

THE EFFECTS OF GLYCAEMIC CONTROL IN CARDIAC PATIENTS UNDERGOING CABG SURGERY

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ABSTRACT

Objective: To see the effect of glycaemic control during and after cardiac surgery in the two groups.

Material and Methods: This randomized clinical control study was conducted in the Department of Cardiothoracic Anesthesia, PGMI/LRH from April 2012 to December 2014. A total number of 100 patients were randomly assigned in one of the two groups, i.e. 50 in Glucose, Insulin, Potassium (GIK) and 50 patients in control group. Patients's demographic data, and the effect of glycaemic control during and after cardiac surgery on clinical outcome was recorded and compared in the two groups. Calculations were done using the SPSS, software package, Version 17.

Results: Glycaemic control reduced the incidence of post-surgical atrial fibrillation in 10 (20%) of GIK group versus 20 (40%) of control group, $P < 0.05$ (Significant). The duration of mechanical ventilation (6.3 ± 1.03 hours GIK versus 8.1 ± 20.9 hours control group, $P < 0.05$ and length of stay in the ICU (intensive care unit) 48 ± 4.5 hours GIK versus control group 60.7 ± 2.89 hours, $P < 0.05$ (Significant).

Conclusion: There may be some benefit to tight glycaemic control during and after cardiac surgery in terms of atrial fibrillation, mechanical ventilation, and length of stay in ICU.

Key Words: Glycaemic, CABG, Cardiac surgery.

INTRODUCTION

Diabetic patients undergoing CABG surgery have increased perioperative mortality and morbidity which significantly reduced long-term survival.¹⁻² Hyperglycaemia after cardiac surgery is a well-documented phenomenon³ resulting in increased gluconeogenesis and glycogenolysis as a result of body's response to stress or surgery.⁴ Uncontrolled blood glucose can lead to: electrolyte imbalance, arrhythmias and an increased risk of ischemic brain injury.⁵ A higher incidence of left ventricular dysfunction, altered endothelial function, more diffuse coronary disease, abnormal fibrinolytic and platelet function, and impaired glucose utilization have been attributed to poorer outcomes in these patients.⁶ In addition, it may predispose patients to an increased risk of post-surgical infections through impaired phagocytic activity and decreased neutrophil function.⁷

To develop new strategies to improve outcomes in diabetic CABG patients, because the above mentioned risk factors were thought to be irreversible, it is important to understand the mechanisms responsible for impaired function in the diabetic ischemic myocardium. As glucose is the preferred metabolic substrate

for the myocardium, its oxidation in the diabetic heart is markedly impaired, during periods of ischemia, not only as a result of impaired glucose transport into the myocyte but also by the reduced rate of phosphorylation of glucose within the cell. Insulin resistance, which is known to occur during cardiopulmonary bypass, also contributes to increased concentrations of free fatty acids and decreased myocardial uptake of glucose.^{8,9}

Malmberg and coworkers reduced mortality after an acute myocardial infarction (MI) by 30% with the infusion of a glucose-insulin solution designed to achieve serum glucose levels < 200 mg/dL.¹⁰ Previously published evidence suggests that glycaemic control in critically ill would result decreased demand for postoperative ventilation, length of stay in ICU, and a decreased incidence of atrial fibrillation, hence improving morbidity and mortality in diabetic CABG patients.^{10,11,12}

MATERIAL AND METHODS

Patients with diabetes mellitus undergoing primary CABG surgery performed on cardiopulmonary bypass were included in the study. This study was conducted in the department of Cardiothoracic Anesthesia PGMI/LRH from April 2012 to December 2014. A total number of 100 patients were randomly assigned in one of the two groups, i.e. 50 in GIK and 50 patients in control group. Approval to use GIK solutions in human subjects was obtained from Institutional Research and Ethical board Post Graduate Medical Institute, Lady Reading Hospital, Peshawar. An informed consent was obtained from each patient enrolled in the study.

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The GIK group received an infusion through a central venous line consisting of 500 mL D5W with 80 U of regular insulin and 40 mEq of KCl infused at 40 mL/h. The GIK was started just before anesthetic induction and continued until 48 hours after arrival in the Intensive Care Unit (ICU). Blood glucose and K⁺ were monitored every hour. Adjustments in the rate of the GIK infusion were made on the basis of the sliding scale. Patients in the Control group received 5% dextrose water infused at 40 mL/h. Blood glucose and K⁺ were also monitored every hour. Insulin was used to administer subcutaneously according to sliding scale. After the 48-hour study period, patients resumed their preoperative diabetic regimens (oral agents or insulin) titrated to keep blood glucose <200 mg/dL.

Patients were anaesthetized with a standard technique including propofol 1-2 mg/kg, morphine 0.1mg/kg, dormicum 0.1mg/kg and atracurium 0.5 mg/kg to facilitate tracheal intubation. Anesthesia was maintained with 2% sevoflurane in 60% oxygen/air mixture together with incremental boluses of atracurium 10 mg when required. Patients were monitored for heart rate, five-lead ECG, pulse oximetry, central venous line pressure, Invasive blood pressure, capnography, urine output, serial blood gas analysis, serum glucose and electrolytes including potassium and magnesium, were monitored continuously from the time of anesthesia induction and every hour to 48 hours after arrival in the ICU in order to monitor oxygenation, ventilation and acid base balance. All vessels with at least 50% stenoses were bypassed, and at least 1 internal mammary artery was used in each patient. Myocardial protection consisted of multidose infusions of antegrade, cold (4°C) blood (hematocrit 20%), potassium (28 mEq/L) cardioplegia supplemented with mild systemic (35°C) and topical (cold saline lavage at 4°C) hypothermia. Inotropic agents were used to maintain systolic blood pressure ≥90 mm Hg after afterload, preload, and heart rate were maximized. ECGs were obtained before CABG, immediately on arrival in the ICU, and on 1st, 2nd, 3rd postoperative days. A perioperative MI was diagnosed either by the appearance of new ECG changes or by the elevation of cardiac enzymes in the immediate 24-hour period after surgery. β-Blockers were instituted before surgery and continued throughout the postoperative period in all patients with a heart rate ≥60 bpm and a systolic blood pressure ≥95 mm Hg.

The time spent on the ventilator was recorded in hours from the time of admission to the ICU to the time of extubation. All patients were placed on standardized “fast-track” protocols. Length of stay in the ICU was defined as time from ICU arrival to transfer to the high dependency unit. Before transfer, patients had to be extubated with stable vital signs and without any inotropic support. Criteria for discharge included a stable cardiac rhythm, temperature < 99°F, a well-healed incision, and oxygen saturations >90% on room air or supplemental oxygen ≤2 L.

Calculations were done using the SPSS, software package, version 17. The student ‘t’ test was performed to compare two data. Results were displayed in figures as mean ± SD. P values of 0.05 or < 0.05 were considered statistically significant.

RESULTS

There was no difference in the incidence of vessels with ≥ 50% stenoses (3.25 ± 0.07 GIK versus 3.15 ± 0.06 control group; *P* > 0.05) or the number of vessels bypassed (3.27 ± 0.09 GIK versus 3.26 ± 0.08, *P* > 0.05). Cross-clamp (47.74 ± 1.55 minutes GIK versus 44.55 ± 1.45 minutes control group; *P* > 0.05) and cardiopulmonary bypass times (89.43 ± 2.45 minutes GIK versus 86.5 ± 2.44 minutes control group; *P* > 0.05) were also similar between two groups.

Mean serum potassium levels were constant in both groups throughout the perioperative period (4.34 ± 0.05 mEq/L GIK versus 4.27 ± 0.04 mEq/L control group; *P* > 0.05). Both groups had similar glucose levels at the time of anesthetic induction (180.4 ± 6.9 mg/dL GIK 179.0 ± 3.8 mg/dL versus control group; *P* > 0.05). However, after the initiation of GIK therapy, GIK-treated patients achieved significantly better glycemic control immediately after induction of anesthesia and was maintained throughout the procedure. Blood glucose was well maintained on 1st postoperative day i-e 131.2 ± 3.5 mg/dL in GIK group versus 256.6 ± 6.4 mg/dL in control group, *P* < 0.05). Similarly there was a significant difference in glucose level on 2nd postoperative day i-e 165.5 ± 6.3 mg/dL in GIK group versus 237.12 ± 5.9 mg/dL in control group, (*P* < 0.05). The postoperative results shows less time spent on the ventilator (6.3 ± 1.03 hours GIK versus 8.1 ± 20.9 hours control group; *P* < 0.05), and had a lower incidence of atrial fibrillation 10 (20%) GIK versus 20 (40%) control group, *P* < 0.05) and length of stay in the intensive care unit (ICU) 48 ± 4.5 hours GIK versus control group 60.7 ± 2.89 control group; (*P* < 0.05, Significant).

DISCUSSION

Diabetic patients with coronary disease have increased levels of proinflammatory cytokines such as interleukin-6 and tumor necrosis factor, which stimulate the synthesis of acute-phase proteins such as C-reactive protein.^{13,14} This increased inflammatory response can contribute to the postoperative capillary leak syndrome, resulting in increased lung water accumulation and altered autonomic tone. As a result, these patients have increased fluid accumulation and require longer periods of ventilatory support. Diabetic patients also have impaired endothelial function. Hyperglycemia depletes NADPH and increases the synthesis of diacylglycerol, both of which result in decreased synthesis of endothelial nitric oxidase synthase, a potent vasodilator.¹⁵ This results in increased production of endothelin-1, a potent vasoconstrictor, which has been shown to increase cell necrosis after

periods of ischemic injury.¹⁶ Bioassays from internal mammary artery and saphenous vein grafts taken from diabetic CABG patients show decreased NO activity and increased production of superoxide and NADPH oxidase.¹⁷ This altered endothelial function during CABG may result in postoperative ischemic necrosis and may contribute to decreased long-term survival and recurrent ischemic events. Patients with diabetes also have impaired platelet function characterized by increased levels of plasminogen activator inhibitor-1 and adhesion molecules.^{18,19} This enhances platelet adhesiveness and hyperaggregability and predisposes to coronary thrombosis, which may ultimately affect long-term vein graft patency.

Intravenous infusions of insulin after CABG surgery have been shown to decrease levels of free fatty acids and increase myocardial uptake of glucose.⁹ Insulin added to cardioplegic solutions in CABG patients enhances aerobic metabolism on reperfusion and improves left ventricular stroke work index.²⁰ Exogenous insulin also decreases oxidative stress and the inflammatory response. Low-dose infusions of insulin (2 IU/h) in obese patients significantly decreased levels of reactive oxygen species, adhesion molecules, and C-reactive protein within 2 hours.²¹ Insulin may also prevent coronary thrombosis by 2 mechanisms. It upwardly regulates the l-arginine–NO pathway, which improves endothelial function, and it decreases serum levels of plasminogen activator inhibitor-1.¹⁸

Several studies have shown that hyperglycemia is associated with adverse outcomes during acute coronary syndromes. Wahab and colleagues²² studied the effects of increased blood glucose in 1664 patients admitted with an acute MI. Patients with a blood glucose >198 mg/dL had higher in-hospital and 1-year mortalities independent of whether or not a history of diabetes was present. Norhammar and coworkers²³ also noted that elevated serum glucose levels in acute MI patients, regardless of a known history of diabetes, was a risk factor for reinfarction, congestive heart failure, and future cardiovascular events. Similar results were noted by Iwakura and colleagues,²⁴ who demonstrated that hyperglycemia in association with acute coronary syndromes predicted larger infarcts, decreased contractility, and less reperfusion by contrast echocardiography. Furnary and coworkers,²⁵ in a retrospective, nonrandomized study of diabetic patients undergoing CABG over a 14-year period, found that patients receiving a continuous insulin drip in the postoperative period had tighter control of serum glucose levels than patients managed with intermittent subcutaneous insulin injections, and as a result, there was a significant decrease in perioperative mortality in the patients treated with a continuous insulin infusion (2.5% versus 5.3%; $P < 0.0001$). The decrease in mortality was primarily because of a decrease in the incidence of cardiac-related deaths.

We hypothesize that by providing Insulin intraoperatively in CABG patients and hence improving endothelial function, decreasing vascular inflammation, and reducing thrombogenicity can contribute to improved early graft patency and enhanced viability of myocardial cells in areas of ischemia. This might explain the improved survival, less time spent on mechanical ventilation, and in ICU and less incidence of atrial fibrillation. A similar early survival benefit was seen in the DIGAMI trial in a group of diabetic patients receiving insulin during an acute MI.⁶ A recent study in rats suggests that it is insulin, and not the glucose or potassium, that confers myocardial protection by enhancing NO synthase.²⁶ A recent study in critically ill patients receiving mechanical ventilation treated with insulin to maintain serum glucose values ≤ 110 mg/dL had significantly decreased morbidity and less multiorgan failure and were less likely to require prolonged ventilation.²⁷

There were five RCTs that examined the time spent on mechanical ventilation following cardiac surgery, with and without tight glycaemic control.²⁸ The four studies that presented their data as mean hours on ventilation were compared in a meta-analysis ($n = 582$), the results of this analysis suggest that patients who experienced tight glycaemic control peri and/or post-operatively spent significantly less time on mechanical ventilation ($p < 0.00001$).^{29,30} We noticed very good results regarding time spent on mechanical ventilator, patients in GIK group spent significantly less time compared to patients in control group ($P < 0.05$) on ventilators, our study was comparable to the ones in previous studies.

Atrial fibrillation, the results of this analysis are heavily weighted by one study, Lazar et al²⁸ and the mean values differ greatly between Lazar et al's, Hoedemaekers et al's²⁹ and Kosenkari et al's³⁰ studies, which is reflected in the heterogeneity analysis. The occurrence of atrial fibrillation (AF), post cardiac surgery, was reported in five of the RCTs (total $n = 488$).^{28,31,32} The results of the meta-analysis revealed a significant reduction in AF in patients with tight glycaemic control during surgery. We noticed a significant reduction in Arrhythmias in our GIK group compared to our Control group ($P < 0.05$). Our results were comparable to the studies done previously.

The duration of time spent in ICU/CCU following cardiac surgery, for patients with and without tight glycaemic control, was reported in five of the RCTs^{30,31,33} there was a significant effect of tight glycaemic control on reducing the time spent in ICU ($p < 0.00001$). Length of stay in ICU was greatly reduced in our GIK group compared to Control group ($P < 0.05$).

CONCLUSION

Tight glycaemic control provides favourable conditions in recovery of the CABG patients during and after cardiac surgery.

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AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

- Laiq N:** Concept and design, drafting the manuscript.
Khan S: Typing the manuscript and making statistical analysis of the results.
Ahmed H: Operating surgeon.
Aslam S: Operating surgeon.
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Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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