EVALUATING THE EFFECT OF GLUCOSE-INSULIN-POTASSIUM INFUSION (GIK) ACCOMPANIED BY THROMBOLYTIC THERAPY ON MORTALITY AND MORBIDITY RATES OF DIABETIC PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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Abstract

INTRODUCTION: **In spite of the current methods of treatment, acute myocardial infarction (AMI) is still associated with high mortality and morbidity rates, especially in diabetic patients. Recent studies have demonstrated the value of glucose-insulin-potassium (GIK) infusion accompanied by thrombolytic therapy in reducing AMI-related mortality and morbidity with statistically meaningful results. This study was conducted to evaluate the effect of GIK infusion accompanied by thrombolytic therapy on mortality and morbidity of diabetic patients with AMI.**

METHODS: **This is a two-year case-control prospective trial involving 300 patients referring to the internal medicine Emergency Services of Chamran and Nour Hospitals. Thrombolytic therapy was indicated for all of these patients. The patients were divided into case and control groups. The case-group comprised patients with acute myocardial infarction who were treated with high doses of GIK accompanied by thrombolytic at the same time. The control group consisted of patients with acute myocardial infarction who were treated only with thrombolytic agent. Upon admission and until 6 months after discharge, the patients were examined and followed up by two cardiology residents working with the study, in respect of physical findings and cardiac arrhythmias. The patients underwent echocardiography upon discharge and after six months.**

RESULTS: **Cardiac arrhythmia during hospitalization was seen in 13.3% of patients in the case group (treated with GIK and thrombolytic agent) and 24.3% of patients in the control group. Mortality rate during the six-month follow-up period was 4.9% in the case group and 12.6% in the control group (P=0.02). Mean ejection fraction of patients before discharge was 44 ± 9.6% in the case group and 40 ± 9.8% in the control group. (P=0.00) Mean ejection fraction after Six months measured 46 ± 8% in the case group and 41.5 ± 9.6% in the control group. (P=0.00).**

DISCUSSION: **This study demonstrated that early infusion of high dose GIK accompanied by thrombolytic agent can have a wide range of beneficial effects in the treatment of diabetic patients with acute myocardial infarction. This method of treatment does not require specialized training or technology; it is associated with few side-effects and leads to a reduction in the frequency of important clinical events such as death and ventricular arrhythmia.**

Keywords • Acute myocardial infarction • Diabetes mellitus • GIK (glucose–insulin–potassium)

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Introduction

Diabetes is the commonest and the most important human metabolic disease affecting more than 15 million people in USA in 2000 year[1] and 6% of the American population, with half of the cases remaining undiagnosed.[2] Impaired glucose tolerance test occurs twice as frequently as overt diabetes.[2]

Regardless of the age of onset of diabetes, the first deaths occur in the fourth decade of life, with cumulative mortality rate increasing with a steady pace over the next twenty years. Hypertension, hyperlipidemia and obesity are common as a cluster in diabetic patients.[3]

Heart disease, particularly coronary heart disease (CHD) is a major cause of morbidity and mortality among patients with diabetes mellitus. Compared to non-diabetics, diabetics are more likely to develop CHD, multi-vessel disease and episodes of silent ischemia. As a result of these and other factors, diabetics with CHD have a worse outcome and poorer long-term survival compared to non-diabetics with CHD. The clinical manifestations of an acute MI are often more severe than in non-diabetics, particularly in women.[4,5] In diabetics, increased incidence of heart failure frequently occurs despite similar infarct sizes and left ventricular ejection fractions.[4,6,7]

The greater extent of coronary disease (i.e. more multi-vessel disease) affects myocardial performance by limiting blood flow to the non-infarcted myocardium.[4,8,9] Diabetic patients also have a higher risk of other complications, including arrhythmias, cardiogenic shock, and recurrent MI.[6,5,10]

There may also be a moderate increase in in-hospital mortality.[4,6,10,11]

Post-MI mortality is related to the severity of left ventricular dysfunction and the quality and timing of remodeling are the most decisive factors. Overall, mortality rate in diabetics is twice as high as in non-diabetics.[12]

Numerous studies have shown that the use of adjunctive insulin favorably affects outcomes in the setting of acute coronary syndromes. Sodi-pallares et al. first described this treatment in 1963. It was initially called "polarizing therapy" and more recently it has become known as GIK therapy.[13]

For the first time, Malmberg in 1994 used insulin-glucose infusions to control diabetes in 327 diabetic patients with acute MI. This study reported more optimal and faster control of diabetes in these patients; however, it did not make any conclusions as to the effect of this method of treatment on mortality rate.[14]

Another study in 1995 by the same group has evaluated the effect of treatment with GIK on the mortality rate of diabetic patients suffering from acute myocardial infarction. 620 diabetic patients were selected on the basis of the estimated risk for cardiovascular accidents and previous treatment with insulin. This study assessed one-year mortality and morbidity rate in these patients with diabetes and acute myocardial infarction. The patients were divided into two groups. Patients in the first group (306 patients) were infused with GIK for 24 hours and were given multiple subcutaneous doses of insulin (MSI) for the period of at least next three months. The remaining 314 patients were treated with the conventional method and were followed up. During the evaluation period, 45% of the patients were treated with oral hypoglycemic agents (OHA) and nearly 33% were treated with insulin. Results showed a significant decrease in morality in the case group (treated with GIK) after one year (26.1% versus 18.6%, P= 0.027). During the course of one year, a 29% reduction of mortality rate was observed in the group treated with GIK and then MSI of insulin. Mortality and morbidity rates decreased most remarkably in patients with low cardiovascular risks who had not received insulin in the past (33% versus 18%, P=0.004). This difference was more prominent after a follow-up period of 3.4 years. The absolute reduction in mortality was 11%. (44% versus 33%, P=0.011).[15]

Materials and methods

This is a case-control prospective clinical trial involving diabetic patients with myocardial infarction referring to the Emergency Services of Nour and Chamran Hospitals, Isfahan, between April 2001 and August 2002. Thrombolytic therapy was indicated for all of the patients with definite ST elevation myocardial infarction (STEMI). The patients were randomly divided into case (to be treated with GIK and thrombolytic agent) and control (to be treated only with thrombolytic agent) groups. Mean age in the case and control groups was 61±11.5 and 61.2±11 years, respectively.

Half of the patients (150 patients) were men and half were women (150 patients). 88 (58%) of 150 men studied were in the case group and 62 (42%) were in the control group. 79 (53%) of 150 women studied were in the case group and 71 (47%) were in the control group. Duration of diabetes in the case and control groups was 6.1 and 5.5 years, respectively.

Two cardiology residents cooperating with the study randomly placed the patients in one of two groups to be studied. The patients' particulars and physical findings were recorded in questionnaires and candidates for receiving high-dose GIK were treated according to the treatment protocol simultaneously with, or some time after the start of thrombolytic therapy. High-dose GIK solution consisted of 30% glucose + 80 meq/lit potassium solutions infused continuously at a speed of 1.5 ml/kg/min for 24 hours. After receiving thrombolytic agent (control group) or thrombolytic agent with GIK (case group), the patients were evaluated by cardiology residents in respect of mortality and complications in and out of the hospital, re-infarction, congestive heart failure, types of arrhythmia, pericarditis, thromboemboli, stroke and major hemorrhage. The patients underwent echocardiography before being discharged. An Acuson XP echocardiograph was used. Simpson's method was used to calculate the ejection fraction. The patients were followed up for six months. Inclusion criteria consisted of type II diabetes mellitus and definite acute ST elevation myocardial infarction (STEMI) and an indication for thrombolytic therapy. Patients whose random blood samples contained equal to, or more than 200 mg/dl glucose irrespective of their last meal and had accompanying polydipsia, polyuria and weight loss, patients whose fasting blood samples (minimum fasting period of eight hours) contained equal to, or more than 126 mg/dl glucose, or those who had credible prescriptions for receiving oral hypoglycemic agents or insulin and had blood glucose levels exceeding 200 ml/dl were considered as having diabetes. HbA1c-levels were measured to rule out stress-induced hyperglycemia. Renal failure or hyperkalemia constituted the criteria of exclusion from the study.

Results

Analysis of findings with SPSS under the supervision of a statistician from the Endocrinology and Metabolism Research Center in Isfahan yielded the following results:

1-There was no significant difference between the case and control groups in respect of age (P-value =0.84) and sex (P-value =0.28).

82 patients in the case group (55%) and 78 patients in the control group (52%) had suffered inferior wall myocardial infarction (P-value =0.64: non-significant).

68 patients in the case group (45%) and 72 patients in the control group (48%) had suffered anterior wall myocardial infarction (P-value =0.90: non-significant).

No significant difference was observed between the two groups in respect of the severity and surface of infarction.

Peak CPK titer measured 1748±1174 u/ml in the case group and 1661±1303 u/ml in the control group (P-value =0.55: non-significant).

Peak LDH titer measured 721±436 u/ml in the case group and 676±368 u/ml in the control group (P-value = 0.35: non-significant). The number of chest leads with Q-wave (average 3 chest leads in each group) was equal in the two groups.
Hyperlipidemia in the control group (treated only with thrombolytic agent) was significantly different from the case group (P-value ~ 0.03).
There was no significant difference between the case and control groups in terms of atherosclerosis risk factors (P-values corresponding to smoking, hypertension, history of myocardial infarction and hyperlipidemia were 0.63, 0.63, 0.49, 1, and 0.03, respectively).

TABLE 1. Frequency distribution of the population under study versus risk factors.

Group	Control		Case	
	%	n/N	%	n/N
Previous MI	4	7/150	4	7/150
Positive FH	6	9/150	8	12/150
Hypertension	40	60/150	37	56/150
Hyperlipidemia	43	65/150	31	47/150
Cigarette smoking	27	41/150	30	45/150

(*Abbreviations*: FH: positive family history of premature coronary heart disease, MI: Myocardial Infarction, n: number of patients displaying a complication in a certain group, N: total number of patients studied in a group)

Overall, 38.7% of patients had hypertension, 37.3% had hyperlipidemia, 28.8% were smokers, and 7% had positive family history for cardiovascular disease. The patients were not different in respect of symptoms, i.e. paroxysmal nocturnal dyspnea (PND), nocturnal coughs, exertional dyspnea (DOE) and other physical findings presented in Table 2.
There was no significant difference between the case and control groups in terms of the following physical findings: S3 (P-value =0.06), crackles (P-value =0.53), elevated JVP (P-value= 0.77), edema (P-value =0.39), and hepatomegaly (P-value =0.08).

TABLE 2. Frequency distribution of the population under study versus physical findings.

Group	Control		Case	
	%	n/N	%	n/N
Hepatomegaly	2	3/150	0	0/150
Edema	5	8/150	3	5/150
Elevated JVP	20	30/150	21	32/150
Crackles	24	36/150	27	40/150
S3	21	31/150	13	19/150

(*Abbreviations:* S3: third heart sound, JVP: elevated jugular vein pressure, n: number of patients displaying a complication in a certain group, N: total number of patients studied in a group)

2- Comparison of laboratory findings in the case and control groups, including levels of creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), blood glucose, and blood potassium showed no significant difference between the two groups upon admission.
3- A comparison between the two groups in respect of in-hospital complications (heart failure, arrhythmia, re-infarction, death in hospital, major bleeding) showed that arrhythmia in the control group was significantly higher than in the case group (case group: 13.3%, control group: 24%, P-value=0.01, Odds Ratio=2.07, Relative Risk: 1.14).
Administration of streptokinase led to one instance of acute abdomen and two instances of hemorrhagic stroke. 1% of patients (1.3% in the case group and 0.6% in the control group) were affected by the adverse effects of streptokinase (P-value = 0.56: non-significant).

TABLE 3. Comparison of the frequency of in-hospital complications between the two groups.

Group	Case		Control		Comparison (P-value)
	%	n/N	%	n/N	
Arrhythmia	13.3	20/150	24	36/150	0.01
Re-infarction	2.7	4/150	6	9/150	0.15
Major bleeding	1.3	2/150	0.6	1/150	0.56
Death	5.3	8/150	9.3	14/150	0.17
CHF	3.3	5/150	2.6	4/150	0.74

(*Abbreviations*: n: number of patients constituting the sample within a group that show complications, N: total volume of sample in a given group)

4- Upon discharge, ejection fraction measured 44±9.7% in the case group and 40±10% in the control group (P=0.01: significant).
Six months later, ejection fraction measured 46±8.3% in the case group and 41.6±9.6% in the control group (P=0.00: significant).
Left ventricular ejection fraction in patients with inferior infarction was the only parameter that had risen to statistically meaningful levels in the case group six months after discharge. No significant difference was observed in respect of other findings (P=0.001).
A comparison of left ventricular ejection fraction (LVEF) between the two groups showed significantly higher levels in the case group, both upon discharge and six months later (upon discharge: P-value=0.001: significant, six months later: P-value= 0.00: significant).
5- There were 7 instances of late mortality in the case group (4.9%) and 17 instances (12.6%) in the control group six months after discharge, hence a significant difference between the two groups (P-value=0.02: significant, Odds Ratio: 2.78, Relative Risk: 1.83).
6- Early mortality before discharge was 5.3% in the case group and 9.3% in the control group, hence no significant difference between the two groups (P-value=0.17: non-significant).

TABLE 4. Glucose lowering agent before admission, during hospitalization, and upon discharge.

	Group	Insulin	Diet	Tablets	P-value
Before admission	Case	24	34	85	
	Control	9	30	91	
During hospitalization	Case	47	22	72	0.008
	Control	23	33	70	
After discharge	Case	36	22	83	0.02
	Control	19	33	71	

7- The two groups were different in respect of oral hypoglycemic agents administered during hospitalization and upon discharge. P-value was 0.008 during the course of hospitalization (significant) and 0.02 upon discharge (significant) (Table 4).
8- Both the case and control groups received ACE inhibitors and beta blockers (P-value=0.27 and 0.27, respectively) with no significant difference between them.
9- 53.5% of patients in the case group and 61.5% of those in the control group received nitrate upon discharge.

Discussion

Several recent epidemiologic reports suggest that hyperglycemia per se could be a determinant for the development of macrovasular disease in patients with diabetes. Biochemical perturbations related to diabetes and hyperglycemia may also be of major importance during the acute infarction period, with subsequent impaired myocardial hemodynamic response to the injury. There is also speculation that insulin treatment in patients with diabetes could favorably affect the coagulation system in the setting of acute coronary syndromes.[13]
In 1996, Malmberg studied the effect of insulin therapy on one-year mortality and morbidity with specific etiology. This study involved the same 620 patients in the previous study, who were divided into case and control groups. The case group was treated with insulin and the control group by oral hypoglycemic agent (OHA). Mortality rate was 19% in the case group and 26% in the control group ($P < 0.05$). CHF was the commonest cause of death in all of the patients. The reductions in in-hospital and one-year morality rates in the case group measured 58% (P 0.05) and 52% ($P<0.02$), respectively.[16]
A different study has assessed the long-term effect of strict blood glucose control with insulin after acute MI in diabetic patients. The absolute reduction in morality rate in this method was 11%.[17]
Authors suggested that the beneficial effects of treatment with GIK were probably due to enhanced glucose oxidation caused by insulin which can increase levels of adenosine triphosphate (ATP) synthesis, a substance with recognized beneficial effects under ischemic conditions.[18]
The difference between our statistics and those of the latter study may be accounted for by lack of treatment with insulin for a minimum period of three months and lack of evaluation of patients for risks of cardiovascular disease. Finally, findings of this study demonstrate that improvement of ventricular performance, as gauged by left ventricular ejection fraction, was significantly higher in the case group compared to the control group. Results of the six-month follow-up showed a significant improvement in ventricular performance, as well as a decrease in late mortality in the case group.
Arrhythmia in the case group was significantly lower than in the control group.
Absence of any significant difference in the case of other complications, such as cerebrovascular accidents and re-infarction can be explained by the assumption that GIK has no obvious effect in preventing obstruction of vessels.
In summary, our findings favor an intervention to regulate the metabolic state of the ischemic heart simultaneously with, or even earlier than the start of treatment with thrombolytic agent. This is in light of the finding that almost in all cases, in-hospital complications, mortality rate, and results of echocardiography in the case group (i.e. patients treated with GIK) were significantly different from those of the control group.

Recommendations:

- Limiting the amount of fluid administered with GIK solution, especially in patients with fluid intake restriction.
- Using the therapeutic effects of GIK solution in other clinical conditions such as cardiogenic shock and unstable angina pectoris.
- Many specialists are aware of the theoretical benefits of GIK solution; hence it seems appropriate to familiarize cardiologists with the practical benefits of treatment with GIK, especially in diabetic patients.

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