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# Effects of Glycemic Level on Outcome of Patients with Traumatic Brain Injury: A Retrospective Cohort Study

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## ABSTRACT

**Objective:** To determine the effects of glycemic level on outcome patients with traumatic brain injury**.**
**Methods:** From September 2010 to December 2012, all medical records of adult patients with TBI admitted to the Emergency Room of Laura Daniela Clinic in Valledupar City, Colombia, South America were enrolled. Both genders between 18 and 85 years who referred during the first 48 hours after trauma, and their glucose level was determined in the first 24 hours of admission were included. Adults older than 85 years, with absence of Glasgow Coma Scale (GCS) score and a brain Computerized Tomography (CT) scans were excluded. The cut-off value was considered 200 mg/dL to define hyperglycemia. Final GCS, hospital admission duration and complications were compared between normoglycemic and hyperglycemic patients.
**Results:** Totally 217 patients were identified with TBI. Considering exclusion criteria, 89 patients remained for analysis. The mean age was 43.0±19.6 years, the mean time of remission was 5.9±9.4 hours, the mean GCS on admission was 10.5±3.6 and the mean blood glucose level in the first 24 hours was 138.1±59.4 mg/dL. Hyperglycemia was present in 13.5% of patients. The most common lesions presented by patients with TBI were fractures (22.5%), hematoma (18.3%), cerebral edema (18.3%) and cerebral contusion (16.2%). Most of patients without a high glucose level at admission were managed only medically, whereas surgical treatment was more frequent in patients with hyperglycemia ($p$=0.042). Hyperglycemia was associated with higher complication ($p$=0.019) and mortality rate ($p$=0.039). GCS was negatively associated with on admission glucose level (r=0.11; $p$=0.46).
**Conclusion:** Hyperglycemia in the first 24-hours of TBI is associated with higher rate of surgical intervention, higher complication and mortality rates. So hyperglycemia handling is critical to the outcome of patients with traumatic brain injury.

**Keywords:** Traumatic brain injury; Hyperglycemia; Polytrauma.

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## Introduction

Traumatic brain injury (TBI) is one of the leading causes of death in people under 40 years in industrialized countries and produces approximately one third of trauma deaths. The overall frequency of TBI in emergency services in Colombia reaches 70%, and its main causes were traffic accidents with 51.2%. According to the National Administrative Department of Statistics (DANE in Spanish) of all deaths in Colombia, trauma ranks first with 40.4% [1].

In the TBI, pathophysiological changes occur that can transcend in time, these changes can happen in two basic forms: primary and secondary injuries; The primary injury, refers to the damage caused by the impact mechanism, causing a skull fracture, vascular and parenchymal damages and concussion, with subsequent increase in brain bleeding and increased intracranial pressure. Secondary injury involves damage in brain tissue caused by different factors such as hypoxia, hypotension, hypoglycemia, hyperglycemia, anemia and others [2].

Although the primary injury is the determinant factor of the outcome of patients with TBI, secondary injury caused by physiological disturbances contributes to poor outcomes in these patients, hypotension and hypoxemia are the main factors associated with increased morbidity and mortality rates of TBI [3]. The primary injury is irreversible, but the events of secondary injury can be manageable, preventing neurological damage or death.

Hyperglycemia is a part of the metabolic response in patients with TBI, especially those with polytrauma. Presence of hyperglycemia is associated with septic complications and a significant high mortality independent of the mechanism of injury [4,5]. An increase in blood glucose level in acute traumatic events occurs as a response to stress and injury severity, even this increase can remain 72 hours after the event. The decrease in blood glucose after intracerebral hemorrhage are associated with reduced risk of expansion of the surrounding tissue edema, cell death and lower intraventricular compromise, which predict best results. An elevated blood glucose level is an independent predictor of early mortality and worse functional outcome in non-diabetic patients who have suffered a TBI [6]. The purpose of this study was to determine the relationship between the outcomes in patients with TBI and their blood glucose levels in Valledupar, Colombia, South America.

## Materials and Methods

### *Study Design and Data Collection*

This was retrospective cohort study which was carried out by analyzing medical records of adult patients with TBI admitted to the Emergency Room of Laura Daniela Clinic in Valledupar City, Colombia, South America, between September 2010 and December 2012. Data collected from medical records included age, sex, mechanism of trauma, classification of trauma such as isolated head trauma or polytrauma, Glasgow Coma Scale (GCS), blood glucose level on admission and brain Computerized Tomography (CT) scans. We included males and females between 18 and 85 years, who referred in 48 first hours after trauma, and their glucose level was measured in the 24 first hours of admission. Adults with and without a diabetic's previous diagnosis were also included. Exclusion criteria were absence of GCS score, absence of a brain CT scan or blood glucose level on the first 24 h of admission and arrival to the hospital after 48 hours post-trauma.

### *Study Protocol*

Severity of TBI was accessed by GCS score on admission. Mild TBI patients were defined as GCS between 13 and 15, moderate between 9 and 12 and severe from 3 to 8. Findings on the brain CT scan considered to be abnormal when any brain lesion was identified (fracture, hematoma, cerebral edema, intracranial hemorrhages, etc.). All the brain CT scans were performed in the same hospital and with the same model of tomography machine. The results were checked by experienced radiologists and neurosurgeons.

Blood glucose levels were determined by capillary blood glucose obtained through fingertips' puncture on the first 24 h of admission. The results were shown in digital blood glucose monitor. The same technique was used in every patient. Clinically significant hyperglycemia was defined as a serum glucose concentration ≥200 mg/dl. The outcome measures included final GCS, duration of the hospital admission, rate of surgical intervention, rate of ICU admission, complication rate and mortality rate. We compared the outcome measures between those who were normoglycemic and those who were hyperglycemic on admission.

### *Statistical Analysis*

The statistical analysis of the data was performed using SPSS software (Version 15.0, SPSS, inc., Chicago, IL, USA). SPSS can take data from almost any type of file and use them to generate tabulated, charts and plots of distributions and trends, descriptive statistics, and complex statistical analysis reports. The menu selections and dialog boxes allowed complex analyzes without typing a single line of command syntax. The Data Editor provided a simple and effective tool type design worksheet, which enabled entering data and browsing the working data file; Feature 1200-SPSS Statistics Base 15.0; Local license for version 15.0-Network Expiration: None. SPSS Statistics is a software package used for statistical analysis. Statistics included in the base software Descriptive statistics: cross tabulation, Frequencies, description, explore, descriptive ratio statistics, bivariate statistics: Means, t-test, ANOVA, Correlation (bivariate,

partial, distances), Nonparametric tests, and prediction for numerical outcomes: linear regression, prediction for identifying groups: Factor analysis, cluster analysis (two-step, K-means, hierarchical) and discriminant.

## Results

A total of 217 patients were identified with TBI. After application of exclusion criteria, 89 patients remained for analysis. Of these patients, 80.9% were males. The mean age was 43.0±19.6 years, the mean time of remission was 5.9±9.4 hours, the mean GCS on admission was 10.5±3.6 and the mean blood glucose level in the first 24 hours was 138.1±59.4 mg/dL. Hyperglycemia was detected in 13.5% of patients.

Regarding to the trauma severity, 41.6% had mild, 15.7% moderate and 42.7% severe TBI. Isolated head trauma was present in 56.2% and polytrauma in 43.8% of all patients. According to the causes of trauma, the most frequent ones were traffic accidents (85.4%) followed by assult trauma (5.6%), falling down (3.4%) and others (5.6%). "Others" included all the patients who were found in public road in which the cause of trauma was unknown (Table 1).

**Table 1.** Baseline characteristics of 89 patients with traumatic brain injury included in the study.

| Variables | Value (n=89) |
|---|---|
| **Age (years)** | 43.0±19.6 |
| **Sex** | |
| Male (%) | 72 (80.9%) |
| Female (%) | 17 (19.1%) |
| **Time of remission (hours)** | 5.9±9.4 |
| **GCS at admission** | 10.5±3.6 |
| **Blood glucose levels in the first 24 h (mg/dL)** | 138.1±59.4 |
| **Hyperglycemia (≥200 mg/dL)** | 12 (13.5%) |
| **TBI severity** | |
| Mild (%) | 37 (41.6%) |
| Moderate (%) | 14 (15.7%) |
| Severe (%) | 38 (42.7%) |
| **Type of trauma** | |
| Isolated head trauma (%) | 50 (56.2%) |
| Polytrauma (%) | 39 (43.8%) |
| **Causes of trauma** | |
| Traffic accident (%) | 76 (85.4%) |
| Assault trauma (%) | 5 (5.6%) |
| Falling down (%) | 3 (3.4%) |
| Patient found on public road (%) | 5 (5.6%) |

The severity of TBI was determined by how much energy the traumatic event did; this energy was directly related to the cause of trauma (eg. traffic accidents) and multiple injuries. In Table 2, the severity of TBI related to the type and the underlying cause was shown. Notably, the severe TBI occurred mainly in patients who suffered traffic accidents (42.1%), while the mild TBI evidenced mostly secondary to physical aggression (60.0%). On the other hand, the type of trauma showed no significant difference in the severity of TBI in patients (Mild TBI 44.0% *vs.* 38.5%, moderate 14.0% *vs.* 17.9% and severe 42.0 *vs.* 43.6% to isolated head trauma and polytrauma, respectively).

The most common lesions presented by patients with TBI, were in order of frequency as fractures (22.5%), hematoma (18.3%), cerebral edema (18.3%) and cerebral contusion (16.2%). Fourteen patients (15.7%) showed no lesion in brain CT. The hematoma and cerebral edema were the most common lesions related to the subsequent hyperglycemia (23.1% and 19.2%, respectively), but it is clear that most of patients had other concomitant lesions, so identifying a direct relationship between these variables was not possible. However, among the patients with high glucose levels (12 patients), 83.3% (10 patients) had some types of lesions associated with trauma in the brain CT (Table 3). An inverse relationship was found between glucose levels at admission and GCS score, using Pearson analysis (r=0.11; $p$=0.46).

Making a comparative analysis of trauma conditions (types and causes) between the patients who presented hyperglycemia and those who did not, it was found that the presence of high glucose levels was more frequent in patients with isolated head trauma (18.0% *vs.* 7.7%; $p$=0.031). Hyperglycemic patients had significantly lower GCS when compared to normoglycemic patients (8.0±1.3 *vs.* 10.9±1.8; $p$<0.001). Hyperglycemia was more common in patients with severe TBI compared to moderate or mild TBI (26.3%, 7.1% and 2.7% respectively) (Table 4).

Regarding treatment and evolution, most patients without high glucose levels at admission were managed only medically (45.5% *vs.* 33.3%), whereas surgical intervention was more frequent in patients with hyperglycemia (66.7% *vs.* 54.5%; $p$=0.042). ICU management was required in 91.7% of patients with hyperglycemia while 76.7% of normoglycemic patients required it ($p$=0.002); however there was no significant

**Table 2.** Frequency of traumatic brain injury according to type and cause of trauma.

| | Mild (n=37) | Moderate (n=17) | Severe (n=35) |
|---|---|---|---|
| **Type of trauma** | | | |
| Isolated head trauma (%) | 22 (44.0%) | 7 (14.0%) | 21 (42.0%) |
| Polytrauma (%) | 15 (38.5%) | 7 (17.9%) | 17 (43.6%) |
| **Causes of trauma** | | | |
| Traffic accident (%) | 32 (42.1%) | 12 (15.8%) | 32 (42.1%) |
| Assault trauma (%) | 3 (60.0%) | 1 (20.0%) | 1 (20.0%) |
| Falling down (%) | 1 (33.3%) | 1 (33.3%) | 1 (33.3%) |
| Patient found on public road (%) | 1 (20.0%) | 0 (0.0%) | 4 (80.0%) |

**Table 3.** Findings on brain CT-scan in hyperglycemic and normoglycemic patients.

| | Total (n=89) | Hyperglycemic (n=12) | Normoglycemic (n=77) |
|---|---|---|---|
| **Without lesion** | 15 (16.9%) | 2 (16.7%) | 13 (16.9%) |
| **With lesion** | 74 (83.1%) | 10 (83.3%) | 64 (83.1%) |
| **Findings** | | | |
| Fractures | 32 (22.5%) | 3 (9.4%) | 29 (90.6%) |
| Hematoma | 26 (18.3%) | 6 (23.1%) | 20 (76.9%) |
| Hemorrhage | 17 (11.9%) | 1 (5.9%) | 16 (94.1%) |
| Contusion | 23 (16.2%) | 2 (8.7%) | 21 (91.3%) |
| Cerebral Edema | 26 (18.3%) | 5 (19.2%) | 21 (80.8%) |
| Pneumocenphalus | 11 (7.7%) | 1 (9.1%) | 10 (90.9%) |
| Others (vascular lesions, neuropathies) | 7 (4.9%) | 1 (14.3%) | 6 (23.0%) |
| **Total** | 142 | 19 | 123 |

**Table 4.** Frequency of hyperglycemia and normoyperglycemia according to type and cause of trauma.

| Type of trauma | Hyperglycemic (n=12) | Normoglycemic (n=77) | *p*-value |
|---|---|---|---|
| Isolated head trauma (%) | 9 (18.0%) | 41 (82.0%) | <0.001 |
| Polytrauma (%) | 3 (7.7%) | 36 (92.3%) | |
| **TBI severity** | | | <0.001 |
| Mild (%) | 1 (2.7%) | 36 (97.3%) | |
| Moderate (%) | 1 (7.1%) | 13 (92.9%) | |
| Severe (%) | 10 (26.3%) | 28 (73.7%) | |

difference between two study groups regarding the ICU admission duration (9.0±2.9 *vs.* 8.4±1.8; $p$=0.086). Patients with hyperglycemia showed significantly higher rates of complications (66.7% *vs.* 50.6%; $p$=0.019) and mortality (16.7% *vs.* 11.7%; $p$=0.039) (Table 5).

## Discussion

TBI includes a broad range of deleterious consequences and high costs on health systems and the patient's rehabilitation [7,8]. The available evidence indicates a mortality of 35% to 42% due to TBI, especially in patients between 15 and 25 years [9-11]. Overall, TBI is divided into two kinds of injuries: primary and secondary. The primary brain injury is the physical damage to parenchyma that occurs during traumatic event, resulting in shearing and compression of the surrounding brain tissue [12,13]. The secondary brain injury, caused by the discharge of active substances, such as excitatory amino acids (eg. glutamate), activated oxygen, neurohormones and signaling molecules, play a key role in the final outcomes [12,13].

Many of the changes during brain injury occur in the energy metabolism. After brain injury, as protection mechanism, glucose intake is increased over a short period of time, followed by declined glucose consumption [4]. Hyperglycemia in patients with trauma can lead to metabolic stress. In experimental studies, hyperglycemia has been related to more pronounced deterioration of brain energy metabolism, cerebral edema, and worse morphological damages [5,14].

Hyperglycemia during the acute phase of critical illness is induced by both increased glucose production and decreased glucose cellular uptake. High levels of glucose are produced through up-regulation of both gluconeogenesis and glycogenolysis. In addition, in critical illness increase in cortisol, catecholamine, and cytokine levels induces hyperglycemia in acute

**Table 5.** Comparing outcome measures between hyperglycemic and normoglycemic patients.

| | Hyperglycemic (n=12) | Normoglycemic (n=77) | *p*-value |
|---|---|---|---|
| **Time of remission (hours)** | 4.72±6.7 | 6.0±9.8 | 0.028 |
| **GCS at admission** | 8.0±2.6 | 10.9±3.5 | <0.001 |
| **Blood glucose levels in the first 24 h (mg/dL)** | 245.8±65.8 | 121.3±36.7 | <0.001 |
| **Treatment** | | | |
| Medical (%) | 4 (33.3%) | 35 (45.5%) | 0.042 |
| Surgical (%) | 8 (66.7%) | 42 (54.5%) | |
| **Requirement ICU** | 11 (91.7%) | 59 (76.7%) | 0.002 |
| Permanence in days (%) | 9.0±7.9 | 8.4±7.9 | 0.086 |
| Complications (%) | 8 (66.7%) | 39 (50.6%) | 0.019 |
| Mortality (%) | 2 (16.7%) | 9 (11.7%) | 0.039 |

injury. Furthermore, cellular glucose uptake is severely diminished in critical injury and illness. In the hypoxia, or other conditions with elevated acute-phase reactants (such as cytokines, angiotensin II, or endothelin I), the Glut 1 and Glut 3 receptor expression and activity are increased, resulting in intracellular glucose accumulation [15].

Hyperglycemia can cause secondary injury by increasing glycolytic rates evidenced by increased lactate/pyruvate ratio, causing metabolic acidosis in the brain parenchyma, increased reactive oxygen species, and will ultimately neuronal cell death [3]. Hyperglycemia affects multiple microvascular and cellular pathways and contributes to pathologic changes after acute injury. Some findings linked with hyperglycemia in the brain injury are acidosis and excitatory amino acid production. Hyperglycemia increase edema formation and the injury to the blood–brain barrier [15].

Multiple studies have evaluated the relationship between hyperglycemia and the evolution of TBI patients and found that hyperglycemia is associated with increased morbidity and mortality in patients with TBI. In a retrospective study by Jeremitsky *et al.,* 77 patients who were admitted in ICU with severe TBI were followed with measurements of serum glucose level for 5 days, finding that among patients who died, the value of mean glucose level was greater than survivors (187.0 mg/dL vs. 153 mg/dL). In the same undertaken study, the hyperglycemia value was ≥ 170 mg/dL and patients who had 2 or more measures of hyperglycemia had less survival [16]. Liu-DeRyke *et al*., [17] developed a retrospective study of 380 ICU patients with TBI and found that levels ≥160 mg/dL in the first 24 hours of admission were associated with a poor outcome in terms of increased mortality or severity of injury. Donald *et al*., [18] did a retrospective cohort study on ICU patients with severe TBI who survived at least 12 hours, and measured the fasting glucose level in the first 10 days. They found that levels of hyperglycemia ≥11.1 mmol/L (≥200 mg/dL) were associated with a 3.6-fold increased risk of death compared to those with lower levels. Rovlias *et al*., [19] in their prospective study on 267 patients with moderate or severe TBI, who underwent surgery, reported that patients with severe TBI had higher levels of hyperglycemia. Their multivariate analysis showed that the levels of hyperglycemia were reliable predictors of severity and neurological damage. So there is a clear association between hyperglycemia and increased morbidity and mortality outcomes and neurological damage in patients with TBI.

Hyperglycemia was shown to be associated with worse outcome in TBI, leading to the conclusion by many that glucose control could improve outcome. It is not clear whether treatment of hyperglycemia improves or exacerbates outcomes in TBI. Because of this limited understanding, some investigators prudent approach to avoid extremes of blood glucose levels by targeting levels from 140 mg/dL to 180 mg/dL [3].

Unfortunately, the exact blood glucose values to be regarded dangerous in severe head trauma have not yet been fully established [20]. Diaz-Parejo *et al*., [21] established cerebral energy metabolism to be affected by transient hyperglycemia only at blood glucose concentration above 270 mg/dL (15 mmol/L). Guidelines from the Brain Trauma Foundation [22] and the European Brain Injury Consortium [23] highlighted the association of hyperglycemia with worse prognosis after severe brain trauma, but do not specify the exact blood glucose values considered as harmful, so it is not clear which level is the trigger for initiating insulin therapy [4].

Yuan *et al*., [24] mentioned that continuous collection of glucose recordings (5 minutes intervals) was more reliable and accurate than routine discontinuous recordings. However, assessing the duration and the amplitude of the episodes using continuous collection of glucose data would help to get better outcomes prediction.

The treatment of hyperglycemia is particularly interesting in patients with severe TBI, due to the high incidence of stress hyperglycemia among these patients, as can be observed in our results. It is important to highlight that in the treatment of these patients it has been identified that some of them may lead to low blood glucose levels (hypoglycemia) triggering a reduction in cerebral glucose, which increases global oxygen extraction fraction and increase markers of cellular distress such as elevations in glutamate and lactate/pyruvate ratio [25-27]. Although hyperglycemia is detrimental, the hypoglycemia, a common complication of tight glucose control, can induce and aggravate underlying brain injury [28]. Vespa *et al*., [29] reported that intensive insulin therapy (IIT) increased oxygen extraction (suggesting ischemia), glutamate, and lactate/pyruvate ratio indicating cellular distress and worse functional outcome.

Oddo *et al*., [25] documented through brain tissue microdialysis of 20 critically ill patients with severe TBI, that tight systemic glucose control was associated with reduced cerebral extracellular glucose availability (<0.7 mmol/L and a lactate/pyruvate ratio >40), related with increasing brain energy crisis and significantly higher adjusted odds of hospital death (OR 7.4, 95% CI, 1.4-39.5). IIT regimen may impair cerebral glucose metabolism after severe brain injury too [25,30].

Bilotta *et al*., [27] compared a regimen of IIT (target blood glucose 4.42–6.63 mmol/L) versus conventional management (target blood glucose 4.42-12.15 mmol/L) in 97 patients with severe TBI. The only favorable endpoint associated with the use of IIT was a shorter stay in the ICU (7.3 vs. 10 days, $p<0.05$). Particularly the incidence of hypoglycemic events was markedly increased for patients treated with IIT ($p<0.0001$). Meier *et al*., [28] compared retrospectively the clinical outcomes before and after

implementation of IIT in 228 severe TBI patients. Target blood glucose levels were 4.97-7.96 mmol/L before utilization of the IIT regimen and 3.48-6.46 mmol/L once this regimen was implemented. Both groups had similar mortality, but insulin therapy was time-dependent. In the first week, IIT was associated with worsened outcome (higher intracranial pressure, greater norepinephrine requirement, and higher rates of bacteremia). These effects appeared to reverse toward the second and into the third week. Episodes of hypoglycemia were significantly more common in the IIT group (52% vs. 26%, $p<0.05$) [28].

Marion *et al*., [18] in their meta-analysis about brain injury revealed that IIT did not appear to decrease the risk of in-hospital or late mortality (RR=1.04, 95% CI=0.75, 1.43 and RR=1.07, 95%CI=0.91, 1.27 respectively). Moreover, IIT did not have a protective effect on long-term neurological outcomes (RR=1.10, 95% CI=0.96, 1.27). However, IIT increased the rate of hypoglycemic episodes (RR=1.72, 95% CI=1.20, 2.46) [31]. Consequently, the majority of currently available clinical evidences did not support tight glucose control (glucose levels below 110-120 mg/dl) in the treatment of patients with severe TBI [32,33].

Our study demonstrated that the main cause of TBI was due to traffic accidents, as referred in others studies, in which the high energy results in a severe or moderate TBI frequently and causing many lesions like fractures, hematomas and cerebral contusions mainly. In the physiological organism responses due to trauma, we found that hyperglycemia was frequent in patients with TBI (13.5%). Patients with more elevated glucose levels were related to worse TBI category (severe-26.3%) and more neurological damage. Additionally those patients required more surgical treatments and ICU management, with consequently more mortality and worsening outcomes.

Metabolic disorders, like hyperglycemia in the TBI context, and more precisely in severe TBI, can be extremely detrimental in the clinical outcome of these patients and furthermore have demonstrated that it is a self-determining mortality indicator in patients with severe TBI. Additional studies are needed to determine the serum glucose levels that elicit harmful biological and statistical effects. Our data confirm the relationship between GCS and hyperglycemia reported by others. Hyperglycemia management is critical in the outcome of patients with TBI.

**Conflict of Interest:** None declared.

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