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Research Article

Effect of perioperative control of blood glucose level on patient's outcome after anesthesia for cardiac surgery

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KEYWORDS

Diabetes;
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Abstract *Background:* Blood glucose control is an important factor in improving outcome of diabetic patients undergoing cardiac surgery.
Objective: Is to estimate the relation between blood glucose control and perioperative outcomes in these patients.
Study design: Prospective cohort study.
Methods: One hundred diabetic patients undergoing cardiac surgery, were divided **equally** into group I (**control group**) in whom no tight glycemic control was done and group II (**study group**) in which tight glycemic control was done. Patients in the study group received intra-operatively an infusion of rapidly acting insulin according to a modified protocol to keep blood glucose level between 80 and 110 mg/dl and continued in the ICU until complete recovery from anesthesia. Patients in the control group followed the same protocol of insulin infusion only if their perioperative blood glucose level exceeded 180 mg/dl.

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Results: There was a rise of blood glucose level in the control group patients till the end of operations (mean level = 227 mg/dl). Mean blood glucose level before CPB was comparable in the two groups, but was significantly different after that until extubation. We reported three cases of delayed recovery in the control group compared to one case in the study group. We also recorded four cases of cardiac problems in group I compared to one case in group II ($P = 0.044$). There was statistically significant difference between groups regarding renal, neurological and surgical post-operative complications.

Conclusion: Tight glycemic control is recommended for better patient's outcome after cardiac anesthesia.

1. Introduction

Diabetes mellitus is a common metabolic and endocrine disorder among the Egyptian population. It represents an independent risk factor for morbidity and mortality in patients undergoing cardiac surgery [1,2]. The severity and duration of diabetes in the diabetic patient determines the severity of complications associated with diabetes such as diabetic peripheral neuropathy, renal dysfunction, fatty liver, optic neuropathy, accelerated atherosclerosis and hypertension. These pathophysiologic changes have their impact on the course of anesthesia and surgery specially cardiac surgery and cardiopulmonary bypass [3]. Studies showed that a fraction of non-diabetic patients were found to have glucose intolerance due to the stressful situation of anesthesia and cardiopulmonary bypass [4,5]. Recent studies showed that although tight euglycemic control has its beneficial effect on reducing neurological and infectious complications yet this was offset by the possibility of hypoglycemia which is more dangerous in case of general anesthesia in the short term view [6].

In a trial to improve the outcome of our practice of cardiac anesthesia and to decrease the length of hospital stay to reduce the costs, we conducted this bi-center study to investigate the value of continuous strict control of blood glucose level perioperatively on the patient's outcome and the incidence of complications whether anesthetic or surgical.

2. Patients and methods

This cohort study was done in Qena, and Mansoura university hospitals from January 2010 to may 2011. It was approved by the ethics committee of Qena and Mansoura faculties of medicine written informed consent was taken from all patients to share in the study. We conducted this study on 100 patients randomly assigned to two groups (50 patients in each group) according to a computer-generated allocation table (graph pad software) [7]. We included patients above 18 years old and below 60 years old: American Society of Anesthesiologists (ASA) classes II and III. Admitted for different cardiac surgical procedures and known to be diabetic. All patients whether insulin dependent or non insulin dependent (on oral hypoglycemic therapy) were shifted to insulin therapy using short acting insulin to control blood glucose (80–110 mg/dl fasting and up to 140 mg/dl random) 2 days before operation as a routine hospital protocol of pre-operative preparation of patients. We recognized diabetic patient if **fasting** (8 h fasting) blood glucose level above 140 mg/dl was measured pre-operatively even if the patient was not treated before surgery for control of high blood sugar (according to the consensus criteria) [8]. We also excluded patients with renal impairment (creatinine level more than 1.6 mg/dl) in whom hyperkalemia may be present that may require insulin – glucose for correction of hyperkalemia. We also excluded patients undergoing off-pump surgery.

The day before surgery, pre-operative evaluation of patients was done which included medical history, clinical examination, chest X-ray examination, ECG, data of cardiac catheterization, echocardiography and laboratory investigations (complete blood count, bleeding time, clotting time, prothrombin time, partial thromboplastin time, blood sugar, Hemoglobin A1c, liver function tests, renal function tests, and urine analysis. Then the study protocol was explained to every patient and consent was taken from him or her.

The **anesthetic technique** was the same for all patients in the study, starting by pre-operative re-examination of the patient, and re-checking his file.

On arrival to the operating room, in the ***fasting*** patient a venous cannula (22 Gauge) was inserted in the non-dominant forearm under complete aseptic technique and 1–2 mg midazolam was injected through it. The non-dominant radial artery cannulation is performed under local anesthesia using lidocaine 2% after doing modified Allen's test, followed by insertion of thoracic epidural catheter with injection of 2–5 mg morphine∗ [***What were the criteria on which epidural morphine dose range (2–5 mg) based?***] (this is from our current practice and clinical experience, variation according to body weight, height, general condition and pre-operative echocardiography data of each patient) diluted with sterile saline solution to 10 ml volume. The patient was put in the sitting position, the anesthetist wearing sterile gloves painted the patient's back with antiseptic solution, the site of epidural needle entry (midline – at the level of the line joining the lower angle of the two scapulae) was infiltrated with 2 ml lidocaine 2% using sterile fine needle of insulin syringe (least painfull) before advancing the epidural needle with loss of resistance test applied till reaching the epidural space.

We gave IV fentanyl at a dose 5-μg/kg, this dose is reduced because patients received thoracic epidural morphine pre-induction of anesthesia, we gave half the dose at induction and a quarter at skin incision and the last quarter before sternotomy. We induced anesthesia with 1–2 mg/kg propofol followed by 0.5 mg/kg atracurium intravenously. After intubation, patients were mechanically ventilated through volume-controlled ventilation with 100% O_2 to maintain the end-tidal

CO_2 at 30–35 mmHg. We continued with isoflurane 0.5–1% (aided by the epidural morphine) and proceeded for central line cannulation of the right internal jugular vein with a 2-way CVP catheter.

2.1. Monitoring

During all procedures, HR, rhythm and computerized ST segment analysis were monitored, pulse oximetry, capnography, CVP, continuous arterial blood pressure (using NIHON KOHDEN monitor – Japan) and activated clotting time (ACT) using hemochron 801 apparatus. Urine output was monitored via urinary catheter. Skin and nasopharyngeal temperature was continuously monitored with thermoster probe.

2.2. Surgical technique

The heart was approached through a standard median sternotomy in all patients. Heparin 300–400 IU/kg was administered i.v. then the ascending aorta, SVC and IVC were cannulated. Cardiopulmonary bypass (CPB) was started when the activated clotting time (ACT) reached more than 400 seconds using a non-pulsatile pump flow rate of 2–2.5 l/m^2/min. Moderate hemodilution with a crystalloid prime and moderate systemic hypothermia (to a lowest temperature of 28 °C) were used. After aortic cross clamping, myocardial protection was achieved with intermittent antegrade cold blood cardioplegia through the aortic root till cardiac arrest occurred and repeated every 25–30 min or on the return of electrical activity of the heart. Myocardial cooling using packed iced saline was done. Hematocrit concentration (HCT) was maintained between 20% and 25%, with addition of blood as necessary. Patients were actively rewarmed to 38 °C before removal of the aortic cross-clamp. Separation from CPB was accomplished with i.v. epinephrine 50–100 ng/kg/min or dobutamine (5–10 μg/kg/min) according to the anesthesiologist managing the case. Heparinization was reversed with an initial dose of i.v. protamine sulfate (0.8–1 mg for 100 IU of heparin administered). An additional dose of 0.5–1 mg/kg of protamine sulfate was given when the ACT remained above 140 s.

Cardiopulmonary bypass was handled by a perfusionist as appropriate with cooperation of the anesthesia team. Serial arterial blood gas analysis and activated clotting time are done as appropriate.

How frequent were you measuring blood sugar in both groups?

Blood glucose was measured (venous blood samples withdrawn and sent to the hospital lab for blood glucose level) just before induction of anesthesia, before skin incision, before initiation of cardio-pulmonary by-pass, every 20 min after start of by-pass till the patient was transferred to the intensive care unit where blood glucose level is measured every 2 h until extubation is done. After extubation blood glucose was monitored every 4 h routinely.

How was blood sugar managed in the control group?

In the control group (group I) no insulin was given to the patient unless blood glucose level exceeded 180 mg/dl. If so, we initiated an infusion of rapidly acting insulin (act rapid) in saline of 6–9 units/h using syringe pump and adjusted the rate of infusion to keep glucose level between 110 and 180 mg/dl [8,9].

While in the study group (group II) where tight glycemic control of glucose level between 80 and 110 mg/dl was targeted we gave a continuous infusion of insulin in saline (50 units of rapidly acting insulin (act rapid) in 50 ml syringe) at a rate of 1–2 units/h if blood glucose between 110 and 150 mg/dl. If blood glucose level was between 150 and 200 mg/dl we increased the rate of insulin infusion to 4–6 units/h. And if it exceeded 200 mg/dl then the insulin infusion rate was 6–9 units/h [from where you got this IV insulin dose 6–9 units/h? I guess from Ref. #9] [this insulin infusion protocol was modified from Cammu et al. [9]].

Post-operative care was standardized for all patients and included epidural morphine (2–3 mg every 8 h) and i.v. midazolam for sedation prior to tracheal extubation when hypertension, tachycardia and/or excessive patient movement occurred. Midazolam was given (increments of 1–2 mg). Sedation was maintained until normothermia, hemodynamic stability and minimal chest tube drainage then extubation was done. The criteria for extubation included normal neurologic status (Glasgow coma scale above 13), stable hemodynamics under minimal inotropic support (< 5 μg/kg/min dopamine or dobutamine and < 50 ng/kg/min epinephrine), adequate pulmonary function (spontaneous ventilation with SIMV for a minimum of 30 min (exhaled tidal volume 6–10 ml/kg), respiratory rate between 12 and 20 breaths/min, $PaCO_2 < 50$ mmHg, pH $>$ 7.3, $PaO_2 > 75$ mmHg on $FiO_2 < 40\%$), normothermia, adequate urine output and minimal chest tube drainage (< 50 ml/h). After extubation, oxygen was delivered to patients through nasal cannula 2–4 ml/min for 24 h. ICU discharge criteria included patient orientation, hemodynamic stability without inotropic or vasoactive drugs, $SaO_2 > 90\%$ on $FiO_2 < 0.5$, no uncontrolled arrhythmia, urine output $\geqslant 0.5$ ml/kg/h. Chest tube, CVP and arterial lines were removed before transfer to the ward.

We followed our patients in the ICU for immediate and delayed post-operative problems including pulmonary complications such as pneumothorax, atelectasis and pleural effusion (by serial X-ray chest examinations).

Neurological complications were also recorded, as well as renal dysfunction diagnosed by any increase of creatinine concentration more than 2 mg/dl.

Surgical bleeding was confirmed if it exceeds 200 ml/h or 1000 ml/day. Infection was diagnosed by lecuocytosis or positive culture of: blood, mediastinal or pleural fluid or urine or discharge from the wound.

Were you able to follow all the 100 patients for 6 months?

All patients were followed up for 6 months for each case using a follow up card through post-operative visits (a weekly visit to the cardiac surgery outpatient clinic in the two surgery departments in Qena and Mansoura or a telephone call contact along 6 months), and data collected from the surgeons [You did not mention the mortality rate if any?], and there were ***no recorded mortality*** nor morbidity other than mentioned in the results.

2.3. Statistical analysis

Sample size calculation was done using online power/sample size calculator (http://www.stat.ubc.ca), we assumed the incidence of adverse events to be 35% according to previously published data [10] and we tested for the frequency of adverse events of 20% considering $\alpha = 0.05$ and power of 0.8, this re-

quired 50 patients in each group. We used SPSS version 16 for statistical analysis, categorical data were compared between the two groups by Chi Square test, parametric data were compared between the two groups by un-paired *t*-test. Mann–Whitney test was used for non-parametric data. Results were considered significant if *P* value less than 0.05.

3. Results

This study was done on 100 patients admitted for different cardiac surgical procedures not involving off-pump surgery. Patients were divided into two groups 50 patients in each group, In group I no tight glycemic control was done, In group II tight glycemic control was done. Patient's characteristics were comparable in the two groups. We had two patients in group I and 1 patient in group II with **history** of myocardial infarction. We had also five patients in group I and six patients in group II on treatment for hypertension. No statistically significant difference was found regarding mean CPB time and length of hospital stay, Table 1.

The total number of cases with complications in the control group was 21 and was seven cases in the study group, this was statistically significant.

Mean blood glucose level before induction of anesthesia and before start of CPB was comparable, but after CPB there was statistically significant difference between the two groups at all measurement points until extubation, Fig. 1.

Delayed recovery (extubation done in the next day of operation) was recorded in three cases in group I (6%) and one case (2%) in group II, these cases required inotropic support for more than 6 h post-operatively and extubation was performed on the second day of operation (after 18 h of intubation). We found statistically significant difference between the two groups (Table 2).

In group I there was four cases (8%) in whom **cardiac problems** were reported in the form of return of atrial fibrillation, in group II we have seen one case of atrial fibrillation and the other suffered from acute myocardial infarction. We found no significant difference between the two groups.

We recorded **pulmonary problems** in five cases in group I (10%) and 2 cases (4%) in group II. Prolonged bronchospasm occurred in three cases in group I, pneumothorax was found in the two cases in group II, bronchitis was recorded in two cases in group I. We found no significant difference between the two groups.

Elevated serum **creatinine** was reported in three cases (6%) in group I compared to one case (2%) in group II (measured the second day of operation). This was statistically significant.

We recorded two cases of post-operative **delirium** and one case of **stroke** 4 days after operation. No neurological complications were recorded in group II. This was statistically significant difference.

Surgically we had three cases (6%) of re-do operation for bleeding in group I and one case in group II (2%) (Table 2). Again we found statistically significant difference between the two groups.

4. Discussion

We conducted this study to investigate the effect of blood glucose level on the course and outcome of cardiac anesthesia and surgery. We put in mind how to improve outcome and decrease

Table 1 Patient's characteristics.

Variable	Group I no = 50	Group II no = 50	*P* value
Age in years	49 ± 8	46 ± 9	0.24
Weight in kg	86 ± 2	83 ± 4	0.33
Height in cm	169 ± 4	167 ± 2	0.09
Body mass index	26 ± 2	28 ± 0.8	0.88
Sex (male/female)	35/15	30/20	0.06
Pre-op. blood glucose level	155 ± 23	147 ± 15	0.07
Length of hospital stay (h)	88 ± 5	83 ± 3	0.078
1-History of:			
Smoking	20 ± 2	17 ± 5	0.07
Hypertension	5	6	0.07
CAD	12	13	0.06
MI	2	1	0.051
LVEF %	52 ± 4	57 ± 7	0.04
AF	4	3	0.12
COPD	3	1	0.048
Stroke	2	-	–
Renal impairment	1	3	0.022
2-type of operation:			
CABG	12	13	0.06
ASD repair	15	17	0.44
Mitral valve replacement	23	20	0.23
3-*Cardio-pulmonary bypass time*-minutes	55 ± 16	59 ± 11	0.66

CAD = coronary artery disease, MI = Myocardial infarction, LVEF = left ventricular ejection fraction, AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, CABG = coronary artery by-pass graft, ASD = atrial septal defect.
Data are expressed as mean ± standard deviation (SD) or number.

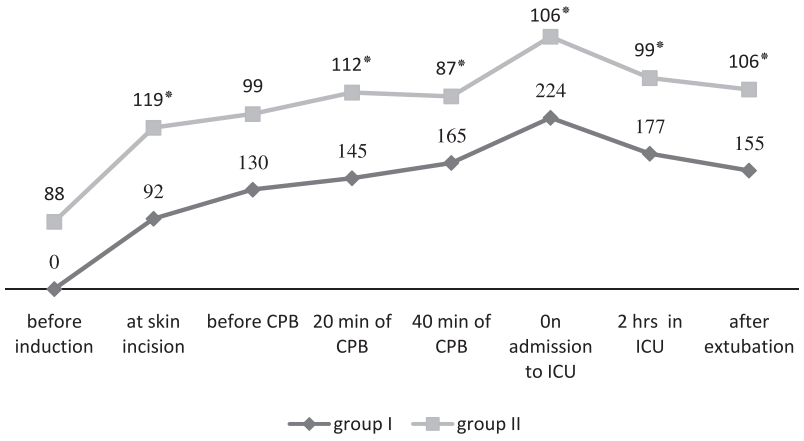

Figure 1 Mean blood glucose level in the two groups (mg/dl). Group I: control group. Group II: tight control group. * = *P* value > 0.05.

Table 2 Post-operative events and complications in the two groups.

Post-operative events	Group I $n = 50$	Group II $n = 50$	*P* value
Delayed recovery	3 Cases	1 Case	0.039*
Pulmonary problems	5 Cases	2 Cases	0.92
Cardiac problems	4 Cases	2 Cases	0.44
Renal problems	3 Cases	1 Case	0.04*
Neurological problems	3 Cases	0	0.032*
Surgical problems	3 Cases	1 Case	0.033*
Total number of cases	21 Cases	7 Cases	0.034*

* = Statistically significant = *P* value < 0.05.

the incidence of peri-operative complications that would result at the end in reduction of length of hospital stay and decrease the cost of these operations both for the hospital and the patient.

Hyperglycemia is considered an important risk factor that contributes to intra and post-operative complications such as infection e.g. wound infection, urinary tract infection, or septicemia [11]. It can be blamed also for the occurrence of stroke, prolonged mechanical ventilation, heart block, cardiac arrest and even death [12].

It has been shown that hyperglycemia is a leading cause for the formation of abnormal proteins through non-enzymatic glycosylation that worsens neurological injury after focal and global cerebral ischemia through anaerobic transformation of glucose to lactate which impairs cellular metabolism [6].

We used insulin infusion in both groups according to a modified protocol [9] but we did not give insulin in the control group unless blood glucose level exceeded 200 mg/dl for patient safety. This occurred early in the ICU at the end of operation, otherwise we did our best to control blood glucose level in the study group between 80 and 110 mg/dl.

It seems from the data you submitted that patients in gp 2 had a significantly better myocardial function and less of pulmonary dysfunction, do you think this impacted on their post-operative course?

The results of follow up of the patients in the two groups showed no statistically significant difference regarding cardiac and pulmonary problems (patients in the study group showed better myocardial and pulmonary functions which was reflected on the post-operative course, while renal, neurological, and surgical problems showed statistically significant difference between the two groups. This is most probably due to the fact that cardio-respiratory problems are more related to the nature of surgical intervention and the mean cardio-pulmonary by-pass time (CPB) that were comparable in the two groups. The delayed recovery that was recorded in the two groups was statistically significant. It was associated with hemodilution and prolonged mechanical ventilation. These results support our assumption that tight glycemic control is beneficial for reduction of post-operative complications regarding neurological, renal and surgical events but it did not differ much regarding cardiopulmonary complications.

What helped us in controlling blood glucose level during operation is that we completely avoided glucose-containing solutions and insulin was diluted in normal saline in contrast to what Azarfarin et al. [13] has done; they gave dextrose 5% solutions and left the surgeon to give dextrose 5% solution in the post-operative period because they wanted to avoid hypoglycemia. However they reported at least one attack of hyperglycemia (above 180 mg/dl) in 55% of non-diabetic patients during the first 24 h after CABG surgery.

We have a number of published studies about the role of blood glucose level control in improving outcome and reducing morbidity after cardiac surgery. Chaney et al. in 1999 [6] reported that the attempt to control blood glucose level carries the risk of hypoglycemia, this finding was not found in our study and on the contrary we found an attempt of blood glucose to rise in the two groups specially during CPB period and in the ICU.

Gandhi et al. [1] found a relation between adverse events and intra-operative glucose concentrations. They reported that for each 20 mg/dl increase in blood glucose level above 100 mg/dl there is 34% increase in the incidence of post-operative complications. In our study the total number of cases with complications was significantly different in the two groups suggesting a strong relation between blood glucose level control and the occurrence of complications though we did not evaluate this relation as Gandhi et al. did.

Another study done by Estrada et al. [11] on diabetic and non-diabetic patients found no difference between diabetic and non-diabetic regarding morbidity and mortality but at the same time they found that diabetic patients stay longer time in the ICU if their blood glucose level was not controlled. In our study no difference was found between the two groups as all our patients were diabetic and although there was statistically significant difference regarding morbidity yet the overall mortality was not different.

Arabi et al. [14]conducted one of the few studies on intensive insulin therapy for patients in medical and surgical ICU and they reported no improvement in survival and that intensive insulin therapy was associated with increased risk of hypoglycemia. This is not in agreement with our study as we did not find any case of hypoglycemia in all patients in the two groups although we followed a protocol to strictly keep blood glucose level between 80 and 110 mg/dl in the study group.

Azarfarin et al. in 2011 [15] studied the effect of blood glucose control in non-diabetic patients undergoing CABG surgery, they found that blood glucose level is increased in these patients though they were not diabetic pre-operatively and that controlling blood glucose level in the study group between 110 and 126 mg/dl is required as it decreased the incidence of complications from 32% in the control group to 16% in the study group. In our study all patients in the two groups were diabetic and we evaluated the effect of blood glucose control on patient's outcome, it can be considered as a continuation of the study of Azarfarin as we found that blood glucose control is essential in diabetic patients as Azarfarin found this control essential for non-diabetic patients.

In conclusion we found that intra-operative tight glycemic control is more beneficial than wide glycemic control in diabetic patients subjected to open heart surgery for decreasing the incidence of post-operative complications as regard to recovery criteria, renal, and neurological complications. However, there was no effect on length of hospital stay between both regimens.

Recommendation: We think that long term follow up on a wider scale of patients may be needed to assure this regimen as standard protocol in cardiac anesthesia of diabetic patients with no fear of hypoglycemia if close monitoring of blood glucose level is done to maintain eu-glycemic stability.

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