Original Article

Effect of glucose–insulin–potassium on Plasma concentrations of C-reactive protein in acute ST- Elevation Myocardial Infarction; A Randomized Clinical Trial

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ABSTRACT

Objective*:* The anti inflammatory effects of glucose-insulin-potassium (GIK) in the management of patients with ST segment elevation myocardial infarction (STEMI) are controversial. We aimed to evaluate anti-inflammatory effect of GIK in STEMI patients treated with streptokinase which is not obvious up to now.

Methodology: This randomized clinical trial enrolled 72 patients who had STEMI that were treated within 12 hours from symptom onset with a high dose of GIK (25% glucose, 50 IU of soluble insulin per liter, and 80 m mol of potassium chloride per liter at 1 ml/kg/hour) (GIK group) or normal saline (control group) as adjunct to thrombolytic therapy. We analyzed Plasma concentrations of high-sensitivity C-reactive protein (HS CRP) at baseline and sequentially for 48 hours.

Results: Baseline HS CRP were significantly increased (2- to 3-fold) at 24 and 48 hours in each group (P<0.01). There was no difference in plasma concentrations of HS CRP between GIK and control patients (P = 0.24). Mean glucose level over 6 hours was higher in GIK group than control group (P=0.006).

Conclusion: GIK therapy offers no anti-inflammatory effect in patients with STEMI treated with streptokinase.

KEY WORDS: Glucose, Insulin, Potassium, STEMI, CRP, Anti inflammatory.

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INTRODUCTION

The effects of glucose–insulin–potassium (GIK) in the treatment of ST segment elevation myocardial infarction (STEMI) are controversial. Fath-Ordoubadi et al published a meta-analysis of GIK treatment and

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showed that GIK infusion could reduce in-hospital mortality.[1] The Glucose–insulin–potassium study-I (GIPS-I) showed that GIK did not reduce mortality in the total population, but it reduced mortality in STEMI patients without signs of heart failure[2], but in the GIPS-II mortality did not differ between groups.[3] In CREATE-ECLA-II and DIGAMI-II,[4,5] no beneficial effects of GIK were observed. In rat model of ischemic myocardial injury, insulin can reduce infarct size.[6]

However, studies about GIK effects are ongoing. On the other hand C-reactive protein (CRP), as an indicator of inflammation is shown to have prognostic value, in acute coronary syndromes.[7-9] Thrombolytic efficacy and a patent infarct-related coronary artery could be realized thorough a reduction in the

rise of CRP.[10-11] A high CRP after MI increases infarct expansion.[7,10,12] The effect of ß-blockers[13] and abciximab, is combined with a reduction of CRP,[14] high CRP in rats with induced MI can increase myocardial infarct size significantly.[15]

But, the influence of high dose GIK on CRP levels in patients with ST-segment elevation MI treated by intravenous thrombolytic agents has not been previously investigated. Evaluating HS CRP concentration is more precise than mortality and could compare GIK therapy with conventional treatment very well. Hence we assessed this effect of GIK in STEMI patients treated with streptokinase.

METHODOLOGY

Study Patients: After approval from university ethic committee, recruitment began. From September 2008 to July 2009, 74 consecutive STEMI patients were randomized to traditional care (N = 39) or additional GIK infusion (N = 35).We missed two patients in the GIK group to follow up. All consecutive patients who had 20 minutes chest pain or its equivalent, time from symptom onset <12 hours, and had ST elevation >1 mm in >2 contiguous electrocardiographic leads were admitted to the Coronary Care Unit of the Vaseie General Hospital (Sabzevar, Iran).[16,17]
Patient with systemic infection, glucocorticoid therapy, hypotension, congestive heart failure, creatinine >2.0 mg/dL, anemia (hemoglobin <11 g/dL), and unwilling to participate were excluded. We obtained Informed consent from the participants or their legal guardians.
Study design: The study was randomized, prospective, and triple blinded. On admission, patients were randomized via block randomization and assigned to the respective group by a closed envelope system. In A group, patients received high-dose GIK infusion (25% glucose, 50 IU of soluble insulin per liter, and 80 mmol of potassium chloride per liter at 1ml/kg/hour) as an adjunct to thrombolytic therapy (1.5 MU of streptokinase/30 to 60 minutes) [GIK group]. In B group 1 L normal saline at 60 mL/h infused in addition to thrombolytic therapy (1.5 MU of streptokinase/30 to 60 minutes) [control group].

Neither the patients nor the researcher nor the statistical consultant knew which group called A and which one called B group (triple blinded). GIK administered in the hospital that initiated the reperfusion therapy. All other medication was standard as ACC/AHA guidelines.[17]
Data collection: Blood was collected at baseline and at 6, 16, 24, and 48 hours. We used an ELISA kit to measure High-sensitivity C-reactive protein (mg/L),

[lowest detection limit 0.35 ng/mL; inter assay coefficient of variation (CV), 3% to 7%; intra-assay CV, <5%]. In each patient, total CK and CK-MB level were measured on admission, 16 and 24 hours thereafter. In all patients, plasma concentrations of glucose and potassium were determined before and at 6 hour after administering therapy.
Study End Points: The primary end point of the study was plasma concentration of HS CRP, and comparing between and within the control and GIK groups. A similar approach was used in Lincroft AM and Chaudhuri studies.[18,19]
Statistical analysis: Data were analyzed thorough the Statistical Package for the Social Sciences (SPSS, version15). Continuous variables were expressed as mean ± SD and were compared using independent t tests and repeated measure ANOVA (such as CK, CK-MB and HS CRP concentration). Categorical data were analyzed by use of chi-square or Fisher exact test. Assuming a power of 80% and α =5%, comparing plasma concentration of HS CRP over the first 48 hours could be demonstrated with a sample size of 32 patients in each group. A p value <0.05 was considered to be statistically significant.

RESULTS

Seventy two patients were enrolled into the study. There was no significant difference between basal data among study groups (Table-I).

The time from chest pain onset to initiation of streptokinase was 4.66±3.81 hours. There was no significant difference between this interval among study groups (P=0.16). Glucose level at baseline was 149±61 mg/dL in controls and 168±83 mg/dL in the GIK

Table-I: Baseline characteristics of 72 patients enrolled in clinical trial of GIK.

	GIK(n=33)	Control (n=39)	P
Age, Years	60±12	57±11	0.3
Sex, M/F, n	8/25	13/26	0.4
Smoker, n (%)	15(45)	17(44)	0.87
Hypertension, n (%)	7(21)	6(15)	0.52
History of CAD, n (%)	1(3)	3((8)	0.62
Glucose, mg/dL	168±83	149±61	0.25
Site of infarct, n (%)			
Anterior	11(33.3)	14(36.8)	0.55
Inferior	12(36.4)	17(44.7)	0.35
Other	10(30.3)	7(18.4)	0.47
Mean peak CK,U/L	2165±149	1830±152	0.13
Mean peak CK-MB,U/L	152±11	138±12	0.30

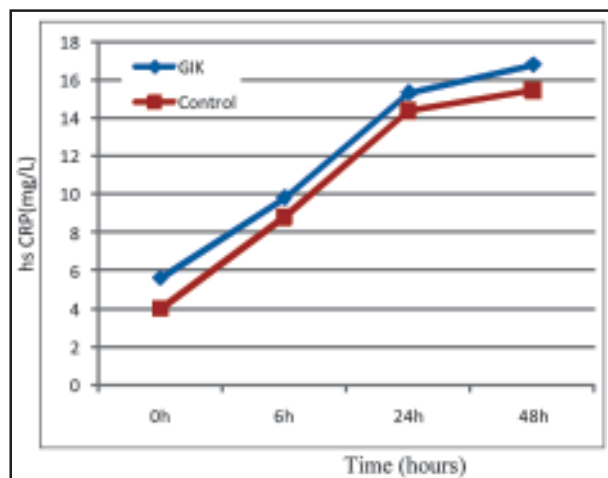CAD, Coronary artery disease; CK, Creatine kinase, Significance at P<0.05

Fig-1: HS CRP concentrations in groups.

Table-II: HS CRP concentrations in groups.

Time, Hours	GIK(n=33)	Control (n=39)	P
HS CRP ,mg/L	4.7±5.1	9.3±6.5	
0	5.6±5.9	4.0±4.3	0.35
6	9.8±6.9	8.8±6.2	0.61
24	15.3±4.4	14.4±3.5	0.46
48	16.8±2.2	15.5±3.2	0.17

CRP, C reactive protein

group (P=0.25). Mean glucose level over 6 hours was higher in GIK group (212± 139 mg/dL) than control group (142±46 mg/dL) (P=0.006).HS CRP level increased significantly (P<0.01) in both groups (Figure-1).

The absolute increases in HS CRP concentrations did not differ significantly (p=0.204) in GIK and control groups (Table-II).

There was no significant difference between groups regarding mean admission serum CK, peak CK, peak CK-MB levels and early peak of CK within 16 hour. Ejection Fraction (39% G vs41% C, p=0.34) and ST segment resolution were similar between the two groups. (p=0.8)

DISCUSSION

Our data suggest that after acute MI, plasma HS CRP concentrations rise, and systemic inflammation enhances. Also GIK therapy offers no anti-inflammatory effect, which is corresponding to large clinical trials that showed no effect of GIK. [3-5]

In an open label study Chaudhuri et al showed that in patients with acute ST-segment elevation myocardial infarction treated with reteplase, GIK infusion reduced levels of C-reactive protein and serum amyloid A and attenuated an increase in plasminogen activator-1, which suggests that GIK has an anti inflammatory and profibrinolytic effect. [19] On the other hand they maintained glucose between 80 and 200 mg/dL but our approach was not tight control of glucose and mean glucose level over 6 hours was higher in GIK group than control group. Therefore the inflammatory effect of glucose could counterbalance the anti-inflammatory effect of insulin and could be the cause of difference between this study and Chaud 's study with tight control of glucose.

Some studies believe that GIK can decrease in free fatty acid concentration and promotion of glycolysis. Therefore an ischemic cell needs less oxygen and produces less toxic intermediates of free fatty acid metabolism [20]. However, while reperfusion therapy can rescue the ischemic myocardium effectively, treatment with GIK has less value. Although before reperfusion therapy GIK might delay ischemic necrosis to some extent, as mentioned in Fath-Ordoubadi study. [1,21]

Furthermore, we should notice side effects of GIK. Hyperglycemia, hyperkalaemia and fluid overload can affect the potential benefits, and could be the cause of difference between this study and Chaud 's study with tight control of glucose. Hyperglycemia and hypoglycemia in some studies had worse outcome in both short- and long-term. [22-26]

Study limitations: The sample size is small and the convenience sampling of consecutive patients assigned from one hospital can limit generalizability. Furthermore, higher baseline HS CRP expressed that our patients were referred late to the hospital and may have led to an underestimation of the advantages of GIK therapy in this study. In addition HS CRP measurement was limited to first 48 hours. Despite these limitations, this pilot study may be helpful in future studies.

In conclusion, in patients with STEMI, the inflammatory factors increase despite the standard fibrinolytics, antithrombotic therapy and GIK infusion. Thus, at least at the present time, there is no role for GIK as adjunctive treatment with streptokinase.

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Maryam Hashemian et al.

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