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Blood Glucose Levels and Outcome in Traumatic Brain Injury: An Observational Study

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Abstract: ***Background: Traumatic brain injury (TBI) has been associated with an acute stress response mediated by the sympathoadrenomedullary axis, which can be assessed by measuring blood glucose level. Blood glucose can serve as a predictor of outcome in TBI. Material and methods: This prospective observational study was conducted between 1 june 2014 and 31 dec 2014.223 patients admitted for TBI in Neurosurgery department, of IMS,BHU were enrolled. Detailed history and data including blood glucose level and Glasgow Outcome Score at 3-month follow-up were taken and analysed. Results: 223 patients were enrolled in the study but 4 died in the first 24 hrs and 3 were lost to follow up ,hence were excluded.216 were included in study : 62 females and 154 males. The majority of cases were young adult patients (mean age of 36.02 ± 16.08 yrs). The mean glucose levels at admission in cases of mild TBI was 70.5± 9.08 and 24 hrs after injury it was 82.94± 18.3.In cases of moderate TBI the mean glucose values were 79.93± 9.18 and 93.72± 10.44 respectively.Severe TBI showed glucose at admission 105.67± 23.81 and higher 24 hrs later, 128.02± 23.99.Higher mean glucose level at admission and 24 hrs after injury was associated with a poor outcome in these patients with isolated TBI.Conclusion: Mild, moderate, and severe TBI were associated with an increase in blood glucose levels during admission, and the mean increase in glucose levels wass based on the severity of the isolated TBI. Surgical intervention did not cause further significant changes in blood glucose levels. Patients with isolated TBI and minimal increases in blood glucose levels were more likely to have a favourable outcome.***

Keywords: traumatic brain injury, head injury, Glasgow Outcome Scale, trauma, prognostic/predictive factor, blood glucose, blood markers, biomarkers

1. Introduction

Traumatic brain injury occurs when an external force mechanically injures the brain.[1] Injury to the brain in TBI is of two types.Primary brain injury is the physical damage to the brain parenchyma that occurs during traumatic event, causing shearing and compression of the surrounding brain tissue. This initiates a complex pathophysiological cascade of cellular events following primary brain injury in the following hours and day.Numerous secondary brain insults- intracranial and extracranial/ systemic occur which result in secondary brain injury. This is mainly ischemic in nature.[2]The main components of this response are increase in cerebral glucose uptake, reductions in cerebral blood flow, indiscriminate excitatory neurotransmitter release, ionic disequilibrium and intracellular calcium accumulation[3].Hyperglycemia aggravates underlying brain damage.By inducing tissue acidosis, oxidative stress, and cellular immunosuppression it leading to multiorgan failure in critically ill patients[4] Changes in blood parameters and biomarkers occur which may provide prognostic information beyond the clinical examination, patient demographics and radiology.These can help in early prediction of outcome of patients with moderate and severe traumatic brain injury. Elevated serum glucose levels after TBI have been considered to be associated with poor neurological outcomes , especially in patients in whom blood glucose levels are >200 mg/dL (11.0 mmol/L). Higher blood glucose levels,>300 mg/dL (16.6 mmol/L), are almost always associated with 100% mortality in paediatric TBI .One study found that persistent hyperglycemia, defined as average daily blood glucose levels >149 mg/dl for the first week after injury, was associated with a five-fold increase in mortality in a cohort of 834 patients with severe TBI [5,6] Different studies show association of hyperglycemia and increased morbidity or mortality. But still the results are not well established.

2. Literature Survey

Studies show increased blood glucose levels is related with poor neurological outcome in traumatic brain injury patients.Also blood glucose levels rise is parallel to the degree of severity of injury.

Aims:

The present study was done with following aims:-

1) To measure random blood glucose levels in TBI patients at admission.
2) To measure random blood glucose levels in TBI patients after 24 hours of injury.
3) To determine the differences between the two and find correlation of blood sugar levels with severity of injury and outcome.

4) T o determine their outcome 3 months after head injury by Glasgow Outcome Scale.

3. Material and Methods

This was an prospective observational study conducted between 1 june 2014 and dec 2014. 223 patients admitted for TBI in the neurosurgery department of IMS,BHU were enrolled in the study but 4 died in the first 24 hrs and 3 were lost to follow up ,hence were excluded.216 were included in study Patients consent and detailed clinical history was taken using a questionnaire. Patients with isolated non-penetrating TB, adults with age between 18 and 65 yrs,brain injury due to mechanical force (trauma) only were included in the study.Patients with penetrating brain injury,brain injury due to causes other than trauma like ischemia, hypertension, infection, brain injury with associated extracranial injuries or systemic diseases, history of diabetes mellitus or on long-term steroid therapy were excluded. Based on the GCS, TBI was divided into three groups - mild TBI with GCS 14-15,moderate TBI with GCS between 9 and 13 and severe TBI with GCS 5 to 8. Blood samples were taken at admission and 24 hours later and blood glucose measured.Glasgow Outcome Score (GOS)was determined at 3-month follow-up. Glucose was measured by glucose oxidase peroxidase method using reagent kits in an autoanalyzer (Randox-2)

4. Results and Observation

223 patients were enrolled in the study but 4 died in the first 24 hrs and 3 were lost to follow up ,hence were excluded.216 were included in study. In the present study the patients belonged to age group 18-65 years.The results and observations are as follows:

Table 1: Demographic and clinical data based on severity of TBI

Type of TBI	*Mild*	*Moderate*	*Severe*
No.of cases	36 (16.7%)	62 (28.7%)	118 (54.6%)
Sex ratio	3.5:1	1.8:1	2.7:1
Age in mean ± SD yrs	36.02 ± 16.08	31.03 ± 18.44	28.18 ± 13.90
GCS in mean ± SD score	14.39 ± 0.49	10.16 ± 1.33	6.01± 1.07

The mean age in the present study was 36.02 .±16.08 yrs in patient with mild TBI, 31.03± 18.44 yr in moderate TBI and 28.18 ±13.9 yrs in severe TBI .Most of the patients were young males in age group 20 to 40 yrs. In this study there were 154 (71.3%) males and 62 (28.7%) females. Most of the patients in the study had severe TBI seen in 118 patients(54.6%). There were 154 total males and 62 total females.Males to female ratio was 2.5:1. Mean GCS in patients with mild TBI was 14.39 ± 0.49,in moderate TBI 10.16 ± 1.33 and in severe cases of TBI 6.01± 1.07.

Table 2: Mode of injury

Mode of injury	*No.of patients*	*Percentage*
RTA	153	70.8
Fall	49	22.6
Assaults	14	6.6

Causes of TBI in this study were - road traffic accidents (RT) in 153 patients (70.8%),fall in 49 patients (22.6%) and assault in14 (6.6%) cases . RTA ,was the most common cause of head injury in this study.

Table 3: CT findings of patients based on severity of TBI

Type of TBI	*Mild*	*Moderate*	*Severe*	*Total patients*
CT Findings				
Brain contusion	12	24	39	75 (34.7%)
Extradural haematoma	19	12	28	59 (27.3%)
Subdural haematoma	5	16	32	53 (24.5%)
Subarachnoid haemorrhage	0	6	10	16 (7.4%)
Diffuse Axonal injury	0	4	9	13 (6.1%)
Total patients	36	62	118	216

In CT scan the most common finding was contusion seen in 75 patients (34.7%).This was followed by extradural haematoma in 59 patients (27.3%),subdural haematoma in 53 patients (24.5%) and subarachnoid haemorrhage in 16 patients (7.4%).Diffuse axonal injury was present in 13 (6.1%) cases.No correlation was seen between different CT findings and blood glucose levels.

Table 4: Comparison of blood glucose levels of patients

Type of TBI	**Mild**	**Moderate**	**Severe**
Glucose level in mean ± SD mg/dl			
At admission	70.5± 9.08	79.93± 9.18	105.67± 23.81
24 hrs after after injury	82.94± 18.38	93.72± 10.44	128.02± 23.99

The mean glucose levels at admission in cases of mild TBI was 70.5± 9.08 mg/dl and 24 hrs after injury it was 82.94± 18.3 mg/dl. In cases of moderate TBI the mean glucose values were 79.93± 9.18 mg/dl and 93.72± 10.44 mg/dl respectively.Severe TBI showed glucose at admission 105.67± 23.81 mg/dl and higher 24 hrs later, 128.02± 23.99mg/dl.

Table 5: Blood glucose levels of patients and their outcome by GOS

GOS	**No of patients**	**Glucose levels (mg/dl)**	
		At Admission	**At 24 hrs after injury**
5 Dead	42(19.4%)	121.10± 16.08)	147.74± 18.82
4 Persistent vegetative state	24(11.1%)	113.20± 9.36)	134.12± 15.34
3 Severe disability	22(10.1%)	106.22± 11.46	128.04± 9.57
2 Moderate disability	28(13.0%)	84.03± 11.48	103.71± 9.37
1 Good recovery	100(46.4%)	74.08± 8.99	89.53± 11.65

In the study it was seen that patients with severe TBI had significantly higher mean blood glucose values both at admission and at 24 hr after injury. Persistent hyperglycemia at 24 hrs showed poor outcome - dead and vegetative state. Good recovery and moderate disability was seen in patients in whom the difference in blood glucose levels at admission and 24 hrs post surgery was <20 mg/dl.

Table 6: Outcome based on severity of TBI

Type of Injury	Mild	Moderate	Severe	Total patients
Outcome				
Favorable	36	62	30	128(59.2%)
unfavourable	0	0	88	88(40.7%)
Total	36(16.7%)	62(28.6%)	118(54.7%).	216

Overall out of 216 patients,128 patients,(59.2%) had a favorable outcome, while 88 patients (40.7%) showed an unfavourable outcome, all of which belonged to category of severe TBI with raised bood glucose levels.

5. Discussion

In the present study most of the patients were young adults in the age group of 20- 40 yrs. The mean age in the present study was 36.02 .±16.08 yrs in patient with mild TBI,31.03± 18.44 yr in moderate TBI and 28.18 ±13.9 yrs in severe TBI. The most common mode of injury was RTA (70.8 %) which accounts for most head injuries in India,followed by fall(22.6%) and assaults . Another Indian study by Saxena et al [7] revealed road traffic injuries as the leading cause (60%) of TBIs, followed by falls (20%-25%), and violence(10%). In study by Haron et al [8] which included 294 patients ,the mean age of the study sample was 34.2 y ±13.0 yrs and about 75% of the study participants were 43 years of age or younger. Of the 294 cases included in the study, 50 patients (17.0%) were females and 244 (83.0%) were males.They reported severe head injury was associated with more than 1 mmol/L elevation in blood sugar in comparison to both mild and moderate head injury. However, the difference in mean blood sugar level between mild and moderate was not more than 1.0 mmol/L As seen in other studies ,we found males to be more commonly involved in traumatic brain injuries than females.The blood glucose levels were significantly higher in patients with severe TBI compared to those with mild and moderate TBI even at admission. Salehpoor et al [9] found that on review of 22 studies which investigated blood glucose levels as a prognostic factor all except three studies, reported that high levels of blood sugar is associated with poor prognosis. Studies done in children with traumatic brain injury achieved significant correlation between blood sugar levels and patient prognosis.All of the studies on adults with traumatic brain injury and studies without a age limit reported a significant relationship between blood glucose levels and prognosis achieved except two studies . The evidence for the prognostic value of blood sugar levels was strong ,both in adults and in children with traumatic brain injury. Comparing the values of blood glucose at admission and 24 hours later >20 mg/dl difference was seen in severe TBI cases whereas, 20mg/dl difference was seen in mild to moderate TBI cases.. Takanashi et al. [10] looked retrospectively at the clinical course of patients with head injury, which have been grouped into various categories on admission. Patients with severe head injury had higher serum glucose levels, at 11.1 mmol/L compared with patients with moderate head injury, at 9.5 mmol/L. Walia et al[11] suggested that hyperglycaemia is more strongly predictive of the outcome of 338 patients with head injury as compared with mean arterial blood pressures. When both factors were included in a regression analysis, each factor was independently associated with mortality; however, there was a stronger relationship between blood glucose and mortality than between mean arterial blood pressure and mortality. The mechanisms of how glucose worsens the ischemic threshold in neurons after injury are not well understood. In neuron cultures exposed to ischemic conditions, post-ischemic superoxide production and cell death are prevented by removing glucose from the medium These studies suggest that glucose is a requisite electron donor for reperfusion-induced neuronal superoxide production.[12] It is also reported that presentation of the ischemic brain with high levels of glucose would drive anaerobic glycolysis, resulting in the accumulation of toxic levels of lactic acid.[13]Thus the neuronal damage that occurs after TBI due to oxidative stress, hypoxia induced apoptosis and neuro inflammation are potentiated by the neurotoxic effects of glucose. There are several evidences to support that, at high concentrations glucose exhibits pro-apoptotic and pro-oxidant properties. Studies have reported that when endothelial cells were incubated with high concentrations of glucose, changes were observed in proliferative, adhesive and synthetic properties. Induction of apoptosis of functional endothelial cells at high glucose concentration in culture has been established. Lorenzi et al states that high glucose interferes with the regulation of cell cycle and brings about programmed cell death.[14] This explains the worse prognosis of TBI patients having hyperglycemia Mortality following head injury has been reported to be in the range of 39-51%.[15]

6. Conclusions

This study demonstrated a significant difference in blood glucose levels among patients with isolated TBI. Severe TBI caused a significant rise in blood glucose levels during admission, and the mean glucose level increased according to the severity of the isolated TBI. Higher blood glucose levels upon admission after isolated TBI were associated with poorer outcomes for patients. Blood glucose level is an important independent predictor of outcome.

7. Future Scope

Further studies are required to establish cleat cut of values for favourable and unfavourable outcomes of blood glucose levels in TBI and more objective results.Other biomarkers are to be investigated.

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