Glucose-Insulin-Potassium Solution Improves The Recovery After Coronary Artery Bypass Grafting

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Abstract

This prospective, randomized, clinical study was designed to determine whether glucose-insulin-potassium solutions would benefit patients undergoing coronary artery bypass grafting (CABG) with cardiopulmonary bypass. The study group was composed of 30 patients who required CABG. In 15 patients, glucose-insulin-potassium (GIK) solution (30% dextrose in water; K+, 80 mEq/L; regular insulin, 50 units) was given intravenously at 1ml/kg per hours after anesthetic induction, and continued to 12 hours after aortic clamping (the GIK group). During aortic clamping, infusion was not administered. Another 15 patients received 5% dextrose in water intravenously at 50 ml/hr at the same periods (the control group).

Patients treated with glucose-insulin-potassium solution had higher cardiac indices (2.8±0.3 vs 2.3±0.2 L/min.m-2, p<0.05 at reperfusion 6th hour), lower inotrope using but statistically insignificant (27% in the GIK group vs. 67% in the control group, p >0.05). There was a slightly lower incidence of rhythm disturbances but insignificant (13% in the GIK group vs. 40% in the control group, p>0.05)

It's concluded that that glucose-insulin-potassium therapy enhanced myocardial performance after elective CABG.

INTRODUCTION

Substrate enrichment with glucose is a method that may enhance the myocardial protection during open heart surgery. Although free fatty acids are main energy source for the nonischemic myocardium, glucose is a more preferable energy source during periods of ischemia and reperfusion and in chronically dysfunctional but viable myocardium 1,2. It was demonstrated that glucose-insulin-potassium (GIK) solution limited electrocardiographic changes in acute myocardial infarctions 3. Subsequent studies showed both clinically and experimentally that GIK solutions enhanced myocardial performance in acute myocardial infarctions 4-11. In an experimental study, hearts treated with GIK solution had lower incidence of ventricular arrhythmia, less myocardial acidosis, better preservation of wall motion, and the lowest areas of tissue necrosis 12. The best protection from ischemic damage was when GIK solution was given before and during the period of coronary occlusion as well as during reperfusion. We thought to assess the effects of GIK solution on the cardiac performance and myocardial protection.

MATERIALS AND METHODS

Study protocol was approved by the local Institutional Committee. An informed consent was obtained from each patient enrolled in the study. All patients with stable angina pectoris who need CABG were eligible in this study. Patients with diabetes mellitus, chronic renal failure (creatinine level > 2.0 mg/dl), hyperkalemia (potassium level > 5.5 mEq/L), or hepatic insufficiency (total bilirubin level > 2.5 mg/ml; levels of transaminases >100 IU) were excluded from study. Patients who could not tolerate the GIK infusion because of hyperglycemia (glucose level > 300 mg/L) or hyperkalemia (Potassium level > 5.5 mEq/L) were also excluded.

Patients who met the eligibility criteria for this study were randomized to the GIK or the control group on the basis of
the last digit of their hospital identification number. All patients underwent placement of a radial artery catheter and Swan-Ganz thermodilution catheter (Baxter Healthcare Corp., Edwards Division, Irvine, Calif.) before induction of anesthesia. After thermodilution catheter insertion, the GIK group received an infusion at 1 ml/kg per hour of GIK solution consisting of a liter bag of 30% dextrose in water with 80 mEq of KCl and 50 units regular insulin. The infusion of the GIK solution continued through the induction period and the time before cardiopulmonary bypass. After cardiopulmonary bypass was initiated, the infusion of the GIK solution was stopped. The infusion was restarted immediately after aortic unclamping and continued for 12 hours. The control group received 5% dextrose in water infused at 50 ml/hr.

Standard operative and anesthetic techniques were used in all patients. Anesthesia was induced with fentanyl (25-50 mcg/kg) and pancuronium bromide (Pavulon, 0.1 mg/kg). An arterial cannula in the ascending aorta and two stage venous cannula in the right atrium were placed and cardiopulmonary bypass established. After cardioplegic induction was achieved by 10 ml/kg cold cristalloid cardioplegia (Plegisol), myocardial protection was achieved by multidose infusions of antegrade cold blood cardioplegic solution (4°C, K:25 mEq, pH:7.6, hematocrit: 20%), systemic (32°C) and topical hypothermia (irrigation with cold saline solution at 4°C).

Cardiac indices, serum glucose and potassium levels were measured before infusion of GIK solution and 6., 12., 18. hour after aortic unclamping. Electrocardiograms were obtained before operation, immediately after operation, and on postoperative days 1, 2, and 7. Creatinine kinase MB (CK-MB), aspartate amino transferase (AST), lactat dehydrogenase (LDH) enzymes levels were measured at 24 hour after operation. A perioperative myocardial infarction was diagnosed either by the appearance of new changes on electrocardiogram (Q waves, ST segment elevation > 1mm, loss of R wave in precordial leads) or by the elevation of creatinine kinase levels to greater than 50 IU in the immediate 24 hour period after operation.

Inotropic agents were used to maintain a cardiac index of 2.0 L/min per square meter or higher and systolic blood pressure of 90 mmHg or higher after afterload, preload, and heart rate were maximized. Inotropic demand was calculated by totally drug amount per patient weight.

Ventricular arrhythmia and atrial fibrillation incidence was assessed and antiarrythmic drug amount was calculated.

**STATISTICAL ANALYSES**

Data are presented as the actual number of occurrences in a group and as the mean plus or minus the standard error. Analysis by x2 test was used to compare occurrences between the GIK and the control groups. Nonpaired Student’s t tests were used to compare measured data between the groups. Data were considered significant at a p value of less than 0.05.

**RESULTS**

Thirty patients were enrolled in the study. They were randomized equally to the GIK and the control group. All of them completed the study protocol.

The mean age (GIK group: 46 years, range 20 to 77, vs control group: 49, range 20 to 73) and ratio of male to female patients (11/4 GIK vs 13/2 control group) were similar in both groups. A slightly higher percentage of patients in the GIK group had a prior myocardial infarction (3/11 vs 1/11). The mean ejection fraction (GIK: 51% range 30% to 65%, vs the control: 53% range 30% to 60%) were similar in the two groups. The incidence of hypertension (7/15 GIK vs 8/15 the control group) and chronic obstructive pulmonary disease (4/15 GIK vs 3/15 the control group) were also similar. There was no need for IABP support in both groups. There was no difference between the groups in the duration of cardiopulmonary bypass (123±2.1 minutes GIK vs 126±4.2 minutes the control group, p>0.05) or the cross-clamp time (54±2.9 minutes GIK vs 56±2.2 minutes the control group, p>0.05). The GIK group had a slightly higher number of vessels grafted, which was non-significant (3.01±0.11 in the GIK group vs 2.97±0.19 in the control group, p>0.05).

Levels of serum K+ remained constant in both the GIK and the control groups during the reperfusion period (4.4±0.2 in the GIK group vs 4.5±0.2 in the control group p>0.05 at 12th hour) There was no difference in serum glucose levels before the infusion of GIK solution (97±10 mg/L in the GIK group, 93±10 mg/L in the control group p>0.05) (Figure1). Glucose levels increased significantly before cardiopulmonary bypass (152±11 mg/L in the GIK group vs 141±5 mg/L the control group; p>0.05) and remained elevated during the infusion of the GIK solution in the reperfusion period (207±11 mg/L in the GIK group vs 146±8 mg/L in the control group, p>0.05, at 6 hours, and 220±12 mg/L vs 143±7, p<0.05, at 12 hours). However, after the
discontinuation of the GIK infusion, there was no difference in serum glucose level between the two groups (168±9 mg/L in the GIK group vs 140±7 mg/L in the control group at 18 hours of reperfusion; p>0.05).

**Figure 1**
Serum glucose levels. 1:Control, 2:Pre-bypass, 3:Reperfusion 6th hour, 4:Reperfusion 12th hour, 5:Reperfusion 18th hour. *: statically significant

There were no deaths in either group. One patient in the control group had a perioperative myocardial infarction. The postoperative cardiac indices for both groups are summarized in Figure 2. Both groups started out with similar indices (GIK group:2.29±0.2 L/min per square meter vs the control group:2.31±0.1 L/min per square meter; p>0.05). But the patients treated with GIK solution had higher cardiac indices during reperfusion that persisted even after the GIK infusion was discontinued (2.8±0.3 vs 2.3±0.2 at 6th hour; 2.8±0.3 vs 2.3±0.2 at 12th hour; 2.9±0.2 vs 2.3±0.1 at 18th hour; in the GIK vs the control group; p<0.05) Patients in the GIK group required less inotropic support (4 patients in the GIK group vs 10 patient in the control group, p>0.05). Patients who received GIK solution had a lower incidence of ventricular arrhythmias but non-significant (2 patients in the GIK group vs 6 patient in the control group, p>0.05).

**DISCUSSION**
GIK solutions enhance the performance of ischemic myocardium. Adenosine triphosphate is very important in maintaining cell membrane function and integrity. It is derived from glycolytic pathways. It was shown that GIK solution increased blood flow and decreased coronary resistance during reperfusion in ischemic hearts 13. During ischemia, oxygen free radicals which is derived from the free fatty acid end products may impair ventricular function and increase the incidence of ventricular arrhythmia 14. Glucose esterifies intracellular free fatty acids and decreases the toxic metabolic end products of them14,15,16. The beneficial effects of GIK solution on the myocardium are different from its hyperosmolarity. Because this protective effect was not achieved experimentally with mannitol 17.

There are interesting studies about the glucose as a substrate in the ischemic myocardium. In coronary artery disease, GIK therapy resulted in more favorable oxygen supply/demand ratio by increasing arterial glucose uptake while decreasing free fatty acid levels 18,19. It was showed that GIK infusions improved global ejection fraction values and better regional wall motion in the infarcted area 6,7. Not only cardiologists but also some surgeons have performed studies on GIK therapy. A higher operative glycogen content and a lower postoperative arrhythmia was seen when it was used 12 hours before a mitral valve replacement 9. GIK infusion significantly decreased the need for inotropic agents in patients who required IABP. In a study, it was observed that there was higher cardiac indices in patients undergoing coronary bypass operation who had pretreatment with GIK.
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10. It was suggested that GIK solution had a beneficial preconditioning effect in ventricular recovery after CPB 20.

Some authors believe that atrial fibrillation may be a manifestation of inadequate atrial protection during myocardial ischemia 21,22. Pretreatment with GIK solution may increase myocardial glycogen stores and result in less atrial ischemia during cardiopulmonary arrest 8. Our patients in GIK group had slightly lower incidence of atrial fibrillation, there wasn’t a statistically significant difference.

Patients with diabetes mellitus might not included in this study. It was suggested that mortality in patients with diabetes and myocardial infarction could be reduced by infusion of glucose insulin solution 23.

GIK therapy was well tolerated. It was only given central line because of hyperosmolarity. And finally we concluded that glucose insulin potassium infusion favorably influenced left ventricular function after coronary artery.

References


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