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Myocardial protection by glucose–insulin–potassium in acute coronary syndrome patients undergoing urgent multivessel off-pump coronary artery bypass surgery

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Editor's key points

- Effects of glucose–insulin–potassium (GIK) infusion on myocardial damage during coronary artery surgery were studied.
- Biomarkers of myocardial damage were measured after reperfusion of the heart in patients with or without the ongoing infusion.
- GIK attenuated the levels of creatinine kinase-MB and troponin-T.
- This study provides biochemical evidence of myocardial protective role of GIK infusion.

Background. The aim of this randomized and controlled trial was to investigate the effect of a glucose–insulin–potassium (GIK) solution on myocardial protection in acute coronary syndrome (ACS) patients undergoing urgent multivessel off-pump coronary artery bypass (OPCAB) surgery.

Methods. Sixty-six patients were randomly allocated either to receive 0.3 ml kg^{-1} h^{-2} GIK solution (potassium 80 mEq and regular insulin 325 IU in 500 ml of 50% glucose) or equivalent volume of normal saline (control) upon anaesthetic induction until 6 h after reperfusion. The primary endpoints were to compare the concentrations of creatine kinase-MB (CK-MB) and troponin-T between the groups after reperfusion. The secondary endpoints were to compare the incidences of postoperative troponin-T >0.8 ng ml^{-1} and myocardial infarction (MI) between the groups.

Results. Highest CK-MB [8.7 (4.4) *vs* 13.1 (7.9) ng ml^{-1}, P=0.006] and troponin-T [0.20 (0.13–0.49) *vs* 0.48 (0.18–0.91) ng ml^{-1}, P<0.0001] values after reperfusion were significantly lower in the GIK group compared with the control group. The area under the curve of serially measured troponin-T was also significantly smaller in the GIK group compared with the control group [0.83 (0.43–1.81) *vs* 0.46 (0.31–1.00), P=0.036]. Significantly fewer patients in the GIK group showed troponin-T >0.8 ng ml^{-1} after reperfusion compared with the control group (3 *vs* 11, P=0.033). The incidence of postoperative MI was similar between the groups.

Conclusions. GIK administration in ACS patients undergoing urgent multivessel OPCAB significantly attenuated the degree of ensuing myocardial injury without complications related to glycaemic control.

Clinical Trial Registry. URL: http://clinicaltrials.gov/ct2/show/NCT01384656?term=GIK+AND+OPCAB&rank=1. Unique identification number NCT01384656.

Keywords: acute coronary syndrome; insulin; myocardial injury; OPCAB; troponin T

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In patients with multivessel coronary artery disease and acute coronary syndrome (ACS), urgent coronary artery bypass surgery (CABG) is a well-established treatment. Unfortunately, these patients are at increased risk of myocardial infarction (MI), rehospitalization, and cardiac death after CABG compared with patients with stable angina pectoris.[1 2]

Recently, off-pump CABG (OPCAB) is gaining renewed interest for being associated with improved outcome in high-risk patients compared with on-pump CABG.[3 4] In patients with ACS presenting for emergent CABG, OPCAB was also associated with improved hospital outcome.[5] Moreover, in the era of dual antiplatelet therapy, OPCAB may especially be valuable for ACS patients, as it has been safely performed without increased risk of procedural bleeding in patients on continued clopidogrel therapy close to surgery.[6 7]

Although different from the global myocardial ischaemia–reperfusion injury observed in on-pump CABG, multivessel OPCAB produces cumulative warm regional myocardial ischaemia–reperfusion injury.[8] Accordingly, the myocardium remains vulnerable to various degrees of injury with unavoidable periods of regional myocardial stunning and impaired cardiac performance.[9] Thus, an effective myocardial

protective strategy, especially in high-risk patients such as ACS patients requiring urgent surgical revascularization, seems to be mandatory.

In order to minimize ischaemic myocardial injury, glucose–insulin–potassium (GIK) solution has been used for almost five decades in various clinical settings for its metabolic and non-metabolic cardioprotective mechanisms. GIK as an adjunct to revascularization after acute MI has been shown to offer significant survival benefit.[10] In the cardiac surgical setting, a recent meta-analysis also showed beneficial effects of GIK solution in terms of reduced myocardial injury and improved haemodynamic performance.[11] Yet, evidence regarding the myocardial protective effect of GIK in ACS patients undergoing OPCAB is lacking.

The aim of this prospective, single-site, double-blind, randomized, and parallel-arm controlled trial was to investigate the effect of a GIK solution on myocardial protection in ACS patients undergoing urgent OPCAB. The primary endpoints were to compare the concentrations of creatine kinase-MB (CK-MB) and troponin-T between the groups during the perioperative period as markers of myocardial injury. The secondary endpoints were to compare the incidences of troponin-T >0.8 ng ml^{-1},[12] postoperative MI, and outcome between the groups.

Methods

Patients

After Institutional Review Board approval and written informed consent was obtained, 66 patients with ACS requiring urgent multivessel OPCAB between February 2011 and October 2011 at Severance Hospital were prospectively studied. This study was registered with ClinicalTrials.gov (*Ref: NCT01384656*). Urgency was defined as OPCAB performed during the index admission within 2 days of diagnosis-confirmation by coronary angiography. Patients were randomly allocated to either the GIK or the control group in 1:1 ratio by means of random numbers generated by a computer. An anaesthesiologist not involved in the current trial performed randomization and assignment. Exclusion criteria were emergent and/or redo surgery, insulin-dependent diabetes, serum fasting blood glucose concentration >13.8 mmol litre^{-1}, liver dysfunction, confirmed renal impairment [serum creatinine (Cr) >2 mg dl^{-1}], mechanical cardiopulmonary support (patients who are already on mechanical ventilation, intra-aortic balloon pump, or both before operation), and emergency conversion to an on-pump CABG. We had not excluded patients with recent MI as we enrolled ACS patients, which encompass patients with non-ST elevation MI, ST elevation MI, and unstable angina (data provided in Table 1). There was no lower limit for the left ventricular ejection fraction (LVEF). However, we excluded patients who were already on intra-aortic balloon pump before operation due to severe heart failure and haemodynamic compromise as described above.

Table 1 Patients' characteristics. Values are mean (range) for age, mean (SD) or number of patients (%). GIK, glucose–insulin–potassium; MI, myocardial infarction

	Control ($n=33$)	GIK ($n=33$)	*P*-value
Age (yr)	67 (7–79)	64 (48–76)	0.157
Gender (M/F)	23/10	20/13	0.606
Body mass index (kg m^{-2})	24 (3)	24 (3)	0.949
Left ventricular ejection fraction (%)	39 (9)	35 (11)	0.089
Diabetes	12 (36)	19 (58)	0.138
Hypertension	17 (52)	19 (58)	0.805
Recent MI (<1 month)	13 (39)	16 (49)	0.620
Unstable angina/non ST-elevation MI	31 (94)	30 (91)	1.000
ST-elevation MI	2 (6)	3 (9)	1.000
Left main disease	3 (9)	5 (15)	0.708
Degree of stenosis (%)			
Left anterior descending	82 (13)	86 (10)	0.195
Left circumflex	80 (21)	77 (26)	0.684
Right coronary artery	83 (14)	85 (15)	0.773
Creatinine (mg dl^{-1})	1.0 (0.2)	1.0 (0.2)	0.321
Medications			
Nitrates	5 (15)	7 (21)	0.751
β-Blockers	22 (67)	22 (67)	1.000
Calcium channel blockers	12 (36)	8 (24)	0.422
Renin–angiotensin system antagonists	17 (52)	20 (61)	0.620
Statins	11 (35)	9 (28)	0.595

Treatment

Patients in the GIK group received 0.3 ml kg^{-1} h^{-2} GIK solution (potassium 80 mEq and regular insulin 325 IU in 500 ml of 50% glucose) via the central venous route upon anaesthetic induction until 6 h after reperfusion. Patients in the control group received equivalent volume of normal saline for the same duration. Solutions were prepared by an anaesthesia nurse and administered by an anaesthesiologist who were both not involved in this study. Attending surgeon and anaesthesiologist involved in the patient care were blinded to the patients' groups.

In all patients, arterial blood gas analyses were performed every hour until discontinuation of the treatment or placebo. Serum glucose concentration was serially measured by arterial blood gas analysis and was maintained between 4 and 11 mmol litre^{-1} using regular insulin or 50% glucose, as necessary. Serum potassium concentration was also serially measured by arterial blood gas analysis and maintained between 3.5 and 5.5 mEq litre^{-1}.

Perioperative management

All patients received standardized perioperative care. Standard monitoring included a pulmonary artery catheter (Swan–Ganz CCOmbo CCO/SvO$_2$^{TM}, Edwards Lifesciences