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Improved myocardial protection during coronary artery surgery with glucose-insulin-potassium: A randomized controlled trial

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See related editorial on page 11.

Supplemental material is available online.

Objective: We sought to assess the role of glucose-insulin-potassium in providing myocardial protection in nondiabetic patients undergoing coronary artery surgery with cardiopulmonary bypass.

Methods: A prospective, randomized, double-blind, placebo-controlled trial was conducted at a single-center university hospital performing adult cardiac surgery. Two hundred eighty nondiabetic adult patients undergoing first-time elective or urgent isolated multivessel coronary artery bypass grafting were prospectively randomized to receive glucose-insulin-potassium infusion or placebo (dextrose 5%) before, during, and for 6 hours after surgical intervention. Anesthetic, cardiopulmonary bypass, myocardial protection, and surgical techniques were standardized. The primary end point was postreperfusion cardiac index. Secondary end points were systemic vascular resistance index, the incidence of low cardiac output episodes, inotrope and vasoconstrictor use, and biochemical-electrocardiographic evidence of myocardial injury. The incidence of dysrhythmias and infections requiring treatment was recorded prospectively.

Results: The glucose-insulin-potassium group experienced higher cardiac indices ($P < .001$) throughout infusion and reduced vascular resistance ($P < .001$). The incidence of low cardiac output episodes was 15.9% (22/138) in the glucose-insulin-potassium group and 27.5% (39/142) in the placebo group ($P = .021$). Inotropes were required in 18.8% (26/138) of the glucose-insulin-potassium group and 40.8% (58/142) of the placebo group ($P < .001$). Fewer patients in the glucose-insulin-potassium group (12.3% [16/133]) versus those in the placebo group (23.4% [32/137]) had significant myocardial injury ($P = .017$). Noncardiac morbidity was not different.

Conclusion: Glucose-insulin-potassium therapy improves early postoperative cardiovascular performance, reduces inotrope requirement, and might reduce myocardial injury. These potential benefits are not at the expense of increased noncardiac morbidity.

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During coronary artery bypass grafting grafting (CABG), the myocardium endures periods of ischemia and reperfusion. For on-pump CABG, ischemic protection is usually afforded by cardioplegia, which establishes electromechanical arrest and reduces myocardial oxygen consumption. Despite this, CABG might be followed by myocardial contractile dysfunction, which is associated with increased early and late morbidity and mortality and necessitates inotropic and mechanical circulatory support.[1,2] Metabolic modulation with glucose-insulin-potassium (GIK) might improve myocardial protection, particularly in diabetic patients.[3] A survival benefit has been noted when early high-dose GIK has been used after acute myocardial infarction,[4-6] and GIK might reduce the requirement for

Abbreviations and acronyms

AF = atrial fibrillation
ANOVA = analysis of variance
CABG = coronary artery bypass grafting
CI = cardiac index
CPB = cardiopulmonary bypass
cTnI = cardiac troponin I
ECG = electrocardiogram
GIK = glucose-insulin-potassium
IQR = interquartile range
ITU = intensive therapy unit
LCOE = episodes of low cardiac output
NYHA = New York Heart Association
PMI = perioperative myocardial infarction
SD = standard deviation
SVR = systemic vascular resistance
SVRI = systemic vascular resistance index
WBG = whole blood glucose

postsurgical circulatory support.[7] Additionally, insulin therapy in intensive care patients has been associated with reduced mortality.[8] A recent meta-analysis of 11 trials (n = 468) of GIK in cardiac surgery suggested that GIK improved cardiac index (CI) and reduced inotrope requirement and the incidence of atrial fibrillation (AF)[9] and called for a multicenter randomized controlled trial of GIK in cardiac surgery. The aim of this study was to examine the effects of GIK on cardiovascular performance and myocardial injury in nondiabetic patients undergoing CABG.

Materials and Methods

A double-blind, prospective, randomized, placebo-controlled trial was conducted in 280 patients undergoing isolated CABG between January 2000 and August 2002. The study was approved by the local research ethics committee, and all patients provided written informed consent. Inclusion criteria were age of 18 years or older and an intention to perform first-time multivessel CABG. Exclusion criteria included diabetes mellitus, serum creatinine level of 200 μmol/L or greater, recent (<6 weeks) cerebrovascular event, and emergency status. Before the trial, computer-generated randomization schedules were generated in advance, stratified by surgeon and left ventricular function, and placed in sequentially numbered sealed envelopes. Trial investigators and medical and nursing staff were blinded to allocation.

Trial Intervention

GIK and placebo (5% dextrose) solutions were independently prepared immediately preoperatively in identical containers and administered from sternotomy to 6 hours after release of the aortic crossclamp as a continuous central intravenous infusion at 0.75 mL $\cdot$ kg^{-1} $\cdot$ h^{-1}. The GIK solution comprised 40% dextrose containing 70 IU/L human Actrapid insulin (Novo Nordisk A/S, Bagsvaerd, Denmark) and 80 mmol/L potassium chloride.

Anesthetic, Operative, and Postoperative Protocols

Anesthesia, cardiopulmonary bypass (CPB), myocardial protection, and surgical techniques were standardized. Anesthesia was induced with intravenous etomidate, fentanyl, and pancuronium and maintained with enflurane, propofol, and alfentanil. CPB (28°C) was instituted with a roller pump and membrane oxygenator with an asanguineous prime. Intermittent antegrade cold blood St Thomas' No. 2 cardioplegia (Martindale Pharmaceuticals, Essex, United Kingdom) containing no glucose was used for myocardial protection (12 mL/kg for induction and 6 mL/kg at 20-minute intervals). Distal anastomoses were constructed during a single crossclamp period, and proximal anastomoses were constructed during partial aortic occlusion. After rewarming with a 37°C maximal heat-exchanger temperature, CPB was discontinued at 36°C-37°C nasopharyngeal temperature. Intraoperative ventricular tachydysrhythmias were treated with internal cardioversion or lidocaine. Intravenous glycopyrollate, atropine, and atrial or dual-chamber epicardial pacing were used to achieve a target heart rate of 70 to 110 beats/min. Arterial whole blood glucose (WBG) samples were drawn at baseline, every half hour before CPB, every 20 minutes during CPB, every hour for the initial 6 hours of reperfusion, and every 2 hours for the subsequent 6 hours. Supplemental insulin (human Actrapid, Novo Nordisk) was administered according to a simple standardized sliding scale with a target WBG value of 180 to 270 mg/dL. Patients with a WBG value of 180 to 270 mg/dL received a 4-IU intravenous bolus of insulin and 5 IU/h continuous intravenous infusion until the next test schedule, and patients with a WBG value of 271 to 360 mg/dL received an 8-IU intravenous bolus and 10 IU/h continuous intravenous infusion. Supplemental infused insulin was stopped 1 hour before trial solution cessation in both groups and restarted 1 hour later according to protocol. Inotropic support, initially with dopamine (3-10 μg $\cdot$ kg^{-1} $\cdot$ min^{-1}) and secondly with epinephrine, was commenced if the mean arterial pressure was less than 65 mm Hg with a CI of 2.2 L $\cdot$ min^{-1} $\cdot$ m^{-2} or less in the presence of a central venous pressure of 12 mm Hg, a pulmonary capillary wedge pressure of 14 mm Hg, and a heart rate of 70 to 110 beats/min. Support was also permitted if the operating surgeon identified poor contractility at separation of CPB or if marginal hemodynamics were noted by attending physicians. Intravenous vasoconstrictors were used for a mean arterial pressure of less than 65 mm Hg, a systemic vascular resistance (SVR) of less than 800 dynes $\cdot$ s^{-1} $\cdot$ cm^{-5}, and a CI of greater than 3 L $\cdot$ min^{-1} $\cdot$ m^{-2}. Bolus phenylephrine was used until the administration of protamine, after which norepinephrine infusion was used as a vasoconstrictor. Extubation, intensive therapy unit (ITU), and hospital discharge criteria and AF management were standardized.

Trial Investigations

Before surgical intervention, baseline demographic and clinical data were recorded. Hemodynamic studies were performed before infusion, before and 15 minutes after protamine administration, and 2, 4, 6, 9, and 12 hours after reperfusion. Cardiac troponin I (cTnI) samples were drawn at baseline and 6, 12, 24, 48, and 72 hours after reperfusion and analyzed in batches with a commercial assay (Bayer Corp, Tarrytown, NY). Preoperative, postoperative day 1, and postoperative 4 electrocardiograms (ECGs) were obtained.