An Observational Study of Blood Glucose Levels during Admission and 24 Hours Post-Operation in a Sample of Patients with Traumatic Injury in a Hospital in Kuala Lumpur

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\textbf{Abstract}

\textit{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.

\textit{Methods:} This prospective observational study was conducted for a year in 2007 among 294 patients who had been treated for TBI in Hospital Kuala Lumpur. Patients fulfilling the set criteria were recruited into the study and data, including blood glucose level and Glasgow Outcome Score at 3-month follow-up, were collected.

\textit{Results:} 294 patients were included in the study: 50 females (17.0\%) and 244 males (83.0\%). The majority of cases were young adult patients (mean age of 34.2 years, SD 13.0). The mean blood glucose level during admission and post-surgery were 6.26 mmol/L (SD 1.30, \(n = 294\)) and 6.66 mmol/L (SD 1.44, \(n = 261\)), respectively. Specifically, the mean admission glucose level associated with mild TBI was 5.04 mmol/L (SD 0.71); moderate TBI, 5.78 mmol/L (SD 1.02); and severe TBI, 7.04 mmol/L (SD 1.18). The mean admission glucose level associated with a poor outcome in patients with isolated TBI was 6.98 mmol/L (SD 1.21). Patients with admission glucose of 5.56 mmol/L (SD 1.21) were more likely to have a favourable outcome.

\textit{Conclusion:} Mild, moderate, and severe TBI were associated with an increase in blood glucose levels during admission, and the mean increase in glucose levels is 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.

\textit{Keywords:} blood glucose, Glasgow Outcome Scale, surgery, trauma, traumatic brain injury, trauma severity index

\textbf{Introduction}

Hyperglycaemia is an important parameter in the prediction of outcomes in traumatic brain injury, TBI (1–3). Studies have assessed the various levels of blood glucose throughout the course of TBI, including at the time of admission, during the course of acute treatment, and during follow-up (4–7). Hyperglycaemia in severe TBI has been associated with detrimental neurological outcomes (8), especially in patients with admission glucose levels of more than 200 mg/dL (11.0 mmol/L). Higher blood glucose levels, that is, more than 300 mg/dL (16.6 mmol/L), are almost always associated with 100\% mortality in paediatric TBI (5).

TBI has been associated with an acute stress response mediated by the sympathoadrenomedullary axis, which can be reflected in an increase in blood glucose level; however, whether isolated TBI by itself results in an increase in glucose level has not been resolved in previous studies. In these studies, the focus was often on various levels of severe head
injury in the presence of other major extracranial injuries (7,9). Chiolero et al. (10) studied plasma cortisol, glucagon, insulin, glucose, free fatty acid, urinary nitrogen, and catecholamine responses in severely traumatised patients. Patients were grouped according to the following classification: severe isolated head injury, multiple injuries combined with severe head injury, and multiple injuries without head injury. The authors found that isolated head injury stimulated increases in the secretion of catabolic counter-regulatory hormones even in the absence of additional non-cranial major injury.

Animal studies have also shown that moderate and severe brain injury could induce increases in blood glucose. He et al. (11) found that the blood glucose increased at different times, and this increase correlated with the severity of brain injury in rats. A marked increase in blood glucose was observed despite high levels of insulin after TBI. By investigating levels of glucose and lactate in cats after 1 hour of simulating direct trauma (concussion) to the brain, Yang et al. (12) found that lactate concentration was increased by almost 3-fold in the cortical regions directly underneath the traumatised area when compared with the control subjects. Thus, TBI can cause derangements in brain energy metabolism.

A study by Young et al. (13) revealed that the sympathetic nervous system works together with the adrenal medullary axis in producing a response to acute severe injury. In their animal study, the authors found reductions in circulating norepinephrine and other catecholamines after the removal of stress. Elevated circulating norepinephrine and other catecholamines in response to acute severe injury play important roles in the survival of injured animals. Elevated catecholamines, which occur during stress responses, induce hepatic gluconeogenesis and result in hyperglycaemia. Stover et al. (14) conducted a prospective randomised controlled study in Sprague Dawley rats and found that norepinephrine elevates extracellular glucose in the injured brain more than in arterial blood and further aggravates post-traumatic oedema formation without changing the lactate concentration. Thus, there is a possibility that norepinephrine facilitates endothelial glucose transport in addition to passive entry, depending on concentration and pressure via a damaged blood-brain barrier.

In a human study, Yang et al. (15) reported that blood glucose and catecholamines were significantly elevated; these levels correlated to the severity of the head injury. The increase in blood glucose was related to the elevation in norepinephrine and epinephrine in response to the stress induced by the head injury. He found that 90% of patients with admission blood glucose levels of 9.6 mmol/L or greater died within 1 month post-injury. Thus, admission blood glucose could be a significant predictor of outcome.

The significant increase in blood glucose has been investigated in medical comorbidities (16,17). Wong et al.'s cohort study of stroke patients in 2008 (17) showed that mean glucose levels on admission remained stable at 6.0 mmol/L in patients with ischaemic stroke without diabetes until at least 48 hours after the stroke. This would suggest that ischaemic injury alone does not raise the blood sugar level on admission. Wintergest et al. (18) showed that increased glucose variability in patients admitted to the Paediatric Intensive Care Unit is highly associated with increased morbidity and mortality.

However, in TBI, the increase in blood glucose level is always complicated by other factors. Walia et al. (19) 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. Vogelzang et al. (20) conducted an analysis on trauma and non-trauma patients and found that hyperglycaemia influenced the outcome, and that the relationship between hyperglycaemia and mortality was more pronounced in trauma patients. Overall, hyperglycaemia correlates better with mortality in trauma patients. Takanashi et al. (21) also 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 (SEM 0.2), compared with patients with moderate head injury, at 9.5 mmol/L (SEM 0.2). Patients with admission glucose levels greater than 13.3 mmol/L had 100% mortality in their study, suggesting that hyperglycaemia on admission could be a significant indicator and potent predictor of head injury severity.

The demographic pattern of brain injury severity has also not been completely elucidated. Studies have reported that females are more likely to have poorer outcomes in severe TBI (22,23); however, epidemiology studies do not support
these observations (24). The age of the patient has also been shown to predict the outcome of TBI due to various factors, such as diminished autoregulatory mechanisms. It is well known that middle-aged men and women, who are also the most productive members of the countries in which they live, sustain the highest rates of head injury and the most severe types of head injury. As a result, head injury and its associated morbidity and mortality create additional economic burden for both the health care system and the country as a poorer outcome could result in significant health care resource needs. The closest description that has been published in Malaysia is the first preliminary report of the National Trauma Database. In this document, the authors reported that there were 120,000 trauma cases per year admitted to a local hospital; however, they did not mention an association between TBI and blood glucose as a stress response (25,26). Another study by Czonyska et al. (27) found that age-related declines in cerebrovascular autoregulation contribute to the relationship between age and outcome in patients following head injury. A demographic study showed that the outcome for head injury is worse as patients get older despite a better Glasgow Coma Scale (GCS) upon admission, which may or may not be a direct reflection of glucose levels on admission (27). Epidemiology studies on gender difference in outcomes after brain injury are limited; however, animal studies revealed higher fatality rates among females (14, 32). Krauss et al. (23) found that females were at least 1.5 times more likely to have poorer outcomes as compared with male. Farace et al. (24) conducted a meta-analysis to investigate possible differences in TBI according to gender. They found that outcomes were worse in women as compared with men in 85% of the measured variables, although this conclusion was limited due to the fact that only a few of the most published reports described gender differences in their outcome. The study may not adequately reflect the possible differences in outcome based on gender in patients with isolated head injury.

This study aims to establish an association between different types of isolated head injury and increased blood glucose levels among those with an isolated head injury without any major extracranial cause. It was hypothesised that higher blood glucose levels would be associated with poorer outcomes in isolated closed TBI and that, as a result, admission blood glucose level could be used as a predictor of outcome among patients with isolated TBI.

**Subjects and Methods**

The primary objective of this study was to determine the differences in blood glucose levels on admission and 24 hours post-operative intervention in a population of adult patients (age 18–65 years) with TBI who were admitted to Hospital Kuala Lumpur and their outcome 3 months after head injury.

This was an observational, prospective cohort study on TBI patients who were admitted to Department of Neurosurgery, Hospital Kuala Lumpur, and registered under the Neurosurgical Head Injury Registration Book from 1 January 2007 until 31 December 2007, with follow-up until 31 March 2008. This study was approved by the local institution and registered under the National Medical Research Register (research protocol ID NMRR-09-265-3254). The inclusion criteria were patients with non-penetrating TBI aged between 18 and 65 years old. Exclusion criteria were as follows: patients who fulfilled the clinical criteria for brain death upon arrival, had other major extra cranial injuries, died within 24 hours of admission, were known to have a history of diabetes mellitus, or were on long-term steroid therapy. Data were collected using a questionnaire; all of the necessary details of the patient were recorded. The selected patients were cross-checked with the Neurosurgical Head Injury Registration Book (2007) for the purpose of follow-up and collecting up-to-date information by tracing the clinical notes to add further details to the questionnaire. Data collected include patients’ demography, description of injuries, computed tomography (CT) findings, Glasgow Coma Scale, blood glucose level during admission and 24 hours post-surgical intervention, and Glasgow Outcome Score. Statistical analyses (mean, standard deviation, and standard error of mean, independent t test, and paired t test) were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL). The level of statistically significant correlations was set at 0.05 in a 2-tailed fashion.

**Results**

Between 1 January 2007 and 31 December 2007, there were more than 50,000 trauma cases admitted to Hospital Kuala Lumpur; however, only 1152 cases were registered in the Neurosurgical Head Injury Registration Book, Department of Neurosurgery, Hospital Kuala Lumpur. Only 294 patients who fulfilled the set criteria were recruited in the study.
The mean age of the study sample was 34.2 years old (SD 13.0). The median age of the patients was 31 years old, with a mode of 22. Approximately 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. Males and females were similarly distributed when categorised according to the admission GCS. The most well-represented ethnic group in the study was Malay (n = 157, 53.4%), followed by Chinese (n = 61, 20.7%), Indian (n = 43, 14.6%), and other races (n = 33, 11.2%). Most of the subjects enrolled in the study were Malaysian (n = 233, 79.2%) while the rest were from other countries. The majority of patients included in the study were either directly admitted through the Emergency Department (n = 170, 57.8%) or as referrals from district hospitals (n = 117, 39.8%). Almost all patients treated in Hospital Kuala Lumpur were involved in road traffic accidents (n = 269, 91.5%). A considerably smaller proportion of the sample were involved in falls (n = 20, 6.8%) or assaults (n = 5, 1.7%).

Patients with a GCS of 7 were highly represented in our sample (n = 69, 23.5%). Mean GCS upon admission was 9.28 (SD 2.53). There was no patient in the study sample with a GCS of less than 5. The majority of patients had severe head injury (n = 140, 47.6%), followed by moderate (n = 104, 35.4%) and mild head injury (n = 50, 17.0%). The majority of CT brain scans (n = 274, 93.2%) had the following findings: most cases were diagnosed with subdural haemorrhage (n = 134, 45.6%), followed by extradural haemorrhage (n = 82, 27.9%) and intraparenchymal haemorrhage/contusion (n = 78, 26.5%). Only 6.8% of the patients were without any findings on imaging.

The mean glucose level on admission was 6.26 mmol/L (SD 1.30) in a bell-shaped distribution. A similar bell-shaped distribution was found for the blood glucose levels of patients (n = 261, 88.8%) within 24 hours after surgical intervention, with a mean of 6.66 mmol/L (SD 1.44). Most of the patients underwent either major operation (n = 242, 82.3%) or minor operation (n = 19, 6.5%). Only a small number of patients were treated conservatively (n = 33, 11.2%).

The highest frequency of cases included patients with severe disability or a Glasgow Outcome Score of 3 (n = 111, 37.9%), followed by moderate disability (n = 82, 28.0%) and good recovery (n = 64, 21.8%). The lowest frequency was seen in patients with a Glasgow Outcome Score of 1 (dead, n = 6, 2.0%).

Table 1 shows details concerning the sample population with respect to the severity of the isolated TBI. Sex distribution, mean age, GCS, CT scan brain findings, serum glucose levels on admission and within 24 hours after operative intervention, and neurological outcome are discussed below.

**Table 1:** Analysis of demographic and clinical data according to the severity of traumatic brain injury

<table>
<thead>
<tr>
<th>Domains</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>50</td>
<td>104</td>
<td>140</td>
</tr>
<tr>
<td>No. according to sex (male/female)</td>
<td>42/8</td>
<td>88/16</td>
<td>114/26</td>
</tr>
<tr>
<td>Age, in mean (SD) years</td>
<td>26.4  (8.6)</td>
<td>31.1 (10.3)</td>
<td>39.3 (14.0)</td>
</tr>
<tr>
<td>Glasgow Coma Scale, in mean (SD) score</td>
<td>13.2  (0.4)</td>
<td>10.4 (1.3)</td>
<td>7.0  (0.8)</td>
</tr>
<tr>
<td>Computed tomography findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extradural haemorrhage</td>
<td>29</td>
<td>48</td>
<td>5</td>
</tr>
<tr>
<td>Subdural haemorrhage</td>
<td>1</td>
<td>42</td>
<td>91</td>
</tr>
<tr>
<td>Intraparenchymal haemorrhage/contusion</td>
<td>20</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td>Glucose level, in mean (SD) mmol/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>5.04  (0.71)</td>
<td>5.78 (1.02)</td>
<td>7.04 (1.18)</td>
</tr>
<tr>
<td>24 hours post-surgery</td>
<td>5.08  (0.71)</td>
<td>5.92 (1.02)</td>
<td>7.46 (0.18)</td>
</tr>
<tr>
<td>Outcomea</td>
<td>50</td>
<td>80</td>
<td>16</td>
</tr>
<tr>
<td>Favourable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unfavourable</td>
<td>24</td>
<td></td>
<td>123</td>
</tr>
</tbody>
</table>

*a* One case in the severe group was missing during follow-up (admission cases = 294, follow-up cases = 293).
Sex distribution was similar in the group stratified by the severity of isolated TBI (mild, moderate, and severe according to GCS). There was no significant difference in age among the patients with differing severities of isolated TBI.

Patient with severe head injury had significantly higher admission and post-operative glucose levels than those with mild and moderate head injury ($P < 0.001$). Within the group themselves, the differences in glucose values were not significant. Further analysis using a paired t test showed that there was no significant difference ($P < 0.01$) in the admission glucose level (6.26 mmol/L, SD 1.3) when compared with the mean glucose level taken 24 hours after surgical intervention (6.66 mmol/L, SD 1.4).

Severe head injury was associated more with subdural haemorrhage and intraparenchymal haemorrhage compared with extradural haemorrhage. There was no relationship between the different types of CT brain scan findings and increased blood glucose levels. In the moderate head injury group with slightly elevated mean blood glucose levels, it seems that mild elevations can be attributed to any pathology. Subdural haemorrhage had the highest number of patients in severe head injury with significant increases in mean blood glucose level. Extradural haemorrhage did not significantly increase the blood glucose level in the severe head injury group.

Further analysis looking at the patients’ outcomes was performed accordingly (Table 2). Both glucose levels on admission and within 24 hours post-surgery were analysed based on the Glasgow Outcome Score at 3-month follow-up of the patients.

### Discussion

Our findings are similar to that of the National Trauma Database Report (26), in which the majority of the population involved in trauma were between 15 and 24 years of age (30.2%). Similar to other studies (24,26), we also found that males were more likely to be involved in TBI; in the National Trauma Database Report (26), 83.5% were males. Although our data showed a male-to-female ratio of 5:1, this study found that the genders were almost equally distributed in terms of admission Glasgow Coma Score. The ethnic group distribution in this study is also comparable with in the National Trauma Database Report (26): majority of patients are Malays, 53.4% versus 58%, followed by Chinese, 20.7% versus 22.5%, and Indians, 14.6% versus 15.6%. With respect to the distribution by gender, race and nationality, the study is comparable with the national data (25,26). Thus, this study may be representative of the demographic involved in isolated TBI in our country.

In this study, there was a significant difference in admission blood glucose level with regard to the different severity of isolated TBI. 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. Glucose levels 24 hours after operation also showed similar differences among the group; only severe head injury patients were elevated by more than 1 mmol/L compared with the other groups, while the different between mild and moderate

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of subjects</th>
<th>Glucose level (mmol/L)</th>
<th>Admission</th>
<th>24 hours post-surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glasgow Outcome Score (GOS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5: Dead</td>
<td>6</td>
<td>7.9 (1.96)</td>
<td>8.5 (1.96)</td>
<td></td>
</tr>
<tr>
<td>4: Persistent vegetative state</td>
<td>30</td>
<td>7.9 (1.10)</td>
<td>8.5 (1.10)</td>
<td></td>
</tr>
<tr>
<td>3: Severe disability</td>
<td>111</td>
<td>6.7 (1.05)</td>
<td>7.0 (1.05)</td>
<td></td>
</tr>
<tr>
<td>2: Moderate disability</td>
<td>82</td>
<td>5.9 (0.91)</td>
<td>6.1 (0.91)</td>
<td></td>
</tr>
<tr>
<td>1: Good recovery</td>
<td>64</td>
<td>5.0 (0.8)</td>
<td>5.0 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Categorisation into two groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable outcome (GOS 1–3)</td>
<td>147</td>
<td>5.5 (1.21)</td>
<td>5.7 (1.21)</td>
<td></td>
</tr>
<tr>
<td>Poor outcome (GOS 4–5)</td>
<td>146</td>
<td>7.0 (1.21)</td>
<td>7.4 (1.21)</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed in mean (SD).
was not more than 1.0 mmol/L. This could mean that the level of blood glucose corresponds to the severity of isolated TBI. Other authors have found similar findings that admission blood glucose level reflects the severity of the TBI (8,20,21,28), specifically the severity of severe head injury (2,7,19). Lam et al. (28) found that the mean admission blood glucose level was 10.7 mmol/L (SEM 0.4) in the severe head injury group, whereas the mean admission blood glucose level for mild head injury was 7.2 mmol/L (SEM 0.4). Rovlias et al. (8) reported a mean admission blood glucose level of 11.3 mmol/L (SEM 0.2) in the severe head injury group, whereas the mean admission blood glucose level for moderate head injury was 9.1 mmol/L (SEM 0.3). Both authors (8,28) documented slightly higher figures compared with the findings in our study.

With regard to the differences in blood glucose levels between the groups (admission versus 24 hours post-surgery), only those with severe TBI had significant but mild (less than 0.5 mmol/L) elevations in mean blood glucose levels. In the mild and moderate head injury group, there was no significant difference in mean glucose levels on admission compared with 24 hours after surgery. Our finding that there was no difference in glucose levels between admission and 24 hours post surgery, but that higher mean glucose levels were associated with poorer outcome, is similar to the findings of other authors (7,28). These findings imply that an isolated traumatic injury can independently and significantly increase blood glucose levels depending upon injury severity; thus, blood glucose level may be an important prognostic factor for predicting outcome among patients with TBI.

With respect to whether there is a relationship between glucose levels at admission or 24 hours post-surgery and the outcome, our study found that glucose levels were significantly associated with outcomes among patients with TBI (Table 2). For glucose levels below 6.0 mmol/L, patients had a better outcome in relation to Glasgow Outcome Score at the 3-month follow-up in the clinic (independent t test, \(P < 0.01\)). Higher blood glucose levels of the patient upon admission (more than 7.9 mmol/L) were associated with poorer outcomes; however, this association was not significant (\(P = 0.98\)). This pattern was also consistent for the relationships between a mean blood glucose level of 8.5 mmol/L within 24 hours post-surgery and poor outcomes: dead, \(P = 0.92\), and persistent vegetative state, \(P = 0.94\) (Table 2). Walia et al. (19) investigated the relationship between blood pressure, blood glucose concentration, and outcome following severe head injury. They found that both mean arterial pressure (MAP) and blood glucose are related to mortality in a linear fashion (\(P < 0.0001\)). Their regression analysis showed that each of the studied factors was an independent predictor of mortality. The relationship between blood glucose and mortality was much stronger than the relationship between MAP and mortality. By grouping the patients together according to the lowest MAP, hyperglycaemia was associated with increasing mortality within each group (\(P < 0.0001\)).

Chiaretti et al. (29) conducted a study among children with head injury and found a similar relationship as the one found in our study: hyperglycaemia occurred more frequently in children with severe head injury than in those with mild and moderate head injury. Their conclusion was that persistent hyperglycaemia beyond 24 hours after injury appears to be an important negative prognostic factor. Cochran et al. (5) found that hyperglycaemia can be an independent predictor of outcomes in paediatric TBI. Patients with admission blood glucose of lower than 7.5 mmol/L were more likely to live, and those with blood glucose of greater than 14.8 mmol/L were more likely to die. Admission blood glucose levels of greater than 16 mmol/L were associated with 100% mortality. An earlier study (30) demonstrated that head injury patients with persistent hyperglycaemia (defined as plasma glucose of more than 15 mmol/L in the study) had grave outcomes (mean time of survival was 2.1 days, SD 1.4). Looking retrospectively at intensive care patients with severe head, Jeremitsky et al. (31) found that hyperglycaemia was an independent predictor of severity and outcome, that is, the higher the score, the poorer the outcome. A study by Salim et al. (2) found that persistent hyperglycaemia may be an independent risk factor for mortality with an odds ratio of 4.91 (95% CI 2.88–8.56, \(P < 0.0001\)). They defined persistent hyperglycaemia as an average daily blood glucose level of equal to or greater than 8.3 mmol/L. Beek et al. (1) found that the predictive value of blood glucose for predicting outcome among those with TBI was strongest for increasing blood levels of glucose (odds ratio 1.7, 95% CI 1.54–1.83).

Kinoshita et al. (32) provided a possible explanation for why early hyperglycaemia might affect outcomes in patients with isolated TBI. In their study, the authors created a rat model of moderate TBI and allocated rats to
of 4 treatment groups: early group given dextrose injection 5 minutes after trauma, delayed group given dextrose injection 4 and 24 hours after trauma, and a control group. They measured contusion areas and volumes, as well as frequency of myeloperoxidase immunoreactive polymorphonuclear leukocytes (PMNLs). They found that acute hyperglycaemia did not significantly affect total contusion volume but did increase contusion area, as well as enhanced accumulation of PMNLs within the contusion area. Delayed induced hyperglycaemia did not produce the same result. The result of their study indicated that early or acute hyperglycaemia aggravates histopathological outcomes and increases the accumulation of PMNLs, leading to worsening of outcomes by enhanced secondary injury, including inflammation.

Instead of using exogenous glucose, Stover et al. (14) used catecholamines (norepinephrine and dopamine) to induce hyperglycaemia, as catecholamines increased hepatic gluconeogenesis in their study in TBI Sprague Dawley rats. They found that norepinephrine and dopamine increased arterial blood glucose, thereby significantly increasing pericontusional cortical glucose and lactate concentrations, but did not increase extracellular lactate concentrations. This leads to aggravation of underlying post-traumatic oedema and further worsens the outcome among patients with TBI. In addition to possibly increasing facilitated endothelial glucose transport, the elevated extracellular to blood glucose ratio suggests passive concentration-dependent and pressure-dependent entry via a damaged blood-brain barrier. This might contribute to the observed reversible increase in extracellular glucose, meaning that the higher the blood glucose level with TBI, the poorer the outcome. Kinoshita et al. (32) has shown earlier that the increased contusion area in vivo also indicates that hyperglycaemia in TBI might also require control treatment to improve the outcome of head injury patients.

Inference of reversibility of the increase in extracellular glucose concentration, which occurs as a result of the damaged blood–brain barrier and leads to poorer outcome in head injury patients, has given others encouragement to find other proof for this reversibility. Zygun et al. (9) further tested the hypothesis that blood glucose levels are associated with brain tissue pH and that the correction of hyperglycaemia would result in improvement of brain tissue pH. They used 428 glucose measurements with pH monitoring and a linear generalised estimating equation model to assess the relationship. They found that the difference between baseline readings of brain tissue pH and glucose with subsequent readings of brain tissue pH and glucose of less than 11.1 mmol/L was not significant (P = 0.29). If the change in blood glucose had been large, there would have been a suggestion of improvement in the brain tissue pH. Thus, there is potential proven benefit for treating hyperglycaemia in TBI.

**Limitations**

The primary limitation of this study was the number of patients recruited. The required sample size, according to calculation, was 445 patients; however, this study assessed only 294 patients. The sample size was small and may not have had a sufficient amount of power to detect significant differences. Furthermore, the study sample collected did not truly reflect the actual number of patients that were eligible for the study within the institution.

The number of cases in the mild head injury group was relatively smaller compared with the number of cases in the severe head injury group. These 2 groups were the groups of interest for determining significant differences in glucose concentration. With such small numbers in each group, further interpretations to the relationship of TBI with different CT scan findings were unsuccessful.

In addition, the measurement of blood glucose level was a source of bias. A standardised method for measuring glucose levels was used consistently in patients who were admitted and underwent surgical intervention. Patients who were treated conservatively may not have received similar lab blood work, thus introducing a source of bias.

**Conclusion**

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. Surgical intervention did not cause any further significant changes in blood glucose levels, suggesting that isolated TBI alone may cause a significant elevation in blood glucose levels. In our study, higher blood glucose levels upon admission after isolated TBI were associated with poorer outcomes for patients.

This study also showed that hyperglycaemia is an important independent predictor of outcome. Blood glucose levels may be a good independent
predictor of outcome in TBI. There is evidence to suggest that tight control of blood glucose in patients with TBI may improve outcomes for these patients. Future research addressing this specific question is warranted.

**Authors’ Contributions**

Conception and design, collection and assembly of the data, drafting of the article: RHH
Analysis and interpretation of the data, statistical expertise: KIM
Provision of study materials or patients, critical revision and final approval of the article, administrative, technical, or logistic support: MSMH

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