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Clinical and hemodynamic outcome following coronary artery bypass surgery in diabetic patients using glucose-insulin-potassium (GIK) solution: a randomized clinical trial

Glicose insulina e potássio (GIK) na revascularização do miocárdio de pacientes diabéticos: ensaio clínico randomizado

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Abstract

Objective: **This study was undertaken to determine whether GIK infusion improves hemodynamic performance by reducing the use of inotropic agents, as well as the morbidity of diabetic patients submitted to CABG.**

Methods: **Patients with type 2 DM referred for CABG were randomized to receive GIK 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; the use of inotropics and vasodilators, the glycemic control (maintenance of plasma glucose levels), and the postoperative morbidity. Hemodynamic and laboratory measurements were performed in the first 24 hours postoperatively, and the patients were followed up for 30 days to detect any surgery-related complications.**

Results: **Twenty-four patients were randomly included in the study. IC did not show significant difference (mean cardiac index at 24 hours in both GIK group 3.49±0.94 and Control group 3.38±0.75; p=0.74). The GIK group revealed lower blood glucose levels in the infusion period (glucose at 12 hours GIK group 195.6±68.25 versus Control group 269.6±78.48; p=0.02), with a lower incidence of hyperglycemia in the GIK group, two (16%) against eight (64%) in the control group (RR 0.25; 95%CI 0.07-0.94; p=0.03). Postoperative infectious complications were less frequent in the GIK group than in Control group, three (25%) against 10 (80%), respectively (RR 0.30; 95%CI 0.11 - 0.83; p=0.01).**

Conclusions: **Studies have proven that GIK improves hemodynamic performance of both patients with or without DM submitted to CABG, what was not confirmed in this study. The use of GIK neither improved the CI improvement nor reduced the use of inotropic drugs, but it provided better glucose control. Secondary clinical outcome, including postoperative infections, was more frequent in the control group.**

Descriptors: **Glucose. Insulin. Potassium. Myocardial revascularization. Diabetes mellitus.**

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Resumo

Objetivos: **Realizou-se um ensaio clínico randomizado a fim de determinar se a utilização de glicose insulina e potássio (GIK) melhora o índice cardíaco (IC), reduz o uso de inotrópicos e a morbidade de diabéticos submetidos à cirurgia de revascularização do miocárdio (CRM).**

Métodos: **Diabéticos referenciados à CRM foram randomizados para receber GIK ou insulina subcutânea, desde a indução anestésica até a 12ª hora de pós-operatório (PO). O desfecho primário foi o IC e, os secundários, os demais parâmetros hemodinâmicos, uso de inotrópicos e vasodilatadores, controle glicêmico e morbidade PO.**

Resultados: **Vinte e quatro pacientes foram randomizados. Não houve diferença significativa no IC (média de IC na 24ª hora no grupo GIK 3,49±0,94 e de controle 3,38±0,75; p=0,74). O grupo de intervenção apresentou glicemias significativamente menores (glicemia 12ª h GIK 195,6±68,25 /Controle 269,6±78,48; p=0,02), com menor ocorrência de hiperglicemias no GIK, dois (16%) contra oito (64%) no grupo de controle (RR 0,25; IC95% 0,07-0,94; p=0,03). Houve menor número de complicações por infecção PO no grupo GIK, três (25%), contra 10 (80%) no grupo de controle (RR 0,30; IC95% 0,11-0,83; p=0,01).**

Conclusão: **Estudos têm demonstrado que a GIK melhora o desempenho hemodinâmico de pacientes diabéticos e não diabéticos submetidos à CRM, o que não foi confirmado neste trabalho. A utilização de GIK não determinou melhora do IC, nem reduziu a necessidade de inotrópicos, mas promoveu melhor controle glicêmico. O desfecho secundário composto por complicações por infecção foi mais freqüente no grupo de controle.**

Descritores: **Glucose. Insulina. Potássio. Revascularização miocárdica. Diabetes mellitus.**

INTRODUCTION

The use of glucose-insulin-potassium (GIK) in myocardial revascularization surgery has been professed as a source of metabolic support to the ischemic myocardium since the 1960s [1], nevertheless remains controversial. The different outcomes published, the variety of protocols, and the administered doses and periods evaluated, make difficult to analyze the significant impact of its usage. Needless to say that the patients with diabetes mellitus (DM) could derive a great benefit from the use of GIK, once the glycemic control, the decreased nonesterified fatty acid of plasma concentrations and the substrate intake to the myocardium at the ischemic transoperative period are important to the patient's postoperative recovery.

An increasingly number of diabetic patients with coronary artery disease have been referred to surgical treatment, considering that the myocardial revascularization surgery is treatment of choice for the majority of these patients [2, 3]. The fact of the diabetes mellitus may be considered as an isolated factor for both mortality and complications after the myocardial revascularization surgery and the motivation to reduce these episodes have recently renewed the interest around the investigation of GIK. Several experimental studies have evaluated the possible action mechanisms of GIK [4-8], and the treatments of acute myocardial infarction in diabetic patients have produced convincing evidence of GIK benefits [9, 10].

Some studies have shown a better hemodynamic performance using the GIK in postoperative of diabetic patients undergone myocardial revascularization surgery [11, 12]. Nevertheless, these results have not repeated in other series [13, 14]. A metaanalysis published in 2004 showed that the GIK use can considerably improve the postoperative recovery of the contractile function and to reduce the incidence of atrial arrhythmias after heart surgery [15]. This was also shown through a randomized clinical trial with nondiabetic patients [16].

The present clinical trial was performed to establish whether the GIK infusion can modify the evolving development of diabetic patients undergone myocardial revascularization surgery. The primary endpoint was the cardiac index, and the secondary endpoints were the remaining hemodynamic variables, the usage of inotropics and vasodilators, the glycemic control and the morbidity postoperative at 30 days.

METHOD

Study Design

This is a randomized clinical trial with building block allocation time and stratified by sex performed before the induction of anesthesia.

Patients with type 2 DM with multiarterial coronary disease, 18 yrs of age or older, admitted to Hospital São Vicente de Paulo, Passo Fundo, RS, Brazil, from January 2002 to June 2003 were eligible. The DM diagnosis was made regarding the patients' clinical history treated with oral hypoglycemic agents or insulin and/or fasting glycemia higher than 126 mg/dL.

Exclusion criteria included the following: patients requiring surgeries associated with myocardial revascularization surgery; emergencies in which clinical, laboratorial, and preoperative hemodynamic evaluation were impossible to be performed; patients with renal failure (creatinine > 2.0 mg/dL) or liver failure (total bilirubin e" 2.5 mg/dL; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) e" 100 IU).

The study was approved by the Institutional Review Board (IRB) of Hospital São Vicente de Paulo, Universidade Federal do Rio Grande do Sul (Project NR 200250). The patients enrolled accepted to participate and written informed consent was obtained from all participants.

Study protocol

The patients were randomly assigned to GIK group (intervention) receiving the infusion of 5% glucose solution (500 mL) associated with 80 IU of regular human insulin (Biohulin®) and 40 mEq potassium. The infusion was started 1 hour before the induction of anesthesia (30 mL/h). The infusion was interrupted during the aortic clamping and restarted just after, lasting up to 12th hour postoperatively. The Control group has received an infusion of 5% glucose solution (30 mL/h) and injections of regular human insulin subcutaneously guided by glycemia or hemoglucotest (HGT). The scales used to adjust the glycemia in GIK group (control group) are shown in Tables 1 and 2.

Estimate of the sample size

It was based on the literature outcomes for the differences between the means of cardiac index (CI) in patients being administered GIK in the postoperative of myocardial revascularization surgery (CI at the 18th hour postoperatively, 2.88 ± 0.5 vs 2.2 ± 0.39 L/min/m^2 in intervention group and control group, respectively), using a type I error (alfa error) < 0.05 and a type II error (beta error) 0f 80%. This has been considered the primary study outcome.

Study variables

The tested hemodynamic variables were as follows: a) cardiac index (CI); b) systemic vascular resistance index (SVRI); c) pulmonary vascular resistance index (PVRI); d) left ventricular stroke work index (LVSWI); e) right ventricular stroke work index (RVSWI); f) stroke volume index (SVI); g) pulmonary capillary pressure (PCP); h) mean pulmonary artery pressure (MPAP); and i) central venous pressure (CVP). These variables were obtained from both the output and the pressures measurements by the Swan-Ganz Continuous Thermodilution Catheter (Edwards Lifesciences, Irvine, CA, model 744HF75®), connected to a continuous cardiac output monitor (Vigilance® - Edwards Lifesciences, Irvine, CA). The mean arterial pressure (MAP) was obtained by catheterization of the radial artery. All hemodynamic measures were recorded as follows: just after the induction of anesthesia; immediately before cardiopulmonary bypass (extracorporeal circulation) (pre-CPB); 30 minutes after its conclusion (post-CPB); on admission to ICU; and the beginning of each hour postoperatively until the 24h hour. The CI was estimated continuously at an average of 60 measures per hour. THe hemodynamic parameters considered as normal were described in Table 3 [17].

Table 1. Schedule to set GIK infusion (intervention)

Glycemia (mg/dL)	Conduct of treatment
> 300	8 IU of human insulin regular in bolus + GIK increase in 6 mL/h
201 a 300	GIK increase in 3 mL/h
126 a 200	KEEP
80 a 125	GIK decrease in 6 mL/h
<79	Stop GIK for 15 minutes repeating the HGT or Glycemia at every 15 minutes up to >125. Then, reinitiate GIK infusion with a rate of 6mL/h lower

Table 2. Schedule for administration of insuline subcutaneoulsy (control)

Glicemia (mg/dl)	Conduct of treatment
80 a 160	Nothing
160 a 200	2 Units of Regular human insulin subcutaneously
200 a 300	4 Units of Regular human insulin subcutaneously
300 a 400	6 Units of Regular human insulin subcutaneously
400 a 500	8 Units of Regular human insulin subcutaneously

Table 3. Hemodynamic Parameters

Estimated/Measured Parameter	Unity and Normal Value
Cardiac Index (CI)	2.4 to 4.0 L/min/m² body surface
Systemic Vascular Resistance Index (SVRI)	1600 to 2400 dynes/sec/m²/cm^5
Pulmonary Vascular Resistance Index (PVRI)	200 to 400 dynes/sec/m²/cm^5
Left Ventricular Stroke Work Index (LVSWI)	40 to 60 g/m²
Right Ventricular Stroke Work Index (RVSWI)	4 to 8 g/m²
Stroke Volume Index (SVI)	40 to 70 mL/beat/m² body surface
Pulmonary Capillary Pressure (PCP)	6 to 12 mm Hg
Mean Pulmonary Artery Pressure (MPAP)	10 to 20 mm Hg
Venous Central Pressure (VCP)	1 to 6 mm Hg
Mean Arterial Pressure (MAP)	70 to 90 mm Hg

The use on inotropics and/or vasodilators was proposed to maintain the following: MAP between 70 and 90 mm Hg; CI of at least 2.4 L/min/m^2; systemic vascular resistance index between 1600 and 2400 dynes/sec/m^2/cm^5; and diuresis of 1 mL/kg/h after regulating both the blood volume (volemia) and heart rate. Dopamine, nitroglycerin, and nitroprusside were administered. The usage dose was recorded pre- and post-CPB, on ICU admission, and at the beginning of each hour postoperatively until the 24th hour.

Glycemias and potassium plasma concentrations were collected pre-CPB, during CPB (trans-CPB) and on 1st, 2nd, 4th, 6th, 8th, 12th, 18th, and 24th hour postoperatively. Hemoglucotests were obtained at each hour until the 6th hour postoperatively and at each 2 hours until the 24th hour.

Plasma concentration of nonesterified fatty acids on operating room admission and in the end of the 1st reperfusion hour was determined.

The clinical variables studied were as follows: a) hyperglycemia (glycemia > 300 mg/dL); b) hypoglycemia (glycemia < 70 mg/dL); c) left heart failure (LHF) established by hemodynamic criteria (PCP > 20 mm Hg and CI < 2.0 L/min/m^2) consistent with radiological and clinical finds; d) intraaortic balloon (IAB) implanted in event of LHF and in the ischemic complications followed by PCP > 20 mm Hg and CI < 2.0 L/min/m^2; e) acute myocardial infarction through the appearance of a new Q wave on electrocardiogram or a new left bundle-branch block in association with enzymatic changes (CPK-MB > 50 IU; CPK > twofold the baseline value; LDH > twofold the baseline value; f) ventricular arrhythmias, supraventricular and atrial fibrillation postoperatively; g) duration of orotracheal intubation; h) ICU length of stay (hours); i) postoperative hospital length of stay (days); and j) postoperative infection. The later outcome gathered the occurrence of surgical wound deep and superficial infection; pneumonia, and urinary tract infection (UTI).

Possible confounding variables pre- and postoperative were controlled. The preoperative glycometabolic state was settled by evaluation time of the DM diagnosis and by the dose of glycolylated hemoglobin (A_{1c}), frutosamine, and glycemia. The water balance was determined between the groups within the 24 hours postoperatively.

Procedures

General anesthesia was induced using fentanyl, etomidate (0.2 to 0.4 mg/kg), and pancuronium bomide (0.1 mg/kg). At the moment of the induction of anesthesia, all the patients were given tranexam acid (50 mg/kg), methylprednisolona (2 g), and ranitidine (50 mg). The maintenance was performed with fentanyl (up to 50 µg/kg of the total dose) and pancuronium associated with 1 to 1.5% enflurane inhalation anesthetic. During CPB, a new dose of pancuronium (0.1 mg/kg),fentanyl (10 µg/kg), and midazolam was given to all the patients.

The Swan-Ganz catheter was inserted, through a midline transsternal incison, just after the induction of anesthesia and baseline homodynamic measures were established. After the arrangement of the grafts, the patients were given 5 mg/kg heparin. They undergone CPB through both ascending aorta and right atrium cannulation by using a standardized centrifugal pump and membrane oxygenator (Medtronic/Trillium Affinity NT®), with pump flow of 2.4 L/min/m^2 of body surface area and temperature at 34ºC. Cardioplegic arrest was promoted by aortic clampling and antegrade cardioplegia followed by the infusion in each graft once the distal anastomosis was performed. The components of the cardioplegic solution used were as follows: potassium chloride, 596 mg; procaine hydrochloride, 136 mg; and magnesium chloride, 1.63 g in 10-mL distilled water (purified water), administered in a blood/solution ratio of 20:1, at 34ºC, in a volume of 250 to 300 mL/dose. All vessels with lesions > 50% were revascularized and, at least, one internal thoracic artery was used in each patient. All patients were given antibiotic prophylaxis with cefazolin 1 g at the 30th minute of CPB and 1-g dose at each 8 hours up to the 24th hour postoperatively. Endovenous nitroglycerin at day 1 postoperatively, beta blocker, and acetylsalicylic acid (325 mg) were administered as soon as the oral pathway is reestablished and there were no contraindication to their use.

Bias control

The randomization was blinded to patients, surgeons, and cardiologists, who were directly involved in the accomplishment of the protocol and in the measurements, such as clinical, laboratory, and hemodynamic data. The participants were randomized to either the intervention group or to the control group. Only the anesthesiologists and the intensivists responsible for glycemic control and for the administration of insulin have had access to the group to which the patients was randomized.

Statistical analysis

Data are expressed as both mean ± standard deviation (SD) and medians for variables normally distributed, and asymmetrical variables are expressed as interquartile range. Continuous variables were tested by means of Student's *t* test and Mann-Whitney *U* test. Qualitative variables were compared by means of χ^2 test and Fisher's exact test. Analysis of variance for repeated measures and the Greenhouse-Geisser test were used to compare intergroup changes over time, the serum levels of glucose and potassium, dose of inotropics, vasodilators, and hemodynamic parameters within 24 hours of the postoperative monitoring.

RESULTS

From January 2002 to July 2003, 32 diabetic patients

were referred to myocardial revascularization surgery. Of these, seven required associated procedures (mitral valve replacement or carotid endarterectomy) and were excluded. One patient refused to participate. Among the 24 eligible patients that consented to participate, 12 were designed to each group. All patients completed the hospital protocol and were followed-up, at least, until the 30th day postoperatively. There were no significant differences in the preoperative evaluation, as shown in Table 1. There were no differences in the intraoperative parameters assessed, as described in Table 2.

The cardiac index increasingly rose over the 24 hours postoperatively; however there was no statistically significant difference between the GIK group and the control group (Figure 1).

The systemic vascular resistance index, the pulmonary vascular resistance index, left ventricular stroke work index, right ventricular stroke work index, stroke volume index, the pulmonary capillary pressure, the mean pulmonary artery pressure, the central venous pressure, and mean arterial pressure did not present statistically significant differences between the GIK group and the control group.

The use of inotropics (dopamina) and vasodilators (nitroglycerin and sodium nitroprusside) was similar between the patients of GIK group and control group. Two patients of the control group required adrenalin over less than 1 hour postoperatively.

The preoperative doses of glycolylated hemoglobin (A_{Ic}), frutosamine, and glycemia were similar between both groups (Table 1). Glycemias were significantly lower in the GIK group compared to the control group when measured pre-CPB (95.2 ± 38.9 vs 194.5 ± 76.2; 95% CI, 150.4 – 48.1; p=0.001) and trans-CPB (143.4 ± 46.5 vs 200.4 ± 45.7; 95% CI, 96.2 – 18.2; p=0.006). The glycemias were also significantly lower in postoperative measurements up to the 12th hour, as shown in Figure 2.

Serum potassium was within normal limits, and did not present significant differences between both groups.

Table 4. Baseline Characteristics of the patients according to the randomization group {mean ± SD, median (IIQ) or N (%)}.

	GIK Group (n =12)	Control Group	*P Value*
Age (years)	60.25 ±9.26	(n =12)	0.7
Gender Male	7 (58%)	58.92 ±6.04	1.0
Female	5 (42%)	8 (66%)	1.0
BMI* (kg/m²)	28.51±4.99	4 (43%)	0.6
Insulin use	3 (25%)	27.63±2.49	0.7
Oral hypoglycemiant use	9 (75%)	5 (42%)	1.0
DM* Time of diagnosis (years)	8.0 (3.25-19.50)	10 (83%)	0.9
Glycosylated Hb* A1c (% of total Hb)	9.5±2.40	9 (4.25-17.50)	0.8
Frucosamine(mmol/l)	2.77±0.53	9.7±1.81	0.2
Glycemia (mg/dl)	129.42±40.47	3.09±0.74	0.5
Ejection fraction (Hemodynamics)	0.60±0.14	143.25±57.05	0,3
Previous acute MI*	6 (50%)	0.54±0.16	1.0
Recent acute MI* (< 30 days)	3 (25%)	7 (58%)	0.5
Stable angina	9 (75%)	1 (8%)	1.0
Unstable angina	3 (25%)	8 (66%)	1.0
Intraaortic balloon (preoperative)	1 (8%)	4 (34%)	1.0
Functional Class (NYHA*)		1 (8%)	0.4
I	6 (50%)	6 (50%)	
II	6 (50%)	4 (34%)	
III	0	2 (16%)	
Systemic arterial hypertension (SAH)	11 (92%)	8 (67%)	0.3
Dyslipidemia	11 (92%)	9 (75%)	0.6
DOPC*	1 (8%)	4 (33%)	0.3
Peripheral vasculopathy	3 (25%)	4 (33%)	1.0

glycolylated hemoglobin (A_{Ic}), frutosamine

* BMI = Body Mass Index; DM = Diabetes mellitus; Hb = Hemoglobin; AMI = Acute Myocardial Infarction; NYHA = *New York Heart Association;* COPD = Chronic Obstructive Pulmonary Disease.

Table 5. Intraoperative parameters according to the randomization group {mean ± SD or median (IIQ)}.

Intraoperative Variables	*GIK Group (n =12)*	*Control Group (n =12)*	*P Value*
Extracorporeal Circulation Time (min)	137.75±37.47	138.67±30.24	0.95
Ischemia Time (min)	89.33±28.95	87.25±22.02	0.85
Reperfusion Time (min)	44.0±15.40	44.17±7.53	0.97
Transoperative Transfusion (ml)	150 (0-825)	0 (0-1125)	0.92
Number of venous grafts	3±0.74	2.58±0.51	0.12
Number of arterial grafts	1.17±0.39	1.08±0.29	0.56
NEFA* - admission (mmol/L)	1.59 (1.01-2.62)	1.42 (0.57-2.62)	0.81
NEFA* - reperfusion (mmol/L)	1.0 (0.63-1.25)	0.98 (0.59-2.09)	1.0

** NEFA = nonesterified fatty acid*

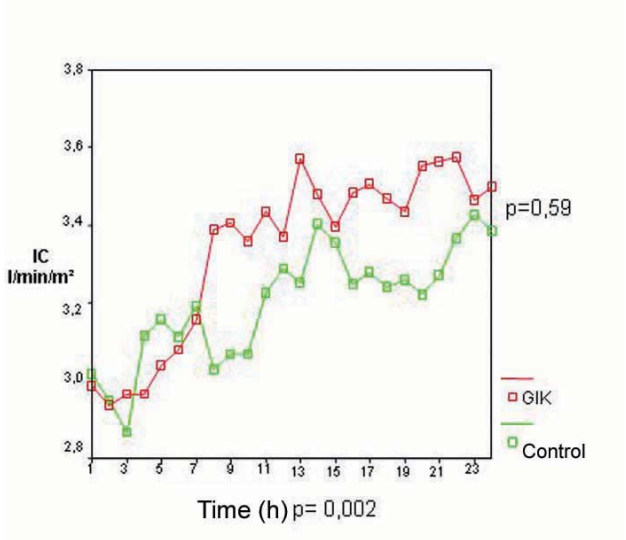

Fig. 1 – Average of Cardiac Index – Chart showing the behavior of cardiac index in the GIK group and in the Control group at 24 hours

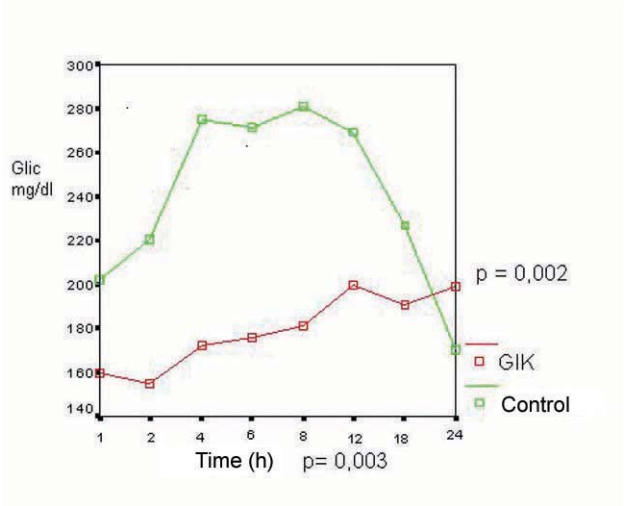

Fig. 2 – Average of Glycemias – chart showing the averages of glycemias in the GIK group and in the control group at 24 hours

The same behavior was presented by hemoglucotests and glycemias. The nonesterified fatty acids were increased in both groups on admission and there was no significant difference between the GIK group and the control group regarding the dose reduction at the first hour after the reperfusion (Table 2).

The event of hyperglycemia transoperatively and postoperatively was significantly higher than in the control group, 8 (64%) vs 2 (16%) in the GIK group (RR 0.25; 95% CI, 0.07-0.94; *p*=0.03). The number of hypoglycemia events was similar in both groups. There were no clinical complications or symptoms caused by hypo- or hyperglycemia. The events were recorded taking into consideration the measurement of plasma glycemia alone.

The left-sided heart failure was similar between the GIK group and the control group. Two patients sustained perioperative acute myocardial infarctions: one patient of the GIK group developed low cardiac output that required insertion of intraaortic balloon postoperatively, and one patient of control group who have required coronary endarterectomy. There was no difference between both groups regarding the occurrence of ventricular and supraventricular arrhythmias, or atrial fibrillation.

The duration of orotracheal intubation and the ICU and hospital length of stay were not significantly different between the allocation groups.

One patient of the control group was readmitted to the hospital on the 28th day postoperatively with mediastinitis.

The primary outcome was a composite of some complications presented by the patients due to infection in both control group and GIK group (10 (80%) vs three (25%), respectively. RR 0.30; 95% CI, 0.11-0.83; $p = 0.01$). The following diagnoses were as follows: a) control group: pneumonia three (25%); urinary tract infection two (16%); and superficial infection in saphenectomy four (32%); b) GIK group: only one (8%) event of each of the above complications.

Two patients in the control group died of multiple organ failure: one patient was readmitted due to mediastinitis, and one patient who during the pneumonia treatment and cellulitis in the saphenectomy presented acute renal failure and cardiac failure. The deaths occurred 120 and 90 days postoperatively. Table 3 shows the postoperative clinical evolution according to the allocation group.

The postoperative water balance was much similar in both groups (Table 4).

DISCUSSION

The infusion of GIK solutions as a metabolic support to myocardium in the perioperative of myocardial revascularization surgery has been recommended many years ago, but there is no consensus regarding to its benefits. Interest has also grown around the potential usage of GIK infusions due to the increasing number of diabetic patients submitted to surgical treatment and the search for better outcomes. The GIK effects in experimental studies have shown its capacity to preserve the contractile function after an ischemia period and a better hemodynamic performance of the heart is expected [4-8].

Table 6. Postoperative clinical outcomes according to the randomization group {N (%) or median (IIQ)}.

Clinical Outcome	GIK Group (n =12)	Control Group (n =12)	*P* Value
Hyperglycemia (>300 mg/dL)	2 (16%)	8 (64%)	0.03
Hypoglycemia (<70 mg/dL)	4 (32%)	2 (16%)	0.64
Heart failure	2 (16%)	3 (25%)	1.0
PO Intraaortic Balloon*	1 (8%)	0	1,0
Perioperative AMI*	1 (8%)	1 (8%)	1.0
Ventricular Arrhythmias	1 (8%)	2 (16%)	1.0
Supraventricular arrhythmias	2 (16%)	3 (25%)	1.0
ACFA	2 (16%)	2 (16%)	1.0
Duration of Orotracheal Intubation (h)	14 (8-17.75)	12.5 (8-16.75)	0.63
Length of ICU Stay* (h)	56.5 (48-135)	55.5 (48-89.5)	0.75
Length of Hospital Stay (days)	7.5 (6-13.25)	7.5 (6-14.75)	0.84
PO Infection	3 (25%)	10 (80%)	0.01

**AMI = Acute Myocardial Infarction; PO = Postoperative; ICU = Intensive Care Unit*

Table 7. Postoperative water balance according to the randomization group {N (%) or median (IIQ)}.

Balance	GIK Group (n=12)	Control Group (n=12)	*P* Value
Colloid Infusion (mL)	1,700 (1,000-2,100)	1,000 (500-1,875)	0.11
Crystalloid Infusion (mL)	6,066.58 ±2,074.53	5,569.67±2,021.64	0.63
Postoperative transfusion (mL)	150 (0-600)	175 (0-450)	0.79
Urinary output (mL)	5,910.08± 2,084.43	5,358.25±1,794.98	0.32
Insensible loss (mL)	559.75 ± 138.47	604±119.85	0.51
Bleeding (mL)	405 (371.3-600)	647.50 (428.5-900)	0.18
Final balance (mL)	2,462.92 ±2,030.60	2,088.67±1,309.98	0.32
Final Balance			
positive	8 (66.7%)	7 (58.3%)	1.0
negative	4 (33.3%)	5 (41.7%)	

The association between low cardiac output and mortality is well-established [18-20] and a normal recovery after a heart surgery is expected when the CI is maintained within the normal parameters [21]. We have established the CI as a primary outcome in our clinical trial, once it is the most sensitive measure of the performance of the heart in the immediate postoperative period. It can be checked by continuous thermodilution using a pulmonary artery catheter. It is simple and adequately accurate [22-24].

Other authors have been using CI to evaluate the benefit from GIK in myocardial revascularization surgery. A randomized clinical trial published in 2000 compared the diabetic patients undergone myocardial revascularization surgery using GIK (n=20) or conventional treatment with insulin subcutaneously (n=20). CI has been shown to increase in the intervention group (CI at the 18th hour postoperative: 2.88 ± 0.50 vs 2.2 ± 0.39 L/min/m^2 in the GIK group and in the control group, respectively; 95% CI, 0.38-0.97; p<0.0001) [11]. Szabó et al., [12] have studied the diabetic patient undergone to myocardial revascularization surgery and randomized to the GIK group with high doses of insulin (n=10) or conventional treatment (n=10). In the GIK group there was a significant increase in the CI (2.3 ± 0.1 to 2.9 ± 0.2 L/min/m^2; p=0.017).

An essay published in 2000 evaluated 45 patients undergone to myocardial revascularization surgery without CPB and randomized to GIK or saline solution. It was not found any difference between the groups regarding CI and SvO_2 (mixed venous oxygen saturation) as well as in the enzymatic variables CPK-MB and troponin 1 [13]. The Insulin Cardioplegia Trial [14] has evaluated the use of a 10-IU insulin-fortified cardioplegia vs placebo in high-risk patients undergone myocardial revascularization surgery due to unstable angina. A total of 1127 patients were randomized. There was no significant difference regarding mortality rate and the event of enzymatic infarction and/or low cardiac output syndrome. This study was criticized by not considering some existing evidences, such as low insulin dose administered in a single moment and not maintained in the postoperative period [25]. A meta-analysis published in 2004, which included 11 studies evaluating the GIK administered in the CBP postoperative or in the valve replacement relating to 468 patients, estimated an 11.4% increment in the CI of patients who received GIK infusion with a decrease in the atrial fibrillation in the postoperative period. Our study has some limitations. The design reduced the ability to analyze these outcomes. Although it was not conclusive, it had strengthened the requirement to perform the clinical trials in order to evaluate the metabolic support in this setting [15]. Finally, the clinical trial published in 2006 appears to have defined the value of GIK therapy in the perioperative surgical myocardial revascularization with the use of CPB in non-diabetic patients revealing a significant increase in the CI, decreased peripheral vascular resistance, lower occurrence of low cardiac output, reduction of inotropes, and reduced lesion of myocardium evaluated by biochemistry and electrocardiographic markers [16].

In our study we did not find any significant difference between the CI and the remaining hemodynamic measures which directly or indirectly influence the CI in patients treated with GIK infusion compared to the patients in the control group. The insignificant difference between the measures obtained and the sample size studied did not provide enough statistical power to confirm whether this difference does not really exist. We have established a CI of less than 2.4 L/min/m^2 as a criterion for the use of inotropics. The CI (2 L/min/m^2) used in the previous studies can be subnormal, which can explain the fact that only higher CI average values were achieved in our patients.

Additionally, our outcomes did not evidence significant difference between the mean inotropic dose and/or vasodilators in both groups.

We believe the adoption of a higher CI did not impair our capacity to evaluate the benefit of GIK as intervention, once both groups were given similar doses of inotropic drugs. In the Lazar et al. study [11], the use of inotropics was lower than in the GIK group. The evaluation of this outcome was performed by means of a unique score, taking into consideration the dose of dopamine, drug association, and inotropic drug support. The use of vasodilators is not reported. Even considering our data analysis by means of a similar score, we did not find differences in our sample. In Lell et al. study [13] it was not observed the hemodynamic profile of the patients treated with GIK. The inotropic dose was similar among the compared groups.

The diabetes mellitus length of time, the glycemia at admission, and the glycolylated Hb (A_{1c}) are considered to be independent predictors of mortality in diabetic patients [10]. The possibility of influence in comparison of patients studied led to an evaluation of the variables and the frutosamine concentrations as well, which reflect the glycemic state within the two weeks prior to myocardial revascularization surgery. There was no difference between these variables of the preoperative glycometabolic state between both groups.

The best glycemic control was obtained in the GIK group with a lower number of hyperglycemia episodes (>300 mg/dL). In a cohort study of 291 diabetic patients submitted to myocardial revascularization surgery, the hyperglycemia occurrence related positively with death and postoperative complications (OR = 2.5%; 95% CI, 1.1-5.3) with a risk increment of 17% for each 18 mg/dL over 110 mg/dL of glycemia [26]. Additionally, the evidences in the literature support that postoperative hyperglycemia (>200 mg/dL) is an independent predictor for the occurrence of mediastinitis in diabetic patients submitted to surgery with CPB [27]. The evidences, in our outcomes, make possible to state that the

better glycemic control was a benefit from the GIK treatment.

Nonesterified fatty acid plasma concentrations in the reperfusion period were statistically similar to the GIK group and the control group in spite of a mean infusion time of GIK of 4 hours and significantly lower transoperative glycemias.

In Rogers *et al.*'s studies [28] the administration of GIK solution composed of 300 g of glucose, 50 IU of insulin, and 80 mEq of potassium in 1000 mL of water at an average infusion rate of 1.5 mL/kg/h was required to significantly reduce the nonesterified fatty acid plasma concentration. In Szabó et al. study [12], the group of diabetic patients receiving high doses of GIK had the substrate consumption patter modified with an increment in the use of lactate and glucose in exchange of nonesterified fatty acid and β-hydroxybutyric acid after one hour of the beginning of the infusion. This metabolic change was followed by the hemodynamic alterations already described. Because we have failed to significantly reduce the nonesterified fatty acid plasma concentrations in reperfusion can explain, in part, why we could not find a significant increase of the cardiac index in the intervention group. It is likely that higher infusion rates provides a more marked reduction of nonesterified fatty acid plasma and enhance the effect of GIK treatment.

Also, left heart failure clinical variables, intraaortic balloon insertion, and acute myocardial infarction did not differ in both groups. There have been, however, a significant amount of complications caused by infection when all were considered as a clustered outcome between individuals of the control group.

It is known that the use of continuous perioperative infusion of insulin and the optimization of glycemic control are related to the reduced occurrence of mediastinitis in diabetic patients [29]. Rassias et al. [30] published in 1999, a clinical trial showing that a continuous insulin infusion and a tight glycemia control in myocardial revascularization surgery transoperative of diabetic patients improve the function of neutrophils, which is determined by the own neutrophils' phagocytic activity increasing the amount of neutrophils, even in non-diabetic patients [31]. Although this was a secondary target of our study and had been significant only as a clustered outcome, the outcome suggests a beneficial effect of GIK once the literature provides theoretical subsidy from the glycemic control effect in the decreased postoperative infection.

Up to present moment, the studies have not evaluated the GIK effect on the mortality of diabetic patients undergoing myocardial revascularization surgery. The current evidences showing that its effect influences the outcome of theses patients, not only by modifying their hemodynamic profile, but also in the maintenance of glycemia and in reduced postoperative infection events making this evaluation to be important for clinical trials designed for mortality outcomes.

Finally, our study failed to determine whether the use of GIK increases the cardiac index, or reduces the need of inotropic and vasodilators agents in myocardial revascularization surgery postoperative of diabetic patients. A large patient population should be studied in order to enlighten this issue. However, it was demonstrated that there is a better glycemic control using GIK. It does not cause hypoglycemic complications. Considering that hyperglycemia alone is a risk factor for postoperative complications, especially those related to infection, our study results suggest that strict glycemic control is highly beneficial to the patients.

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