

Study of Intraoperative Tight Control of Blood Sugar Level in Patients Undergoing Off Pump Coronary Artery Bypass Grafting in View of Inotropic Requirement and Cardiac Index

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ABSTRACT

Introduction: Perioperative hyperglycemia can have detrimental effects on myocardial preservation in coronary revascularization procedures. Aim of this study was to compare effectiveness of tight control of blood sugar during off pump coronary artery bypass grafting in reducing myocardial damage and improve cardiac performance.

Material and methods: A prospective comparative study was done in 60 nondiabetic patients of age group 35-75 years of ASA grade II and III posted for off pump coronary arteries bypass grafting. Patients were randomized into Group I (30 patients) for tight control of blood sugar level (80-120 mg / dl) with the help of continuous insulin infusion protocol intraoperatively; up to 8 hrs. in postoperative period and Group II (30 patients) for conventional control of blood sugar level (200 mg/dl) with the help of insulin infusion, started when blood sugar level was more than 200 mg/dl. Blood sugar concentration measured with handheld glucometer half hourly. Cardiac indices were monitored every hourly till 8 hour postoperatively. Inotropic score was calculated in both the groups.

Results: Mean blood sugar level in group I was 115+/- 6.63 mg /dl and in group II was 191+/-45.49 mg/dl without any incidence of hypoglycemia. Mean insulin required for group I was 3.77+/-2.2 U and for group II was 2.27+/-0.87 U. The patients in group I had higher cardiac indices at all-time intervals which is statistically significant. At the end of 8 Hours cardiac index in group I was 3.78+/- 0.54 and in group II was 3.15+/- 0.74. % change in cardiac index from baseline in group I was 55.56% and in group II was 21.96%. The “p” value was 0.001 by “t” test which was highly significant. Comparison of inotropic scores revealed no statistical significance difference.

Conclusion: Hyperglycemia can be tightly controlled (80-120mg/dl) with insulin infusion protocols in non-diabetic patients undergoing off pump CABG. Tight glycaemic control was having beneficial effects on contractile function of heart as revealed by significantly better cardiac indices and trend towards lesser need of inotropic support.

Keywords: Tight Glycaemic Control, Coronary Artery Bypass Grafting, Glucose-Insulin- Potassium Infusion

INTRODUCTION

Technological advances and fewer complications are advantages of myocardial revascularization without cardiopulmonary bypass [off pump coronary artery bypass (OPCAB). But patients remain to have unpredictable ischemic reperfusion damage to myocardium and impaired cardiac performances during OPCAB. This implies an

ongoing need to develop strategies for myocardial protection during these procedures.

First time in 1962, Sodi-Pallares et al¹ showed in patients with acute myocardial infarction that infusion of glucose – insulin- potassium (GIK) reduces electromyographic signs of ischemia, reduces ventricular ectopy, limits infarct size & improves survival. Majority of the patients without diabetes have derangement of glucose metabolism due to surgical and anesthesia stresses perioperatively. Tight glycaemic control in perioperative period especially with high dose insulin (hyperinsulinemic normoglycaemic clamp) significantly decrease incidence of ventricular arrhythmias, less myocardial acidosis, better preservation of wall motion and decrease area of tissue necrosis in myocardium subjected to ischemia and reperfusion (2, 3, 4, 5).

These favorable results prompted us to study tight glycaemic control with modified GIK regimen (Adopted from Gandhi et al Feb.2007)⁶ in improving cardiovascular performance in OPCAB.

Aim of this study was to compare the effectiveness of intraoperative tight control of blood sugar (80 to 120 mg%) with that of conventional blood sugar (200 mg%) control in OPCAB in reducing myocardial damage and improving cardiac performance. Objectives of this study are to study effectiveness of tight glycaemic control in view of,

1. Cardiac performance in the form of any improvement in cardiac index.
2. Inotropic requirement.

MATERIAL AND METHODS

After institutional ethical committee approval, adults patients scheduled for elective primary myocardial revascularization without cardiopulmonary bypass were included in this prospective comparative, randomized control

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study. Patients were randomly divided into two groups of 30 each.

Group I: -n=30 (study group)

These patients received continuous infusion of insulin (50 IU of Actrapid HM in 50 ml of 0.9% of normal saline) at rate of 2 IU/ hr with help of infusion pump started just after induction of anesthesia.

A separate infusion of 5% dextrose 500 ml with 80 meq of potassium chloride at rate 100 ml / hr started so as to avoid any hypoglycemia. Half hourly blood sugar estimation was done with hand held glucometer, and insulin infusion rate was then adjusted according to algorithm (TABLE 1) (adopted from Gandhi et al 2007)⁶ so as to maintain blood sugar level between 80 to 120 mg/d. If previous 2 hrs trend was increasing blood sugar then infusion rate was increased accordingly from column 1 to column 2 and then column 2 to column 3.

When glucose level is < 80 mg/dl, insulin infusion is stopped & 50ml/h of 10% dextrose infusion initiated. Glucose is checked every 30 minutes until glucose level is \geq 80mg/dl then 10% dextrose infusion discontinued. Insulin infusion is restarted, always in COLUMN 1 of protocol.

Group II: -n = 30 (Control Group)

Patients in the conventional treatment group did not receive insulin during surgery unless their glucose levels exceeded 200 mg/dl. If glucose concentration was between 200 mg/ dl and 250 mg/dl, patients received an intravenous infusion of insulin starting with 2 ml/hr, then titrating infusion rate until the glucose concentration was around 200 mg/dl. If the intraoperative glucose concentration was greater than >250 mg/dl, patients received an intravenous infusion of insulin at a rate, increased 50% to 100% of previous rate and continued until the glucose level was around 200 mg/dl. A separate infusion of 5% dextrose 500 ml with 80 meq of potassium chloride at rate 100 ml / hr. started so as to avoid any hypoglycemia.

Insulin infusion & control of blood sugar were continued during post-operative period till patients were extubated from elective ventilation, in both study and control group or till 8 hrs. from induction time.

Inclusion criteria

- Surgery under general anesthesia.
- ASA status II and III
- Age group 35 to 75 yrs.
- Sex both male and female
- weight 45 to 75 kg

Exclusion criteria

- Patients with diabetes mellitus type I and II either on diabetic diet, oral hypoglycemic drugs or insulin
- Patients with chronic renal failure with creatinine clearance > 2mg /ml
- Patients with acute renal failure with urine output < 20 ml /kg /24 hr.
- Patients with hepatic insufficiency with sr. bilirubin > 2.5 mg /ml, AST or ALT > 100 IU.

- Patients with hyperkalemia serum Poassium >5.5 meq /L.
- Patients with emergency CABG.
- Redo CABG.
- Combined CABG with any other cardiac procedure.

Patient under study underwent thorough preoperative assessment including detailed history, clinical examination & all necessary investigations including blood sugar profile so as to evaluate any unknown diabetes status and written informed consent is taken from each patients.

Anesthetic technique

Previously prescribed cardiovascular medications were continued until the time of operation. After premedication with midazolam 0.03mg/kg and fentanyl 1mcg/kg, pulmonary artery catheter was inserted through right internal jugular vein (CCOMBO- EDWARD LIFE SCIENCES). Standardized anesthetic and surgical management protocols were used in all patients and no interventions were withheld during the study period. including the use of cardiopulmonary bypass. Major goals of hemodynamic management were to maintain cardiac index greater than 2.2 L/min/m² and systolic blood pressure >100 mm of Hg; when afterload, preload and heart rate were optimized. Warmed lactated ringer saline and packed cells were used to replace fluid losses and maintain hemoglobin at 10 gm/dl. Following parameters were monitored - continuous cardiac output, ECG, pulse oxymeter, end tidal carbon dioxide, temperature (both surface and core temperature).

Induction: Induction of anesthesia was done with Thiopentone Na (3-5 mg/kg.) & fentanyl 25 to 50 μ /kg in titrated doses. Under direct laryngoscopic vision, tracheal intubation done after Vecuronium.

Maintenance of Anaesthesia:- Anesthesia was maintained on O₂ (50%) + N₂O (50%) + Vecuronium as skeletal muscle relaxant + Sevoflurane as anesthetic agent + continuous infusion of Midazolam 1mg /hr + fentanyl 1 to 2 μ g/kg/hr + Intermittent positive pressure ventilation.

Arterial blood samples obtained at ½ hrs interval during CABG to measure blood sugar concentration with hand held glucometer. Subsequent administration of insulin was given as per the protocol. After revascularization, all patients were transferred to the cardiac intensive care unit intubated.

Parameters measured

- Glucose concentration was measured every ½ hourly intra operatively & hourly post operatively for 8 hrs.
- Cardiac index (CI) was compared in both the groups with the help of continuous cardiac output monitor every hourly.
- Inotropic agents were used to maintain cardiac index 2.2 L/min/m² Or higher and systolic blood pressure of 100 mm of Hg or higher in presence of central venous pressure 12 mm of Hg, pulmonary capillary wedge pressure of 14 mm of Hg and heart rate 70 to 100/min. For use of inotropic agents, an inotropic score was used to quantify the number of inotropes used, dosage & length of administration.

The score ranges from 0 to 5 where,

- 0 - No inotropic support or dopamine < 2 µg/kg/min
- 1- Inotropic support 2 µg /kg/min. or more for 24 hrs.
- 2 - Use of two inotropes.
- 3 - Use of epinephrine
- 4– Use of three inotropes.
- 5 – Inotropic support for 24 hrs or more

RESULTS

All patients were non diabetic, underwent off pump coronary artery bypass grafting (OPCAB). The two groups were demographically identical. (Table 2). The two groups were also comparable regarding h/o recent myocardial infarction (Recent M I), h/o congestive cardiac failure (CCF), h/o hypertension (HT), ejection fractions, number of coronary vessels involved and involvement of left anterior descending artery (LAD) > 50%. (table 2).

Both groups had similar baseline blood sugar level just after anesthetic induction. After induction glucose concentrations were lower in the intensive treatment group than in the conventional treatment group at all-time intervals. At end of 8 hrs, mean blood sugar concentration in group I was 114 ± 9.01 and in group II was 213 ± 10.65. 'p' value was highly significant by 't' test. (table 3). No patient in either group developed hypoglycemia intraoperatively or postoperatively. Van Den Berghe and colleagues in 2001 reported incidence of hypoglycaemia to be 5% without significant sequelae, in their study of maintaining blood sugar level 80 to 110 mg /dl in critically ill patients⁷ whereas that reported by Chaney et al. is in 40% of patients in the "tight control" group required treatment.⁸ Several studies using a modified insulin clamp technique, reveal the safe and effective use of this treatment in cardiac surgical patients without hypoglycaemia with effective glycemic control.^{9,10} Mean glucose levels were 115.50 ± 6.63 mg / dl in the intensive treatment group (group I) and 191.62 ± 45.49 mg/dl in the conventional treatment group (group II). (table 3)

Maximum insulin required in group I was 9 U/ hr. and in group II was 3 U/hr. (table 5). Mean insulin required in Group I was 3.77 ± 2.2 IU at the end of eight hour and in Group II was 2.27 ± 0.78 IU at end of eight hour. 'p' value

was 0.001 which was highly significant.

Both groups started with similar cardiac indices. The patients in group I (tight sugar control) had higher cardiac indices at all-time intervals vs. cardiac indices of patients in group II (conventional sugar control). At end of 8 hrs. cardiac index in group I was 3.78 ± 0.54 and in group II was 3.15 ± 0.74. The 'p' value was 0.001 by 't' test which

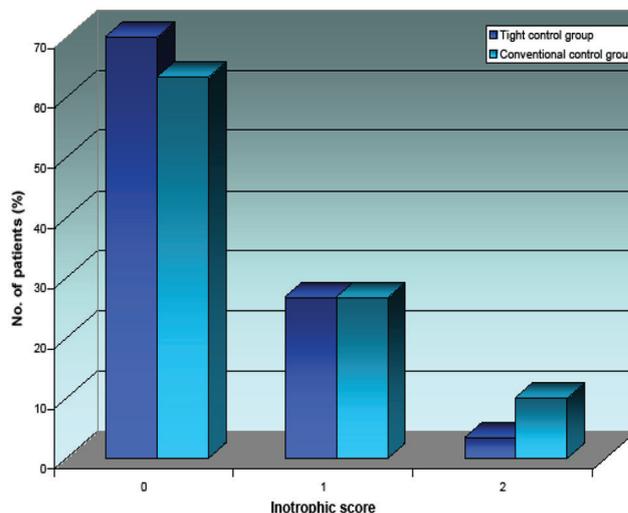


Figure-1: Comparison of inotropic score in both groups

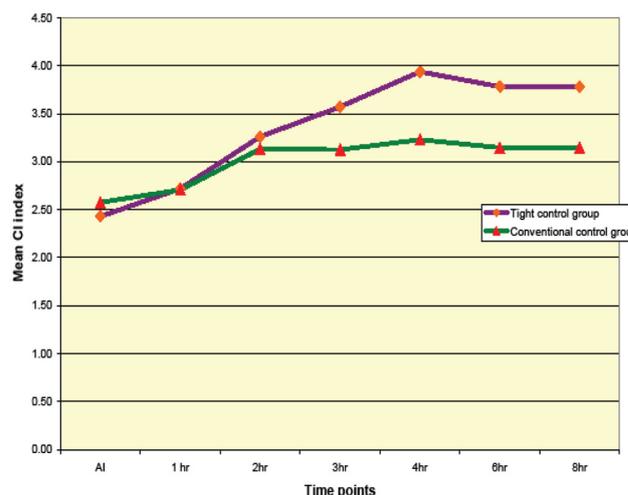


Figure-2: Comparison of cardiac index in both groups

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

Table-1: Insulin infusion protocol

Parameter	P value		Significance	
	Group I	Group II		
Age	60.60 ± 9.78	60.23 ± 9.24	0.88	NS
Weight	61.93 ± 7.41	62.93 ± 6.49	0.58	NS
Height	156.13 ± 6.73	157.27 ± 6.60	0.51	NS
BMI	25.47 ± 3.26	25.50 ± 2.79	0.96	NS
Male	23 (76.66 %)	24 (80 %)	0.754	NS
Female	7 (23.33 %)	6 (20 %)		
H/O recent MI < 90 days				
Yes	7 (23.33 %)	6 (20 %)	0.754	NS
No	23 (76.66 %)	24 (80 %)		
H/o CCF				
Yes	3 (10 %)	3(10 %)		NS
No	27 (90 %)	27 (90 %)		NS
EF Gradation				
Grade 1 > 60	8(26.66 %)	8(26.66 %)	0.73	NS
Grade 2: 40-59	18 (60 %)	18 (60 %)		
Grade 3: 20-39	4(13.33 %)	4(13.33 %)		
No. of vessels involved				
1	9 (30 %)	11(36.66 %)	0.73	NS
2	7 (46.66 %)	8 (36.66%)		
3	14(23.33 %)	11(26.66%)		
LAD > 50% lumen involved				
Yes	16(53.33 %)	17(56.67 %)	0.795	NS
No	14 (46.67 %)	13 (43.33%)		

Table-2:

Time points	BSL Mean ± SD		Significance
	Tight controlgroup I	Conventional control group II	
After induction	104.17±12.86	100.33± 12.55	0.25
1Hr	119.80±13.45	164.23± 18.24	0.00
2Hrs	119.60±14.96	202.37± 29.81	0.00
3Hrs	122.03±20.12	207.53± 24.46	0.00
4 Hrs	109.60±12.90	224.20± 18.78	0.00
6 Hrs	119.13±14.91	229.63± 14.35	0.00
8 Hrs	114.17±9.01	213.07± 10.65	0.00

Table-3:

Time points	CI Mean ± SD		Significance
	Tight controlgroup	Conventional control groups	
After induction	2.43±0.46	2.58±0.61	0.30
1Hr	2.72±0.53	2.71±0.57	0.93
2Hrs	3.26±0.39	3.13±0.67	0.36
3Hrs	3.57±0.50	3.13±0.56	0.001
4 Hrs	3.94±0.53	3.23±0.64	0.001
6 Hrs	3.78±0.58	3.15±0.63	0.001
8 Hrs	3.78±0.54	3.15±0.74	0.001

Table-5:

is highly significant statistically. % change in cardiac index after induction in group I was 55.56% and in group II was 21.96%. The 'p' value was 0.001 by 't' test which was highly significant. (table 4).

Comparison of inotropic scores revealed no statistical significance as number of patients with inotropic score 0

were 21(70%) in group I and in group II were 19 (63.3%), with inotropic score 1 were 8 (26.7%) in group I and in group II were 8 (26.7%), and with inotropic score 2 was 1(3.3%) in group I and in group II were 3 (10%). (figure 2). The 'p' value was 0.351 which was insignificant (table 26). The mean inotropic score in Group I was 0.33± 0.55 and in Group II

Time points	Insulin Mean \pm SD		Significance
	Tight control group	Conventional control groups	
After induction	2.00 \pm 0.00	0.00 \pm 0.00	-
1Hr	2.87 \pm 1.11	0.00 \pm 0.00	-
2Hrs	2.90 \pm 1.27	0.97 \pm 1.16	0.001
3Hrs	3.50 \pm 2.56	1.07 \pm 1.05	0.001
4 Hrs	2.77 \pm 1.94	2.00 \pm 0.64	0.04
6 Hrs	3.73 \pm 2.26	2.27 \pm 0.45	0.001
8 Hrs	3.77 \pm 2.22	2.27 \pm 0.78	0.001

Table-5:

was 0.47 ± 0.68 . But there is trend towards lesser need of inotropic agents with tight control of blood sugar than conventional control.

DISCUSSION

Hyperglycemia in perioperative period is caused or exacerbated by surgical stress and anesthesia because of counter regulatory hormones. Acute hyperglycemia occurring intraoperatively abolishes ischemic preconditioning [11] and amplifies reperfusion injury to heart (12). During ischemia, glucose is preferred substrate for myocardium, but marked insulin resistance leads to hyperglycemia & impaired cellular uptake of glucose & increase FFA concentrate. Free fatty acids are detrimental to the ischemic myocardium because increased oxygen consumption required for metabolizing the new substrate (i.e. FFA). Hyperglycemia also leads to increased free radical release & increasing oxidative stress causing endothelial dysfunction which may affect myocardial ischemia.^{13,14,15}

There are several mechanisms by which GIK solutions enhance the performance of the ischemic myocardium.^{16,17,18}

1. The increased supply of adenosine triphosphate derived from glycolytic pathways helps to maintain cell membrane function and integrity, which is critical to the preservation of myocytes, endothelial and vascular smooth muscle cells.
2. In patients with coronary artery disease, GIK therapy resulted in a more favorable oxygen supply/demand ratio by increasing arterial glucose uptake while decreasing free fatty acid levels.
3. Membrane stabilization and anti-arrhythmic effects.⁷ Presumably, insulin improves the potassium uptake of the myocyte reducing the incidence of ventricular arrhythmia.
4. Improved myocardial glycogen content enabling prolonged synthesis of adenosine triphosphate and creatin triphosphate during anaerobic conditions.
5. Postoperative insulin resistance This can be reduced by using individually administered, high-dose insulin for maintaining euglycemia.
6. Reduction of free fatty acids (FFA) with its negative consequences.

In a retrospective observational study of 409 patients undergoing cardiac surgery, Gandhiet al, found that a 20mg/dL increase in the mean intraoperative glucose level

was associated with increased postoperative mortality and morbidity¹⁹. Ouattara et al demonstrated that adverse events after CABG was 7.2% more likely in those patients with poorly controlled intraoperative blood glucose levels²⁰

Benefits of GIK solution and tight glycemic control in cardiac surgical patients, we hypothesized that with tight control of blood sugar with a modified GIK infusion during OPCAB would protect the heart from ischemic-reperfusion damage resulting in improved cardiac performance.

In present study, the patients were randomly divided into two groups of 30 each. (TABLE 1).

GROUP I- Tight control of blood sugar (80-120 mg /dl)

GROUP II- Conventional control of blood sugar (200 mg/dl)

All patients were non diabetic, underwent off pump coronary artery bypass grafting (OPCAB).

The two groups were demographically identical. The age, weight, height, BMI distribution were also statistically insignificant as shown in (table 2). The two groups were also comparable regarding certain baseline characteristics like h/o recent myocardial infarction (Recent M I) (table 2), h/o congestive cardiac failure (CCF) (table 5), h/o hypertension (HT) (table 2). Preoperative h/o drug intake like ACE inhibitors (angiotensin converting enzyme inhibitors), β blockers, diuretics, nitrates was also comparable in both groups.

Both groups were also comparable regarding ejection fractions, and number of coronary vessels involved and involvement of left anterior descending artery (LAD) > 50%. (table 2).

Both groups had similar baseline blood sugar level just after anesthetic induction. Afterwards glucose levels were lower in the intensive treatment group than in the conventional treatment group at all-time intervals. (table 3) At end of 8 hrs mean blood sugar concentration in group I was 114 ± 9.01 and in group II was 213 ± 10.65 . 'p' value was highly significant by 't' test. (table 3). No patient in either group developed hypoglycemia intraoperatively or postoperatively. Van Den Berghe and colleagues in 2001 reported incidence of hypoglycaemia to be 5% without significant sequelae in their study of maintaining blood sugar level 80 to 110 mg / dl in critically ill patients⁷. Chaney et al. reported that 40% of patients in the "tight control" group required treatment for postoperative hypoglycaemia⁸. Similar study using a modified insulin clamp technique, s reveal the safe and

effective use of this treatment in cardiac surgical patients¹⁰ without hypoglycaemia with effective glycemic control.

Mean glucose levels were 115.50 ± 6.63 mg / dl in the intensive treatment group (group I) and 191.62 ± 45.49 mg/dl in the conventional treatment group (group II). (table 3)

Maximum insulin required in group I was 9 U/ hr. and in group II was 3 U/hr. (table 5). Mean insulin required in Group I was 3.77 ± 2.2 IU at the end of eight hour and in Group II was 2.27 ± 0.78 IU at end of eight hour. 'p' value was 0.001 which was highly significant. So to maintain the tight control of blood sugar intraoperatively insulin requirements are nearly doubled than conventional control.

Both groups started with similar cardiac indices, group I- 2.43 ± 0.46 L/min/m² vs. group II- 2.58 ± 0.61 L/min/m². (table 4). The 'p' value was 0.30 by 't' test which was statistically not significant. The patients in group I (tight sugar control) had higher cardiac indices at all time intervals vs. cardiac indices of patients in group II (conventional sugar control). At end of 8 hrs. cardiac index in group I was 3.78 ± 0.54 and in group II was 3.15 ± 0.74 . The 'p' value was 0.001 by 't' test which is highly significant statistically. % change in cardiac index after induction in group I was 55.56% and in group II was 21.96%. The 'p' value was 0.001 by 't' test which was highly significant. (table 4, figure 1).

Comparison of inotropic scores revealed no statistical significance as number of patients with inotropic score 0 were 21(70%) in group I and in group II were 19 (63.3%), with inotropic score 1 were 8 (26.7%) in group I and in group II were 8 (26.7%), and with inotropic score 2 was 1(3.3%) in group I and in group II were 3 (10%). (figure 2) The 'p' value was 0.351 which was insignificant. The mean inotropic score in Group I was 0.33 ± 0.55 and in Group II was 0.47 ± 0.68 . But there is trend towards lesser need of inotropic agents with tight control of blood sugar than conventional control.

Juha K. Koskenkari and colleagues (2005)³ have done study to evaluate the effects of high-dose insulin 1U /kg /hr. in 40 patients scheduled for combined aortic valve replacement and coronary artery bypass surgery. The blood glucose levels were maintained within a targeted range at 108 to 180 mg/dl. There was lesser need for dobutamine support and a trend toward better cardiac indices ('p' value = 0.053).

In study done by Turki Albacker et al⁵ have shown that high dose insulin therapy (hyperinsulinemic normoglycemic clamp) was cardio protective, high dose insulin group had lower troponin I level 4 hours postoperatively, with greater improvement in cardiac indices.

Harold L. Lazar and colleagues¹⁶ study patients undergoing CABG who were treated with glucose-insulin-potassium solution had higher cardiac indices (2.8 ± 0.1 vs. 2.0 ± 1 L/min per square meter; $p < 0.001$), lower inotrope scores. David W. Quinn and colleagues²¹ have done study to assess the role of GIK in providing myocardial protection in nondiabetic patients undergoing coronary artery surgery. The results were, the GIK group had higher cardiac indices throughout infusion and reduced vascular resistance. Inotropes were required in 18.8% of the glucose-insulin-potassium group and 40.8% of the placebo group. Fewer patients in the glucose-

insulin-potassium group (12.3%) versus those in the placebo group (23.4%) had significant myocardial injury.

Harold L. Lazar and colleagues⁹ did a study of effect of tight glycemic control in diabetic CABG patients which showed lower inotropic score GIK -1.18 ± 0.06 vs. Standard therapy- 2.16 ± 0.08 .

The possible explanation to higher cardiac indices in group I than in group II but having similar inotropic scores in our study could be, as both groups received insulin infusion, cardiac indices were maintained above the critical value i.e. > 2.2 L/min/m² and the protective effect was demonstrated in both group. As there was tight glycemic control in group I, the required amount of insulin was almost doubled in group I than in group II, so the cardiac indices were maintained at higher levels group I than in conventional control group i.e. group II. This has been shown by various studies which demonstrate the cardio protective effects of high dose insulin (hyperinsulinemic normoglycemic clamp)^{4,5,6,15}.

CONCLUSION

1. There was considerable level of hyperglycemia in non-diabetic patients undergoing off pump CABG.
2. Blood sugar levels can be tightly controlled (80-120mg/dl) with the help of separate and continuous insulin infusion protocol in non-diabetic patients undergoing off Pump CABG without inducing hypoglycemia as compared to conventional GIK drip.
3. Tight control of blood sugar intraoperatively in off pump CABG patients was having beneficial effects on contractile function of heart as revealed by better cardiac indices in group I and group II.
4. Inotropic requirements and arterial and arterial pH were comparable in both the groups because both the groups were treated with insulin which causes early clearance of lactate, early shifting towards aerobic metabolism and better myocardial preservation.
5. There was no patient with wound gaping or sternal wound infection in either of two groups, again due to protective effects of insulin in controlling blood sugar.

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