Does Glucose–Insulin–Potassium Infusion during on-pump Coronary Revascularization Affect Perioperative Inotropic Requirements?

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ABSTRACT

Background: During coronary artery bypass grafting (CABG), the myocardium is subjected to endure periods of ischemia and reperfusion, which may result in post-ischemic contractile dysfunction. That is a major contributor to early and late morbidity and mortality and increased requirement of pharmacologic and mechanical circulatory support. Glucose insulin potassium (GIK) infusion was thought to provide a cardioprotective effect.

Objective: To investigate whether the use of GIK solution in patients undergoing on-pump CABG affects requirements of inotropes.

Patients and Method: In this prospective, randomized placebo-controlled trial, 64 patients were assigned into two groups: the GIK group in which glucose-insulin and potassium infusion was given during CABG surgery, and the non-GIK group in which only saline infusion was given during the procedure.

Results: In the GIK group, all patient needed not more than two inotropes with mean of 1.28 ± 0.46, while in the non-GIK group there were patients who need up to three inotropes with mean of 1.56 ± 0.56 (P. value of 0.032).

Conclusion: GIK infusion during on-pump CABG reduces perioperative inotropic requirements.

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

INTRODUCTION

More than 1.5 million open-heart operations are performed annually worldwide [1, 2]. During cardiac surgery, it is often necessary that patients are operated on cardiopulmonary bypass. In this process, patients encounter myocardial ischemia and thus it is required that protective measures are taken to preserve the myocardium and prevent further damage [3]. Since 1962, the cardioprotective effect of glucose-insulin–potassium (GIK) infusion has generated interest in the treatment of patients with acute coronary syndrome and those undergoing cardiac surgery [4, 5].

Beyond the well-known metabolic insulin effects, myocardial contractile function benefits directly from -insulin-induced- increased expression of glucose transporters and improved turnover of Na-K-ATPases, mediating positive inotropic effects [6]. Preventive GIK supply before myocardial ischemia increases myocardial glycogen content, enabling prolonged synthesis of adenosine triphosphate and creatin triphosphate during anaerobic conditions [7]. Consequently, perioperative insulin application should improve both tolerances towards ischemia and recovery of contractile function [8].

Aim of the present study was to investigate whether the use of GIK solution in patients undergoing on-pump CABG affects requirements of inotropes.

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.

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.

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 assigned into two equal groups (using sealed envelopes): 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 100 ml/ hour 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.

Received:11 /1 /2021
Accepted:8 /3 /2021

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.

Inotropic drugs used were recorded for dose and duration, intraoperatively and during ICU stay.

In agreement with expert-based guidelines [9]. The administration of inotropic drugs aimed to optimize circulatory preload and vascular resistance based on invasive pressure monitoring.

Statistical analysis and sample size:

A sample size of 32 patients in each group was determined with 80% power to detect a 5 ng ml^{-1} (SD 7 ng ml^{-1}) difference of epinephrine dose 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 $\chi 2$ 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 were 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 the table (1).

Table (1): Demographic data

		Group A "GIK" (N=32)		Group B "Non-GIK" (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 (Meter)		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	

Independent-samples T-Test and Chi-square test were used; Data are given as Mean±SD or number (%) as indicated.
Abbreviations: N.: number, BMI: body mass index.

Hemoglobin level, hematocrit value, platelets count, total bilirubin, liver enzymes (Alt and Ast), prothrombin concentration (PC), INR, blood urea nitrogen, serum creatinine, serum levels of Na^{+} and Ca^{+2} showed no statistically significant difference between the two groups (Table 2).

Table (2): Preoperative laboratory investigations

	Group A "GIK" (n=32)	Group B "Non-GIK" (n=32)	P. value
	Mean ± SD	Mean ± SD	
Hb (g/dl)	13.47 ± 1.62	13.52 ± 1.09	0.885
HCT	39.09 ± 4.56	39.49 ± 3.24	0.686
PLT (mcL)	206.84 ± 47.82	217.56 ± 50.62	0.387
BUN (mg/dL)	21.56 ± 1.57	22.72 ± 3.96	0.643
S. Creatinine (mg/dl)	0.96 ± 0.2	0.98 ± 0.18	0.785
T. Bilirubin (mg/dl)	0.79 ± 0.02	0.74 ± 0.07	0.587
ALT (U/L)	24.41 ± 5.04	25.97 ± 5.39	0.421
AST (U/L)	23.56 ± 4.06	23.25 ± 4.6	0.874
PC	94.76 ± 6.18	94.62 ± 8.26	0.940
INR (U/L)	1.04 ± 0.06	1.04 ± 0.07	1.000
Na^{+} (mEq/L)	139.47 ± 3.6	137.81 ± 3.98	0.086
Ca^{+2} (g/mol)	1 ± 0.09	1.04 ± 0.12	0.095

Used Independent-samples T-Test; Data are given as Mean±SD.
Abbreviations: Hb: hemoglobin, Hct: hematocrit, Plt: platelets, BUN: blood urea nitrogen, Alt: alanine aminotransferase, Ast: aspartate aminotransferase, PC: prothrombin concentration, INR: international normalization ratio

Comparison of the two groups for preoperative cardiac specification regarding the history of hypertension, history of diabetes mellitus, history of myocardial infarction, and the history of CCU admission showed no statistically significant differences. Also, preoperative evaluation of left ventricular ejection fraction and number of diseased vessels showed no statistically significant difference between the two groups (Table 3).

Table (3): Preoperative cardiac specifications and patient comorbidities

		Group A "GIK" (N=32)		Group B "Non-GIK" (N=32)		P. value
		Mean ± SD		Mean ± SD		
Preoperative LVEF%		58.5 ± 6.68		58.84 ± 6.15		0.831
Catheter (number of vessels diseased)		3.15 ± 0.72		3.09 ± 0.73		0.618
		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	

Used Independent-samples T-Test and Chi-square test; Data are given as Mean±SD or number (%) as indicated.
Abbreviations; N: number, LVEF: left ventricular ejection fraction, CCU: cardiac care unit.
There was no statistically significant difference regarding intraoperative heart rate, mean arterial blood pressure (MBP) and central venous pressure (CVP) between the study groups (Figures 1, 2 and 3).

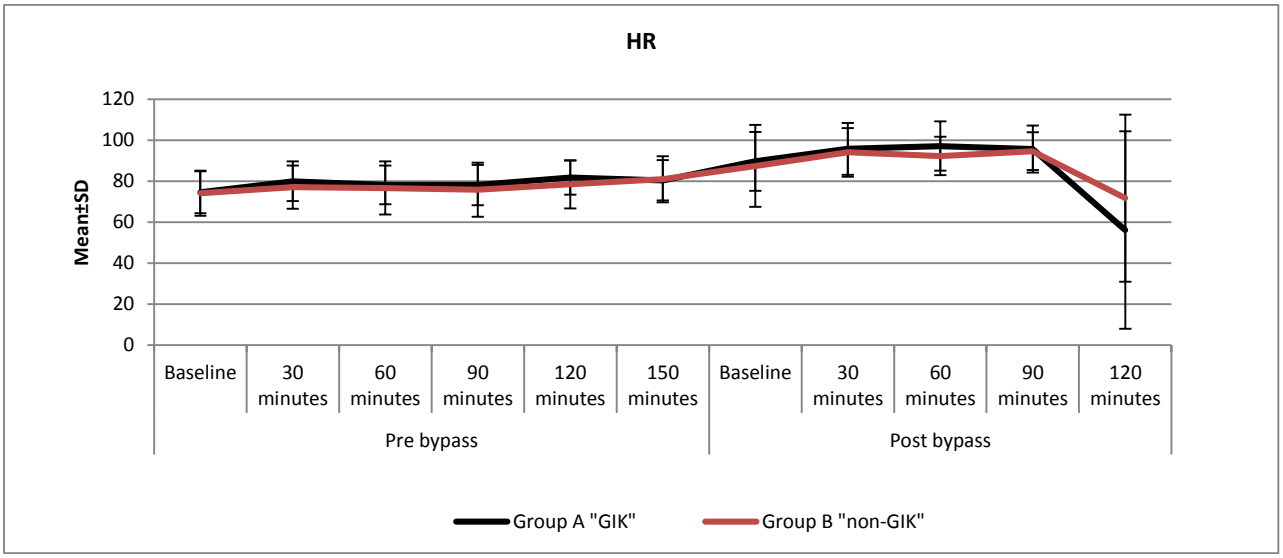

Figure (1): Intraoperative heart rate.

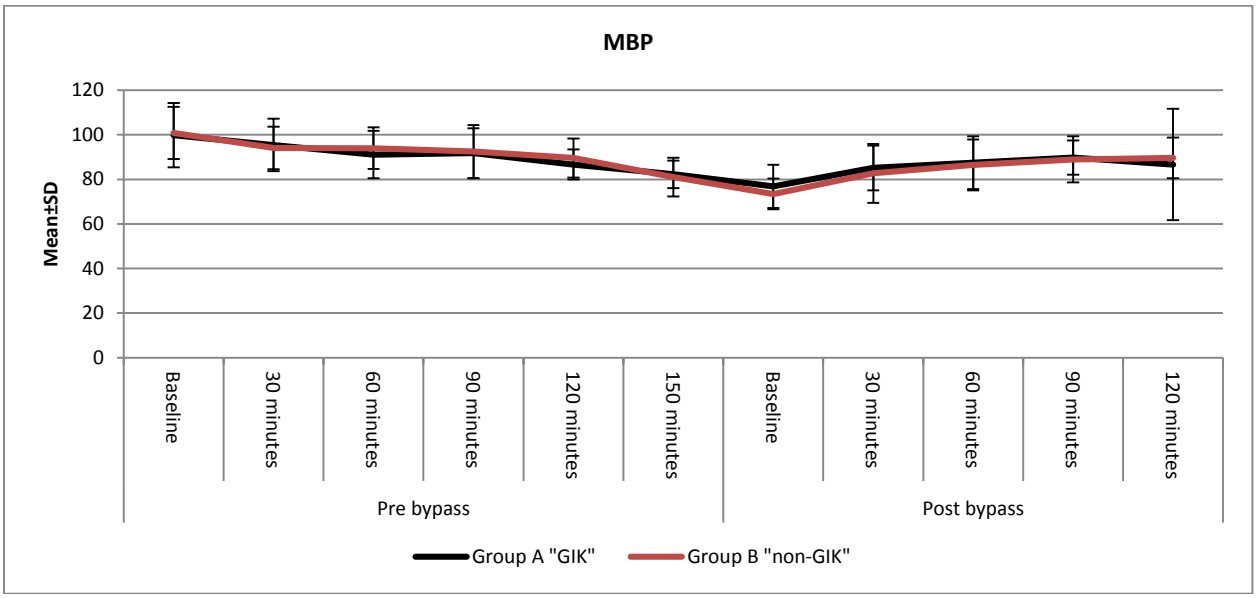

Figure (2): Intraoperative mean arterial blood pressure.

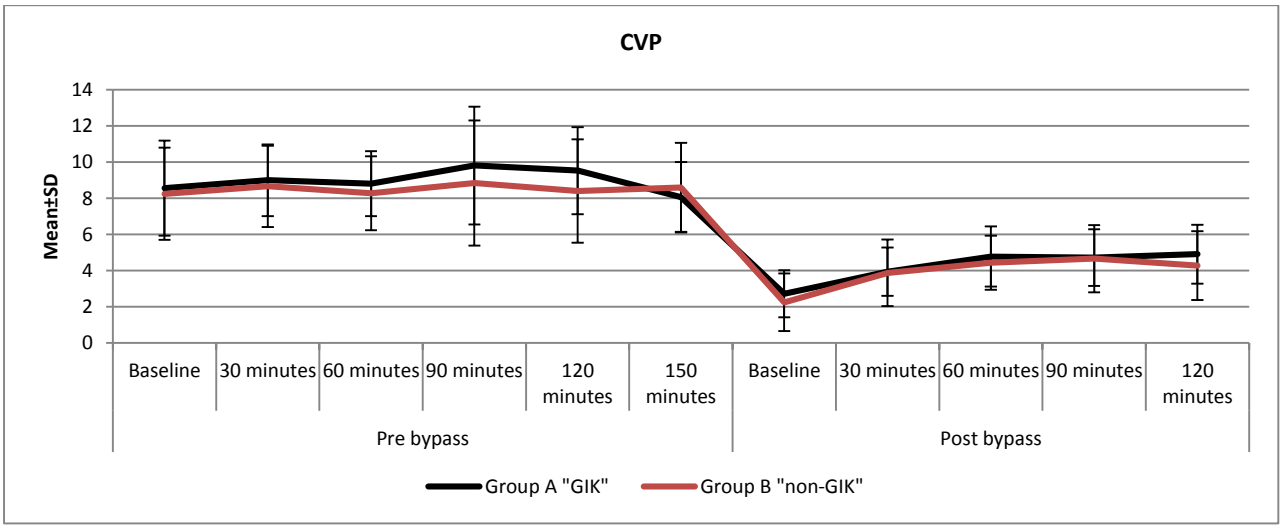

Figure (3): Intraoperative central venous pressure.

All of the 64 patients included in this study received epinephrine at the start of weaning from the CPB. There was a statistically significant difference between the two groups at 30 and 60 minutes intraoperative and postoperatively at 12, 18, 24, 30 and 36-hours (P values<0.05). As regards total duration of epinephrine support, it was statistically significant with P-value of 0.001. (Table 4)

Table (4): Epinephrine

Epinephrine (ng/Kg/min)	Group A ''GIK'' (n=32) Mean ± SD	Group B ''Non GIK'' (n=32) Mean ± SD	P. value
Intraoperative			
Start	50.94 ± 5.3	51.88 ± 8.96	0.612
30 minutes	57.81 ± 9.13	67.81 ± 8.96	**0.040***
60 minutes	56.56 ± 9.61	67.5 ± 2.85	**0.039***
90 minutes	55 ± 2.64	65.94 ± 5.25	0.062
120 minutes	45 ± 3.86	63.46 ± 9.79	0.068
Postoperative			
6 hours	44.53 ± 9.97	54.69 ± 4.62	0.075
12 hours	27.5 ± 2.4	41.56 ± 2.16	**0.012***
18 hours	13.28 ± 1.93	28.91 ± 2.35	**0.002***
24 hours	5.81 ± 1.19	14.69 ± 1.82	**0.021***
30 hours	1.77 ± 0.05	7.81 ± 1.02	**0.030***
36 hours	0.32 ± 0.08	3.71 ± 0.06	**0.031***
42 hours	0 ± 0	0.67 ± 0.04	0.155
Duration (hours)	19.59 ± 7.63	26.84 ± .27	**0.001***

Independent-samples T-Test and Chi-square test. Data are given as Mean ± SD. *Significant P. value

There was no statistically significant difference between the two groups regarding either norepinephrine or dobutamine support of the doses and duration (Tables 5 & 6).

Table (5): Nor-epinephrine

	Nor-epinephrine (ng/Kg/min)	Group A ''GIK'' (n=32) Mean ± SD	Group B ''Non GIK'' (n=32) Mean ± SD	P. value
Intraoperative	Start	6.25 ± 1.4	9.69 ± 1.09	0.431
	30 minutes	10 ± 1.01	19.38 ± 3.85	0.087
	60 minutes	9.69 ± 1.87	18.28 ± 3.44	0.104
	90 minutes	8.75 ± 1.18	17.97 ± 4.16	0.083
	120 minutes	4 ± 1.00	11.11 ±1.87	0.108
Postoperative	6 hours	5 ± 1.36	10.47 ± 1.8	0.148
	12 hours	1.56 ± 0.15	6.41 ± 1.6	0.082
	18 hours	1.07 ± 0.27	3.28 ± 0.58	0.197
	24 hours	0 ± 0	0.63 ± 0.04	0.321
Duration(hours)		2.69 ± 5.41	6.14 ± 8.58	0.059

Independent-samples T-Test and Chi-square test. Data are given as Mean ± SD.

Table (6): Dobutamine

	Dobutamine (mcg/kg/min)	Group A ‘’GIK’’ (n=32) Mean ± SD	Group B ‘’Non-GIK’’ (n=32) Mean ± SD	P. value
Intraoperative	Start	0 ± 0	0 ± 0	-
	30 minutes	0.38 ± 0.05	0.63 ± 0.11	0.586
	60 minutes	0.47 ± 0.05	0.7 ± 0.01	0.663
	90 minutes	0.63 ± 0.06	0.7 ± 0.01	0.896
	120 minutes	0.31 ±0.07	0.52 ± 0.06	0.675
Postoperative	6 hours	0.38 ± 0.05	0.41 ± 0.02	0.93
	12 hours	0.22 ± 0.04	0.31 ± 0.03	0.733
	18 hours	0.08 ± 0.01	0.28 ± 0.01	0.341
	24 hours	0 ± 0	0.19 ± 0.04	0.156
	30 hours	0 ± 0	0.09 ± 0.01	0.179
	36 hours	0 ± 0	0.06 ± 0.01	0.321
Duration (hours)		1.22 ± 4.84	2.53 ± 9.03	0.471

Independent-samples T-Test; Data are given as Mean ± SD.

The number of inotropes used for each patient showed a statistically significant difference between the two groups. In the GIK group, all patient needed not more than two inotropes with mean of 1.28 ± 0.46, while in the non-GIK group, there were patients who needed up to three inotropes with mean of 1.56 ± 0.56 (P. value of 0.032) as shown in table (7).

Table (7): Number of Inotropes used

	Group A ''GIK'' (n=32)	Group B ''Non-GIK'' (n=32)	P. value
	Mean ± SD	Mean ± SD	
Number of inotropes used	1.28 ± 0.46	1.56 ± 0.56	**0.032***

Independent-samples T-Test Data are given as Mean ± SD *Significant P. value

DISCUSSION

Glucose–insulin–potassium (GIK) infusion is thought to provide cardioprotective benefits by increasing myocardial glucose uptake and improving the coupling of glycolysis and glucose utilization [10, 11].

Several experimental studies reported that administration of GIK therapy may preserve myocardial perfusion and left ventricular function, as determined by hemodynamic parameters [10, 11, and 12].

In our study, less requirement of epinephrine intraoperatively and postoperatively was observed in the GIK group, while there was no difference in requirement of either norepinephrine or dobutamine between the two groups. Also, the Number of inotropes used for each patient showed a significant difference between the two groups in favor of the GIK group over the non-GIK group. **Lazar *et al.*** [13] operated on forty consecutive coronary artery bypass grafting patients with diabetes mellitus and reported that diabetic patients who received GIK solution had a higher postoperative cardiac index, lower inotrope scores, shorter times of ventilator support, and lower incidence of atrial fibrillation and ventricular arrhythmias after coronary artery bypass grafting. Moreover, In a prospective, randomized, double-blind, placebo-controlled trial of two hundred eighty non-diabetic adult patients undergoing first-time elective or urgent isolated multivessel coronary artery bypass grafting, **Quinn *et al.*** [14] stated that GIK therapy improved early postoperative cardiovascular performance, reduced inotrope requirement, and might reduce myocardial injury. In addition, **Ellenberger *et al.*** [15] in their randomized controlled trial concluded that the administration of GIK before aortic cross-clamping resulted in a lesser requirement for inotropes in moderate- to high-risk patients undergoing on-pump cardiac surgery. In a prospective, randomized study by **Jovic *et al.*** [16] on 49 patients scheduled for CABG surgery with poor left ventricular function (EF < 40%). They found that a significant recovery of cardiac function was evident in GIK-treated patients. A significant difference in ICU stays and the need for inotropic support was demonstrated, which may indicate favorable effects of GIK.

On the other hand, some studies failed to prove that GIK infusion has such an effect. **Barcellos *et al.*** [17] in their clinical trial on twenty-four patients with type 2 DM referred for CABG were randomized to receive GIK infusion or subcutaneous insulin from anesthetic induction up to 12 hours postoperatively. The primary clinical outcome was the cardiac index (CI) and the secondary clinical outcomes were the remaining hemodynamic parameters and the use of inotropes and vasodilators. They failed to prove that the use of GIK neither improves CI nor reduces the use of inotropic drugs in cardiac diabetic patients undergoing cardiac surgery but it provided better glucose control with fewer postoperative infections [17]. Moreover, **Shim *et al.*** [18] in their randomized, double-blind, placebo-controlled study found no significant difference in hemodynamic parameters, use of vasoactive, inotropic, and/or anti-arrhythmic agents, insulin, and supplemental glucose was not significantly different between the groups. In another prospective randomized clinical trial by **Suhail *et al.*** [19] on one hundred and sixty patients that were randomized into two equal groups; GIK group and non-GIK group. They found no difference in requirements of inotropic support between the groups but the duration of inotropic support was longer in the non-GIK group as compared to the GIK group.

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