Original Article

Effects of Glargine Insulin on Glycemic Control in Patients with Diabetes Mellitus Type II Undergoing Off-pump Coronary Artery Bypass Graft

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Abstract

Background: The prevalence of diabetes mellitus in patients requiring coronary artery bypass grafting (CABG) is noticeably high (20%–30%). These patients have inferior perioperative outcome, reduced long-term survival, and high risk of recurrent episodes of angina. To improve perioperative outcome surgical unit defined satisfactory glycemic control is desired during this period. Hence, the aim of our study is to compare the efficacy of glargine insulin combination with continuous human insulin infusion for perioperative glycemic control in patients with diabetes undergoing CABG. **Materials and Methods:** Fifty Patients, who were posted for off-pump CABG with diabetes mellitus type II, were randomized in two group, Group I normal saline + human insulin infusion during the perioperative period, Group II (glargine group): Glargine + human insulin infusion during perioperative period. **Results:** During surgery and in the postoperative period, random blood sugar and human insulin requirement are significantly higher in control group than glargine group. Other infection, step-up antibiotics, intensive care unit (ICU) stay, and hospital stay were significantly higher in control groups in postoperative period. **Conclusion:** Our study results suggest that glargine effectively manages blood glucose level with significantly greater control over postoperative morbidity.

Keywords: *Diabetes mellitus Type II, glargine insulin, human insulin, off-pump coronary artery bypass grafting*

Introduction

Recently, the incidence of diabetes is increasing strikingly, and the World Health Organization estimates that by 2025, there will be 300 million patients with diabetes (5.4% of the world population) The prevalence of diabetes mellitus in patients requiring coronary artery bypass grafting (CABG) is noticeably high (20%–30%) Associated with high risk of recurrent episodes of angina.[1-3] Hyperglycemia is a major risk factor for increased postoperative morbidity and mortality among patients undergoing cardiovascular (CV) surgery.[4] These patients have inferior perioperative outcome, reduced long-term survival, and high risk of recurrent episodes of angina.[1,5,6] Latham *et al*.,[7] found that hyperglycemia in the immediate postoperative phase increases the risk of infection in both diabetic and nondiabetic patients and the higher the level of hyperglycemia, the higher the potential for infection in both patient populations. Growing evidence suggests that achieving glycemic control in patients with diabetes decreases perioperative morbidity and improves short-term and long-term survival. Increased fasting glucose levels before surgery and persistently elevated glucose levels during and immediately after cardiac surgery are predictive of increased perioperative complications in patients with and without diabetes.[8,9]

Recently, a long-acting insulin analog (glargine; lantus, SoloSTAR®Pen) has been developed with pharmacokinetic profile with an onset of action at 2 h and duration of action about 24 h without peak effect.[10,11] It is expected that glargine insulin administration as basal insulin once a day causes reduction in blood glucose (without causing hypoglycemia). Combination of glargine with continuous insulin infusion in patients undergoing CABG surgery will prevent blood glucose levels fluctuation and provides better glycemic control. It is unknown whether weight-based dosing of insulin glargine within 24 h of cardiac surgery is effective

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for maintaining blood glucose values within a target range of 80–140 mg/dL.

There are very few literature reports available on the use of glargine insulin in patients with diabetes during perioperative period in CABG. One study has shown that a combination of continuous insulin infusion and glargine insulin can improve glycemic control in patients with diabetes undergoing CABG.[12] In other study, dosing insulin glargine by weight proved to be safe, but larger scale studies are needed before adopting weight-based dosing in this patient population.[13] In this prospective, case–control study, we aimed to compare the efficacy of glargine insulin combination with continuous human insulin infusion for perioperative glycemic control and postoperative complication rate in patients with diabetes undergoing CABG.

Materials and Methods

A prospective randomized control study of 50 patients with diabetes mellitus type II, who underwent CABG between January 1, 2015 and July 31, 2015 were enrolled in the study. Patient with diabetes mellitus type II, patient on preoperative oral hypoglycemic drug, coronary artery disease, without valve involvement, age group between 40 and 70 years were included. Patients with a history of previous cardiac operation, age >70 years or <40 years, liver and renal dysfunction, lung disease, and carotid intervention were excluded from the study.

Institutional Ethics Committee had reviewed and cleared (UNMICRC/ANAES/2014/20) the study, a written informed consent was taken from all patients, and 50 patients were randomly allocated into two groups. Group I (control group): Normal saline + human insulin infusion during perioperative period, Group II (glargine group): Glargine + human insulin infusion during perioperative period [Figure 1]. Continuous human insulin infusion (HUMAN ACTRAPID, Abbott, India.) was used for blood glucose control, according to earlier reported Van den Berghe protocol,[5] which has been modified slightly. Modified Van den Berghe protocol at our institution was used to calculate insulin recommendations based on these protocols. The hourly blood glucose values during treatment were compared with the other 11 protocols using a blood glucose goal of 120–180 mg/dl. The major assumption was that the change in glucose would be the same for all of the protocols, allowing comparison of recommended insulin dosing. In control group, normal saline was given (1 unit/kg) subcutaneously with glargine insulin syringe. In glargine group, glargine (BASALOG, Biocon, India) was given (1 unit/kg) subcutaneously before 2 h of surgery. Normal saline was taken in glargine insulin syringe so dose was given as 1 unit/kg in syringe for measurement of dose. This was done to maintain study blindness. In all patients, we have checked fasting blood sugar before giving glargine. In the background for satisfactory glycemic control, we have given rapid-acting insulin. We want to check in the study after giving glargine, requirement of rapid-acting insulin is reduced or not. As the surgical stress increase the rapid-acting insulin requirement for satisfactory glycemic control. For all patients, posted in the study were kept fasting for 8 h. For the first patient, it is from 12 am and the second patient in list, from 4 am on the day of surgery. All patients were kept on subcutaneous insulin (human actrapid) with sliding single from 5-day before surgery.

Variables used in this study were as follows:

- Preoperative variables: age, gender, body mass index, hypertension, family history, diabetes mellitus duration, oral hypoglycemic agents, insulin with oral hypoglycemic agents, levels of fasting blood sugar levels, postprandial blood sugar, glycosylated hemoglobin, serum creatinine, serum acetone, and serum glutamic-pyruvic transaminase
- Postoperative variables: levels of total count, serum acetone, serum creatinine, serum glutamic-pyruvic transaminase, and incidence of complications (infections, step-up in antibiotic), intensive care unit (ICU) stay, and hospital stay. Random blood sugar (RBS) and total units of human actrapid infusion were measure during surgery and at ICU, every 2 h up to 24 h. The reason for increase in the ICU stay and hospital stay were (1) increasing total count or infection required step-up in antibiotic for more days (2) acute renal failure in few patients.

Statistical analysis

Statistical analysis was performed using SPSS, Version 20.0 (IBM, Armond, ny, United States of America). Qualitative data were expressed as proportions, whereas the quantitative data were expressed as mean ± SD Continuous variables were compared by Student's *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. The level of significance was accepted at $P < 0.05$.

Results

Fifty patients with type II diabetes mellitus, who underwent CABG were enrolled in this study, of whom 25 were randomly assigned into control group and 25 into glargine group. The demographic and surgical features of the patients are summarized in Table 1. Demographic variables, risk factor profile, and preoperative biochemical variable in both the groups were comparable ($P > 0.05$) Family history of diabetes mellitus type 2 and hypertension were consider as a risk factor and noted.

Between the groups

During surgery, at 0 h and after 2 h, RBS and human insulin requirement are comparable in both groups. But after 4 h, RBS (after 4 h: 218.76 ± 45.58; 186.76 ± 48.45,

P = 0.0201) and human insulin requirement (after 4 h: 4.4 ± 2.58; 1.92 ± 2.03, *P* = 0.0004) are significantly higher in control group than glargine group. After surgery, 24 h in ICU, RBS (24 h in ICU: 200.68 ± 36.76; 170.12 ± 48.33, *P* = 0.0153) and human insulin requirement (24 h in ICU: 3.6 ± 2.25; 1.92 ± 2.39, *P* = 0.0137) are significantly higher in control group than glargine group [Table 2].

Within the groups

During surgery in glargine group, 0 h compare with 2 h, RBS (0 h: 179.4 ± 37.61; 2 h: 208.48 ± 49.09, *P* = 0.0229) and human insulin requirement (0 h: 1.48 ± 2.00; 2 h: 3.68 ± 2.07, *P* = 0.0004) are significantly higher and 0 h compare with 4 h, RBS, and human insulin requirement are comparable. During surgery in control group, 0 h compare with 2 h and 4 h, RBS is comparable, but human insulin requirement (0 h: 2.11 ± 2.04;2 h: 3.68 ± 2.07, *P* = 0.0095) are significantly higher. After surgery in glargine group, postoperatively human insulin requirement (0 h: 2.11 ± 2.04; 12 h: 1 ± 1.87 *P* = 0.050) are significantly lower [Table 2].

Postoperative investigations are comparable in both the groups. Other infection (control group; 6: Glargine group; 0, *P* = 0.0296) step-up antibiotics (control group; 10: Glargine group; 2p = 0.0205), ICU stay (control group; 3.92 ± 1.84: Glargine group; 2.76 ± 0.43, *P* = 0.0035), and hospital stay (control group; 6.36 ± 1.03: Glargine group; 5.0 ± 0.86, *P* > 0.0001) were significantly higher in control groups in postoperative period [Table 3].

Discussion

The prevalence of diabetes mellitus in CABG patients is associated with poorer surgical outcome; and hence, strict glycemic control is highly advocated in this population.[14] Uncontrolled glycemic index often exerts deleterious effects on CV system by triggering various inflammatory pathways.[15] It also alters free radical balance,[16] induces

Table 1: Demographic data (*n*=50)

Variable	Control group (*n*=25)	Glargine group (*n*=25)	*P*
Age (year)	59.36±6.27	58.12±7.97	0.5438
Male (%)	17 (68.0)	21 (84.0)	0.3205
Female (%)	8 (32.0)	4 (16.0)	0.3205
Body mass index	25.48±3.98	25.42±2.66	0.9503
Hypertension (%)	11 (44.0)	10 (40.0)	1
Family history (%)	2 (8.0)	1 (4.0)	1
Diabetes mellitus type 2	1	0	1.00
Hypertension	1	1	0.4705
Diabetes mellitus duration (year)	8.28±6.14	6.56±4.85	0.2772
Oral agents (%)	22 (88.0)	24 (96.0)	0.6022
Insulin + oral agents (%)	5 (20.0)	0	0.0593
Fasting blood sugar levels (mg/dl)	167.32±64.49	173.08±50.88	0.7274
Postprandial blood sugar (mg/dl)	220.86±88.25	190.26±116.10	0.2994
HbA1c (%)	7.52±2.92	7.34±2.78	0.8243
Serum creatinine (mg/dl)	1.08±0.27	1.08±0.28	1
Serum acetone (mg/dl)	<10	<10	
SGPT (unit/liter)	25.48±20.48	21.20±7.18	0.329

SGPT: Serum glutamic pyruvic transaminase, HbA1c: Hemoglobin A1c

Table 2: Random blood sugar and insulin requirement (*n*=50)

	RBS (mg/dl)			Insulin requirement (unit/kg)		
	Control group (*n*=25)	Glargine group (*n*=25)	*P*	Control group (*n*=25)	Glargine group (*n*=25)	*P*
During surgery						
0 h	197.72±72.87	179.4±37.61	0.2695	2.2±3.16	1.48±2.00	0.3406
2 h	232.84±52.36	208.48±49.09#	0.0962	4.64±2.91#	3.68±2.07#	0.1852
4 h	218.76±45.58	186.76±48.45*	0.0201	4.4±2.58#	1.92±2.03*	0.0004
After surgery (ICU)						
0 h	209.52±58.39	175.79±53.53*	0.0384	3.64±2.82	2.11±2.04*	0.0328
6 h	233.08±64.67	173.08±54.81*	0.0005	4.44±2.61	2.04±2.58*	0.002
12 h	226.12±69.13	165.80±38.43*	0.0004	3.84±2.89	1±1.87*,#	0.0001
18 h	208.68±51.45	169.92±38.03*	0.0039	3.4±2.38	1.28±1.92*	0.0011
24 h	200.68±36.76	170.12±48.33*	0.0153	3.6±2.25	1.92±2.39*	0.0137

#Comparison with 0 h significant, *Comparison between control and glargine significant. ICU: Intensive Care Unit, RBS: Random blood sugar

Table 3: Postoperative data (*n*=50)

	Control group (*n*=25)	Glargine group (*n*=25)	*P*
Investigation			
Total count (cmm)	15236.00±3569.86	13904.80±4111.19	0.2275
Serum creatinine (mg/dl)	1.20±0.50	1.08±0.27	0.2963
Serum acetone (mg/dl)	<10	<10	
SGPT (unit/liter)	25.36±13.51	24.00±14.80	0.7358
Complication			
Wound infection	0	0	0
Other infection (%)	6 (24.0)	0	0.0296
Lower respiratory track (%)	4 (60)	0	0.1589
Urinary track infection (%)	1 (20)	0	0.9842
Bacteremia (%)	1 (20)	0	0.9842
Step in antibiotics (%)	10 (40.0)	2 (8.0)	0.0205
Acute renal failure (%)	3 (12.0)	0	0.2337
Stay			
ICU stay (day)	3.92±1.84	2.76±0.43	0.0035
Hospital stay (day)	6.36±1.03	5.0±0.86	<0.0001

SGPT: Serum glutamic pyruvic transaminase, ICU: Intensive Care Unit Stay

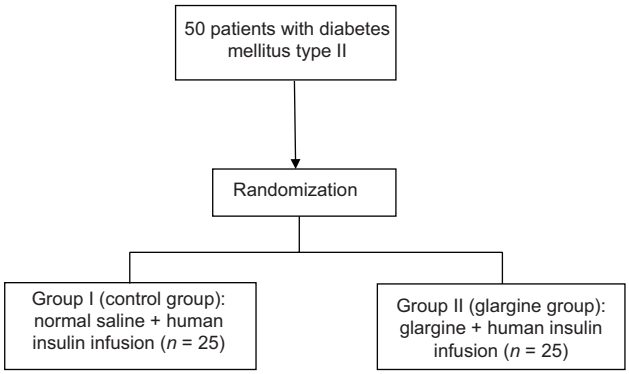

Figure 1: Consort diagram

endothelial dysfunction,[17] and reduces nitric oxide activity, collectively leading to reduced graft patency[18] and increased incidences of procedural failure, Potential benefits of insulin to reduce hyperglycemia-related complications in CABG patients could be explained by the fact that it increases myocardial glucose uptake, reduces oxidative stress, and inflammatory responses. Several prospective randomized studies have documented its role in reducing levels of free-fatty acids and free radicals and ultimately improving the surgery outcome.[19]

Insulin glargine is an analog of human insulin and have low solubility at neutral pH and high solubility at pH 4. The subcutaneous tissue injection leads to neutralization of acidic solution causing the formation of microprecipitates, from which small amounts of insulin glargine are slowly released, resulting in a relatively constant concentration/time profile over 24 h with no pronounced peak. Slow peaking provides glucose control in single daily dose. Basically, it lowers glucose levels by stimulating peripheral glucose uptake, inhibiting lipolysis in the adipocyte, inhibiting proteolysis, and enhancing protein synthesis. The median time between injection and the end of pharmacological effect was 14.5 h (range: 9.5–19.3 h) for NPH human insulin and 24 h (range: 10.8–>24.0 h) (24 h was the end of the observation period) for insulin glargine.

Pharmacokinetic studies in healthy and diabetic population showed that insulin glargine gets absorbed at relatively slower and constant rate over 24 h with no pronounced peak. Hence its serum concentration was consistent with time profile of the pharmacodynamic activity of insulin glargine. In type 1 diabetic patient also relatively constant concentration-time profile of insulin glargine (subcutaneous injection of 0.3 U/kg) is reported. It gets metabolized rapidly at the carboxyl terminus of the beta-chain with the formation of two active metabolites M1 (21A-Gly-insulin) and M2 (21A-Gly-des-30B-Thr-insulin). The duration of action is not affected by the root of administration.

Insulin glargine injection is a human-made form of a hormone that is produced in the body used to treat type 1 (insulin-dependent) or type 2 (noninsulin-dependent) diabetes. The most common side effects of glargine are hypoglycemia or low blood sugar. Symptoms include a headache, hunger, weakness, sweating, tremors, irritability, trouble concentrating, rapid breathing, fast heartbeat, fainting, or seizure (severe hypoglycemia can be fatal). Other common side effects of glargine include pain, redness, swelling, itching, or thickening of the skin at the injection site. These side effects usually go away after a few days or weeks.

Our study is a prospective randomized study designed to demonstrate better glycemic control in diabetic patients with glargine insulin as basal insulin along with continuous human insulin infusion as compared to continuous human insulin infusion only. The routine practice of administration of subcutaneous insulin for glycemic control is less

preferred method as it leads to fluctuating and improper absorption rate.[20] We herewith report that through glargine as basal insulin along with continuous regular insulin infusion, glucose level could be maintained up to 24 h postsurgery along with less fluctuation in glycemic control. 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, but we were unable to achieve this target because this study was designed for blood glucose level between 120 and 180 mg/dl.[4] According to Yeldandi *et al*., once daily glargine insulin provides good glycemic control in hyperglycemic patients after CV surgery which is comparable to twice-daily NPH/regular insulin.[21]

Moreover, Furnary *et al*. reported reduction in the incidence of deep sternal wound infection and mortality with continuous intravenous insulin infusion in patients with diabetes after cardiac surgical procedures.[22,23] Recent studies have shown reduction in the incidence of sternal wound infection, length of ICU stay and mortality, by normalization of postoperative blood glucose in patients with diabetes undergoing CABG.[22-27]

Forouzannia, *et al*. done the same study and concluded that a combination of continuous insulin infusion and glargine insulin as main basal insulin can improve glycemic control in patients with diabetes undergoing CABG, but no significant reduction in postoperative morbidity. In our study, we reported better perioperative glycemic control with significant reduction in postoperative morbidity.[12]

Conclusion

Our study, results suggest that preoperative glargine effectively controls the blood glucose level and reduces the daily requirement of human insulin infusion. It also shows significantly greater control over postoperative morbidity.

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Conflicts of interest

There are no conflicts of interest.

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