

# Combination of GIK and Magnesium as a Solution of Choice to Protect Myocardium in High-Risk CABG

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## Abstract

**Background-** CABG is one of the most common surgical procedures, especially among heart surgeries. Protection of the myocardium during and after the early stages of operation has special importance. Different medical and drug techniques have been used for this purpose. One of these techniques is infusion of glucose-insulin-potassium (GIK) solution. We compared the efficacy of GIK solution and GIK- magnesium (Mg) in two groups. The first group received GIK solution without Mg and the second group GIK plus Mg solution, to protect the function of the myocardium.

**Method-** In a double-blind randomized study, we selected 50 patients as candidates for CABG with left ventricular ejection fraction (LVEF) less than 30% and without any severe lung, kidney and blood diseases. These 50 patients were divided in two equal groups. After induction of anesthesia with the same method for both groups, we infused 10 ml/hr GIK in the first group and the same amount of GIK-Mg in the second group for 10 hours in each group and the length of the time and the amount of solution were equal and also stages of induction and maintenance of anesthesia in both groups were similar. We studied vital signs, hemodynamic parameters and complications in both groups during induction, cardiopulmonary bypass (CPB), during stages of weaning these patients from CPB, during their stay in the ICU and until discharge from the hospital.

**Results-** Complications such as sudden fibrillation, arrhythmias, ST elevation during weaning the patients from CPB, intubation time and stay in hospital and ICU in the GIK-Mg group were significantly less than the GIK without Mg group. More importantly, the average percentage of LVEF on discharge in the GIK-Mg group was higher than the group without Mg solution.

**Discussion-** Our study demonstrated that infusion of GIK-Mg is more effective in protection of myocardial function and decreasing complications in CABG patients with LVEF less than 30% than GIK without Mg solution. So, it is recommended that in such patients, GIK-Mg solution should be used routinely (*Iranian Heart Journal 2005; 6 (3): 15-21*).

**Key words:** glucose ■ insulin ■ potassium ■ magnesium ■ myocardial protection ■ coronary artery bypass

Cardiovascular diseases are one of the most important causes of death in Iran and throughout the world. Over recent years, with excellence advances in the fields of cardiac surgery and anesthesiology, a great number of these patients are undergoing operation and their lives are being saved.

During cardiac surgery it is sometimes necessary that patients are taken on cardiopulmonary bypass.<sup>1</sup> In this process patient encounter myocardial ischemia and thus it is required that protective measures be taken to preserve the myocardium and prevent further damage.<sup>2</sup>

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Nowadays, multiple numbers of protocols in line of myocardial support have been developed such as using whole body hypothermia, local myocardial hypothermia, use of cardioplegic injection methods in antegrade and retrograde forms, utilization of cold and warm blood in cardioplegic solutions, use of medications like calcium channel-blocking agents, as well as GIK solution (glucose, insulin, potassium) which serves to fortify cellular reserves and enhance myocardial protection.<sup>3</sup>

In our study, we attempted to conduct a clinical investigation regarding two compositions: GIK (glucose, insulin, potassium) and GIK-Mg (glucose, insulin, potassium and magnesium) so as to support and sustain viability of myocardium in intra- and postoperative periods in coronary bypass surgery.

Many studies having discussed the pathophysiology of myocardial ischemic damage and reperfusion injury, suggest that the use of Mg is supported by several logical reasons. Although results of several clinical trails on acute myocardial infarction show variations and some contradictions, but these differences are explainable with regard to the time of administration of the solution.<sup>9</sup>

As we know, one of proposed features of GIK solution is that it offers a protective effect against myocardial damage often occurring in the perioperative period in CABG surgery. Furthermore, Mg has proved to have a protective effect on the heart and prevent myocardial injury and limit extension of necrotic areas, shown in AMI studies.<sup>7</sup> Hence, we concluded that the combination of these two substances may exert a more pronounced effect on protection of ischemic and injured myocardium. Also, we know that one of the important effects of Mg is its anti-arrhythmic effect. In some studies, GIK has led to more frequent occurrence of postoperative arrhythmias, particularly atrial fibrillation. Therefore, a combination of GIK and Mg may also perhaps reduce the arrhythmogenic effects of GIK.<sup>13</sup>

In 1965, Polaruss and co-workers applied GIK solution in acute MI patients and demonstrated that utilization of this solution caused limitation of electrophysiological changes in these patients. In initial studies, application of this solution for isolated hearts with regional ischemia resulted in reduction of the size of the infarct zone and on the other hand, led to elevation of high energy phosphate levels, consequently improving ventricular function.<sup>15</sup> Furthermore, under severe ischemic conditions and prolonged periods of transfusion, GIK solution caused lactate accumulation and cardiac function deterioration. Interest in GIK solution faded after three clinical trials on patients with myocardial infarction in England demonstrated no positive results on patients' survival.<sup>10</sup>

After introduction of newer and more effective cardioplegic solutions, the role of GIK in heart surgery was dismissed, but recently with the appearance of new modern surgical techniques for therapy of unstable angina, interest has again turned toward this solution. In one experimental study based on a pig model for revascularization of ischemic myocardium, it was demonstrated that the heart receiving GIK develops ventricular arrhythmia less frequently and shows better preservation of heart wall functions with less areas of necrosis. Human studies by the same group showed also that patients receiving GIK manifest a higher cardiac index, less need for inotropic drugs, shorter time on the ventilator, lower rate of occurrence of atrial fibrillation and shorter duration of stay in the ICU and hospital.<sup>17</sup>

## Methods

In this study, fifty volunteer patients who were candidates for CABG surgery with LVEF less than 30% and without progressive pulmonary, renal or hematological diseases, were selected for a randomized, double-blind clinical trial and placed into two treatment groups of GIK and GIK-Mg. After obtaining

informed consent from the patients, diazepam 5mg orally was given the night before surgery as premeditation. One hour prior to operation, morphine, 0.05mg/kg and promethazine, 0.5mg/kg were injected IM, and after arrival to the operating room, they were visited again. In this visit, specifications like age, sex, associated diseases such as diabetes, thyroid diseases, history of MI, history of hospitalization in CCU, history of hypertension, surgery, and several parameters were measured before starting anesthesia including pulse rate, arterial blood pressure, respiratory rate, etc. were recorded. Before induction of anesthesia, preoxygenation with 100% oxygen with help of an oxygen mask was performed, and then fentanyl 4 µg/kg and midazolam 30 µg/kg (as premedication) plus ethomidate 0.2 mg/kg and 0.1 mg/kg pavulon (as muscle relaxant) were administered. Maintenance of anesthesia was with fentanyl, midazolam and pavulon in the form of TIVA.<sup>3</sup> The composition of glucose-insulin-potassium or glucose-insulin-potassium plus magnesium was started at a rate of 10ml/hr for 10 hrs during the operation and continued in the surgical ICU.

Our composition of GIK solution contains 50ml of 50% hypertonic glucose, 10 units regular insulin and 5mEq potassium, brought to 100ml volume by normal saline. GIK-Mg also had the same composition, in addition to 20mEq magnesium in normal saline to reach 100 ml.

Hemodynamic criteria such as blood pressure, heart rate, ST-T segment changes, arrhythmias, sudden fibrillation, intra- and post-CPC, duration of intubation and discharge time were assessed following anesthesia and in the ICU and recorded.

On discharge, patients underwent echocardiography by a cardiologist and were then discharged. We used patient's LVEF measured prior to operation and at discharge as a worthy criterion in our study. It is necessary to mention that monitoring and follow-up of patients was performed by one

surgeon, one anesthesiologist and one cardiologist.

Comparing preoperative statistical parameters of the two groups was done using independent t-test and Mann-Whitney test. Comparing parameters in different phases of the study was performed using analysis of variance. Chi-square and Fisher exact tests were utilized for comparison of nominal variables of both treatment groups.

## Results

Comparison of the two groups showed no significant differences in terms of specifications including age, weight, previous heart surgery, history of stay in CCU, diabetes, hypertension and/or history of myocardial infarction (Table I).

**Table 1.** Comparison of preoperative specifications of the two patient groups.

Treatment Group	GIK	GIK-Mg	P-Value
Number	25	25	
Age (Mean ± SD)	57.3 ±10.8	55.3 ±12.3	0.54
Weight (Mean ± SD)	73. ± 9.7	71.8 ±10	0.61
Hgb (Mean ± SD)	14.3 ± 1.8	14.7 ±1.8	0.49
Htc. (Mean ± SD)	42.3 ±4.7	43.2 ±4.6	0.50
FBS (Mean ± SD)	138 ±80	131 ±53	0.75
Na (Mean ± SD)	141 ±4.7	139 ±4.7	0.29
K (Mean ± SD)	4.33 ±0.43	4.28 ±0.47	0.69
BUN (Mean ± SD)	24.7 ±9.1	21 ±7.6	0.12
Creatinine (Mean ±SD)	1.24 ±0.31	1.26 ±0.23	0.64
Sys. BP (Mean ± SD)	133 ±30	122 ±13	0.08
Dias. BP (Mean ± SD)	79 ±17.6	77 ±9	0.56
HR (Mean ± SD)	81.8 ±14.6	78.6 ±6.7	0.33

In comparison of laboratory tests and preoperative hemodynamics of understudied groups, about hemoglobin level before operation, hematocrite, fasting blood sugar, serum levels of Na, K, BUN, and Creatinin, systolic blood pressure, diastolic blood pressure, heart rate and EF value before operation, no significant difference was found. Also, left heart functioning in both two groups were similar and all subjects in either group manifested an cardiac EF level less than 30% (Table II).

**Table II.** Comparison of cardiac specifications and associated diseases in the two treatment groups.

Treatment Group	GIK	GIK-Mg	P-Value
EF% (Mean $\pm$ SD)	28.1 $\pm$ 4.6	27.7 $\pm$ 5.2	0.59
History of operation	62.5%	56.5%	0.19
History of MI	60%	68%	0.047
History of CCU stay	60%	56%	0.31
History of Diabetes	36%	28%	0.54
History of Hypertension	52%	44%	0.57

ST-segment elevation during CPB withdrawal was observed in 12% of GIK patients, but in about 2% of the GIK-Mg patients ( $P=0.003$ ). Occurrence of arrhythmias during weaning from CPB was seen in 8% of the GIK group subjects while in the GIK-Mg group, it was seen in 1.7% of subjects ( $P=0.005$ ). Furthermore, sudden fibrillation during CPB weaning was seen in 10% of subjects in the GIK group, while in the GIK-Mg group this event was seen in 2.5% of subjects ( $P=0.007$ ). Relative frequency of hypotension during CPB separation in GIK patients was 12%, while in the GIK-Mg group it was observed in 3% of patients ( $P=0.004$ , Table III).

**Table III.** Comparison of ST segment alteration, hemodynamics and arrhythmias during operation between the GIK and GIK-Mg groups.

Criteria	GIK	GIK-Mg	P-Value
ST-Segment elevation at CPB weaning	12%	2%	0.003
Sudden fibrillation at CPB weaning	10%	2.5%	0.007
Arrhythmia at CPB weaning	8%	1.7%	0.005
BP Decline at CPB weaning	12%	3%	0.004

### Duration of stay in the ICU

48% of GIK patients had a duration of stay of 48 hours, and 52% of them had been hospitalized for a duration of more than 48 hours. These numbers for GIK-Mg patients were reported to be 67% and 25%, respectively. Therefore, in the latter group, 8% of subjects had hospitalization for a period of 24 hours as well. This observed difference is statistically significant ( $P=0.004$ ).

### Hospital stay

GIK patients had an average stay in hospital of 9.3 days, and GIK-Mg patients 8.4 days ( $P=0.004$ ), which is statistically significant.

### Ejection fraction

Statistical investigation for ejection fraction values among patients in the pre- and postoperative periods revealed that in the GIK group before operation, LVEF ranged from 15 to 30%, with a mean of 28.1%. In this group, after operation, these numbers were 15%, 55% and 39.8%, respectively. For the GIK-Mg group, before operation, EF ranged from 15% to 30%, with a mean of 27.7%. Postoperatively, the figures were 25%, 60% and 47.9%, respectively, the difference between the two groups being statistically significant.

### Discussion

In the human body, magnesium works as a physiological antagonist for calcium. A wide variety of biological effects could be explainable based on this fact.<sup>2</sup> Magnesium functions as a cofactor for more than 300 biological reactions, most of which are essential for cellular homeostasis. Chronic Mg deficiency is often associated with multifocal cellular necrosis, intracellular calcium accumulation, increased platelet aggregation, coronary artery constriction and cardiac arrhythmias.<sup>1</sup> In experimental studies, magnesium has led to improved endothelium function, prevention of adverse effects of oxygen free radicals and prevention of increased blood calcium levels which appears upon tissue reperfusion.<sup>19</sup> Magnesium administration can offer myocardial protection against ischemia and limit myocardial reperfusion injury.<sup>20</sup> Recent studies have highly emphasized the role of Mg in platelet-dependent thrombosis.<sup>16</sup> Mg levels have a negative correlation with platelet aggregation and ATP release. According to clinical studies, magnesium supplementation inhibits platelet-dependent

acute thrombosis. It is this potential mechanism which explains the low survival rate in patients with low serum Mg levels who are otherwise free of disorders.

Another potential mechanism involved in Mg deficiency is its probable relationship with cardiac arrhythmias. There is evidence showing that low Mg levels are associated with ventricular arrhythmias after acute MI.<sup>18</sup> Some authors have demonstrated that low Mg levels can lead to a higher incidence of atrial arrhythmias seen after CABG operation.<sup>14</sup>

For optimal and appropriate utilization of GIK solution in cardiac surgery, the following considerations are essential:

- 1) Insulin administration should be done in sufficient doses so as to limit free fatty acid levels. Smith, in spite of measuring free fatty acids (FFA) levels and assuring the sufficiency of insulin dose, did not report any significant difference regarding duration of stay in hospital and ICU, and cardiac markers.<sup>18</sup>

In our study, FFA levels have not been measured, and assurance of sufficiency of administered insulin dose was not possible. Therefore, the influence of GIK solution or superiority of GIK-Mg could not be considered on account of lack of usefulness of GIK or lack of effectiveness of Mg content of GIK solution. Yet, in this research, insulin was administrated for both groups in equal doses, thus compensating to some extent this disadvantage.

- 2) Administration of GIK solution must be continued throughout the reperfusion phase because myocardial ischemia occurs with the highest prevalence rate in this phase.

- 3) There must exist enzymatic cofactors for GIK solution effective action. One of these are 2- valence cations, including Mg. Measurements of patients' Mg levels could primarily be very useful for this assessment.

During the different phases of operation, a significant difference was found between the treatment groups in terms of minimum duration of CPB, the intra-CPB urinary volume, the first 24 hours urine volume and blood sugar level.

The minimum temperature during CPB in the GIK-Mg group was reportedly higher compared with the GIK group. The reason which may be set forth is the influence of Mg on improvement of cellular metabolism.

Urine volume during CPB in the GIK-Mg group was less than that of the GIK group. The effect of Mg on urine volume has not yet been clarified in importance and/or has not been reported. Nevertheless, Mg is a Ca antagonist and calcium promotes diuresis. Perhaps, it is by this reason that Mg resulted in lower urine volumes observed in that group. However, we must recall that Mg blocks L-type Ca channels and these channels solely exist in the myocardium, necessitating more investigation of this potential mechanism. The discussion will be verified greatly when we acknowledge that the first 24 hr urine volume was greater in the group receiving GIK-Mg throughout the operation than that of GIK group, indicating occurrence of diuresis after depletion of Mg levels.

One of the important effects of Mg being investigated is its anti-arrhythmic effect in the postoperative period. In this study, the incidence of arrhythmia after separation from CPB in patients of the GIK-Mg group was 1.7%, but in the GIK group, arrhythmia has been reported to be observed in about 8%. This difference is highly significant statistically and can propose the protective effect of magnesium. This hypothesis is further supported when we note that in the GIK group, frequency of fibrillation was 10% while in the GIK-Mg group, it was 2.5%. In the GIK group, the mean values of LVEF before and after operation were 28.1 and 39.8%, respectively and in the GIK-Mg group, they were 27.7 and 47.9%, respectively, with a significant P-value (0.004).

One notable point in this study is the very poor functioning left ventricle seen in all of the patients under study, such that the LVEF values in all of them was lower than 30%. This fact alone can explain the appearance of complications in this patient population, but on the other hand provides a background for the manifestation of positive effects due to the presence of Mg. Since the maximum useful effects of Mg are found in high-risk patients who are at risk of major severe adverse effects, hence it would be a rational conclusion to accept the superiority of GIK-Mg over GIK solution. The present study delivers good support in line of demonstrating this action.

In this study, investigation of GIK and GIK-Mg effects on cardiac muscle injury was not possible because sensitive markers of heart injury like biochemical indicators particularly troponin I<sup>4</sup> had not been measured and as a result, the influence of GIK-Mg on limiting myocardial injury secondary to CABG was not delineated. Further, presence of infarct zones surrounding the operation site had not been evaluated, and no judgment can be made in this regard. These issues remain to be discussed in the future research.

Of notable issues in this study is higher level of blood sugar in most phases of the operation and afterwards observed in the GIK-Mg compared to GIK group. In some studies, GIK treatment has caused a blood sugar increment compared to the control group and by the same reason follow-up and frequent measurements of blood sugar in patients under GIK treatment have been under consideration. Yet, serum glucose levels of patients in the GIK-Mg group have never exceeded this notable amount. Very high levels of blood sugar have rarely been observed in a minority of patients. The mechanism of action is unknown and perhaps the re-testing of this observation at future studies can assist testing the above hypothesis.

Mg supplementation therapy affords the best benefits to that group of patients that, 1) have

low Mg deposits in their bodies, 2) have therapy commenced at initial reperfusion, 3) are at high risk of complications. Therefore, measurement of baseline levels and intra- and postoperative levels of Mg may help to determine whether all of the patients benefited from this treatment or the observed but non-significant effects are in relation to mixing patients with normal and high serum Mg levels. Therefore, it is recommended that in future studies, the magnesium levels and better yet, urine Mg level which is considered as a better marker indicating whole body magnesium content, be measured.

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