ORIGINAL ARTICLE

Predictive power of neuron specific enolase for traumatic brain injury in patients with head trauma

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Abstract

Introduction: The presence of a predictor for traumatic brain injury (TBI) in patients with head trauma could play a crucial role in the identification of patients at higher risk of brain injury. The use of serum biomarkers like enolase to predict TBI in patients with head trauma is under investigation. Regarding this, the aim of the present study was to explore the association of neuron specific enolase (NSE) with TBI in patients with head trauma.

Methods: This observational study was conducted on patients with isolated blunt head trauma. A total of 168 subjects were enrolled in the study, 84 cases of whom had isolated blunt head trauma, and 84 individuals had no head trauma (i.e., control group). The serum concentration of NSE in all included subjects was measured within the first 6 h. All patients underwent brain computed tomography (CT) scan. Statistical analysis was carried out using SPSS software, version 19.0. Independent t-test, one way ANOVA, and Chi-square test were used for statistical analysis. The receiver operating characteristic curve was plotted, and cut-off values of serum NSE were calculated to determine the sensitivity and specificity of this biomarker in the prediction of intracranial injuries.

Results: The mean serum NSE concentrations for patients with head trauma and controls were 23.14±22.63 (95% CI: 18.77-28.39) and 7.00±4.42 ng/ml (95% CI: 3.67-10.33), respectively, which were not significantly different (P=0.049). Furthermore, the serum NSE level was significantly higher in the group with severe trauma, compared with that in the group with mild trauma (P=0.023). According to our findings, the NSE of ≤ 15.5 ng/ml can rule out the likelihood of brain injury associated with head trauma with a sensitivity of 100% and a specificity of 88%.

Conclusions: The NSE can be helpful to predict severe brain injury in patients with head trauma where CT scan or other diagnostic tools are not available. According to our results, clinicians can rule out the possibility of a severe head injury after head trauma when having a case with a serum NSE level of ≤ 15.5 ng/ml.

Key words: Brain injury, Head trauma, Neuron specific enolase (NSE), Prognosis

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Introduction

Traumatic brain injury (TBI) is one of the leading causes of death and disability and accounts for up to about one-third of all trauma-related deaths (1). Early prognosis in patients suffering from head trauma is of critical importance in the reduction of associated morbidity and mortality. The Glasgow Coma Scale (GCS) is one of the most common systems used for this purpose; however, it has some limitations. For instance, in hemodynamically unstable (e.g., those with hypotention), poisoned, and intubated patients, the scale has a low precision (2, 3).

Currently, decisions in dealing with a patient with head trauma are made based upon various factors, including trauma mechanism, initial level of consciousness, clinical manifestations, and other associated injuries (4). According to the existing guidelines, patients classified as severe or moderate groups (GCS<13) should undergo further assessments, such as cranial computed tomography (CT) scans (5-7). Nonetheless, a normal CT finding is not sufficient for the discharge of a patient and cannot independently predict the likelihood of subsequent physical and cognitive impairments which may occur in many patients (8, 9). Therefore, the patients should be intensively observed in the emergency department for a certain period of time.

The available guidelines have not clearly specified the duration of the observation period and risk level to determine the required level of services in the emergency department; accordingly, decisions are inevitably made at the discretion of the physician. However, such decisions can be regarded as a challenging dilemma when there is a high volume of workloads or overcrowding in emergency departments (10).

A large number of patients with a mild head trauma admitted to the emergency departments are asymptomatic at the time of admission or will be symptomatic in spite of normal clinical findings upon admission. This issue complicates the process of deciding on the way of dealing with such referrals, constituting the majority of the patients admitted to emergency departments. Moreover, in this group of patients, GCS has a low sensitivity (5, 11). Even though numerous studies have been conducted in this field, they have failed to establish a definite strategy to manage the issue. The existing guidelines delegate the responsibility of making decisions about having a brain CT scan or discharging the patient to the physician (11).

Regarding the above-mentioned data, the availability of prognostic biomarkers for patients with head trauma can play a key role in the identification of the patients who are at higher risk of brain injuries. The identification of such biomarkers also leads to a lower workload in the emergency department and efficient prioritization for the staff involved in the care of trauma patients. The use of serum biomarkers, such as neuron specific enolase (NSE), to determine the prognosis in patients with head trauma is in progress (12).

The NSE is found in high concentrations in neuronal cytoplasm and in a lower quantity in the peripheral nerves of the endocrine cells and blood platelets. According to various studies, after brain injuries, NSE is elevated in the blood circulation and cerebrospinal fluid. Accordingly, this can be used as a tool to predict the severity of brain injury (13-15). The results of the current study can contribute to the clinicians to determine head trauma prognosis using serum biomarkers like NSE.

Methods

This descriptive cross-sectional study was conducted on the patients with isolated blunt head trauma admitted to the Emergency Department of Hazrat Rasoul-e-Akram Hospital, as a tertiary level teaching center in Tehran, Iran, from March 2016 to December 2017. The project was approved by the Ethics Committee of Iran University of Medical Sciences, Tehran, Iran (code: 91/D /130/3075). A total of 168 subjects were included in the study among whom 84 (50%) participants suffered from isolated blunt head trauma, and 84 (50%) subjects had no head trauma (i.e., control group). The control group consisted of the patients admitted to the emergency department of the hospital for reasons other than trauma.

Altman's nomogram was employed to calculate the sample size, estimated at 160 individuals using the standardized difference of 0.5. The inclusion criteria for the case group were: 1) isolated blunt head trauma, 2) age of ≥ 18 years, and 3) satisfaction of the patient or her/his next of kin to participate in the study. In addition, regarding the control group, the inclusion criteria were: 1) patient's satisfaction to donate a blood sample, 2) age of ≥ 18 years, and 3) lack of any trauma.

All patients were examined by the third-year residents of emergency medicine. The patients with head trauma were classified into three groups of mild (GCS ≥ 14), moderate (8 < GCS < 14), and severe (GCS < 8) (16). Initial physical examination findings, including the level of

consciousness and demographic information, were recorded in data collection forms. To assay the serum concentration of NSE in all patients, along with other necessary tests (i.e., complete blood count, blood glucose, and rhesus factor), blood samples were obtained within the first 6 h after head trauma.

All patients with head trauma underwent head CT scan, and the images were interpreted by highly skilled radiology specialists. The control group did not undergo the head CT scan. Serum levels of NSE (ng/ml) were measured using a diameter kit (Milano, Italy). According to the manufacturer's instruction, an NSE level of 0-12 ng/ml was considered normal, while values higher than 12 ng/ml were regarded as abnormal.

Statistical analysis

Data analysis was performed using SPSS software, version 18.0. The data were subjected to quantitative and qualitative analyses. The quantitative variables were reported as 95% confidence interval (CI) of the mean, and the qualitative variables were expressed as frequency and percentage frequency. The ROC curve was plotted, and the cut-off values of serum NSE were calculated to determine the sensitivity and specificity of this biomarker in the prediction of intracranial injuries. Normality of the quantitative data was investigated using the Kolmogorov-Smirnov test. The data were analyzed using the t-test, one-way ANOVA, and Chi-square test. A p-value less than 0.05 was considered statistically significant.

Results

A total of 168 individuals, consisting of 84 cases and 84 controls, were entered into the study. Among the patients with head trauma, 20, 32, and 32 participants were classified into mild, moderate, and severe head trauma groups, respectively. The mean age of the patients was 31.11±12.78 years (age range: 5-66 years). The results of the t-test revealed no significant difference between the case and control groups in terms of age (P=0.34).

The studied population consisted of 18 (21.42%) females and 66 (78.57%) males. Based on the results of the Chi-square test, the two groups were comparable in terms of gender distribution (P=0.51). The mean serum NSE concentration in patients with head trauma was 23.14±22.63 ng/ml (IQR=10-24). The NSE level was within the normal range for 27 (32.14%) patients (95% CI: 22.2-41.7) and greater than normal in 57 (67.85%) patients (95% CI: 57.5-77.6).

Regarding the four studied groups, the mean serum NSE levels in the control, mild head trauma, moderate head trauma, and severe head trauma groups were 7.00±4.42 (95% CI: 3.67-10.33), 14.2±8.54 (95% CI: 10.85-18.25), 20.15±17.14 (95% CI: 14.56-26.77), and 31.71±29.94 (95% CI: 22.34-42.9), respectively. In the control group, there was one subject with a mean serum NSE concentration higher than normal (Figure 1).

With regard to the patients with mild head trauma, the mean serum NSE concentration in 11 out of 18 subjects (55%) was higher than normal, while this value was within the normal range in 9 participants. Regarding the patients with moderate head trauma, the mean serum NSE level in 18 (56.3%) subjects was higher than normal; however, this value was in the normal range in 14 (44.7%) subjects. In the patients with severe head trauma, the mean serum NSE level was found to be higher than and within the normal range in 28 (87.5%) and 4 (12.5%) subjects, respectively.

The results of the one-way ANOVA test demonstrated that the mean serum NSE concentration was significantly different among all groups. In addition, Turkey and post hoc analysis revealed a significant difference in NSE serum levels between the control group and the groups with severe and mild head trauma. In this respect, the serum NSE level was significantly higher in the group with severe trauma, compared to those in the control (P=0.049) and mild trauma groups (P=0.023).

However, the difference was not statistically significant between other groups including, the control and mild trauma groups (P=0.88), control and moderate trauma groups (P=0.5) and severe and mild trauma groups (P=0.135). The mean serum NSE concentration was obtained as
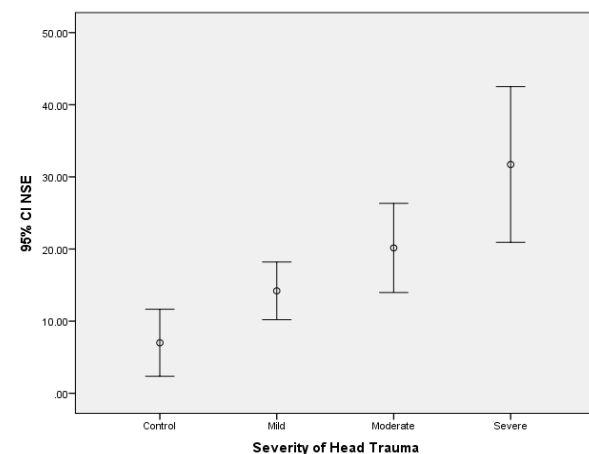

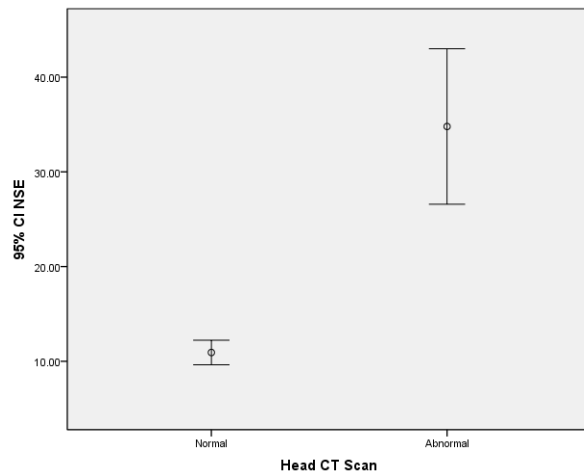**Figure 1: Comparison of neuron specific enalose serum levels in terms of trauma severity**

17

Figure 2: Comparison of neuron specific enalose serum levels between patients with intracranial hemorrhage and subjects with normal computed tomograhy findings

28.54±38.3 and 20.24±14.82 ng/ml in women and men, respectively. According to the results of the Mann-Whitney U test, this value was not significantly different between the two genders (P=0.888).

Among the 84 studied trauma patients, 43 (51.2%) subjects had abnormal head CT scan findings (95% CI: 40.5-61.9) that were classified into three groups. In this regard, 3 (15%), 15 (46.9%), and 25 (78.1%) patients were included in the mild, moderate, and severe head trauma groups, respectively. The results of the Chi-square test revealed a significant relationship between initial GCS and head CT scan findings (P<0.001). In this respect, decreased GCS was associated with increased abnormal brain CT findings (Figure 2).

In addition, a comparison was made between the groups with normal and abnormal head CT scan findings in terms of the serum levels of NSE. As the results indicated, the mean serum concentration of NSE was significantly higher in the group with abnormal findings in the brain CT scan (34.79±26.68 ng/ml; IQR=18-4), compared with that in the group with normal findings (10.92±4.1 ng/ml; IQR=13-8; P<0.001).

Another part of the analysis included the plotting of the ROC curve, and determining the cut-off values of serum NSE predicting the head trauma-associated intracranial injuries. The accuracy was measured by the area under the ROC curve of 0.981. It was demonstrated that an NSE level of ≤ 15.5 ng/ml can rule out the likelihood of the brain injury associated with head trauma with a sensitivity of 100%. Moreover, an NSE level of > 15.5 ng/ml had a specificity of 88%

to rule in the brain injuries associated with severe head trauma. Therefore, according to our findings, an NSE level of > 15.5 ng/ml was proposed as a prognostic biomarker with high sensitivity (100%) and specificity (88%).

Discussion

This cross-sectional observational study was targeted toward the investigation of the serum level of NSE in patients with head trauma. It was intended to determine the correlation between the serum concentration of this biomarker and the severity of brain injuries, as well as its prognostic potentiality. Our findings demonstrated that the mean serum NSE concentration in the patients with severe trauma was significantly higher than that in the patients with moderate and mild trauma.

Over the past decades, search for the biomarkers contributing to the prediction of the severity of brain injuries has attracted the attention of scientists and clinicians. Numerous biomarkers, including NSE and S100 protein, have been introduced as prognostic markers in clinical practice. These markers can also monitor the course of some diseases, including ischemic stroke, subarachnoid hemorrhage, and brain injuries, following head trauma (13, 14).

In order to clinically use NSE in the prediction of the severity of head trauma, it is required to determine the concentration at which predicting brain injuries in patients with head trauma with high sensitivity is possible. Various studies have reported different cut-off values for serum NSE levels to determine the neurologic prognosis in patients with head trauma; therefore, an exact cut-off value has not been presented yet.

Some studies have reported a cut-off value of 20 ng/ml for predicting poor neurologic outcomes in patients with head trauma (21-17). Guan et al. (2003) conducted a study on 41 patients with closed-head injury and a GCS of ≤ 8. They reported a cut-off value of 60 ng/ml for predicting poor neurologic outcomes (e.g., death and a GCS of < 3) in patients with head trauma (22). Olivecrona et al. also stated that in 48 patients with head trauma and a GCS of ≤ 8, an NSE level of > 9.52 ng/ml is an indicator of poor neurologic outcomes (e.g., GCS ≥ 3) (23). Rodríguez et al. also performed a survey on patients with severe head trauma (GCS < 8) and declared a level of > 6.0 ng/ml as the cut-off value facilitating the prediction of mortality within the first six months after trauma with the sensitivity and specificity of 75% and 66.1%, respectively (24).

In our study, a concentration of > 22.5 ng/ml was determined as acceptable to rule in brain injuries following head trauma. Moreover, according to the ROC analysis, a serum NSE level of ≤ 15.5 ng/ml could rule out the possibility of serious TBI following head trauma with 100% sensitivity. The results of the present study showed no significant difference between the two groups of patients with moderate and mild head trauma in terms of the NSE level. Moreover, this variable was not significantly different between the control and mild trauma groups.

In a systematic review performed by Papa Linda et al. (2015) on athletes with mild head trauma, there was no significant correlation between the increased level of NSE and mild brain injuries (25). However, Guan et al. (2003) investigating 78 patients with head trauma reported a significant difference between moderate and mild head trauma patients in terms of the NSE level (22).

In another study carried out on 80 patients with general trauma and head trauma, Meric et al. (2010) indicated a significant difference between the patients with mild head trauma (GCS of > 13) and moderate head trauma (GCS of 9-13) and between patients with moderate and severe head trauma regarding the NSE level (20).

The results of the current study were indicative of a significant difference between the patients with moderate and severe head trauma in terms of the NSE level. To the best of our knowledge, this study is unique due to presenting a cut-off value to rule out severe brain injuries with 100% sensitivity. One of the limitations of the present study was its small sample size. Furthermore, we investigated only one biomarker, and no comparison was performed with other biomarkers.

Conclusions

Serum NSE level can be used to predict severe brain injuries in patients with head trauma when other diagnostic tools like CT scan are not available. As the results indicated, the clinicians can rule out serious traumatic brain injuries following head trauma when the serum level of NSE is ≤ 15.5 ng/ml with 100% sensitivity. Regarding the high sensitivity and specificity of NSE, this biomarker can be addressed as a promising indicator to determine the prognosis and outcomes of the head injuries.

Acknowledgments

Conflict of Interest

There is no conflict of interests to be declared.

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