

Significance of Random blood sugar in traumatic brain injury.

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Abstract

Traumatic brain injury(TBI) occurs when an external force traumatically injures the brain. TBI is a leading cause of death and disability. A complex pathophysiological cascade of cellular events is involved in it. Experimental models have shown that TBI results in a significant increase in glucose utilization following injury. Hyperglycemia aggravates underlying brain damage by causing free radical injury, apoptosis and lactic acidosis. The aim of our study is to estimate the random blood sugar levels in TBI patients within 24 hours of injury and to find its correlation with the level of consciousness (Glasgow coma scale) if any. The study involves 30 TBI patients who were admitted to P.I.M.S hospital within 24 hours of injury (group I) and 30 healthy age and sex matched controls (group II). Random blood glucose was estimated in both the groups and Glasgow coma scale was noted in group I. Data was analyzed by unpaired t test. Pearson's Correlation coefficient was measured between RBS and GCS. TBI patients had blood sugar 189.93 ± 51.74 mg/dl and controls had 106.47 ± 18.32 mg/dl. The random blood sugar was elevated significantly ($P < 0.0001$) in Gp I compared to Gp II. GCS was bearing a negative correlation with the blood sugar ($r = -0.7043$). From the elevated blood glucose levels and its negative correlation with Glasgow coma scale we conclude that strict blood glucose regulation is essential in TBI patients for the better outcome after head injury.

Keywords. Traumatic brain injury, hyperglycemia, apoptosis, acidosis

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Introduction

Traumatic brain injury(TBI) occurs when an external force traumatically injures the brain. TBI can be classified based on severity, mechanism (closed or penetrating head injury), or other features (e.g., occurring in a specific location or over a widespread area). Head injury usually refers to TBI, but is a broader category because it can involve damage to structures other than the brain, such as the scalp and skull. TBI is a leading cause of death and disability.

Although the head, face and neck comprise only 12% of the total body surface area exposed during an accident, these areas sustain disproportionately more injuries leading to death at the time of a crash [1]. Males are more at risk than females. The increased frequency of head injuries observed in men is consistent with the existing literature with a male to female ratio 6.1:1 [2].

Brain trauma can be caused by a direct impact or by acceleration alone. In addition to the damage caused at the

moment of injury, brain trauma causes secondary injury, a variety of events that take place in the minutes and days following the injury. These processes, which include alterations in cerebral blood flow and the pressure within the skull, contribute substantially to the damage from the initial injury.

Traumatic brain injury induces a complex pathophysiological cascade of cellular events. Central components of this response include increase in cerebral glucose uptake, reductions in cerebral blood flow, indiscriminate excitatory neurotransmitter release, ionic disequilibrium and intracellular calcium accumulation.

Restoration of homeostasis requires significant increase in glucose metabolism. Experimental models have shown that TBI results in a significant increase of glucose utilization within the first 30 minutes post-injury, after which glucose uptake diminishes and then remains low for about 5-10 days [3,4]. The initial hyperglycolysis described above results from disruption of ionic gradients across the neuronal cell membrane, activating energy-dependent ionic pumps [5].

Hyperglycemia aggravates underlying brain damage and influences both morbidity and mortality in critically ill patients [6] by inducing tissue acidosis, oxidative stress, and cellular immunosuppression [7] which in turn promote the development of multiorgan failure [8]. Hypoglycemia impairs energy supply causing metabolic perturbation [9] and induces cortical spreading depolarizations [10].

Studies have mentioned that intensive glycemic control is essential following traumatic brain injury for a better clinical outcome, controversially the majority of currently available clinical and preclinical evidence does not support tight glucose control (maintenance of blood glucose levels below 110-120 mg/dl) during the acute care of patients with severe TBI [11].

The aim of our study is to (i) estimate the random blood sugar (RBS) levels in TBI patients within 24 hours of injury and to assess the level of consciousness by taking Glasgow coma scale (GCS) (ii) to find the correlation between RBS and GCS if any.

Methodology

The study was conducted in Pondicherry Institute of Medical Sciences (P.I.M.S), Pondicherry. Institutional ethical committee approval was obtained and informed consent was taken from the relatives or patients' by-standers.

Study design

Our study involves two groups, Gp I & Gp II. Gp I involves 30 TBI patients (all were male patients coincidentally) in the age group of 26 ± 7 years who were admitted to P.I.M.S hospital within 24 hours of sustaining injury. In Gp II, we selected 30 age and sex matched healthy controls. We ensured by history and a few basic investigations, that they were not suffering from any illnesses.

Table 1. Comparison of Random Blood Sugar: Traumatic brain injury patients Vs Healthy controls

	TBI patients	Controls	P value
Random blood sugar (mg/dl)	$189.93 \pm 51.74^{**}$	106.47 ± 18.32	< 0.0001
Correlation of RBS with GCS (r)	-0.7043^*	---	< 0.05

**p - Highly significant

*p - Significant

Discussion

Seventy eight percent elevation was observed in the random blood sugar values of TBI patients as compared to the controls. Specific metabolic events like glucose production, utilization are explained by the physiological state of accelerated metabolism which may be associated with insulin resistance [13]. Persistent elevation of serum glucose in the first week after injury was shown to be fatal as increased rate of mortality was reported [14].

Inclusion criteria for group I

Brain injury cases due to mechanical force (trauma) only.

Exclusion criteria

Brain injury due to other causes like ischemia, hypertension, infection. Brain injuries associated with other soft tissue/musculoskeletal injury, liver disorders, renal diseases, hyperuricemias.

Random blood Glucose was estimated immediately at admission, within 24 hours of injury by glucose oxidase peroxidase method [12] using reagent kits in an autoanalyzer (Cobas integra 400). The severity of brain injury was assessed clinically by Glasgow coma scale, blood pressure and CT findings.

Statistical Analysis

Data obtained was analysed by using graph pad statistical analysis software. Unpaired 't' test was used for comparing the values. $P < 0.05$ is considered to be significant. Pearson's correlation coefficient, r (between -1 and +1) is calculated to find the correlation of RBS with Glasgow coma scale.

Results

Random Blood Sugar (RBS) was 189.93 ± 51.74 mg/dl in patients and 106.47 ± 18.32 mg/dl in healthy controls (shown in table 1). Blood sugar is significantly elevated in TBI patients compared to controls ($P < 0.0001$). GCS of patients ranged from 3-14. Correlation study showed that Glasgow coma scale bears a strong negative correlation ($r = -0.7043$) with blood sugar which is statistically significant ($p < 0.05$). This implies that higher the Random Blood Sugar, worse is the patient's status of consciousness and vice versa.

Several mechanisms may be explained for the toxic effects of glucose. Hyperglycemia sets in neuronal death by releasing extracellular zinc and activation of neuronal NADPH oxidase [15]. Elevated serum glucose levels is considered deleterious as it results in anaerobic glycolysis leading to accumulation of lactic acid in toxic levels which lowers the neuronal threshold and brings about astrocyte cell death [16]. However lactate produced from astrocytes is shuttled to the neurons to facilitate energy

production at need [17]. Accumulation of lactate may cause neuronal damage as a result of acidosis, membrane damage, disruption of blood brain barrier and cerebral edema [18].

Van den Berghe et al have demonstrated that tightly controlled blood glucose levels with intensive insulin therapy improved outcome in intensive care patients and this may confer some benefit in head injured patients [19].

It has already been proved in TBI that in the primary phase, due to the localized neuronal death at the impact site, there is reduction in the cerebral blood flow and anaerobic glycolysis causing hypoxia and ischemia [20]. This effect could be potentiated by hyperglycemia induced anaerobic glycolysis. Ischemia will enhance the generation of reactive oxygen species (ROS) [21]. ROS has a major role in activating caspases and bringing about apoptosis [20,22]. Neuroinflammation is well established fact in TBI which results in excessive cell apoptosis and neuronal necrosis [23]. During cell death there is breakdown of DNA, RNA and excessive purine catabolism. This provides a large amount of substrate to the enzyme xanthine oxidase which produces superoxide radicals along with uric acid which itself has both prooxidant and antioxidant properties.

Thus the neuronal damage that occurs after TBI due to oxidative stress, hypoxia induced apoptosis and neuroinflammation 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 [24]. The exact mechanism is explained as retardation of cell cycle transition from S to G2 phase by glucose which takes the cell to death [25].

Another theory explains the progressive down regulation of Bcl-2 and increased expression of Bax during cultures causing apoptosis of cells [26]. This finding was supported by another experiment on renal proximal tubular cells, when cultured in high glucose concentrations decreased Bcl-2 expression [27]. Sharifi et al investigated whether glucose could induce apoptosis in neuronal cells and role of glucose in the expression of anti-apoptotic (Bcl-2) and pro-apoptotic (Bax) genes [28]. He also demonstrated the neuronal death by cleaved DNA fragments and increased ratio of Bax:Bcl-2. This fact is supported by a report, good glucose control at early stage of diabetes

mellitus can decrease the number of apoptotic cells in the retina because of down regulation of Bax:Bcl-2 ratio [29].

The likely mechanism of neurotoxicity of glucose can also be attributed to the elevated ROS, oxidative stress and nitrosative stress [30]. Now it is clearly evident that oxidative stress that is set in TBI due to hypoxia, ischemia, apoptosis, inflammation etc is further accentuated by hyperglycemia induced ROS, apoptosis and ultimately cell death.

This explains the worse prognosis of TBI patients having hyperglycemia. In our study we have noted the negative correlation between Glasgow coma scale and blood sugar, which implies that higher the sugar, poorer is the level of consciousness. Our finding is in accordance with the results of several studies. Deep coma was seen in patients with a high blood sugar and consciousness was regained with a decrease in blood sugar [31]. Brain lesions which affect the level of consciousness influence the fasting blood glucose. Pentelenyi et al reports a quantitative correlation between the alterations in the levels of consciousness and FBS in brain injury patients. Deep coma was associated with high blood sugar level and clear consciousness with normal glucose levels [32].

Conclusion

From the elevated blood glucose levels and its negative correlation with Glasgow coma scale we conclude that strict blood glucose regulation is essential for the better outcome after the traumatic brain injury, as hyperglycemia potentiates the damaging events, like neuroinflammation, apoptosis and oxidative stress.

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