

Effects of Controlling of Post Operative Hyperglycemia (Stress Induced Hyperglycemia) in Adult Non-Diabetic Patients Undergoing Mitral Valve Replacement Surgery Under Cardiopulmonary Bypass

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Abstract:

Objectives: The objective of this study was to see whether there is an association between high blood glucose levels after operation under CPB and post operative morbidity and mortality.

Methodology: This cohort study was carried out in the Department of Cardiac Surgery at National Institute of Cardiovascular Diseases (NICVD), Sher-e-Bangla Nagar, Dhaka from January, 2012 to December, 2013 for a period of twenty four (24) months. A total number of 110 patients who underwent MVR operation with CPB were enrolled in this study as per inclusion and exclusion criteria. Patients were divided into two groups according to their post operative blood glucose levels, recorded within first 60 hrs after mitral valve replacement surgery under cardiopulmonary bypass. Patients having blood glucose level of less than 10.1 mmol/L (unexposed) and patients having blood lactate level of 10.1 mmol/L or more (exposed) were grouped. Post operative variables were observed and recorded during the hospital course of the patient.

Result: A total number of 110 patients were enrolled in this study. Blood glucose levels lower than or equal to 10 mmol/L after MVR were present in 55(50%) patients (Group A) Blood glucose levels higher than 10 mmol/L after MVR were present in 55(50%) patients. Postoperative morbidity was higher in this group (Group B) than in the patients who had peak blood glucose levels of less than or equal to 10 mmol/L MVR (p 0.001). Postoperative ICU stay was prolonged in patients with elevated levels of blood glucose after MVR under CPB compared with of patients with lower blood glucose levels (p 0.001). Other common morbidities are neurological complication (p 0.04), renal dysfunction (p 0.01), wound infection (p 0.04), post-operative hospital stay (p 0.004). also higher in group B patient, as well as mortality.

Conclusions: Blood glucose concentration of 10.1 mmol/L or higher after MVR under CPB is an important issues related to postoperative morbidity and mortality.

Key words: Non diabetic patient, mitral valve replacement, post operative blood glucose control.

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Introduction:

Over the last decade, the incidence of diabetes mellitus has increased markedly both in developed and developing

countries¹ Diabetes mellitus has been associated with a poor clinical outcome after cardiac surgery, including a

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higher incidence of wound infections, ischemic events, neurological and renal complications, and mortality². Nevertheless, derangement of glucose metabolism after surgery is not specific to patients with DM³.

Hyperglycemia is present in up to 80% of patients after cardiac surgery, about 80% of ICU patients with hyperglycemia have no history of diabetes prior to admission. The risk of hospital complications relates to the severity of hyperglycemia, with a higher risk observed in patients without a history of diabetes compared to those with known diabetes. Improvement in glycemic control reduces hospital complications and mortality. A target glucose level between 7.8 and 10.0 mmol/l (140 and 180 mg/dl) is recommended for the majority of ICU patients⁴.

Hyperglycemia is a marker of in-hospital morbidity and mortality⁵. Observational studies showed that hyperglycemia predicted mortality and infections after surgery⁶. Intravenous insulin regimens to reduce blood glucose immediately after surgery decreased the incidence of infection⁷. Intensive insulin therapy markedly decreased septicemia and mortality among critically ill patients in a surgical ICU⁸.

In recent years, it has also been recognized that tight glucose control markedly improves acute outcomes of hospitalized diabetic patients, including lowering the risk of infection and death. Reports have demonstrated that tight glucose control with continuous intravenous insulin in diabetic cardiac surgery patients reduces mediastinitis, mortality, costs, and length of stay⁹. Lazar and colleagues showed there was also a reduction in postoperative atrial fibrillation and ischemia in cardiac surgery patients. There are now reports demonstrating the outcome benefits of tight glucose control in hospitalized patients, even in the absence of diabetes¹⁰. For this reason, many researchers have proposed tight glucose control as an effective tool to prevent the deleterious effects of glucose unbalance¹¹.

The disturbances in blood glucose homeostasis have been attributed to insulin resistance and/or a failure of pancreatic β -cell function caused by the systemic inflammatory response syndrome after cardiopulmonary bypass (CPB) and its effects on systemic temperature¹². Hyperglycemia is associated with poor outcomes in critically ill and post surgical patients³.

Acute hyperglycemia may also have its own deleterious effects that can lead to poor peri-operative outcomes. Once the renal threshold is crossed osmotic diuresis leads to dehydration, electrolyte and acid base imbalance. Hyperosmolarity leads to central nervous system dysfunction and its rapid correction can worsen cerebral oedema¹³.

Acute hyperglycemia occurring intra-operatively abolishes ischemic preconditioning and amplifies reperfusion injury

to the heart. In addition, during ischemia, glucose is the preferred substrate for the myocardium, but marked insulin resistance leads to hyperglycemia as a result of impaired cell uptake of glucose which in turn leads to increased concentrations of free fatty acids. Fatty acids are detrimental to the ischemic myocardium because of the increased oxygen consumption required to metabolize the new substrate. Hyperglycemia also leads to increased free radical release and hence increased oxidative stress, causing endothelial dysfunction, which may further affect myocardial ischemia¹.

Hyperglycemia has a pro-inflammatory action that is normally restrained by the anti-inflammatory effect of insulin secreted in response to that stimulus. Free fatty acids (FFAs) also induce pro-inflammatory changes. During illness, stress increases the concentration of counter-regulatory hormones (mainly glucagon, an epinephrine). Given this background, it is plausible that in the presence of high concentrations of both glucose and FFA, inflammation is more prominent. High circulating concentrations of glucose and FFAs may explain, at least in part, the oxidative and inflammatory derangements during acute illness; insulin may exert its anti-inflammatory action by ameliorating glucose and lipid parameters¹⁴.

Cardiopulmonary bypass increases post-operative glycemia and insulin consumption in both diabetic and non-diabetic patients. The use of cardiopulmonary bypass during cardiac surgery diabetic patients is associated with more difficult glycemic control in early post operative period¹⁵.

Material & Method:

This Prospective, Observational study was conducted in the department of cardiovascular surgery, National Institute of Cardiovascular Diseases (NICVD), Sher-e-Bangla Nagar, Dhaka from January 2012 to December 2013. The study was approved by Ethical review committee of NICVD. Informed written consent was obtained from each patient and data will be collected in approved data collection form. The participants had the right to withdraw himself or herself from the study at anytime during study. Interest of study was given highest priority and confidentiality was maintained with safe guard of the right and health of the participants.

Inclusion Criteria:

All non-diabetic adult patients undergoing mitral valve replacement surgery with the use of cardiopulmonary bypass both who are either normoglycemic or developed hyperglycemia postoperatively.

Exclusion Criteria:

Age: Below 18 yrs, above 65years, all diabetic patients, emergency cardiac surgery, patients with poor LV

function. (LVEF<30%), patients with redo-valve surgery, patient with LA thrombus, patient with congestive cardiac failure, patients with cardiomyopathy, patient with renal failure, patients with stroke, Patients with prolonged cardiopulmonary bypass(>120 mins).

Study population: The study was carried out on non-diabetic adult patients undergoing mitral valve replacement surgery with the use of cardiopulmonary bypass developing postoperative hyperglycemia fulfilling the inclusion and exclusion criteria.

Preoperative characteristics of study patient: Each patient was assessed by history, clinical examination, and pre operative investigations (All routine investigation and was recorded in the preformed data.

Grouping of the Patients.

Group: A (n=55) Patients with good post operative blood glucose control(10 mmol/l or less).

Group: B (n=55) Patients with poor post operative blood glucose control(blood glucose >10 mmol/l).

Anesthesia, surgical technique and postoperative management

Standard anesthetic and surgical techniques was followed, heparin was given to maintain the activated clotting time at 480 seconds throughout CPB. A standard CPB circuit was used with non pulsatile flow at a rate through out bypass of 2.4 L / min / m² and a mean arterial pressure kept 50 to 60 mm Hg. Myocardial protection was achieved with intermittent ante grade cold-blood cardioplegia. For all cases, myocardial protection was predominantly maintained by intermittent antegrade with moderate systemic hypothermia (28°C to 32°C).

For all patients mechanical bi-leaflet valve prosthesis was used. At the end of mitral valve replacement, adequate de-airation was ensured, patients were weaned from CPB, then patients was transferred to the intensive care unit and ventilated with 70% oxygen using volume-controlled ventilation. Patients were extubated after fulfilling the criteria for extubation. Proper peri-operative analgesia and sedation was ensured. Patient was discharged from ICU after attainment of haemodynamic stability, weaning from all inotropic support and removal of chest drain.

Per-operatively CPB time , X-clamp time , post operatively highest post operative (venous) blood glucose value (within first 60 hrs), mechanical ventilation time(hrs), ICU stay (hrs), neurological complications (stroke), renal failure (elevated serum creatinine two times preoperative value), post surgical infection (wound infection)and in-hospital mortality were recorded and were compared

between two groups. Proper management of all these complications were be done accordingly. After achieving target INR patients were discharged. Patients developing complications were kept in hospital for adequate management.

Post-operative Glucose Measurement:

Venous sample of blood will be taken to measure blood glucose. Blood glucose measurement was done by enzymatic colourimetric method with DIMENSION X-PAND, PLUS, SIEMENS analyzer.

Post-operative Glucose Management:

All MVR patients developing post operative hyperglycemia (blood glucose>10mmol/L) were started on a sliding-scale insulin infusion as well as iv bolus soon after surgery to maintain blood glucose levels less than 10mmol/L according to a standard protocol. Multiple samples were collected according to the protocol for blood glucose measurement. The highest blood glucose value was recorded within 60 hrs after surgery.

Protocol for blood glucose management: (Bojar 5th edition P 755)

Blood Sugar	Regular Insulin IV Bolus	Infusion Rate
151-200 8.3-11.11mmol/l	No bolus	2Units/h
201-240 11.12-13.33mmol/l	4 Units	2 Units/h
241-280 13.34-15.55mmol/l	6 Units	4 Units/h
281-320 15.56-17.77mmol/l	10 Units	6 Units/h

This infusion was continued for the first 24 hours and blood glucose measurement was done hourly. Then, patients were switched to subcutaneous soluble insulin, and blood sugar levels were monitored every 8 hours.

Data Collection: Data were collected by interview of the patients , clinical examination, laboratory investigation, hospital records peroperative and postoperative findings . Then data was put in data master sheet using SPSS.

Statistical Analysis:

After processing all available data, statistical significance was analyzed. Data were expressed as mean \pm SD, frequency, percentage as applicable. Intergroup comparisons of BGC after surgery was done using 2-tailed t tests to determine the significance of difference. To show the relationship between the variables Pearson correlation analysis was performed. P-value <0.05 will be considered statistically significant. All the data entry and analysis were done by using SPSS (latest version) soft ware program.

Results:

A total number of 110 elective MVR patients were enrolled for this study and divided into two groups according to the post operative blood glucose level. Those patients

who were below ≤ 10 mmol/L were designated as Group A and those patients who were above 10mmol/L were designated as Group B.

Table-I
Age distribution of the study patients (n=110)

Age in years	Group A (n=55)		Group B (n=55)		Total (n=110)		p value
	Number	%	Number	%	Number	%	
20 – 30	12	21.8	14	25.5	26	23.6	
31 – 40	31	56.4	31	56.4	62	56.4	
41 – 50	12	21.8	10	18.2	22	20.0	
Mean \pm SD(Range)	36.4 \pm 6.7(20-50)		35.3 \pm 6.2(22-50)		35.9 \pm 6.5(20-50)		0.34 ^{ns}

Table-II
Distribution of study patients according to sex (n=110)

Sex	Study group		Total	P value
	Group A(n=55)	Group B(n=55)		
Male	25 (45.5%)	26 (47.3%)	51 (46.4%)	0.84 ^{ns}
Female	30 (54.5%)	29 (52.7%)	59 (53.6%)	
Total	55(100.0%)	55(100.0%)	110(100.0%)	

Table-III
Distribution of BMI and BSA status of the study patients (n=110)

Categories	Study group		p value
	Group A(n=55)mean \pm SD	Group B(n=55)mean \pm SD	
BMI (kg/m ²)	21.4 \pm 1.7	21.5 \pm 1.4	0.82 ^{ns}
BSA (m ²)	0.7 \pm 0.1	0.7 \pm 0.1	0.91 ^{ns}

Table-IV
Distribution of pre-operative biochemical parameters among the study patients (n=110)

Variables	Glucose Group		p value
	Group A(n=55)mean \pm SD	Group B(n=55)mean \pm SD	
HbA _{1c} (%)	5.22 \pm 0.35	5.22 \pm 0.38	0.98 ^{ns}
S. Creatinine (mg/dl)	0.78 \pm 0.08	0.81 \pm 0.07	0.10 ^{ns}
RBS (mmol/L)	6.24 \pm 0.59	6.36 \pm 0.57	0.30 ^{ns}

Table-V
Echocardiographic results (LVEF) among the study patients (n=110)

Variable	Study group		p value
	Group A(n=55)mean \pm SD	Group B(n=55)mean \pm SD	
LV EF %	52.29 \pm 5.01	52.36 \pm 4.46	0.93 ^{ns}

Table-VI
Comparison of per-operative variables between groups

Duration	Study group		p value
	Group A(n=55) Mean±SD	Group B(n=55) Mean±SD	
CPB time (min.)	85.07±8.46	88.65±14.42	0.04 ^s
X clamp time (min.)	57.21±6.03	60.05±6.66	0.02 ^s

Table-VII
Distribution stress induced hyperglycemia among the post surgical patients (n=110).

Stress induced hyperglycemia	Post operative Blood Glucose		Total
	Hyperglycemic >7.80mmol/L (n=82)	Normoglycemic ≤7.80mmol/L (n=28)	
Frequency (%)	84 (76.4)	26 (23.6)	110 (100.0)

Table-VIII
Comparison of highest post operative blood glucose value among the study patients (n=110)

Highest post operative blood glucose value	Study Group		p value
	Group A(n=55)	Group B(n=55)	
Mean±SDmmol/L	9.12±1.42	14.18±2.24	0.001 ^s

Table-IX
Comparison of Mechanical Ventilation Time (MVT) and Duration of ICU stay among the study population (n=110)

Variables	Study group		p value
	Group A(n=55) Mean±SD	Group B(n=55) Mean±SD	
Mechanical Ventilation Time (min.)	8.94±2.47	13.02±10.42	0.02 ^s
Duration of ICU stay in days	1.47±0.50	2.00±0.66	0.001 ^s

Table-X
Comparison of post operative complications among the study patients (n=110)

Variables	Study group				p value
	Group A(n=55)		Group B(n=55)		
	No.	%	No.	%	
Neurological Complications (Present)	3	5.5	11	20.0	0.04 ^s
Renal Dysfunction (Present)	3	5.5	13	23.3	0.01 ^s
Post operative Hospital stay in days	Mean±SD 8.89±1.81		Mean±SD 10.38±3.28		0.004 ^s
Post surgical infection(Present)	No.	%	No.	%	
	4	7.3	12	21.8	0.04 ^s
Mortality (Yes)	1	1.8	3	5.5	0.31 ^{ns}

Table-XI
Distribution of adverse in-hospital outcome among the study patients (n=110)

Adverse outcome	Study group				p value
	Group A(n=55)		Group B(n=55)		
	No.	%	No.	%	
Present	5	9.1	23	41.8	0.001 ^s
Absent	50	90.9	32	58.2	

Table-XII
Comparison of highest post operative blood glucose value among the study patients according to hospital outcome (n=110)

Highest post operative blood glucose value	Hospital outcome		p value
	Adverse(n=28)	Good(n=82)	
Mean±SDmmol/L	15.18±3.05	10.44±2.12	0.001 ^s

Discussion:

The present study performed in NICVD, Dhaka, included a total number of 110 mitral valve replacement surgery patient under CPB and was divided into two groups according to post operative blood glucose level. Those patients whose highest blood sugar level were below or equal to 10 mmol/L were designated as group A and those patients whose highest blood sugar level were above 10 mmol/L were designated as group B. The distribution of study population is recorded according to age. All patients in group A 55(50.0%) and group B 55(50.0%) are within less than 60 years group. It has been found that middle aged people or young adult persons most commonly underwent mitral valve replacement surgery in this study.¹⁶

The mean age of the studied patients were 35.9±6.5 years ranging from 20 to 50 years. The mean age was found 36.4±6.7 years in group A and 35.3±6.5 years in group B. There was no significant difference of age distribution between two groups (P>0.05) (table 1). In the study of Chowdhury et al¹⁶ mean age was 33.08 years. Our observation was similar to these studies.

There was no significant sex difference between two groups (P>.05). Males were 45.5% in group A and 47.3% in group B. On the other hand female were 54.5.8% in group A and 52.7% in group B (table 2). Females were more with mitral valve disease in the study of Shrestha et al¹⁶. Our findings were similar to those studies.

The distribution of stress induce hyperglycemia among the study population 85(78.54%), (table- 7). This result

is consistent with other studies. Farnoosh et al,⁴ showed in one study that 80% non diabetic patients develop stress induced hyperglycemia after cardiac surgery during their ICU stay in their early post operative days.

The distribution of BMI, BSA, HbA1C, LVEF, Serum Creatinine and RBS between Blood Glucose groups were recorded (Table 3-6). Most of the patients were non smokers. The left ventricular ejection fraction was observed in group A and group B (52.29±5.01 vs 52.36±4.46) with statistically insignificant difference (p>0.05). Body mass index and body surface area were almost identically distributed in both groups insignificant difference (p>0.05).

The biochemical parameters were similar in the both groups. HbA1C was found in group A and group B (5.22±0.35 vs 5.22±0.38) with statistically insignificant difference. Serum creatinine was observed in group A and group B (0.78±0.08 vs 0.81±0.07) with statistically insignificant difference. Random blood sugar was also observed in group A and group B (6.24±0.59 vs 6.36±0.57) with statistically insignificant difference.

Mechanical ventilation time was observed significantly greater in group B than group A (8.94±2.47vs13.02±10.42) minute with p=0.02(Table-9). It was also observed that duration of ICU stay was observed (1.47±0.50vs2.00±0.66) days which was significantly higher in group B (p=0.001), (Table-9). Similar result was published by Ascione, et al.,¹, Ouattara, et al.².

Neurological complication (Table-10) was observed 20% in group B and 5.5% in group A with statistically significant

difference ($p=0.04$). Capes and his associates showed poor prognosis for poor postoperative blood glucose controlled individuals¹⁸.

Renal dysfunction (Table-10) was also observed 23.3% in group B and 5.5% in group A with statistically significant difference ($p=0.01$). Similar result was published by Ascione et al¹. They showed that in post operative poor blood glucose control patients the renal dysfunction is about 25%. Which is almost same as our study results.

Post operative hospital stay was observed in group B and group A (10.38 ± 3.28 vs 8.89 ± 1.81) days with significant difference ($p=0.004$). Ascione and associates in 2008 observed increased hospital stay in post operative hyperglycemic population. This finding is consistent with our study.

Post operative surgical infection (Table-10) was observed significantly greater in group B than group A (21.8% vs 7.3%) with $p=0.04$. 3 (5.5%) Ascione, et al., 2008 also showed significant wound infection resulted in post operative poor blood glucose group. Dandona and his colleagues explained this in their study¹⁴.

Patient's post operative death 3 (5.5%) in group B and 1 (1.8%) in group A (table-10) which was found statistically insignificant ($p=0.31$). Capes et al.,¹⁸ and Ascione, et al.¹ showed significant mortality in poor post operative blood glucose control group of patients.

Highest post operative blood glucose level was observed significantly higher in adverse hospital outcome patients than good hospital outcome patients (15.18 ± 3.05 vs 10.44 ± 2.12) mmol/L with $p=0.001$. Similar result was published by Ascione et al¹. Dandona et al¹⁴. So, controlling of post operative blood glucose level is an important factor to reducing adverse in hospital outcome.

Conclusion:

In conclusion, the findings of this study permit to conclude that a peak blood glucose level of 10.1 mmol/L or higher during CPB is associated with an increased risk of perioperative morbidity. Most common morbidities are infection, neurological complication and renal dysfunction. Post operative ICU stay and hospital stay is also longer in higher blood glucose group. Although mortality is higher in the high blood glucose group of patients operated under CPB during mitral valve surgery difference between higher and lower blood glucose group is not significant. Although initially we thought that a high blood glucose level could be an independent predictor of in-hospital mortality, but the

study showed insignificant result. It would be worth mentionable that a higher proportion of mortality is observed in the higher post operative blood glucose group, a further study with larger sample size could be done to see the consequence.

Limitations:

There are some limitations in this study. Some are mentioned below. It was a purposive non-random sampling method. The proposed post operative blood glucose control threshold value differed from the threshold value chosen by other authors for different clinical setup.

For further study, the following recommendations are proposed: Further large scale study should be carried out. Further studies should be carried out to determine level of blood glucose control during and after CPB time and interventions based on blood glucose values to improve survival in adult non-diabetic cardiac surgical patients.

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