International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Glycemic Variability in Postoperative Major Oncosurgery Patients and its Effect on Patient Outcomes - A Prospective Observational Study

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Abstract: ***We conducted the study for evaluating effect of glycemic variability in postoperative major oncosurgery patients. We collected data for 104 patients (February, 2017 to December, 2018) with gastrointestinal neoplasm undergoing surgery for more than 4 hours. We used iPro^{TM} 2 Continuous Glucose Monitoring System to collect values for Mean and Standard Deviation of glucose within 24 hours (Glu1Ave and Glu1SD) and Maximum glucose, Mean glucose, Standard Deviation of glucose, Coefficient of variance of glucose in 72 hours (GluMax, GluAve, GluSD and GluCV). The association of GluSD, GluCV and Glu1SD with mortality and morbidity was statistically significant irrespective of diabetic status.***

Keywords (MESH): Blood glucose, Glycemic variability, Oncosurgery, Postoperative, Logistic regression

1. Introduction

Importance of glycemic variability in the outcome of different subsets of patients has been a matter of speculation in recent studies. Studies have been undertaken to find out the adverse effects of large excursions of glucose on patients' health during their hospital stay. [1] These studies compared the risk of glucose variability in causing morbidity and mortality vis - à - vis the deleterious effects of extremes of glucose levels, namely hyperglycemia and hypoglycemia. Glycemic variability can be described as fluctuations of blood glucose over a defined time. Amongst different statistical methods to measure glucose variability, Standard Deviation (SD) was found to be the best predictor of mortality. [2]Several studies had been done to evaluate relationship between glycemic variability and outcome after major surgeries. [3]In these previous studies, glycemic variability in the perioperative period was found to have adversely affected patient outcomes after major surgeries. A large number of oncosurgeries took place in our hospital and data were insufficient regarding glycemic variability and postoperative outcome in this subset of patients. Therefore we undertook this prospective study with an objective to assess the impact of glycemic variability on patients' morbidity and mortality after major oncosurgeries. In addition, we also aimed at finding appropriate indices to predict outcome after oncosurgeries.

2. Methods

Approval from ethical committee was obtained and written informed consents from the scheduled participants were taken for the study. We undertook this prospective observational study over a specified period of time (February, 2017 to December, 2018) in which we included all patients in our hospital who fulfilled the inclusion criteria and did not fall into the exclusion category. We assessed a total of 109 patients, of which none were excluded by us. No new patient was recruited, but 5 patients were lost tofollow up. Therefore, the sample size stands at 104. Within this period of time 104 patients with American Society of Anesthesiologists (ASA) Physical Status I and II could be included who fulfilled following inclusion criteria –patients with gastrointestinal neoplasm and surgery duration of more than 4 hours with anticipated significant fluid shift and with at least 72 hours hospital stay. Patients of more than 18 years of age were included in the study. Unwilling patients and patients below 18 years were excluded from the study. All patients selected for the study after due consideration of the inclusion and exclusion criteria were interviewed, examined and investigated as per the study proforma. The study was conducted as a prospective observational study. We adopted quantitative research methodology. Patient demographic, diabetic status, HbA1c, Basal Metabolic Index (BMI) and type and duration of the oncosurgery performed were noted for each patient. Fingerstick blood glucose testing was done in the patients at the time of admission. The value was taken as GluAdm. Glucose measurements were done in the patients in study population using iPro2 Professional Continuous Glucose Monitoring (CGM) which was inserted

after the completion of the surgery. The data collected were measured for maximum glucose in 72 hours (GluMax), mean glucose (GluAve), Standard Deviation of glucose (GluSD), coefficient of variance of glucose (GluCV), and mean and Standard Deviation of glucose during first 24 hours (Glu1Ave and Glu1SD, respectively). The Standard Deviation (SD) is the square root of variance, which quantifies the variation or dispersion of a set values. The coefficient of variation (CV) is the ratio between the standard deviation and the mean. GluSD, GluCV and Glu1SD were the indices for glycemic variability. Any incidence of infections, cardiovascular complications, neurological complications and other complications were noted in each patient. Hyperglycemia was managed as per standard ICU/ward protocol. Follow up after 28 days was done to check for mortality. For measuring the glucose parameters, iPro2 Professional Continuous Glucose Monitoring System or CGMS system (iPro2^{TM}, Medtronic Minimed, Inc. Northridge, CA, USA) was used. The CGMS has been found to be reliable for measuring the glucose fluctuations in the critically ill and values measured by CGMS had a good correlation with arterial blood glucose, taken as reference. [3] Food and Drugs Administration (FDA), U. S. A. in June 1999 approved its use in the measurement of continuous daily glucose levels. The CGMS unit consisted of a glucose sensor (to be placed in subcutaneous tissue) which sensed the glucose levels in interstitial fluid by electrochemical methods every 10 seconds and recorded an average value every 5 minutes and gave 288 values per day. The iPro2 takes one hour to start up a sensor. If the patient does the first Blood Glucose meter reading too soon, sensor data will not be available for calibration. Therefore, blood glucose was tested at least one hour after sensor was inserted. Another blood glucose reading was done two hours after the first one. This reading is a backup, in case the first reading was a few minutes too early. The sensor emits a green light upon successful application. The iPro2 was removed (but the sensor was left in) prior to an X - ray, Computed Tomography scan or Magnetic Resonance Imaging. The iPro2 was reconnected afterward. A minimum of four capillary blood glucose were needed to be measured for calibration purposes. Insulin, if needed, was injected at least 3 inches (7.5 centimeters) away from the sensor insertion site. During the time patient was continuously wearing it, occlusive dressing was kept applied. The sensor was removed after 72 hours and the data were downloaded into a computer. The data were of glucose values over 72 hours along with a continuous graph. Continuous variables were calculated as Mean ± Standard Deviation and they were compared across groups using unpaired ttest. Categorical variables were calculated as number of patients and percentage of patients and they were compared across groups for both mortality (Alive & Dead) and morbidity (patients with morbidity & without morbidity) using Chi Square test. The area under the receiver operator characteristics (ROC) curves were calculated for seven blood glucose control indices, mentioned above. Separate Logistic Regression Analysis were performed entering the age, sex, diabetic status, HbA1c, ASA physical status, BMI, duration of surgery, duration of stay in the Intensive Care Unit (ICU) as well as the glucose indices as the independent variables and patient morbidity and mortality as the dependent variables. The statistical software SPSS version 2.0 was used for the analysis.

3. Results

Total number of non - survivors were 10 and total number of patients with morbidity were 34. The age distribution in survivor and non - survivor were 66.13± 8 and 70.2±8.41 (p=0.287).54 out of 94 survivors were male while 6 out of 10 non - survivors were male (p=0.913).44 out of 94 survivors were of ASA PS I while 2 out of 10 non - survivors was ASA PS I. Rest of the patients were of ASA PS II (p=0.251).34 out of 94 survivors and 8 out of 10 non - survivors were diabetic (p=0.058). The BMI distribution in survivor and non - survivor were 25.14±1.73 and 27.16±1.89 (p=0.018). In survivors and non survivors, surgery hours were 5.03±0.5 and 5.1±0.65 (p=0.781) respectively.

Table 1 showed that HbA1c and all the seven blood glucose indices were significantly more in survivors than non - survivors. It also showed that 3 indices of glycemic variability (GluSD, GluCV&Glu1SD) and GluMax were significantly more in morbids than non - morbids, however HbA1c did not have any significant association. In addition, it compared the variation of glucose indices with individual morbidities. (Please see Table 1 here).

Table 1: Variation of Glucose Indices in Patients with Mortality and Morbidity

		HbA1c	GluAve	GluSD	GluCV	GluMax	GluAdm	Glu1Ave	Glu1SD
Mortality	Alive (mean±SD)	6 ± 1.47	126.02 ± 38.66	20.81 ± 14.08	15.67 ± 8.05	172.51 ± 59.72	127.94 ± 42.73	126.4 ± 38.55	17.43 ± 12.35
	Dead (mean±SD)	8.6 ± 1.67	178.4 ± 42.07	56.2 ± 24.8	29.68 ± 10.33	283.4 ± 77.66	181.6 ± 63.59	182.8 ± 49.25	182.8 ± 49.25
	p Value	0.001	0.006	<0.001	0.001	<0.001	0.014	0.004	<0.001
	Significance	significant	significant	significant	significant	significant	significant	significant	significant
Morbidity	YES (mean±SD)	5.97±1.48	124.31±39.72	16.14±9.03	12.54±4.56	160.29±49.94	127.4±39.82	127.4±37.34	15.37±8.99
	NO (mean±SD)	6.82±1.91	144.94±43.1	40.82±21.65	26.23±9.49	230.29±80.19	145.35±58.89	140.94±51.81	31.71±23.95
	p Value	0.084	0.094	<0.001	<0.001	<0.001	0.194	0.286	0.001
	Significance	Not significant	Not significant	significant	significant	significant	Not significant	Not significant	significant
Infection	p Value		0.13	<0.001	<0.001	0.006	0.483	0.387	0.008
	Significance		Not significant	significant	significant	significant	Not significant	Not significant	significant

CVS Complication	p Value		0.277	0.001	0.000	0.016	0.162	0.135	0.010
	Significance		Not significant	significant	significant	significant	Not significant	Not significant	significant
CNS Complications	p Value		0.234	0.019	0.093	0.075	0.331	0.247	0.030
	Significance		Not significant	significant	Not significant	Not significant	Not significant	Not significant	significant
Other Complications	p Value		0.132	0.007	0.013	0.027	0.099	0.481	0.009
	Significance		Not significant	significant	significant	significant	Not significant	Not significant	significant

In our study, 16 cases of infective complications were there which included 11 cases of surgical site infections, 3 cases of pulmonary infections and 2 cases of genitourinary infections.10 cases of cardiovascular complications were there which included 7 cases of uncontrolled hypertension, 2 cases of arrhythmia and 1case of heart failure. All indices of glycemic variability (GluSD, GluCV& Glu1SD) were significantly associated with infections and cardiovascular complications.6 cases of central nervous system complications included 4 cases of ischemic stroke and 2 cases of seizure disorder. Central nervous system complications were having statistically significant association with GluSD and Glu1SD but not with GluCV. Rest were miscellaneous complications of other systems (2 cases).

The calculation of area under the ROC curve revealed that the measures of glycemic variability (GluSD, GluCV and Glu1SD) had an area under curve are 0.860, 0.851 and 0.826. The area under curve for GluSD was greater than that of GluCV and Glu1SD. **(Please see Figure 1 here)**

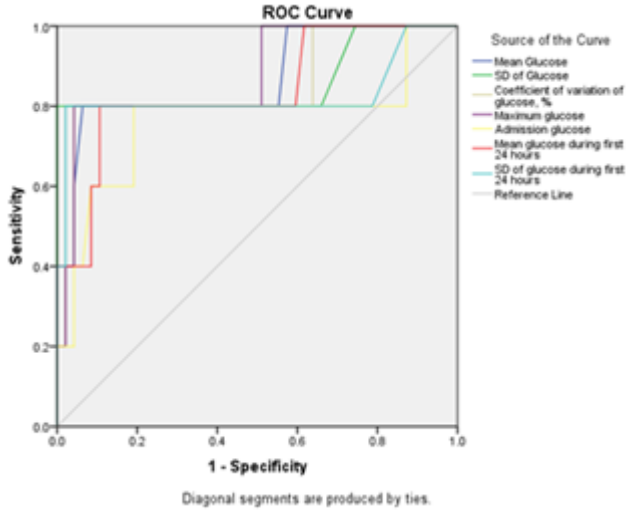

Figure 1: The Receiver Operator Characteristics Curve for mortality

The Logistic Regression Analysis for mortality showed that the Odds Ratios for GluAdm, GluMax, GluAve, GluSD, GluCV, Glu1Ave, and Glu1SD were 1.03, 1.03, 1.04, 1.10, 1.19, 1.04 and 1.10 respectively. (Please see Table 2 here)

Table 2: The Logistic Regression Analysis for Mortality

	B	P value	Odds Ratio
GluAdm	0.03	0.03	1.03
GluMax	0.03	0.01	1.03
GluAve	0.04	0.03	1.04
GluSD	0.10	0.00	1.10
GluCV	0.17	0.01	1.19
Glu1Ave	0.04	0.02	1.04
Glu1SD	0.09	0.00	1.10

Table 3 showed that there was no significant variation in diabetic status between survivor and non - survivor group. It also showed that there was no significant variation in diabetic status between morbid and non - morbid group (Please see Table 3 here).

Table 3: Variation of Diabetic Status with Mortality and Morbidity

		Diabetic Status		Total	P Value	Significance
		NO	YES			
Mortality at 28 Days	Alive	60 (96.77)	34 (80.95)	94 (90.38)	0.058	Not Significant
	DEAD	2 (3.23)	8 (19.05)	10 (9.62)		
Total		62 (100)	42 (100)	104 (100)		
Morbidity	No	44 (70.97)	26 (61.9)	70 (67.31)	0.494	Not Significant
	YES	18 (29.03)	16 (38.1)	34 (32.69)		
Total		62 (100)	42 (100)	104 (100)		

The calculation of area under the ROC curve revealed that the measures of glycemic variability (GluSD, GluCV and

Glu1SD) had an area under curve are 0.825, 0.861 and 0.671 respectively. (Please see Figure 2: The Receiver Operator Characteristics curve for morbidity)

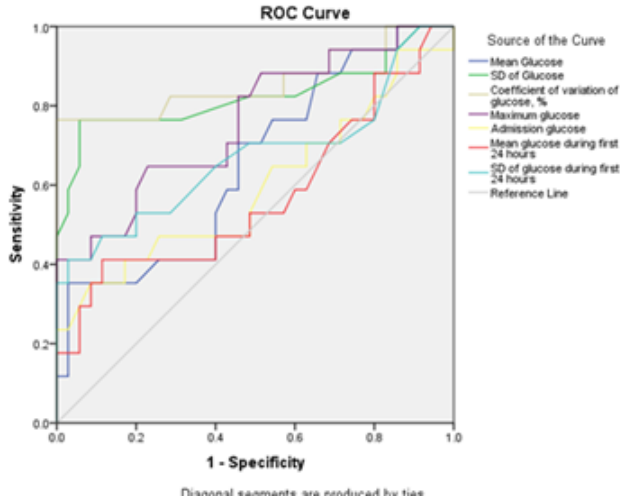

Figure 2: The receiver operator characteristics curve for morbidity

The Logistic Regression Analysis of Morbidity showed that the Odds Ratios for GluAdm, GluMax, GluAve, GluSD, GluCV, Glu1Ave and Glu1SD were 1.008, 1.017, 1.013, 1.106, 1.263, 1.008 and 1.063 respectively. (Please see Table 4 here)

Table 4: The Logistic Regression Analysis for Morbidity

	B	S. E.	Wald	df	Sig.	Exp (B)
GluAdm	.008	.006	1.693	1	.193	1.008
GluMax	.017	.005	9.429	1	.002	1.017
GluAve	.012	.008	2.760	1	.097	1.013
GluSD	.101	.029	12.100	1	.001	1.106
GluCV	.233	.061	14.470	1	.000	1.263
Glu1Ave	.008	.007	1.160	1	.281	1.008
Glu1SD	.061	.022	7.697	1	.006	1.063

4. Discussion

The research question was whether the outcomes of patients undergoing major oncosurgeries involving fluid shift and significant perioperative in - hospital stay could be influenced by peri - operative glycemic variability or not. In addition, we also aimed to find out the most appropriate blood glucose indices to predict outcomes. Therefore, we enrolled such postoperative patients in our study as their perioperative blood glucose variability could be measured during their stay in the hospital. Glycemic variability is defined as a standard of intraday variation which reflects the swings of blood glucose as a consequence of diminished or absent autoregulation and/or the shortcomings of insulin therapy. [1] Previous studies have shown that glucose control cannot be estimated by mean glucose alone and glycemic variability has been put forward as an optimum measurement for that. [2]Out of the seven blood glucose indices, GluSD, GluCV and Glu1SD were taken as measures of glycemic variability. These measures were found to have affected the outcome in our study. It was found that complications related to infections, CVS, CNS were also influenced by peri - operative glucose variability. Further, GluSD and GluCV had good accuracy to predict mortality and morbidity. Diabetic status did not influence mortality or morbidity. The strengths of the study could be attributed to several points. Firstly we were targeting "Glycemic Variability" rather than "Glycemic Control" in the study group and to assess that, continuous monitoring of glucose is preferable to intermittent blood glucose checking (as done by capillary blood glucose) [1]Secondly CGMS provides fairly accurate measurement and its accuracy is constant at all glucose levels. [4] Thirdly the use of CGMS is an almost painless procedure as compared to fingerpick glucose measurement or glucose values determined by blood gas analyzers. Therefore, patient adherence is better. Fourthly, the study was undertaken in a multi - specialty hospital having a bed capacity of more than 550 and which caters to a large pool of cancer patients coming for surgery. Therefore, we could include of a large variety of patients fulfilling the inclusion criteria in this study. The study had its share of limitations as well. Firstly, the time frame of the study was short for conducting this prospective study. Increasing time frame could have helped us to incorporate a larger number of patients in this study. Secondly, the high cost of CGMS was a restraining factor for using this tool in every patient fulfilling the inclusion criteria. Thirdly, we did not evaluate whether addition of a display unit to CGMS could change the outcomes. Addition of a display unit or an Insulin pump guided by it could have helped us to evaluate the efficacy of this system in changing the patient outcome. Our study corroborated with previous studies done on patients undergoing surgeries other than oncosurgeries. In 4302 patients after major cardiac surgery, Duncan et al found that increased glycemic variability was associated with increased risk for adverse outcomes in postoperative period. These adverse effects were not influenced by diabetic status. [4]The study by Jeon et al on 13800 post - surgery patients revealed that increased in - hospital mortality was associated with high glucose variability. [OR=1.14, 95% CI (1.03, 1.27) for 10% increase in coefficient of variation]. [5] Eshuis et al found association of increased risk for adverse outcomes in terms of both morbidity and mortality on 330 patients after pancreatic oduodenectomy where patients with high variability had an Odds Ratio of 3.6 (95% CI) for complications. An interesting finding that mortality and morbidity were associated with increased glycemic variability irrespective of the preoperative diabetic status of the patients was supported by the study by Eshuis et al on pancreatic oduodenectomy patients where pre - operative glucose values were not associated with postoperative complications. [6] A study by Bansal et al on postoperative cardiac surgery patients showed that glycemic variability as measured by standard deviation, was a predictor of increased length of stay, rise in creatinine and acute kidney injury after cardiac surgery. They concluded that glycemic variability was therefore a new dimension in postoperative glycemic management in cardiac surgery patients, which needed to be explored. [7]Contrary to popular belief that diabetic patients had increased micro/macrovascular complications, we did not find any significant difference in outcome among patients who were diabetic vis - à - vis those who were not. Irrespective of diabetic status, blood glucose variability affected outcome significantly. The wider implication of the study was that the Standard Deviation (SD) and the Coefficient of variation of glucose (GluCV) can predict mortality and morbidity in patients after major oncosurgery

irrespective of their diabetic status, therefore measures to reduce glycemic variability could be a judicious step to prevent postoperative complications including mortality and morbidity in this group of patients. Insulin Therapy guided by Continuous Glucose Monitoring System may be adopted for this purpose.

Hence our study shows that postoperative mortality and morbidity were associated with increased glycemic variability. We also concluded that this association was significant, irrespective of the diabetic status of the patients. Among the indices for glucose variability, Standard Deviation of glucose (GluSD) and Coefficient of Variation of glucose (GluCV) were found to be most accurate. These indices for glucose variability could be used to predict postoperative outcome in patients after major oncosurgeries.

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Author Profile

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Dr. Chandrashish Chakravarty during his undergraduate tenure received multiple gold medals and awards. He was awarded MD (Anesthesiology) at first attempt from AIIMS, New Delhi and went to University of Miami for his fellowship in Critical Care Medicine after ECFMG (USA) certification. He completed his European Diploma in Intensive Care (EDIC). Royal College of London, UK also certifies him in Specialty Examination for Respiratory Medicine and MRCP (UK). Currently he is working as a consultant in Critical Care in the Apollo Gleneagles Hospital, Kolkata since 2011. He is involved in training DNB, FNB and IDCC students as teacher and guide for DNB dissertation. He is also ACLS, ATLS certified and National CTLS instructor and faculty in trauma. He has attended different National Conferences of Indian Society of Anesthesiologists and Indian Society of Critical Care Medicine as faculty.

Dr Tanmoy Das is Senior Consultant & HOD Anesthesiology, Perioperative Medicine & Pain at Apollo Gleneagles Hospitals, Kolkata. India. He has 30 years Post MD experience in Anesthesia and has independently anesthetized more than 35000 Surgical cases of all types. Have had the opportunity thrice of setting up and organizing a Departments of Anesthesia, Cardiac Anesthesia& Postoperative Cardiac Care Services at: Trichur Heart Hospital, Thrissur, Kerala., Suraksha Hospital, Kolkata and Apollo Gleneagles Hospitals Kolkata

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Preoperative assessment, anesthetic management and postoperative care of around 1400 surgical cases per month.
Full fledged Postgraduate teaching program for DNB Anesthesia
Operation Theatre Management: Chief of Operating Room Services. Scheduling, Planning & Management of the entire OR Complex on a day to day basis and long term management.

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Pediatric Anesthesia
Regional Anesthesia
Trauma Anesthesia
Trauma Care Involvement:
On call Airway Doctor and also for Initial Assessment in Emergency Department
More than 60% of OR cases are trauma related coming for surgery & pain relief at various stages of trauma care.
Integral part of critical care team involved in the care of trauma patients in the ICU
Principal Investigator for CRASH 2 Trial.
Organization and opening of the Kolkata Chapter of ITACCS INDIA in March 2008.
Organizing Chairman, ITACCS INDIA 2009, 13th Annual Conference of International Trauma Care, Indian Chapter.
Regular CME programs on Trauma Management as per CTLS guidelines.

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Chapters in text book: 14
Special awards and recognition:
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Kops Award ISA 2003
Sarojini Devi Award ISA 2003
Gold Medal & T N Jha Fellowship 1997
H. M. Desai Award 1996 & 1997
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Legal & Ethical issues
Teaching & Training