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STUDY OF STRESS HYPERGLYCEMIA AS A PREDICTOR OF OUTCOME IN CRITICALLY ILL PATIENTS WITH SEPSIS

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ABSTRACT

Background: In hospital hyperglycemia (Stress Hyperglycemia) is defined as any glucose value >7.8 mmol/l (140 mg/dl. Hyperglycemia is a common finding in patients with severe sepsis and is related with higher mortality rates. We aimed to evaluate the effects of SH in critically ill patients with sepsis.

Methods: In this observational study, non-diabetic critically ill patients with sepsis admitted to our facility over a 1-year period were included.

Results: Out of 62 patients (n=62) who met the inclusion criteria 31 patients (n=31) were found to have stress hyperglycemia and 31 patients (n=31) were non-stress hyperglycemic. There were no statistically significant difference in Mean duration of complaints, Hemodynamic variables, Laboratory parameters, Requirement of mechanical ventilation, Hypoglycemic episodes, Hemodialysis; Blood/urine infections between the two groups. Rate of insulin requirement was significantly higher in patients of stress hyperglycemia as compared to without hyperglycemia. SOFA score and procalcitonin levels of patients of both the groups were found to be comparable. Proportion of patients without hyperglycemia was higher as compared to those with stress hyperglycemia among discharged (64.52% vs. 61.29%) and vice-versa among expired patients (29.03% vs. 38.71%). Difference in outcome of patients of both the groups was not found to be statistically significant.

Conclusion: On the basis of the study it was concluded that clinical and laboratory characteristics of patients with sepsis and stress hyperglycemia do not differ substantially from those patients of sepsis who do not have stress hyperglycemia.

KEYWORDS :

1. INTRODUCTION

Sepsis is a condition in which the body is challenged by foreign microbial agents and body's homeostatic mechanisms come into play that attempt to rid the body of the foreign agent without damaging the host (1). Sepsis continues to cause significant morbidity and mortality despite advances in supportive treatments (2). The main pathophysiological feature of sepsis is the uncontrollable activation of both pro- and anti-inflammatory responses arising from the overwhelming production of mediators such as pro- and anti-inflammatory cytokines. Such an uncontrollable inflammatory response would cause many kinds of metabolic derangements. One such metabolic derangement is hyperglycemia (3) and could be a predictor of outcome (4).

Claude Bernard in the late nineteenth century was one of the first who recognized that acute injury was associated with the development of hyperglycemia. When faced by external aggression, such as shock, sepsis, burns or surgery, the body develops a response, known as stress, comprising hyper metabolism and hyper catabolism (5). Critically ill patients (including those with severe sepsis) who have been previously euglycemic tend to have hyperglycemia and insulin resistance. Even a modest degree of hyperglycemia occurring after ICU admission is associated with a substantial increase in hospital mortality and blood glucose values serve as independent predictors of mortality (5).

Hyperglycemia is a common finding in patients with severe sepsis. It is related with higher mortality rates, especially when it is the result of sepsis-induced state of stress rather than a result of preexisting diabetes mellitus. The American Diabetes Association and American Association of Clinical Endocrinologists consensus on in-patient hyperglycemia defined stress hyperglycemia or hospital related hyperglycemia as any blood glucose concentration >7.8mmol/l (140 mg/dL) without evidence of previous diabetes (6). Stress hyperglycemia is almost a universal finding in patients with sepsis and multiple pathogenic mechanisms are responsible for this syndrome.

Hyperglycemia in critical illness, such as severe sepsis, is not only a marker of severity of illness and the predictor of poor outcome but also has many kinds of adverse effects on vital organs. Recently it has also been reported that the variability of the glucose level in blood is independently associated with hospital mortality in septic patients (7) and that severity of sepsis has a strong effect on glycemic variability in blood (8) and risk of hypoglycemia too (9). The purpose of the present study is to study the clinical and laboratory characteristics of patient suffering from sepsis with hyperglycemia and to investigate the effect of hyperglycemia on outcome.

2. MATERIALS AND METHODS:

It is a prospective observational study that was conducted in Department of Medicine, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun. A total of 75 critically ill, non-diabetic patients were recruited for the study purpose over a period of 1 year. Patients of sepsis were defined based on the criteria in the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock (10). Immunocompromised patients and patients with severe underlying comorbidities, like malignancies, connective tissue diseases, chronic renal failure, cirrhosis, immunosuppressive treatment, etc. were excluded from the study.

Demographic data, history, clinical examination and details of investigations were recorded. Variables included were age, Pao2, PaCo2, pH, heart rate, Blood Pressure, Temperature and organs failed during the first 24 hours of admission. Alterations in mental status were evaluated through the Glasgow Coma Score, whereas severity of sepsis was classified by the sepsis-related organ failure assessment score (SOFA). On admission random blood sugar was determined as early as possible and patients of Sepsis were stratified as either having Stress Hyperglycemia and those without Stress hyperglycemia. HbA1C levels determined on admission were used to rule out patients with pre-diabetes and Diabetes. Stress hyperglycemia was defined according to the American Diabetes Association and American Association of Clinical Endocrinologists consensus on inpatient hyperglycemia as any random blood glucose concentration > 7.8 mmol/ L (140mg/dl).

Of the total 75, critically ill non-diabetic patients recruited for the study, over the period of 1 year, 13 patients were excluded because they met the exclusion criteria. The remaining patients were stratified as either having stress hyperglycemia (SH, n=31) and those without stress hyperglycemia (NSIH, n=31).

2.1 Data Management and Statistical Analysis:

Data was analyzed by using statistical software SPSS 22. Qualitative variables were represented in form of frequency and percentage. Quantitative data was represented in form of mean±standard deviation. Data was analyzed using Independent Samples 't'-test, and

Chi-square test. A 'p' value less than 0.05 was considered to indicate a statistically significant association.

3. RESULTS:

Of the total 75, critically ill non-diabetic patients recruited for the study, over the period of 1 year, 13 patients were excluded because they met the exclusion criteria. The remaining patients were stratified as either having stress hyperglycemia (Group I, n=31) and those without stress hyperglycemia (Group II, n=31). Age of patients included in the study ranged from 18 to 87 years.Difference in age of patients of Group I and Group II was not found to be statistically significant (p=0.926). Though proportion of males was higher in Group I (48.39%) as compared to Group II (45.16%). Difference in gender of patients in both the groups was not found to be statistically significant (p=0.799).

Duration of ICU stay of overall as well as of patients of Group I and Group II ranged between 1 & 30 days. Median duration of patients of Group I was 7 days while that of Group II was 5 days. Difference in mean duration of complaints among patients of Group I (8.65±6.30 days) and Group II (7.74±6.78 days) was not found to be statistically significant. Difference in hemodynamic variables (Pulse rate, SBP, DBP, MAP, RR) and body temperature of patients of both the groups was not found to be statistically significant.

Laboratory findings of patients of both the groups were found to be similar except raised TLC (23.13±11.17 vs. 16.96±9.77), low lymphocyte levels (8.29±7.17 vs. 14.26±12.92) and higher pO2 (104.42±34.44 vs. 84.87±31.24) among patients with stress hyperglycemia (Group I) as compared to non-hyperglycemic patients (Group II). Though mechanical ventilation was required in higher proportion of patients of Group II (51.61%) as compared to Group I (41.94%) but differences in requirement of mechanical ventilation among patients of Group I and Group II was not found to be statistically significant (p=0.445) (TABLE 1)

Insulin was required by only 4 patients, all belonging to Group I. Proportion of patients requiring insulin was higher in Group I (12.90%) as compared to Group II (0.00%) and this difference was found to be statistically significant (p=0.039). Difference in proportion of Group I (25.81%) and Group II (22.58%) patients who faced hypoglycemic episode was not found to be statistically significant (p=0.767). Difference in proportion of Group I (35.48%) and Group II (29.03%) patients requiring hemodialysis was not found to be statistically significant (p=0.587). Inotropic intervention was required in higher proportion of patients of Group II (70.97%) as compared to Group I (67.74%) but this difference was not found to be statistically significant (p=0.783)(TABLE 2)

Table 1: Between Group Comparison of Hematological and Biochemical Variables

	Group I (n=31)		Group II (n=31)		Statistical significance	
	Mean	SD	Mean	SD	't'	'p'
Hemoglobin	11.03	1.98	10.51	1.87	1.052	0.297
TLC	23.13	11.17	16.96	9.77	2.316	*0.024
Platelet Count	118.48	96.89	108.03	103.78	0.410	0.683
Neutrophil	86.23	10.20	80.58	13.97	1.817	0.074
Lymphocytes	8.29	7.17	14.26	12.92	-2.249	*0.028
Monocytes	4.61	3.59	4.35	2.14	0.344	0.732
Eosinophil's	0.52	1.09	0.71	1.53	-0.573	0.569
Basophils	0.00	0.00	0.06	0.25	-1.438	0.156
S.creat	3.21	2.36	3.13	2.00	0.155	0.877
Sodium	139.18	6.35	137.77	8.60	0.734	0.466
Potassium	4.14	1.06	4.29	1.05	-0.531	0.597
T.Bil	3.60	4.68	2.76	2.11	0.912	0.366
D.Bil	1.86	2.41	1.62	1.59	0.458	0.649
I.Bil	1.74	2.80	1.08	0.66	1.279	0.206
ALT	640.71	1976.16	324.16	950.18	0.804	0.425
AST	533.19	1323.09	794.06	3001.34	-0.443	0.659
Serum Albumin	2.23	0.65	2.30	0.56	-0.454	0.652
pH	7.29	0.13	7.29	0.14	-0.140	0.889
pCO2	34.43	11.77	36.81	17.70	-0.623	0.535
pO2	104.42	34.44	84.87	31.24	2.341	*0.023
FiO2	56.84	27.41	46.55	22.03	1.630	0.108
PaO2/Fio2	232.74	103.84	256.41	98.24	-0.922	0.360

* $p < 0.05$

Table 2: Between Group Comparison of Clinical Findings

	Total (N=62)	Group I (n=31)		Group II (n=31)		Statistical significance	
		No.	%	No.	%	x^2	'p'
Mechanical ventilation	29	13	41.94	16	51.61	0.583	0.445
Insulin requirement	4	4	12.90	0	0.00	4.276	0.039
Hypoglycemic episode	15	8	25.81	7	22.58	0.088	0.767
Hemodialysed	20	11	35.48	9	29.03	0.295	0.587
Inotrope intervention	43	21	67.74	22	70.97	0.076	0.783
Blood/Urine Infection*	28	14	48.28	14	46.67	0.015	0.902

***(N=59; Group I n=29 and Group II n=30)**

SOFA score of patients of Group II (12.90±3.29) was found to be higher than that of Group I (12.71±3.88) but this difference was not found to be statistically significant (p=0.833). Procalcitonin levels of patients of Group I (41.06±69.60 units) was found to be higher than that of Group II (20.02±27.33 units) but difference in mean Procalcitonin levels of patients of above two groups was not found to be statistically significant (TABLE 3)

Table 3: Between Group Comparison of Level of Sepsis

	Group I			Group II			Statistical significance	
	n	Mean	SD	n	Mean	SD	't'	'p'
SOFA score	31	12.71	3.88	31	12.90	3.29	0.212	0.833
Procalcitonin	17	41.06	69.60	29	20.02	27.33	1.456	0.152

Proportion of patients of Group II was higher as compared to Group I with outcome Discharged (64.52% vs. 61.29%) and DOPR (6.45% vs. 0.00%). Expiry was higher in Group I (38.71%) as compared to Group II (29.03%). Difference in outcome of patients of both the groups was comparable (p=0.293; non-significant) (TABLE 4).

Table 4: Between Group Comparison of Outcome of Study Population

Outcome	Group I (n=31)		Group II (n=31)		Total (N=62)	
	No.	%	No.	%	No.	%
Discharged	19	61.29	20	64.52	39	62.90
DOPR	0	0.00	2	6.45	2	3.23
Expired	12	38.71	9	29.03	21	33.87
x^2=2.454 (df=2); p=0.293						

DISCUSSION:

The present study was carried out with an aim to study the association between stress hyperglycemia & outcome in critically ill patients with sepsis and to differentiate the clinical and laboratory characteristics of those critically ill patients with sepsis having stress hyperglycemia and those not having stress hyperglycemia. In present study, age of patients ranged from 18 to 87 years with a mean age of 45.89 years. Though mean age of SIH patients was higher (47.55 years) as compared to that of NSIH patients (44.23 years) yet this difference was not significant statistically. As far as gender of patients was concerned, although majority of patients in both the groups were males yet proportion of females was relatively lower in SIH group (51.61%) as compared to non-SIH group (54.84%) but this difference was not significant statistically.

In Indian (11,Present study) studies the mean age of critically ill patients with sepsis is relatively much lower than the age of patients in Western studies. One of the reasons for this could be difference in life expectancy. It can be seen that the mean age of patients is maximum in the study from Japan (12), which might be attributed to the high life expectancy in Japan. The gender profile of patients in present study differs from all the studies reported above. In present study, females dominated over the males. However, in other series majority of patients were females. Closest to our series, Leonidou *et al.* (13) in their study reported the proportion of males to be 49.2% and Godinjak *et al*. (14) reported the proportion of males in their series to be 55%. One of the reasons for higher proportion of females in present study could be referral from obstetrics and gynecology department of our

facility where a number of cases of post-partum sepsis contributed to the total load of patients in present series, and thus contributed towards a skewed gender picture as compared to other studies. However, notwithstanding the age and sex differences in different case series, the present study found no impact of age and sex on stress hyperglycemia occurrence. Similar to findings of present study, none of the studies have reported any impact of age and gender on stress hyperglycemia occurrence.

In present study, duration of ICU stay ranged from 1 to 30 days with a mean of 8.19±6.51 days (Median 7 days). Statistically, no significant association between duration of ICU stay and stress hyperglycemia was seen in present study. However, Sharma *et al.* (11) in their study found the duration of ICU stay to be significantly longer in patients with stress hyperglycemia as compared to those who did not develop stress hyperglycemia. Although, in present study, the mean duration of ICU stay was slightly longer in SIH group as compared to NSIH group yet the difference was not significant statistically. One of the reasons for this could be less number of cases in each group. However, Ali *et al.* (7) in their study showed that increased glucose levels in patients with sepsis prolong the duration of ICU stay. However, Leonidou *et al.* (13), similar to our study did not see any influence of stress hyperglycemia on the duration of hospital stay in their study despite finding the mean duration of hospital stay to be slightly longer in SIH group (7.7±6.2 days) as compared to non-SIH group (5.6±3.8 days). As such some of the researchers are of the view that stress hyperglycemia in critically ill patients with sepsis may not be harmful at all (15). Godinjak *et al.* (14) in their study also did not find a significant difference in ICU stay of patients with or without stress hyperglycemia. From the point of view of duration of ICU stay, in present study we also conclude that stress hyperglycemia in critically ill sepsis patients did not prolong the duration of ICU stay significantly.

The present study did not show a significant difference in hemodynamics and vitals (Pulse rate, SBP, DBP, MAP, Respiratory rate, and body temperature) of patients in SIH and NSIH groups. Thus showing that stress hyperglycemia did not influence the hemodynamic parameters of the patients either. Similar to findings of present study Tiruvoipati *et al.* (15) also did not find a significant difference in hemodynamic parameters (Pulse rate, SBP, DBP, MAP, Temperature, Respiratory rate).On hematological and biochemical assessment too, we did not find a significant difference between two groups for any of the parameters except mean TLC count, which was significantly in SIH as compared to non SIH group. Mean lymphocyte count was lower in SIH cases as compared to non-SIH cases. These findings are similar to the findings of Tiruvoipati *et al.* (15) who also found no significant difference between two groups for any of the hematological and biochemical parameters except TLC count. The lowered TLC count in both the studies could be indicative of a stress hyperglycemia induced protective response against inflammatory activity. It seems that with the rapid stress release of glucose levels, the protective mechanism of the body seems to balance against the inflammatory stresses. Glucose is largely utilized by tissues that are non-insulin dependent, and these include the central and peripheral nervous system, bone marrow, white and red blood cells and the reticulo endothelial system (16).

In present study, no significant difference between two groups was observed with respect to outcomes like need for mechanical ventilation, hypoglycaemic episodes, hemodialysis, ionotropic intervention and blood/ urine infection. The only difference between two groups was in the need for insulin which was significantly higher in SIH group as compared to NSIH group. Tiruvoipati *et al.* (15) in their study also did not find a significant difference between two groups with respect to requirement of mechanical ventilation and inotropes. As far as insulin need is concerned, it is indicated only for the group having hyperglycemia and this difference could be set aside as a protocol difference instead of an outcome difference. Godinjak *et al.* (14) too in their study did not find a significant impact of stress hyperglycemia on the mechanical ventilation need, however, in their study they reported vasopressor need to be more than three times in SIH group (68.4%) as compared to NSIH group (21.2%). Similar to present study, no significant difference in bacteremia episodes was observed between hyperglycemic and normoglycemic group was observed by Leonidou *et al.* (13). In effect all these studies show that stress hyperglycemia has a very limited role in critically ill patients with sepsis.

In present study, no significant difference in disease severity as measured by SOFA severity and inflammatory activity as measured by procalcitonin levels could be seen. Similar to present study, Tiruvoipati *et al.* (15) also failed to see a significant difference in severity of disease as measured by APACHE III and SAPS 2 scores in their study as well as for inflammatory marker as measured by C-reactive protein levels. In another study, Waeschle *et al.* (17) too did not find a significant difference in blood glucose levels of patients with different severity of sepsis thus indicating that the severity levels of Sepsis were independent of glycemic status of patients.

In present study, although in hospital mortality rate was slightly higher in SIH group as compared to NSIH group yet the difference between two groups was not significant statistically. Contrary to this Tiruvoipati *et al.* (15) in their study reported mortality rates to be significantly lower in SIH as compared to non-SIH group. However, Godinjak *et al.* (14) found mortality rates to be significantly higher in SIH as compared to non-SIH groups, thus showing that SIH was significantly associated with higher risk of mortality. Thus, there was variable evidence regarding the risk of mortality owing to stress hyperglycemia in different study populations. The findings of present study thus showed that stress hyperglycemia in critically ill sepsis patients is an interesting phenomenon and unlike traditionally conceived as a marker of deteriorating health condition, in sepsis cases it is an essential survival response (18) .The findings of present study thus endorse the unique behavior of stress hyperglycemia in critically ill sepsis patients and indicated that stress hyperglycemia alone should not be considered as a risk factor for adverse outcomes in sepsis patients and focus should be kept on other factors such as severity of disease and other patient characteristics. Further studies to substantiate the findings of present study are recommended in a larger sample size.

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