A study on the Outcomes of Modified Tight Glucose Control for the Management of Glycemic Control in Diabetic Patients Undergoing Cardiac Surgery

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ABSTRACT

Background and Objective: Diabetes mellitus is associated with increased surgical morbidity and mortality. Its relatively high risk may be related to the level of perioperative hyperglycemia. This study was aimed to compare the outcomes of patients undergoing open cardiac surgery by glucose control in two ways: modified tight versus conventional method.

Methods: This open-labeled, randomized control trial was conducted on 75 diabetic patients (18-70 years old) with ASA II-III undergoing open cardiac surgery from Shahid Faghihi Hospital, Shiraz, Iran. The patients were randomly divided into modified tight control (Blood Sugar maintained between 100-120 mg/dl) and conventional method (Blood Sugar < 200mg/dl). Primary end points included: hospital mortality, sternal wound infection, duration of mechanical ventilation, cardiac arrhythmia, cerebrovascular attack and acute renal failure. The secondary end point was length of ICU staying. Complications after 30 days of surgery were recorded. We used student’s t test, chi-square and repeated measurement tests.

Results: Although the trend of change in blood glucose during surgery and in ICU was not significantly different between groups, blood sugar measurement showed a significant difference at the different times (P<0.001). In terms of primary end points and secondary end points were not significantly different between two groups. The occurrence of hypoglycemia was low in both groups (one patient in each group) and were not significantly different between two groups. Hypokalemia was the most prominent side effect in the 34 patients of modified tight control group compared with eight patients in the conventional group (P<0.001). After 30 days sternal wound infection was seen in 1 patient of treatment group versus 7 in control group (P<0.05), which was significant.

Conclusion: Modified tight control of blood glucose close to normal values during cardiac surgery was associated with decreased occurrence of episodes of hypoglycemia and hyperglycemic complications.

KEYWORDS: Cardiac surgery, Diabetes; outcome, Glycemic control

1. INTRODUCTION

Diabetes mellitus is associated with increased surgical morbidity and mortality. Its relatively high risk may be related to the level of perioperative hyperglycemia. About 30-40% of patients, who are undergoing coronary artery bypass graft, have diabetes mellitus or metabolic syndrome and are at risk for hyperglycemia events[1].

Hyperglycemia leads to increased susceptibility to infection of the surgical wound, neurological injury, cardiac and renal damage, increased need for inotropic support and death[2-3]. Hyperglycemia is a major cause of formation of abnormal proteins through non-enzymatic glycosylation that leads to the worsening of neurological damage, global and focal cerebral ischemia through anaerobic conversion of glucose to lactate, thus disrupting the cellular metabolism[4].

Furthermore, hyperglycemia increases the duration of hospital stay and costs. On the other hand, diabetic patients are more likely to revascularization, 24% more risk of readmission for heart-related problems and 44% more risk of readmission[5].

The incidence of coronary artery disease is greater in diabetic patients. Furthermore, impaired platelet function, fibrinolytic and impaired endothelial function are more common in these patients which leads to less graft patency, increased preoperative mortality, and reduced short and long term post-operative survival[6].

Insulin acts as an anti-inflammatory agent by inhibiting proinflammatory factors and reduces inflammatory mediators[7].
Insulin regulates the L-arginine nitric oxide pathway, therefore, improves vasodilatation and endothelial function, and increasing prostacyclin release, thus improves platelet function. On the other hand, insulin reduces apoptosis.[8] Several studies have shown that patients with acute coronary syndrome who present with hyperglycemia are at higher risk of inhospital mortality.[9,10] Hyperglycemia is important in determining the outcome of acute coronary syndrome in diabetic and non-diabetic patients.[9,11] Doenst, assessed the outcome of 6280 patients undergoing cardiac surgery and found that patients with blood glucose levels greater than 360 mg/dl had higher intra-operative morbidity and mortality.[4] In similar findings, increased post-operative complications were observed due to increased blood glucose levels.[12-15] These studies strongly suggested that the increased levels of blood glucose in the preoperative period contribute to higher postoperative morbidity and mortality in both diabetic and non-diabetic patients undergoing cardiac surgery. However, tight control of blood glucose can lead to hypoglycemia that can be associated with neurological damage.[16]

According to some other studies, this method cannot improve the outcome in patients with open heart surgery.[17] Modified tight control method has been proposed as a method to overcome this limitation. Therefore, the aim of this study was to compare the postoperative outcome of patients undergoing open cardiac surgery in two methods of blood glucose control: modified tight control versus conventional methods.

2. MATERIALS AND METHODS:

2.1. Study design and population:
This open-labeled, randomized control trial was conducted on 75 diabetic patients, aged 18-70 years with ASA II-III undergoing open heart surgery from Shahid Faghihi Hospital, Shiraz, Iran. Patients were divided into modified tight control (Blood Sugar maintained between 100-120 mg/dl) and conventional method (Blood Sugar < 200 mg/dl).

2.2. Inclusion criteria:
Diabetic patients scheduled for non-emergency open cardiac surgery and aged between 18 to 70 years, were included.

2.3. Exclusion criteria:
Patients with ketoacidosis or hyperosmolar coma, Redo surgery, patients with a history of cerebrovascular accident (CVA) or transient ischemic attacks (TIA), patients with EF<30% and patients with a history of liver or kidney disease, were excluded from the study.

2.4. Study procedure:
After arrival to the operation room, standard monitoring included five-lead electrocardiography, pulse oximetry and arterial line for continuous monitoring of blood pressure and blood gases were used. After general anesthesia the patients were randomly allocated in two groups: modified tight glycemic control (MTGC), and conventional glucose control (CGC). After induction of general anesthesia, central venous catheter inserted, and baseline BS via an ACCU- check Active glucometer (Roche, Germany) was checked. In MTGC, if the blood sugar was above 120 mg/dl, an infusion of 50 units of regular insulin in 50 ml saline was started in order to maintain blood glucose between 100-120 mg/dl. Insulin dose was adjusted according to the Table 1. In CGC if blood glucose was equal or higher than 200mg/dl, patients were treated with insulin as follows: If blood sugar was 200-250 mg/dl, 4 units of regular insulin per hour will be administered until the blood glucose reached to 200mg/dl. If blood glucose was greater than 250 mg/dl, 4 units of regular insulin per hour began and continued until blood glucose became less than 150 mg/dl and maintained<200 mg/dl.[18]

Table 1. Insulin infusion protocol in modified tight glucose control group (19)

<table>
<thead>
<tr>
<th>Serum Glucose Level, mg/Dl</th>
<th>Insulin Infusion Rate, U/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70</td>
<td>Off</td>
</tr>
<tr>
<td>70-109</td>
<td>1</td>
</tr>
<tr>
<td>110-119</td>
<td>2</td>
</tr>
<tr>
<td>120-149</td>
<td>3</td>
</tr>
<tr>
<td>150-179</td>
<td>4</td>
</tr>
<tr>
<td>180-209</td>
<td>5</td>
</tr>
<tr>
<td>210-239</td>
<td>6</td>
</tr>
<tr>
<td>240-269</td>
<td>8</td>
</tr>
<tr>
<td>270-299</td>
<td>10</td>
</tr>
<tr>
<td>300-329</td>
<td>12</td>
</tr>
<tr>
<td>330-359</td>
<td>14</td>
</tr>
<tr>
<td>&gt;360</td>
<td>16</td>
</tr>
</tbody>
</table>

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 MTCG patients was discontinued after the surgery.

ICU glycemic controls in both groups were performed by conventional methods and BS level was maintained ≤200 mg/dl as the protocol used in operation room in CGC group. In the ICU, blood glucose was checked every two hours until 20 hours after the operation. During this period, subcutaneous insulin or oral anti-diabetic medication was not prescribed. The insulin administration...
protocol was discontinued 24 hours after surgery in both MTCG and CGC.

3. RESULTS:
Variables such as mortality, sternal wound infection, duration of mechanical ventilation, cardiac arrhythmias (Atrial fibrillation, Cardiac arrest, Heart block which require pace maker), cerebrovascular attack and acute renal failure (two-fold increase in baseline creatinine) were the primary outcomes and length of ICU stay was evaluated as a secondary outcome. Occurrence of hypoglycemia (blood glucose less than 60 mg/dl that treated with 50 cc of dextrose 50%) and hypokalemia (serum potassium less than 3meq/dl, so corrected with 20meq of potassium) were noted. Outcomes were determined by the ICU general practitioner that was unaware of the treatment. Furthermore, 30 days after discharge, patients were visited by the surgeon and adverse events (the same as the primary outcomes) were recorded. This study was approved by the ethics committee of Shiraz University of medical sciences and all patients signed the informed consent before study.

3.1. Statistics:
Statistical analyses were performed using SPSS V19. The results are expressed as mean ± SD, and P<0.05 was considered as significant. Data about patients’ baseline characteristics in MTGC and CGC, including age, weight, preoperative blood glucose, preoperative ejection fraction, duration of surgery were analyzed using Student’s t-test. Chi-square analyses were performed to detect the need to inotropic support, the incidence of hypoglycemia and hypokalemia, early postoperative events (sternal wound infection, cardiac complication, atrial fibrillation, stroke, acute renal failure and death) and morbidity after one month in MCGC and CGC. For comparing blood glucose in MCGC and CGC during surgery and in ICU repeated measurement test was used. Duration of themechanical ventilation and stay in ICU under the Mann Whitney U test were compared in MCGC and CGC.

This clinical study comprised 75 diabetic patients who underwent open cardiac surgery, and were divided into two groups: Thirty eight patients in the MTGC group and 37 patients in the CGC.

In terms of baseline characteristics including age, weight, preoperative blood glucose, ejection fraction no statistically significant differences were found between the two groups (Table 2).

<table>
<thead>
<tr>
<th>Details</th>
<th>Modified Tight glucose control</th>
<th>Conventional glucose control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean±SD (Year)</td>
<td>58.18±10.77</td>
<td>59.18±8.91</td>
<td>0.66</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>17 (44)</td>
<td>13 (35)</td>
<td>0.72</td>
</tr>
<tr>
<td>Weight, mean±SD (kg)</td>
<td>65.55±12.65</td>
<td>66.13±9.85</td>
<td>0.82</td>
</tr>
<tr>
<td>Preoperative BS, mean±SD (mg/dl)</td>
<td>190.68±81.04</td>
<td>192.41±80.47</td>
<td>0.92</td>
</tr>
<tr>
<td>EF, mean±SD (%)</td>
<td>51.05±9.94</td>
<td>50.02±8.30</td>
<td>0.63</td>
</tr>
<tr>
<td>History of hypertension, N (%)</td>
<td>26 (68)</td>
<td>24 (63)</td>
<td>0.74</td>
</tr>
<tr>
<td>History of MI, N (%)</td>
<td>18 (47)</td>
<td>12 (32)</td>
<td>0.18</td>
</tr>
<tr>
<td>History of arrhythmia, N (%)</td>
<td>2 (5)</td>
<td>2 (5)</td>
<td>1.00</td>
</tr>
<tr>
<td>History of AF, N (%)</td>
<td>0 (0)</td>
<td>1 (2.7)</td>
<td>0.49</td>
</tr>
<tr>
<td>History of smoking, N (%)</td>
<td>6 (16)</td>
<td>8 (21)</td>
<td>0.24</td>
</tr>
<tr>
<td>Duration of surgery, mean±SD(min)</td>
<td>221±77</td>
<td>231±82</td>
<td>0.65</td>
</tr>
</tbody>
</table>

SD: Standard deviation; BS: Blood sugar; EF: Ejection Fraction; MI: Myocardial Infarction; AF: Atrial Fibrillation

The mean duration of surgery was similar in both groups (221±77 in MTGC versus 231±82 min in CGC). In MTGC group, 29 patients required inotropic support compared with 26 patients in CGC (P=0.55).

Although the trend of change in blood glucose during surgery was not significantly different between groups, BS measurement showed a significant difference at the different times (P<0.001, Figure 1).

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, Figure 2).

Figure 1. Comparison of trend of changes in the mean ± SD of the blood glucose levels in diabetic patients during cardiac surgery between Modified Tight glucose control and Conventional glucose control.* mean significant differences (P < 0.001).
4. DISCUSSION:

The current clinical study was designed to compare the effect of glycemic control by two methods: modified tight glycemic control and conventional on post-operative outcomes in diabetic patients after open cardiac surgery. We used insulin for modified tight glucose control through a designed protocol to maintain BS in a range of 100-120 mg/dl in MTGC and <200mg/dl in CGC. In ICU both groups treated as a conventional method.

On the basis of previous studies\textsuperscript{[7,9,14,18]}, our hypothesis was based on improving outcomes and reducing complications and thus, reducing the duration of mechanical ventilation and length of ICU staying following TGC. It is reported that the adjustment of blood sugar in the range of 80-110 mg/dl through TGC and subsequent hypoglycemic episodes are responsible for the higher mortality rates.\textsuperscript{[12,17,20,21]}

Severe hypoglycemia is a medical emergency that may cause seizures and permanent brain damage. Likewise, hypoglycemia was defined as BS less than 40 mg/dl by Vandenberg. Also, physiological changes occur as follows: increasing the counter regulatory hormones if BS reaches to the 65 mg/dl, adrenergic symptoms if BS was about 55mg/dl, and cognitive dysfunction in the BS around 45mg/dl.\textsuperscript{[22]}

Except for significant sternal wound infection, one month after surgery (seven cases in a conventional versus one case in modified tight control) no differences between other complications in both groups were observed (P<0.05) (Table 4).

Table 3. Comparison of outcome in intensive care units in Modified Tight glucose control and Conventional glucose control

<table>
<thead>
<tr>
<th>Complication in ICU</th>
<th>Modified Tight Glucose control (n=38)</th>
<th>Conventional Glucose control (n=37)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternal wound infection</td>
<td>0</td>
<td>2</td>
<td>0.24</td>
</tr>
<tr>
<td>AF</td>
<td>4</td>
<td>5</td>
<td>0.73</td>
</tr>
<tr>
<td>Cardiac complication</td>
<td>3</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>0.50</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>34</td>
<td>8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>1</td>
<td>1</td>
<td>0.49</td>
</tr>
</tbody>
</table>

In contrast to the previous studies that intra-operative tight glucose control (TGC) reduced the complications, in our study early post-operative complications (sternal wound infection, atrial fibrillation, cardiac complications, stroke, acute renal failure and death) did not show any significant differences in the two groups (10 patients in MTGC 26% compared with 19 patients in CGC 51%). Hypokalemia in MTGC was significantly higher than in CGC (34 Versus 8 P<0.001). Insulin infusion results in hypokalemia and increase risk of dangerous arrhythmia as AF\textsuperscript{[23]}. In our study, a significant increase in the incidence of hypokalemia was found in the treatment group (34 patients compared with eight patients) which caused slower number of AF rhythm (four cases compared with five cases) and lower incidences of sinus tachycardia than in control groups. In the present study, despite of hypokalemia in MTGC 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 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 hours 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 hours after surgery. So, in such cases administration of the potassium with insulin is recommended. Vandenberg reported that 50 mg/dl lowering of blood sugar lead to 34% reduction of ICU mortality. In our study, although the mean blood glucose in MTGC group at the end of surgery was approximately 38 mg/dl lower than the mean of CGC, postoperative complications in the ICU in both groups were not significantly different.

Our findings about primary outcomes were consistent with the results of Gunjan. 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 control group (114 mg/dl compared to 157 mg/dl). Forty 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 stay of two days in both groups. In spite of the continuing insulin infusion in ICU, the post-operative mortality and morbidity was not reduced.

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. Gandis suggested that 20 mg/dl increase in the average blood glucose leads to increase probability of post-operative complications for 34%. In our study, the mean blood glucose levels were 160.64 ± 53 mg/dl intra-operatively, and 208.20 ± 66.49 mg/dl post-operatively. While, the average blood sugar in Ghandi’s study was 133 mg/dl. Complications such as death, stroke, and cardiac complications in TGC group were more than the control group.

Salah divided 100 diabetic patients into two groups of TGC and common method that, tight control of blood glucose was continued from the beginning of anesthesia to complete recovery of patients and extubation. Increasing in blood glucose level was continued until the end of the operation in the control group (with a mean of 227 mg/dl). Mean blood glucose levels were similar in both groups before the start of CPB. However, significant differences were found between the two groups from the start of the CPB until extubation.

These findings were similar to our results at min of 90 (roughly the start of CPB) till the fourth postoperative hour (roughly the time of extubation).

Azarafarin 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%), maintaining the blood glucose levels in the range of 110-126 mg/dl is needed.

We believe that the effect of mean BG levels according to the protocol was a definite determining factors in the dramatic decrease our infection rates. Deep sternal wound infection can cause increased mortality, length of hospital staying and retrieval of patient to the operating room. Moreover, hyperglycemia increases the risk of deep sternal wound infection by two folds. Insulin administration can enhance phagocytic functions of neutrophils and thus reduced infection in these patients. High blood glucose levels within the first 48 hours after surgery associated with sternal wound infection. Long term follow up (after one month), showed one patient with sternal infection in MTGC and seven cases in CGC that was statistically significant result. It was similarly the study of Hruska, Smith et al. (2005). They indicated that continuous infusion of insulin administration to maintain BS=100-120 mg/dl significantly reduced the rate of sternal wound infection in the diabetic patients who underwent the CABG. Zerr, Furrnary et al. (1997), divided 1585 patients with diabetes into the 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 were decreased from 2.4% in the control group to the 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.

Similar results were found by Furrnary, Zerrand Kramer. While, they noticed that sternal wound infection rate reduced in TGC method in diabetic patients in their center, who underwent open heart surgery (from 2.6% prior to the start of TGC method to 1% after TGC method). Our study had some limitation, including small numbers of patients, this number does not represent the definite and accurate result;
therefore, further study is recommended with larger populations. In addition, one of the indices of cardiac event measurement is serum troponin level, it is recommended to evaluate this marker in future studies. We can conclude that the blood glucose can be maintained in 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 surgery and to get better results, insulin infusion should be continued in the ICU at least until the need for inotropic support.

4. CONCLUSION:
We concluded that using a modified tight control of blood glucose level 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.

Abbreviations:

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

Authors contributions:
FJZ is responsible for the design of the research; MGN performed the experiments.

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References:


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