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EFFECTS OF STRICT GLYCEMIC CONTROL ON MORBIDITY & MORTALITY OF DIABETIC PATIENTS POST-CABG

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Objectives: Diabetic mellitus is a risk factor for morbidity and mortality following CABG. Its relative risk may be related to the level of peri-operative hyperglycemia. We hypothesized that strict glucose control with a continuous insulin infusion in the peri-operative period would reduce hospital morbidity & mortality.

Background: There is a general consensus that hyperglycemia should be avoided. However, there is disagreement about the acceptable lower level of serum glucose.

Methods: The study was done at the National Institute Of Cardiovascular Diseases (NICVD). From June 2009 to June 2011 all diabetic patients who had CABG alone without a concomitant procedure were included. Patients were divided in two groups, on the basis of minimum sugar level; 80mg/dl (Group I) and 180mg/dl (Group II).

Results: All these patients were followed up till 30th post-operative day. Following endpoints were assessed; superficial infection, mediastinitus, ICU stay, total hospital stay and death. Results showed significant association with superficial infection. Mediastinitis, ICU stay, total hospital stay and death were statistically insignificant between the two groups.

Conclusion: Strict glycemic control is not associated with a significant improvement in outcome when compared with moderate glycemic control. However, there is significant chance of hypoglycemia with its associated complications when strict glycemic control is undertaken.

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INTRODUCTION

Hyperglycemia is a normal response to physical or metabolic stress. It leads to release of stress hormones like cortisol, glucagon, epinephrine, and growth hormone. These agents are responsible for up-regulation of hepatic gluconeogenesis and glycogenolysis. This raised serum glucose is available to organs which have an increasing demand like the brain and heart. However body‘s own response is to try to regulate serum glucose level with help of release of insulin. This regulatory mechanism is impaired in diabetic patients. Primary culprit lesions are vascular atherosclerotic disease & peripheral and autonomic neuropathies in Diabetic mellitus. These increase the susceptibility of patients to hyperglycemia associated complications. Patients admitted with acute Myocardial Infarction having undiagnosed hyperglycemia (untreated) have a more adverse outcome compared to non diabetic and diabetics(treated): 16% mortality vs 1.7% and 3% respectively.[1]

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There is a very high incidence of diabetic mellitus in patients presenting for coronary artery disease. About 44% of patients presenting for cardiac surgery were diabetic with 48% of possible diabetic undiagnosed preoperatively[2]. While Pears et al. mentioned 25% to 30% patients operated for CABG have diabetic mellitus[3]. Diabetic mellitus is a sole predictor of not only non-operative but also postoperative adverse events, significantly reduced long-term survival, and less freedom from recurrent episodes of angina[4] following surgery. Van den Berghe et al showed improved outcome with 34% decrease in hospital mortality in ICU setting in a mixed patient's population by maintaining a serum glucose level of 80 to 110 mg/dl[5]. However role of strict glycemic control in cardiac surgery patients is still controversial due to possible hypoglycemic events.

Controlling serum glucose level in open heart surgery patients is quite different from other surgical patients. Possible causes of hyperglycemia include: Pump associated release of Inflammatory cytokines, insulin resistance due to hypothermia ,absorption of insulin by plastic material in the extracorporeal circuit causing relative deficiency, ongoing glucose administration in the cardioplegia solution and use of drugs with hyperglycemic effect (Adrenalin, Steroids)[6]. Intra-operative serum glucose also has an influence on operative outcome irrespective of whether the patient is diabetic or not.[7]

Non diabetic cardiac surgery patients showed better survival and fewer septic complications when their serum glucose level was controlled between 4.4 and 6.1mmol/l; had 46% fewer septic complications and 34% lower mortality than patients managed in the conventional manner (mean fasting blood glucose level averaged 8.5 mmol/l during the ICU stay)[8].

There are differences of opinion regarding optimal serum glucose level in post pump CABG patients in ICU settings. There are different glycemic controls protocols like absolute glucose (Matias) protocol[9], a relative glucose change (Bath) protocol[10], and an enhanced model predictive control (eMPC)[11] algorithm.

We were using the moderate glycemic control protocol in our ICU setting with blood glucose range of 150 to 180mg/dl. With this background we had hypothesized that strict glycemic control with blood glucose range of 80 to 110mg/dl would have a better outcome. Our primary endpoint was to check the safety of adopting strict glycemic protocol while secondary endpoints were to document efficacy of this protocol in terms of ICU and total hospital stay, septic complications and mortality compared to moderate glycemic control defined as 150 to 180 mg/dl.

MATERIAL AND METHODS

It was an interventional randomized trial , carried out from June 2009 to June 2011, in intensive care unit at department of Cardiac Surgery, National Institute Of Cardiovascular Diseases, Karachi . Non-probability Purposive sampling was done while randomization was achieved by envelop technique that was chosen by on-call resident . Primary endpoint of study was to document the safety of strict glycemic protocol in post CABG patients . Secondary endpoint was to observe the adverse outcomes defined as mortality , wound infection ,duration of ICU stay and total hospital stay . After getting approval from institutional ethical review Committee all diabetic patients who had CABG alone, without a concomitant procedure were included in this study. All non diabetics , failed PCI , acute evolving myocardial infarction, patient requiring mechanical cardiac support were excluded from study.

Patients were randomly divided in two groups; control group and study group. Intravenous insulin was used as a sliding scale or an infusion pump & insulin therapy stopped once blood sugar fall below 150mg/dl in control group . Blood sugar

PJC Vol 24, No. 3 & 4
July — December 2013

was checked every hour by glucometer strip or as part of arterial blood gases analysis report. In the Study group Insulin infusion pumps were used to control hyperglycemia. The Pump was only stopped once blood sugar fall below 80mg/dl. Infusion dose of insulin is shown in Table I.

TABLE-I: INSULIN REGIME USED IN ICU

Glucose range	Insulin infusion
250 mg/dl more	Inc by 3 units/h
200 to 250mg/dl	Inc by 2 unit/h
150 to 200mg/dl	5unit/hour
120 to 150mg/dl	4units/hour
80 to 120mg/dl	2units/hour
<80mg/dl	Repeat after 30 min

All the patients were operated with standard on- pump technique. All vessels with at least 60% stenoses were bypassed, and internal mammary artery was used to bypass left anterior descending artery whenever possible in each patient. Myocardial protection consisted of multiple infusions of antegrade, cold (4°C) blood, potassium (28 mEq/L), Hco_3, cardioplegia supplemented with moderate systemic (28 to 30°C) and topical (cold saline lavage at 4°C) hypothermia. Patients were shifted to ICU on ventilator support. Inotropic agents were used to maintain a systolic blood pressure of 90 mm Hg after afterload, preload, and heart rate were optimized. All patients were placed on standardized "fast-track" protocols for extubation.

Length of stay in the ICU was defined as time from ICU arrival to transfer to the floor or step-down unit. A stay of more than 72 hours was considered a prolonged stay. Before transfer, patients had to be extubated with stable vitals and without any inotropic support. Hospital length of stay was defined as the time from the date of surgery to the day of discharge. Criteria for discharge included a stable cardiac rhythm, temperature of 99°F, a well-healed incision, and oxygen saturations of 90% on room air or supplemental oxygen of 2 L. Superificial wound infection was defined as localized erythmia or superficial wound discharge. Deep infection was present when associated with sternal dehiscence.

RESULTS

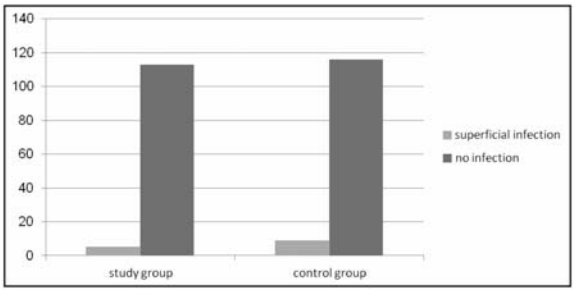
The baseline characteristics of patients at the time of admission to the ICU are listed in Table II.

TABLE-II: PREOPERATIVE VARIABLES

	Control group	Study Group
N	125	118
M:F	99:26	94:24
Age yrs	59+/ 7	61+/6
Hypertension	75	69
left main+ 3VD	37	37
EF% < 30%	33	37
EF% 30% TO 50%	49	59
EF% > 50	43	22
ELECTIVE	102	87
Urgent	23	34

All diabetic patients were on preoperative oral hypoglycemic agents. Patients with poorly controlled glycemic control were managed and optimized with insulin in the pre-operative period. However, this protocol could not be followed in patients undergoing urgent CABG. Urgent CABG was done in patients with left main disease.

FIGURE-I: INCIDENCE OF INFECTION IN THE TWO GROUPS



When comparing the ICU stay, total hospital stay and mortality, the difference was statistically insignificant. However, the incidence of infection was higher in the control group. Superficial infection defined as localized wound hyperemia or swelling or superficial discharge occurred in 9 (7%) patients in control group compared to 5(4%) patients in the study group. (Figure I)

TABLE-III: RESULTS

Outcome	Control group (n=125)	Study group (n=118)
Superficial infection	09 (7%)	05 (4%)
Deep infection	01	00
ICU STAY > 72h	0 4	03
Total hospital stay	09 days (+ -05 days)	08 days (+-03days)
Deaths	02	01
Hypoglycemic episode	00	05

Final outcome has been shown in Table III. Five patients of the study group required 25% D/W solution intravenously to manage the episodes of hypoglycemia.

DISCUSSION

Our results showed that strict glycemic control is relatively feasible to achieve normoglycemia. However this protocol has possible adverse results as shown in the study: 5 patients had episodes of hypoglycemia despite hourly sugar monitoring. None of these patients had any adverse sequeale and they were managed with 25% D/W solution. Hypoglycemia is a major concern with aggressive insulin administration in anesthetized and sedated patients who cannot report symptoms of low blood glucose. There are more chances of hypoglycemia post CPB-pump; as the patient continues to rewarm insulin resistance decreases, there is potential for hypoglycemia and aggressive insulin therapy makes these patient extremely vulnerable to hypokalemia associated arrhythmias. There was no significant difference in outcome when compared in terms of overall hospital stay and mortality. A significant difference was observed as regards superficial wound infection in control group (7%, much higher than that reported in litrature of 3.6 %[12]).

Cardiac surgery particularly with the use of hypothermic CPB is associated with metabolic derangements. Insulin resistance results from counter regulatory mechanisms invoked by the stress of surgery and hypothermia including increased plasma levels of glucagon, catecholamines, growth hormone, and cortisol[13]. This leads to decreased insulin stimulated skeletal muscle glycogen synthesis, which can mostly be attributed to decreased glucose transport (Glut 4) receptor sensitivity[14].

Trained nursing staff is a pre- requisite for control of serum glucose in post CPB pump cardiac surgical patients . This is important for regular monitoring of serum glucose levels and appropriate responses in case of any adverse sequeale. Patients with post operative serum blood glucose level more than 220mg/dl had more septic complications compared to better glycemic control[15]. Gandhi et al. failed to document any beneficial effect of strict glycemic control on the incidence of mortality, sternal infections, cardiac arrhythmias, prolonged ventilation, and renal failure in patients undergoing on-pump cardiac surgery. Although the mean blood glucose levels in their treatment group were significantly lower than in their control group, the mean blood glucose level of their treatment group did not reach the preset target of 80–100 mg/dL during surgery as well as in the ICU[16].

CONCLUSION

Strict glycemic control is not a superior tool when compared to moderate glycemic control as regards patient outcome. There is always the possibility of hypoglycemic episodes in post pump patients when managed with strict glycemic control.

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