Comparative study between tight and moderate glycemic control in non-diabetic patients undergoing coronary artery bypass grafting using cardiopulmonary bypass

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Abstract:

Background: The non-diabetic patients undergoing coronary artery bypass graft (CABG) operation show injurious hyperglycemia, so it is very important to make dynamic glycemic control. The choice between tight and moderate glycemic control is controversy. Using the insulin has many benefits as it reduces the plasma level of the proinflammatory cytokines such as TNF-α, IL-6, IL-8 and ICAM-1 by inhibition of their transcription. Our aim is to compare between both tight and moderate glycemic control for these patients regarding hazards and benefits.

Methods: This prospective, descriptive study with purposive sampling evaluated 60 consecutive patients without diabetes, undergoing CABG surgery. The patients were with normal left ventricular function and randomly distributed into two groups, tight (blood glucose 80-120 mg/dl) and moderate (blood glucose 120-180 mg/dl) glycemic group. Systemic inflammatory markers (IL-6, IL-8 and CRP plasma levels), blood glucose levels, number of blood sugar measurements within target value, incidence of hypoglycemia, the inotropic support need and its duration, the ventilatory support duration, surgical wound infection incidence, renal impairment, the need for renal replacement therapy were measured.

Results: There was higher statistically significance in plasma level of pro-inflammatory cytokines IL-6, IL-8 and CRP in group I (P=0.001). The duration of use of inotropic support was significantly higher in group I (P=0.002). There was no statistically significant difference between two groups regarding the other measurements.

Conclusion: superiority of the moderate glycemic control in the non-diabetic patients undergoing CABG was clear and it achieved better results as it had less inflammatory response, less inotropic support time and avoiding aggressive hypoglycemia side effects.
Keywords: systemic inflammatory response, CABG, glycemic control, insulin, diabetes, cardiovascular, IL-6, IL-8 and CRP.

Background:

Even the non-diabetic patients undergoing CABG operation show perioperative hyperglycemia especially during and after cardiopulmonary bypass (CPB) usage [(1)]. Rising evidence contacts that hyperglycemia with insulin resistance and increased inflammatory state resulting in inflammatory cytokines release such as IL-6, TNF-α, , IL-1β, IL-8 and resistin from macrophages and/or adipocytes ***(2)*****.** Increased plasma and/or tissue concentrations of these cytokines are thought to have a negative effect on metabolism and stimulation of peripheral insulin resistance ***(3)*****.**

Perioperative hyperglycemia is a chief hazard factor for death, cardiovascular, renal, respiratory, and infectious complications ***(4)*****.** So dynamic glycemic control prevents damage to vital organs and thereby improve critically ill patients outcome ***(5)*****.**
The insulin has immunoregulatory effects and expected to decrease the formation of CRP and proinflammatory cytokines by inhibition of their transcription**.** But, aggressive insulin infusion could lead to hazardous hypoglycemia ***(6)***.
Serum IL-6 and IL-8 levels are clear indices of inflammatory cascade activation and analyst of subsequent organ dysfunction. Continued increases of IL-6 levels are linked with postoperative morbidity and mortality [(7)].
CRP is a sensitive but non-specific marker of tissue damage, infection and systemic inflammation. The inflammation markers are important predictors of bad prognosis and post-operative outcome in patients undergoing on-pump CABG [(8)].
Controlling blood glucose especially during cardiopulmonary bypass (CPB) is difficult. This is due to many contributing factors such as insulin resistance and hypothermia during CBP [(9)].
Insulin resistance plus hypothermia may be provoked by insulin adherence to the extracorporeal circuit plastic material and by the steroids that may be used to suppress inflammatory reaction of CPB [(10)]. Although transmembrane protein defects are

thought to play a role in insulin resistance, the underlying molecular mechanisms are not fully understood [11].

Aim of the Work:

To compare between outcomes and safety of both tight and moderate glycemic control in non-diabetic patients undergoing CABG surgery perioperatively especially regarding inflammatory cytokines.

Patients and Methods: This prospective, descriptive study with purposive sampling evaluated 60 consecutive patients without diabetes, undergoing CABG surgery. This study was conducted in Fayoum University hospitals, Cairo University hospitals and National Heart Institution. Approval was obtained from the research ethics committee of the anesthesia department of Fayoum University, Cairo University and National Heart Institution and written consent was obtained from all patients. Sixty adult patients of the same age group with diabetes who had undergone on-pump coronary artery bypass grafting were registered in this study.

Emergency CABG, redo CABG, combined CABG and any other cardiac procedure, patients with poor ventricular function (Ejection Fraction < 40% and patients with impaired liver or kidney functions were the exclusion Criteria.

Study groups

The Patients were randomly allocated into two groups, 30 patients each: ***Group (I)*** as the tight glycemic control group (target blood glucose 80-100 mg %) and ***Group (II)*** as the moderate glycemic control group (target blood glucose < 180 mg %)

Preoperative Management of blood glucose:

24 hours prior to surgery, oral hypoglycemic agents were discontinued. Diabetic patients on insulin had their daily dose of insulin held the evening before surgery and a standard subcutaneous insulin sliding scale was begun until the intraoperative insulin infusion protocol was started.

Intraoperative management of blood glucose:

Each study group followed a separate intraoperative insulin infusion protocol (or method) as shown below:

Group I (Tight dynamic glycemic control method):

The patients in this group followed a dynamic protocol of insulin infusion. The goal of this protocol was to keep blood sugar level between 80-120 mg/dL**.**

Blood glucose levels were tested every 30 minutes. The patients received a regular insulin continuous infusion (Actrapid insulin, Novo Nordisk, Copenhagen, Denmark) in 50ml of 0.9 % NaCl) using a syringe pump. The dose was adjusted under strict supervision of a team of anesthetists and ICU nurses assisted by ICU physicians. Serial blood glucose measurements were achieved by ***(Accucheck Go, Roche, Germany)*** glucose meters.

We were following the protocol by ***Ghandi and coworkers*** [(2)] shown in Table (1) [(2)]:

Column 1		Column 2		Column 3	
Serum glucose Level, mg/dL	Insulin infusion Rate, U/h	Serum glucose Level, mg/dL	Insulin infusion Rate, U/h	Serum glucose Level, mg/dL	Insulin infusion Rate, U/h
>400	18	>400	25	>400	30
351-400	16	351-400	22	351-400	27
301-350	14	301-350	20	301-350	24
251-300	12	251-300	18	251-300	21
201-250	10	201-250	15	201-250	18
176-200	8	176-200	12	176-200	15
151-175	6	151-175	9	151-175	12
121-150	4	121-150	7	121-150	9
101-120	2	101-120	4	101-120	6
80-100	1	80-100	2	80-100	3
<80	Off	<80	Off	<80	Off

Column 1: All patients started in column 1 and restarted in this column when glucose level <80 mg/dL.

Column 2: If patient had not reached glucose level range of 80-120 mg/dL within 2 hours after column 1 usage and glucose level has decreased by <50 mg/dL over preceding 1 hours, column 2 was used.

Column 3: Was used if patients had not achieved blood glucose level range of 80-120 mg/dL within 2 hours of using column 2 and glucose level had decreased by <50 mg/dL over preceding 1 hour.

If glucose level was <60 mg/dL, treatment of hypoglycemia protocol had initiated by 50ml of 10% dextrose infusion. Glucose was then monitored every 30 minutes till

glucose level was >80 mg/dL. Then dextrose 10% was discontinued and insulin infusion was always resumed in column 1.

Group II (The moderate glycemic control):

Group II received the intravenous insulin infusion titrated to maintain blood glucose level from 120 - 180 mg/dL. Preparation of this insulin infusion was the same as in group I and blood glucose measurements were also performed by ***Accucheck Go, Roche, Germany*** glucose meters.

The regimen was applied as follows:

- If baseline blood glucose level > 180 mg/dL, a bolus of 2 units was started followed by insulin infusion at 2 units/ hours. Blood glucose measurement was done every 30 minutes.

The regimen is demonstrated in table (2) below:

Table (2): moderate glycemic control regimen

> 180 mg/dl	Increase infusion by 2 units/hour
Between 108 and 180 mg/Dl	Maintain current infusion rate
< 108 mg/Dl	Stop insulin infusion
< 72 mg/dL	Stop insulin infusion and administer 25 mL of Dextrose 50%

Maximum insulin infusion = 20 unit per hour [(8)].

Postoperative management of blood glucose

In the ICU, the tight glycemic control protocol was continued at least 24 hours postoperatively for both study groups until enteral feeding was started. The insulin infusion was prepared and checked as was stated above. Then diabetic patient restarted their preoperative insulin regimen of oral hypoglycemic [(2)].

Measurements

Blood glucose levels, number of blood sugar measurements within target value, hypoglycemia incidence, the inotropic support need and its duration,

the ventilatory support duration, surgical wound infection incidence, systemic inflammatory response (IL-6, IL-8 and CRP), renal impairment and the need for renal replacement therapy were measured. Renal impairment is defined as increase in serum creatinine by more than or equal to 0.3mg/dL.

IL-6 and IL-8 Assay: Citrated 4.5-mL blood samples were drawn during and after CPB. These were immediately centrifuged (3500*g*, 10 minutes), and plasma was separated and frozen at 220°C until analysis. Using commercially available enzyme-linked immunosorbent assay (ELISA) kits (DuoSet, R & D Systems, Minneapolis, MN), IL-6 and IL-8 concentrations (pg/ml) were determined according to the manufacturer's instructions. IL-6 and IL-8 concentrations were measured by using a standard commercial assay (R&D Systems) by a staff blinded to all subject data. Interassay and intra-assay coefficients of variation were 5% and 3%, respectively.

Statistical Analysis: Statistical presentation and analysis of the present study was conducted, using the mean, standard error, student t- test, paired t-test, Chi-square and Linear Correlation Coefficient by SPSS V17. Unpaired Student T-test was used to compare between two groups in quantitative data.

Results:

Between April 2012 and December 2014, a total of 60 participants were recruited to this study and were randomly allocated to group I (30 participants) or group II (30 participants). The results revealed no significant changes between both groups regarding demographic characteristics as shown in Table (3).

Tab (3): Demonstration data in both groups

Demonstration data		Group I (N=30)	Group II (N=30)	P value
Age		53.700 ± 5.342	54.060 ± 4.838	0.72
Gender	Male	21 (76%)	19 (74%)	1.00
	Female	9 (24%)	11 (26%)	
Weight		86 ± 13.67	81 ± 9.20	0.71

BMI	33.5 ± 7.08	29.66 ± 5.32	0.67

Comparing between the systemic inflammatory response in the tight and moderate group (group I and group II respectively), there was higher statistically significance in plasma level of pro-inflammatory cytokine IL-6 and IL-8 in group I (P=0.001) as shown in figure 1 and 2. Also, there was higher statistically significance in plasma level of CRP in group I (P=0.001) as shown in figure 3.

Figure (1): Primary outcome; IL-6 in both groups:

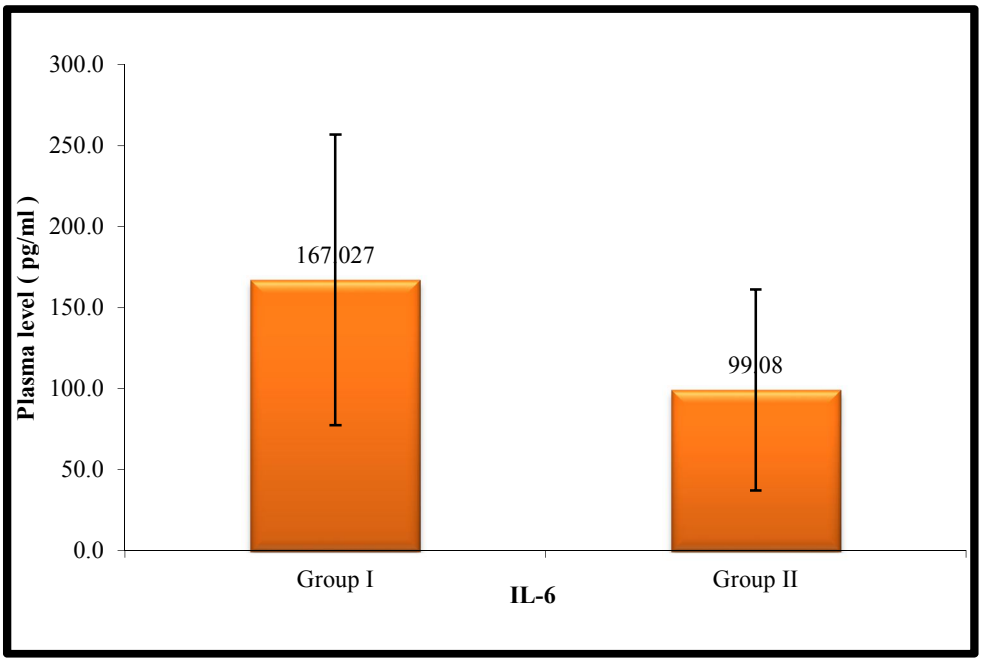


Figure (2): Primary outcome; IL-8 in both groups:

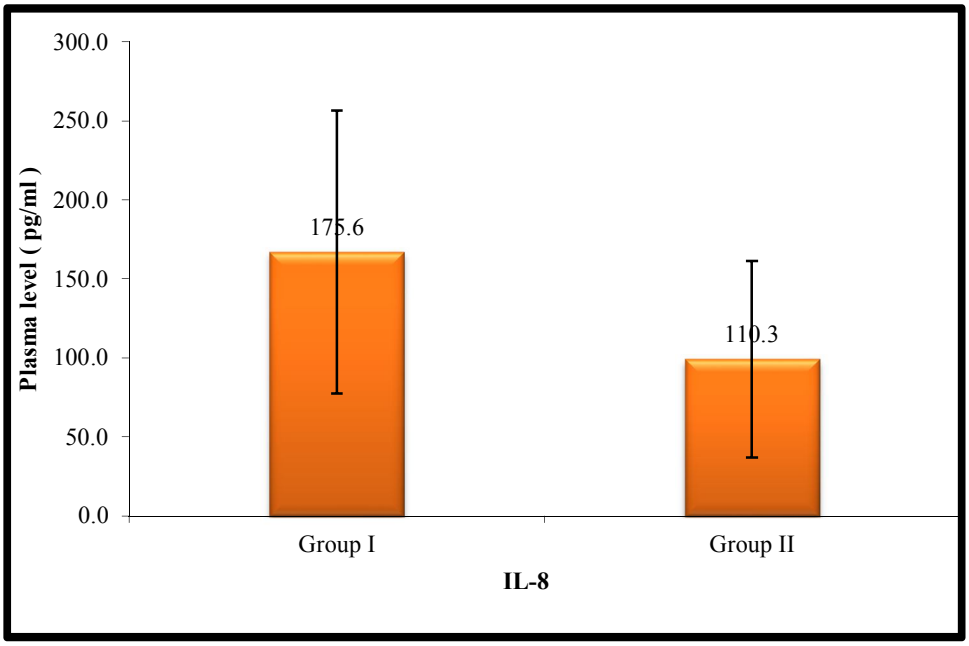
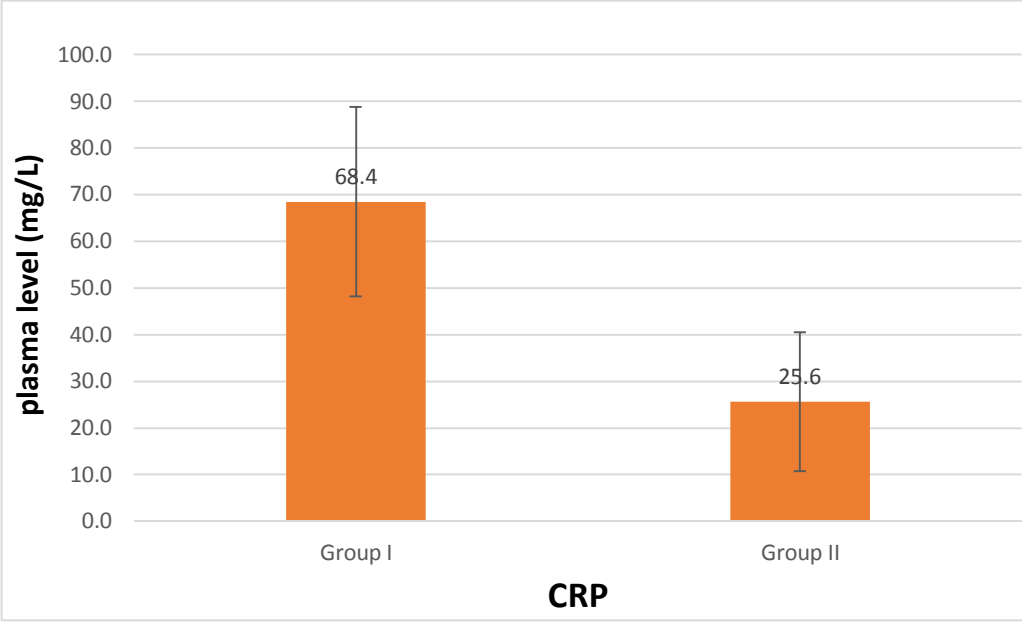


Figure (3): C - reactive protein (CRP) in both groups:



There was a statistically significant difference regarding the duration of inotropic support use (median value of the number of hours) in group I and group II. The duration of use of inotropic support was significantly higher in group I (P=0.002).

There was no statistically significant difference between two groups regarding number of measurements of blood sugar within target value, incidence of hypoglycemia, need of inotropic support, duration of ventilation, renal impairment and wound infection.

Tab (4): Secondary outcomes in both groups:

Secondary outcomes	Group I (N=30)	Group II (N=30)	P value
Number of measurements of blood sugar within target value	78.180 ± 11.317	82.000 ± 13.406	0.1296
Incidence of Hypoglycemia	5 (16.66%)	1 (3.33%)	0.084
Need of inotropic support	28 (93.33%)	27 (90.00%)	0.640
Duration of Inotropic support	11.20 ± 4.21	7.26 ± 3.45	0.002*
Duration of ventilation	8.600 ± 2.231	9.720 ± 3.676	0.069
Renal impairment	1 (3.33%)	1 (3.33%)	1.000
Wound infection	1 (3.33%)	1 (3.33%)	1.000
Intraoperative mortality	None	None	---

Discussion:

The main finding of this study was that moderate glycemic control is better than tight glycemic control for non-diabetic patients undergoing CABG operation.
Like our study, many studies on cardiac surgical non-diabetic patients classified the patients into two groups, intensive and liberal glycemic control groups like Thomas [(9)], Lazar HL [(10)] and Gandhi and coworkers [(2)].

Thomas and coworkers study [(9)] indicated that a moderate glycemic control strategy during CABG leads to improvement in health-related quality of life and survival rates that are similar to those achieved with a tight target range. In addition, the liberal strategy has superiority in glucose control and target range management.

As regard the safety of glycemic control, statistically significant more incidences of hypoglycemia were detected in the tight glycemic group (4 patients) 14% versus (1 patient) 3% in the moderate group in our study. Azam and coworkers [3] in their study exposed that hypoglycemia has harmful effects on the brain as it is an obligate glucose metabolizer. Severe hypoglycemia can cause neuronal necrosis by increased excitatory amino acids concentrations, with more affection of the superficial layers of the cortex and the dentate gyrus of the hippocampus; however, the cerebellum and brainstem are spared injury [17] .

In our study, we demonstrated that maintenance of blood glucose in a moderate glycemic control perioperatively in CABG using CBP led to perioperative results similar to those achieved with a tight control but also was superior in glucose control, target range management, less duration of inotropic support and suppressed inflammatory response.

Our study matched with Castigliano and coworkers [11], Griesdale and coworkers [12] and Lazar and coworkers [6].

In our study, regarding the need of inotropic support, there were no statistically significant differences between group I and group II regarding the need of inotropic support. But the moderate glycemic control has statistically significant reduction in the duration of inotropic support use (being < 12 hours or > 12 hours) in group II versus group I (P = 0.022).

As some studies prove while others fail to prove that insulin decreases the need of inotropic support, we have found no studies on the insulin effect on the duration of inotropic support use. Our study proved that insulin had no outcome on the need but decreased the duration of inotropic support use. We need to conduct further studies aiming to discover and explicate how insulin may affect the duration of inotropic support use in CABG patients.

As regards the duration of ventilation there was no statistically significant between group I and group II.

Desai et al [13], Bhamidipati et al, [14] and Pezzella et al [19] study demonstrated that the moderate group was also superior to the tight group in the perioperative results of

prolonged ventilation, pneumonia, deep sternal wound infection, perioperative renal failure, and operative mortality. On the basis of these results, it seems reasonable to set the target BG range to between 121 and 180 mg/dL for this group of patients undergoing first-time isolated CABG.

On the other hand, the study by Gandhi and coworkers [2] and Giakoumidakis and coworkers [18] demonstrated that there was no difference in the incidence of prolonged ventilation 19% in tight group versus 20% in conventional group (P = 0.82).

Our study may presume that perhaps higher doses of insulin usage may incompletely counteract these harmful effects of insulin deficiency and/or resistance on the lung. Also it suppose that the insulin inotropic and vasodilator effects may decrease lung congestion.

In our study there was no statistically significant difference between the incidence of renal impairment in both groups (P=1.000). Only one case of renal impairment occurred in group I (TGC) and also one case of renal impairment occurred in group II. The study by De la Rosa and coworkers [15] and Gauthier et al, [20] was similar to our results but against our results was the study by Van den Berghe and coworkers [16].

As regards wound infection in our study , the tight glycemic control group showed one case incidence of wound infection and also the moderate group showed one case incidence of wound infection (p=1.000).

With regard to the systemic inflammatory responses, our study proved a decrease of inflammation with the 2 groups but there was major reduction of inflammatory cytokine mediators such as IL-6, IL-8 and CRP in the moderate glycemic control group.

Comparing between the systemic inflammatory response in the tight and moderate groups, there was higher statistically significance in plasma proinflammatory cytokine IL-6 and IL-8 levels and CRP plasma level in group I (P=0.001).

Our results agreed with Desai et al, [13] Bhamidipati et al, [21] and Haga et al, [22] study results as they found significant decrease in inflammatory mediators as IL-6, IL-1, IL-8, CRP and ESR in moderate glycemic control.

Against our study, Lazar et al, [6] had shown in their series that one of the aggressive glycemic control benefits is that inflammation markers, such as free fatty acids, are markedly reduced.

References:

1- 1- Krinsley JS, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, et al. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. Crit Care. 2013; 17(2):R37.

2- Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC, Johnson MG, Williams AR, Cutshall SM, Mundy LM et al., Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Ann Intern Med 2007; 146(4):233-243.

3- Azam AL, Zachary S, Craig RN: Effectiveness of tight glycemic control on mortality and morbidity. JBI Database of Systematic Reviews & Implementation Reports 2014; 12(9) 132 – 145.

4- Krinsley JS, Meyfroidt G, Van den Berghe G, Egi M, Bellomo R. The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. Curr Opin Clin Nutr Metab Care. 2012; 15(2):151–60.

5- Shalin P. Desai, MD, Linda L. Henry, PhD, Sari D, Sharon L, Hunt, MBA, Chidima T. Martin, BS, CCRP, Shrinivas Hebsur, MD, and Niv Ad: Strict versus liberal target range for perioperative glucose in patients undergoing coronary artery bypass grafting: A prospective randomized controlled trial: J Thorac Cardiovasc Surg: 2012;143:318-25.

6- Lazar HL, McDonnell M, Chipkin S, Fitzgerald C, Bliss C, Cabral H. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary bypass graft patients. Ann Surg: 2011; 254:458-64.

7- The NICE-SUGAR study investigators. Intensive versus conventional glucose control in critically ill patients. NEJM: 2009; 360:1283–97.

8- Leibowitz G, Raizman E, Brezis M, Glaser B, Raz I, Shapira O. Effects of moderate intensity glycemic control after cardiac surgery. Ann Thorac Surg. 2010; 90(6):1825–32.

9- Thomas P, Holmes, Graciela, Speir, and Niv Ad: Impact of Perioperative Glycemic Control Strategy on Patient Survival after Coronary Bypass Surgery. The Society of Thoracic Surgeons. (Ann Thorac Surg 2014; 98:1281–5).

10- Lazar HL: Glycemic Control during Coronary Artery Bypass Graft Surgery. International Scholarly Research Network ISRN Cardiology, Volume 2012, Article ID 292490, doi:10.5402/2012/292490

11- Castigliano M. Bhamidipati, DO,Damien J. LaPar, MD, George J. Stukenborg, MA, PhD, Christine C. Morrison, MSN: Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg; 2011; 141:543-51.

12- Griesdale DE, de Souza RJ, van Dam RM, Heyland DK: Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009; 180:821-827 discussion 799–800.

13- Desai, MD, Shalin P. Linda L. Henry, PhD, Sari D. Holmes, PhD, Sharon L. Hunt, MBA, Chidima T. Martin, BS, CCRP, Shrinivas Hebsur, MD, and Niv Ad, MD: Strict versus liberal target range in patients undergoing CABG: A prospective randomized controlled trial. J ThoracCardiovascSurg 2012; 143:318-25.

14- Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, Ailawadi G: Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J ThoracCardiovascSurg 2011; 141:543-551.

15- De la Rosa G, Danado JH, Restrepo AH, Quintero AM: Strict glycemic control in patients hospitalized in a mixed medical and surgical intensive care unit: a randomized clinical trial. Critical Care 2008; 12(5):1-9.

16- Van den Berghe G: Does tight blood glucose control during cardiac surgery improve patient outcome? Ann Intern Med 2007; 146:307–8.

17- Hargraves JD. Glycemic control in cardiac surgery: implementing an evidence-based insulin infusion protocol. Am J Crit Care. 2014; 23(3):250–8.

18- Giakoumidakis K, Eltheni R, Patelarou E, Theologou S, Patris V, Michopanou N, et al. Effects of intensive glycemic control on outcomes of cardiac surgery. Heart Lung. 2013; 42(2):146–51.

19- Pezzella AT, Holmes SD, Pritchard G, Speir AM, Ad N. Impact of perioperative glycemic control strategy on patient survival after coronary bypass surgery. Annal Thorac Surg. 2014; 98(4):1281–5.

20- Pezzella AT, Holmes SD, Pritchard G, Speir AM, Ad N. Impact of perioperative glycemic control strategy on patient survival after coronary bypass surgery. Annal Thorac Surg. 2014; 98(4):1281–5.

21- Bhamidipati CM, LaPar DJ, Stukenborg GJ, Morrison CC, Kern JA, Kron IL, et al. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg. 2011; 141(2):543–51.

22- Haga KK, McClymont KL, Clarke S, Grounds RS, Ng KY, Glyde DW, et al. The effect of tight glycaemic control, during and after cardiac surgery, on patient mortality and morbidity: a systematic review and meta-analysis. J Cardiothorac Surg. 2011; 6:3.

23-