±0,32	1,05±0,43	<0,001
Peak creatine kinase-MB (U/L)	213,6±170	235,4±210,3	0,006
Admission blood glucose concentration (mg/dl)	141,4±53,9	187,9±101,8	<0,001
Hemoglobin (g/dl)	13,72±1,68	13,4±1,77	<0,001
Admission blood Urea concentration (mmol/L).	15,3±5,2	19,2±10,5	<0,001
Admission plasma sodium level (mEq/ dl)	134,1±3,6	139,3±3,5	<0,001
Plasma osmolarity (mosm/l)	281,6±6,8	295,9±6,01	<0,001

Data are expressed as mean ± SD for normally distributed data.

Table 3. Angiographic and Procedural Characteristics of Patients.

Variables	Low group (N=1669)	High group (N=834)	P value
Preprocedural TIMI grade 0-1 n (%)	1461 (58,3)	732 (29,2)	0,84
Postprocedural TIMI grade 3 n (%)	1465 (58,5)	608 (24,2)	<0,001
3 of diseased vessels n (%)	390(%15,2)	241(%9,6)	0,008
Tirofiban use, n (%)	817 (%32,6)	380 (%15,1)	0,132

TIMI, thrombolysis in myocardial infarction.

Cardiovascular mortality was defined as unexplained sudden death, death due to acute myocardial infarction, heart failure, and/or arrhythmia. Reinfarction was defined as serum creatine kinase-MB enzyme levels at least 2 times of the upper limit of normal and new ST-segment elevations. We set the repeat target vessel revascularization (TVR) as the need for PCI or coronary surgery because of restenosis or reocclusion of the IRA. Major adverse cardiac events (MACEs) were defined as cardiovascular mortality, reinfarction, repeat target vessel revascularization (percutaneous or surgical), or acute stent thrombosis. Quantitative variables are expressed as mean ± SD and qualitative variables as percentages. Comparison of the parametric values between the 2 groups (high and low blood levels of hyp) was performed using 2-tailed Student's t tests. Categorical variables were compared by chi-square and Fisher exact tests. Backward elimination multivariate logistic regression analysis including variables with p values <0.10 was performed to identify independent risk factors of MACEs during in-hospital and long-term follow-up. The cumulative survival curve for long-term cardiovascular mortality was constructed using the Kaplan-Meier method, with differences assessed with log-rank tests. A p value < 0.05 was considered statistically significant. Analyses were performed using SPSS Statistics, version17.0 (SPSS Inc, Chicago, Illinois).

Results

Overall 2.518 patients, 1.669 patients in the low - group and 834 patients in the high-group.2.076 (82.9%) males and 427 (17.1%) females, participated in this study. Mean age of the participants was 56.6 + 11.9 years. Baseline characteristics are summarized in Table 1. Patients with high- group tended to be older and more commonly had histories of diabetes and had admission shock. Smoking was more frequently in patients with low- group (Table 1). Serum osmolarity levels were 281,6±6,8 mosm/l in low-group and 295,9±6,01 mosm/l in the high -group (p <0.001). Baseline serum creatinine, sodium, glucose, BUN were higher in the high- group (p <0.001 for each; (Table 2). Post procedural Thrombolysis in Myocardial Infarction 3 flow, which is defined as patients with normal perfusion in whom the contrast is minimally persistent at the end of the washout phase in the coronary angiography (22), were less frequently seen in the high-group (p <0.001) With respect to trofiban use, there was no statistically significant difference between groups (p=0.132) (Table 3). The in-hospital mortality rate was significantly higher in patients with high-group in those with low-group (2.4% vs 1.5%, p <0.001), MACEs were more frequent (3.9% vs 3.8%, p <0.001) (Table 4). Median follow-up time was 23 (1-54) months. Cardiovascular mortality (p <0.001) and severe heart failure (p <0.001) were higher in high-group (Table 5). The Kaplan-Meier survival plot for cardiovascular mortality in both the groups is presented in Figure 1. In a stepwise multivariate Cox-regression analysis, high- group was an independent predictor of long-term MACEs (odds ratio 1.72, 95% confidence interval 1.07 to 2.77, p 0.02) (Tables 6). Age, DM, Killip class > 1, post procedural TIMI grade < 3 and hemoglobin were also independent predictor of MACEs during the long-term follow-up periods.

Table 4. In-hospital cardiac events and complications

Inhospital events	Low group (N=1669)	High group (N=834)	P value
In-hospital mortality, n (%)	38 (1,5)	62 (2,4)	<0,001
Reinfarction, n (%)	31(1,2)	20(0,7)	0,37
Target-vessel revascularization, n (%)	65 (2,5)	45 (1,7)	0,08
MACE, n (%)	100 (3,9)	97 (3,8)	<0,001
Cardiopulmonary resuscitation, n (%)	47 (1,8)	70 (2,7)	<0,001
Dialysis, n (%)	3 (0,1)	13 (0,5)	<0,001
Serious ventricular arrhythmia, n (%)	48 (1,9)	68 (2,7)	<0,001
Inotrope use, n (%)	101 (4,03)	107 (4,2)	<0,001
IABP using, n (%)	47 (1,8)	71 (2,8)	<0,001
Temporary pacemaker, n (%)	48(1,9)	45 (1,7)	0,002
LVEF	47.85±11.11	46.5±11.44	0.04
Time of hospital stay, (days)	6,97±3,65	7,86±4,7	<0,001

Mean values (standard deviation) and % (n) are reported for continuous and categorical variables, respectively. MACE, major adverse cardiac events (cardiovascular death, reinfarction, target-vessel revascularization, LVEF, left ventricular ejection fraction, IABP, Intra-aortic balloon pump.

Discussion

The major findings of the present single center study, the first to date examining the impact of hyperosmolarity in patients undergoing primary PCI for STEMI. Hyperosmolarity was independently associated with an increase in in-hospital, long-term mortality, and longer hospital stay. Hyperosmolarity was one of the strongest independent predictors of diminished survival. Plasma sodium, glucose and BUN are the primary components driving plasma osmolarity. Hypernatremia produce changes in hemostatic function consistent with a hypercoagulable state (Increase in factor VIII coagulant acitivity, the ristocetin co-factor, von Willebrand antigen, plasminogen activator activity and fibrinopeptide A concentration with shortening of the activated partial thromboplastin time) (23). The mechanisms of the effect are unclear. These changes in hemostatic function might contribute to the thromboembolic complications of conditions such as hyperosmolar coma in diabetes mellitus or severe heatstroke in which degrees of hypernatremia occur. Acute hyperglycaemia is associated with worse in-hospital in patients with STEMI (24). Hyperosmolarity due to hyperglycaemia has been shown to have detrimental effects on survival of ACS patients, especially in nondiabetics (11-13). In the same way, elevated levels of BUN, a major contributory to plasma osmolality, were considerable predictive of mortality, recurrent myocardial infarction, and congestive heart failure after 30 days amongst patients with ACS (16,25). Gasior et al. (26) found that acute hyperglycaemia in patients with ACS was associated with an increased risk of both in-hospital and long-term adverse outcomes. Bhalla et al. (27) showed that the impact of hyperosmolality in patients admitted for acute stroke. Osmolality greater than 296 mosmol/kg upon admission therefore resulted in a 2.4-fold increased risk of death (27).

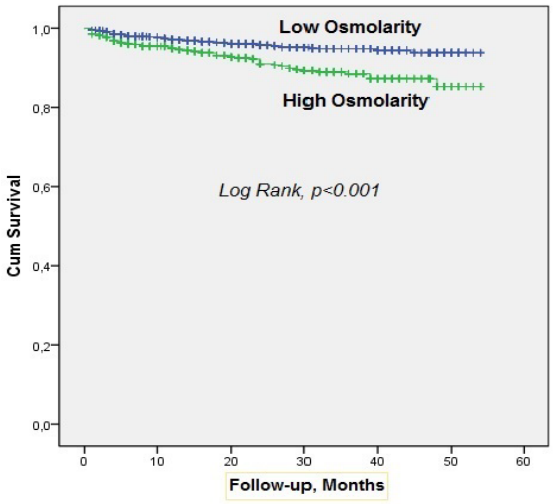

Figure 1. Kaplan-Meier cumulative curves for long-term survival according to high versus low osmolarity groups.

Table 5. Long-term cardiac events

Variable	Low group (N=1602)[a]	High group (N=755)[b]	P value
Cardiovascular mortality, n (%)	60 (2,5)	65 (2,7)	<0,001
Severe Heart failure, n (%)	95 (4,03)	84 (3,5)	<0,001
Reinfarction, n (%)	126 (5,3)	66 (2,8)	0,49
TVR, n (%)	255 (10,8)	127 (5,3)	0,62
MACEs, n (%)	334 (14,1)	187 (7,9)	0,05

TVR, target vessel revascularization; MACE, major adverse cardiovascular event (cardiovascular death, reinfarction, target vessel revascularization.) a .n =1602 for low group (there is no follow-up for 29 patients). b . n=755 for high group (there is no follow-up for 17 patients).

The impact of renal insufficiency on in-hospital and long-term mortality of patients with acute ST-elevation myocardial infarction is well established (28). Even though serum blood urea nitrogen (BUN) concentrations themselves, serum creatinine, estimated creatinine clearance and estimated GFR are defective measures of renal function, the specific pattern of BUN reabsorption plays a pivotal role for its predictive value (16). BUN as an independent marker of subsequent mortality among patients with acute coronary syndromes (16). Angiotensin-II regulated urea reabsorption in the distal tubule is closely linked to water reabsorption under the influence of antidiuretic hormone (16,29,30). Therefore, heart failure or neurohumoral alterations resulting in renal hypoperfusion are indicated by BUN, regardless of alters in serum creatinine or GFR, as urea reabsorption is augmented by the sympathetic nervous system and renin–angiotensin–aldosterone system, both established correlates of cardiovascular risk (16,30–32).

Table 6. Multivariate predictors of long-term follow-up major adverse cardiac events.

Variables	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.077 (1.060-1.095)	<0.001	1.051 (1.028-1.074)	<0.001
Diabetes mellitus	2.92 (2.02-4.20)	<0.001	2.62 (1.62-4.23)	<0.001
Hypertension	2.18 (1.5-3.17)	<0.001	-	-
Female	2.31 (1.55-3.44)	<0.001	-	-
Killip class >1	5.93 (3.57-9.83)	<0.001	4.18 (2.32-7.54)	<0.001
Anterior myocardial infarction	1.67 (1.16-2.42)	0.006	-	-
Current smoker	0.63 (0.43-0.91)	0.015	-	-
Hemoglobin (g/dl)	0.76 (0.69-0.84)	<0.001	0.83 (0.72-0.94)	0.006
High osmolarity	2.42 (1.69-3.48)	<0.001	1.72 (1.07-2.77)	0.02
Postprocedural TIMI grade <3	3.96 (2.66-5.88)	<0.001	2.35 (1.40-3.95)	0.001
3 of diseased vessels, n (%)	2.4 (1.66-3.48)	<0.001	-	-
Creatinine concentration at admission (mg/dl)	2.87 (1.71-4.8)	<0.001	-	-
BUN	1.049 (1.028-1.071	<0.001	-	-
Admission blood glucose concentration (mg/dl)	1.006 (1.004-1.008)	<0.001	-	-

Mean values (standard deviation) and % (n) are reported for continuous and categorical variables, respectively R: Odds ratio; Abbreviations: CI, confidence interval;

The relationship established between hyperosmolarity and survival after an STEMI is striking. Serum hyperosmolarity also remained as an independent prognostic factor of cardiovascular mortality after multivariable analysis. However it is difficult to determine whether it is hyperosmolarity by itself or the more serious comorbidities and worst underlying disease what influence in-hospital and/or long-term survival of patients after STEMI. Future studies predicting osmolarity in a prospective way will be needed to confirm our results. This is the first study, to our knowledge, to disclose the association of osmolarity with post-STEMI prognosis after primary PCI. Osmolarity could be utilized as a simple prognostic and diagnostic test after primary PCI in coronary care unit, and it helps for strict control of complications and preventive strategies.

This study has several limitations. Firstly, data from the present study were collected in a single center and analyzed retrospective design without randomization and thus subject to selection bias. However, consecutive patients were selected in order to mitigate possible effects of selection bias. Despite adjusting for multiple risk factors, it is possible that there might have been residual confounding conditions and medications.

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