Effects of glucose-insulin-potassium solution on acute myocardial infarction outcome in patients received streptokinase according to Killip classes

Glikoz insülin potasyum solüsyonunun streptokinaz alan çeşitli Killip sınıflı miyokart infarktüslü hastaların üzerindeki etkisi

Zeynab Soltani, Jahanbakhsh Samadikhah, Rasoul Azarfarin, Bahram Hashemi**, Nariman Nezami***,[1]*

From Departments of Cardiology, *Anesthesiology, **Medical Research, and
***Drug Applied Research Center, Tabriz University (Medical Sciences), Tabriz, Eastern Azerbaijan
[1]Young Researchers Club, Tabriz Islamic Azad University, Tabriz, Eastern Azerbaijan, Iran

Acute myocardial infarction (AMI) is associated with a high mortality rate and a large number of complications (1). The AMI mortality rate is directly related to the severity of hemodynamic deterioration and can be reduced by rapid reperfusion with chemical agents or mechanical procedures (2). The main mechanism of improvement is myocardial salvage (3). However, restoration of myocardial function does not depend only on the success of reperfusion therapy. Glucose-insulin- potassium solution (GIK) was proposed for the first time as a polarizing agent promoting electrical stability and protecting heart during AMI (4). Although a meta-analysis of subsequent randomized trials found a 28% reduction of in hospital mortality rates (5), there are controversial reports about the GIK effect in AMI management. The present study aimed to evaluate the effects of GIK on AMI patients received streptokinase and compare its effects on patients with different Killip classes (KC I vs. II /III).

Present single-blind clinical trial evaluated the effects of GIK on AMI patients admitted to Tabriz Shahid Madani Hospital, Feb 2006-Jul 2007. Study protocol was approved by the ethic committee of Tabriz University of Medical Sciences.

Patients who had symptoms consistent with AMI 20 minutes in duration, presented within 12 hours of symptom onset, and had ST elevation ≥1 mm in two contiguous electrocardiographic leads were enrolled. Exclusion criteria were serum creatinine ≥3 mg/dl, hyperkaliemia, and severe heart failure (KC IV). Patients with diabetes mellitus or plasma glucose level ≥300 mg/dl were also excluded.

One hundred AMI cases were enrolled; 50 patients into KC-I group and remainder into KC-II/III. The patients underwent streptokinase thrombolytic therapy after admission during at least 12 hours after onset of the symptoms. B group was divided into two subgroups including 25 patients (GIK vs. Placebo group). All included patients received standard therapies for AMI according to European Society Guidelines. The GIK (25 % glucose, 50 IU insulin and 80 mmol/lit potassium chloride) infused with 1mg/kg/h speed for 24 hours simultaneously with streptokinase (1.5 MU during 30-60 minutes).

Left ventricle ejection fraction (LVEF) was determined using transthoracic echocardiography by Simpson's method. Post AMI recurrent MI, mechanical complications, cardiogenic shock, arrhythmia, heart failure (HF), mortality and revascularization were surveyed during hospitalization period, at 1st, 3rd and 12th months after discharge.

Statistical analyses were performed using SPSS software 13.0. Statistical significance between groups of evaluation was estimated using one-way repeated measures ANOVA and Chi-square tests. The p value <0.05 was considered significant.

There were no significant differences between groups in demographic characteristics and clinical manifestation of AMI. Table 1 shows infarct locations and primary LVEF in the study's groups. Considering study design, subjects of KC-I group have high LVEF (p=0.024). The outcome of GIK infusion during follow up period is presented in Table 2.

During hospitalization. Only three subjects from KC-I 's placebo subgroup complicated with HF (p=0.022), while there were

Address for Correspondence/Yazışma Adresi: Dr. Nariman Nezami, Clinical Pharmacy Laboratory, Drug Applied Research Center, Tabriz University (Medical Sciences), Pashmineh, Daneshgah Street, Tabriz, Eastern Azerbaijan, Iran Phone: +98(411)333 87 89 Fax: +98(411)336 32 31 E-mail: dr.nezami@gmail.com

doi:10.5152/akd.2010.120

Table 1. Infarct location and primary ejection fraction in the study population

Variables		Groups				Total (n=100)	p*
		Killip class II/III (n=50)		Killip class I (n=50)			
		GIK (n=25)	Placebo (n=25)	GIK (n=25)	Placebo (n=25)		
Infarct location	Inferior, n (%)	2(8)	7(28)	2(4)	2(4)	13(13)	0.072
	Inferior right ventricular, n(%)	1(4)	0(0)	3(12)	1(4)	5(5)	
	Inferior lateral, n(%)	3(12)	3(12)	3(12)	8(32)	17(17)	
	Anteroseptal, n(%)	3(12)	2(8)	4(16)	5(20)	14(14)	
	Antero lateral, n(%)	16(64)	12(48)	13(52)	9(36)	50(50)	
	Inferior posterior, n(%)	0(0)	2(8)	0(0)	0(0)	2(2)	
LVEF	≥50%	3(12)	5(20)	0(0)	0(0)	8(8)	0.024
	≥40-50%>	16(64)	12(48)	9(32)	10(40)	47(47)	
	≥30-40%>	5(20)	4(16)	10(40)	10(40)	29(29)	
	30%>	1(4)	4(16)	6(24)	5(20)	15(15)	

Data are presented as proportions/percentages
*Chi-square test
GIK - glucose- insulin-potassium, LVEF - left ventricular ejection fraction

six subjects with HF in both GIK and placebo subgroups of KC-II/III group (p=0.463). Comparison of mortality rate was non-significant.

One month after discharge. Three participants deceased. All these deceased subjects were belonged to KC-II/III in which one had received GIK infusion. Although mortality rate was not different between Placebo and GIK subgroups (p=0.261), it was higher in KC-II/III group (p=0.035).

Three months after discharge. Mortality rate was not different between GIK and Placebo subgroups, and even between KC-I and -II/III groups (p=0.387, 0.815).

Twelve months after discharge. The mortality rate had not changed regarding the rates of previous follow up.

Totally, six participants died; five belonged to KC-II/III group and one was from KC-I (p=0.029). Out of five deceased subjects from KC-II/III group, three and two cases belonged to the Placebo and GIK subgroups, respectively. Mortality rate was not different between subgroups of different KC groups (p=0.315).

Study results showed that the rate of post AMI complications and mortality was not different between GIK and Placebo subgroups according to KCs during follow up, except the rate of HF during hospitalization which was significantly lower in KC-I received GIK.

Initially, Sodi-Pollares et al. (4) showed that GIK reduced mortality rate of AMI patients during hospitalization and then another study (6) showed 6% lower mortality rate in GIK group. Consistently, inpatient mortality rate was non-significantly low with GIK in both KC-I and -II/III in present study. ECLA trial (7) revealed that GIK infusion significantly decreases 30 day mortality of AMI patients, more prominent with thrombolytic. Another recent study reported that GIK reduced significantly one month mortality rate of AMI patients (1), while present study failed to show any effect for GIK. Solely, Pache et al. (8) found out non-significant reduction in the six month mortality rate of MI patients by GIK infusion. The present study not only evaluated the 3rd, 6th and 12th month outcomes, and did not found any effect of GIK on post AMI complications and mortality rate.

Turel et al. (9) reported that GIK with reperfusion therapy significantly decreases post MI HF. In present study, GIK also reduced post AMI HF rate among KC-I, but had no impact on post MI HF in higher KC. Krljanac et al. (6) showed that GIK reduces significantly inpatient recurrent MI in AMI patients (6), but the present study did not show such effect during follow up. The major study by Diaz et al. (10) was not show any effect of GIK on the one month mortality rate and HF, even outcome in GIK group was worsen during 0-3 days of hospitalization. Differences in the results during early hospitalization may arise from different GIK infusion rate, study population and interval of symptoms onset to treatment. GIK is supposed to provide myocardial protection in patients with AMI during both periods of ischemia and reperfusion (11), but it was reduced the rate of HF during hospitalization in KC-I group.

Finally, the present study is suffering from some limitations including small sample size, undetermined levels of brain natriuretic peptide, C-reactive protein, tumor necrotizing factor alpha, cardiac troponin T, alkaline phosphatase and lactase dehydrogenase.

GIK have not any significant effect on post MI complications and mortality rate during hospitalization, one, three, 12 months after discharging patient from hospital, but it was reduced the development rate of HF during hospitalization in patients with KC-I.

Conflict of interest: None declared.

Table 2. Clinical out come in the study population during hospitalization, 1 month, 3 and 12 months after MI

Time of evaluation	Complications		Groups				Total (n=100)	p*
			Killip class I (n=50)		Killip class II/III (n=50)			
			GIK (n=25)	Placebo (n=25)	GIK (n=25)	Placebo (n=25)		
During hospitalization	Recurrent MI, n(%)		0(0)	1(4)	0(0)	1(4)	2(2)	0.564
	Consistent ischemia, n(%)		8(32)	6(24)	1(4)	3(12)	18(18)	0.771
	Heart failure, n(%)		0(0)	3(12)	6(24)	6(24)	15(15)	0.035
	Arrhythmia, n(%)		4(16)	1(4)	3(12)	5(20)	13(13)	0.359
	MC, n(%)		1(4)	0(0)	0(0)	2(8)	3(3)	0.096
	MCAEs, n(%)		13(52)	11(44)	10(40)	17(68)	51(51)	0.410
	Mortality, n(%)		0(0)	1(4)	0(0)	1(4)	2(2)	0.564
	Revascularization	PCI, n	5	8	8	11	32	0.194
		CABG, n	2	3	5	5	15	
1 month after discharge	Recurrent MI, n(%)		0(0)	0(0)	1(4)	0(0)	1(1)	0.387
	Rehospitalization, n(%)		1(4)	0(0)	0(0)	2(8)	3(3)	0.096
	Heart failure, n(%)		0(0)	2(8)	2(8)	2(8)	6(6)	0.510
	Continuous chest pain, n(%)		1(4)	0(0)	0(0)	2(8)	3(3)	0.096
	Arrhythmia, n(%)		1(4)	0(0)	0(0)	1(4)	2(2)	0.564
	MCAEs, n(%)		3(12)	2(8)	3(12)	8(32)	16(16)	0.085
	Mortality, n(%)		0(0)	0(0)	1(4)	2(8)	3(3)	0.261
	Revascularization	PCI, n	4	1	6	4	15	0.250
		CABG, n	1	0	2	1	4	
3 months after discharge	Recurrent MI, n(%)		0(0)	0(0)	1(4)	1(4)	2(2)	0.564
	Rehospitalization, n(%)		1(4)	1(4)	0(0)	1(4)	3(3)	0.643
	Heart failure, n(%)		1(4)	1(4)	1(4)	1(4)	4(4)	0.510
	Arrhythmia, n(%)		0(0)	1(4)	1(4)	1(4)	3(3)	0.643
	MCAEs, n(%)		2(8)	3(12)	3(12)	4(16)	12(12)	0.528
	Mortality, n(%)		0(0)	0(0)	1(4)	0(0)	6(6)	0.815
	Revascularization	PCI, n	0	1	0	3	4	0.441
		CABG, n	0	0	1	0	1	
12 months after discharge	Recurrent MI, n(%)		0(0)	1(4)	1(4)	0(0)	2(2)	0.564
	Rehospitalization, n(%)		3(12)	2(8)	2(8)	2(8)	9(9)	0.771
	Heart failure, n(%)		0(0)	2(8)	2(8)	1(4)	5(5)	0.794
	Arrhythmia, n(%)		1(4)	0(0)	0(0)	1(4)	2(2)	0.564
	MCAEs, n(%)		4(16)	5(20)	5(20)	4(16)	18(18)	0.510
	Mortality, n(%)		0(0)	0(0)	0(0)	0(0)	0(0)	1
	Revascularization	PCI, n	2	2	0	1	5	0.470
		CABG, n	0	0	1	2	3	

Data are presented as proportions/percentages
*Chi-square test
CABG - coronary artery bypass grafting, GIK - glucose-insulin-potassium, MC - mechanical complications, MCAEs - major cardiac adverse events, MI - myocardial Infarction, PCI - percutaneous coronary intervention,

References

1. Van Der Horst IC, Timmer JR, Ottervanger JP, Bilo HJ, Gans RO, De Boer MJ, et al. GIPS Investigators. Glucose-insulin-potassium and reperfusion in acute myocardial infarction: rationale and design of the Glucose-Insulin-Potassium Study-2 (GIPS-2). Am Heart J 2005; 149: 585-91.
2. Hanefeld M, Temelkova-Kurktschiev T. Control of postprandial hyperglycemia-an essential part of good diabetes treatment and prevention of cardiovascular complications. Nutr Metab Cardiovasc Dis 2002; 12: 98-107.
3. Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival: should the paradigm be expanded? Circulation 1989; 79: 441-4.

4. Sodi-Pallares D, Testelli MR, Fischleder BL, Bisteni A, Medrano GA, Friedland C, et al. Effects of an intravenous infusion of a potassium-glucose-insulin solution on the electrocardiographic signs of myocardial infarction. Am J Cardiol 1962; 9: 161-81.
5. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation 1997; 96: 1152-6.
6. Krljanac G, Vasiljevic Z, Radovanovic M, Stankovic G, Milic N, Stefanovic B, et al. Effects of glucose-insulin-potassium infusion on ST-elevation myocardial infarction in patients treated with thrombolytic therapy. Am J Cardiol 2005; 96: 1053-8.
7. Díaz R, Paolasso EA, Piegas LS, Tajer CD, Moreno MG, Corvalán R, et al. Metabolic modulation of acute myocardial infarction. The ECLA (Estudios Cardiológicos Latinoamérica) Collaborative Group. Circulation 1998; 98: 2227-34.
8. Pache J, Kastrati A, Mehilli J, Bollwein H, Ndrepepa G, Schühlen H, et al. A randomized evaluation of the effects of glucose-insulin-potassium infusion on myocardial salvage in patients with acute myocardial infarction treated with reperfusion therapy. Am Heart J 2004; 148: 3.
9. Türel B, Gemici K, Baran I, Yeşilbursa D, Güllülü S, Aydınlar A, et al. Effects of glucose-insulin-potassium solution added to reperfusion treatment in acute myocardial infarction. Anadolu Kardiyol Derg 2005; 5: 90-4.
10. Díaz R, Goyal A, Mehta SR, Afzal R, Xavier D, Pais P, et al. Glucose-insulin-potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA 2007; 298: 2399-405.
11. Apstein CS. Glucose-insulin-potassium for acute myocardial infarction: remarkable results from a new prospective, randomized trial. Circulation 1998; 98: 2223-6.