Comparing Effects of Continuous Insulin Infusion with or without Subcutaneous Glargine Insulin on Glycemic Control in Diabetic Patients Undergoing Coronary Artery Bypass Graft (CABG)

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ABSTRACT

OBJECTIVE: Hyperglycemia is associated with increased morbidity and mortality in diabetic patients following coronary artery bypass grafting. Tight glycemic control in perioperative period can reduce these events. The goal of this study was to determine whether combination of continuous infusion and subcutaneous glargine as a basal insulin could improve glycemic control.

MATERIAL AND METHODS: Diabetic patients who were candidate for CABG were randomized to receive continuous insulin infusion with or without subcutaneous Glargine insulin for at least 72 hours which started 24 hours before surgery and continued for 48 hours after surgery.

RESULTS: A total 84 subjects were required. In group A (n = 45) continuous insulin infusion was used for glycemic control and in group B (n = 39) we used continuous insulin infusion with subcutaneous glargine insulin. Blood glucose level was significantly better in desirable range in group B in comparison to group A. Total mean blood glucose level in group A was 186.1 mg/dl and in group B was 174.3 mg/dl ($P = 0.008$). Frequency of hypoglycemia (blood glucose <70 mg/dl) was 0.66% in group A and 0.5% in group B that was similar ($P = 0.530$). The mean length of stay in the hospital was not different between two groups ($P = 0.288$).

CONCLUSION: We found out that a combination of continuous insulin infusion and glargine insulin as main basal insulin can improve glycemic control in diabetic patients undergoing coronary artery bypass grafting.

KEY WORDS: CABG, Continuous insulin infusion, Glargin insulin, Diabetes.

INTRODUCTION

Diabetes mellitus is an important risk factor for coronary artery disease that require coronary artery bypass grafting (CABG). Hyperglycemia is a major risk factor for increased postoperative morbidity and mortality among patients undergoing cardiovascular (CV) surgery (1). The risk decreases by better control. It's commonly defined as the maintained blood glucose level below 200 mg/dl (2,3). So far many protocols have been considered for glycemic control in diabetic patients undergoing CABG. Numerous studies have shown that continuous insulin infusion is preferred for perioperative glycemic management (4,5,6 and 7).

Recently a long-acting insulin analog (glargine; lantus) has been developed in the pharmacokinetic profile with an onset of

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action at 2-hours, without peak, and duration of action about 24-hours (8,9). It is proposed that by using this analog as main basal insulin in the form of subcutaneous, a fixed level of insulin can be created in blood (10,11). It is expected that glargine insulin administration as basal insulin once a day puts blood glucose in a lower level and combines it with continuous insulin infusion in patients undergoing CABG prevents blood glucose levels fluctuation and provides better glycemic control in these patients. The aim of this study is to evaluate two methods of continuous insulin infusion with or without glargine insulin to control blood glucose levels in diabetic patients undergoing CABG.

MATERIAL AND METHODS

We conducted a clinical trial study at the Department of Cardiac Surgery in Afshar Hospital and Yazd Diabetes Research Center from July 2006 to October 2007. We studied 84 patients with diabetes mellitus who were undergoing CABG for the first time. In all patients the diagnosis of diabetes had been made before admission for surgery. We used two methods for control of perioperative hyperglycemia in target range (120-180 mg/dl). Patients were randomized into two groups, in group A continuous insulin infusion (CII) was used for blood glucose control level according to modified Van den Berghe protocol (appendix). Continuous insulin infusion was initiated 24 hours before the surgery and continued for 48 hours after admission to ICU. In group B, in addition to Continuous insulin infusion, patients received 15 units of subcutaneous glargine insulin at night, 12-hours before initiation of CII and repeated the dose at the same time for 4 consecutive days. Blood glucose level was measured every 2 hours before and after operation and 2 times during operation infusion rate titrated according the result of glucose testing to maintain blood glucose in target levels. Family daily mean blood glucose, frequency of hypoglycemic (blood glucose level <70) and significant hyperglycemia (blood glucose level >200) were determined for all the patients.

Variables used in this study were as follows:

1. **Preoperative variables:** age, sex, weight and Body Mass Index (BMI), type of diabetes, duration of diabetes, family history of diabetes, current method of diabetic control, hypertension, hyperlipidemia, previous myocardial infarction, ejection fraction, previous cerebrovascular accident and smoking.
2. **Intraoperative variables:** mean blood glucose, off pump procedure, duration of cardiopulmonary bypass and duration of aortic cross-clamp time.
3. **Postoperative variables:** intubation time, need for inotropic agents, sternal wound infection, length of hospital stay and death.

Data were analyzed using SPSS 13. Continuous variables were compared by T-test. The mean value of daily blood glucose was compared between the two groups by means of Independent-sample T-test. Above variables were analyzed by means of Chi-square test and Fisher's exact test. A P value of <0.05 was considered significant.

RESULTS

84 patients with type 2 diabetes mellitus were enrolled in this study, of whom 45 were randomly assigned into group A (continuous insulin infusions) and 39 into group B (continuous insulin infusion with subcutaneous glargine). The mean age was 58.6 years, 59.5% were male, and the mean BMI was 26.2. The demographic data of the two groups are shown in Table 1. There was no significant difference between the groups in sex distribution, age and prevalence of other underlying diseases. Oral hypoglycemic agent was the most common agent used preoperatively by patients; as it was used by 38 of 45 patients in group A (84.4%) and by 32 of 39 patients in group B (82.1%). In group "A" 13.3% and in group "B" 12.8% received insulin. The needs for inotropic agents were significantly higher in group A (P = 0.039). One patient in each group had sternal wound infections (P = 1.000). The mean length of stay in the hospital was 7.1 days for group A and 6.5 days for group B (P = 0.288) (Table 2).

Glycemic control: Overall glycemic control was significantly better in group B. Total mean blood glucose was 186.1 mg/dl (SE 3.6; range 140-237) in group A and 174.3 mg/dl (SE 2.2; range 142-197) in group B (P

= 0.008) (Table 3). Postoperative mean blood was 174.9 mg/dl (SE 3.7; range 146-249) in group A and 166.6 mg/dl (SE 2.4; range 140-218) in group B (P = 0.072). The daily mean blood glucose levels for both groups are shown in Table 3.

Percentage of blood glucose values above 200 mg/dl: Overall, 31.3% of blood glucose values were above 200 mg/dl in group B that was significantly less common compared with 34.9% in group A (P = 0.02) (Figure 1).

Frequency of hypoglycemia: Overall, hypoglycemia (blood glucose <70 mg/dl) was 0.66% during group A and 0.5% during group B that was similar between two groups (P = 0.53) (Figure 2).

Table1- Characteristics of the diabetic patients

	Group A	Group B	*P* value
Number of patients	45 (53.6%)	39 (46.4%)	----------
Age (years)	58.1 (SE:1.4) (range 38-85)	59.1 (SE:1.5) (range 37-85)	0.638
Gender (male %)	25 (55.6%)	25 (64.1%)	0.506
BMI	26.3 (SE:0.7) (range 17-40)	26.1 (SE:0.4) (range 20-32)	0.796
Duration of DM (year)	8.1 (SE:1.3 (range 1-47)	7.1 (SE:0.8 (range1-20)	0.249
Family history of DM	24 (53.3%)	26 (66.7%)	0.267
Oral agent	38 (84.4%)	32 (82.1%)	----------
Insulin	6 (13.3%)	5 (12.8%)	----------
Diet	0 (0.0%)	1 (2.6%)	----------
Uncontrolled	1 (2.2%)	1 (2.6%)	----------
Hypertension	23 (51.1%)	22 (56.4%)	0.666
Hyperlipidemia	28 (62.2%)	22 (56.4%)	0.659
Smoking	13 (28.9%)	5 (12.8%)	0.109
Stroke	0 (0.0%)	2 (5.1%)	0.213
Myocardial infarction	14 (31.1%)	15 (38.5%)	0.500
Ejection fraction (%)	48.1 (SE:1.2) (range 25-60)	48.2 (SE:1.5) (range 20-60)	0.962
Preoperative Cr (mg/dl)	1.06	1.06	0.995

Group A: Continuous insulin infusions, group B: Continuous insulin infusion with subcutaneous glargine, DM: Diabetes Mellitus, BMI: Body Mass Index

Table 2- Complications during operation and postoperative

	Group A	Group B	P value
Off pump procedure (%)	11.1%	30.8%	0.031
Cardiopulmonary bypass duration (min)	53.5	54.1	0.838
Cross clamp duration (min)	26.2	26.7	0.692
Intubation time >6 h (%)	27 (60.0%)	20 (51.3%)	0.510
Postoperative inotropic agent (%)	15 (33.3%)	5 (12.8%)	0.039
Sternal wound infection	1 (2.2%)	1 (2.2%)	1.000
Length of hospital stay (days)	7.1	6.5	0.288
Death	0	0	-------

Group A: Continuous insulin infusions, group B: Continuous insulin infusion with subcutaneous glargine

Table 3- Daily mean blood glucose level (mg/dl) before and after operation

	Group A	Group B	All	*P* value
Day of operation				
Preoperation day	208.7	189.4	199.7	0.030
Intraoperative	182.6	171.6	177.5	0.250
First day after operation	183.8	174.7	199.7	0.204
Second day after operation	165.2	157.8	179.6	0.171
First & second day	174.9	166.6	171.0	0.072
Total	186.1	174.3	180.6	0.008

Group A: Continuous insulin infusions, group B: Continuous insulin infusion with subcutaneous glargine

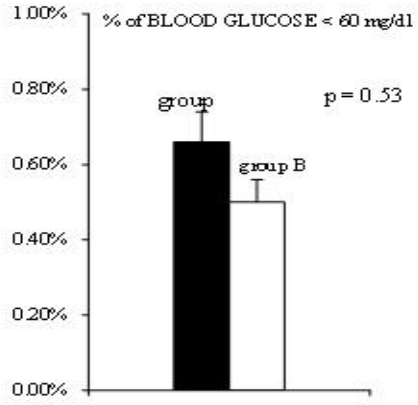

Figure 1- Percentage of blood glucose values above 200 mg/dl

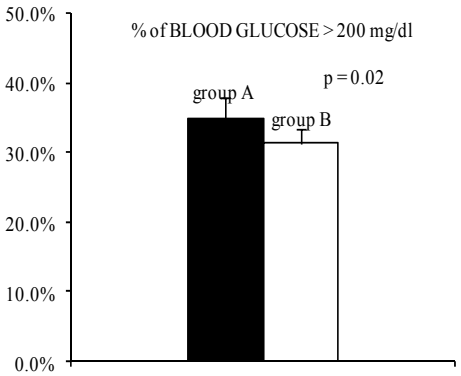

Figure 2 - Frequency of hypoglycemia (BG <70 mg/dl)

CONCLUSION

Many recent studies have shown reduction in mortality, incidence of sternal wound infection and length of stay by normalization of post-operative blood glucose in diabetic patient undergoing CABG (2,6,12,13,14 and 15). The usual regime of sliding scale subcutaneous insulin for preoperative glycemic control is not a preferable method because of unreliable absorption rate. The newer long-acting insulin analog (glargine) may be appropriately administrated for basal insulin coverage throughout the surgical period (16). Many studies have shown that continuous insulin infusion provides better control of preoperative blood glucose level in patients with diabetes after CABG (4, 5 and 6). Our study is a prospective randomized study to significantly demonstrate better blood glucose in diabetic patients by continuous insulin infusion with glargine insulin as basal insulin. In one study Yeldandi et al. evaluated comparison of once-daily glargine insulin with twice-daily NPH/Regular insulin; they achieved that once-daily glargine insulin provides good glycemic control in hyperglycemic patients after cardiovascular surgery (17). In our study, continuous insulin infusion was initiated 24 hours before surgery and continued for 72 hours. The importance of glycemic control in the first postoperative day reported in retrospective review by McAlister et al.; an increase of 18 mg/dl of average blood glucose on the first postoperative day was significant associated with a 17% increase in the risk of adverse outcome (3). Furnery et al. found out that continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection and mortality in diabetic patients after cardiac surgical procedures (2,6). Through continuous insulin infusion with glargine insulin, we achieved better adequate glycemic control and maintained glucose level 48 hours post surgery. However, sternal wound infection and mean length of stay in the hospital are not different. Percentage of blood glucose value less than 70 mg/dl is not different in neither of the groups. In the recent study, blood glucose level below 200 mg/dl reduced postoperative morbidity and mortality among

patients undergoing cardiovascular surgery (2,3 and 18); in our study percentage of blood glucose value above 200 mg/dl was lower in the group that received glargine insulin with continuous insulin infusion. However, Vandenberg et al. recommended that the goal of blood glucose control for patients in surgical ICU should be no higher than 110 mg/dl (1), but we were unable to achieve this target because this study was designed for blood glucose level between 120-180 mg/dl. It is concluded that continuous insulin infusion with glargine insulin as basal insulin provides better control of perioperative blood glucose level in diabetic patients after CABG than continuous insulin infusion alone**.**

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Appendix

ICU Blood Glucose (BG) GOAL: 120 -180 mg/dl

- Prepare Insulin for infusion by diluting 50 units in 50 ml saline.
- Start 1 unit/h insulin infusion for every 100 mg/dl BG >100 mg/dl.

A. If current BG is <80 then

- STOP insulin infusion
- Give 50 ml D50 IV push
- Notify MD/HO
- Check BG every 30 minutes until BG >120 mg/dl
- When BG >120 mg/dl. restart drip at 50% of previous rate (0.50 x previous rate)

B. If current BG is 81 to 120 and previous BG was	**Action Step 1**	**Action Step 2 check BG in**
81-100	↓ rate by 0.6 unit	2 hr
101-120	↓ rate by 0.4 unit	2 hr
121-160	↓ rate by 0.8 unit	2 hr
161-200	↓ rate by 1.2 unit	2 hr
201-250	↓ rate by 1.5 unit	2 hr
251-400	↓ rate by 2 unit	2 hr
>400	↓ rate by 3 unit	2 hr
C. If current BG is 121 to 160 and previous BG was	**Action Step 1**	**Action Step 2 check BG in**
≤120	↑ rate by 0.1 unit	2 hr
121-160	No change	2 hr
161-200	↓ rate by 0.3 unit	2 hr
201-250	↓ rate by 0.6 unit	2 hr
251-400	↓ rate by 1 unit	2 hr
>400	↓ rate by 2 unit	2 hr
D. If current BG is 161 to 200 and compared to previous BG it has	**Action Step 1**	**Action Step 2 check BG in**
Remained the same or increased	↑ rate by 0.5 unit	2 hr
Decreased by ≥ 1 but <10 then	↑ rate by 0.3 unit	2 hr
Decreased by ≥ 10 but <50 then	No change	2 hr
Decreased by ≥ 50but <100 then	↓ rate by 0.8 unit	2 hr
Decreased by ≥ 100	↓ rate by 2 unit	2 hr
E. If current BG is >200 and compared to previous BG it has	**Action Step 1**	**Action Step 2 check BG in**
Remained the same or increased	↑ rate by 0.8 unit	2 hr
Decreased by ≥ 1 but <30 then	↑ rate by 0.5 unit	2 hr
Decreased by ≥ 30 but <100 then	↓ rate by 0.3 unit	2 hr
Decreased by ≥ 100	↓ rate by 1 unit	2 hr

Individualized algorithm for very Insulin resistant subjects (insulin Infusion >2O units/hr or BG >3OO for more than 4hr).

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