# THE INVESTIGATION OF THE EFFECTS OF GLUCOSE-INSULIN-POTASSIUM-MAGNESIUM SOLUTION IN PATIENTS SUFFERING FROM ACUTE MYOCARDIAL INFARCTION WHICH WERE GIVEN THROMBOLYTIC THERAPY

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***The main purpose of the MI treatment are to limit the infarct zone, to prevent from the complications and to improve the prognosis. In the ischemic period of the myocardium until the vessel patency has been obtained, we tried to give a dense metabolic support to the myocardium and thus to protect the contractile mass. To reach this aim, 46 consecutive patients with acute MI who were given thrombolytic therapy simultaneously with the Glucose-Insulin-Potassium-Magnesium (GIK-Mg) solution, were divided into GIK-Mg (n=21, 6 male) and the control group which were not given the GIK-Mg solution (n=25, 8 male). All the laboratory results (CPK, Mg++, K+, glycemia), and the other data (systolic arterial tension, ejection fraction) were recorded (safety measurements; serum glucose, K, Mg and efficacy measurements; SBP, CPK, EF, Arrhytmia) for three days.***

***Hyperglycemia, hypermagnesemia, a slight decrease in systolic blood pressure at the twelth hour and an increase in ejection fraction at the third day proportionally to the first day was recorded for the whole GIK-Mg group (p<0,05). There is no statistical difference regarding with the potassium level, infarct expansion and arrhytmia incidence (p>0,05). No comment was made regarding with the mortality rate. Other than the two patients who needed extra insulin for blood sugar regulation, all laboratory parameters were within the physiologic ranges and the whole working group tolerated this solution very well. We can conclude that GIK-Mg solution, which was given simultaneously with thrombolytic therapy to acute MI patients is cheap, safe, well tolerated, free of side effects, has no effect on arrhytmia incidence and infarct expansion. We still need further investigations with larger clinical trials regarding with GIK.***

***Key Words: Acute Myocardial Infarction, Thrombolytic therapy, Glucose-Insulin-Potassium-Magnesium***

Normally perfused myocardium uses free fatty acids (FFA) in the fasting, glucose in the nonfasting and lactate in the exercise state(1,2).

In the early stages of the myocardial infarction and serious ischemic conditions, there is an increase in the serum levels of the catecholamines and FFA which were liberated from the adipose tissue (3). Myocardial infarction (MI) causes a decrease in the pancreas perfusion and this leads to a decline in insulin release from B cells causing low serum insulin level as well as decreased uptake of the glucose by the myocardium(3). Finally liver increases its glycogenolysis for compensation.

There is a switch from reversible to an irreversible ischemia period in the first three hours of ischemia. If the glycolytic ATP can be provided to the myocardial cell, the mitochondria keep its metabolism and this leads to preservation of the energy cycle, membrane function, perfusion and globally contraction of the myocardium(2,3).

Glucose-Insulin-Potassium-Magnesium (GIK-Mg) solution was used as an adjuvant therapy for the treatment of acute MI patients in this regard(4,5,6,7,8,9,10).

*The clinical indications of GIK-Mg are;*

**1-**Refractory heart failure after cardiopulmonary bypass

**2-**Acute ischemic syndromes(11,12).

*The effects of GIK-Mg are;*

***a)*** Metabolic Effects:

**1-** It increases glucose, insulin and lactate.

**2-** It decreases the FFA levels of the plasma.

**3-** It increases the shift of potassium (K) inside to the myocardial cells.

***b)*** Hemodynamic Effects:

**1-** It increases the cardiac output(CO).

**2-** It decreases the peripheral resistance (PR).

**3-** It increases the blood flow into the skeletal muscle.

**4-** It increases the renal blood flow.

***c)*** Other Effects:

**1-** It has controversial effects on ventricular arrhytmias(11, 12, 13, 14, 15, 16, 17).

**2-** It has a controversial effect on the infarct expansion (18).

In acute MI patients, the use of GIK-Mg provides an increase in serum levels of the insulin contributing to the uptake of glucose in terms of the source of energy for the cell mitochondrial and membrane function.

We can hypothesize that Glucose-Insulin-Potassium-Magnesium (GIK-Mg) solution can be used as an adjuvant medical therapy in the early period of acute MI because of the metabolic effects of insulin(12, 13, 19, 20, 21).

The aim of this study is to investigate the clinical and metabolic effects of the GIK-Mg in the early period of acute MI patients which were given thrombolytic therapy.

## MATERIAL AND METHODS

Each patient who was included in this study has signed a consent form and hospital ethical committee approval has been provided.

*Inclusion criteria for the study:*

**1-** The patient who admits to the emergency room in the first 6 hours after the onset of typical chest pain.

**2-** MI diagnosed and confirmed by clinical and laboratory findings.

**3-** Age < 65 years.

**4-** First diagnosed MI in his/her life.

*Exclusion criterias for the study:*

**1-** Age > 65 years.

**2-** Heart rate < 40/min.

**3-** Serum glucose level > 180 mg/dl.

**4-** Serum K level > 5 mEq/lt.

**5-** Serum Creatinine level > 3 mg/dl.

**6-** Serum Magnesium level > 5 mg/dl.

**7-** Acute or chronic renal failure.

**8-** Pulmonary edema, congestion and cardiopulmonary shock.

**9-** Uncontrolled hypertension and arrhytmias

**10-** Patients who underwent recuscitation.

All patients who were admitted to the coronary care unit (CCU) were monitored for the rhythm of the heart, an access for an intravenous line for both arms with 21 no gauge, transthoracic echocardiographic measurements, manual blood pressure measurements from the right arm every six hours, thrombolytic therapy (TT) either with streptokinase (SKZ) or tissue plas-

minogen activator (t-PA) starting with heparin and GIK-Mg solution simultaneously (4, 5, 6, 7, 11, 12).

The patients were divided into the study group which were given GIK-Mg as GIK-Mg(+) and GIK-Mg(-) for the control group.

*The GIK-Mg solution composed of the following:*

**1-** 250 gr of glucose.
**2-** 80 mEq K.
**3-** 50 units of crystallised insulin.
**4-** 18 gr Mg(12).
**5-** This mixture was complemented with physiologic serum (% 0.9) up to 1000 ml.

GIK-Mg were given to patients simultaneously with TT from their contralateral antecubital vein.

*GIK-Mg infusion protocol was as follows:*

**1-** 250 ml/h for an hour
**2-** 150 ml/h for two hours
**3-** 100 ml/h for two hours
**4-** 30 ml/h for ten hours (12).

Heparin infusion protocol was 5000 units of bolus with 1000 U/h continous infusion for a total of 5 days (13).

*GIK-Mg safety measurements were:*

**1-** Serum glucose level
**2-** Serum K level
**3-** Serum Mg level

*GIK-Mg efficacy measurements were:*

**1-** Systolic blood pressure (SBP)
**2-** Serum total creatinephosphokinase level (CPK)
**3-** Left ventricle ejection fraction (EF)
**4-** Arrhytmia detection on the monitor.

All these serum measurements were made in the first 6, 12, 24 and 48 hours after admission to CCU by utilising Olympus AV800 auto-analyser. Serum glucose levels were assessed according to first assay, serum K and Mg levels were assessed according to Olympus ISE mid-standart-Olympus ISE buffer-Olympus ISE reference solutions with ion selective membrane technique. Serum total CPK were taken as the marker of infarct expansion.

Utilising 2.5 mHz probe of the Toshiba SSH-160 A echocardiography machine, ejection fractions were assessed in the first and third days after admission to CCU according to the American Society of Echocardiography guidelines utilising Teicholz measurement system and reported as % change (22).

Statistical Analysis

All statistical analysis were made by utilising student t-test, fisher exact test and chi-square test. The data was presented as ± standart deviation.

## RESULTS

The study group (n=21) consisted of 6 males and 15 females (28.5 %) and the control group (n=25) consisted of 8 males and 17 females (32 %).

The age of the study group was 55.2±9 and for the control group 58.5±6.2.

In the study group 11 patients were diagnosed with anterior and 10 patients were diagnosed with inferior MI. All anterior MI patients were given t-PA and all inferior MI patients were given SKZ (Table I).

**Table I:** Features of the study and control group.

| | GIK-Mg | Control |
|---|---|---|
| No.of patients | 21 | 25 |
| Sex (Male/Female) | 6/15 | 8/17 |
| t-PA/SKZ | 11/10 | 14/11 |
| Anterior | 11/10 | 14/11 |

*GIK-Mg side effects:*

**1-** No allergic reactions were detected.
**2-** No pain at the infusion site were detected.
**3-** Four patients of the study group and seven patients of the control group were dead. (Table II).

**Table II:** Etiologies for the death

| | GIK-Mg | Control | P value |
|---|---|---|---|
| Cardiopulmonary arrest | 1 | 1 | >0.05 |
| Heart failure | 2 | 3 | >0.05 |
| Arrythmia | 1 | 2 | >0.05 |
| Cerebral Hemorrhage | - | 1 | >0.05 |
| Total | 4 | 7 | >0.05 |

Total CPK for the infarct expansion, EF, SBP (efficacy measurements) and serum glucose, K, Mg levels (safety measurements) were represented in tables III, IV, V, VI and graphics I and II respectively (Table III).

**Table III:** Total CPK for infarct expansion

| U/I | GIK-Mg | Control | P value |
|---|---|---|---|
| 6th hour | 442.09±82.30 | 432.92±56.39 | >0.05 |
| 12th hour | 841.9±402.75 | 751.48±406.52 | >0.05 |
| 24th hour | 1300.61±657.95 | 1070.28±808.65 | >0.05 |
| 48th hour | 1467.4±797.83 | 1190.33±562.24 | >0.05 |

The left ventricular ejection fraction and systolic blood pressure shows the most significant statistical change among all measurements. The most significant change regarding with systolic blood pressure was seen in the first 12 hour period which correlates with the EF (Table IV, V, VI).

**Table IV:** Ejection Fraction

| % | First day | Third day | P value |
|---|---|---|---|
| GIK-Mg | 56.9±7.6 | 58.83±8.38 | <0.05 |
| Control | 55.68±3.87 | 55.1±4.64 | >0.05 |
| P value | >0.05 | <0.05 | |

**Table V:** Systolic Blood Pressure

| MmHg | GIK-Mg | Control | P value |
|---|---|---|---|
| 6th hour | 130.23±12.09 | 135.1±2.24 | >0.05 |
| 12th hour | 125.47±10.47 | 132.4±12.59 | <0.05 * |
| 24th hour | 123.8±8.04 | 129.16±11.09 | <0.05 * |
| 48th hour | 122.1±8.54 | 127.39±9.75 | <0.05 * |

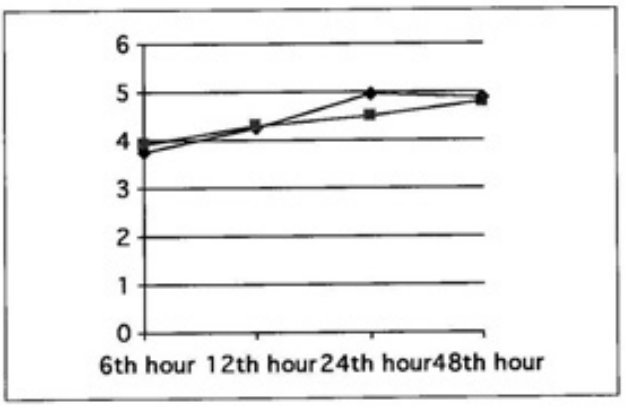
* The most significant reduction of the SBP started to occur after the 12th hour (p=0.02).

**Table VI:** Serum Glucose Levels

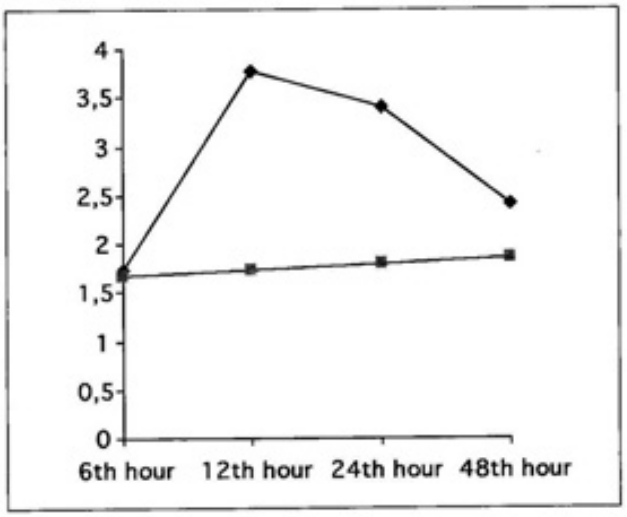
| mg/dl | GIK-Mg | Control | P value6th |
|---|---|---|---|
| hour | 107.85±25.77 | 110.2±21.24 | >0.05 |
| 12th hour | 155.61±28.72 | 101.92±11.98 | <0.001 |
| 24th hour | 127.95±46.48 | 90.68±9.12 | <0.05 |
| 48th hour | 111.71±39.49 | 85.12±7.04 | <0.05 |

Graphic I and II represents the change of both of the K and Mg levels by hours.

**Graphic I.** K levels of GIK-Mg and Control Groups




**Graphic II.** Mg levels of GIK-Mg and Control Groups




## DISCUSSION

The main purposes of the MI treatment are limiting the infarct zone, prevention from the complications and improving the prognosis(13, 20, 21). Multiple invasive and noninvasive treatment strategies have been utilised in this regard(13, 20, 21). Because of its positive hemodynamic and metabolic effects on the myocardium, this solution has been used in the classical treatment scheme of MI starting with Sodi-Pallares et al. and Mittra et al. (4, 12, 13, 16, 17, 18, 19, 20, 26). The aim of adding Mg to GIK is to get the beneficial effects of the Mg for the ischemic syndromes (1, 2, 3, 6, 8, 9, 10, 17, 23, 24) and also promoting the activation of the insulin(1, 2).

*There are two clinical scenarios in the reperfused myocardium:*

1- If the Crebs cycle works regularly, then pro-

tons and oxygen come together to form water.
2- If ischemia prolongs and disturbs the Crebs cycle, protons and oxygen can't come together to form water and these metabolites starts to accumulate causing intracellular acidosis and free radical formation (1, 2)
After the coronary occlusion, the first pathologic changes start to appear after the 20th minute(13, 25). The irreversible changes can be seen grossly by the end of the 5th and 6th hours. For this reason the 70 % of the GIK-Mg solution was infused in the first 5 hours and finished at the 15th hour (12).
All the GIK-Mg group tolerated this volume overload without any need for a diuretic.
Two patients from the GIK-Mg group needed extra insulin for serum glycemia regulation. This may be due to pancreatic hypoperfusion, elevated adrenegic nervous system activity and its effects on insulin release or high stress state related to acute MI.
The low dose extra insulin requirement only in two patients for GIK-Mg solution represents the good tolerability and safety of this particular solution.
Mg and K levels were also elevated during GIK-Mg infusion but none of the patients achieved the critical pathologic level which represented itself with any clinical or electrocardiographic findings. We assume that, when K and Mg levels stay constant, all the given K have moved into the intracellular space by the help of glucose, insulin and Mg. This K shift inside the cell and calcium blockade by Mg, makes them electrically more stable (7,26).
In the GIK-Mg group, one patient has suffered from ventricular fibrillation(VF) on the second day and two patients from the control group have suffered from VF (one in the first and the other in the second day, after admission to CCU).
It's effect on mortality is stil contoversial(11, 12, 13, 18, 19, 29, 30). Because of our limited patient population both for the control and the study group, we reported only the death causes in this paper.
None of the patients complained about the infusion site pain.
We can conclude that GIK-Mg is safe and tolerable and arrythmia pathogenesis in acute MI has much more mixed and complex mechanisms than our knowledge(12, 13, 27, 28, 29, 31). We couldn't find any total CPK level change regarding with the infarct extension(11,12, 13, 18).
SBP started to decline after the 12th hour probably related to the GIK-Mg's lowering effects on the serum osmolarity and systemic vascular resistance (6). The EF for both groups didn't show any statistical difference on the first day ($p>0.05$) but it started to show improvement ($p<0.05$) on the third day of the acute MI. This is consistent with the time need for the beneficial effects of GIK-Mg which are the preservation of the tissue glycogen and high energy stores for the continuation of the mitochondrial and membrane activation of the myocardial cell and left ventricular afterload reduction which leads to an increase in EF in time (1, 2, 12).
Although it is hypertonic in nature, none of our patients developed pulmonary congestion or heart failure symptoms and signs. This may be due to our rigid patient inclusion criteria or age distribution of our patient population.
We can conclude that GIK-Mg solution as an adjuvant therapy to standart acute MI protocol is cheap, safe, well tolerated, free of serious life threatening effects, and it decrease the SBP and increases the EF; which are known as the beneficial effects on acute MI therapy. We still need further investigations and larger clinical trials for the evaluation of GIK on acute MI therapy.

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