



EFFECT OF DIFFERENT PERIOPERATIVE GLYCEMIC PROTOCOLS IN NONDIABETIC PATIENTS UNDERGOING OPEN HEART SURGERY: A COMPARATIVE STUDY

Anaesthesiology

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ABSTRACT

Hyperglycemia during cardiac surgery is common due to stress response and cardiopulmonary bypass. Increased blood glucose is associated with poor outcomes, more complications and increased mortality in diabetic as well as nondiabetic patients due to negative effect on endothelial function, myocardium and inflammatory response. Perioperative blood glucose control and correct target value in cardiac surgery patients remain an ongoing controversy. This study was conducted to observe the effect of two different glycemic protocols in non-diabetic patients undergoing on pump cardiac surgery. A total of 102 nondiabetic patients were randomly distributed into two groups: Group A, Group B. After induction a continuous insulin infusion at the rate of 0.1 unit/kg/hr was started in both groups when blood glucose level (BGL) was $>140\text{mg/dl}$ in Group A and $>180\text{mg/dl}$ in Group B. The infusion rate was adjusted to maintain BGL at $120\text{--}140\text{mg/dl}$ in Group A and $160\text{--}180\text{mg/dl}$ in Group B. BGL was measured at different points of time. Perioperative effects, requirement of cardiac drugs, insulin used and infection related complications were assessed. Finally data of 100 patients were analyzed. Rate of deep sternal wound infection [Group A:B= 3(6.12%):4(7.84%)] and other infection related complications were similar in both the groups ($p>0.05$). Length of ICU stay was significantly longer in Group B than Group A ($p=0.013$). Perioperative infection rate in nondiabetic cardiac patients is not higher when target blood glucose level is $160\text{--}180\text{mg/dl}$ as compared to $120\text{--}140\text{mg/dl}$. Though length of ICU stay is less in lower blood glucose group; perioperative morbidities and 30day mortality is similar in both blood glucose range.

KEYWORDS

nondiabetic, hyperglycemia, cardiac surgery, deep sternal wound infection.

INTRODUCTION

Hyperglycemia during cardiac surgery is associated with poor outcomes, more complications and increased mortality, not only in diabetic patients but also in patients who are not previously diagnosed as diabetics. In long back, it has been established that hyperglycemia is an independent risk factor for postoperative surgical wound infection.^[1-3]

Stress response and cardiopulmonary bypass can induce profound hyperglycemia in cardiac surgery which provokes numerous deleterious effects on myocardium subjected to ischemia-reperfusion process. Myocardial infarct size is strongly correlated with blood glucose concentration.^[4] Hyperglycemia causes impaired glucose transport into the myocardium, leads to the formation of advanced glycation end products (AGE) and its cell surface receptor (RAGE).^[5] RAGE increases the inflammatory response by activating three key pro-inflammatory transcription factors which are normally suppressed by insulin: NF κ B (nuclear factor), AP-1 (activated protein), and EGR-1 (early growth response).^[6] Because hyperglycemia provokes coronary endothelial dysfunction^[7], it may further increase the incidence of myocardial ischemic events. Hyperglycemia also directly affects pathways responsible for changes in endothelial function, inflammation and oxidative stress by altering the polyol pathway and increasing the synthesis of diacylglycerol which activates protein kinase-C^[8]. The beneficial effects of glycemic control may be a decrease in concentration of free fatty acids and the scavenging of free radicals.^[9] Clinical trials have shown a reduction in morbidity with a lesser impact on mortality using tight blood glucose control.^[10] Though previously it was thought that tight glycemic control during cardiac surgery is associated with decreased infection rates and improved survival.^[11], benefit of tight blood glucose control have shown a negative impact on mortality due to hypoglycemia and contribute to the body of evidence disputing the need for tight blood glucose control^[12]. Due to such conflicting results of these recent trials, the target blood glucose range for cardiac surgery patients is still not clearly defined. It is still a question whether rigorous perioperative glycemic control reduces death and morbidity in cardiac surgery patients.

We shall compare the perioperative outcomes of two different glycemic protocols in non-diabetic patients undergoing on pump cardiac surgery.

MATERIAL AND METHODS

After obtaining the institutional ethics committee approval and written informed consent from all patients, the study was conducted.

Inclusion criteria: Non diabetic patient with NYHA $<IV$, 25-60 years scheduled for elective open heart surgery under cardiopulmonary bypass were included in this study.

Exclusion criteria:

Patients with Parsonnet score >10 , on chronic steroid therapy, diabetes mellitus, epilepsy, pregnant, hematological disease, impaired hepatic, renal function and aortic cross clamp time $>2\text{ h}$ were excluded from the study.

In the preanesthetic check-up, all patients were explained the procedure. All patients were instructed to follow the fasting guideline. Angiotensin-converting enzyme inhibitor was suspended the day before surgery. CCB and β -adrenergic blockers were continued till the morning of surgery. Patients of both the groups were premedicated with lorazepam 1 mg, ranitidine 150 mg, and metoclopramide 10 mg orally, the night before surgery. Patients were wheeled into operating room and standard ASA monitors (pulse oxymeter, NIBP till the IBP was done, ECG) were attached. Lactated Ringers' solution was started through an intravenous line with 18 G intravenous (iv) cannula at the anterior aspect of right dorsum or forearm. All patients received piperacillin and tazobactam intravenously (iv) (4.5 gm). Arterial cannulation was established in the left radial artery under local anaesthesia. Induction of Anaesthesia was done by IV inj of midazolam (0.01 mg/kg), fentanyl (2-3 $\mu\text{g/kg}$) and sleep dose of thiopentone sodium till loss of eyelash reflex.

Neuromuscular blockade was achieved by 1 mg/kg of rocuronium to facilitate rapid endotracheal intubation and intraoperative relaxation was maintained with rocuronium. The lungs were ventilated with nitrous oxide in oxygen (50: 50). End-tidal CO $_2$ was maintained between 35 and 40 mmHg throughout. Anaesthesia was maintained with isoflurane at 0.8–1.0 minimal alveolar concentration. Pulmonary artery catheterization and central venous cannulation were performed thereafter and surgery was started. All the drugs were repeated as bolus, before incision, before sternotomy and every 30 minutes interval. Baseline ABG and pre-heparin activated clotting time (ACT) were checked. In both groups blood glucose level was checked preoperatively and was evaluated after skin incision, after sternotomy, after cross clamp application, after cross clamp release and after return from CBP. Insulin infusion was started if any reading showed more value than the predetermined target blood glucose level. After starting of insulin infusion, blood glucose was checked at 30 minutes interval to maintain the target blood glucose range. ABG was done hourly to check acid base imbalance and electrolytes mainly K $^+$ level and corrected accordingly. Urine output was also monitored. Patients of

Group A received insulin infusion at the rate of 0.1unit/kg/hr when blood glucose level >140mg/dl and the dose of insulin infusion was adjusted to maintain the blood glucose level 120-140mg/dl. Group B received insulin infusion at the rate of 0.1unit/kg/hr while blood glucose level >180mg/dl and the dose of insulin infusion adjusted to maintain the blood glucose level 160-180mg/dl after induction of anaesthesia. All patients received the routine drugs of GA along with vasoactive drugs if required. The CPB circuit was primed with priming fluid Ringers' Injection and sodium bicarbonate, mannitol, and heparin. No dextrose containing fluid was used in the study. If any of the blood glucose value becomes <70 mg/dl, 25% dextrose solution was administered to the patient immediately. If two blood glucose reading >200 mg/dl even after increasing the dose of insulin infusion, it was considered as poor control. If consecutive three blood glucose level comes >200 mg/dl without responding to increasing insulin dose, it was considered as insulin resistance. Those patients were excluded from the study. Heparin (400 units/kg) was administered before aortic purse string to achieve an ACT of > 480s before commencement of cardiopulmonary bypass. Hematocrit was maintained at 25% during CPB. Mild to moderate hypothermia was initiated. Myocardial protection was achieved by antegrade cold cardioplegia (at 4°C, St. Thomas' solution-based crystalloid-blood cardioplegic solution PLEGIACARD as 1:4 ratio) after aortic cross clamp and the cardioplegia was repeated every 20 minutes. The cardiac repair or valve replacement was carried out under CPB with mild hypothermia using standard extracorporeal techniques. Nitroglycerine infusion 0.5µg/kg/min, adrenaline 0.05µg/kg/min and dopamine 5µg/kg/min were started at the onset of rewarming as per the institutional protocol. Infusion of milrinone, noradrenaline and amiodarone was also initiated according to the need to maintain mean arterial pressure >70mmHg, pulmonary artery pressure below 30mmHg and normal sinus rhythm. All the patients were rewarmed to 37°C. Serum potassium levels were optimized to 4-4.5 mEq/L throughout surgery. Ventricular fibrillation (VF) or ventricular tachycardia (VT) was treated with inj Xylocard (1.5mg/kg), MgSO₄ (2gm), amiodarone (3mg/kg) as appropriate and in cases refractory to medical management internal defibrillation with 20-50 J was administered. Protamine sulphate 1.3 times the heparin dose was given to reverse the effect of heparin and return the activated clotting time to within 20% of the preoperative value. At the end of surgery, patients were shifted to the intensive care unit (ICU). In the post-operative period, blood glucose was evaluated hourly for first 6 hours and then 2 hourly for next 18 hours. The adverse events like cardiac morbidity, new onset arrhythmia, hypoglycaemia, electrolyte imbalance, bleeding, infections, acute renal failure was noted and managed accordingly.

Statistics:

It was estimated that 49 subjects would be required per group in order to detect a reduction of one third in the frequency of infection assuming that the rate in the control group would be 36% on the basis of earlier study^[8]. This sample size was provided with 80% power and at 5% probability of type I error. Considering 10% drop out, we had included 110 patients (55 patients in each group) in this study.

Statistical Analysis was done using standard statistical software Statistica version 6 [Tulsa, Oklahoma: StatSoft Inc., 2001] and Graph Pad Prism version 5. Haemodynamic parameters and other variables normally distributed values were analysed by Student's unpaired t test. Mann-Whitney U test was used for variables which were not normally distributed. A p-value <0.05 was considered as statistically significant.

RESULTS

The study was conducted in 102 patients 51 in each group according to a computer generated randomization chart. Two patients in Group A were excluded because of aortic cross clamp time more than 2 hours. So, data of remaining 100 patients were finally analyzed [Group A (n=49), Group B (n=51)]. Postoperative infection rate in terms of deep sternal wound infection, UTI, sepsis, RTI, culture positive ETT tip, arterial catheter, CV catheter, pulmonary artery catheter, urinary catheter and positive sternal wound swab are found to be similar in both the groups (p>0.05) (Table 1).

Table 1	Group A (n=49)	Group B (n=51)	p value*
Deep sternal wound infection	3(6.12%)	4(7.84%)	1.000
UTI	1(2.04%)	2(3.92%)	1.000
Sepsis	2(4.08%)	3(5.88%)	1.000
RTI	5(10.20%)	5(9.80%)	1.000

Culture positive ETT tip	2(4.08%)	0(0.00%)	0.238
Culture positive arterial catheter tip	1(2.04%)	1(1.96%)	1.000
Culture positive central venous catheter tip	1(2.04%)	2(3.92%)	1.000
Culture positive pulmonary artery catheter tip	1(2.04%)	1(1.96%)	1.000
Culture positive sterna wound swab	3(6.12%)	4(7.84%)	1.000
Culture positive urinary catheter tip	1(2.04%)	2(3.92%)	1.000
Total requirement of insulin in unit	100.14±13.46	83.47±10.81	0.000

Values represent mean±SD. *p<0.05 is statistically significant. SD: Standard deviation.

In the intraoperative period blood glucose level was estimated after skin incision, after sternotomy, after CPB on, after Axcl on and off, after weaning of CPB. After skin incision blood glucose level was similar in both the groups (p=0.544). However, it was significantly high (p<0.05) in Group B throughout the intraoperative period to maintain the target glucose level as per protocol. Total requirement of insulin was significantly high in Group A (p=0.000) as compared to Group B to maintain predetermined blood glucose level. However, the incidence of hypoglycemia was not significant in between the groups. Only 2 patients (4.08%) in Group A and 1 patient (1.96%) in Group B suffered from hypoglycemia in the postoperative period which is neither statistically (p=0.614) nor clinically significant. Requirement of dopamine and other cardiac drugs are found to be similar (p>0.05) in both the groups as shown in. Length of ICU stay was significantly longer in Group B as compared to Group A (p=0.013) though duration of surgery and time for extubation were similar in both the groups (p>0.05).

DISCUSSION:

Post sternotomy mediastinitis and deep wound infection in cardiac surgery patients increases operative mortality two to threefold due to hyperglycemia^[13]. "Stress hyperglycemia" is exacerbated by factors specific to cardiopulmonary bypass including heparin administration, hypothermia and administration of glucose-containing cardioplegic solutions^[14]. Other factors include increased renal absorption of glucose, increased substrate availability in the form of lactate and decreased exogenous insulin activity^[15]. Perioperative hyperglycemia itself induces inflammation and expression of proinflammatory cytokines^[16]. We have selected continuous insulin infusion (CII) rather than intermittent bolus dose. CII provides better control of perioperative blood-glucose level in patients than does conventional intermittent injection of insulin. In 2006 Li JY and coworkers^[17] reported the advantages of continuous infusion as they found that on the 1st and 2nd postoperative days, the mean value for the CII group was significantly lower than that for the glucometer guided injection of insulin (GGI) group. In our study in Group A the requirement of total insulin was much higher (100.14±13.46 unit) as compared to Group B (83.47±10.81 unit) (p=0.000). This is because of relatively strict target blood glucose control (120-140mg/dl) in Group A than Group B (160-180mg/dl). This study shows that two different glycemic protocol has no significant effect on 30 days mortality (p=1.000) after open heart surgery. However the ICU stay was significantly less in Group A (p=0.013) as found previously in many studies with targeted predetermined intraoperative blood glucose levels with variable targeted blood sugar. There is a common consensus of many previously done studies that tight glycemic control has no proven benefit in cardiac surgery, but it in turn increases the episodes of perioperative hypoglycemia which increases the overall 30 day mortality.

Table 2	Group A(n=49)		p value*	U	Z
Duration of surgery(hour)	2456.00	2594.00	0.899	1231.00	-0.128
Time for extubation(hour)	2569.00	2480.00	0.899	1154.500	0.655
Length of ICU stay (day)	2114.500	2935.500	0.013	889.5	-2482

Values represent in sum. *p<0.05 is statistically significant.

Limitations of our study:

One of the most important limitations of our study is that we could not

measure the plasma concentration of insulin. Thereby patients may suffer from hyperinsulinemic normoglycemia which has adverse effect on neurocognitive function and can cause perioperative delirium

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