Original Article

Perioperative Glycemic Control in Patients who Underwent Cardiac Transplantation and Effect on the Outcome at Discharge in a Tertiary Care Centre

Lohit Kumbar, Sandeep Donagaon[1], Nagamalesh UM[2], Ravi Shankar Shetty[3], Pramila Kalra

Department of Endocrinology, Ramaiah Medical College and Hospital, Bengaluru, [1]Department of Endocrinology, SDM College of Medical Sciences and Hospital, Dharwad, [2]Department of Cardiology, Ramaiah Medical College and Hospital, [3]Department of Cardiothoracic Surgery, Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India

Abstract

Objectives: To study the glycemic status and insulin requirements in patients who underwent cardiac transplantation and to compare it among patients with and without diabetes mellitus. To compare preoperative glycemic status and perioperative insulin requirements with the outcome. **Methods and Materials:** The retrospective data of the glycemic status of patients before and after cardiac transplantation were collected and analyzed. Different variables like HbA1c, creatinine, age, BMI, and glycemic status were compared with the outcome. **Results:** A total of 18 patients with a mean age of 46.72 ± 16.94 years (mean ± SD) and a median age of 48.5 years underwent cardiac transplantation. The mean preoperative glycosylated hemoglobin (HbA1c) was 8.75 ± 2.15% (72 ± 2.36 mmol/mol) and 5.82 ± 0.45% (40 ± 4.89 mmol/mol) in patients with and without diabetes mellitus, respectively. The mean insulin requirement of insulin on postoperative days 0, 1, 2, and 3 was 1.396, 0.503, 0.490, and 0.537 (IU/kg/day) in patients with diabetes, whereas in patients without diabetes mellitus it was 1.955, 0.561, 1.19, and 0.61 (IU/kg/day), respectively. The mean insulin requirement at the time of discharge was 0.698 ± 0.43 IU/kg/day (mean ± SD) and 1.285 ± 1 IU/kg/day (mean ± SD) ($p = 0.36$) in patients with and without diabetes mellitus, respectively ($p = 0.53$, 0.11, 0.41, and 0.32, respectively). There was no association with the outcome when analyzed with different variables like HbA1c, creatinine, BMI, age, hemoglobin, insulin requirements, and glycemic status. **Conclusions:** Perioperative glycemic control is crucial for successful cardiac transplantation irrespective of diabetic status.

Keywords: Cardiac transplantation, diabetes mellitus, insulin, perioperative

Introduction

Diabetes mellitus is associated with the higher incidence of preoperative comorbidities, including obesity, small vessel coronary artery disease, more severe and extensive atherosclerosis, peripheral vascular disease, renal insufficiency, hypertension, and increased rates of life-threatening postoperative infection.[1]

The risk for postoperative complications and increased mortality relates to both long-term glycemic control and the severity of hyperglycemia on admission and during the hospital stay.[1]

Postoperative and perioperative hyperglycemia in critically ill patients are associated with increased risks of infection, inpatient mortality, and other adverse events in both patients with and without diabetes mellitus.[2]

Access this article online

Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_121_20

Survival of cardiac transplant patients in the long term has improved significantly in the modern era, mainly due to the more proficient immunosuppressive regimens available now.[3] However, the diabetogenic effects of these immunosuppressive agents have contributed to the increased rates of posttransplant diabetes mellitus.[4]

Insulin exerts cardioprotective effects via glucose-dependent and -independent mechanisms, including aversion of glucose

Address for correspondence: Dr. Pramila Kalra, Department of Endocrinology, Ramaiah Medical College and Hospital, Mathikere, Bengaluru - 560 054, Karnataka, India.
E-mail: kalrapramila@gmail.com

Submitted: 12-Mar-2020 **Revised:** 20-Mar-2020
Accepted: 25-Apr-2020 **Published:** 30-Jun-2020

How to cite this article: Kumbar L, Donagaon S, Nagamalesh UM, Shetty RS, Kalra P. Perioperative glycemic control in patients who underwent cardiac transplantation and effect on the outcome at discharge in a tertiary care centre. Indian J Endocr Metab 2020;24:270-4.

Table 1: Baseline characteristics of patients

Number of patients	Baseline characteristics of patients						*P*
	Diabetes mellitus[11]			Without Diabetes mellitus[9]			
	Mean	Median	IR (25-75)	Mean	Median	IR (25-75)	
Age (years)	55.20±10.11	55.50	45.75-66	36.13±18.29	36.50	20-54	0.012
BMI (kg/m^2)	23.26±4.64	22.48	19.38-27.07	18.96±2.25	19.77	16.88-59	0.02
Haemoglobin (gm/dl)	12.5±1.62	12.5	11.45-13.9	9.86±4.32	11.2	9.02-11.97	0.13
Creatinine (mg/dl)	1.13±0.32	1.03	0.93-1.32	0.96±0.37	1.03	0.67-1.23	0.30
Glycosylated Haemoglobin -HbA1c -% (mmol/mol)	8.75±2.15 (72+2.36)	8.05 (64.5)	7.2-9.95 (55-85.251)	5.82±0.45 (40+4.89)	5.8 (40)	5.4-6.2 (36-44)	0.02
Length of stay in hospital (days)	33.90±18.61	24.50	23-54	33.38±30.91	23.5	17.25-35.50	0.96

Table 2: Insulin requirements in the perioperative period

Diabetes Mellitus	Insulin requirement (IU/kg/day) (mean±SD) in the perioperatve period			
	Day 0	Day 1	Day 2	Day 3
Yes	1.221±0.720	0.551±0.534	0.552±0.712	0.537±0.749
No	1.661±1.60	0.144±0.243	0.249±0.528	0.207±0.289
P	0.53	0.11	0.41	0.32

Table 3: Insulin requirements at discharge

Diabetes Mellitus	Insulin requirement at discharge (IU/kg/day)		
	Mean±SD	Median	IR (25-75)
Yes	0.773±0.481	0.593	0.44-1.38
No	0.395±0.877	0	0-0.68
P	0.36		

toxicity, positive inotropy, the interrelated modulation of oxidative stress, inflammation, and apoptosis, and regulation of blood flow. These effects may account for the clinical benefits of intensive insulin therapy observed in cardiac surgery patients.[5]

Glycemic management in patients undergoing cardiac transplantation poses specific challenges, especially with cardiac tissue acceptance. These patients are being exposed to massive doses of steroids and immunosuppressive drugs. This is a retrospective analysis of peri-operative glycemic control in patients who underwent cardiac transplantation.

Objectives

The primary objective was to study the glycemic status and insulin requirements in-patients who underwent cardiac transplantation and the secondary objective was to compare the insulin requirements among patients with and without diabetes mellitus and to compare preoperative glycemic status with the outcome at discharge.

Subjects and Methods

Methods

A retrospective analysis of cardiac transplant patients admitted in our hospital from 2015 to 2019 was done. A total of 18 cases who underwent cardiac transplantation were included. Data obtained from the records included age, gender, height, weight, BMI, hemoglobin, serum creatinine, glycosylated hemoglobin (HbA1c), diabetic status, insulin infusion dose, insulin requirement at discharge, and length of stay in hospital. Insulin infusion dose during the perioperative period was collected from day zero to day three. Insulin infusion was given as per the institute protocol. Blood glucose levels were maintained in the range of 140–180 mg/dl. Patients had received injectable methylprednisolone 500 mg at induction and 500 mg before clamp release. Methylprednisolone was reduced to 125 TID on day one postoperatively and the dose was reduced by 50 mg per day depending on the patient's condition. Tacrolimus was added on the seventh or eighth day post cardiac transplantation. A cardiac biopsy was done after the first week post cardiac transplantation. The primary outcome measured was death and secondary outcomes were the duration of hospital stay and incidence of infection. Glycemic status of patients was compared with the outcome at discharge. The other factors which may affect the outcome like serum creatinine, hemoglobin, gender, BMI, and age were analyzed using linear regression analysis.

Statistical methods

- Statistical analysis of data: All the continuous variables such as insulin, HbA1c, etc., are expressed as mean and SD. Alternatively, in case of non-normality are expressed as median with interquartile range. The difference in the mean/median values was tested for statistical significance by independent student t-test. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS software version 18.0.

Results

The study cohort comprised of 18 patients, which included 14 male and four female patients with a mean age of 46.72 ± 16.94 years (mean ± SD) and a median age of 48.5 years [Table 1]. Ten patients were diagnosed of diabetes mellitus preoperatively and eight were without diabetes mellitus. The preoperative mean HbA1c in patients with diabetes mellitus was 8.75 ± 2.15% (72 ± 2.36 mmol/mol), while in patients without diabetes mellitus, it was 5.82 ± 0.45% (40 ± 4.89 mmol/mol). The mean insulin

requirement of insulin on postoperative day 0, 1, 2, and 3 was 1.396, 0.503, 0.490, and 0.537 (IU/kg/day) in patients with diabetes mellitus, whereas in patients without diabetes mellitus it was 1.955, 0.561, 1.19, and 0.61 (IU/kg/day), respectively [Table 2]. The higher requirements of insulin in patients without diabetes mellitus was probably due to outliers and small sample size. Median insulin requirement on day zero to day three were 1.667, 0.386, 0.328, and 0.333 (IU/kg/day) in patients with diabetes mellitus and 1.085, 0.000, 0.000, and 0.108 (IU/kg/day) in patients without diabetes mellitus, respectively. The insulin requirements in the perioperative period in patients with or without diabetes mellitus were not significant (p = 0.53, 0.11, 0.41, and 0.32). The range of blood glucose levels were between 140 mg/dl and 180 mg/dl. There was no incidence of hypoglycemia in any of the patients while on insulin infusion. The mean insulin at the time of discharge in patients with diabetes mellitus was 0.698 ± 0.43 IU/kg/day (mean ± SD), while in patients without diabetes mellitus it was 1.285 ± 1 IU/kg/day (mean ± SD) [Table 3]. The insulin requirements upon discharge in patients with and without diabetes mellitus were not significant (p = 0.36). The mean length of stay in the hospital in patients with diabetes mellitus was 33.90 ± 18.61 days (mean ± SD) and median of 24.5 days while in patients without diabetes mellitus it was 33.38 ± 30.91 days (mean ± SD) and median of 23.5 days. The various factors like creatinine, HbA1c, age, BMI, and hemoglobin did not affect the outcome (p = NS).

Two of the patients died in the postoperative period.

The cause of death was pneumonia and sepsis in one patient and other had vasogenic shock in the postoperative period.

None of the patients had any infections or increased requirements for antibiotics in the perioperative period. The cultures taken from blood, urine, and endotracheal tube did not isolate any organism in any of the patients.

Discussion

In this study, we observed that insulin infusion was required in high doses during the perioperative period, i.e., 1.396, 0.503, 0.490, and 0.537 (IU/kg/day) in patients with diabetes mellitus, whereas in patients without diabetes mellitus it was 1.955, 0.561, 1.19, and 0.61 (IU/kg/day), respectively, on day zero to day three. There was no significant difference in insulin infusion dose between the patients with and without diabetes mellitus. The higher mean insulin requirement in patients without diabetes mellitus is due to the outliers. A study done by Furnary *et al*.[1] observed significant lower mortality with continuous insulin infusion (2.5%, n = 65/2612) than with subcutaneous insulin (5.3%, n 50/942, *P* 0.0001) and better glycemic control with continuous insulin infusion (177 ± 30 mg/dLvs 213 ± 41 mg/dL, *P* 0.0001). In a study[6] done in patients with liver transplantation, mean insulin (units) requirement during the first, middle, and last 24 hr of hospital stay was 57, 86, and 59 in pretransplant diabetes mellitus and 15, 23, and 17 units in patients without pretransplant diabetes mellitus, respectively.

In our study, patients, blood sugar levels were between 140 mg/dl to 180 mg/dl in both patients with and without diabetes mellitus. In a study by Walia *et al*.,[2] the mean morning fasting plasma glucose level following conversion (subcutaneous Day 1) was 124.7 ± 35.4 mg/dL (134.9 ± 52.5 mg/dL diabetes mellitus, 120.9 ± 26.4 mg/dL without diabetes mellitus, *P* = 0.14). Pre-drip blood glucose levels in patients with and without diabetes mellitus were 244.7 ± 71.6 mg/dl and 265.3 ± 75 mg/dl (p = 0.30), respectively. On day 1, insulin drip was 153.8 ± 28.5 mg/dl and 165.8 ± 34.6 mg/dL (p = 0.18), respectively. In the transition from day zero to day 4, the subcutaneous insulin blood glucose levels on Day zero were 160.7 ± 49.5 mg/dl, 137 ± 23.9 mg/dl (p = 0.008), Day 1 155 ± 38.8 mg/dl, 131.3 ± 26.1 mg/dl (p = 0.004), Day 2 143 ± 31.7 mg/dl, 126 ± 28.5 mg/dl (p = 0.034), Day 3 147.8 ± 48.9 mg/dl, 128 ± 23 (p = 0.026), and Day 4 147.1 ± 42 mg/dl, 128.7 ± 23.8 mg/dl (p = 0.029), respectively, in patients with and without diabetes mellitus. Insulin glargine dose in patients with and without diabetes mellitus were not significantly different on the conversion day to subcutaneous insulin from the intravenous route or subsequent subcutaneous protocol days 1 to 4. In a study[6] done in liver transplant patients, the blood glucose levels were higher in pretransplant diabetes mellitus than in patients without diabetes mellitus (163 mg/dl vs 147 mg/dl). In a study by Garcia *et al*.,[7] glycemic control was performed used intravenous (IV) and subcutaneous (SQ) insulin protocols with a glucose target of 80–110 mg/dL. There were no significant differences between patients with and without diabetes mellitus in mean glucose levels on the intravenous and subcutaneous insulin protocols.

None of our patients had hypoglycemia during insulin infusion. In a study done by Wallia[2] *et al*. in cardiac transplantation, no patients developed severe hypoglycemia (blood glucose ≤40 mg/dL) while on the drip, and only 2.8% experienced hypoglycemia on subcutaneous insulin. In a study done by Garcia[7] *et al*. in cardiac transplantation, severe hypoglycemia (blood glucose ≤40 mg/dL) did not occur on the intravenous protocol and was experienced by only three patients without diabetes mellitus on the subcutaneous protocol. Moderate hypoglycemia (blood glucose >40 and <60 mg/dL) occurred in 17 (19%) patients on the intravenous protocol and 24 (27%) on the subcutaneous protocol.

As per the protocol of our institute, patients undergoing cardiac transplantation patients had received injectable methylprednisolone 500 mg at induction and 500 mg before clamp release. Methylprednisolone was reduced to 125 TID on day one postoperatively and the dose was reduced by 50 mg per day depending on the patient's condition. Tacrolimus was added on the seventh or eighth day post cardiac transplantation. In a study[6] in patients undergoing liver transplantation, 500 mg of intravenous methyprednisolone was given preoperatively, 50 mg, and 25 mg twice daily on postoperative day zero and day one, respectively. 20 mg, 15 mg, and 10 mg twice daily was given on postoperative days 2 and 3, days 4–6, and days

7–10, respectively, followed by tapering of dose to stop at four months postoperatively.

In our study, there were two deaths in the postoperative period. In a study by Garcia[7] *et al*., 30-day mortality in patients with diabetes mellitus was nil, while in patients without diabetes mellitus it was 1 (2%). In a study done by Wallia[2] *et al*. only one patient (diabetes mellitus) died in the first year following cardiac transplantation

In our study mean length of stay in the hospital in patients with diabetes mellitus was 33.90 ± 18.61 days (mean ± SD) and median of 24.5 days while in patients without diabetes mellitus it was 33.38 ± 30.91 days (mean ± SD) and median of 23.5 days. In a study by Garcia[7] *et al*., the mean duration of hospitalization was 18 ± 11 days (mean ± SD) in patients with diabetes mellitus and 14 ± 8 days (mean ± SD) in patients without diabetes mellitus. In a study by Wallia[2] *et al*., the mean average days of hospitalization were 12.6 ± 4.6 days (mean ± SD) and 12.6 ± 5.4 days (mean ± SD) in patients with and without diabetes mellitus, respectively.

In our study, none of the patients had any infections or increased requirements for antibiotics in the peri-operative period. In a study by Garcia[7] *et al*., the incidence of infections was 2/26 and 4/66 in patients with and without diabetes mellitus, respectively.

When analyzed for various factors like creatinine, BMI, age, hemoglobin, and glycemic status with the outcome, i.e., the length of hospital stay, we found that none of the factors were significantly associated with the outcome. In a study by Garcia[7] *et al*., there were no significant differences between patients with and without diabetes mellitus within 30 d of surgery in all-cause mortality, treated heart transplant rejection episodes, reoperation, prolonged ventilation, 30-day readmissions, ICU readmission, number of ICU hours, hospitalization days after HT, or infections.

Two of the patients who were without diabetes mellitus during the preoperative period developed diabetes mellitus and required insulin at discharge.

Strict blood glucose control with intensive insulin therapy in critically ill patients proved to be beneficial concerning mortality and morbidity of critically ill patients in surgical as well as medical ICU, irrespective of previously diagnosed diabetes.[8]

Immunosuppressive therapy in post-heart transplant can complicate diabetes mellitus. However, many studies show no difference in survival compared with recipients without diabetes mellitus. The percentage of patients with diabetes mellitus among heart transplant recipients (29%)[9] was higher than in many published studies.[10,11] Nevertheless, global survival at a one-year follow-up (83%) was similar to that of patients without diabetes mellitus. Neither fasting glucose impairment nor pre-transplantation diabetes mellitus were independent predictors of one-year mortality.[12] The three- and five-year mortalities observed in one study[9] had already evolved to lower survival in individuals with diabetes mellitus. Statistically significant differences in the incidences of infection, acute rejection, or renal dysfunction during the first year and this appeared to persist up to five years. In one study[9] centre, 23% of deaths at the one-year follow-up were due to infection, but there was no difference between patients with and without diabetes mellitus. The same was true for death due to cardiovascular causes (23%), acute rejection, hemorrhage, and cardiovascular or cerebrovascular causes (15% each). By contrast, renal insufficiency (CrCl <60 ml/min) was confirmed as a significant predictor of one-year mortality.[9]

Compared to the usual cardiac surgery patients, cardiac transplant patients have significantly more severe medical comorbidities, underlying heart disease/heart failure before surgery, fluctuating renal function, and receive high-dose steroids. They have very high surgical stress, making glycemic management very difficult.[2]

Tacrolimus causes hyperglycemia by enhanced glucose absorption in the jejunum by the upregulated expression of SGLT1 and also by increasing insulin resistance.[13] Since all the patients in our study were on tacrolimus, the effect of tacrolimus on the outcome could not be assessed.

Limitations of the study

This study is a retrospective study. Glycemic status was not compared with long-term outcomes. There were some of the missing data on insulin infusion in the perioperative period. Other factors which could affect the outcome like size of the heart, status of donor heart, and comorbidities in donor were not studied.

Conclusion

Perioperative hyperglycemia in patients with diabetes or nondiabetic can be managed with insulin infusion. Perioperative glycemic management plays an important role irrespective of the glycemic status preoperative. Glycemic status in the perioperative period is one of the determining factors for successful cardiac transplantation. A proper glycemic control has a great impact on the outcome and survival of the patients.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Frisch A, Chandra P, Smiley D, Peng L, Rizzo M, Gatcliffe C, *et al*. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010;33:1783-8.
2. Wallia A, Gupta S, Garcia C, Schmidt K, Oakes DJ, Aleppo G, *et al*. Examination of implementation of intravenous and subcutaneous insulin protocols and glycemic control in heart transplant patients. Endocr Pract 2014;20:527-35.

3. Rana A, Gruessner A, Agopian VG, Khalpey Z, Riaz IB, Kaplan B, *et al*. Survival benefit of solid-organ transplant in the United States. JAMA Surg 2015;150:252-9.
4. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva C. Posttransplantation diabetes: A systematic review of the literature. Diabetes Care 2002;25:583-92.
5. Ng KW, Allen ML, Desai A, Macrae D, Pathan N. Cardioprotective effects of insulin: How intensive insulin therapy may benefit cardiac surgery patients. Circulation 2012;125:721-8.
6. Werner KT, Mackey PA, Castro JC, Carey EJ, Chakkera HA, Cook CB. Hyperglycemia during the immediate period following liver transplantation. Future Sci OA 2016;2:FSO97.
7. Garcia C, Wallia A, Gupta S, Schmidt K, Malekar-Raikar S, Johnson Oakes D, *et al*. Intensive glycemic control after heart transplantation is safe and effective for diabetic and non-diabetic patients. Clin Transplant 2013;27:444-54.
8. Vanhorebeek I, Ingels C, Van den Berghe G. Intensive insulin therapy in high-risk cardiac surgery patients: Evidence from the Leuven randomized study. Semin Thorac Cardiovasc Surg 2006;18:309-16.
9. Saraiva J, Sola E, Prieto D, Antunes MJ. Diabetes as an outcome predictor after heart transplantation. Interact Cardiovasc Thorac Surg 2011;13:499-504; discussion 504.
10. Higgins J, Pflugfelder PW, Kostuk WJ. Increased morbidity in diabetic cardiac transplant recipients. Can J Cardiol 2009;25:e125-9.
11. Moro JA, Martínez-Dolz L, Almenar L, Martínez-Ortiz L, Chamorro C, García C, *et al*. [Impact of diabetes mellitus on heart transplant recipients]. Rev Esp Cardiol 2006;59:1033-7.
12. António N, Prieto D, Providência LA, Antunes MJ. Diabetes mellitus does not affect one-year outcome after heart transplantation. Rev Port Cardiol 2010;29:205-20.
13. Li Z, Sun F, Zhang Y, Chen H, He N, Chen H, *et al*. Tacrolimus induces insulin resistance and increases the glucose absorption in the Jejunum: A potential mechanism of the diabetogenic effects. PLoS One 2015;10:e0143405.