Adjusted tight control blood glucose management in diabetic patients undergoing on pump coronary artery bypass graft. A randomized clinical trial

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Abstract

Background Many of the patients who are undergoing Coronary Artery Bypass Graft have diabetes mellitus or metabolic syndrome and are at risk for hyperglycemia events.

Objective The present study aimed to compare conventional glucose control with adjusted tight control in patients undergoing on-pump CABG.

Methods This double –blind randomized clinical trial study was conducted in Shiraz, Iran, from September 2017–March 2018. Two consecutive groups of 75 patients undergoing elective on- pump coronary artery bypass graft surgery.

Intervention The patients were divided into adjusted tight control of the blood glucose between 100 and 120 mg/dl and conventional method that the blood glucose maintained ≤ 200 mg/dl.

Primary outcomes were mortality, sternal wound infection, cardiac arrhythmia, cerebrovascular attack, and acute renal failure.

Secondary outcomes included duration of mechanical ventilation and length of ICU staying. The same main outcomes were evaluated after one month.

Statistical analysis The data were analyzed using SPSS version 20(SPSS, Chicago, IL). Group comparisons were performed using t-tests and Chi-square tests. Repeated measurement test was used for comparing blood glucose in two groups. Mann Whitney U test was compared duration of the mechanical ventilation and length of ICU staying. Statistical significance was defined as a p value < 0.05 .

Results There were no significant differences between main and secondary outcomes. About late outcomes, sternal wound infection was in the control group (7 patients) more than intervention (1 patient) ($P < 0.05$). No differences between other complications in both groups were observed. The occurrence of hypoglycemia was low in both groups. Hypokalemia was significantly higher in the intervention than in control ($P < 0.001$).

Conclusions The findings showed using adjusted tight glycemic control to a level that is nearby to normal values during cardiac surgery may reduce episodes of hypoglycemia and thus reduces its side effects. As well as reduce hyperglycemic complications such as sternal wound infection.

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Keywords Cardiac surgery · Diabetes · Tight control of glucose · Critically ill patient

Abbreviations

CABG	Coronary Artery Bypass Graft
CVA	cerebrovascular accident
TIA	transient ischemic attacks
MDAS	Memorial Delirium Assessment Scale
BS	Blood glucose
AF	Atrial Fibrillation

Introduction

About 30–40% of patients who are undergoing Coronary Artery Bypass Graft (CABG) have diabetes mellitus or metabolic syndrome and are at risk for hyperglycemia events [1]. The incidence of coronary artery disease is greater in diabetic patients [2]. Furthermore, impaired platelet function, fibrinolytic and impaired endothelial function is more common in these patients which leads to less graft patency, increased pre-operative mortality, and reduced short and long term postoperative survival [2].

Diabetes is a common life-long healthiness condition and the most important risk factor for coronary artery disease. Newest estimates show an overall incidence of 382 million in 2013, with a predictable rise to 592 million by 2035 [3]. Average yearly increases in insulin-dependent Diabetes of 3% global and 4% in Europe are described. In the Islamic Republic of Iran incidence of diabetes, 7% to 8% are described [4]. Currently, 3.2 million people diagnosed with Diabetes, while another 630,000 remain undiagnosed [3]. Due to the slow onset of non-insulin dependent Diabetes, and long pre-detection period, up to one-half of cases may be undiagnosed. Hyperglycaemia and uncontrolled glucose is a major cause of disrupting the cellular metabolism due to the formation of abnormal proteins through non-enzymatic glycosylation, thus that increases the duration of hospital stay and costs [5]. Hyperglycemia is important in determining the outcome of the acute coronary syndrome in diabetic and non-diabetic patients [6].

Insulin acts as an anti-inflammatory agent by inhibiting pro-inflammatory factors and reduces inflammatory mediators [7].

Tight control of blood glucose is a method for reduced of hyperglycemia side effects [8]. This method can lead to hypoglycemia; that may be associated with neurological damage [9, 10]. According to some other studies, this method cannot improve the outcome after cardiac surgery [11, 12]. Adjusted tight control method has been proposed as a method to overcome this limitation.

Objective The present study aimed to compare conventional glucose control with adjusted tight control in patients undergoing on-pump CABG.

Methods

Study population

This double-blind randomized clinical trial study was conducted in from Shahid Faghihi Hospital, Shiraz, Iran, from September 2017–March 2018 (Ethics code: 91-01-60-5268).

Two consecutive groups of 75 patients undergoing elective on-pump coronary artery bypass graft surgery.

Setting and patients

Inclusion criteria Non-insulin dependent diabetic patients, aged 18–70 years with ASA II–III, Ejection Fraction $\geq 30\%$, undergoing elective CABG.

Exclusion criteria included Ketoacidosis or hyperosmolar coma, Redo surgery, history of cerebrovascular accident (CVA) or transient ischemic attacks (TIA), liver or kidney disease.

Randomization Randomization was performed using a computer-generated random digits to ensure that patients and investigators were blind to the treatment assignment before study entry; and the allocation was done 1:1 to receive either adjusted tight control of the blood glucose or conventional. Randomization was not performed until electronically confirming the eligibility criteria in the web-based case report form. Randomization was performed centrally without stratification. The sequence was generated by an independent statistician using a random number generator with a 1:1 allocation using random block sizes of 2.

Sample size The study population consisted of 75 patients. Based on the previous data and according to complication of tight glycemic glucose [13] the study required a sample size of 30 patients per intervention group to provide the statistical power of 90% with a two-sided significance level of 0.05. However, we increased our sample size to 37 patients in each study group to accommodate any withdrawal or missing data points.

Assessments After arrival to the operation room, standard monitoring included five-lead electrocardiography, pulse oximetry and arterial line for continuous blood pressure monitoring and blood gases were inserted. After induction of general anesthesia, a central venous catheter was introduced, and baseline BS (via an Accu-check Active glucometer Roche, Germany) was checked. General anesthesia was induced and therefore the patients were randomly allocated into two groups: adjusted tight glycemic regimen (intervention group), and conventional (control group).

Interventions

In the intervention group, if the BS ≥ 120 mg/dl, an infusion of 50 units of regular insulin in 50 ml saline was started in order to maintain blood glucose between 100 and 120 mg/dl. Insulin dose was adjusted according to the method described by Gandhi GY [11]. In control group if blood glucose was

≥ 200 mg/dl, patients were treated with insulin as follows: If BS was 200–250 mg/dl, 4 units/h will be administered until the blood glucose reached to 200 mg/dl. If blood glucose was greater than 250 mg/dl, 4 units/h began and continued until blood glucose became less than 150 mg/dl, and maintained ≤ 200 mg/dl (Insulin dose was adjusted according to the method described by Gandhi [11]).

The dose and type of inotropes during weaning from CPB were recorded. In both groups, blood glucose was measured every 30 min until the end of the surgery. Insulin infusion in intervention group of patients was discontinued the end of surgery. ICU glycemic controls in both groups were performed by conventional method and BS level was maintained ≤ 200 mg/dl as the protocol used in the operation room in the control group. In the ICU blood glucose was checked every 2 h until 20 h after the operation. During this period, subcutaneous insulin or oral anti-diabetes medication were not prescribed. The insulin administration protocol was discontinued 24 h after surgery in both groups.

Primary outcomes Mortality, sternal wound infection, cardiac arrhythmia, cerebrovascular attack and acute renal failure (as identified by; two-fold increase in baseline creatinine).

Secondary outcomes Duration of mechanical ventilation and length of ICU staying.

Adverse events Occurrence of hypoglycemia (blood glucose less than 60 mg/dl that need to treated), hypokalemia (serum potassium less than 3 meq/dl, that were corrected with Kcl based on deficit, and re-check) and delirium based on Memorial Delirium Assessment Scale (MDAS) were noted. Outcomes were determined by physician of ICU that was unaware of the protocol 30 days after discharge, patients were visited by the surgeon and adverse events (the same as the primary outcomes) were recorded.

Statistical analysis

The data were analyzed using SPSS version 20 (SPSS, Chicago, IL). Group comparisons were performed using t-tests and Chi-square tests. Repeated measurement test was used for comparing blood glucose in two groups. Mann Whitney U test was compared duration of the mechanical ventilation and length of ICU staying. Statistical significance was defined as a p value < 0.05 .

Results

During the study period from September 2017–March 2018, 200 patients undergoing elective CABG were

eligible to participate in the trial. After initial screening, 120 patients agreed to participate and provided informed consent. They were randomly assigned to adjusted tight control blood glucose ($n = 60$) or conventional treatment ($n = 60$). Among them, 5 patients did not have inclusion criteria. We excluded 15 randomly assigned patients (8 in the adjusted tight control blood glucose group and 7 in the conventional treatment group) from the final intention-to-treat analyses (see statistical analysis) because their glucose levels were less than 100 mg/dL during surgery. We withdrew 5 patients in each group after randomization because surgery was canceled. Among the patients who received study interventions, 7 of 45 patients in the adjusted tight control blood glucose group and 8 of 45 patients in the conventional treatment group were lost to follow-up after being discharged from the hospital. Because we do not have follow-up data on these patients, we could not include them in our primary efficacy analyses.

Finally, of the patients, 75 patients were enrolled in the study that included in two groups adjusted tight control blood glucose and conventional). (Fig. 1).

There were no significant differences between them in terms of demographic characteristics including age, weight, preoperative blood glucose, ejection fraction, duration of the surgery and requiring for inotropic support ($P > 0.05$) (Table 1).

Although the trend of change in blood glucose during surgery was not significantly different between groups, BS measurement showed a significant difference at different times ($P < 0.001$, Fig. 2).

Blood glucose level did not differ between the two groups in the ICU, but measuring the BS during several hours showed a significant difference ($P < 0.001$, Fig. 3).

Primary outcomes

During the ICU stay, no significant different about; mortality rate, sternal wound infection, cardiac arrhythmia, stroke, acute renal failure were observed between groups (Table 2).

Secondary outcomes Two parameters of the duration of mechanical ventilation and length of ICU stay were compared in the two groups by Mann Whitney U test. The median duration of mechanical ventilation in the intervention group was 7.5 h versus 8 h in the control group (mean rank 35.95 versus 40.11 $p = 0.40$). Median ICU staying in the intervention group was 2 days versus 2 days in the control group (mean rank 34.46 versus 41.64 $p = 0.07$) that do not sign.

Late outcomes: Except for significant sternal wound infection [7 cases in control group versus 1 case in the intervention

Fig. 1 Flow chart of study inclusion criteria

($P < 0.05$)] no differences between other complications in both groups were observed (Table 3).

Adverse events The occurrence of hypoglycemia was low in both groups (one patient in each group). Hypokalemia was significantly higher in the intervention than in control (34

versus 8 $P < 0.001$). The lower number of AF rhythm was seen in the intervention group (4 cases in the intervention vs 5 cases in the control group but did not significant), and lower incidences of sinus tachycardia than in control groups was shown. Delirium was higher in the intervention group than control but did not sign. (8 versus 6 $P > 0.05$).

Table 1 Baseline data of patients in two groups

	Intervention (n = 38)	Control (n = 37)	P
Age, mean $\pm$ SD (Year)	10.77 $\pm$ 58.18	8.91 $\pm$ 59.18	0.66
Gender male/female (%)	(44)17	(35)13	0.56
Weight, mean $\pm$ SD (kg)	12.65 $\pm$ 65.55	9.85 $\pm$ 66.13	0.82
Preoperative BS, mean $\pm$ SD (mg/dl)	81.04 $\pm$ 190.68	80.47 $\pm$ 192.41	0.92
EF, mean $\pm$ SD (%)	9.94 $\pm$ 51.05	8.30 $\pm$ 50.02	0.63
History of MI, N (%)	(47)18	(32) 12	0.18
Duration of Aortic cross-clamp time(min), mean $\pm$ SD(min)	55.11 $\pm$ 38.61	49.47 $\pm$ 30.73	0.09

SD Standard deviation; BS Blood sugar; EF Ejection Fraction; MI Myocardial Infarction

Fig. 2 Comparison of trend of changes in the mean $\pm$ SD of the blood glucose levels in patients during surgery between two groups. * mean significant differences ($P < 0.001$)

Discussion

Tight control of blood glucose can cause a further lowering of blood glucose during surgery. Therefore, we decided to keep BS in the range of 100–120 mg/dl (adjusted tight glycemic control) to avoid hypoglycemia and its complications; in addition to the benefit of maintaining normal intraoperative blood glucose range. In contrast to the previous studies that intraoperative tight glucose control can be reduced the complications, the our results showed that the early postoperative complications (sternal wound infection, Atrial fibrillation, cardiac complications, stroke, acute renal failure, and death) did not any significant differences in two groups 10 patients in intervention (26%) compared with 19 patients in control (51%).

On the other hand sternal wound infection was lower in intervention group than conventional group ($p < 0.05$).

It is reported that the adjustment of blood sugar in the range of 80–110 mg/dl through attuned tight glycemic control. Subsequent hypoglycemic episodes are responsible for the higher mortality rates [11]. The signs and symptoms of hypoglycemia in patients undergoing surgery under general anesthesia and sedation in ICU is extremely difficult to determine [11].

Insulin infusion can be caused hypokalemia, and increase the risk of dangerous arrhythmia as AF [14]. In the present study, despite hypokalemic in the adjusted tight glycemic

control group, AF rhythm and sinus tachycardia were lower in this group. This may be due to better glucose control in this group and the desirability of controlling the blood glucose during the surgery. However, it deserves further study. Lazer and his team divided 141 diabetic patients undergoing CABG into two groups (administered infusion of the glucose-insulin-potassium with aims BS = 125–200 mg/dl and standard with BS < 250). Glucose Insulin Potassium (GIK) infusion started before induction of anesthesia and continued for 12 h after surgery. Patients, who received GIK, significantly had fewer AF rhythms (17% compared with 42%) and duration of hospital stay (6.5 vs. 9.2 days) was shorter. It should be considered that in their study GIK was continued for 12 h after surgery. So, in such cases administration of the potassium with insulin is recommended [15].

Vandenberg reported that 50 mg/dl lowering of blood sugar leads to a 34% reduction of ICU mortality [16]. In our study, although the mean blood glucose in the adjusted tight glycemic control group at the end of surgery was approximately 38 mg/dl lower than the mean of CGC, postoperative complications in the ICU were not significantly different in both groups.

Our findings of primary outcomes were consistent with the results of Gunjan and colleagues. They studied 400 diabetic and non-diabetic patients who were divided into two groups of the TGC group with the BS range of 80–100 mg/dl. Mean of BS at the end of surgery in the treatment group was less than

Fig. 3 Comparison of trend of changes in the mean $\pm$ SD of the blood glucose levels in patients in ICU between two groups.* mean significant differences ($P < 0.001$)

Table 2 Comparison of outcome in intensive care units in two groups

Complication in ICU	Intervention (<i>n</i> = 38)	Control (<i>n</i> = 37)	<i>p</i>
Sternal wound infection	0	2	0.24
AF	4	5	0.73
Cardiac complication	3	6	0.3
Stroke	1	1	1
Acute renal failure	1	1	1
Death	1	0	0.50
Hypokalemia	34	8	<0.001*
Hypoglycemia	1	1	0.49
Delirium	8	6	0.54

*=*means significant differences*

the control group (114 mg/dl compared to 157 mg/dl). Forty-four percent of patients in the treatment group and 46% of patients in the control group encountered one of these complications: Death (4 vs. 0), stroke (8 vs. 1) and a mean ICU stays of 2 days in both groups. In spite of continuing insulin infusion in ICU, the postoperative mortality and morbidity were not reduce [11].

Although in the present study, the trend of change in blood glucose levels during surgery was not significantly different in each group, they were significantly different from each other at different times of measurement (from 90 to 240 min of starting the operation) Therefore, differences in the blood glucose at the different hours of the surgery may not adequately reflect the favorable impact of modified tight control of blood sugar. Gandhi and colleagues suggested that 20 mg/dl increase in the average blood glucose lead to an increase in the probability of postoperative complications for 34% [17]. In our study, the mean blood glucose levels were 160.64 ± 53 mg/dl intra-operatively, and 208.20 ± 66.49 mg/dl postoperatively. While the average blood sugar in their study was 133 mg/dl. Complications such as death, stroke, and cardiac complications in the TGC group were more than the control group.

Azarafarin et al. studied the effect of tight control of blood glucose in non-diabetic patients undergoing CABG. They concluded that for reducing complications of post-cardiac surgery (from 32% to 16%), they needed to maintain blood

glucose levels in the range of 110–126 mg/dl. The difference in our study with them was the diabetics of our patients, but postoperative complications did not show differences [13].

We believe that the effect of mean BS levels according to the protocol was a definite determining factor in the dramatic decrease in our infection rates. Deep sternal wound infection can cause increased mortality, length of hospital staying and retrieval of the patient to the operating room. Moreover, hyperglycemia increases the risk of deep sternal wound infection by two-fold. Insulin administration can enhance the phagocytic functions of neutrophils and thus reduced infection in these patients. High blood glucose levels within the first 48 h after surgery associated with sternal wound infection [18].

Long term follows up (after one month), showed one patient with sternal infection in adjusted tight glycemic control and seven cases in the control group that was a statistically significant result. It was similar to the study of Hruska et al. They indicated that continuous infusion of insulin administration to maintain BS = 120–160 mg/dl, significantly reduced the rate of sternal wound infection in the diabetic patients who undergo CABG [19].

Zerr and coworkers divided 1585 diabetic patients into two groups of control and protocol groups. The mean of BS in the protocol group was maintained within a mean of 176 mg/dl compared with the 195 mg/dl in the control group. The incidence of wound infection in both sternal or foot ulcers was

Table 3 Comparison of complications between Adjusted Tight glucose control and control groups

Complication after one month (<i>n</i> = 37)	Modified Tight Glucose control (<i>n</i> = 38) <i>P</i>	Conventional Glucose control	
Sternal wound infection	1	7	<0.05 *
Foot infection	2	5	0.43
Cardiac complication	3	1	0.61
Stroke	0	1	1
Acute renal failure	1	3	0.6
Death	1	1	1

*=*means significant differences*

decreased from 2.4% in the control group to 1.5% in the treatment group. The sternal wound infection rate in the control group was only 2.8% compared with 0.74% in the treatment group [18].

Similar results were found by Furnary et.al and Kramer et .al.While, they noticed that sternal wound infection rate reduced in tight glycemic control method in diabetic patients in their center, who underwent open heart surgery (from 2.6% prior to the start of tight glycemic control method to 1% after tight glycemic control method) [20].

In a meta-analysis by Zhou-Qing Kang and coworkers about the effects of perioperative tight glycemic control on postoperative consequences, they found compared to generous control, perioperative TGC (the upper level of glucose goal ≤ 150 mg/dL) was related with substantial reduction of short-term mortality, cardiac surgery mortality, non-diabetic patients mortality, and some postoperative complications [21]. This was similar to our results.

In Saager study about the effect of tight control of blood glucose under CABG on delirium; they have found that this method can be caused higher this complication than control. This in line with our study [14].

Limitations

Our study had some limitations, including small numbers of patients, this number does not represent the definite and accurate result, and therefore, further study is recommended with a larger population. In addition, one of the indices of cardiac events measurement is serum troponin level, it is recommended to evaluate this marker in future studies. The third limitation in this study was Patients HbA1C levels that we are not included in our data. This data is recommended to evaluate in future studies.

Conclusion

We can conclude that blood glucose can be maintained at the close range of normal by using a standard protocol with insulin infusion. In the present study, insulin infusion was discontinued at the end of the surgery and to get better results, insulin infusion should be continued in the ICU at least until the need for inotropic support. In conclusion, using adjusted tight glycemic control to a level that is close to normal values during cardiac surgery may reduce episodes of hypoglycemia and thus reduces its side effects. As well as reduce hyperglycemic complications such as sternal wound infection. It seems that more studies are required for achieving the desired level of blood glucose during surgery and in the ICU setting.

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Authors' contributions FJ and SA collaborated equally. They conceived and designed the analysis, and collected and analyzed the OCT-data; SA performed the statistical analysis. FJ and SA drafted the paper. All authors read and approved the final manuscript.

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Data availability Data are available on request to the corresponding author.

Compliance with ethical standards

Ethics approval and consent to participate All of the procedures of this study were approved by the local Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Ethics code: 91–01-60-5268).

This study was designed as a placebo-controlled, clinical trial (Code: IRCTID: IRCT2013041713052N1. Informed consent form was obtained from all patients.

Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

Conflicting interest There is no conflict of interest to be declared.

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