

Myocardial Protection with Glucose-Insulin-Potassium Infusion during Cardiopulmonary Bypass for Coronary Revascularization

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ABSTRACT

Background: Sodi-Pallares and colleagues first time introduced use of glucose-insulin and potassium (GIK) solution for myocardial protection. They used this solution in patients with acute myocardial infarction and concluded that GIK solution limited electrocardiographic changes in these patients.

Objective: To investigate the effectiveness of the GIK solution regarding myocardial protection evaluated by postoperative creatine kinase MB (CKMB) and cardiac troponin I levels.

Method: In this prospective, randomized clinical trial, sixty-four patients were assigned into two groups: GIK group, in which glucose-insulin and potassium infusion were given during surgery, and non-GIK group in which only saline infusion was given during the procedure.

Results: All CK-MB values were lower in the GIK group than the Non-GIK group in the postoperative period (6, 12 and 24 hours' samples) with statistically significant results. Troponin values were lower in the GIK group versus the Non-GIK group after 6 and 12 hours with statistical significance ($P < 0.001$ and 0.022 respectively).

Conclusion: The addition of GIK infusion throughout the operation to standard myocardial protective techniques in patients undergoing on-pump coronary artery bypass graft (CABG) surgery attenuates myocardial ischemic injury.

Keywords: CABG, Cardiac Protection, Inotropic support, GIK.

INTRODUCTION

The heart is separated from the circulation during cardiac surgery with cardiopulmonary bypass (CPB). This causes myocardial ischemia, inevitably. In addition to this ischemic insult, upon reperfusion, an extra hit will occur, which may intensify the magnitude of cardiac dysfunction⁽¹⁾. The loss of high-energy phosphates and disruption of normal intracellular calcium homeostasis is central to the pathogenesis of ischemic myocardial injury⁽²⁾. Myocardial ischemia causes extreme release of catecholamines within minutes and induces hormonal and metabolic changes, such as a major decrease in insulin secretion and rise in free fatty acids (FFAs)⁽³⁾.

Several techniques have been developed over the years to reduce and/or modulate the magnitude of this ischemia-reperfusion injury associated with the cardiopulmonary bypass episode⁽¹⁾. The early years of myocardial protection studies during CPB largely focused on the quest for the exact formulation of solutions to satisfy the optimal demands of cardioplegic solutions⁽⁴⁾.

Therapy with glucose-insulin-potassium (GIK) is associated with a decreased level of circulating FFAs and facilitates the use of glucose as the main energy source of cardiac myocytes^(3,5).

In contrast with FFAs, glucose is less oxygen-consuming and has favorable impacts on myocardial function and integrity of the membrane^(3,6). Besides, insulin activates pathways of intracellular signaling that promote cell survival and inhibit apoptosis-related events⁽⁷⁾. During ischemia, intracellular

potassium levels are decreased, whereas the delivery of potassium raises its levels inside myocardial cells, thus increasing the threshold against ventricular arrhythmias⁽³⁾.

Ethical approval:

This prospective randomized clinical trial was conducted after approval of the Ethical Committee board of Sohag University and obtaining informed written consent from each patient.

PATIENTS AND METHODS

Patients aged more than 30 years undergoing coronary artery bypass grafting (CABG) on cardiopulmonary bypass. The study was conducted in the period from January 2019 until January 2020 at Sohag University Hospital.

Exclusion criteria: Patients who underwent off-pump surgery, poorly controlled diabetes mellitus (glucose >12 or < 3 mmol/L), patients with preoperative renal dysfunction (creatinine > 1.2 mg/dl), those with a previous stroke, those with severe liver disease (Child-Pugh C stage), emergency CABG surgery and those with concomitant valvular heart diseases or poor cardiac functions (EF less than 50%).

Patients were randomly (using sealed envelopes) assigned into two equal groups: GIK group in which patients were given GIK solution (50 IU of regular insulin and 50 mEq of potassium were added to 1000 ml of 5% Dextrose solution) at a rate of 100ml/ hour



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after induction of anesthesia and continued till the end of the operation, and non-GIK group in which only 0.9% normal saline infusion was given with the same volume and rate of infusion as in GIK group.

Perioperative Management:

After reviewing patients’ charts: Age, sex, body mass index, and associated diseases such as a history of hypertension, diabetes mellitus, myocardial infarction, and admission to the cardiac care unit were recorded.

Laboratory investigations, left ventricular ejection fraction (LVEF) and the number of vessels diseased by cardiac catheter were recorded.

Immediately before surgery in the preoperative holding room, a peripheral I.V. line was inserted under complete aseptic technique. After this, all patients were premedicated with midazolam 20-40 µg/kg I.V. before pushing them inside the operating room.

In the operating room, all patients were connected to baseline monitors. Under complete aseptic technique and local skin infiltration with lignocaine 1%, an arterial line was inserted through the right or left radial artery and a triple lumen central venous line was inserted through the right internal jugular vein with the aid of ultrasound guidance.

Anesthesia was induced with fentanyl 2 µg/kg, midazolam 0.1- 0.2 mg/kg, and propofol 0.5 mg/kg, and tracheal intubation was facilitated with rocuronium bromide 0.6 mg/kg. Anesthesia was maintained with fentanyl infusion 1-2 µg/kg/h, and sevoflurane inhalation end-tidal 0.5-1.0% as required. The lungs were mechanically ventilated (tidal volume 6–8 mL/kg of predicted body weight, ventilatory rate 10-12/m, and PEEP 5 cm H₂O) to maintain end-tidal CO₂ at 30-35 mmHg. Muscle relaxation was maintained with rocuronium infusion of 0.5 mg/kg/h throughout the surgery. After this, the nasopharyngeal temperature probe was inserted.

The operative technique was started by a full midline sternotomy, followed by harvesting the left internal mammary artery (LIMA) and greater saphenous vein grafts as conduits. All operations were performed using non-pulsatile cardiopulmonary bypass.

Cold blood cardioplegia was used to achieve complete cardiac arrest (insulin and glucose were not added to the cardioplegia solution). Additionally, Ice slush was used to achieve local cooling of the heart.

At the end of the operation and when bleeding was controlled, the chest was closed, and the patient was transferred to the ICU.

During ICU stay; CKMB and troponin-I levels were measured after 6, 12, and 24 hours of admission.

Statistical analysis and sample size:

A sample size of 32 patients in each group was determined with 80% power to detect a 5ng ml⁻¹ (SD 7 ng ml⁻¹) difference of CK-MB between the groups at α-level of 0.05 using the independent t-test.

Continuous variables were presented as Mean ± SD, while categorical variables were presented as number (percentage). Categorical variables were compared using the χ² or Fisher’s exact tests, as appropriate. For continuous variables, the normality of distribution was tested with the Kolmogorov–Smirnov test. Intergroup comparisons of parametric data were performed by the independent t-test, while non-parametric data was performed by the Mann–Whitney U-test. All statistical tests were two-tailed. P-values of ≤ 0.05 were considered statistically significant.

All statistical analyses were performed using IBM SPSS statistics version 20 for windows.

RESULTS

There was no statistically significant difference between the two groups regarding patients’ demographics (age, sex, weight, height, and BMI) as shown in table (1).

Table (1): Patients demographic data

		GIK group (N = 32)		Non-GIK group (N = 32)		P. value
		Mean ± SD		Mean ± SD		
Age (years)		57.19 ± 7.9		54.34 ± 7.79		0.152
Weight (kg)		80.47 ± 12.44		81.28 ± 10.82		0.781
Height (m)		1.63 ± 0.07		1.67 ± 0.08		0.097
BMI		30.12 ± 4.06		28.67 ± 3.59		0.136
		N	%	N	%	
Sex	male	26	81.2	30	93.8	0.131
	female	6	18.8	2	6.2	

Data were given as Mean ± SD or number (%) as indicated. BMI: body mass index, N: number

Preoperative patient clinical characteristics and laboratory results showed no statistically significant differences. In addition, preoperative evaluation of left ventricular ejection fraction (LVEF) and the number of vessels diseased showed no statistically significant difference between the two groups as shown in table (2).

Table (2): Preoperative Patients Characteristics

		GIK Group (N = 32)		Non-GIK Group (N = 32)		P. value
		N	%	N	%	
Hypertension	No	11	34.4	12	37.5	0.794
	Yes	21	65.6	20	62.5	
Diabetes mellitus	No	24	75.0	21	65.6	0.412
	Yes	8	25.0	11	34.4	
Myocardial Infarction	No	18	56.3	15	46.9	0.453
	Yes	14	43.7	17	53.1	
CCU admission	No	18	56.3	13	40.6	0.211
	Yes	14	43.7	19	59.4	
		Mean ± SD		Mean ± SD		P. value
Hb (mg/dl)		13.47 ± 1.62		13.52 ± 1.09		0.885
S. Creatinine (mg/dl)		0.96 ± 0.2		0.98 ± 0.18		0.785
T. Bilirubin (mg/dl)		0.79 ± 0.12		0.74 ± 0.17		0.587
INR		1.04 ± 0.06		1.04 ± 0.07		1.000
Preoperative LVEF%		58.5 ± 6.68		58.84 ± 6.15		0.831
Catheter (number of vessels)		3.15 ± 0.72		3.09 ± 0.73		0.618

Data were given as Mean ± SD or number (%) as indicated. Abbreviations: N: number, CCU: cardiac care unit, Hb: hemoglobin, INR: international normalization ratio, LVEF: left ventricular ejection fraction.

As regards anesthesia time, CPB time, ischemia time (aortic cross-clamp time), and the number of grafts done; there were no statistically significant differences between the two groups as shown in table (3).

Table (3): Intraoperative characteristics

	GIK group (n = 32)	Non-GIK group(n = 32)	P. Value
	Mean ± SD	Mean ± SD	
Anesthesia time(hours)	5.75 ± 0.43	5.82 ± 0.6	0.577
Bypass time(min)	99.78 ± 14.46	104.03 ± 16.36	0.275
Cross clamp time(min)	56.47 ± 11.28	60.84 ± 16.89	0.228
Number of grafts	2.96 ± 0.64	2.87 ± 0.65	0.578

Data were given as Mean ± SD.

All CK-MB values were lower in the GIK group than in the Non-GIK group in the postoperative period with statistically significant results (Table 4).

Table (4): Postoperative CK-MB

CK-MB	GIK group (n = 32)	Non-GIK group (n = 32)	P. value
	Mean ± SD	Mean ± SD	
6 hours	29.81 ± 9.24	37.83 ± 12.9	0.006*
12 hours	25.55 ± 4.18	35.65 ± 18.68	0.004*
24 hours	23.34 ± 2.75	32.43 ± 17.14	0.004*

Data were given as Mean ± SD. *P-value significant.

Troponin values were lower in the GIK group versus the Non-GIK group after 6 and 12 hours with statistical significance. While, there was no statistically significant difference between the two groups in troponin values at 24 hours samples as shown in table (5).

Table (5): Postoperative Troponin I

Troponin I	GIK group (n = 32)	Non-GIK group (n = 32)	P. value
	Mean ± SD	Mean ± SD	
6 hours	1.45 ± 0.19	1.8 ± 0.45	<0.001*
12 hours	2.54 ± 0.17	3.41 ± 2.09	0.008*
24 hours	2.86 ± 0.68	5.67 ± 8.68	0.073

Data were given as Mean ± SD. *P-value significant.

DISCUSSION

Despite all advancements in techniques of myocardial protection, perioperative myocardial damage is still the most important cause of cardiovascular morbidity and mortality after technically successful CABG (8).

Infusion of glucose-insulin-potassium (GIK) was supposed to have cardioprotective advantages by increasing myocardial glucose absorption and enhancing glycolysis and glucose consumption (9, 10). Several clinical studies have documented that GIK therapy can maintain myocardial perfusion and left ventricular function (9, 11).

In our study, all CK-MB values were lower in the GIK group than in the non-GIK group in the postoperative period. Troponin values were lower in the GIK group versus the non-GIK group after 6 and 12 hours, while there was no difference between the two groups in troponin values at 24 hours samples.

One or a combination of GIK mechanisms has been suggested to achieve cardiac protection in most research. Myocardial contractile activity directly benefits from insulin-induced both increased glucose transporter expression and enhanced Na-K-ATPase turnover, mediating beneficial inotropic effects (12).

Precautionary GIK supply before myocardial ischemia increases the content of cardiomyocyte glycogen, allowing for continued synthesis of adenosine triphosphate and creatine triphosphate throughout anaerobic conditions (13).

The increased release of stress-induced catecholamines not only inhibits the favorable effects of insulin but also causes systemic lipolysis, resulting in increased levels of FFA with its negative implications (14). Excessive FFA results in increased free oxygen radicals generation, worsened ATP-production efficiency with fairly high consumption of oxygen compared to glucose oxidation (15), and cell membrane damage due to increased acyl-carnitine levels (16).

Each of these effects can be avoided by adequate insulin that inhibits adipose tissue hormone-sensitive lipase and activates mitochondrial acetyl-CoA-carboxylase, while directly inhibiting FFA oxidation (17).

The main result of the GIK solution was thought to be increased membrane polarization. (17, 18). Generally, insulin increases the myocytes potassium uptake (13), which allows sinus rhythm to stabilize

more rapidly postoperatively (19). As conduction abnormalities and postoperative arrhythmias are common complications after coronary bypass surgery, these protective effects are crucial (17, 20).

One essential myocardial metabolic response following ischemia is temporary insulin resistance. It is part of an overall hormonal stress reaction that reportedly has a high potential to induce hyperglycemia (21).

Previous studies had divergent results; **Shim et al.** (22) found a significant reduction of both CKMB and troponin after infusion of GIK. A prospective randomized clinical trial by **Suhail et al.** (23) found that in the early postoperative period, peak CKMB levels were high in the non-GIK group versus the GIK group. Another prospective and randomized study by **Lazar and colleagues** (24) found better cardiac output and faster recovery from urgent coronary bypass grafting in patients with unstable angina given GIK infusion for 12 hours after the operation (24). **Jovic et al.** (25) in their study concluded that GIK treatment has a potential cardioprotective effect in coronary surgery. The effect is independent of the amount and concentrations of glucose-insulin and potassium.

On the other hand, some studies failed to prove that GIK infusion has a cardiac protective effect during cardiac surgery. **Bruemmer et al.** (26) did not find a significant difference in postoperative cardiac troponin I (cTn I) concentration between the two groups. **Shim et al.** (27) reported no significant difference in cardiac enzymes, hemodynamic parameters, and blood glucose in patients treated with GIK during cardiac surgery (27).

Our results to be interpreted within the confines of some limitations. Firstly, the GIK solution was given at a fixed dose and limited only to the operative period. It remains questionable if the continuation of GIK infusion in the postoperative period may provide more protection.

Secondly, because the decision to extubate the patients and discharge them from the ICU were all dictated by established protocols this may influence the results. Finally, we used this strategy in patients with good cardiac functions. It might be more effective if it is used in patients with poor cardiac function.

CONCLUSION

In conclusion, the addition of GIK infusion to standard cardioprotective techniques in patients undergoing CABG surgery on CPB attenuates myocardial cell injury.

It would be useful to conduct a larger study to warrant the long-term clinical impact of GIK infusion. In addition, further studies are necessary to discover the optimal timing, dosage, and duration of GIK solution administration.

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