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Original Article

Role of Glucose Variability in the Diagnosis of Septic Patients

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Abstract:

Background: *Glucose variability is an indicator and independent predictors of mortality and severity of sepsis in critically septic patients of intensive care unit.*

Objectives: *This study evaluated the relationship of glucose variability in critically ill septic patients in relation with serum lactate.*

Method: *It is a prospective observational study was conducted in the Intensive Care Unit (ICU) in Department of Anesthesia, Pain, Palliative Care and Intensive Care, Dhaka Medical College hospital, Dhaka over a period of one year in between 1st January- 31st December, 2015. Total 51 septic adult patients were included in the study according to the selection criteria. In this study, 8 consecutive capillary blood samples were taken with a periodic interval of 3 hours starting from admission. Mean and standard deviation (SD) blood glucose were computed to see the glucose variability and agreement done with serum lactate and severity of sepsis. All collected data were registered documented and analyzed in the statistical program Statistical Package for Social Science (SPSS) version 20.0.*

Result: *Among total 51 patients, 52.9% study cases were of 4th decade with a mean age of 46±12 years had a mild female predominance. Glycemic variability was taken as >2SD. High glycemic variability observed in 70.6% cases. Good agreement observed in glucose variability with serum lactate by Kappa Statistics.*

Conclusion: *Glucose variability shows the prediction of sepsis and it could be used as a useful alternative tool to predict sepsis and severity of sepsis.*

Introduction

Severe sepsis (acute organ dysfunction secondary to infection) and septic shock (severe sepsis plus hypotension not reversed with fluid resuscitation) are major healthcare problems, affecting millions of individuals around the world each year, killing one in four (and often more), and increasing in incidence[1,2]. These patients are particularly prone to hyperglycemia and insulin resistance because of a number of pathophysiologic changes associated with sepsis[3]. More recently, biological laboratory markers (biomarkers) have been used, ranging from the relatively simple white blood cell count and C-reactive protein (CRP) to more complex biomarkers, such as pro calcitonin (PCT) or cytokine levels and (to some extent) coagulation markers. Importantly, all of these markers are more helpful at ruling out than at ruling in an infection. Virtually, all patients in the ICU have some inflammatory response associated with fever at one time or another, but these responses do not all require antibiotic administration[4]. Hence, sepsis biomarkers could be helpful to decrease the use of antibiotics or unnecessary diagnostic tests, such as CT scans, to identify a source of sepsis. Landmark studies in this area support the use of serum lactate in both the diagnostic and treatment phases for septic shock. Lactate levels are a critical parameter indicating sepsis induced hypo-perfusion and triggering guideline driven early goal directed therapy (EGDT) in the Surviving Sepsis Campaign[5]. In addition to aiding diagnosis, biomarkers of sepsis can potentially be used for prognostication to predict the development of organ dysfunction, to guide antibiotic therapy and to evaluate the response to therapy. Many biomarkers have been proposed over the years, but there is little consensus on which is best and the exact role of individual markers remains uncertain. Many of the biomarkers that have been proposed are mediators of the inflammatory response to sepsis, that is, they are essential players in the development and promulgation of the syndrome of sepsis; others are merely present as a consequence of the sepsis process. Because of the complexity of the sepsis response, different markers may have different roles in terms of diagnostics, prognostics and therapeutic guidance; some may even express different elements at different times during the sepsis response in the same patient.

Serum Lactate is recognized as a potentially useful prognostic marker to risk stratify patients with severe sepsis and elevated serum lactate is found to be strongly associated with morbidity and mortality in various populations with sepsis. Landmark studies in this area support the use of serum lactate

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in both the diagnostic and treatment phases for septic shock[6]. Lactate levels are a critical parameter indicating sepsis induced hypo-perfusion and triggering guideline driven early goal directed therapy (EGDT) in the Surviving Sepsis Campaign[7].

Extreme elevations of blood glucose are associated with excess mortality in various groups of hospitalized patients. Targeting normoglycemia with the use of continuous insulin infusions (intensive insulin therapy [IIT]) improves outcomes in a selected group of critically ill patients[8]. Patients with severe sepsis, IIT did not improve survival, but significantly increased the number of hypoglycemic events[9]. The current recommendation from the Surviving Sepsis Campaign is that insulin therapy be used to maintain glucose below 150 mg/dL in septic patients[7].

In a prospective study of septic critically ill patients a significant association between high glycemic variability and mortality was found[10].These results are consistent with in vitro data showing that short-time fluctuations of glucose levels induce endothelial cell damage and apoptosis[11]. Moreover, a significant association between glycemic variability and 8-iso prostaglandin F2a, a marker of oxidative stress and potential mediator of organ dysfunction, has been shown in diabetic type 2 patients[12]. Minimal glycemic variability has been proposed to become the gold standard of glycemic control in diabetic patients. Glycemic variability depends on both endogenous patient-specific factors such as severity of disease and diabetes status as well as exogenous factors such as type and quality of glucose monitoring, the glucose algorithm used for the calculation of the insulin rate, compliance of the nursing staff with the recommendations of the protocol and application of medication including enteral and parenteral nutrition. As the endogenous glucose regulation system can hardly be influenced, glycemic variability needs to be improved by acting on the exogenous factors[13].

The measure glycemic variability describes fluctuations of blood glucose over time. As glucose fluctuations are not covered by mean glucose, glycemic variability has been suggested as an additional measure for glucose control. Glycemic variability is represented by standard deviation (SD), mean daily δ blood glucose or glucose liability index (GLI). SD is the most commonly used parameter and is calculated as the square-root of the average of the squared differences between individual glucose values and the mean. Mean daily δ blood glucose describes the mean of the daily difference between minimum and maximum blood glucose. These two measures do not take order and timing of measurements into account. GLI is the squared difference between consecutive blood glucose levels per unit of actual time between the samples. GLI considers the time between and the order of measurements[14]. Although no gold standard of measuring glycemic variability has been established yet, SD seems to be the best predictor of mortality.

Materials and Methods:

This prospective observational study was carried out in the Intensive Care Unit (ICU), Department of Anaesthesiology, Pain, Palliative Care and Intensive Care, Dhaka Medical College hospital, Dhaka, during the period from 1st January-31st December, 2015. Total 51 patients were included in the study according to the selection criteria.

Inclusion Criteria: Septic patients who were admitted to the ICU with age >18 years.

Exclusion criteria: Age under 18 years, have a hospital length of stay of<24 hours, patients having diabetes mellitus and who already received steroid before admission.

All suspected septic patients were examined to find out Sepsis, severe sepsis & septic shock were defined using the criteria of the American College of Chest Physicians and the Society of Critical Care Medicine Consensus Conference. After meeting inclusion and exclusion criteria and who fulfilled the diagnostic criteria for sepsis was evaluated by the ICU team and all patients were treated following the Surviving Sepsis Campaign guidelines. After written informed consent was obtained, each patient was equipped with an arterial cannula and a central venous catheter.

In addition, all patient data, including vital parameters and laboratory results, were collected. Blood glucose levels were measured predominantly in capillary blood on admission and in every three hours thereafter (every 30 to 60 minutes in the case of hypoglycemic values) with Accu-Check Active glucometer. As an index of glycaemic variability, mean and the standard deviation (SD) of all blood glucose values for each patient were calculated. All analyses were performed separately for septic episodes and for the group stratified by the severity of sepsis. Blood lactate level was measured after enrollment. To prevent an in vitro rise in blood lactate levels, the sample were immediately analyzed.

Statistical analysis:

Data were presented as mean with SD, unless otherwise indicated. Kappa statistic was calculated as a measure of agreement between glucose variability and serum lactate level. Kappa value > 0.6 was considered as good agreement. A P value less than 0.05 was considered to indicate statistical significance.

Results:

The study sample consisted of a total of 51 patients with sepsis in whom data was collected to obtain glycemic variability and its relation in the diagnosis of sepsis January 2015 to December 2015. Observation and results are as follows-

Among the study participants, mean age observed 46 years with a standard deviation of 12 years. Most of the cases (around 76%) belong to 4th and 5th decades. Blood sugar level >2SD of mean was taken to see the blood glucose variability. Glucose variability was present in 70.59% patients. All of the study populations were hyper-lactatemic. Serum lactate more than 4 mmol/l were considered lactate positive and Serum lactate less than 4 mmol/l considered lactate negative. Agreement test between serum lactate and

glucose variability in different septic patients was tested with Serum lactate level by Kappa Statistics, as neither of these tests is not gold standard for diagnosis of sepsis. Good agreement was observed. Among different category of sepsis there was significant difference observed. This result indicates that glucose variability was increasing with severity of sepsis. Also there was significant difference observed in Serum lactate among different category of sepsis. This result indicates that serum lactate positivity was increasing with severity of sepsis.

Table I shows age distribution of study patients. (n=51)

Table 1

Age Groups			
Mean±D	46±12 Years	Min.-Max.	18-65Years

Table II shows Glucose variability of study patients. (n=51)

Table II

Glucose Variability	Frequency	Percent (%)
Absent	15	29.41
Present	36	70.59
Total	51	100

Table III shows serum Lactate positivity of study patients. (n=51)

Table III

Serum lactate	Frequency	Percent (%)
Negative	14	27.5
Positive	37	72.5
Total	51	100

Table IV shows agreement test between serum lactate and glucose variability in different septic patients. (n=51)

Table IV

Lactate Positivity in different category of Sepsis		Glucose Variability ≥ 2SD Glucose Variability Absent	Glucose Variability Present	Total	Ƙ-value
Negative	n	12	2	14	
	%	23.5%	3.9%	27.4%	
Positive	n	3	34	37	0.759
	%	5.9%	66.7%	72.6%	
Total	n	15	36	51	
	%	29.4%	70.6%	100.0%	

Table V shows glucose variability among different category of sepsis. (n=51)

Table V

Glucose Variability		Category of sepsis Sepsis	Sever Sepsis	Septic Shock	Total	P-value
Absent	n	8	2	5	15	
	%	15.7%	3.9%	9.8%	29.4%	
Present	n	3	15	18	35	0.001
	%	5.9%	29.4%	35.3%	70.6%	
Total	n	11	17	23	51	
	%	21.6%	33.3%	45.1%	100.0%	

Table VI shows serum Lactate among different category of sepsis. (n=51)

Table VI

Serum Lactate		Category of sepsis Sepsis	Sever Sepsis	Septic Shock	Total	P-value
Normal	n	11	3	0	14	
	%	21.6%	5.9%	0.0%	27.5%	
Positive	n	1	14	22	37	0.001
	%	2.0%	27.5%	43.1%	72.5%	
Total	n	12	17	22	51	
	%	23.5%	33.3%	43.1%	100.0%	

Table VII shows agreement test between serum lactate and glucose variability in sepsis patients.(n=12)

Table VII

Lactate Positivity in Sepsis patients		Glucose Variability ≥ 2SD Glucose Variability Absent	Glucose Variability Present	Total	Ƙ- value
Negative	n	7	1	8	0.542
	%	63.6%	9.1%	72.7%	
Positive	n	1	2	3	
	%	9.1%	18.2%	27.3%	
Total	n	8	3	11	
	%	72.7%	27.3%	100.0%	

Table VIII shows agreement test between serum lactate and glucose variability in sever sepsis patients. (n=17)

Table VIII

Lactate Positivity in Severe Sepsis		Glucose Variability ≥ 2SD			
		Glucose Variability Absent	Glucose Variability Present	Total	Ƙ- value
Negative	n	2	1	3	
	%	11.8%	5.9%	17.6%	
Positive	n	0	14	14	0.767
	%	0.0%	82.4%	82.4%	
Total	n	2	15	17	
	%	11.8%	88.2%	100.0%	

Table IX shows agreement test between serum lactate and glucose variability in septic shock patients. (n=22).

Table IX

Lactate Positivity in Septic Shock		Glucose Variability ≥ 2SD			
		Glucose Variability Absent	Glucose Variability Present	Total	Ƙ- value
Negative	n	3	00	3	
	%	13%	0.0%	13%	
Positive	n	2	18	22	0.701
	%	8.7%	78.3%	100%	
Total	n	5	17	22	
	%	21.7%	78.3%	100%	

Discussion:

Primary objective of the study was to find out the diagnostic value of glycemic variability in septic patients. In this study, a total 51 non-diabetic septic patients were allocated purposively on the basis of sepsis criteria in the ICU.

More than 50 % patients were of 4th decades among 51 non diabetic septic patients of this study. Mean age was 46 years with a SD of 12 years but age of most study patients in the study were of 6th decades in study of Egi, M. et al.[15].Most of the sepsis patients of this study were from Surgical, Casualty and Gynae & Obstetric wards. Probably younger age in my study was due to poor isolation facility and poor hygienic conditions and lack of awareness of our patients increases septic condition even in younger ages.

This study slight female predominance but sex distribution in study of Egi, M. et al.[15] male predominance. As it was a single center study with small number of study cases; reflection of sex distribution may not be accurate here.

Glycemic variability describes fluctuations of blood glucose over time and is influenced by endogenous and exogenous factors. To see the glycemic variability total 8 blood samples were taken at an interval of 3 hours started from admission. Total 408 capillary blood samples were taken for this study. Mean and SD glucose were measured to see the glucose variability. Among the patients, 35 expressed high glucose variability. Increased lactataemia indicate cellular hypo-perfusion. In 72.5% patient's serum lactates were more than 4 mmol/L. Still there is no study to evaluate glycemic variability for the diagnosis of septic patient. Although serum lactate is being used widely as a marker of sepsis. In table IV we found good agreement between high glycemic variability and serum lactate (kappa value=0.759). High glycemic variability indicate >2SD blood glucose concentration. Among the study population, 36 were exhibit high glycemic variability. So it can be used as a predictor of sepsis like serum lactate where resource allocation is less or limited because glycemic variability can be obtain by using simple tool of blood glucose measurement which is easily available in the context of our country.

Among the category of sepsis, septic shock was the predominant category (43%), least was sepsis (24%) and shows that, there was significant difference in glucose variability among different category of sepsis (p-value =0.001). This result indicates that glucose variability also predict severity of sepsis. Pisarchik AN et al. [16] showed in a retrospective study, glycemic variability, rather than a mean glucose level, is an important factor associated with sepsis and hospital mortality in critically ill patients. The analysis identified significant association of increasing daily glucose excursion (DELTA) accompanied by evident episodes of hyperglycemia (>11 mmol/l) and hypoglycemia (<2.8 mmol/l), with sepsis and forthcoming death, even when the mean daily glucose was within a range of acceptable glycaemia. It was found that significant association (p =0.001) between serum lactate positivity and severity of sepsis. Positivity of serum lactate was increased in severe sepsis and septic shock. It indicates the possibility of alternate use of glucose variability in prediction of severity of sepsis

In this study kappa statistics between serum lactate and glucose variability revealed good agreement as the severity of sepsis increases. Among different category of sepsis, fair agreement observed in sepsis and good agreement was observed in severe sepsis and in septic shock.

Limitations Of The Study:

Like other scientific study, the present study is not without limitations:

- The major limitation of this study was lack of randomization.
- Another limitation was its observational design.
- Sample size was small, so the findings derived from the study cannot be generalized to reference population.

Conclusion:

Since Serum lactate is used as a diagnostic marker of sepsis, glucose variability can be used reliably as an alternative.

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