

Effects of glucose-insulin-potassium solution added to reperfusion treatment in acute myocardial infarction

Akut miyokard infarktüsü reperfüzyon tedavisine ilave edilen glikoz-insülin-potasyum solüsyonun etkileri

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ABSTRACT

Objective: Reperfusion treatment modalities used in the routine treatment protocols of acute myocardial infarction (AMI) were found to be ineffective in establishing the nutritional cellular reperfusion in the microvascular environment even they succeed to open the infarct related artery. Glucose-insulin-potassium (GIK) solution, which is presumed to stimulate the glycolytic pathway, is experimentally proven to be the most efficacious substrate for the preservation of energy production and therefore the myocardial viability, in the setting of acute ischemia.

Methods: We compared, 54 patients who suffered AMI and received GIK solution (300 g glucose+50 IU crystallized insulin+80 mEq potassium chloride in one liter solution) in addition to conventional treatment (GIK group) with 27 patients who were traditionally treated (control group) for in-hospital and early-term (1 month) cardiac morbidity. We also compared the two groups in terms of heart rate variability (HRV).

Results: Eight patients in the control group, developed new-onset symptomatic congestive heart failure whereas only 5 patients in GIK group were found to have such a cardiac morbidity ($p=0.01$). Reduced HRV (<50 ms) was found in 3 patients of control group whereas no patient in GIK group had abnormal HRV ($p=0.01$).

Conclusion: The GIK solution decreased the incidence of new-onset symptomatic congestive heart failure and low HRV after myocardial infarction. Larger multicenter trials need to resolve the questions on the efficiency of metabolic intervention with GIK solution in acute myocardial infarction. (*Anadolu Kardiyol Derg 2005; 5: 90-4*)

Key Words: Glucose, insulin, potassium, myocardial infarction, heart rate variability.

ÖZET

Amaç: Akut miyokard infarktüsünde (AMI) rutin tedavi protokolü olarak kullanılan reperfüzyon tedavisi yöntemlerinin, infarkt ile ilgili damarın açıklığı sağlanmış olsa bile hücrenin beslenmesini sağlayan mikrovasküler ortamı yeterli ölçüde sağlanmadığı saptanmıştır. Akut iskemi gibi durumlarda enerji üretiminin ve miyokardiyal canlılığın korunmasında en etkili yol olduğu deneysel olarak ispatlanan glikolitik yolun, glikoz-insülin-potasyum solüsyonu ile uyarılabileceği öne sürülmüştür.

Yöntem: Akut miyokard infarktüsü geçiren hastalarda, geleneksel tedaviye ek olarak glikoz-insülin-potasyum solüsyonu (GIK - 1 litre solüsyon içinde 300 g glikoz+50 IU kristalize insulin+80 mEq potasyum klorür) verilen 54 hasta (GIK grubu) ile geleneksel tedavi uygulanan 27 hastada (kontrol grubu) hastane içi ve erken dönem (1 ay) kardiyak morbidite karşılaştırıldı. İki grup arasında kalp hızı değişkenliği (KHD) de karşılaştırıldı.

Bulgular: Kontrol grubunda yer alan 8 hastada yeni başlangıçlı semptomatik konjestif kalp yetersizliği gelişirken, GIK grubunda ise kardiyak morbidite olarak 5 hastada konjestif kalp yetersizliği saptandı ($p=0.01$). Düşük (<50 ms) KHD kontrol grubunda 3 hastada saptanırken, GIK grubunda ise hiç bir hastada izlenmedi ($p=0.01$).

Sonuç: Glikoz-insülin-potasyum solüsyonunun, AMI sonrasında yeni başlangıçlı semptomatik kalp yetersizliği sıklığını ve düşük KHD insidansını azalttığı saptandı. Çok merkezli büyük ölçekli çalışmalar, akut miyokard infarktüsünde GIK solüsyonu ile metabolik tedavinin etkinliği ile ilgili soruları ortadan kaldıracaktır. (*Anadolu Kardiyol Derg 2005; 5: .90-4*)

Anahtar kelimeler: Glikoz, insülin, potasyum, miyokard infarktüsü, kalp hızı değişkenliği

Introduction

Cardiovascular heart disease is the leading cause of death in the developed and developing countries. Among all the deaths due to cardiovascular heart diseases (41.6%) in the United States, 22.8% are related to acute myocardial infarction

(AMI) (1). The latter is the first presentation of coronary heart disease in 30% of men and 20% of women (2).

The mortality from AMI has reduced from 30% to 15% as the coronary care units had merged into the clinical practice during 1960's. With the approval of reperfusion therapies as a routine treatment modality; one-month early-term mortality has reduced to 6.5% (3).

Such a reduction of mortality in AMI shifted all the attention to development of congestive heart failure (CHF) due to systolic dysfunction, which is the only cardiovascular heart disease with increasing prevalence (4).

The flow restored in the epicardium does not always equally mean nutritional cellular reperfusion in the microvascular area (no-reflow phenomenon). Still reperfusion may also have deleterious effects on microvascular integrity generally named as "reperfusion injury".

These limitations of reperfusion therapies were also proven by myocardial contrast echocardiography and coronary Doppler ultrasound studies.

Adjuvant therapy modalities have been brought forward to further decrease mortality and morbidity in AMI. Fath-Ordoobadi and Beatt (5) in their meta-analysis called into attention glucose-insulin-potassium (GIK) infusion, which was firstly used by Sodi-Pallares (6) in 1962 and then was forgotten after the thrombolytic era.

The GIK infusion is called to be the most optimal nutritional support for the myocardium in the setting of a severe ischemic metabolism. It is also thought to prolong the time till the irreversible myocardial injury, to preserve the cellular integrity by various mechanisms and to prevent the reperfusion injury and electrical instability.

In our study we evaluated the effects of high dose GIK solution on in-hospital and one-month early-term cardiac morbidity in a randomized prospective study.

Material and Methods

Patients: Eighty-one patients who were hospitalized for Q-wave AMI and planned to be treated with a reperfusion therapy were randomized into two groups. Local ethic commission approved the study protocol before the start of the study.

At least two of these criteria were required for AMI diagnosis: 1) Typical chest discomfort that lasts more than half an hour. 2) At least two creatine kinase (CK) and creatine kinase myocardial band (CK-MB) values above normal (normal value+2 standard deviation) 10-16 hours after the onset of symptoms. 3) ≥ 2 mm ST elevation in at least two contiguous precordial derivations or ≥ 1 mm ST elevation in at least two extremity derivations.

Those who have acute or chronic renal failure or prominent hyperkalemia (potassium > 5.5 mEq/L) and those who presented in cardiogenic shock were excluded from the study.

Therapy: All the patients received a reperfusion therapy (thrombolytic, primary PTCA or primary PTCA+stent implantation) as soon as possible. All the patients also received aspirin and heparin infusion. Those who had no any contraindication also received a beta-blocker. Other medications (calcium channel blocker, angiotensin converting enzyme inhibitor, diuretic, inotropic agents) were used according to their indications. Intravenous GIK solution (300 g glucose+50 IU crystallized insulin+80 mEq potassium chloride) was infused to every two patients out of three (patients were respectively randomized according to their hospitalization sequence). The solution was given via central vein route if present otherwise from peripheral venous one in the following dose: 200 ml was infused in the first hour and 150ml/hour in the next 2 hours and then 1.5ml/kg/hour till the end of the first 24 -hour. If patients had

had a pain at the infusion point, infusion rate was reduced first by half and stopped if the pain did not resolve or the heart rate drops below 40/minute or pauses lasting more than three seconds appear, plasma glucose increases above 400mg/dl or decreases below 60mg/dl. During the first 24 hours creatine kinase (CK), CKMB fraction, potassium and glucose levels were checked in every three hours.

New onset symptomatic heart failure was defined as development of paroxysmal nocturnal dyspnea and/or orthopnea accompanied by heart failure physical examination signs (third heart sound, crepitation in the lungs, sinus tachycardia at rest) or complaints on prominent exertional dyspnea (NYHA Class II-III) after discharge from the hospital.

Recurrent angina was defined as typical chest pain in the hospital after the first 24 hours. Less than 50% resolution of ST segment on the ECG taken 2 hours after the beginning of treatment was defined as "delay in ST segment resolution".

The 24-hour ECG recordings were taken with Biosensor Holter instruments in the period after the first 24 hours till discharge. We assessed heart rate variability using time domain index SDNN (standard deviation of normal to normal intervals).

Echocardiographic evaluation was made by Hewlett Packard Sonos 2000 machine with a 2.5 MHz transducer 30 days after AMI. Ejection fraction (EF) was measured with a modified Simpson method by a cardiologist who was unaware of the patient's treatment.

Statistical Methods: SPSS and Epiinfo computer programs were utilized for the statistical analysis. Mann-Whitney test was used to compare continuous variables and Chi-square test was used to compare categorical variables. $p < 0.05$ was taken as statistically significant.

Results

Fifty-four patients were included into GIK group and 27 patients were included into the control group (totally 81 patients). No statistical significant differences were found between two groups in terms of baseline characteristics and treatment, as shown in the Table 1.

One patient from either group died during 30-day follow-up period. The patient from GIK group died because of deteriorating pump failure while a patient from the control group was lost due to sudden death.

During 30-day follow-up period 5 of 54 patients in the GIK group and 8 of 27 patients in the control group developed symptomatic CHF ($p=0.01$, Table 2). All of 5 patients in GIK group that developed symptomatic CHF had anterior AMI, whereas among 8 patients in the control group 7 had anterior AMI and 1 had inferior AMI.

During monitorization in the coronary care unit and according to Holter analysis data, 15% of patients in the control group and 9% of patients in GIK group developed complex arrhythmias but this difference did not reach statistical significance.

The 24-hour Holter analysis revealed that SDNN was lower than 50 ms in 3 of 27 patients in the control group whereas no patient from GIK group had such a low SDNN ($p=0.01$). Ejection fraction $< 40\%$ was detected in 13% of patients from GIK group and 26% of patients in the control group, but difference was insignificant ($p > 0.05$).

Other parameters such as recurrent angina, delay in ST-segment resolution, need for inotropic agent support and higher peak CK/ peak CK-MB values were much more common in GIK group though they were statistically insignificant.

Two patients had pain at infusion point, which was resolved by stopping the infusion in one patient and halving the dose in another. During the infusion period only one patient had blood glucose level of >400 mg/dl. No patient developed hypoglycemia.

Discussion

Our study demonstrated that GIK solution decreased the incidence of symptomatic heart failure, which is an important morbidity of AMI. Even remained statistically insignificant, higher EF in the GIK group might point out the efficiency of GIK infusion for myocardial salvage in acute ischemia. These results are concordant with the findings of ECLA study (7) and Arsenian et al. (8).

Another finding was that patients who had SDNN <50ms were much more common in the control group. Depressed heart rate variability after AMI has a very important role for predicting mortality and arrhythmic complications. This predictive value of heart rate variability is independent from other established risk predictors such as depressed left ventricular EF, increased ventricular ectopy and presence of late potentials. The predictive value of heart rate variability for all cause mortality is similar to left ventricular EF, while its value for predicting arrhythmic events is greater than that of the left ventricular EF (9). It is generally accepted that SDNN lower than 50 ms

in 24 hour Holter analysis after AMI could identify patients at increased risk of death (10).

A subgroup study of the European Myocardial Infarct Amiodarone Trial (EMIAT) showed that low heart rate variability might help to distinguish patients with low EF (<40%) who may benefit from amiodarone treatment (11).

As much as we know no study has been reported till now on the effects of GIK solution on heart rate variability.

Although, statistically insignificant, complex arrhythmias were much more common in the control group. Altogether these results might point out that GIK solution establishes the electrical stabilization in infarcted hearts.

Sodi-Palleres (6) was the first who showed that GIK infusion decreased ventricular arrhythmias and improved the early-term survival during AMI. Other trials that followed this first one revealed compromising results mostly because of their poor methodology. For example in some of these trials, treatment had been initiated after the first 48 hours of chest pain that is too late to affect the myocardial infarct area, while in others insufficient for reduction of plasma fatty acids doses of glucose and insulin were used (5).

One of the best early studies by Rackley et al. (12) showed that GIK (300 g glucose+50 IU regular insulin and 80 mEq potassium chloride) infusion resulted in increase of myocardial glucose uptake by 250%, decrease of myocardial free fatty uptake by 90% and decrease of blood free fatty acid levels by 70%. Despite a large volume of infusion in the first 24-48 hours, pulmonary capillary wedge pressure decreased and cardiac output and ejection fraction increased (12). These findings are concordant with experimental studies that showed glucose-insulin treatment might heal both systolic and diastolic dysfunction (13).

Later in 1995, Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study (14) has broken up the silence in this field. In this study the patients who were hospitalized for AMI and received a thrombolytic therapy were randomized to receive glucose plus insulin and multidose insulin therapy afterwards or standard therapy. One -year mortality decreased by %29 in glucose plus insulin group (14). Although DIGAMI study specifically covered only diabetic patients its results might also be extrapolated to non-diabetic patients beca-

Table 1. Baseline characteristics

	Control group (n=27)	GIK group (n=54)	p
Age, (years)	60±11	56±11	NS
Men/Women	23/4	44/10	NS
Anterior/Inferior MI	16/11	30/24	NS
Previous MI, n (%)	6 (22)	9 (17)	NS
Hypertension, n (%)	8 (30)	21 (39)	NS
IDDM, n (%)	1 (4)	1 (2)	NS
NIDDM, n (%)	6 (22)	3 (6)	NS
Smoker, n (%)	18 (67)	37 (69)	NS
Time to treatment, hours	3.8±2.2	3.5±2.4	NS
Accelerated t-PA, n (%)	9 (33)	23 (43)	NS
Streptokinase, n (%)	12 (44)	26 (48)	NS
PTCA, n (%)	1 (4)	1 (2)	NS
PTCA+Stent, n (%)	5 (19)	4 (7)	NS
Aspirin, n (%)	27 (100)	53 (98)	NS
Nitrate, n (%)	24 (89)	50 (88)	NS
Beta-blocker, n (%)	18 (67)	39 (72)	NS
Calcium channel blocker, n (%)	1 (4)	3 (6)	NS
Heparin, n (%)	26 (96)	52 (96)	NS
ACE-inhibitor, n (%)	15 (56)	28 (52)	NS

ACE: Angiotensin converting enzyme; GIK: Glucose-insulin-potassium; IDDM: Insulin dependent diabetes mellitus; MI: Myocardial infarction; NIDDM: Non-insulin dependent diabetes mellitus; NS: Non-significant; PTCA: Percutaneous transluminal coronary angioplasty; t-PA: tissue plasminogen activator

Table 2. Outcomes of both groups during follow-up period

	Control group (n=27)	GIK group (n=54)	p
New onset symptomatic congestive heart failure, n (%)	8 (30)	5 (9)	0.01
HRV (SDNN)<50msec, n (%)	3 (11)	0	0.01
Need for inotropic agent support, n (%)	4 (15)	3 (6)	NS
Ejection fraction≤40%, n (%)	7 (26)	7 (13)	NS
Complex arrhythmia, n (%)	4 (15)	5 (9)	NS
Recurrent angina, n (%)	2 (4)	1 (2)	NS
Delay in ST resolution, n (%)	6 (22)	9 (17)	NS
Average peak CK, (IU)	4366±2779	3916±3117	NS
Average peak CK-MB, (IU)	439±323	368±271	NS

CK=Creatin kinase; CK-MB=Creatin kinase-myocardial band; GIK: Glucose-insulin-potassium; HRV=Heart rate variability; NS: Non-significant ; SDNN=Standard deviation of normal to normal interval;

use the most beneficial effect in glucose-insulin group was for mild diabetic patients who did not use insulin before hospitalization. In this subgroup glucose and insulin decreased in -hospital mortality by 58% and one- year mortality by 52%.

The strongest call for reevaluation of GIK infusion in the reperfusion era came from Fath-Ordoubadi and Beatt (5). In their meta-analysis that covers 9 studies, which included 1932 patients, hospital mortality was reduced by 28%. When only 4 studies that used high dose (Rackley regimen) GIK infusion were analyzed, this ratio increased to 48%.

In another study, a group of 44 patients who also received GIK, carnitine and magnesium in addition to thrombolytic therapy was compared with group who received only the classical therapy (8). Death and development of CHF were seen to decrease significantly in the patient group who received metabolic support (8).

The most convincing evidence about the use of GIK in the reperfusion therapy era came from the study "Estudios Cardiológicos Latinoamerica" (ECLA) (7). In this study the largest randomized trial after reperfusion therapies, were established in routine treatment protocols of AMI, GIK infusion in addition to reperfusion therapy reduced in hospital mortality by 66% and this beneficial effect on survival was shown to be maintained if high dose GIK was used. Severe heart failure (Killip Class>2) and ventricular fibrillation incidence reduced in the subgroup that received GIK solution in addition to reperfusion therapy.

Several theories based on experimental observations have been developed to explain beneficial effects of GIK solution. Free fatty acid levels increase during acute ischemia by the effect of catecholamines and/or heparin whether endogenously produced or therapeutically given. High levels of free fatty acids depress the myocardial contractility, inhibit glycolytic flux, increase c-AMP levels, accumulate as toxic fatty acid derivatives, cause membrane damage, generate arrhythmias, and increase myocardial oxygen consumption (15,16). Decreased beta -oxidation of free fatty acids during ischemia cause accumulation of acylcarnitine and acylcoenzyme-A. Acylcarnitine inhibits calcium pump of sarcoplasmic reticulum, sarcolemmal sodium-calcium exchanger and sodium pump. They activate calcium channels and increase c-AMP levels. All of these cause excessive intracellular calcium accumulation and arrhythmias (13).

In the presence of high levels of glucose and insulin, the inhibition of glycolysis by free fatty acids is minimal and high levels of glucose and insulin decrease plasma levels of free fatty acids and depress myocardial free acid uptake at any plasma free fatty acid level (15,16).

In well oxygenated adult hearts, ATP whether produced in the mitochondrion or glycolytically produced resides in the same compartment (17). However during ischemia, glycolytically produced ATP is maintained in another compartment without interfering with ATP produced in the residual mitochondrion (16). All of these support theories that put forward different gradients in the cytoplasm (18). Glycolytic ATP rather than mitochondrial ATP is shown to supply the energy for closure of potassium channels and ATP has a protective effect on myocardial membrane during ischemia (19).

It is also known that glycolytic ATP production has an important role for preventing ischemic contracture (20-22).

Although glycolysis supplies a small amount of ATP that is negligible when compared with the total tissue ATP, it is specifically used for the energy required for uptake by the sarcoplasmic reticulum and calcium extraction by the sarcolemma because of the formed subcellular compartmentation.

Contractile function and calcium release are impaired because of the rapidly consumed glycogen during ischemia. Glucose plus insulin also partly preserves myocardial glycogen stores (23).

A small amount of oxidative metabolism continues during real clinical ischemia. As a result of augmented glycolysis, substrate (piruvate) provided to citric acid cycles increases. Cycles are also supported with anaplerosis by the production of intermediate products of citric acid cycles (24).

Optimal GIK dosage is still in debate. High dose GIK (Rackley regimen) and low dose GIK regimens were compared in the ECLA study. At the end of a one-year follow-up period, survival rates of patients who received high dose GIK remained higher when compared with the control group. This result shows that high dose GIK is more effective for myocardial salvage (7). The superiority of high dose GIK was also shown in a recent meta-analysis. Mortality was reduced by %48 in four studies where high dose GIK solution was used during AMI. However mortality benefit was only %28 in 9 studies in which low dose GIK solution was used (5). In another Polish trial that was recently reported, low dose GIK did not show any beneficial effect (25). The optimal infusion rate to depress fatty acid levels was shown to be 1.5 ml/kg/hour, used in Rackley's protocol (26). In our trial we used a front-loaded Rackley regimen.

In conclusion: 1) High- dose GIK solution usage in AMI decreased the rate of the development of symptomatic CHF 2) Depressed heart rate variability (SDNN<50 msec), which is considered a prominent negative prognostic sign after AMI, was much more common in the control group when compared with GIK group.

The most prominent limitation of our study was the small patient number. Obtained data should be supported with larger and multicenter trials in the future.

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