"Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing on pump CABG surgery."

Thesis submitted for the partial fulfillment for the requirement of the degree of DM (Cardiothoracic and Vascular Anesthesia)

of

SCTIMST

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DIVISION OF CARDIOTHORACIC AND VASCULAR ANESTHESIA

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Dr. Manmohan Singh, the then Honorable Finance Minister of Government of India, laid the foundation stone of the third dimension of the Institute, Achutha Menon Center for Health Science Studies (AMCHSS) on June 15, 1992. Dr. Murali Manohar Joshi, the then Honorable Minister of Science and Technology and Human Resource Development, Government of India, dedicated the AMCHSS to the nation on January 30, 2000.

DECLARATION

I hereby declare that this thesis entitled, "**Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing on pump CABG surgery",** has been prepared by me under the capable supervision and guidance of Dr.Thomas Koshy, Professor,Divisionof Cardiothoracic & Vascular Anesthesiaand Dr.Jaya Kumar.K, Professor and Head, Department of Cardiovascular &thoracic surgery,at Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram.

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Date:

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CERTIFICATE

This is to certify that this thesis entitled, "**Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing on pump CABG surgery",** is a bonafide work of Dr.Dinesh Kumar.U.S, DM Cardiothoracic & Vascular Anesthesia Resident,. It was done under my direct guidance & supervision at the Division of Cardiothoracic & Vascular Anesthesia&Department of Cardiovascular &Thoracic Surgeryat Sree Chitra Tirunal Institute for Medical Sciences & Technology, Thiruvananthapuram. He had shown keen interest in preparing this project.

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CONTENTS

INTRODUCTION

Diabetes mellitus is one of the major risk factors for ischemic heart disease &atherosclerosis. It is a systemic disease involving all the systems of the body. Various studies have shown uncontrolled diabetes to be associated with many macro vascular complications like coronary artery disease, stroke & micro vascular complications like nephropathy, neuropathy, retinopathy etc.[1-5] Studies have also shown that glycosylated haemoglobin (HbA1C) level is an indicator of blood sugar control over the last 3-4 months and it predicts both micro & macro vascular complications. The American diabetes association has recommended the use of HbA1C levels as a method of assessing long term glycemic control in diabetic patients. HbA1C more than 7% is an independent risk factor for micro vascular & macro vascular complications in diabetic patients. American Association of clinical endocrinologist's medical guidelines for clinical practice for management of diabetes mellitus recommends to maintain glycosylated haemoglobin less than 7%.[13]

The optimal control of blood sugar in the perioperative period during cardiac surgery is a very controversial topic and many studies have addressed it differently. Perioperative hyperglycemia is an independent risk factor for increased morbidity & mortality during cardiac surgery. Various retrospective studies have shown that perioperative hyperglycemia is associated with increased inotropic requirement, increased ICU & hospital stay, higher infection rate, delayed wound healing, renal failure & cerebrovascular accidents. [1-5]Van Den Berg et al has recommended tight control of blood sugar between 80-120 mg/dl in critically ill patients.[9]Finfer S et al studied intensive versus conventional glucose management in critically ill patients & concluded that tight control is associated with increased risk of hypoglycemia & neurological complications. [10]Griesdale et al, in their meta-analysis titled‘*Intensive insulin therapy and mortality among critically ill patients’*reported increased risk of hypoglycemia & neurological complications with intensive insulin therapy [11]Currently Society of thoracic surgeon’s guidelines recommends maintaining blood sugars less than 180mg/dl in the perioperative period. [12]

The objective of this project is to find out whether long term preoperative blood glucose control as indicated by the HbA1C (blood sugar levels over last 3-4 months) level influence the perioperative blood sugar levels, insulin requirement, inotropic requirement, incidence of atrial fibrillation, infection rate & duration of ICU & hospital stay in patients undergoing on pump CABG surgery.

There are many retrospective observational studies which have shown that elevated HbA1C is associated with adverse outcome in cardiac surgery & percutaneous coronary revascularization. [14-16]There are no prospective studiescorrelating HbA1C & outcomes in patients undergoing on pump CABG. So we want to do a prospective observational study whether HbA1C levels influence the above mentioned outcomes in patients undergoing CABG on pump.

OBJECTIVES

To test the hypothesis that higher glycosylated haemoglobin levels are associated with perioperative hyperglycaemia, higher insulin requirement, inotropic requirement, higher incidence of infections, atrial fibrillation, and increased duration of ICU & hospital stay in patients undergoing on pump CABG.

Objectives:

1. To assess whether patients with HbA1C more than 7% have higher blood sugar & insulin requirements perioperatively.
2. To evaluate whether patients with HbA1C more than 7% require higher inotropic support.
3. To assess whether patient with HbA1C more than 7% have higher incidence of atrial fibrillation, infections & prolonged ICU & hospital stay.

REVIEW OF LITERATURE

The prevalence of diabetes mellitus in patients requiring cardiac surgery is rapidly increasing. These patients have higher perioperative morbidity and mortality, significantly reduced long-term survival. There is now evidence to suggest that achieving glycaemia controlin patients with diabetes decreases perioperative morbidity and improves short-term and long-term survival. Despite the emerging recognition of the importance of glycaemia control, there are no specific guidelines for cardiac anaesthetist as to what the optimal level of glucose should be during the perioperative period, and the best method to achieve these target values.

Detrimental Effects of Hyperglycaemia in the Perioperative Period in CABG patients.

- **Salomon NW, Page US, Okies JE, Stephens J, Krause AH, Bigelow JC. Diabetes mellitus and coronary artery bypass: short-term risk and long-term prognosis. Journal of Thoracic Cardiovascular Surgery 1983; 85:264-271**

  Salomon et al studied retrospectively3,707 patientsundergoing CABG over a 12 year period which included 250 diet/oral medication-controlled and 162 insulin-dependent patients with diabetes mellitus. Analysis of 20 pre- and 18 intra-operative variables revealed a higher incidence of hypertension, left ventricular hypertrophy, and tobacco consumption in diabetic groups. The extent of diffuse coronary disease as judged angiographically and at operation was significantly greater in diabetic groups than in non diabetic CABG patients. No difference was noted inthe incidence of localized coronary disease between the groups. Average number of graft was more in diabetic patients. The perioperative mortality was greater for diabetic patients (5.1% for non-insulin-dependent diabetes, 4.5% for insulin-dependent diabetes) than for non diabetic CABG patients (2.5%). The incidences of sternotomy complications and renal insufficiency were significantly greater in the diabetic group. The number of total hospital days was also greater in diabetic groups. Actuarially determined survival and cardiac event-free curves revealed a significant difference between diabetic groups as compared to the non diabetic

patient population, with follow-up extending to 10 years after CABG. Results indicate that diabetic patients have quantitatively and qualitatively more coronary artery disease than non diabetic patients and have higher perioperative morbidity and mortality and a lower long-term survival rate than non diabetic patients. However, results continue to justify selection of patients for CABG based on clinical and anatomic criteria regardless of diabetic status. *Diabetes mellitus should be considered a patient-related risk factor, for both short- and long-term outcomes following CABG.*

- **Thourani VH, Weintraub WS, Stein B, et al. Influence of diabetes mellitus on early and late outcome after coronary artery bypass grafting. Annals of Thoracic Surgery 1999; 67:1045-1052.**

  Thourani et al studiedretrospectivelythe impact of diabetes on short- and long term outcomes after coronary artery bypass grafting by comparing the outcomes between 9,920 patients without diabetes mellitus and 2,278 patients with diabetes from 1978 to 1993. Compared with non diabetic patients, the group with diabetes was older (62+/-10 years versus 60+/-10 years), comprised more women (31% versus 19%), and had a greater incidence of hypertension (61% versus 44%) and previous myocardial infarction (51% versus 48%).The diabetic patients alsohad class III-IV angina more commonly (69% versus 63%), higher incidence of congestive heart failure (11% versus 5%) or triple-vessel or left main disease (60% versus 50%), and had lower ejection fractions (0.54 versus 0.57). Furthermore diabetic patients had a higher incidence of postoperative death (3.9% versus 1.6%) and stroke (2.9% versus 1.4%) but not Q wave myocardial infarction (1.8% versus 2.9%). Diabetics had lower survival (5 years, 78% versus 88%; 10 years, 50% versus 71%; both, $p \leq 0.05$) and lower freedom from percutaneous transluminal coronary angioplasty (5 years, 95% versus 96%; 10 years, 83% versus 86%; latter, $p \leq 0.05$), but diabetics did not have lower freedom from either myocardial infarction (5-years, 92% versus 92%; 10-years, 80% versus 84%) or additional coronary artery bypass grafting (5-years, 98% versus 99%; 10-years, 90% versus 91%). Multivariate correlates of long-term mortality were diabetes, older age, reduced ejection fraction, hypertension, congestive heart failure, number of vessels diseased, and urgent or

emergent operation. *They concluded from their study that Diabetics have a worse hospital and long term outcome after coronary artery bypass grafting.*

- **McAlister FA, Man J, Bistritz L, Amad H, Tandon P. Diabetes and coronary artery bypass surgery: an examination ofperioperative glycemic control and outcomes. Diabetes Care2003; 26:1518 –1524.**

  McAlister and co-workers in a retrospective study of 291 patientsundergoing CABG surgery showed that average serum glucose level on the first postoperative day significantly predicted the development of an adverse outcome.

- **Anderson RE, Brismar K, Barr G, Ivert T. Effects of cardio-pulmonary bypass on glucose homeostasis after coronary artery bypass surgery. European Journal of Cardiothoracic Surgery2005; 28:425–430.**

  Anderson and coworkers studied the effect of elevated fasting blood glucose levels prior to surgery in a group of 1,375 CABG patients. Patients with elevated fasting blood glucose had a 1-year mortality that was twice as great as patients with normal fasting values and equal to that of patients who were suspected, or known to have diabetes mellitus.*Collectively, these studies strongly suggest that increased fasting glucose levels prior to surgery, and persistently elevated glucose levels during and immediately after cardiac surgery, are predictive of increased perioperative morbidity and mortality in patients with and without diabetes & influences the early & late outcomes after coronary artery bypass surgery.*

- **Gandhi GY, Nuttall GA, Abel MD, et al. Intraoperative hyperglycaemia and perioperative outcomes in cardiac surgery patients. Mayo Clinical Proceedings 2005; 80:862-866.**

  In this study the authors objective was to evaluate the association between intraoperative hyperglycemia and perioperative outcomes in patients who underwent cardiac surgery. They conducted a retrospective observational study of consecutive adult patients who underwent cardiac surgery between June 10, 2002, and August 30, 2002, at the Mayo Clinic, a tertiary care center in Rochester, Minn. The primary independent variable was

the mean intraoperative glucose concentration. The primary end point was a composite of death and infectious (sternal wound, urinary tract, sepsis), neurologic (stroke, coma, delirium), renal (acute renal failure), cardiac (new-onset atrial fibrillation, heart block, cardiac arrest), and pulmonary (prolonged pulmonary ventilation, pneumonia) complications developing within 30 days after cardiac surgery. Among 409 patients who underwent cardiac surgery, primary end points were more commonly seen in male and older patients with diabetes mellitus, undergoingcoronary artery bypass grafting and receivinginsulin during surgery ($P \leq 05$ for all comparisons). Atrial fibrillation (n=105), prolonged pulmonary ventilation (n=53), delirium (n=22), and urinary tract infection (n=16) were the most common complications.

The initial, mean, and maximal intraoperative glucose concentrations were significantly higher in patients experiencing the primary end point ($P < 0.01$ for all comparisons). In multivariable analyses, mean and maximal glucose levels remained significantly associated with outcomes after adjusting for potentially confounding variables, including postoperative glucose concentration. Logistic regression analyses indicated that a

20 mg/dL increase in the mean intraoperative glucose level was associated with an increase of more than 30% in outcomes (adjusted odds ratio, 1.34; 95% confidence Interval, 1.10-1.62). *They concluded that it is not just postoperative hyperglycemia but intraoperative hyperglycemia is also an independent risk factor for complications, including death, after cardiac surgery.*

Beneficial Effects of Glycemic Control on Clinical Outcomes & Various insulin protocols to control blood sugars during Cardiac Surgery

- **Furnary AP, Gao G, Grunkemeier GL, et al. Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. Journal of Thoracic Cardiovascular Surgery 2003; 125:1007–1021**

  This study involved 3,554 patients who underwent CABG surgery from 1987 to 2001. Patients were divided into three groups based on the year of surgery, the method of glycemic control, and the targeted glucose levels. From 1987 to 1991, patients received subcutaneous insulin, given every 4 hours to keep serum glucose < 200 mg/dL. From 1991 to 1998, a continuous intravenous (IV) insulin infusion was used to keep serum glucose between 150 and 200 mg/dL. From 1998 to 2001, the Portland protocol was instituted, which used a continuous insulin drip to keep serum glucose between 100 and 150 mg/dL. Continuous insulin infusions resulted in significantly lower mean glucose levels than could be obtained with intermittent subcutaneous insulin therapy. The perioperative mortality in CABG patients with diabetes was decreased by 50% after 1992 (4.5% vs. 1.9%; $p < 0.0001$) when continuous insulin protocols were instituted, and it was similar to that for non diabetic CABG patients. There was also a significant decrease in the incidence of deep sternal wound infections ($p < 0.001$). *They concluded that Continuous insulin infusions resulted in significantly lower mean glucose levels than could be obtained with intermittent subcutaneous insulin therapy*

- **Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project.Endocrinology Practice2004; 10 (supplement 2):21-33.**

  Furnary and coworkers expanded their original series to include an additional 1,980 patients managed with the Portland protocol from 2001 to 2005. They introduced a new method to assess glycemic control called 3-blood glucose or "3-BG," consisting of the average of all glucose values obtained on the day of surgery and the first and second postoperative days. *An increase in 3-BG was an independent predictor of perioperative mortality ($p < 0.001$). Mean 3-BG was also significantly related to the incidence of deep*

sternal wound infections, hospital length of stay, blood transfusions, new onset atrial fibrillation, and low cardiac output syndrome.

- **Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative out-comes and decreases recurrent ischemic events. Circulation 2004; 109:1497–1502.**

  In this trial involving 141 patients with diabetes undergoing isolated CABG surgery, patients were prospectively randomized to receiveglucose-insulin–potassium to keep serum glucose between 120 and 180 mg/dL, or sliding scale insulin coverage to maintain glucose < 250 mg/dL. The glucose-insulin–potassium was started on induction of anesthesiaand continued for 12 hours in the intensive care unit(ICU). The glucose-insulin–potassium-treated patientsachieved significantly better glycemic control immediately prior to cardiopulmonary bypass (169 mg/dL vs. 209mg/dL; $p < 0.0001$), and after 12 hours in the ICU (134mg/dL vs. 266 mg/dL; $p < 0.0001$). Patients treated withtight glycemic control had significantly higher cardiacindices ($p < 0.0001$) and less need for inotropic support ($p < 0.05$) and pacing ($p < 0.05$). Tighter glycemic controlalso resulted in a lower incidence of infections (0% vs.13%; $p < 0.01$) and atrial fibrillation (15% vs. 60%; $p < 0.007$). All this contributed to a shorter hospital length ofstay (6.5 days vs. 9.2 days; $p < 0.0003$). After 5 years, theKaplan-Meier curves showed a significant survival advantage ($p < 0.04$) for patients receiving better glycemic control. They had a significantly lower incidence of recurrent ischemia ($p < 0.01$) and wound infections ($p < 0.03$), and were able to maintain a lower angina class ($p < 0.03$).

- **Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients New England Journal of Medicine2001; 345:1359-1367**.

  Hyperglycemia and insulin resistance are common in critically ill patients, even if they have not previously had diabetes. Whether the normalization of blood glucose levels with insulin therapy improves the prognosis for such patients is not known. They performed a prospective, randomized, controlled study involving adults admitted to the surgical intensive care unit who were receiving mechanical ventilation. On admission, patients

were randomly assigned to receive intensive insulin therapy (maintenance of blood glucose at a level between 80 and 110 mg per deciliter [4.4 and 6.1 mmol per liter]) orconventional treatment (infusion of insulin only if the blood glucose level exceeded 215 mg per deciliter [11.9 mmol per liter] and maintenance of glucose at a level between 180 and 200 mg per deciliter [10.0 and 11.1 mmol per liter]). At 12 months, with a total of 1548 patients enrolled, intensive insulin therapy reduced mortality during intensive care from 8.0 percent with conventional treatment to 4.6 percent ($P<0.04$, with adjustment for sequential analyses). The benefit of intensive insulin therapy was attributable to its effect on mortality among patients who remained in the intensive care unit for more than five days (20.2 percent with conventional treatment, as compared with 10.6 percent with intensive insulin therapy, $P=0.005$). The greatest reduction in mortality involved deaths due to multiple-organ failure with a proven septic focus. Intensive insulin therapy also reduced overall in-hospital mortality by 34 percent, bloodstream infections by 46 percent, acute renal failure requiring dialysis or hemofiltration by 41 percent, the median number of red-cell transfusions by 50 percent, and critical-illness polyneuropathy by 44 percent, and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care. Intensive glycaemia control had no effect on morbidity and mortality in those patients spending < 3 days in the ICU.*Their conclusion was intensive insulin therapy to maintain blood glucose at or below 110 mg per deciliter reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.*

- **Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients New England Journal of Medicine2009; 360:1283-1297.**

  Finfer S et al compared intensive & conventional glucose control in critically ill patients. Within 24 hours after admission to an intensive care unit (ICU), adults who were expected to require treatment in the ICU on 3 or more consecutive days were randomly assigned to undergo either intensive glucose control, with a target blood glucose range of 81 to 108 mg per deciliter (4.5 to 6.0 mmol per liter), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). They defined the primary end point as death from any cause within 90 days after randomization. Of the

6104 patients who underwent randomization, 3054 were assigned to undergo intensive control and 3050 to undergo conventional control; data with regard to the primary outcome at day 90 were available for 3010 and 3012 patients, respectively. The two groups had similar characteristics at baseline. A total of 829 patients (27.5%) in the intensive-control group and 751 (24.9%) in the conventional-control group died (odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02). The treatment effect did not differ significantly between operative (surgical) patients and nonoperative (medical) patients (odds ratio for death in the intensive-control group, 1.31 and 1.07, respectively; P=0.10). Severe hypoglycemia (blood glucose level, < or = 40 mg per deciliter [2.2 mmol per liter]) was reported in 206 of 3016 patients (6.8%) in the intensive-control group and 15 of 3014 (0.5%) in the conventional-control group (P<0.001). There was no significant difference between the two treatment groups in the median number of days in the ICU (P=0.84) or hospital (P=0.86) or the median number of days of mechanical ventilation (P=0.56) or renal-replacement therapy (P=0.39).

In this large, international, randomized trial, they found that intensiveglucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

- **Griesdale DE, De Souza RJ, Van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009; 180: 821-827.**

  Griesdale et al conducted a meta-analysis to update the totality of evidence regarding the influence of intensive insulin therapy compared with conventional insulin therapy on mortality and severe hypoglycemia in the intensive care unit (ICU). They conducted searches of electronic databases, abstracts from scientific conferences and bibliographies of relevant articles. They included published randomized controlled trials conducted in the ICU that directly compared intensive insulin therapy with conventional glucose management and that documented mortality. They included in their meta-analysis the data from the recent NICE-SUGAR (Normoglycemia in Intensive Care Evaluation - Survival Using Glucose Algorithm Regulation) study. They included 26 trials involving a total of 13,567 patients in their meta-analysis. Among the 26 trials that reported

mortality, the pooled relative risk (RR) of death with intensive insulin therapy compared with conventional therapy was 0.93 (95% confidence interval [CI] 0.83-1.04). Among the 14 trials that reported hypoglycemia, the pooled RR with intensive insulin therapy was 6.0 (95% CI 4.5-8.0). The ICU setting was a contributing factor, with patients in surgical ICUs appearing to benefit from intensive insulin therapy (RR 0.63, 95% CI 0.44-0.91); patients in the other ICU settings did not (medical ICU: RR 1.0, 95% CI 0.78-1.28; mixed ICU: RR 0.99, 95% CI 0.86-1.12). The different targets of intensive insulin therapy (glucose level < or = 6.1 mmol/L vs.< or = 8.3 mmol/L) did not influence either mortality or risk of hypoglycemia. *The interpretation of the above Mata-analysis was Intensive insulin therapy significantly increased the risk of hypoglycemia and conferred no overall mortality benefit among critically ill patients. However, this therapy may be beneficial to patients admitted to a surgical ICU.*

- **Harold L. Lazar, Marie McDonnell, Stuart R. Chipkin, et al. The Society of Thoracic Surgeons Practice Guideline Series: Blood Glucose Management during Adult Cardiac Surgery Annals of Thoracic Surgery 2009; 87: 663–669.**

  They authors have recommended maintaining blood sugar levels < 180 mg/dl perioperatively using continuous insulin infusion in diabetic patients. All patients who require > 3 days in the ICU because of ventilatory dependency or requiring the need for inotropes, intraaortic balloon pump, or left ventricular assist device support, antiarrhythmics, dialysis, or continuous venovenous hemofiltration should have a continuous insulin infusion to keep blood glucose <150 mg/dL, regardless of diabetic status (Class-I, level of evidence B).The HbA1c level should be obtained prior to surgery in patients with diabetes or those patients at risk for postoperative hyperglycaemia to characterize the level of preoperative glycaemia control (level of evidence C) based on the recommendation of American diabetic association.

Glycosylated haemoglobin (HbA1C) is a form of haemoglobin that is formed from non-enzymatic glycosylation pathway. Once glycosylated they remain in the RBC, which has a life span of 120 days. So they serve as a marker of average blood glucose levels over the previous 3-4 months. 2010 American diabetic association standards of medical care in diabetes have recommended HbA1C > 6.5% as another criterion for the diagnosis of diabetes. HbA1C was first separated from other forms of haemoglobin by Huisman &Meyeringin 1958 using a chromatographic column. Its increase in diabetes was first described in 1969 by Samuel Rahbar et al. The use of HbA1C for monitoring the degree of glucose control was proposed in 1976 by Anthony Cerami, Ronald Koenig & co-workers.It can be measured using high performance liquid chromatography, immunoassay & capillary electrophoresis in laboratory & point of care device using immunoassay & borate affinity chromatography. Results may be unreliable in circumstances like blood loss; blood transfusion, anaemia & high erythrocyte turn over.

- **Halkos ME et al. Elevated preoperative HbA1C level is predictive of adverse events after coronary artery bypass surgery. Journal of thoracic & cardiovascular surgery 2008; 136(supplement 3):631-640.**

  Of 3555 consecutive patients who underwent primary, elective coronary artery bypass grafting at a single academic centre from April 1, 2002, to June 30, 2006, 3089 (86.9%) had preoperative HbA1C levels obtained and entered prospectively into a computerized database. All patients were treated with a perioperative intravenous insulin protocol. A multivariable logistic regression model was used to determine whether HbA1C, as a continuous variable, was associated with in-hospital mortality, renal failure, cerebrovascular accident, myocardial infarction, and deep sternal wound infection after coronary artery bypass grafting.

  In-hospital mortality for all patients was 1.0% (31/3089). An elevated HbA1C level predicted in-hospital mortality after coronary artery bypass grafting (odds ratio 1.40 per unit increase, P = .019). Receiver operating characteristic curve analysis revealed that HbA1C greater than 8.6% was associated with a 4-fold increase in mortality. For each unit increase in HbA1C, there was a significantly increased risk of myocardial infarction and deep sternal wound infection. By using receiver operating characteristic value

thresholds, renal failure (threshold 6.7, odds ratio 2.1), cerebrovascular accident (threshold 7.6, odds ratio 2.24), and deep sternal wound infection (threshold 7.8, odds ratio 5.29) occurred more commonly in patients with elevated HbA1C. Elevated HbA1C level was strongly associated with adverse events after coronary artery bypass grafting. *Preoperative HbA1C testing may allow for more accurate risk stratification in patients undergoing coronary artery bypass grafting.*

- **Moitra VK, Greenberg J, Arunajadai S, Sweitzer B et al. Therelationship between glycosylated haemoglobin and perioperativeglucose control in patients with diabetes. Canadian Journal of Anaesthesia 2010; 57(supplement 4):322-329.**

  This was a prospective observational study of 244 adult patients with type 2 diabetes who were evaluated before elective non-cardiac surgery at a preoperative medicine clinic in a tertiary care medical centre during the period September 2004 to May 2005. Preoperative HbA1C levels were determined, and preoperative and postoperative glucose values were measured on the day of surgery. The primary outcome variables were preoperative and postoperative blood glucose values. 122 patients had an HbA1C $\geq$ 7%, including 23% of patients with HbA1C $\geq$ 8%. HbA1C levels predict preoperative glucose levels and duration of surgery predicts postoperative glucose levels. Glucose levels in one-third of the patients with type 2 diabetes decreased during surgery without administration of insulin or glucose-regulating medications.*HbA1C values may serve as biomarkers for glucose control during the immediate perioperative period in patients with type 2 diabetes undergoing elective surgery.*

- **Hudson CC, Welsby IJ et al. HbA1C levels & outcome in non-diabetic cardiac surgery patients. Canadian journal of anaesthesia 2010;57(supplement 6):565-572**

  In this retrospective observational study, Hudson et al accessed data from a prospectively collected quality assurance database for a cohort of 1,474 non-diabetic elective cardiac surgery patients with documented preoperative HbA1C levels. The relationship of HbA1C with death within 30 days of surgery was examined using logistic regression modelling. Acute kidney injury and infection were similarly assessed using multivariable linear and logistic regression. Thirty-one per cent of patients (n = 456) had elevated

HbA1C values (>6.0%). Patients with elevated HbA1C had higher fasting and peak intraoperative blood glucose values. Also, an elevated HbA1C level was independently associated with increased 30-day mortality (odds ratio 1.53 per cent increase [1.24-1.91]; P = 0.0005). This relationship persisted even after "borderline" diabetics were excluded. Furthermore, acute kidney injury was associated with elevated baseline HbA1c (P = 0.01). No association was found between HbA1C and postoperative infection risk (P = 0.48). In non-diabetics, an elevated preoperative HbA1C level (>6.0%) is independently associated with significantly greater early mortality risk after elective cardiac surgery.*Their findings suggested that HbA1Cmight have value as a screening tool to identify high-risk non-diabetic cardiac surgery patients.*

SUMMARY OF LITERATURE

Various studies had demonstrated increased morbidity and mortality in post-surgical patients with diabetes. Such patients have not only higher preoperative blood glucose levels, but blood sugar levels were high in the intraoperative and postoperative period's also requiring higher dose of insulin. Gandhi et al reported in 2005 that it was not just postoperative hyperglycemia but intraoperative hyperglycemia was also an independent risk factor for complications, including death, after cardiac surgery.[(5)]Another study demonstrated that continuous insulin infusions in the postoperative period resulted in significantly lower mean glucose levels than could be obtained with intermittent subcutaneous insulin therapy.[(6)]Van de berghe et al from their landmark study showed intensive insulin therapy to maintain blood glucose at or below 110 mg per decilitre, reduces morbidity and mortality among critically ill patients in the surgical intensive care unit.[(9)]In contrast, Finfer et al in there large, international, randomized trial, found that intensive glucose control increased mortality among adults in the ICU: a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.[(10)]The Society of Thoracic Surgeons Practice Guideline Series have recommended maintaining blood sugar levels < 180 mg/dl perioperatively using continuous insulin infusion in diabetic patients.[(12)]

Preoperative HbA1C values has gained acceptance as an index of long-term glucose control in patients undergoing surgery. It was also found to be a predictor of perioperative morbidity and mortality in many retrospective series. In a large retrospective study involving 3000 diabetic and non-diabetic, on-pump and off-pump CABG patients, the authors have reported an association between elevated HbA1C levels and several short-term adverse outcomes.[14]Another retrospective study reported prolonged hospital stays in patients with elevated HbA1C undergoing CABG.[18] In a prospective study of 244 type 2 diabetic patients, Moitra VK et al concluded that HbA1c levels may serve as biomarker for glucose control during the immediate perioperative period.[15] There are no prospective studies correlating HbA1C values & outcomes in patients undergoing on pump CABG.

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MATERIALS AND METHODS

Study design: Prospective Randomised controlled observational, single centre study conducted at SCTIMST hospital wing.

Subject/participants selection- Patients who were scheduled for elective coronary artery bypass grafting on cardiopulmonary bypass, who met all the inclusion criteria and did not have any exclusion criteria and were willing to participate in the study were included. Minors, neonates, person**s** incompetent to give informed consent, prisoner**s**, normal/healthy volunteer**s**; pregnant women,staff & students of the institute were not included in the study. Staff and students of this institute were excluded as subjects because their ability to refuse consent might be impaired.

Number-Total numbers of patients were120 as calculated by power analysis.

Inclusion criteria: Patients aged 40-80 yrs of either sex, with triple vessel diseases & ejection fraction of > 30% undergoing elective on pump CABG.

Exclusion criteria: Age < 40yrs or > 80yrs, Emergency surgery, Co existing valvular disease, preoperative renal failure, EF < 30 %, LMCA lesion, large LA Size (> 4 cms), h/o of atrial fibrillation & those unwilling to give consent.

Recruitment: Principle investigator recruited the participants for this study. Adult patients who were posted for elective coronary bypass grafting and had already given consent for the surgical procedure were included. Those patients who met all the inclusion criteria and did not have any of the exclusion criteria were approached. The study process; the data researchers wanted to collect; right to refusal were explained to the patients. Informed written consent was taken if the patient agrees to participate in the study. The patient was then considered as a subject in the present study and relevant data needed for the study were collected.

Conduct of the study: After the approval of technical advisory committee & institutional ethical committee this study was started. Informedwritten consent was taken from participants who were willing to participate in the study. Those meeting all of the inclusion criteria and did not have any of the exclusion criteria were selected. HbA1C levels were done as a part of routine CABG workup. Depending on HbA1C levels they were divided into two groups.

Group I: HbA1C $\geq$ 7%.

Group II: HbA1C < 7%

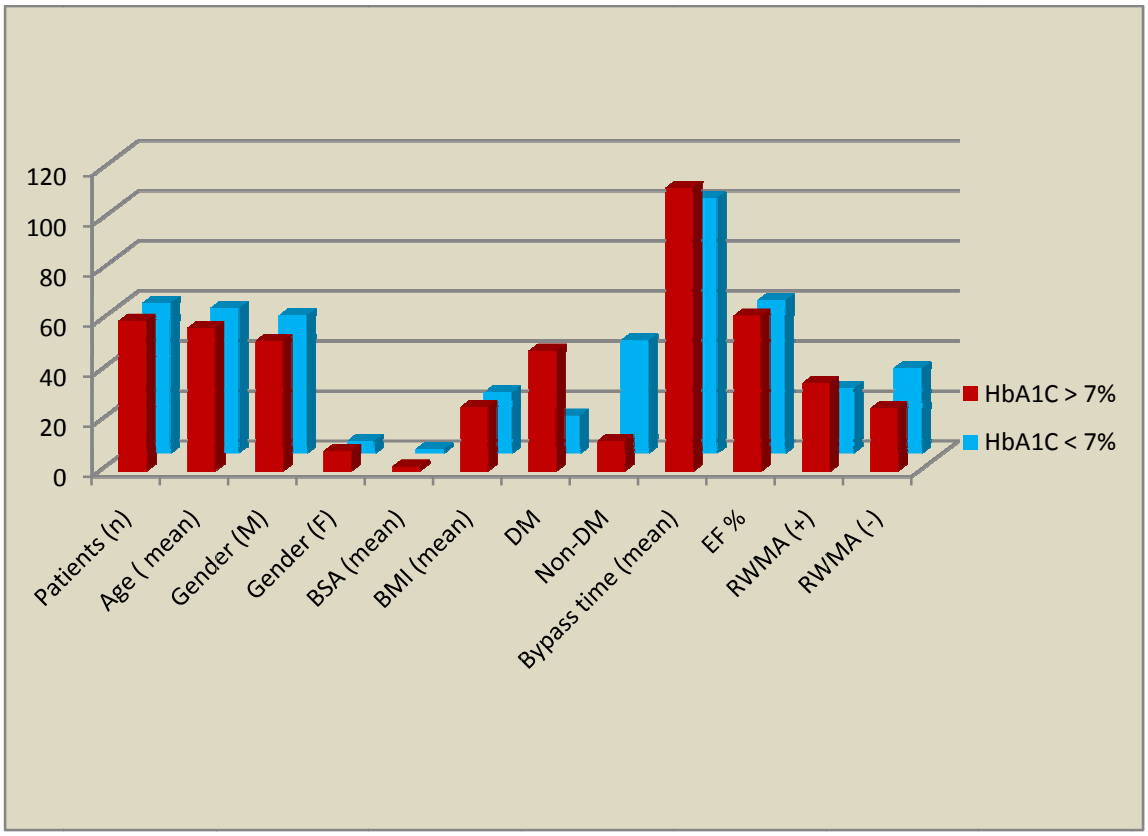
One day prior to surgery fasting blood sugar & random blood sugars were determined. If it was more than 180 mg/dl, patient was treated according to sliding scale as per our institute protocol. Patient with history of DM, oral hypoglycaemic drugs & insulin were stopped on the day of surgery as per institute protocols.For all patients FBS was estimated on the day of surgery and further blood sugar estimations were done in the pre CPB, CPB and post CPB periods. If blood sugar was more than 180mg/dl, patients were treated uniformly withhuman regular Insulinusingmodified Cleveland clinic protocol. Postoperatively blood sugar levels were monitored every hourly, if blood sugar levels more than 180 mg/dl; it was treated as per modified Cleveland clinic protocol for insulin dose. All patients were treated to maintain blood sugar levels less than 180 mg/dl as per society of thoracic surgeon's guidelines. [7]

Data analysis: Preoperatively demographic data like age, sex, history of diabetes, duration of diabetes & treatment, Ejection fraction, Regional wall motion abnormality, blood sugar & HbA1C levels were recorded.Perioperatively blood sugar levels, total insulin requirement during surgery & first 48 hrspost-operatively, inotropic requirement (To calculate the Wernovsky inotropic score = Dobutamine (µg/kg/min) + Dopamine (µg/kg/min) + 100 X adrenaline (µg/kg/min) + 100 X nor adrenaline (µg/kg/min) + 10 X milrinone (µg/kg/min) + 10,000 X vasopressin dose (U/kg/min)[17]& any episode of atrial fibrillation were recorded.

Postoperatively patients were followed up till discharge from hospital. Superficial or deep sternal wound infections, duration of ICU & hospital stay, any episodes of atrial fibrillation, were recorded. These data were collected from the patient's charts and files in the intensive care unit (ICU) & ward.

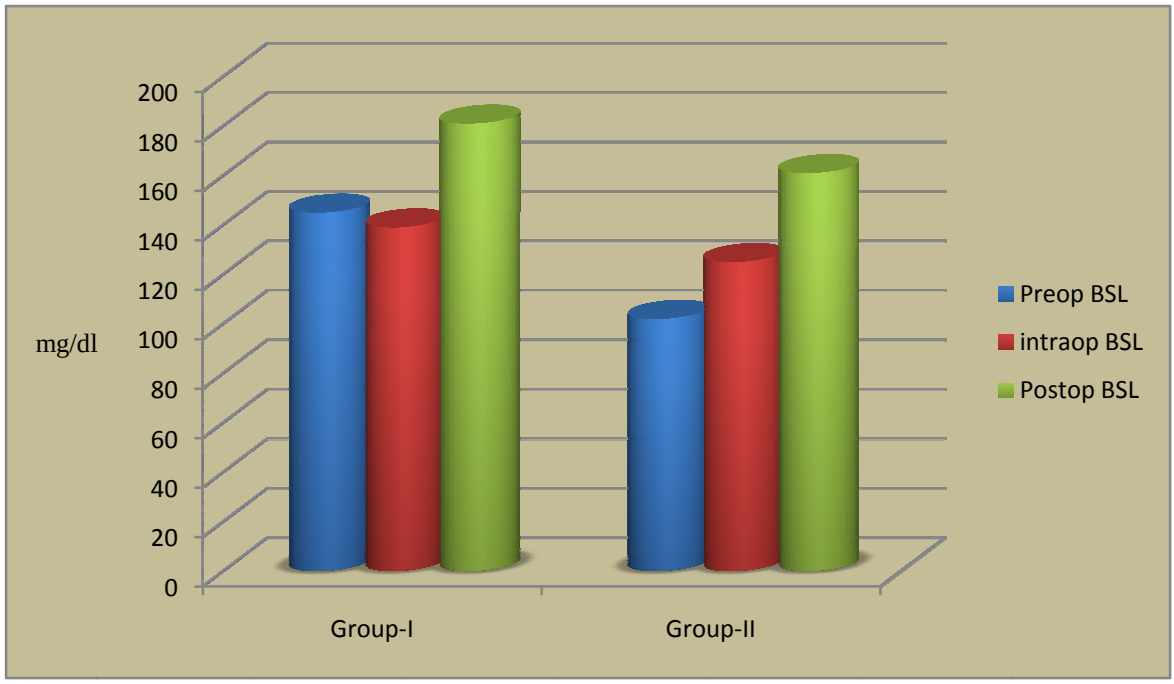
Stastical analysis was performed with SPSS 11th edition for windows. P value < 0.05 was taken as significant.

GRAPHS

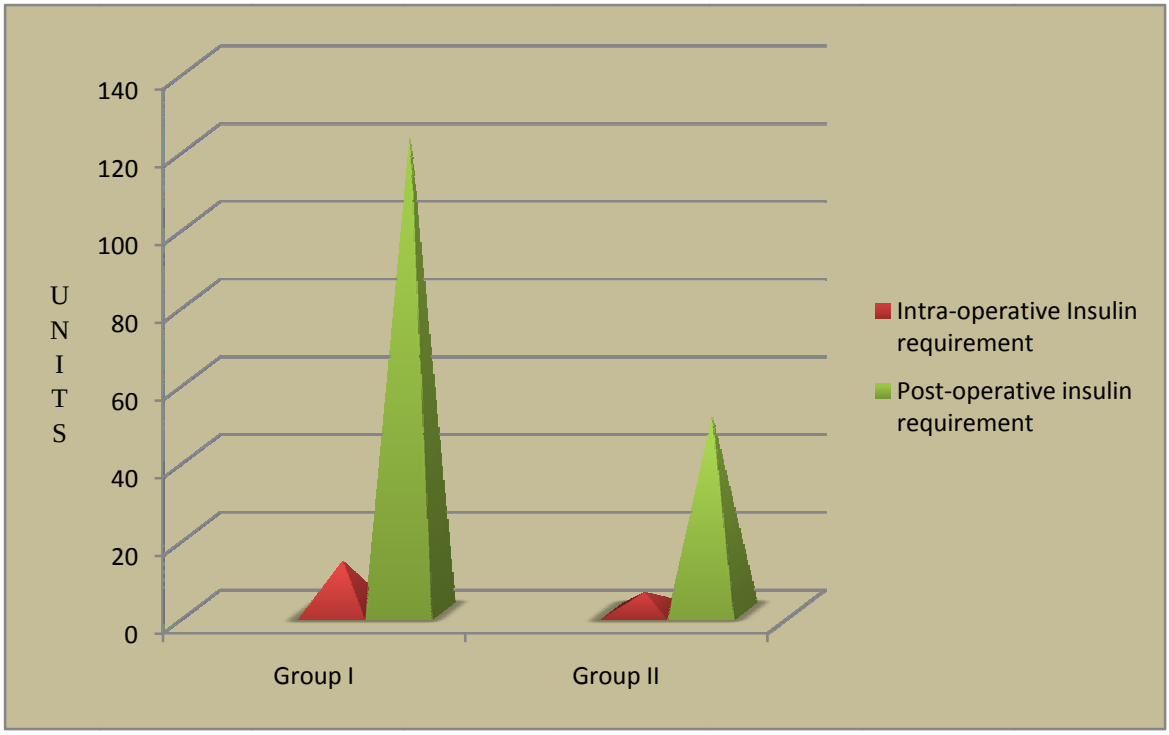


BSA- Body surface area, BMI- body mass index, DM- diabetes mellitus, EF- ejection fraction, RWMA- regional wall motion abnormality.

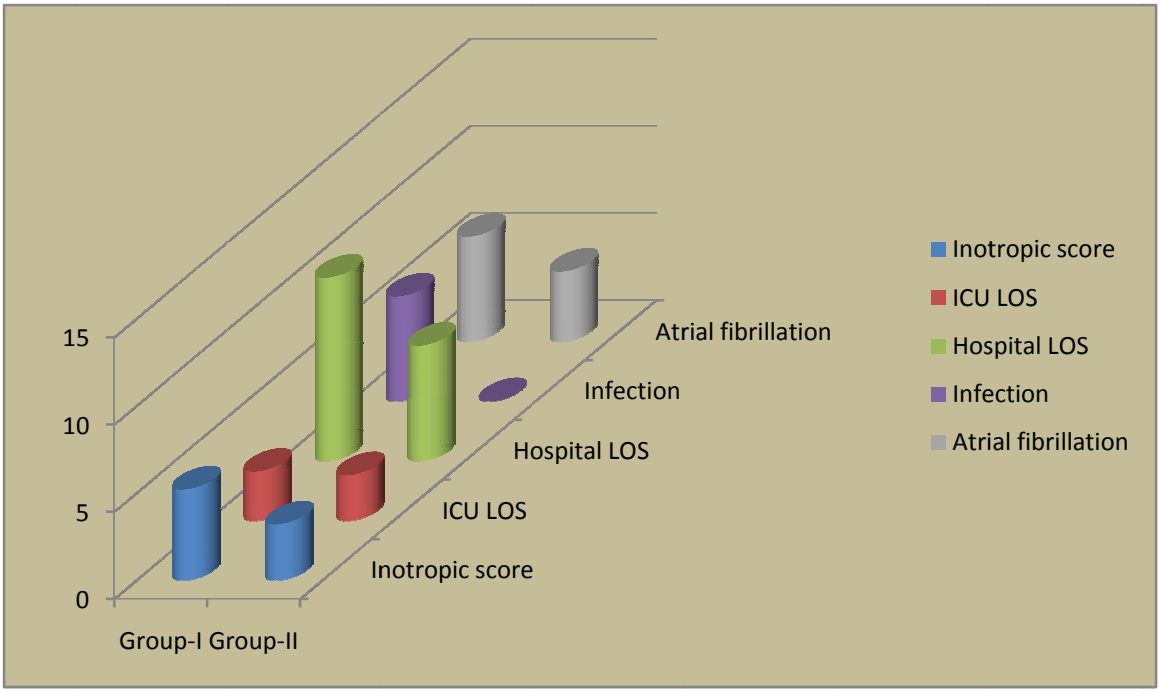
Graph: 1 Demographic variables



Graph- 2 Perioperative blood sugar levels

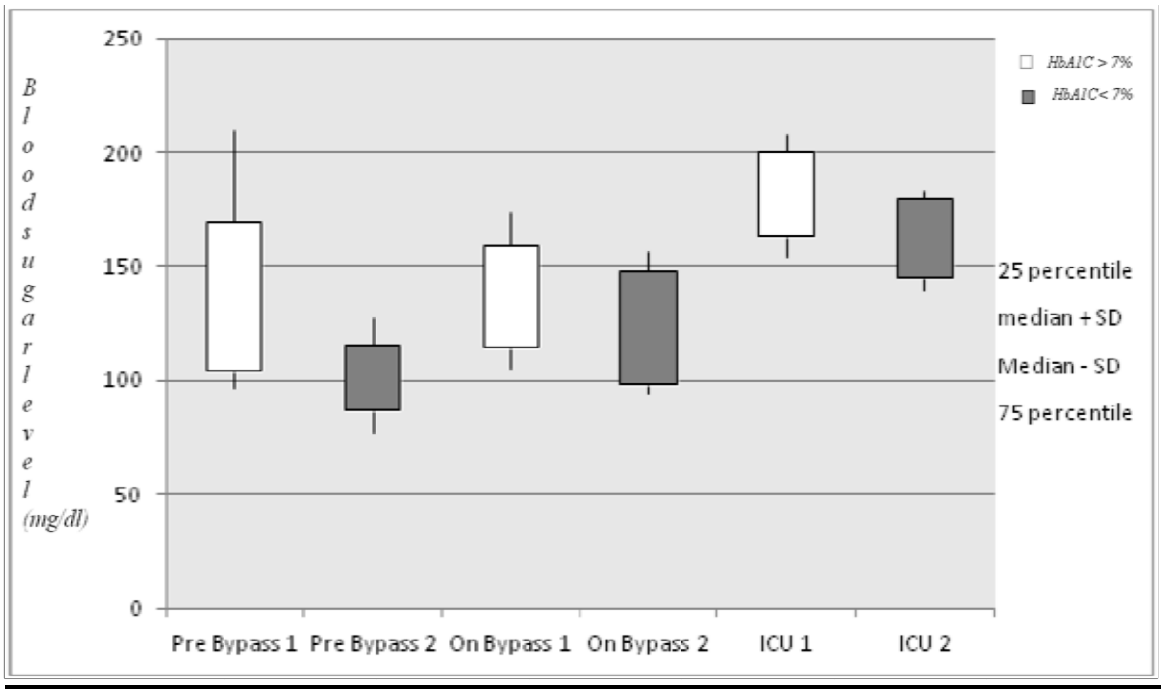


Graph-3 Perioperative insulin requirement to maintain BSL < 180mg/dl



LOS- length of stay

Graph 4 Perioperative outcomes following on pump CABG



Graph-5 Perioperative blood sugar levels & variability

OBSERVATION AND RESULTS

Stastical analysis was performed with SPSS 11th edition for windows.P value < 0.05 was considered as significant.One hundred & twenty patients who were undergoing on pump CABG in our institute satisfying the inclusion & exclusion criteria were randomly included our study. After the informed consent based upon their HbA1C levels patients were grouped into two groups.

Group-I HbA1C ≥ 7%

Group-II HbA1C < 7%

Groups	Patients (n)	Age (years)	Gender (n) (male/female)	BSA(m^2) Mean ± SD	BMI(Kg/m2) Mean ± SD	Number of patients with/without diabetes	Bypass time (minutes) Mean ± SD	EF% Mean ± SD	Number of patients with/without RWMA
I (HbA1C ≥7%)	60	57± 8	52/8	1.71± 0.2	25.5 ± 3.5	48/12	113 ± 30	62 ± 11%	35/25
II (HbA1C <7%)	60	58± 8.6	55/5	1.68± 0.2	24.4± 4.8	15/45	102 ± 25	61±11%	26/34
P- value		0.51	0.55	0.46	0.24	0.0	0.37	0.62	0.1
Test		Paired T-test	Chi-square	Paired T-test	Paired T-test	Chi-square	Paired T-test	Paired T-test	Chi-square

Abbreviations: BSA- body surface area, BMI- body mass index, EF- ejection fraction, RWMA- regional wall motion abnormality

Table-1 Demographic data

Group-I (HbA1C > 7%) included patients in the age group 57 ± 8 yrs. 52 were males & 8 females. 48 patients had diabetes whereas 12 patients had no past h/o diabetes. Group-II (HbA1C < 7%) included patients in the age group 58 ± 8.6 yrs. 55 were males & 5 females, only 15 patients had diabetes while the rest had no h/o diabetes.Demographic variables between group-I & group-II were compared using Chi-square test for variables with nominal scale (gender, diabetic status & RWMA) & paired T-test for variables with interval scale & normal distribution (age, BSA, BMI, EF & bypass duration).Table-1 shows P value is > 0.05 for all variables except diabetic status meaning both the groups are comparable with regard to demographic data.

Graph-1 shows comparison of the demographic variables between the two groups.

Groups	Preoperative BSL(mg/dl) (Median±SD)	Intraoperative BSL(mg/dl) (Median±SD)	Postoperative (First48 hrs.) BSL(mg/dl) (Median±SD	Intraoperative Insulin requirement (Units) (Mean ± SD)	Postoperative Insulin requirement (Units) (Mean ± SD)
I (HbA1C ≥ 7%)	145 ±49	139 ±34	181 ±27.5	3.2 ±9	122 ±89
II (HbA1C < 7%)	102 ±20	125 ±31	161 ±22	1 ±3.5	50 ±43
P value	0.00	0.04	0.00	0.08	0.00
Test	Paired T-test	Paired T-test	Paired T-test	Paired T-test	Paired T-test

Abbreviations: BSL-blood sugar levels

Table-2-Perioperative blood sugar levels & insulin requirement

Preoperative, intraoperative & postoperative blood sugars levels for the first 48 hrs, intraoperative & postoperative insulin requirement were compared using Paired T-test. Table-2 & Graph-2 & 3 shows that perioperative blood sugar levels & postoperative insulin requirement were higher in group-I & statistically significant as compared to group-II.Intraoperative insulin requirement was not statistically significant.

Groups	Inotropic Score (n) (mean ± SD)	ICU length of stay (Days) (mean ± SD)	Hospital length of stay (Days) (mean ± SD)	Infections n (percentage)	Atrial fibrillation n (percentage)
I (HbA1C > 7%)	5.2 ± 7	2.8 ± 0.8	7.1 ± 3.5	6 (10%)	6 (10%)
II (HbA1C < 7%)	3.2 ± 4.3	2.6 ± 0.4	6.2 ± 0.4	0	4 (6.7%)
P- value	**0.05**	**0.08**	**0.02**	**0.03**	**0.74**
Test	**Paired T test**	**Paired T test**	**Paired T test**	**Fisher's T test**	**Fisher's T test**

Table-3 Perioperative outcomes following on pump CABG

Perioperative outcomes were compared using Paired T-test (inotropic score, ICU & hospital length of stay) & Fisher's test (atrial fibrillation & infection rate). Table-3 & Graph-4 shows that inotropic score (based on inotropic dose) was higher in group-I patients during first 48 hrs. in the ICU. Six patients in group-I & four patients in group-II developed atrial fibrillation which was not statistically significant. Duration of stay in the ICU in group-I (2.8 ± 0.8 days) was longer than group-II (2.6 ± 0.4 days) but not statistically significant (p = 0.08). Length of stay in the hospital was longer in group- I (7.1 ± 3.5 days) as compared to group-II (6.2 ± 0.4) & was statistically significant. (p = 0.02). Six patients postoperatively developed deep sternal wound infection & three patients had to undergo pectoral flap surgery. All the six patients were from group-I & had high HbA1C levels preoperatively.Graph-5 shows the glucose variability between the two groups during pre-bypass, bypass & ICU for the first 48 hrs. Glucose variability is more in group-I as compared to group-II.

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DISCUSSION

The objective of our study was to determine whether preoperative glycosylated haemoglobin levels (HbA1C) could predict the probability of perioperative hyperglycaemia, duration of stay in the ICU & hospital, inotropic requirement & the incidence of infection & atrial fibrillation in the postoperative period. During cardiac surgery there is alteration in the glucose metabolism. Many factors like surgical stress, exposure to CPB, inotropes, insulin resistance;predisposes both diabetic & non-diabetic patients for hyperglycaemia. Various studies have shown that perioperative hyperglycaemia & glucose variability is associated with prolonged ICU & hospital stay & increased mortality & morbidity perioperatively during cardiac surgery. Perioperative hyperglycaemia & glucose variability influence the outcome in critically ill patients.However, their extent of perioperative hyperglycaemia can only be determined afterwards, which limits their use as a clinical predictor. Identifying relevant patient characteristics that are connected to and could possibly predict intra- and postoperative hyperglycaemia is an important step toward improved medical management. The importance of preoperative HbA1C levels, whether surgery should be delayed in patients with higher values & can HbA1C levels can be used to predict perioperative hyperglycaemia & post-operative outcomes following on pump CABG are the questions we have tried to answer from our study.

Perioperative blood sugar levels till first 48 hrs. postoperatively& glucose variability were higher in group-I (HbA1C > 7%) patients. Patients with HbA1C > 7% required a higher insulin doses postoperatively for the first 48 hrs.to maintain blood sugars less than 180mg/dl. Inotropic score [17] of group-I was higher postoperatively though preoperative EF, RWMA, duration of CPB & aortic crossclamp were comparable between both the groups. Patients with HbA1C > 7% probably had more severe coronary artery disease. All patients who developed deep sternal wound infection were from group-I, three patients underwent pectoral flap surgery had HbA1C > 10%. Duration of stay in the hospital was longer in group-I patients. Intraoperative insulin requirement, duration of ICU stay & atrial fibrillation rate, there was no statistically significant difference between the two groups. Thus preoperative HbA1C levels can be used as a clinical predictor of perioperative hyperglycaemia, insulin requirement, duration of stay in the hospital & infection rate postoperatively.

LIMITATION AND STRENGTH

This study had certain limitations. It was a small observational single centre study. Inotropic score that is the maximum dose of inotrope used in the ICU during first 48 hrs.was used to calculate inotropic requirement in both the groups. The duration of inotrope used couldn't be compared as there was no cardiac output monitoring postoperatively in all patients.

Compared with other studies, it was a prospective study with a homogenous cohort from single centre. All data was manually collected; so there was no issue of data loss through automatic data collection. Blood sugar level was maintained less than 180 mg/dl in both the groups as per the present STS guidelines. Modified Cleveland clinic insulin dose protocol was used in both the groups to maintain blood sugar levels less than 180 mg/dl perioperatively.

CONCLUSION

In conclusion, this prospective study proved that preoperative HbA1C levels predicted the degree of perioperative hyperglycaemia, insulin requirement perioperatively & duration of stay in the hospital. Furthermore, patients with HbA1C> 7% had an increased risk of infections &required higher inotropic support. We also noticed that patients who underwent pectoral flap surgery for deep sternal wound infection with more than one month hospital stay had a preoperative HbA1C > 10%. In patients with high HbA1C levelspreoperatively, the risk benefit ratio is to be considered before taking up for CABG surgery. In this subset of patients surgery may be delayed until the blood sugars are controlled for a better outcome.

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MODIFIED CLEVELAND CLINICOPERATING ROOM INSULIN THERAPY

Blood Glucose Goal: < 180mg/dl. Regular Insulin 100 units/100 ml in 0.9% normal saline in a concentration of 1 unit/ml will be used.

Starting Insulin: Start if pre CPB blood glucose > 180 mg/dl and if on pump or post pump blood glucose > 180mg/dl.

- Bolus dose: 0.03 units/kg (maximum bolus is 3 units)
- Initiate continuous infusion: initial rate 0.03 units/kg/hr (maximum initial rate is 3 units/hr)
- See Table 1 (Insulin Infusion adjustment) for adjustment of insulin rate.

Blood glucose monitoring: Measure blood glucose every 30 to 60 minutes.

Hypoglycaemia protocol:

- If blood glucose ≤ 60 mg/dL: stop insulin infusion, give 25 – 50 mL of 50% dextrose solution, obtain blood glucose level every 30 minutes until blood glucose > 80 mg/dL for three consecutive levels, and then check blood glucose every 30 – 60 minutes.
- If blood glucose 60 – 70 mg/dL, or 71 – 85 mg/dL and decreasing: stop insulin infusion, obtain blood glucose level every 30 minutes until blood glucose > 85 mg/dL for three consecutive measurements, then check blood glucose every hour.

Resuming insulin infusion:

- Restart at half the previous rate when blood glucose rises above 180 mg/dL.

Insulin Infusion Adjustment (Do not adjust insulin rate every hour - only make adjustments to the insulin rate every two hours)

Blood Glucose	**If BG <u>DECREASES</u> ≥ 30 mg/dl since last level**	**If BG is <u>STABLE</u> (change in BG < 30 mg/dl) since last level**	**If BG <u>INCREASES</u> ≥ 30 mg/dl since last level**
≤ 60	Stop insulin infusion See Hypoglycaemia Protocol	Stop insulin infusion See Hypoglycaemia Protocol	––
61 – 70	Stop insulin infusion See Hypoglycaemia Protocol	Stop insulin infusion/ See Hypoglycaemia Protocol	––
71-85	Stop insulin infusion See Hypoglycaemia Protocol	Decrease rate by 50%	––
86 – 100	Decrease rate by 50%	Decrease rate by 50%	––
101 – 115	Decrease rate by 50%	Continue current rate	––
116 – 150	Decrease rate by 50%	Increase rate by 25%	Increase rate by 25%
151 – 200	Decrease rate by 25%	Increase rate by 25%	Bolus 2 units/ Increase rate by 25%
201 – 250	Continue current rate	Bolus 2 units/ Increase rate by 25%	Bolus 4 units/ Increase rate by 25%
251 – 300	Continue current rate	Bolus 4 units/ Increase rate by 50%	Bolus 6 units/ Increase rate by 50%
301 – 350	Continue current rate	Bolus 6 units/ Increase rate by 50%	Bolus 8 units/ Increase rate by 50%
351 – 400	Continue current rate	Bolus 8 units/ Increase rate by 50%	Bolus 10 units/ Increase rate by 50%
> 400	Notify staff anaesthesiologist	Notify staff anaesthesiologist	Notify staff anaesthesiologist

MODIFIED CLEVELAND CLINIC INTENSIVE CARE UNIT INSULIN THERAPY PROTOCOL.

Day of surgery (until Midnight): Blood Glucose Goal: < 180 mg/dl; Post-operative day one (beginning at midnight) until discharge from ICU, Blood Glucose Goal: < 180mg/dl. If blood glucose is within target range upon arrival to the ICU, reduce the infusion by 50% upon admission unless the rate has already been reduced by 50% in the OR.

Starting Insulin: If blood glucose > 180 mg/dl for 4 consecutive measurements:

- Bolus dose: 0.05 units/kg (maximum bolus is 5 units)
- Initiate continuous infusion: initial rate 0.05 units/kg/hr (maximum initial rate is 5 units/hr).
- Please see Table 2 (Insulin Infusion adjustment) for adjustment of insulin rate.

Blood glucose monitoring: Measure blood glucose every hr.

Hypoglycaemia protocol:

- If blood glucose ≤ 60 mg/dL: stop insulin infusion, give 25 – 50 mL of 50% dextrose solution, obtain blood glucose level every 30 minutes until blood glucose > 80 mg/dL for three consecutive levels, and then check blood glucose every two hours.
- If blood glucose 61 – 70 mg/dL, obtain BG level every 1 hour until BG > 80 mg/dL for three consecutive measurements, then check blood glucose every 2 hours.
- If blood glucose 61 – 70 mg/dL – stop insulin infusion.

- If blood glucose decreases ≥ 30 mg/dL since last level and blood glucose = 71 – 85 mg/dL – stop infusion, obtain blood glucose level every one hour until blood glucose > 80 mg/dL for three consecutive levels, then check blood glucose every two hours.

- If enteral nutrition or total parenteral nutrition is stopped, decrease insulin infusion rate by 50% and monitor blood glucose levels every 1 hour until BG > 80 mg/dl for three consecutive levels, then check blood glucose every 2 hours

Resuming insulin infusion: Restart at half the previous rate when blood glucose ≥ 180 mg/dL. Do not give bolus. Obtain blood glucose in one hour and re-evaluate

Insulin Infusion Adjustment **(**Do not adjust insulin rate every hour - only make adjustments to the insulin rate every two hours)

Blood Glucose	**If BG <u>DECREASES</u> ≥ 30 mg/dl since last level**	**If BG is <u>STABLE</u> (change in BG < 30 mg/dl) since last level**	**If BG <u>INCREASES</u> ≥ 30 mg/dl since last level**
≤ 60	Stop insulin infusion See Hypoglycaemia Protocol	Stop insulin infusion See Hypoglycaemia Protocol	––
61 – 70	Stop insulin infusion See Hypoglycaemia Protocol	Stop insulin infusion/ See Hypoglycaemia Protocol	––
71-85	Stop insulin infusion See Hypoglycaemia Protocol	Decrease rate by 50%	––
86 – 100	Decrease rate by 50%	Decrease rate by 50%	––
101 – 115	Decrease rate by 50%	Continue current rate	––
116 – 150	Decrease rate by 50%	Increase rate by 25%	Increase rate by 25%
151 – 200	Decrease rate by 25%	Increase rate by 25%	Bolus 2 units/ Increase rate by 25%
201 – 250	Continue current rate	Bolus 2 units/ Increase rate by 25%	Bolus 4 units/ Increase rate by 25%

251 – 300	Continue current rate	Bolus 4 units/ Increase rate by 50%	Bolus 6 units/ Increase rate by 50%
301 – 350	Continue current rate	Bolus 6 units/ Increase rate by 50%	Bolus 8 units/ Increase rate by 50%
351 – 400	Continue current rate	Bolus 8 units/ Increase rate by 50%	Bolus 10 units/ Increase rate by 50%
> 400	Notify ICU Resident*	Notify ICU Resident*	Notify ICU Resident*

(Note: if insulin rate is ≥ 30 units/hr, notify ICU resident*)

PROFORMA FOR DATA COLLECTION

- **Patient ID :**
- **Age:**
- **Sex:**
- **Weight**
- **Height**
- **BMI:**
- **BSA**
- **Diagnosis:**
- **Proposed Surgery:**
- **Diabetic or Non Diabetic:**
- **Diabetic medication:**
- **Group:**
- **Pre-operative echo:**
- **Preoperative blood glucose:**
- **Duration of Bypass:**

- **Intra operative blood sugar: median + SD**

- **Post-operative blood sugar: median + SD,**

- **Insulin requirement intra op:**

- **Post op insulin requirement:** **POD 0**

  POD 1

- **Inotropic requirement:** Inotropic score = Dobutamine (µg/kg/min) + Dopamine (µg/kg/min) + 100 X adrenaline (µg/kg/min) + 100 X nor adrenaline (µg/kg/min) + 10 X milrinone (µg/kg/min) + 10,000 X vasopressin dose (U/kg/min).

- **Any AF intra or post-operative:**

- **Any infection:**

- **Duration of ICU stay:**

- **Duration of hospital stay:**

- **Any complications:**

Technical Advisory Committee (Clinical Studies)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCE & TECHNOLOGY
THIRUVANANTHAPURAM – 695011, INDIA

TAC Registration No: SCT-/S/2011/94 **Date: 21.10.2011**

TITLE: Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing onpump CABG surgery.

Principal Investigator:	
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(2) Name: Dr. Jaya Kumar .K	Degree: M.S. (General Surgery), MCH (CVTS)
Address: Professor and Head, Department of CVTS, SCTIMST	

Members who participated in TAC meeting

Dr. V. Mohan Kumar (Chairman)
Dr. R. Sankar Kumar
Dr. C. Kesavadas
Dr. K. Srinivasan
Dr. T. V. Kumary
Dr. Narayanan Namboodiri
Dr. K. Shivakumar (Member Secretary)

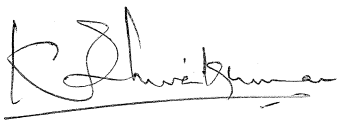
Risk Classification of the project (Minimum/ Moderate/ High): Minimum

Requirement of DSMB: No

Recommended members of DSMB: Not applicable

Recommendations of TAC:

Recommended for consideration of IEC in the light of the responses received from the investigator.



Signature of the Member Secretary, TAC (Clinical Studies)

Note for IEC
Copy of the investigator's responses to questions/suggestions from TAC is attached (Appendix-1).

INSTITUTIONAL ETHICAL COMMITTEE APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान

तिरुवनन्तपुरम - 695 011, केरल, भारत

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM - 695 011, INDIA

(An Institute of National importance under Govt. of India)

Institutional Ethics Committee

SCT/IEC/392/NOVEMBER -2011 21-12-2011

Dr. Dinesh Kumar U.S
Resident
DM. (Cardiac Anaesthesia)
SCTIMST.

Dear Dr. Dinesh Kumar,

The Institutional Ethics Committee reviewed and discussed your application to conduct the clinical trial titled " Preoperative glycosylated Haemoglobin Levels Predict Perioperative Hyperglycemia, Insulin Requirement & Prolonged Hospital Stay in Patients Undergoing On - pump CABG Surgery" IEC/392/ to the IEC with the following documents on 19th November, 2011.

The following documents were reviewed:

1. *Covering letter dated 24/08/2011.*
2. *Study proposal.*
3. *IEC Application form.*
4. *TAC Approval.*
5. *Monitoring chart.*
6. *Modified Cleveland Clinic protocol.*

तार : चित्रमेट Grams : Chitramet | फोन Phone : 2443152 | फाक्स Fax : (91)471-2446433 2550728 | ई-मेइल E-mail : sct. @sctimst.ac.in वेबसाईट Website : www.sctimst.ac.in

7. *Consent- Malayalam and English.*
8. *CV of Investigators.*
9. *Covering letter dated 10 December, 2011 from Dr. Dinesh Kumar U.S. Resident. DM (Cardiac Anaesthesia), Department of Anaesthesiology, SCTIMST addressed to Dr. Anoopkumar Thekkuveettil, Member Secretary, IEC – SCTIMST submitting the Modified Application for Ethics Review and Modified Information to Participants and Consent form.*
10. *Modified Application for Ethics Review and Modified Information to Participants and Consent form submitted on 10-12-2011.*
11. *Covering letter dated 20 December, 2011 from Dr. Dinesh Kumar U.S. Resident. DM (Cardiac Anaesthesia), Department of Anaesthesiology, SCTIMST addressed to Dr. Anoopkumar Thekkuveettil, Member Secretary, IEC – SCTIMST submitting the Modified Information to Participants and Consent form.*
12. *Modified Information to Participants and Consent form submitted on 20-12-2011.*

The following members of the Ethics committee were present at the meeting held on 19th November, 2011 at Director's Conference Hall.

Sl. No	Member Name	Highest Degree	Gender	Scientific / Non-scientific	Affiliation with Institution (s)
1.	Justice M.R. Hariharan Nair.	MA BL	Male	Legal Expert (Chairperson)	No
2.	Prof. K. Radhakrishnan	MD	Male	Clinician (Neurologist)	Yes
3.	Dr. G. S. Bhuvaneshwar	PhD	Male	Basic Scientist (Biomedical Expert)	Yes
4.	Dr. K. A. Kumar	MD	Male	Clinician (Psychiatrist)	No
5.	Dr. Rema M. N	MD	Female	Pharmacologist	No
6.	Ms. Seema Bhaskar	MA	Female	Lay Person (Social Science)	No

7.	Dr. Girish Menon	MCh	Male	Neurosurgeon/Ethicist	Yes
8.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro Enterologist)	No
9.	Dr. Anoopkumar Thekkuveettil	PhD	Male	Basic Scientist (Molecular Biology) / Ethicist (Member Secretary)	Yes

IEC Decision

IEC approved the study to be conducted in the present form.

Remarks:

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Yours Sincerely

Dr. Anoopkumar Thekkuveettil
Member Secretary, Ethics Committee.

ABBREVATIONS AND SYMBOLS

BSA- Body surface area

BMI- Body mass index

BSL- Blood sugar levels

CABG- coronary artery bypass grafting

DM- Diabetes mellitus

EF- ejection fraction

LOS- length of stay

HbA1C- Glycosylated haemoglobin

RWMA- Regional wall motion abnormality

< - less than

>- more than

Non-DM- Non diabetic

INFORMATION TO PARTICIPANTS & CONSENT FORM

Title of Project: "Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing on pump CABG surgery**."**

Name of Researcher: Dr. Dinesh Kumar.U.S, Dr.Thomas Koshy, Dr.Jaya Kumar.

Name of the participant:

You are invited to take part in this research study conducted at Sree Chitra Tirunal Institute for Medical Sciences and Technology. The information in this document is meant to help you to understand about the present study and to help you to decide whether to take part in it or not. Please feel free to ask if you have any questions or concerns.

Back ground of the present study

Many patients presenting for CABG (Bypass surgery) have diabetes & it has to be well controlled before taking up for surgery. So we measure blood sugar levels (Fasting & postprandial) as part of routine investigation. Many studies have shown that glycosylated haemoglobin levels predict blood sugar levels over the past 2-3 months. In this study we are evaluating whether long term control of blood sugars (glycosylated haemoglobin levels) will it predict blood sugar levels, insulin requirement & prolonged hospital stay in CABG patients. The results of research may provide benefit to the society in terms of better understanding and advancement of medical knowledge for future application.

Why are you selected as a potential participant?

You are being asked to participate in this study because you satisfy our eligible criteria of adult patients undergoing coronary artery bypass grafting.

Is there any extra discomfort to you by being a participant in the study?

There is no extra discomfort to you by being a participant in the study. There won't be any extra checkups, investigations, need for follow-up (before and after discharge) because of the study.

What are the possible risks to you by being a participant in this study?

There is no additional risk to you by participating in this study.

What is the extra cost to you by being a participant in this study?

There is no additional cost to you by participating in this study

Are there any complications that can happen to a participant due to study?

There are no complications that can happen to the participant due to the study process.

What are the possible benefits to you from being a participant in this study?

You are not expected to get any benefit from being participant in this research study.

Who will benefit from this study?

The results of research may provide benefit to the society in terms of better understanding and advancement of medical knowledge for future application.

Will the personal details and information obtained from you be kept confidential?

You have the right to confidentiality regarding your medical information (personal details, results of examinations, investigations and history). By signing this document you are permitting the research team members to view and use your data. The information from this study can be presented in scientific journals and meetings by the researchers, however your personal identity will not be revealed.

How will your decision of not to participate in the study will affect you?

It will not affect you in any means. You will still get the standard treatment and care you are entitled to get. It will not affect your relationship with the institute, treating doctor, staff members & researcher.

Can you decide to stop participating in the study once you start?

The participation in this study is purely on voluntary basis. You have the right to withdraw from this study at any time during the course of study without giving any reasons. You will still get the standard treatment and care you are entitled to get. It will not affect your relationship with the institute, treating doctor, staff members & researcher.

Can the investigator take you off the study?

The investigator has the right to take you off the study without your consent to do so.

Right to new information

If the research team gets any new information during the course of the study that may affect your decision to continue to participate in the study, you will be told about that information.

The following persons can be contacted in case if the participant needs to discuss anything about the study. Dr.Dinesh Kumar.U.S, Department of anaesthesiology, SCTIMST. (Mobile number 9645358182). Dr.Thomas Koshy, Department of anaesthesiology, SCTIMST.(mobile number 9847064457).

In case of conflict the participant can contact the institutional ethics committee chairman of SCTIMST

Dr. Anoop kumar .T,

Scientist – F,

Molecular medicine,

B.M.T wing (SCTIMST),

Pojappura,

Trivandrum. Phone – 0471 – 2520256 .

CONSENT FORM

Title of Project: Preoperative Glycosylated haemoglobin levels predict perioperative hyperglycemia, insulin requirement & prolonged hospital stay in patients undergoing onpump CABG surgery.

Names of Researchers:
Dr. Dinesh kumar.U.S, Dr.Thomas Koshy, Dr. Jaya Kumar. K

I confirm that I have been explained that glycosylated haemoglobin levels is a routinely do investigation as per hospital protocol during CABG surgery. I understand that relevant sections of any of my data and medical notes collected during the study will be used by the doctors' team doing this research. I was told that the purpose of the present research is for better understanding and advancement of medical knowledge for future application. I also understand that there won't be any change in the treatment I receive, for me being a participant in the study.

I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily in a language understandable to me.

I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

I was told that there is no additional risk to me by being a subject in the study. I have also been explained that I will not be getting any benefit for participating in the study

I have also been explained that my identity will not be disclosed. I give permission for these individuals to have access to my records and present in scientific journals and meetings.

I have been provided with the contact numbers of principle investigator in case I want to know more about study and participants rights.

I agree to take part in the above research study.

Name of Patient	Date	Signature
Name of researcher	Date	Signature