CORONARY ARTERY BY PASS GRAFTING
EARLY MORBIDITY AND MORTALITY IN PATIENTS WITH TIGHT GLYCAEMIC CONTROL VERSUS STANDARD CONTROL

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ABSTRACT... Background: Several studies have suggested superiority of tight glycaemic control in reducing the incidence of surgical site infection and mortality after cardiac surgery. **Objective:** To compare the frequency of post operative surgical site infections after CABG in patients with tight glycamic control and those with standard glycamic control. **Setting:** Shaikh Zayed Hospital, Lahore. **Period:** June 2008 to March 2010. **Methods:** Total of 496 patients were included, they were randomized to tight glycaemic control group (TGC ,n =248) or standard control group(SC, n=248).In TGC group blood glucose was maintained between 90 – 130 mg/dl, while in SC group blood glucose was maintained between 131- 190mg/dl for 48 hours post surgery. Results were prospectively evaluated. **Results:** Demographic and surgical data was similar in both groups. Patients in TGC group showed significant reduction in post operative superficial sternal wound infection (4 vs 12 , $p < 0.05$) , deep sternal wound infection (1 vs 7, $p <0.05$) and leg wound infection (2vs 9, $p<0.05$).There was also non significant reduction in the incidence of post operative mediastinitis (1 vs 3), new myocardial infarction (2 vs 3),and atrial fibrillation (10 vs 12). Mortality was equal in both groups (1 in each). **Conclusions:** Significant reduction in SSI was observed in TGC group and no change was seen in other morbidities and short term mortality in the study.

Key words: Surgical site infection, Continuous insulin infusion, Glucose insulin potassium infusion

INTRODUCTION

Clinical benefits of long term tight glucose control has been demonstrated in diabetic patients in reduction of chronic complications such as retinopathy, neuropathy and nephropathy[1]. In recent years it is recognize that tight glucose control markedly improves early out come of hospitalized diabetic patients, including lower the risk of infection and death[2-7]. Lazer and colleague[5] showed reduction in atrial fibrillation and ischemia in post operative cardiac surgery patients. Out come benefits of tight glucose control in cardiac surgery patients, even in the absence of diabetes has been demonstrated[9-16].

Diabetic patients present specific challenge in post surgical period especially surgical site infections (SSI). It is well established that patients with diabetes mellitus (DM) are at increase risk of both surgical and nosocomial infection[17-19]. Infection rate has been quoted to be 2-5 times more prevalent in diabetic than in non diabetic populations[20].

In cardiac surgical patients, complications of infection has mortality as high as 14 percent[21-23]. Study published by Van der Burgh and coworkers[10] showed that tight glycaemic control with targeted blood glucose level between 80-110 mg/dl reduced one year mortality from 8 to 4.6 percent.

In a retrospective study, Zerr and colleagues[24] at the Portland Diabetic Project established that increased mean glucose levels for the first two days following cardiac surgery is an independent risk factor for deep sternal wound infection in diabetics. Improved glycaemic control decreased deep sternal wound infections from 2.4% to 1.5%.

A prospective study of 761 cardiac surgery patients showed not only that diabetics were at increased risk of wound infections but also that strict glucose control using an insulin infusion to maintain glucose between 120-160 mg/dl significantly reduced the risk of wound infection in diabetics[19].

This study was designed to compare the results of TGC

(90-120) and SC(131-190) and to see the outcome difference in terms of morbidity and mortality.

MATERIALS AND METHODS

This study was conducted in Shaikh Zayed Hospital from June 2008 to march 2010. All the patients undergoing CABG (coronary artery bypass grafting), were included. The patients undergoing combined CABG with valvular surgery, correction of congenital anomalies, and patients undergoing emergency operations were excluded. Total of 496 patients were included in the study. Two groups of the patients were formed, 1) tight glycaemic control (TGC) and 2) standard control (SC). Patients were randomized to each group on the basis of 496 serial numbers, issued prior to the commencement of the study. The study was approved by the ethical committee of our hospital. Written consent was taken from each patient. CABG was performed by the same surgical team.

Intra operatively blood glucose was monitored and intravenous bolus of insulin were given according to the set protocol. Continuous intravenous insulin infusion was not used during surgery. Repeated dozes of iv regular insulin were given at 20 minutes intervals pre CPB (Cardio Pulmonary Bypass) and during CPB to maintain blood glucose in target range. Initial IV bolus dozes are shown in the table I. In general, if the insulin sensitivity is unknown, it is assumed that 1 unit iv insulin decreases anesthetized patients blood glucose by 10 mg/dl. Therefore to lower the blood glucose from 250mg/dl to a target of 100mg/dl, 15 units of bolus IV insulin was given. Subsequently bolus dozes were given depending on individual patient's response to the previous dozes.

During 48 hours post cardiac surgery, blood glucose was maintained in the range of 90-130 mg/dl in TGC group while blood glucose of 131 – 190 was maintained in SC group. Blood glucose was measured at hourly intervals for the first 12 hours , 2 hourly for the next 12 hours and 4 hourly in the next 24 hours with the help of Dimension RX machine (venous blood) and "On Call Plus " glucometer (capillary blood).Blood glucose levels were checked more frequently if there was hypoglycemia , patients were administered 25 % DW and glucose was rechecked.

Table-I. Intra operative insulin bolus therapy

BG mg/dl	Insulin Bolus low (Units)	Insulin Bolus medium (Units)	Insulin Bolus high (units)
125-140	5	10	15
140-180	8	12	20
180-200	10	15	20
200-225	15	20	25
225-250	20	25	30
250-350	25	30	35

Table-II. Intensive care unit insulin protocol for TGC group

BG (mg/dl)	Infusion rate (units/hour)	Bolus (units)
110-125	1	1
126-150	2	2
151-200	3	3
201-250	5	5
251-350	10	10

Table II shows the ICU protocol that was used for TGC group. Table III shows the ICU protocol for insulin in SC group. glucose monitoring protocol is shown in table IV.

STATISTICAL ANALYSIS

Data was entered to SPSS version 14. Chi square test was applied to compare the occurrence of superficial and deep sternal and leg wound infections, mediastintis, atrial fibrillation, stroke, new myocardial infarction and mortality in both groups. P value< 0.05 was considered significant.

RESULTS

As shown in table V, significantly less number of patients in TGC group developed wound infections. 4 patients developed superficial wound infection in TGC group as compared to SC group were 12 patients developed superficial wound infection (p =0.046). 1 patient developed deep wound infection in TGC group as compared to 7 in the SC group (p= 0.034). 2 patients in

Table-III. ICU protocol for patients in standard control group

BG (mg/dl)	Infusion rate (units/hour)	Bolus
110-125	-	-
126-150	-	2
151-200	1	2
201-250	5	5
251-350	10	10

Table-IV. Monitor glucose hourly

BG (mg/dl)	Insulin infusion	Administer	Recheck BG
<60	Off	1 amp 25% DW	Every 30 mins
61-80	Stop infusion	-	Every hr
81-120	No change	-	Every hr
121-150	Increase 1 unit/hr	-	Every hr
151-200	Increase 2 unit/hr	Bolus 2 units	Every hr
201-250	Increase 2-3 unit/hr	Bolus 4 units	Every hr
251-300	Increase 3-4 unit/hr	Bolus 6 units	Every hr
301-400	Increase 4-5 unit/hr	Bolus 8 units	Every hr
>400	Consult DR	-	-

the TGC group developed leg wound infection as compared to 9 in the SC groups (p= 0.035).

Non significant difference was seen in occurrence of mediatinitis, atrial fibrillation, stroke, and new myocardial infarction. Mediatinitis was seen in 1 patient in TGC group and 3 patients in SC group. (p= 0.317). atrial fibrillation was seen in 10 patients in TGC group and 12 in SC group (p= 0.67). 2 patients developed stroke in TGC group and 1 in SC group (p = 0.54). Average of 423 minutes were spent on ventilator in TGC group in 437 minutes in SC group (p =0.63). 2 patients developed new myocardial infarction in TGC group as compared to 3 in SC group. (p =0.655).

Table-V. Results

	Tight glycamic control	Standard glycaemic control	X^2- value	P- value
Superficial wound infection	4	12	4	0.046
Deep wound infection	1	7	4.50	0.034
Mediastinitis	1	3	1.00	0.317
Leg wound infection	2	9	4.45	0.035
Sternal infection	1	2	0.33	0.564
Atrial fibrillation	10	12	0.18	0.670
Stroke	2	1	0.33	0.564
Time on ventilator (minutes)	423	437	0.23	0.6333
New myocardial infarction	2	3	.20	0.655
Mortality	1	1	0.000	1.000

DISCUSSION

A Cohort study of 411 patients undergoing coronary artery bypass graft surgery demonstrated a significant increase in the risk of developing infections including leg and sternal wound, urinary tract infections, and pneumonia when serum glucose levels were higher than 200mg/dl. Yet another retrospective study of diabetics undergoing CABG found not only poor glycamic control in their population , but also an increase in adverse outcome including sepsis and infection in the patients with elevated blood glucose within first 24 hours after surgery[25].

Although many investigators have elicited numerous details regarding the role of diabetes and impaired glucose control on post operative SSI, several questions remain unanswered , particularly regarding the use of continuous insulin infusion (CII). Although most studies of CII have been performed in cardiothoracic surgery population, it remains theoretically plausible that this strategy may be expanded to other surgical patients; however, special data on the use of CII use in these populations are lacking. Studies are still needed to define the optimal threshold of glucose control that apparently balances the reduced infection risk with the risk of hypoglycemia. The Portland group has progressively lowered the target range for use in their CII protocol, from 150 – 200 mg/dl on its onset to the most recently published level of 100 - 150 mg/dl, with conquest lowering of infection rate and mortality.

However the impact on other adverse outcomes related to reduced glucose targets is unclear. The specific solution used in CII has also been questioned.

Lazer at al have studied the use of potassium, glucose and insulin CII solution (GIK) given during and the 12 hours following CABG surgery in diabetic population. The hypothesis was that GIK, especially the insulin component, improves endothelial function, decrease vascular inflammation, and reduces thrombogenicity. They found fewer post operative wound infection and pneumonia in GIK treated group verses those who received subcutaneous insulin (0% vs 13 %, p =0.01). Of note, the target glucose levels for these studies was ranged from 120 -200 mg/dl while the vender Bergh studies , the targets were in the lower range of 80 -110 mg/dl.

Postoperative hypoglycemia may also increase infections in non diabetics cardiac patients. One prospective study of diabetic and non diabetic patients undergoing CABG, found that those non diabetics with postoperative hyperglycemia had an increased incidence of mediastinitis[26]. Thus postoperative glucose control may not only benefit the diabetics but also non diabetic patients. There is little data refuting the correlation of hyperglycemia and infection in cardiac surgery, however one large study in 2003 of 1574 patients , undergoing CABG did not find a statistically significant increase in surgical and nosocomial infections in the patients with post operative hyperglycaemia[27]. The author confirmed that the diabetes was associated with prolonged hospital stay. one important feature of the study was , large percentage of non diabetics (65%). Whether the non diabetic patients benefit from tight glycaemic control post operatively, is less certain. Despite of this study, majority of the investigators have shown improved infectious outcome with aggressive glucose control, with the data being stronger in diabetics.

While most of the studies demonstrate increase infection rate in cardiac surgery with elevated post operative hyperglycaemia , the evidence for improved outcome with intraoperative tight glucose control is less compelling. A retrospective study by Gandhi in 2005, found that increased mean intra operative blood glucose was not associated with post operative infection. A more recent study conducted by the same investigators, examined 400 diabetic and non diabetic cardiac surgery patients. They investigated tight intra operative blood glucose control (80-100mg/dl) versus treatment of intra operative glucose when levels exceed 200mg/dl[25]. Post operatively all patients received tight blood glucose control to maintain normoglycaemia. Though not adequately powered to detect differences in deep sternal wound infections, aggressive intra operative insulin therapy did not reduced the incidence of sternal wound infections. They found a statistically significant increased risk of stroke in the intensive glucose control groups.

When looking at long term glucose control, Hb A1C is used as a surrogate measure. Its accepted that HbA1C levels reflects average glucose levels over a time period of 90 days.

As illustrated above diabetes mellitus has an extensive impact on the development of post surgical wound infection after cardiac surgery. Fortunately, at least some degree of increased risk of SSI may be eliminated via a aggressive perioperative glucose control. As prevalence of Diabetes continues to climb, clinicians must remain vigilant and continue to identify patients with previous undiagnosed diabetes to regulate perioperative glucose levels tightly in both diabetic patients and hyperglycemic

non diabetic patients and to ensure optimization of any modifiable SSI risk factors.

A majority 57.2% of our patients were already on antihyperglycaemic agents before presenting to us. The rest were either unaware of their diagnosis or not compliant with their medications. Of those 57.2% only 21.4% had an optimal control of their blood glucose levels as demonstrated by Hb A1C levels.

Previously diagnosed patients required, on the average, greater amount of insulin compared with newly diagnosed patients or non diabetics. Our protocol included optimizing blood glucose levels before surgery.

This study sought to define the value below which the glucose levels results in the reduction in the variety of morbidities and short term mortality.

We found maintaining blood glucose levels <130 mg/dl, in first 48 hours after CABG, results in significant reduction in incidence of superficial sternal wound infection, deep sternal wound infection and leg wound infection.

There was no significant change in occurrence of sternal infection, stroke, atrial fibrillation, time spent on ventilator, mew myocardial infarction, and short term mortality.

The study was limited in time scale for long term effects. Further studies are required to define the effect of blood glucose levels on long term morbidity and mortality. Large scale multi center studies are needed before adoption of these results internationally.

CONCLUSIONS

This study concludes that there was significant reduction in the superficial, deep sternal and leg wound infection in the group with tight glycaemic control but no change in the incidence of other morbidities and short term mortality.

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