Original Article

Blood Glucose Variability as a Predictor of Mortality for Septic Patients in Intensive Care Unit

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Abstract

Background: *One of the ways of modulation of septic response is glycaemic control. Increased Blood glucose variability rather than mean glucose level in critically ill patients is an important factor associated with sepsis.*

Objective: *Objective of this study was to find out whether the increased blood glucose variability predicts mortality for septic patients in Intensive Care Unit.*

Methods: *Purposively allocated 40 septic patients in Intensive Care Unit of Dhaka Medical College Hospital, Bangladesh were observed prospectively from January 2012 to July 2013. Glucose variability was assessed within first twenty four hours of recruitment of septic patients. By considering a target blood glucose level (5 - 8 m mol/L), the assigned patients were separated into three groups (according to blood glucose variability). Group I (mild variable group) included those patients having less than two blood glucose values not within the target blood glucose level. Group II (moderate variable group) included those patients having more than two to four blood glucose values not within the target range. Group III (more variable group) included those patients having more than four blood glucose values out of range of target glucose level. Chi- square test along with a p-value (< 0.05) was done to assess which group of blood glucose variability best reflects the association of mortality. Logistic regression was used to determine the odds ratio of ICU death in relation to blood glucose variability.*

Results: *Out of all the septic patients, the more blood glucose variability group (37.5%) more reflected the blood glucose variability than the others. Using the Chi-square, it was found that a highly significant difference (x2-14.56, p-value 0.001) was existed between three blood glucose variability groups with respect to mortality. Logistic regression analysis demonstrated that more glucose variability group had predicted higher mortality rate with a p- value of 0.007 and an odds ratio of 16.0. Result is significant. On the other hand, significant effect of moderate glucose variability group on mortality was not found with a p-value of 0.665 and an odds ratio of 0.667.*

Conclusions: *The septic patients having more blood glucose variability had predicted higher mortality rate than that of moderate and less blood glucose variability in Intensive Care Unit. This observation indicates that blood glucose variability should be included as a future approach to glucose management of septic patients as a target for therapeutic intervention.*

Key Words: *Blood Glucose Variability, Septic Patients, Intensive Care Unit, Mortality*

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Introduction

Severe sepsis and Septic shock are major risks of mortality in Intensive Care Unit patients. It still remains one of the leading causes of death. This unacceptable high mortality can only be reduced if there is greater awareness and understanding of the condition and knowledge of most effective treatment measure available. Closer observation and earlier treatment can influence the outcome of sepsis. Diagnosis of sepsis is not easy. Making an early, accurate diagnosis of septic shock is a key to increasing survival rates. The most adopted system to predict mortality is Acute Physiology and Chronic Health Evaluation (APACHE) Scores. Although useful to evaluate outcome, these cumbersome tools are of limited use in day to day practice. A number of biological markers have been tried to be used as reliable prognostic tools for the above purpose. Blood glucose has recently emerged as an important variable in critical care.

Patients with sepsis, a manifestation of infection where systemic signs of inflammation are present and vital organ function may be impaired; are at greater risk of death than those suffering from uncomplicated infection. These patients are particularly prone to hyperglycemia and insulin resistance because of a number of pathophysiologic changes associated with sepsis.

In the acute stress response, neuroendocrine stimulations with high levels of counter regulatory hormones glucagon, catecholamines, glucocorticoids, growth hormone leads to upregulation in hepatic gluconeogenesis and glycogenolysis and peripheral insulin resistance considered as a beneficial adaptation intended to supply energy to vital organs in critically illness Although the adaptive rationale for the hyperglycemic response is not well understood, acute hyperglycemia has many deleterious effects leading to increased inflammation (by pro-inflammatory cytokines- TNF-alpha, IL1 beta, IL8), vulnerability to infection and multiorgan system dysfunction (Turina, Fry & Polk 2005). Hyperglycemia is thought to induce oxidative stress and interfere with normal endothelial function by overproduction of reactive oxygen species, which results in diabetic complications through several molecular mechanisms: the polyol pathway, the hexoamine pathway, protien kinase C pathway and formation of advanced glycation end products.

One of the ways to modulate septic response is tight glucose control. Close control of blood glucose has been shown to increase survival in critically ill septic patients. Increased blood glucose variability rather than mean blood glucose level in critically ill patients is an important factor associated with sepsis. If we can forecast about the upcoming outcome of septic patients by the help of blood glucose variability, it will help us to improve the outcome of sepsis. Hence, it was appropriate to study that glucose variability can predict the mortality for septic patients in Intensive Care Unit.

Materials and Methods:

This Prospective Observational Study was carried out in a 20 bed mixed Medical-Surgical Intensive Care Unit in the Department of Anaesthesia, Analgesia and Intensive Care of Dhaka Medical College Hospital, Dhaka over a period of 19 months starting from January 2012 to July 2013. Prior to commencement of this study, the research protocol was submitted to the Ethical Review Committee of Dhaka Medical College Hospital and was approved. Patients admitted in ICU for more than 24 hours who fulfilled the criteria of sepsis either on admission or at any time during their ICU stay were purposively recruited. No randomization was performed. The study was strictly observational.

Subjects having length of stay in ICU less than 24 hours and other critically ill patients having no criteria of sepsis were excluded.

Study Procedure:

Total 40 patients were recruited after fulfilling the inclusion and exclusion criteria. At the time of admission and again after 24 hours patients were examined for vital signs and symptoms of systemic inflammatory response syndrome (SIRS), organ failure and/ or infection. Infection was defined by presence of clinical signs of systemic inflammatory response syndrome along with an identified source of infection and/ or positive blood cultures. An observation checklist was used by an unblinded observer (i.e. the researcher who knows which patient belongs to which group) to collect data on study parameters.

In all patients after getting proper treatment and nutritional support, blood glucose level was measured from finger capillary sampling at every 4 hours intervals using glucometer. There is no universally accepted gold standard method to measure blood glucose variability. Glycemic variability is considered as a standard of intra -day variation, reflecting the swings of blood glucose as a consequence of diminished or absent auto regulation and the short comings of insulin therapy. In this study, a target blood glucose level was 5-8 mmol/ L (Colledge, Walker & Ralston 2010)[31]. Blood glucose level was measured every 4 hours interval for the 1st 24 hours of recruiting patient, as such 6 glucose values were within the 1st 24 hours were included in this study. The glucose values that were not within the range of operational blood glucose level (5-8 mmol/L) were considered as values of glucose variability. The assigned patients were divided into three variable groups: Group I (mild variable group) – when less than 2 glucose values were not within the target glucose level (5-8 mmol/L); Group II (moderate variable group) - when 2-4 glucose values were not within the range (5-8mmol/L); Group III - (more variable group) – when more than four glucose values were not within the range.

Statistical Analysis:

Patients were separated into three different blood glucose variability groups: Gr.I (mild variable group), Gr.II (moderate variable group) and Gr.III (more variable group).They were also separated into ICU survivors and non-survivors. Data was processed and analyzed by SPSS (Statistical package for Social Sciences) software, 20th version. Categorical data were presented as frequency and percentage. Numerical data were presented as mean and age was presented both with (mean ± SD). Chi-square test, multiple logistic regression analysis was performed. The level of significance was at 5%, 95% confidence interval and a p-value <0.05 was considered as significant.

Table I. *Distribution of age of the study group*

	Mean ± SD	Minimum	Maximum
Age (yrs)	46.03±15.13	20	75

Table II: *Gender distribution of the study group*

Gender	Frequency	Percentage
Male	18	45
Female	22	55
Total	40	100.00

Data was expressed as frequency and percentage

Table III: *Distribution of the patients by clinical classification*

Clinical classification	Frequency	Percentage
Medical	21	52.5
Surgical	19	47.5
Total	40	100.00

Data was expressed as frequency and percentage

Table IV: *Distribution of patients into different blood glucose variability group*

RBS group	Frequency	Percent
Mild	14	35.0
Moderate	11	27.5
More	15	37.5
Total	40	100.0

Data was expressed as frequency and percentage

Table V: *Distribution of patient's status of the study group*

Status	Frequency	Percent
Non- survivors	22	55
Survivors	18	45
Total	40	100

Table VI: *Chi- square analysis of status of the patients among glucose variability groups*

Glucose variability group	N	Non-survivors	Survivors	X^2	p-value
Gr.I (mild)	14(35%)	2(14.29%)	12(85.71%)	14.56	0.001
Gr.II (moderate)	11(27.5%)	8(72.73%)	3(27.27%)		
Gr.III (more)	15(37.5%)	12(80%)	3(20%)		
Total	40(100%)	22(55%)	18(45%)		

Data was expressed as number (within parenthesis was percentage over column total)
Data here analyzed by Chi-square test.

Table VII: *Effect of Blood glucose variability on mortality by Multiple Logistic regression analysis*

Glucose variability Groups	OR	p-value
Gr.I (mild) (Reference)		0.004
Gr. II (moderate)	0.667	0.665
Gr.III (more)	16.000	0.007

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	Nrbs			11.303	2	0.004	
	nrbs (1)	2.773	1.021	7.380	1	0.007	16.000
	Nrbs (2)	-0.405	0.935	0.188	1	0.665	0.667
	Constant	-0.981	0.677	2.099	1	0.147	0.375

Fig : Variables in the Equation

Discussion

Most common cause of mortality in ICU is septic shock. One of the ways of modulation of septic response is tight glycemic control. The tight control of blood glucose level will improve the outcome of sepsis. Different authors have tried to find out the relation between blood glucose variability and mortality. If we can to seek a link between sepsis and upcoming death by the help of glucose variability, it will help us to improve the outcome of sepsis.

Hence I thought it would be appropriate to study that glucose variability can predict the mortality for septic patients in Intensive Care Patients.

This study shows that the mean age of the study subjects was 46.03±15.13 years and the youngest and the oldest patients were 20 and 75 years old respectively. Among total, 45% of all study subjects were male and 55% were female. Medical patients (52.5%) were recruited more than that of surgical (47.5%)

Also shown that 35% of all patients were in mild glucose variability group, 37.5% were in more group and 27.5% were in moderate glucose variability group.

On the other hand, 55% of all patients were non-survivors and 45% were survivors.

This study shows that a highly significant difference between three blood glucose variability groups exist with respect to mortality. Moderate and more glucose variability groups do not differ with respect to mortality but they differ with respect to mild glucose variability group. The result was highly significant (p- value 0.001).

It was revealed that more glucose variability group was a highly significant predictor of mortality with a p- value of 0.007 and an odds ratio of 16.0 while significant effect of moderate glucose variability group on mortality was not found with a p-value of 0.665 and an odds ratio of 0.667.

Various types of literature defined the association of GV with mortality in different populations of critically ill patients in different ICU. Most of the studies were retrospective observational cohorts except Waeschle et al. (2008).

This study was consistent with the study of Waeschle et al. (2008) showed that the relation between glycemic control and the severity of sepsis in a prospective observational cohort of patients treated with IIT. In addition they showed that significant association of SD levels >20mg/dl with mortality rate (p=0.0195). They included patients with sepsis, severe sepsis or septic shock.

It was consistent to the study of Ali et al. (2008). They also worked with septic patients and their aim was to determine association between GV and hospital mortality. Main results of that study was subjects with increased Glycemic lability index, but lower average glucose values had almost five-fold increased odds of hospital mortality (odds ratio = 4.73, 95% confidence interval=2.6-8.7) compared with those with lower Glycemic lability index.

This study was also consistent to the study of Pisarchic et al. (2012). They analyzed another retrospective study about mortality of burned patients. Their observation was, increasing glucose variability is independently associated with sepsis [majority of non-survivors had Delta (Daily glucose excursions)>8 m mol/L one day before death while the absolute majority of the survived patients on the day when sepsis was detected had Delta >6 m mol/L.]

Limitations:

The major limitation of our study was lack of randomization. Another limitation was its observational study design. Sample size was small, so the findings derived from the study cannot be generalized to reference population. The accurate picture of glucose variability was not drawn as this study was carried out only in an Adult Intensive Care Unit. So, the picture of paediatric group was not known.This was a single centre study.

Conclusions:

The septic patients having more blood glucose variability predicted mortality more than that of moderate and less blood glucose variability in ICU. If, we know about the propensity of death from the glycemic picture of septic patients within the 1st 24 hours of detection of sepsis, it will be easy to treat the patient and easily improve the outcome of sepsis that is death.

Patient with septic shock have a high mortality and as yet there is no accurate prediction scoring system which gives accurate prediction of outcome for individual patient. In that case, Glucose variability can see the way to improve the outcome of sepsis.

Our observation is prospectively confirmed, would indicate that Glucose variability should be included as a future approach to glucose management of septic patients as a target for therapeutic intervention.

References:

1. Brun-Buisson C, Meshaka P, Pinton P, et al. EPISEPSIS: A reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med. 2004; 30:527-529. [PubMed: 14985955]
2. Russell JA. Management of sepsis. N Engl J Med. 2006; 355:1699-1713. [PubMed: 17050894]
3. Sablotzki A. Muhling J, Czeslick E: [sepsis and multiple organ failure - update of current therapeutic concepts]. Anaesthesiol intensivmed Notfallmed Schmerzther 2005, 40: 511 - 520 .

4. Marik PE, Raghavan M. Stress-hyperglycemia, insulin and immunomodulation in sepsis. Intensive Care Med. 2004; 30: 748-756. [PubMed: 14991101]

5. Rusavy Z, Sramek V, Lacigova S, et al. Influence of insulin on glucose metabolism and energy expenditure in septic patients. Crit Care. 2004; 8:R213-R220. [PubMed: 15312220]

6. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. Crit Care Clin. 2001; 17: 107-124. [PubMed: 11219223]

7. Van den Berghe G, Wouters PJ, Bouillon R, Weekers F, Verwaest C, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P: Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med

8. Ellger B, Debaveye Y, Vanhorebeek I, Langouche L, Giulietti A, Van Etten E, Herijgers P, Mathieu C, Van den Berghe G: Survival benefits of intensive insulin therapy in critical illness: Impact of maintaining normoglycemia versus glycemiaindependent actions of insulin. Diabetes 2006; 55: 1096-105

9. Vanhorebeek I, Langouche L, Van den Berghe G: Glycemic and nonglycemic effects of insulin: How do they contribute to a better outcome of critical illness? Curr Opin Crit Care 2005; 11: 304-11

10. Bagry HS, Raghavendran S, Carli F: Metabolic syndrome and insulin resistance: Perioperative considerations. ANESTHESIOLOGY 2008; 108: 506-23

11. Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R: Intensive insulin therapy in the critically ill patients. N Engl J Med 2001; 345: 1359-67

12. Furnary AP, Gao G, Grunkemeier GL, Wu Y, Zerr KJ, Bookin SO, Floten HS, Starr A: Continuous insulin infusion reduces mortality in patients with diabetes undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2003; 125: 1007-21

13. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, Van Wijngaerden E, Bobbaers H, Bouillon R: Intensive insulin therapy in the medical ICU. N Engl J Med 2006; 354: 449-61

14. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. Mayo Clin Proc 2004; 79:992-1000

15. Turina M, Fry DE, Polk HC Jr: Acute hyperglycemia and the innate immune system: Clinical, cellular, and molecular aspects. Crit Care Med 2005; 33: 1624-33

16. Langouche L, Vanhorebeek I, Vlasselaers D, Vander Perre S, Wouters PJ, Skogstrand K, Hansen TK, Van den Berghe G: Intensive insulin therapy protects the endothelium of critically ill patients. J Clin Invest 2005; 115: 2277-86

17. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van den Berghe G: Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet 2005; 365: 53-9

18. Mesotten D, Swinnen JV, Vanderhoydonc F, Wouters PJ, Van den Berghe G: Contribution of circulating lipids to the improved outcome of critical illness by glycemic control with intensive insulin therapy. J Clin Endocrinol Metab 2004; 89: 219-26

19. Langouche L, Vander Perre S, Wouters PJ, D'Hoore A, Hansen TK, Van den Berghe G: Effect of intensive insulin therapy on insulin sensitivity in the critically ill. J Clin Endocrinol Metab 2007; 92: 3890-7

20. Yu WK, Li WQ, Li N, Li JS**:** Influence of acute hyperglycemia in human sepsis on inflammatory cytokine and counter regulatory hormone concentrations.World J Gastroenterol 2003; 9: 1824-7

21. Esposito K, Nappo F, Marfella R, Giugliano G, Giugliano F, Ciotola M, Quagliaro L, Ceriello A, Giugliano D: Inflammatory cytokine concentrations are acutely increased by hyperglycemia in humans: Role of oxidative stress. Circulation 2002; 106: 2067-72

22. Brownlee M2001 Biochemistry and molecular cell biology of diabetic complications. Nature 414: 813-820

23. Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E,Ceriello A 2003 Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)Hoxidase activation. Diabetes 52: 2795-2804

24. Piconi L, Quagliaro L, Assaloni R, Da Ros R, Maier A, Zuodar G, Ceriello A 2006 Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. Diabetes Metab Res Rev 22: 198-203

25. Takeuchi A, Throckmorton DC, Brogden AP, Yoshizawa N, Rasmussen H, Kashgarian M 1995 Periodic high extracellular glucose enhances production of collagens III and IV by mesangial cells. Am J Physiol 268: F13-F19

26. Mauer SM, Steffes MW, Ellis EN, Sutherland DE, BrownDM, Goetz FC 1984 Structural-functional relationships in diabetic nephropathy. J Clin Invest 74:1143-1155

27. Steffes MW, Bilous RW, Sutherland DE, Mauer SM 1992 Cell and matrix components of the glomerular mesangiumin type I diabetes. Diabetes 41:679-684

28. Horvath EM, Benko R, Kiss L, Mura´nyi M, Pe´k T, Fekete K, Ba´ra´ny T, Somlai A, Csorda´ **s A,** Szabo C 2009 Rapid'glycaemic swings' induce nitrosative stress, activate poly-(ADP-ribose) polymerase and impair endothelial function in a rat model of diabetes mellitus. Diabetologia 52:952-961

29. Ceriello A, Esposito K, Piconi L, Ihnat MA, Thorpe JE,Testa R, Boemi M, Giugliano D 2008 Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients.Diabetes 57: 1349-1354

30. Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol JP, Colette C 2006 Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 295:1681-1687

31. Colledge, NR. , Walker, BR. and Ralston, SH.(2010) Davidson's Principles and Practice of Medicine. Edinburgh: Charchill Livingstone.

32. Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. Anesthesiology. 2006; 105:244-252. [PubMed: 16871057]

33. Hirsch IB, Brownlee M. Should minimal blood glucose variability become the gold standard of glycemic control? J Diabetes Complications. 2007; 19: 178-181. [PubMed: 15866065]

34. Devos P, Preiser JC, Melot C, et al. Impact of tight glucose control by intensive insulin therapy on ICU mortality and the rate of hypoglycaemia: final results of the Glucontrol study. Intensive Care Med. 2007; 33(suppl 2): S189.

35. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. New Engl J Med. 2008; 358:125-139. [PubMed: 18184958]

36. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med. 2008; 36: 296-327. [PubMed: 18158437]

37. Reiner M Waeschle, Onnen Moerer, Reinhard Hilgers, Peter Herrmann, Peter Neumann and Michal Quintel : The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability. Crit Care2008,12:R129

38. Reinhart K, Brunkhorst FM, Bone HG, Gerlach H, Grundling M,Kreymann G, Kujath P, Marggraf G, Mayer K, Meier-Hellmann A, Peckelsen C, Putensen C, Quintel M, Ragaller M, Rossaint R, Stüber F, Weiler N, Welte T, Werdan K: [Diagnosis and Therapy of Sepsis: Guidelines of the German Sepsis Society Inc. and the German Interdisciplinary Society for Intensive and EmergencyMedicine.]. Internist (Berl) 2006, 47:356-373.

39. Alexander N, Pisarchik 1 , Olga N. Pochpen@, Lindmila A. Pisarchyk : Increasing Blood Glucose Variability Is a precursor of Sepsis and Mortality in Burned patients : PLos ONE 7(10) : C46582. doi : 10.1371/ journal. pone 0046582

40. Monnier L, Colettle C, Owens DR(2004) Glycaemic variability :the third component of the dysglycaemia in diabetes. Is it important ? How to measure it ? S Diabetes Sci Technol 2 : 1094- 100

41. Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: A severity of disease classification system. Crit Care Med 1985; 13:818-29

42. Waeschle, RM, Moerer, O, Hilgers, R, Herrmann, P, Neumann, P, and Quintel, M. (2008) `The impact of the severity of sepsis on the risk of hypoglycaemia and glycaemic variability', Crit Care, 12, pp.R129.

43. Ali, NA, O'Brien, JM Jr, Dungan, K, Phillips, G, Marsh, CB, Lemeshow, S, Connors, AF, Jr, and Preiser, JC. (2008) 'Glucose variability and mortality in patients with sepsis', Crit Care Med, 36, pp. 2316–2321.

44. Pisarchik, AN., Pochepen, ON. and Pisarchyk, LA. (2012) `Increasing Blood Glucose Variability Is a Precursor of Sepsis and Mortality in Burned Patients', PLoS ONE 7(10), e46582. doi: 10.1371/journal.pone.0046582