Determinants of Glasgow Outcome Scale in patients with severe traumatic brain injury for better quality of life

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Abstract. Primary and secondary brain injury may occur in severe traumatic brain injury. Secondary traumatic brain injury results in a more severe effect compared to primary traumatic brain injury. Therefore, prevention of secondary traumatic brain injury is necessary to obtain maximum therapeutic results and accurate determination of prognosis and better quality of life. This study aimed to determine accurate and noninvasive prognostic factors in patients with severe traumatic brain injury. This was a cohort study on 16 subjects. Intracranial pressure was monitored within the first 24 hours after traumatic brain injury. Examination of Brain-Derived Neurotrophic Factor (BDNF) and S100B protein were conducted four times. The severity of outcome was evaluated using Glasgow Outcome Scale (GOS) three months after traumatic brain injury. Intracranial pressure measurement performed 24 hours after traumatic brain injury, low S100B protein (<2µg/L) 120 hours after injury and increased BDNF (>6.16pg/ml) 48 hours after injury indicate good prognosis and were shown to be significant predictors (p<0.05) for determining the quality of GOS. The conclusion is patient with a moderate increase in intracranial pressure Intracranial pressure S100B protein, being inexpensive and non-invasive, can substitute BDNF and intracranial pressure measurements as a tool for determining prognosis 120 hours following traumatic brain injury.

Keywords: cohort study, severe traumatic brain injury, GOS, intracranial pressure, S100B protein, BDNF

1. Introduction

Traumatic brain injury is one of the most common contributing factors of morbidity and mortality due to trauma. According to the 2004 Indonesian Survey on Household Health, there were 132,367 cases of traumatic brain injury in every population of 100,000 [1]. Based on the resulting damage, traumatic brain
injury may involve all components of the head, from the skin and skull, to brain tissue as well as its blood vessels and layers [2].

In the evaluation of tissue damage, early clinical conditions such as Glasgow Coma Scale (GCS), pupil reactions, and motor strengths are used. However, there are limitations in evaluating deeper pathological conditions, such as those occurring at the cellular level. In intracranial monitoring, the increase of intracranial pressure within three to seven days indicates a poor prognosis. Although intracranial pressure measurement is categorized as an invasive procedure, it cannot describe the events occurring within the brain cells. The same applies to the CT-scan radiological parameter. Some cases with Diffuse Axonal Injury (DAI) show normal appearance. However, the injury can result in permanent brain damage [3-4]. Monitoring of early clinical signs can provide a good final GOS.

Modalities able to describe the brain’s intracellular condition are required to determine the prognosis of traumatic brain injury [2]. A cellular biomarker can show pathological conditions of nerve cells. Some cellular biomarkers that have been increasingly studied include S100B protein and Brain Derived Neurotrophic Factor (BDNF) [3].

This study aimed to determine the association between severe traumatic brain injury and its outcome using GOS examination three months after injury. Prognostic parameters of this study were 24 hour-intracranial pressure, the level of S100B and BDNF 24, 48, 72 and 120 hours after injury.

2. Method
2.1. Subject
This was a cohort study performed at the Emergency Department, Intensive Care Unit (ICU), and Inpatient Department of Malahayati Islamic Hospital, Medan, North Sumatera. The sample size of this study using 5% for significance level and 90% for confidence level, with dropout rate 10%. Based on the calculation, this study included 16 subjects, during the period of April-November 2011. The inclusion criteria were men or women, aged 20-60 years old, and admitted with a GCS of 5-8. A written informed consent was obtained for intracranial pressure monitoring and for participating in the study. For this purpose, the patient was represented by family members responsible for the patient.

Exclusion criteria were patients with bilateral mydriasis, patients with operative lesion based on CT scan; and patients with multiple trauma, history of chronic disease, cerebral tumor, and infection. Patients were categorized as dropouts if they were represented by family members who refused to continue participating in the study and if the patient passed away within three months.

Intracranial pressure which is a pressure inside cranial cavum filled with a brain, liquor cerebrospinal, and blood vessels in its brain [4-7]. Intracranial pressure value using mmHg, normal/low intracranial pressure was less than 20 mmHg, moderate was 20-30 mmHg, the high was more than 30 mmHg.

2.2. Laboratory analysis
At the start of the study, subjects with severe traumatic brain injury without effects or risk factors were identified. Subsequently, serum S100B and BDNF was measured at 24, 48, 72 and 120 hours after injury. An association between these findings and GOS was assessed after three months to identify the extent of influence as a prognostic factor.

S100 B protein is a protein binding calcium that involved into signal transduction and found in the glial cell in the nervous system. S100B protein release into perifer circulation. S100B protein measured in ug/liter units [8-10]. Measurements were performed using a regularly calibrated 450 nm Elisa reader. Initial examination of S100B protein with a level of more than 2.5 ug/l showed a high risk of worsening outcome. A concentration of serum S100B >2 ug/l is a high risk of poor outcome or even death [11-15].

Brain Derived Neurotrophic Factor is an endogen protein that produced by endoplasmicreticulumand Golgi apparatus in the cell, hippocampus is the highest organ that produced BDNF, and keeps neuron cell
function. Analysis of BDNF using pg/millimeters units [16]. Using Reader Elisa with wave length 450nm that had been routine scale. In normal condition, BDNF level concentration in cerebrospinal fluid is 6.16 pg/mL [17].

Analysis of Glasgow Outcome Scale is a scale used to evaluate the outcome of patients with traumatic brain injury after treatment. GOS is classified as good if the patient recovered (GOS 5) or if the patient can perform mild daily routine independently/moderate disability (GOS 4). GOS is classified as poor if the patient cannot perform daily routines without assistance/severe disability (GOS 3), if the patient is in a persistent vegetative state (GOS 2), or if the patient passed away (GOS 1) [12].

Glasgow Outcome Scale (GOS) is a scale used to evaluate the outcome of patients with traumatic brain injury after treatment. GOS is evaluated one month, three months, six months and 12 months after the injury. Among those choices, the 3-month evaluation is the most significant GOS measurement. It's based on the duration of recovery from traumatic brain injury and the rehabilitation process of patients with traumatic brain injury [18].

2.3. Statistical Analysis
Data were analyzed using Statistical Package for Social Science (SPSS) version 15. To determine normal distribution, Kolmogorov-Smirnoff test was performed analytically. If p value was <0.05, the distribution was considered abnormal. To determine differences in mean, which will be used to differentiate outcome, unpaired T-test was performed on normally distributed data. In data without normal distribution, Mann-Whitney test was performed. Level of significance in this study was 5%, p>0.05 was considered not significant and p<0.05 was considered significant.

3. Results and Discussion
Table 1 showed the characteristic of study subjects, most of the subject were 20-39 years (68.7%) and 50-60 year (31.3%). This could be related to the higher cause of head injury that found the highest cause of injury was motor cycle accident. In severe head injury, most of the study subjects were in GCS 6 and 7 and GOS after three months showed the higher percentage (68.6%). Most of the patient showed Diffuse Injury II in a CT-Scan examination.

Table 1. Distribution of study subjects according to demographic characteristic and parameters.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Frequencies (f)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GCS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>□ 6</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>□ 7</td>
<td>5</td>
<td>31.3</td>
</tr>
<tr>
<td>□ 8</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td><strong>GOS in three months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ 1</td>
<td>2</td>
<td>12.5</td>
</tr>
<tr>
<td>□ 2</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>□ 3</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>□ 4</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>□ 5</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td><strong>GOS categorized in three months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>□ Bad</td>
<td>4</td>
<td>31.3</td>
</tr>
<tr>
<td>□ Good</td>
<td>12</td>
<td>68.6</td>
</tr>
<tr>
<td><strong>CT-Scan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse Injury II</td>
<td>11</td>
</tr>
<tr>
<td>------------------</td>
<td>-------------------</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td>Diffuse Injury III</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2 showed fluctuating data for S100B protein, for the first 24 hours it showed the higher mean but in 120 hours, there was a decrease of S100B protein. Table 2 also showed the mean of BDNF for the first 24 hours but showed fluctuating data.

**Table 2.** Mean of CT-Scan, S100B Protein, and BDNF serum level.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Mean±standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 hours</td>
</tr>
<tr>
<td>CT-Scan</td>
<td>27.8±3.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>S100B Protein (µg/L)</td>
<td>2.9±0.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>BDNF (pg/mL)</td>
<td>7.0±0.9&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Normally distributed data: mean ± standard deviation
<sup>b</sup>Not-normal distribution data: median (minimum-maximum)

Table 3 showed intracranial pressure level could be the most significant predictor compared to S100B protein and BDNF.

**Table 3.** Analysis of the association among 24 hour-intracranial pressure, S100B Protein, and BDNF with good GOS after three months.

<table>
<thead>
<tr>
<th>Time assessment</th>
<th>24-hour pressure (p-value)</th>
<th>intracranial Protein S100B (p-value)</th>
<th>BDNF (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td>0.01&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.41</td>
<td>0.23</td>
</tr>
<tr>
<td>48 hours</td>
<td>0.05</td>
<td>0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>0.11</td>
<td></td>
<td>0.22</td>
</tr>
<tr>
<td>120 hours</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>0.74</td>
</tr>
</tbody>
</table>

<sup>a</sup>p = significance value (p<0.05)

Previous study found no significant difference regarding of intracranial pressure measurement in patients with severe traumatic brain injury[19]. This differs from our findings, probably because of in that study, severe traumatic brain injury cases studied included cases with intracranial lesion requiring decompression craniectomy. On the contrary, the subjects of this current study were patients suffering from severe traumatic brain injury without operable lesions. Thus, it can be concluded that patient outcome in the study was influenced by various factors. Some of these factors include the size of the hemorrhagic lesion and the size of craniectomy defect in the surgical procedure[19].

S100B protein measurement showed an initial increase within the first 24 hours, which decreased on subsequent measurements. However, increase of S100B after initial measurement was observed in several
patients. This indicates a secondary traumatic brain injury that was continuous and unstoppable in nature. Subjects tend to suffer from the poor outcome. This result was consistent with the previous studies, which found out that an increase in S100B protein started from the first minute after traumatic brain injury[20–21]. In accordance with that study, we found an increase in S100B protein within the first 24 hours in all subjects, indicating that S100B protein was increased in every case of traumatic brain injury.

Previous study found that the level of S100B protein could decrease rapidly, it may even reach the normal level within 4-6 hours [28], contrary to our findings. The level of S100B protein decreased 48 hours after injury, but did not reach anormal level and could still be classified as within dangerous range (>2 μg/l). The decrease was only temporary, as it increased 72 hours after injury and decreased 120 hours after injury. S100B protein level increased and remained above normal value until the fifth day of observation. Moreover, consistent with our findings, other previous studies found that the level of S100B protein increased on the first measurement [10]. The occurrence of secondary increase on subsequent examination can predict poor outcome of subjects with traumatic brain injury [10, 22-26].

A decreased level of S100B protein reaching below 2 μg/l at 120 hours after injury determined good GOS. Increased S100B indicates an ongoing secondary brain injury. S100B Protein may be a good initial marker in determining the prognosis of traumatic brain injury. In the patient with severe head injury, there was an increased in S100B protein serum level, in this study, found that the reduction of S100B protein serum level would show the good prognosis response. The reduction of S100B protein serum level at 120 hours post severe head injury would be biomarker to predict

Previous study showed that the increase in BDNF level after traumatic brain injury contributed to the healing process, decreased the cognitive decline effect, and increased the formation of nerve cells [27,28]. An increase in BDNF level as a feedback marker of traumatic brain injury recovery process occurred since the initial measurement. An increasing trend was observed in the process of brain injury decreased. However, a trend towards a decrease in BDNF level indicates a failure of the recovery process and an ongoing secondary brain injury (48-72 hours after injury). A BDNF level of ≤6.16 pg/ml as measured at 48 hours after trauma followed by a decrease on subsequent examinations may determine the patient’s GOS. This occurred concurrently with brain edema process which reaches its peak 48-72 hours after trauma.A limitation of this study was that we did not assess the quality of life by using quality of life questionnaire.

4. Conclusions
The conclusions was there should be a treatment protocol that emphasize the intracranial pressure checks in the first 24 hours (lower than 30 mmHg), S100B protein level at 120 hours (less than 2 μg/liter) or BDNF level at 48 hours (more than 6.16 pg/ml) as a predictor of severe head injury to predict good GOS after three months, but intracranial pressure level could be the most significant predictor compared to S100B protein and BDNF.

References


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