# The efficacy of pharmaceutical combination of glucose, insulin, potassium, and magnesium along with thrombolytic therapy on the mortality of patients with acute myocardial infarction

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## Abstract

**BACKGROUND:** Despite conventional treatment methods of acute myocardial infarction, its complications and mortality rates are still very high. Finding new cost-effective treatments like regulation of ischemic muscle metabolism at the time of thrombolytic therapy can meet this requirement to some extent. This study investigated the efficacy of the pharmaceutical combination of glucose, insulin, potassium (GIK) and magnesium along with thrombolytic therapy.

**METHODS:** In a double-blind, controlled clinical trial, 200 patients with acute myocardial infarction who had the indication for thrombolytic treatment were selected and divided to 6 groups of almost 30 people. A specific treatment protocol was designed for each group. The patients in the first 5 groups were compared with the ones in the sixth group as the control group in terms of frequency of complications and in-hospital mortality and also mortality during 3 and 6 months after the treatment.

**RESULTS:** Mean age of the patients was 58.77 ± 2.6 years. Males constituted 77% of the study population. Heart failure, in-hospital arrhythmia and ejection fraction (EF) at discharge showed favorable results in the five groups which received metabolic regulations as compared to the control group. In-hospital mortality of no groups was different from that of the control group ($P > 0.05$). Three months after the treatment, mortality of the group that received GIK and magnesium was lower than that of the control group ($P < 0.05$). After 6 months, none of the patients who received high-dose GIK and magnesium along with thrombolytic therapy died while the mortality rate of the control group was 44.4% ($P < 0.05$).

**CONCLUSION:** The infusion of GIK and magnesium solution along with thrombolytic therapy can lead to a decrease in the long-term mortality and complications in patients with acute myocardial infarction.

**Keywords:** Acute Myocardial Infarction, Glucose, Insulin, Potassium, Magnesium, Thrombolytic Therapy, Cardiovascular Diseases, Clinical Trial.

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## Introduction

Despite conventional treatment methods for acute myocardial infarction, its complications and mortality rates are still very high.[1] Therefore, it is essential to find new and cost-effective treatments in this regard. Besides conventional treatments (like thrombolytic therapy), two metabolic treatments have been introduced for treating the patients with acute myocardial infarction. These two methods include the infusion of a solution of glucose, insulin, potassium (GIK), and magnesium (Mg). Recently, the perfusion measurement of myocardial tissue has shown that at the beginning of acute myocardial infarction, perfusion of myocardial tissue is at a very low level but it is not zero.[2] Since the infarction area has the minimum sufficient flow for the release of substrate, lactic acid wash would provide a basis for the intervention in the infarction flow using GIK method. The studies conducted by insulin and glucose with low-flow ischemia have shown that at the time

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of acute myocardial infarction, the increase of glycosylated substrate, which is accessible by the tissue, has useful effects.[3] High glucose substrate has been found to cause an increase in resistance of myocytes to toxic effects of cellular calcium which is produced during hypoxia.[4] The results of a review study in 1997 demonstrated that GIK prescription led to 28-42% reduction in the in-hospital mortality of myocardial infarction patients.[5] However, thrombolytic therapy was not conventional at that time and it is not evident whether using GIK in treating myocardial infarction was essential at the presence of current thrombolytic treatments or not. After this study, only one other study in 1998 in South America evaluated the value of using high-dose GIK along with thrombolytic therapy and angioplasty in treating acute myocardial infarction.[6]

The indication for using Mg in treating myocardial infarction is the overall reduction of Mg in the body.[7] The reasons for this reduction include receiving insufficient Mg, taking diuretics, old age, and trapping free Mg in fat cells as a result of released fatty acids by fat cells at the beginning of infarction.[7,8] Various researches in 1996 have suggested Mg infusion immediately after myocardial infarction and adding Mg salts to the diet of the patients for 2 years after myocardial infarction to possibly decrease the mortality and complications of the condition.[9] Nevertheless, the results of some other studies have indicated ineffectiveness of Mg on decreasing of the mortality and complications of myocardial infarction.[10]

In the present study, the effects of the combined usage of GIK and Mg with thrombolytic therapy was compared with thrombolytic therapy alone.

## Materials and Methods

This study was a double-blind clinical trial. Participants were patients who referred to the emergency department and coronary care unit (CCU) of Noor, Feiz, and Alzahra Hospitals, affiliated to Isfahan University of Medical Sciences (Isfahan, Iran), between late January 2000 and late July 2001. All subjects suffered from acute myocardial infarction and had the indications for thrombolytic treatment.

A total number of 240 patients were enrolled in the study. They were randomly divided into 6 groups using sealed envelopes in which the number of group was randomly placed. Moreover, each envelop was numbered between 1 and 240 to correspond the 240 patients. After obtaining informed consent forms signed by patients, two residents of internal medicine who participated in this study opened the envelopes related to each patient and placed the subjects in one of the six treatment groups based on the number inside the envelope.

The six treatment groups included: 1) low-dose GIK + thrombolytic; 2) high-dose GIK + thrombolytic; 3) low-dose GIK + Mg + thrombolytic; 4) high-dose GIK + Mg + thrombolytic; 5) Mg + thrombolytic; and 6) thrombolytic alone (control group).

Low-dose GIK contained 1 liter of 10% glucose solution plus 20 units of insulin crystal (human or non-human) plus 40 MEq potassium, which were infused at the rate of 1 ml per kg of body weight per hour.

High-dose GIK contained 1 lit of 25% glucose solution plus 50 units of insulin crystal (human or non-human) plus 80 milliequivalents (mEq) of potassium which were infused at the rate of 1.5 ml per kg of body weight per hour. Mg solution contained 8 grams of magnesium sulfate in 1 liter of 5% serum dextrose which was infused for 24 hours.

After determining the treatment group of the patients, all characteristics, symptoms, and examination results of the patient were recorded in a questionnaire by internal medicine residents. The patients were then treated according to the protocol designed for their own groups either simultaneous with or shortly after the beginning of thrombolytic therapy.

Thrombolytic therapy was performed using 1.5 million units of intravenous streptokinase. GIK, Mg and streptokinase were infused via separate veins. To maintain double-blindness, the placebo (5% glucose serum) was used. Therefore, each patient received three solutions. In other words, only one solution of 5% glucose serum was used in the first, second, and fifth treatment groups.

On the other hand, the sixth treatment group received glucose serum through 2 veins while the third and fourth groups did not receive any 5% glucose serum.

After infusing the solutions, the patients were examined by two internal medicine residents participating in the study for mortality and in-hospital complications including a second myocardial infarction, congestive heart failure, secondary arrhythmia, in-hospital death, cerebrovascular complications, and major bleeding. Echocardiography was also performed by a heart specialist before the patients were discharged and the results (ejection fraction) were recorded in the questionnaire.

The patients were followed for mortality and percutaneous transluminal coronary angioplasty (PTCA) requirement. Echocardiography was repeated at 3 and 6 months after the discharge. All echocardiograms were performed by a specific specialist at Isfahan Cardiovascular Research Center (Isfahan, Iran). Each patient was provided with a special follow-up card on which the dates of the 3- and 6-month reference were written. If the patients did

not show up on the determined days, the information was achieved by phone calls or referring to their address.

Considering the exclusion criteria (kidney failure, hyperkalemia, bradycardia, and hypotension) and unavailability during the follow-up, 40 patients were excluded from the study. Consequently, the data of 200 patients was analyzed.

To analyze the data, Fisher's exact, chi-square, Dunnett's, Kruskal-Wallis, Dunn's, and Mann-Whitney tests were used. The minimum error of less than 0.05 was considered for rejecting the null hypothesis.

## Results

The mean age of the patients (77% males and 23% females) was 58.7 ± 2.6 years. The characteristics of the patients in terms of risk factors and conducted clinical examinations in each group are demonstrated in table 1.

The results obtained from 6 types of mentioned treatments were compared with one another in three stages. No significant difference was observed between the 6 treatment groups with regard to mortality rate during their hospital stay. The lowest mortality rate (none out of 32 patients) was in the fourth treatment group (high-dose GIK + Mg + thrombolytic). The highest mortality rate (8 from 36 patients) was observed in the sixth treatment group (only thrombolytic therapy) (Table 2).

Minimum and maximum numbers of patients with heart failure were detected in the fourth treatment group (with 2 cases) and in the sixth treatment group (with 20 cases), respectively.

Using Dunnett's test to compare groups 1 to 5 with group 6 (control group), it was found that heart failure rate in the control group was higher than that in treatment groups 1 (low-dose GIK + thrombolytic), 2 (high-dose GIK + thrombolytic), and 4 (high-dose GIK + Mg + thrombolytic) ($P < 0.05$). However, no significant difference was observed between the control group and treatment groups 3 (low-dose GIK + Mg + thrombolytic) and 5 (Mg + thrombolytic) ($P > 0.05$). Moreover, no difference was found between treatment groups 1 and 2 (Table 2).

**Table 1.** Frequency distribution of risk factors, physical findings, and demographic characteristics among patients who received low-dose glucose, insulin, and potassium (GIK), high-dose GIK, low-dose GIK and magnesium, high-dose GIK and magnesium, magnesium, and placebo plus thrombolytic therapy (groups 1-6, respectively)

| Variables | Treatment groups | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Total number | 22 | 24 | 22 | 22 | 24 | 36 |
| Age (year) | 55.80 ± 2.15 | 59.70 ± 2.00 | 59.30 ± 2.70 | 57.90 ± 2.70 | 2.40 ± 60.20 | 59.40 ± 2.90 |
| Male gender | 26 | 26 | 24 | 28 | 24 | 26 |
| Diabetes Mellitus | 6 | 12 | 4 | 6 | 6 | 12 |
| Smokers | 14 | 16 | 18 | 12 | 14 | 16 |
| Hyperlipidemia | 6 | 8 | 6 | 10 | 8 | 10 |
| Obesity | 2 | 10 | 4 | 4 | 2 | 10 |
| Hypertension | 10 | 22 | 16 | 10 | 16 | 12 |
| Family history of cardiovascular diseases (Yes) | 12 | 12 | 6 | 14 | 2 | 6 |
| Myocardial Infarction | 4 | 4 | 2 | 4 | 8 | 6 |
| $S_3$ | 6 | 4 | 6 | 4 | 6 | 22 |
| $S_4$ | 28 | 18 | 28 | 16 | 26 | 26 |
| Rhonchus | 12 | 14 | 10 | 8 | 6 | 20 |
| JVP | 6 | 4 | 6 | 4 | 6 | 16 |
| Edema | 2 | 6 | 2 | 2 | 2 | 2 |
| Hepatomegaly | 2 | 4 | 0 | 2 | 0 | 0 |

Values are expressed as mean ± SD or frequency.

**Table 2.** Relative frequency of in-hospital complications among patients who received low-dose glucose, insulin, and potassium (GIK), high-dose GIK, low-dose GIK and magnesium, high-dose GIK and magnesium, magnesium, and placebo plus thrombolytic therapy (groups 1-6, respectively)

| Treatment group | Total number | Heart failure* | Arrhythmia | Repeated myocardial infarction | Stroke | Death | Major bleeding | PTCA |
|---|---|---|---|---|---|---|---|---|
| 1 | 32 | 4 | 2 | 0 | 0 | 2 | 2 | 0 |
| 2 | 34 | 4 | 6 | 0 | 0 | 2 | 2 | 0 |
| 3 | 22 | 4 | 6 | 0 | 0 | 2 | 2 | 0 |
| 4 | 32 | 2 | 0 | 0 | 0 | 2 | 0 | 0 |
| 5 | 34 | 6 | 4 | 2 | 0 | 0 | 3 | 6 |
| 6 | 26 | 20 | 12 | 0 | 0 | 2 | 8 | 2 |

*Heart failure based on clip criterion (higher than 2); PTCA: Percutaneous transluminal coronary angioplasty

The maximum and minimum frequencies of arrhythmia were observed in the control group (14 cases from 32 patients) and of the fourth group (no cases), respectively (Table 2). While the frequency of arrhythmia decreased in the fourth group, it did not differ significantly between other groups and the control group. No differences were observed between the treatment groups regarding the frequencies of repeated myocardial infarction, stroke, in-hospital major bleeding, and PTCA requirement during the hospital-stay ($P > 0.05$).

Left ventricular ejection fraction was different in the six treatment groups (Table 3). The maximum (49%) and minimum (37%) mean values of ejection fraction belonged to groups 2 and 4 and the control group, respectively. A significant difference was seen between treatment groups 2 and 4 and the control group in terms of left ventricular ejection fraction (Table 2).

Mortality rate after discharge until the 3-month follow-up was not different between the 6 groups (Table 4). The maximum and minimum mortality rates were seen in the control group (27.8%) and group 4 (no cases), respectively. Only mortality rate of group 4 was different from that of the control group ($P < 0.05$).

The need for PTCA from admission until 3 months after discharge was not different between the 6 groups. The minimum and maximum rates of needed PTCA were observed in treatment groups 1 (35.7%) and 5 (64.3%), respectively.

At the 3-month follow-up, left ventricular ejection fraction was different between the 6 treatment groups (Table 3). The maximum and minimum mean values were calculated in treatment groups 2 (50%) and 4 (51%) and in the control group (37.9%), respectively. In all groups except group 3, left ventricular ejection fraction was different from that of the control group ($P < 0.05$).

Mortality rate during 3 to 6 months after discharge was not different between the 6 treatment groups. The highest and lowest mortality rates from admission until the 6-month follow-up were found in the control group (16 cases) and group 4 (zero cases). The mortality rate in groups 2 and 4 was significantly lower than the control group ($P < 0.05$).

With regard to the need for PTCA from admission until discharge, there was no difference between groups 1 to 5 and the control group ($P > 0.05$). The maximum and minimum need for PTCA were in the treatment group 5 (24 cases from 28 people) and in group 4 (8 cases from 26 people), respectively (Table 4).

**Table 3.** Left ventricular ejection fraction before discharge, and 3 and 6 months after the treatment in patients who received low-dose glucose, insulin, and potassium (GIK), high-dose GIK, low-dose GIK and magnesium, high-dose GIK and magnesium, magnesium, and placebo plus thrombolytic therapy (groups 1-6, respectively)

| Treatment group | Before discharge | 3 months after discharge | 6 months after discharge |
|---|---|---|---|
| 1 | 47 ± 2.6 | 46.1 ± 2.59 | 48.65 ± 2.51 |
| 2 | 49.06 ± 2.15 | 50.62 ± 2.28 | 5 ± 2.51 |
| 3 | 42.5 ± 1.72 | 44.63 ± 2.19 | 44.58 ± 2.08 |
| 4 | 49.22 ± 2.19 | 51.88 ± 2.41 | 52.46 ± 2.68 |
| 5 | 46.66 ± 2.53 | 49.63 ± 1.99 | 51.36 ± 2.44 |
| 6 | 27.67 ± 2.53 | 37.86 ± 2.71 | 29.38 ± 2.58 |

**Table 4.** Relative frequency of mortality and percutaneous transluminal coronary angioplasty (PTCA) requirement 3 and 6 months after discharge in patients who received low-dose glucose, insulin, and potassium (GIK), high-dose GIK, low-dose GIK and magnesium, high-dose GIK and magnesium, magnesium, and placebo plus thrombolytic therapy (groups 1-6, respectively)

| | 3 months after discharge | | | 3 to 6 months after discharge | | | |
|---|---|---|---|---|---|---|---|
| Treatment group | Total number | Death | PTCA requirement | Number | Death | PTCA requirement | Number |
| 1 | 30 | 4 | 10 | 26 | 0 | 16 | 6 |
| 2 | 22 | 0 | 16 | 2 | 0 | 14 | 4 |
| 3 | 28 | 0 | 14 | 4 | 2 | 18 | 18.7 |
| 4 | 32 | 0 | 13 | 0 | 0 | 8 | 0 |
| 5 | 30 | 2 | 18 | 6 | 0 | 23 | 6 |
| 6 | 28 | 2 | 16 | 10 | 6 | 10 | 16 |

The maximum and minimum left ventricular ejection fraction values after 6 months of follow-up were observed in the treatment group 4 (53.5%) and control group (39.4%), respectively. Left ventricular ejection fraction was higher in group 4 compared to the control group ($P < 0.05$).

## Discussion

The results of this study revealed that the in-hospital complications of secondary arrhythmia and severe heart failure decreased in the groups that received metabolic intervention in addition to thrombolytic therapy. Furthermore, ventricular function at the time of discharge showed considerable improvement as compared to the control group. Long-term mortality of the patients with acute myocardial infarction also significantly decreased in these patients as compared with the group that only received thrombolytic therapy. Moreover, the ventricular function of the people in the mentioned groups increased as compared to the control group. The fourth treatment group which received high-dose GIK and Mg demonstrated favorable results in general while in some cases, other groups did not show any differences with the control group.

Although no significant difference was found among the groups that received high and low doses of GIK, it is difficult to reach a final conclusion and more precise studies on larger sample sizes are required. In a similar study entitled ECLA in Latin America, two groups received high and low doses of GIK without Mg and were compared with a control group that only received thrombolytic therapy. The results showed that high-dose GIK was more effective for decreasing long-term mortality after treatment as compared with the low-dose GIK. In addition, in comparison with the control group, high and low doses of GIK significantly decreased both mortality and in-hospital complications and also the mortality of the patients one year after the treatment.[6]

Another similar study entitled DIGAMI demonstrated reduced mortality in patients who received insulin and glucose at the time of infarction and also received long-term insulin in addition to thrombolytic treatment.[11]

It is noteworthy that the above-mentioned studies were conducted while using thrombolytic as a treatment for acute myocardial infarction. Thus far, no studies have been undertaken based on simultaneous application of GIK and Mg. However, the LIMIT-2 study reported a significant decrease in in-hospital mortality during 4.5 years after thrombolytic therapy accompanied by Mg compared to thrombolytic therapy alone.

Moreover, in a study in India, patients were compared in 4 groups. Thrombolytic therapy was combined with Mg in one group and with potassium in another. Considerable reductions in mortality, cardiovascular events, and ventricular ectopy were detected in the mentioned groups compared to the placebo group.[12]

In another study, the effects of intravenous Mg in acute myocardial infarction were investigated randomly and in a double-blind way. Since no difference was observed between the group that received Mg and the control group in terms of mortality and conduction disorders, it was concluded that the study was not comprehensive enough.[10]

Considering the findings of this study, metabolic intervention is recommended to be performed in combination with other conventional treatments of acute myocardial infarction, especially thrombolytic therapy. In addition, to obtain stronger results about the required dose of GIK, comparisons should be made between groups receiving high and low doses of GIK + Mg and a group receiving Mg along with thrombolytic therapy.

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## Conflict of Interests

Authors have no conflict of interests.

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