Original Research Article

Association between the glycemic variability and mortality in critically ill neurological patients - A hospital based observational study

Shaik Afsar Pasha[1*], Shaik Arif Pasha[2], Bala Kusuma[3], T. Suhasini[4]

[1]Assistant Professor, Department of Neurology, NRI Medical College, Mangalagiri, chinakani, Guntur, Andhra Pradesh, India
[2]Associate Professor, Department of Critical Care Unit, NRI Medical College, Mangalagiri, Chinakakani, Guntur, Andhra Pradesh, India
[3]Department of Anesthesiology, NRI Medical College, Mangalagiri, Chinakakani, Guntur, Andhra Pradesh, India
[4]Professor, Department of Critical Care Unit, NRI Medical College, Mangalagiri, Chinakakani, Guntur, Andhra Pradesh, India
[*]Corresponding author email: **afsarpasha81@gmail.com**

International Archives of Integrated Medicine, Vol. 3, Issue 7, July, 2016.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 14-06-2016 **Accepted on:** 20-06-2016
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Pasha SA, Pasha SA, Kusuma B, T. Suhasini. Association between the glycemic variability and mortality in critically ill neurological patients - A hospital based observational study. IAIM, 2016; 3(7): 42-49.

Abstract

Background: In diabetic patients, the glycemic control is usually represented by hemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG), which are usually referred as the "glucose triad". Apart from these three, "glucose variability" (GV) has been considered as an additional marker, and may be equally important.

Materials and methods: The study was a prospective observational study conducted in critical care unit of NRI General Hospital. The study has included all the critically ill neurological patients admitted in the study setting during the study period. A total of 114 participants were included in the study. All critically ill neurological patients were included in the study and were assessed with hourly Glucometric random blood sampling (GRBS) for 6 hours for initial 15 days of admission. Glycemic

variables have been recorded including Mean blood glucose (MBG), Glycemic liability index (GLI), Standard deviation of blood glucose. APACHE II scores were also recorded.

Results: The mean age of the study participants was 51.69 (±20.21) years. Males constituted 57% and females constituted 43% of study population. The proportion of subjects with diabetes was 51.8%.The mean days of ICU stay was 8.19 (±3.86) days. The morality risk in study population was 28%. Univariate logistic regression analysis showed highest mortality in < 30 year age group. When compared to below 30 year age group, the risk of mortality in 30 to 49 year group was 44%, was 27.6% in 50 to 69 years age group and 71.4% in above 70 years age group. The mortality was almost similar in both genders. The mean APACHE II score was 4 units higher in mortality group, compared to non-mortality group (95% CI 1.64 to 6.37, p value 0.001). Even though the mean GLI, SD GLI values were 39.24 and 73.67 times higher in people with mortality these differences were statistically not significant. The differences in the mean values of mean blood glucose and SDBG were very negligible between the subjects with and without mortality.

Conclusion: The study findings reveal that though, APACHE II scores seem to positively associated with mortality among critically ill neurological patients, the glycemic variability though positively influenced the mortality, it is not significant. Further studies assessing the role of GV specifically among such patient groups with a larger sample might reveal the true influence of such interaction.

Key words

Glycemic variability, Mortality, Neurological patients, Critically ill, APACHE II.

Introduction

In diabetic patients, the glycemic control is usually represented by hemoglobin A1c (HbA1c), fasting plasma glucose (FPG) and postprandial glucose (PPG), which are usually referred as the "glucose triad". Apart from these three, "glucose variability" (GV) has been considered as an additional marker, and may be equally important.

The Diabetic Control and Complications Trial [1] was one of the first studies that envisaged GV as an independent risk indicator for complications in diabetic patients. The study concluded that even after controlling for HbA1c values among conventionally treated diabetic patients and intensively treated subjects; the former group had a higher risk of developing retinopathy over time. In fact GV is considered to be one of the three domains of glycemic control apart from hyperglycemia and hypoglycemia, which are essential prognostic markers in critically ill patients [2].

Considerable research evidence has linked the detrimental effect of hyperglycemia and its consequential effect on morbidity and mortality in the form of numerous adverse neurological outcomes and multi-organ failures [3-5]. The common neurological complications include elevated intracranial pressure, higher risk of epileptic seizures, and cerebral herniation among others [6]. By controlling glycemic variability, it is possible to reduce these complications and to set the therapy for all patients with diabetes.

The glycemic excursion among the critically ill patients in intensive care units may also influence the occurrence of adverse outcome [5, 7]. The low levels of extracellular glucose in the brain resulting due to intensive insulin therapy have been one of the attributable factors for such bad outcomes [8].

Hence, the intensivists usually face the dilemma to maintain the balance between the two dangerous scenarios of hyperglycemia and hypoglycemia. In spite of the hard evidence from observational and multi-centric trials, the required glucose levels to be maintained for optimum prognosis are still debatable. Hence the present study was undertaken with the objective

of assessing the role of GV on mortality among critically ill neurological patients.

Objectives

- To assess the impact of glycemic variability on mortality in critically ill neurological patients, admitted to a tertiary care teaching hospital.
- To assess the association between APACHE II score and mortality in critically ill neurological patients admitted to a tertiary care teaching hospital.

Materials and methods

Study design: The study was a prospective observational study.

Study setting: The study was conducted in critical care unit of NRI General Hospital, which is a tertiary care teaching hospital.

Study population: The study has included all the critically ill neurological patients admitted in the study setting during the study period.

Study duration: The data collection for the study was done for a 1 year period.

Sample size: A total of 114 participants were included in the study.

Sampling method: All the eligible participants were included in the study, hence no sampling was done.

Ethical considerations: Approval of institute Human Ethics committee was obtained. Informed written consent was obtained from all the participants, after explaining the objectives of the study, risks and benefits involved. The personal details of the patients were kept confidential throughout the study.

Study procedure: All critically ill neurological patients were included in the study and were assessed with hourly Glucometric random blood sampling (GRBS) for 6 hours for initial 15 days of admission. Glycemic variables have been recorded including Mean blood glucose (MBG), Glycemic liability index (GLI), Standard deviation of blood glucose. APACHE II scores were also recorded.

Statistical analysis

Mortality was considered as the primary outcome variables. Glycemic variability as assed by Mean GLI, SD GLI, mean and SD blood glucose were the primary explanatory variables. Duration of ICU and ventilator stay, APACHE II score etc were considered as other explanatory variables. Descriptive analysis was done by means and standard deviations for quantitative variables and frequency and percentage for categorical variables. The association between explanatory and outcome variables was assessed by comparing the mean differences of quantitative variables across the groups and their 95% CI. Univariate logistic regression analysis was used to compare the risk of mortality in relation with glycemic variability variables and other explanatory variables. P value 0.05 was considered as statistically significant.IBM SPSS version 21 was used for statistical analysis.

Results

A total of 114 participants were included in the study. The mean age of the study participants was 51.69 (±20.21) years. Males constituted 57% and females constituted 43% of study population. The proportion of subjects with diabetes was 51.8%.The mean days of ICU stay was 8.19 (±3.86) days. The morality risk in study population was 28% (**Table – 1**).

Table - 1: Descriptive analysis of study population.

Characteristics	Study population (N=114)
Age (mean±SD)	51.69±20.21
Gender {Frequency (%)}	
➢ Female	49 (43.0)
➢ Male	65 (57.0)
DM {Frequency (%)}	59 (51.8)
APACHE II Score (Mean±SD)	17.07±6.85
DOSICU (Mean±SD)	8.192±3.86
Mean of GLI (Mean±SD)	204.65±288.80
SD of GLI (Mean±STD)	.40±832.16
MBG (Mean±STD)	156.89±29.645
Crude Mortality	26 (22.8)

Univariate logistic regression analysis showed highest mortality in < 30 year age group. When compared to below 30 year age group, the risk of mortality in 30 to 49 year group was 44%, was 27.6% in 50 to 69 years age group and 71.4% in above 70 years age group. Hence it can be concluded that mortality was higher in both the extremes of age (**Table – 2**).

The mortality was almost similar in both genders. There was slightly higher risk of mortality in diabetic subjects (OR 1.337, 95% CI 0.55 to 3.21), but this association was statistically not significant. There was no increase in mortality with each one unit increment in any of the glycemic variability indices in the study population (**Table – 2**).

The risk of mortality increased 1.12 times with each unit increase in APACHE II score (OR 1.128, 95% CI 1.04 to 1.21), which was statistically significant (p value 0.002). There was 2.33 time higher risk of mortality with each day increase in ventilator stay (OR 2.33, 95% CI 1.69 to 3.21), which was statistically significant (P value < 0.001). The risk of mortality increased 1.13 times with each day increase in ICU stay (OR 1.13, 95% CI 0.99 to 1.29), which was statistically not significant (p value 0.055) as per **Table – 2**.

Table - 2: Factors influencing the mortality in study population (n=114).

Parameter	**Un Adjusted odds ratio**	**P- value**	**95% C.I. for odds ratio**	
			Lower	**Upper**
I. Age group				
< 30 years (baseline)	1			
30 to 49 years	.440	.276	.100	1.930
50 to 69 years	.276	***.030***	.086	.881
70 years and above	.714	.669	.153	3.334
II. Gender				
Female (baseline)	1			
Male	1.036	.937	.428	2.511
III. Diabetes				
No (baseline)	1			
Yes	1.337	0.516	0.556	3.21
III. Glycemic variability Indices				
Mean GLI	1.001	0.360	0.999	1.003
SD GLI	1.00	0.54	0.999	1.001
Mean BG	1.001	0.923	0.986	1.015
SD BG	1.00	0.998	0.979	1.021
IV. Other parameters				
APACHE II score	1.128	***0.02***	1.04	1.21
Number of days on ventilator	2.331	***<0.001***	1.69	3.21
Days of ICU stay	1.134	***0.055***	0.997	1.29

The mean APACHE II score was 4 units higher in mortality group, compared to non-mortality group (95% CI 1.64 to 6.37, p value 0.001). Even though the mean GLI, SD GLI values were 39.24 and 73.67 times higher in people with mortality these differences were statistically not

significant. The differences in the mean values of mean blood glucose and SDBG were very negligible between the subjects with and without mortality (**Table – 3** and **Figure – 1 to 5**).

Figure - 1: Box Plot of APACHE II SCORE distribution in study population (N=114).

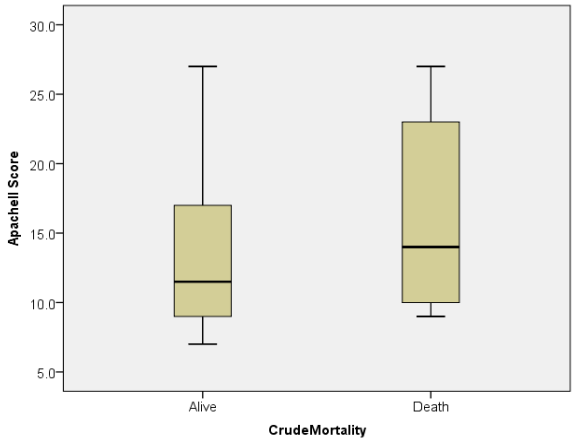


Figure - 2: Box Plot of MEAN OF GLI in study population (N=114).

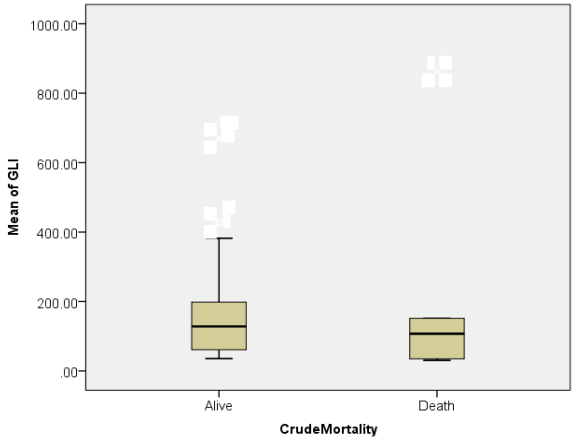


Figure - 3: Box Plot of SD OF GLI in study population (N=114).

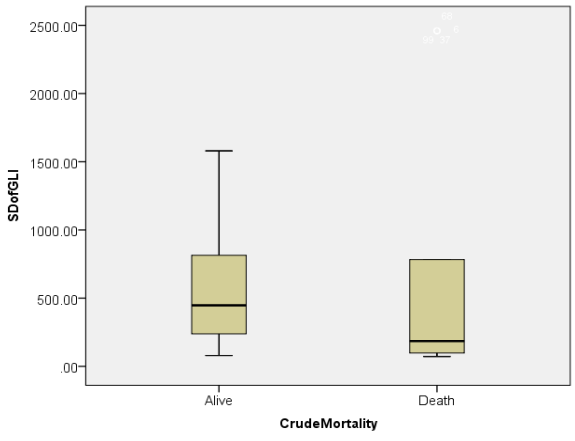


Figure - 4: Box Plot of MBG in study population (N=114).

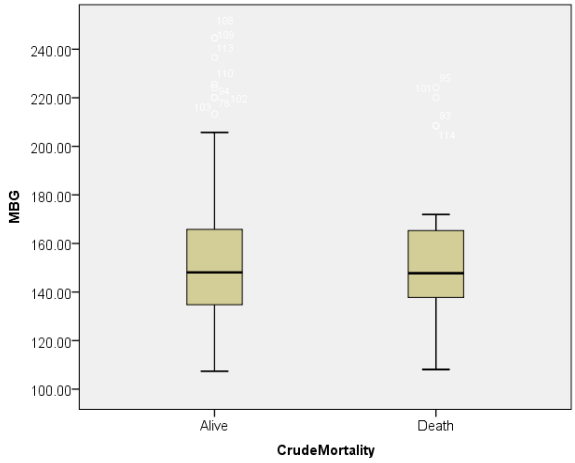
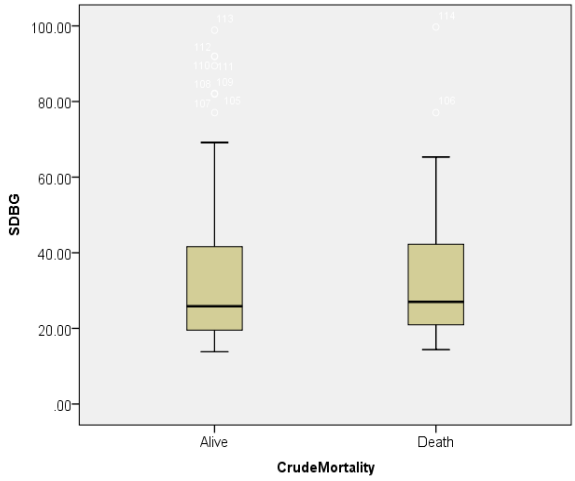


Figure - 5: Box Plot of SDBG in study population (N=114).



Discussion

The intensivists have long been puzzled by the niggling issue of what constitutes optimal level of glucose for the critically ill patients in the ICU. Though, physiological stress naturally induces hyperglycemia, in the critically ill patients it has been ascribed to the inflammatory response, insulin resistance, medication induced or due to the role of hormones countering the effects of insulin [9]. The prevalence of hyperglycemia seems to be on the higher side among such patients ranging from 50-75%, which has been linked to the occurrence of organ dysfunction, higher mortality, being more prone for infections and neurological complications [9, 10].

Table - 3: Comparison of glycemic apachelle score and glycemic variability indicators in people with and without mortality (n=114).

Parameter	Morality	Mean	Mean difference	P value	95% CI	
					Lower	Higher
APACHE II SCORE	Yes (n=26)	17.07	4.00	0.001	1.64	6.37
	No (n=88)	13.068				
Mean GLI	Yes (n=26)	204.69	39.24	0.359	-45.10	123.59
	No (n=88)	165.41				
SDLI	Yes (n=26)	640.40	73.67	0.54	-165.92	313.27
	No (n=88)	566.72				
MBG	Yes (n=26)	156.89	0.649	0.924	-12.78	14.08
	No (n=88)	156.24				
SDBG	Yes (n=26)	34.68	-0.01	0.998	-9.38	9.36
	No (n=88)	34.69				

The inconsistency and unreliable results from studies that assessed the glucose control have off late highligtened the influencing role of GV among ICU populations. Chang, et al. [11], reported that the unpredictable rapid changes of glycemic levels enhance the risk of oxidative stress and in turn are more damaging than persistent hyperglycemia among patients with type 2 diabetes mellitus.

The mean age of the study participants was 51.7years. Males constituted 57% and females constituted 43% of study population. Similar gender ratio was reported by Todi and Bhattacharya [2] in their retrospective assessment of 2208 patients, however, their patients' mean ages was higher (61years).

Even though the mean GLI, SD GLI values were 39.24 and 73.67 times higher in people with mortality these differences were statistically not significant. The differences in the mean values of mean blood glucose and SDBG were very negligible between the subjects with and without mortality. The evidence relating the impact of GV exclusively on critical ill neurological patients has been sparse. Many of the studies, which have assessed such relation, have done by linking hypo/or hyperglycemia or intensive insulin therapy (IIT) with mortality among neurological patients. In the prospectively collected database about the management of subarachnoid hemorrhage Lattore, et al. [12], concluded that aggressive hyperglycemia management results in good glucose control and reduced risk of adverse outcomes. IIT seem to have no effect in improving the mortality, neurological outcome or infections among a small group of head trauma patients as it induced hypoglycemia [13], but among patients with a cardiovascular event or neurological surgery, it resulted in reduced intracranial pressure, epileptic episodes, critical illness polyneuropathy and diabetes insipidus [9].

Schlenk in their longitudinal micro dialysis study [14] of SAH patients, reported hyperglycemia being associated with increased lactate/pyruvate ratios and the resultant higher mortality. One of the limitations of our study may be a smaller sample, which could explain the non-significant association between GV and mortality.

Conclusion

The study findings reveal that though, APACHE II scores seem to positively associated with mortality among critically ill neurological patients, the glycemic variability though positively influenced the mortality, it is not significant. Further studies assessing the role of GV specifically among such patient groups with

a larger sample might reveal the true influence of such interaction.

Limitations

- Multivariate analysis to assess the variables, which can strongly predict the mortality could not be done due to low effective sample size
- Lack of statistical significance can be attributed to the lower sample size, as no prior sample size calculation was done in the study basing on expected magnitude of the estimate

Acknowledgement

We sincerely acknowledge the support given by our staff of critical care unit in NRI Medical College, Mangalagiri, Chinakakani, Guntur, Andhra Pradesh.

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