Original Article

Comparison of intensive insulin therapy and conventional glucose management in patients undergoing coronary artery bypass grafting

Vaishali Mohod, Veena Ganeriwal, Juilee Bhange

Department of Anaesthesiology and Critical Care, Grant Medical College and Sir JJ Group of Hospital, Byculla, Mumbai, Maharashtra, India

Abstract

Background and Aims: Hyperglycemia during cardiac surgery is a risk factor for postoperative outcomes. Because incidence of diabetes mellitus is increasing in Indian population, we tried to evaluate the western protocol for strict control of blood sugar perioperatively. The main aim of the study was to evaluate glycemic control during coronary artery bypass grafting and to determine whether intensive insulin therapy (IIT) is better than the conventional one.

Material and Methods: A prospective randomized comparative study was conducted to evaluate IIT and conventional management of glucose in 40 patients undergoing on-pump coronary artery bypass grafting. Outcomes measured were incidence of hyperglycemia or hypoglycemia, incidence of hypokalemia, prolonged intubation, wound infections, strokes, acute renal failure, new onset arrhythmias, length of stay in ICU and hospital, cardiac arrest and mortality. The statistical analysis was done by using Chi-square test, and paired and unpaired *t* test.

Results: The diabetic patients had significantly higher mean blood sugar and insulin requirement. The incidence of hyperglycemia was significantly higher in conventional management of blood sugar ($P = 0.001$), whereas hypoglycemia ($P = 0.047$) and hypokalemia ($P = 0.020$) were significantly higher in IIT. There were no significant difference in the incidence of prolonged intubation, wound infection, length of ICU and hospital stay, strokes, acute renal failure, new onset arrhythmias, cardiac arrest, and mortality.

Conclusion: The IIT did not improve the morbidity and mortality in our patients undergoing coronary artery bypass grafting.

Keywords: Coronary artery bypass grafting, glycemic control, intensive insulin therapy

Introduction

Intraoperative glucose control during cardiac surgery is often difficult. Intraoperative blood glucose control for good postoperative outcome in the cardiac surgery depends on preoperative control of diabetes, intraoperative management of blood sugar, duration of cardiopulmonary bypass, use of inotropic agents, other co-morbidities, etc. Hyperglycemia in response to stress during on-pump coronary artery bypass grafting (CABG) increases vulnerability to surgical site infection, neurological damage, cardiac and renal injury, and perioperative mortality.[1,2]

Intense blood glucose control targeting blood glucose levels between 80 and 110 mg/dl resulted in a reduction in morbidity and mortality in the critically ill patient population including cardiovascular surgery patients.[3,4] Intensive insulin therapy (IIT) has been shown to reduce infection rates, improve outcomes in acute neurologic injury and acute myocardial infarction, and

Address for correspondence: Dr. Vaishali Mohod,
4/31, Swastik Building, J J Hospital Campus, Byculla, Mumbai-8, Maharashtra, India.
E-mail: vamohod2001@yahoo.co.in

Access this article online	
Quick Response Code:	Website: www.joacp.org
	DOI: 10.4103/joacp.JOACP_61_17

How to cite this article: Mohod V, Ganeriwal V, Bhange J. Comparison of intensive insulin therapy and conventional glucose management in patients undergoing coronary artery bypass grafting. J Anaesthesiol Clin Pharmacol 2019;35:493-7.

improve survival after cardiac surgery.[5,6] However, recent evidence of severe hypoglycemia associated with IIT brings its safety and efficacy into question.[7,8] Some clinical trials evaluating other patient populations have also shown a reduction in morbidity with a lesser impact on mortality using tight blood glucose control. In addition, it has been observed that blood glucose variability is an independent predictor of ICU and in-hospital mortality.[9]

This study was designed with the primary objective to study glycemic control during on-pump CABG and to compare conventional versus IIT in these patients. Secondary objective was to evaluate whether IIT is better than conventional management of glucose in the terms of various outcomes in postoperative period.

Material and Methods

After institutional ethics committee approval, a prospective randomized comparative study was conducted in 40 adult diabetic and non-diabetic patients posted for on-pump CABG. Patients with diabetic ketoacidosis or hyperosmolar coma were excluded from the study. Preoperatively patients were evaluated as per the study protocol. They were divided into two groups of 20 by computer based random tables.

Group I (IIT):[7] Patients received continuous intravenous infusion of 50 units of recombinant human insulin diluted in 50 ml of 0.9% sodium chloride solution, to maintain tight control of blood sugar level between 80 and 110 mg/dl. Insulin infusion was started after induction of anesthesia and continued intraoperatively as well as for 48 h postoperatively in the intensive care unit (ICU). The required rate of insulin infusion was calculated according to the standardized algorithm [Table 1].

Insulin infusion was started as per the corresponding blood sugar values given in column 1. If insulin infusion had to be discontinued because of blood sugar levels below 80 mg/dl and later restarted, when the blood sugar levels were above 80 mg/dl, it was always restarted according to this column.

Insulin infusion was given as per column 2, if the patient did not reach blood sugar level in the range of 80–110 mg/dl within 2 h of using column 1 protocol, or if blood sugar levels decreased by less than 50 mg/dl over the preceding 2 h of using column 1 protocol.

Insulin infusion was given as per column 3, if the patient did not reach blood sugar level in the range of 80–110 mg/dl within 2 h of using column 2 protocol, or if blood sugar levels decreased by less than 50 mg/dl over the preceding 2 h of using column 2 protocol.

When blood sugar levels dropped below 80 mg/dl, insulin infusion was stopped, and 50 ml/h of 5% dextrose infusion was initiated. Thereafter, blood sugar was checked every 30 min until the sugar level was more than or equal to 80 mg/dl (however, these 30 min readings have not been entered in our monitoring charts, and only the next value as per the study protocol time intervals have been entered). When blood sugar level ≥80 mg/dl was achieved, dextrose infusion was discontinued. Insulin infusion was then resumed, always as per column 1 of the algorithm.

This protocol was followed for maintaining tight control of blood sugar levels between 80 and 110 mg/dl throughout the intraoperative as well as the 48 h postoperative period.

Group II (Conventional insulin therapy): Patients received conventional treatment of insulin i.e., they were not given insulin unless blood sugar levels were more than 200 mg/dl. If blood glucose concentration was between 200 and 250 mg/dl, the patients received an intravenous bolus of 4 units of insulin every hour until the glucose concentration was below 200 mg/dl. If the blood glucose levels were above 200 mg/dl despite bolus dose, then the patients received an intravenous infusion of

Table 1: Insulin infusion protocol

Column 1		Column 2		Column 3	
Serum glucose level (mg %)	Insulin infusion rate (U/h)	Serum glucose level (mg %)	Insulin infusion rate (U/h)	Serum glucose level (mg %)	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

insulin, which was continued until the blood glucose level was below 200 mg/dl. This was carried out intraoperatively as well as up to 48 h postoperatively in the ICU.

In both the groups, blood glucose levels were measured on induction, on bypass, at the end of first hour, second hour, and third hour on bypass, off bypass, postoperatively on admission to ICU, during the first 24 h at 2 hourly intervals and next 24 h at four hourly intervals. Arterial blood samples were drawn for each of the blood glucose measurements through an arterial line. The blood glucose concentration was measured with the help of One Touch Horizon blood glucose monitor, and same sample was subjected to arterial blood gas and electrolyte analysis.

Dextrose containing fluids were avoided and administered only during episodes of hypoglycemia. Patients were kept nil by mouth depending on the individual duration of postoperative intubation and ventilation. Thereafter starting with clear liquids, patients were shifted on soft diet within the next 24 h. Patients were not given any oral diabetic medications or subcutaneous insulin during this period. Diabetic patients were put on oral hypoglycemic agents and/or insulin 48 h postoperatively as per the recommendation of physicians. The patients were followed up till discharge from the hospital.

The primary outcomes studied were incidence of hyperglycemia (blood sugar ≥200 mg/dl) and hypoglycemia (blood sugar ≤80 mg/dl), and requirement of total insulin during perioperative period. The secondary outcomes studied were incidence of hypokalemia, prolonged intubation, wound infections, strokes, acute renal failure, new onset arrhythmias, length of stay in ICU and hospital, cardiac arrest, and mortality. Observed data were compiled and statistically analyzed using Chi-square test and paired and unpaired *t* test.

Results

Both groups were comparable in their baseline characteristics [Table 2].

The mean as well as total insulin requirement was significantly higher in the intensive group than the conventional group intraoperatively as well as postoperatively ($P = 0.001$). In the diabetic patients of both the groups, the mean insulin requirement was significantly higher in the intensive group during the postoperative period. In the non-diabetic patients of both the groups, the total as well as the mean insulin requirement was significantly higher in the intensive group than the conventional group during the intraoperative as well as postoperative periods ($P = 0.001$) [Table 3].

Eleven patients out of 20, in the conventional group developed hyperglycemia (blood sugar >200 mg/dl), where as none of the patients in the intensive group developed hyperglycemia ($P = 0.001$) [Table 4]. It was also found that five out of 20 patients (25%) in the intensive group developed hypoglycemia ($P = 0.047$). Hypokalemia (serum $K+ < 3.5$ mEq/L) occurred in six out of 20 patients in the intensive group. It was noted that this hypokalemia was mild and did not lead to any ECG changes or arrhythmias. Two patients in the conventional group (10%) developed renal failure and received hemodialysis. Two patients in the intensive treatment group and four patients in the conventional treatment group developed sternal wound infections. The incidence of prolonged intubation (>48 h) was not significantly different in the two groups. Three patients in the intensive treatment group and four patients in the conventional group required prolonged intubation. The mean length of ICU stay for patients in the intensive group and conventional group was not significantly different ($P = 0.097$).

Table 2: Demographic characteristics and co-morbidities

	Group I		Group II	
	n	%	*n*	%
Mean age (SD)	54.1 (9.9)		56.1 (8.0)	
Mean body mass index (SD)	28.6 (3.7)		27.5 (2.7)	
Sex				
M	18	90	17	85
F	2	10	3	15
Diabetes	8	40	8	40
H/O smoking				
Current	1	5	0	0
Past	7	35	9	45
Never	12	60	11	55
H/O AMI	11	55	13	65
H/O stroke	0	0	1	5
ASA class				
II	0	0	0	0
III	18	90	17	85
IV	2	10	3	15
Type of surgery				
Only CABG	18	90	16	80
CABG with other procedure	2	10	4	20

H/O=History of, AMI=Acute myocardial infarction

Table 3: Comparison of insulin requirement

Study Groups	Diabetic status	Intraoperative	Postoperative	Total
Group I	Diabetics	24.5±2.6	128±45	152±45.6
	Nondiabetics	17.33±3.7	88.67±28.9	106±29.5
Group II	Diabetics	16.7±11.9	14±5.3	30.75±14
	Nondiabetics	2±3.7	2±4	4±7.4
	Mean insulin requirement			
Group I		20.20±4.8	104.4±40.3	124±42.3
Group II		7.9±10.7	6.8±7.5	14.7±16.9

Table 4: Comparison of outcomes in intensive therapy and conventional therapy

Outcomes	Group I	Group II
Mean Length of ICU stay (days)	3.3	4.2
Mean Length of hospital stay (days)	11.0	17.2
Hyperglycemia	0	11 (55%)
Hypoglycemia	5 (25.0%)	0
Hypokalemia	6 (30%)	0
Renal failure	0	2 (10%)
Prolonged intubation	3 (15%)	4 (20%)
Wound infection	2 (10%)	4 (20%)
New onset arrhythmias	3 (15%)	3 (15%)
Stroke	0	1 (5%)
Cardiac arrest	3 (15%)	4 (20%)
Mortality	3 (15%)	4 (20%)

Two patients in intensive group required re-exploration for postoperative bleeding. One more patient had sudden onset arrhythmias and cardiac arrest. In conventional group, two patients had renal failure, one patient had stroke, and one patient had sepsis. Out of these four, three had new onset arrhythmias leading to cardiac arrest to which they succumbed ($P = 0.677$).

Discussion

It has been found in number of studies that maintaining a tight control of blood sugar between 80–110 mg/dl is difficult despite an IIT.[3,7,10] Some studies observed that IIT was not only related to a reduction in the average glucose level but also reduction in the variability of glucose levels perioperatively along with duration of hyperglycemia.[11,12] Hypoglycemia is a major concern with aggressive insulin administration in anesthetized and sedated ICU patients who cannot report symptoms of low blood glucose. As such, there is no consensus definition of hypoglycemia; we considered <80 mg/dl as hypoglycemia. Brunkhorst *et al*. terminated a study of IIT for critically ill patients after the first safety analysis, in view of significant incidence of hypoglycemia in the intensive treatment group (12.1%) compared to the conventional therapy group (2.1%) ($P < 0.001$).[13,14] The principal investigators of the Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation study also found that severe hypoglycemia (glucose less than or equal to 40 mg/dl) occurred in 6.8% of those in the intensive therapy group, compared with 0.5% in the conventional therapy group ($P = 0.03$). Gandhi *et al*. found that the intraoperative insulin requirement in the intensive group was 19 ± 16 units, whereas in the conventional group it was 2 ± 5 units.[7] Their postoperative insulin requirement was similar in both the groups because they maintained tight control of blood sugar in both the groups in the postoperative period.

In this study, every blood sample taken for blood sugar measurement was subjected to electrolyte analysis to measure the potassium levels. Thus, early detection of hypokalemia was possible and prompt correction could be instituted. Earlier study by Van den Berghe found that 41% reduction in the incidence of renal failure in patients receiving IIT as against those on conventional glucose management.[3] LeComte *et al*. reported that in non-diabetics, strict perioperative blood glucose control was associated with a significantly reduced incidence of renal impairment ($P = 0.01$), renal failure ($P = 0.02$), and acute postoperative dialysis (from 3.9% in control group to 0.7% in insulin group ($P < 0.01$).[9] Their scoring was according to RIFLE (Risk, Injury, Failure, Loss of kidney function, End stage kidney disease) criteria [an international consensus classification for acute kidney injury, which defines three grades of severity – risk (class R), injury (class I), and failure (class F)]. Azevedo *et al*. did not find a significant difference in renal function outcome in the two groups ($P = 0.37$)[10], which correlated with the results of the present study.

Furnary AP *et al*. conducted a follow-up study evaluating the effect of continuous insulin infusion found significant decrease in deep sternal wound infections with IIT ($P = 0.005$).[2] Vora *et al*. assessed the effects of tight blood glucose control of 120 to 200 mg/dl, using continuous insulin infusion in diabetic patients after cardiac surgery, reported a decrease in the incidence of deep surgical wound infections in the intensive group (4.63% versus 4.94% in the conventional group).[5] Van den Berghe *et al*. found that patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care along with decreased in hospital mortality by 34%.[3] Lazar HL *et al*. (2000) also found that patients treated with GIK (Glucose Insulin Potassium) infusion had a significantly shorter duration of ventilator support (8.35 ± 2.60 versus 13.45 ± 7.33 h; $P = 0.0128$) and hospital stay (6.70 ± 1.52 versus 10.15 ± 6.62 days; $P = 0.02$) than the patients on conventional glucose management after CABG.[15,16]

The benefits of strict glycemic control during cardiac surgery was questioned by Gandhi *et al*., suggesting higher mortality for patients receiving IIT to achieve tight control of blood glucose levels between 80–100 mg% (four deaths vs. 0 deaths in the conventional group; $P = 0.061$). In meta-analysis of various RCTs, it has been suggested that there may be a significant reduction in early mortality in the tight glycemic control groups.[17-20] In the Action to Control Cardiovascular Risk in Diabetes study, there was no significant difference in the rate of nonfatal stroke (1.3% vs. 1.2%; $P = 0.74$) between the two study groups.[18]

When the present study was started, the existing guidelines for blood sugar control were from the American Association of Clinical Endocrinologists for in-hospital management of blood glucose in critically ill patients that suggested a goal blood sugar of 80 to 110 mg/dl.[21] Later in 2009, it was recommended that blood glucose should be maintained between 140 and 180 mg/dl in critically ill patients admitted in ICU, with increased benefits in maintaining blood glucose closer to 140 mg/dl. The Society of Thoracic Surgery workforce on evidence based surgery recommended maintenance of intraoperative as well as postoperative blood sugar <180 mg/dl for 24 h in diabetic patients by continuous insulin infusion and in non-diabetics by intermittent or continuous insulin to maintain the same level.[22] Maintenance of blood glucose below 110 mg/dl is no longer recommended.

Limitations: The study included diabetics and non-diabetic patients who received IIT irrespective of diabetic status. This study included small Indian population and can be used to design a future larger study in same population.

Conclusion

We noted that maintenance of strict glucose control is very difficult in conventional glucose management than with IIT in on-pump CABG patients. The IIT did not significantly improve the morbidity and mortality in Indian patients undergoing on pump CABG as compared to conventional glucose management.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Herlitz J, Wognsen G, Emanuelsson H, Haglid M, Karlson BW, Karlsson T, *et al*. Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. Diabetes Care 1996;19:698-703.
2. Furnary AP, Changle H, Zerok J. Post-operative hyperglycemia prolongs length of stay in diabetic CABG patients. Circulation 2000;290:1868-74.
3. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, *et al*. Intensive insulin therapy in the critically ill patients. N Engl J Med 2001;34:1359-67.
4. Szabo Z, Hakanson E, Svedjeholm R. Early post-operative outcome and medium-term survival in 540 diabetic and 2239 non-diabetic patients undergoing coronary artery bypass grafting. Ann Thorac Surg 2002;74:712-9.
5. Vora AC, Saleem TM, Polomano RC, Eddinger VL, Hollenbeak CS, Girdharry DT, *et al*. Improved perioperative glycemic control by continuous insulin infusion under supervision of an endocrinologist does not increase costs in patients with diabetes. EndocrPract 2004;10:112-8.
6. Carr JM, Sellke FW, Fey M, Doyle MJ, Krempin JA, de la Torre R, *et al*. Implementing tight glucose control after coronary artery bypass surgery. Ann ThoracSurg 2005;80:902-9.
7. Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery. Ann Int Med 2007;146:233-43.
8. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, *et al*. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.
9. Lecomte P, Van Vlem B, Coddens J, Cammu G, Nollet G, Nobels F, *et al*. Tight perioperative glucose control is associated with a reduction in renal impairment and renal failure in non-diabetic cardiac surgical patients. Crit Care 2008;12:R154.
10. Azevedo JR, Lima ER, Cossetti RJ, Azevedo RP. Intensive insulin therapy versus conventional glycemic control in patients with acute neurological injury: A prospective controlled trial. Arq Neuropsiquiatr 2007;65:733-8.
11. Egi M, Bellomo R, Stachowski E, French C, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology 2006;105:244-52.
12. GirishG, Agrawal K, Satsangi DK, Tempe D, Dutta N, Pratap H. Glycemic control in cardiac surgery: Rationale and current evidence. Ann Card Anaesth 2014;17:222-8.
13. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, *et al*. German Competence Network Sepsis (SepNet): Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.
14. DeSantis AJ, Schmeltz LR, Schmidt K, O'Shea-Mahler E, Rhee C, Wells A, *et al*. Inpatient management of hyperglycemia: The northwestern experience. Endocr Pract 2006;12:491-505.
15. Lazar HL, Chipkin S, Philippides G, Bao Y, Apstein C. Glucose-insulin-potassium solutions improve outcomes in diabetics who have coronary artery operations. Ann Thorac Surg 2000;70:145-50.
16. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann ThoracSurg 1997;63:356-61.
17. 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.
18. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, *et al*. Effects of intensive glucose lowering in type 2 diabetes. Action to control cardiovascular risk in diabetes study group. N Engl J Med 2008;358:2545-59.
19. Ouattara A1, Lecomte P, Le Manach Y, Landi M, Jacqueminet S, Platonov I, *et al*. Poor intra-operative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. Anesthesiology 2005;103:687-94.
20. Mechanick J, Handelsman Y, Bloomgarden Z. Hypoglycemia in the intensive care unit. Curr Opin ClinNutr Metab Care 2007;10:193-6.
21. American Association Of Clinical Endocrinologists Medical Guidelines For Clinical Practice For The Management Of Diabetes Mellitus AACE Diabetes Mellitus Clinical Practice Guidelines Task Force Endocrine Practice. vol. 13, May/June 2007.
22. Lazar HL, McDonnell M, Chipkin MD, Furnary AP, Engelman RM, Sadhu AR, *et al*. The society of thoracic surgeons practice guideline series: Blood glucose management during cardiac surgery. Ann Thoracic Surg 2009;87:663-9.