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Prognostic Importance of Serum S100 Protein (B Dimer) in Patients with Severe Head Trauma

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The serum level of S100B has been proposed as an indicator of prognosis in head trauma; however, there are scant reports in this regard. This study aimed to investigate the prognostic value of serum S100B in patients with severe head trauma. In a cross-sectional, prospective study, 72 patients with severe head trauma (Glasgow coma scale = 8) were recruited from Tabriz Imam Reza Teaching Center from September 2009 to December 2011. Serum level of S100B was measured on admission, 48 h later and at discharge/decease by enzyme-linked immunosorbent assay (ELISA) method. According to their in-hospital outcome, the patients were categorized as discharged (group A, n = 42), expired due to cerebral injury (group B, n = 16) and expired due to non-cerebral causes (group C, n = 14). The three groups were comparable in terms of age and sex. While the mean level of serum S100B was not significantly different between the three groups on admission and at the time of discharge/decease, it was significantly higher in group B (2.4±1 μU mL^{-1}) than in groups A (1.0±0.5 μU mL^{-1}) and C (1.5±0.5 μU mL^{-1}) 48 h after discharge ($p = 0.001$). Serum S100B levels on all three occasions were significantly correlated with Glasgow Coma scale in a reverse fashion. According to the Marshall grading system, the brain trauma was of grade I, II, III, IV and V in 18, 16, 13, 13 and 12 cases, respectively. The mean level of the serum S100B was significantly higher in grade V only when it was measured 48 h after admission ($p = 0.02$). In conclusion, serum level of S100B is a significant predictor of in-hospital mortality in patients with severe head trauma, when it is measured after 48 h of admission. It is also correlated with radiologic grade of the brain injury in such cases.

Key words: S100B protein, traumatic brain injury, prognosis

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INTRODUCTION

Cardiovascular diseases, traumatic accidents and malignancies are three major causes of mortality in developing countries. The deaths after traumatic accidents are usually due to the brain injury. Thus, many investigators have been trying to define accurate prognostic factors in such cases. A factor that is directly connected with brain cell death has been always tempting (Grossman and Loftus, 1999; Winn and Youmans, 2004; Korfias *et al*., 2006; Somi *et al*., 2008; Fattahi *et al*., 2011; Hashemzadeh *et al*., 2012). S100 is a calcium binding, dimeric protein, which is found in cytosole of astroglial and Schwann cells in the Central Nervous System (CNS). Previous reports have shown high concentrations of this protein in the cerebrospinal fluid (CSF) of patients with neurological diseases and brain damage (Raabe *et al*., 2003).

Some investigators have proposed the level of S100 may be correlated with the brain cell damage. They have suggested that measuring this protein in the plasma could be used as a noninvasive tool for predicting outcome in cases with traumatic and non-traumatic brain injuries (Pelinka *et al*., 2003; Rothermundt *et al*., 2003; Goncalves *et al*., 2008). Although, this association between serum S100 and prognosis of brain injury has been investigated, there are many limited studies available in this regard. Likewise, due to methodological shortcomings, conducting other studies has been suggested in these cases (Townend *et al*., 2002; Lomas and Dunning, 2005). Therefore, the objective of the present work was to examine the prognostic value of serum B dimer of S100 protein (S100B) measured in different occasions after severe brain trauma in in-hospital mortality. In addition, association between serum level of S100B protein and radiologic severity of the brain injury was investigated.

MATERIALS AND METHODS

In this cross-sectional, prospective study, 72 patients with severe head trauma (Glasgow Coma Scale, GCS = 8) who were admitted to the department of emergency in Tabriz Teaching Imam Reza Hospital within 2 h of trauma were recruited from September 2009 to December 2011. Patients with neurological diseases, hemodynamic shock, hypotension, hypoxia, severe accompanying/ spinal cord injuries; child cases (<5 years); patients in need of resuscitation at the time of admission and who expired within the first 24 h of hospitalization were not included. This study was approved by the ethics committee of Tabriz University of Medical Sciences. The patients were categorized in three groups: Who were discharged; who were expired due to the brain trauma; and who were expired due to other causes.

Serum levels of B dimer of S100 protein (S100B) were measured using an enzyme-linked immunosorbent assay (ELISA) method (Human S100B ELISA kit, Bio-vendor Research and Diagnostic Products) on admission, 48 h later and at the time of discharge/decease.

All patients were intubated and mechanical ventilation was employed if indicated. Severity of brain trauma was documented on brain Computer Tomography (CT) scans according to the Marshall Grading System (Saatman *et al*., 2008).

STATISTICAL ANALYSIS

The SPSS Software for Windows (ver.16.0, SPSS Inc., IL, USA) was used for analysis. One-way analysis of variance (ANOVA) along with Tukey *post hoc* test and the Chi-square (χ^2) or Fisher's exact tests were used. Correlation was examined using Pearson coefficient (r). A p-value = 0.05 was considered statistically significant.

RESULTS

During the study period, 42 patients were discharged, while 16 and 14 cases expired due to brain or other injuries, respectively. General data of the three mentioned groups are summarized in Table 1. While the three groups were comparable in terms of age ($p = 0.08$) and sex (0.10), surgical treatment was significantly more frequent in discharged patients comparing with expired ones ($p = 0.01$).

Potential prognostic factors in the three studied groups are summarized and compared in Table 2. Accordingly, abnormal pupil reaction on admission was observed significantly more frequent in the cases expired due to cerebral injury comparing with that in the other two groups ($p = 0.03$). The mean GCS on admission was significantly the lowest in the same group of the patients ($p<0.001$). The mean final GCS was significantly higher in the discharge cases ($p<0.001$). For the mean serum S100B, only 48 h after admission it was significantly higher in the cases expired due to cerebral injury ($p = 0.001$). There was no significant difference between the three groups in terms of on admission and final levels of the serum S100B ($p = 0.11$ and 0.09, respectively).

Negative, statistically significant correlations were documented between GCS and early, 48 h and final levels of the serum S100B ($r = -0.23$ with $p = 0.02$; $r = -0.29$ with $p = 0.01$ and $r = -0.92$ with $p = 0.01$, respectively).

Table 1: Demographic and general data of the three studied groups

Variable	Discharged (n = 42)	Expired		p-value
		Cerebral etiology (n = 16)	Non-cerebral etiology (n = 14)	
Age (year)	26.8±11.8	29.4±12.1	23.2±11.7	0.08
Sex				
Male	25 (59.5)	14 (87.5)	11 (78.6)	0.10
Female	17 (40.5)	2 (12.5)	3 (21.4)	
Mechanism of trauma				
MVA*	36 (85.7)	12 (75)	12 (85.7)	-
Fall	5 (11.9)	2 (12.5)	1 (7.1)	
Quarrel	3 (7.1)	2 (12.5)	2 (14.3)	
Treatment				
Nonsurgical	36 (85.7)	9 (63.3)	8 (57.1)	0.01*
Surgical	6 (14.3)	7 (46.7)	6 (42.9)	

Data are presented as mean±standard deviation (fro age) and frequency (%), MVA: Motor vehicle accident, *p<0.05 is significant

Table 2: Potential prognostic factors in the three studied groups

Variable	Discharged (n = 42)	Expired		p-value
		Cerebral etiology (n = 16)	Non-cerebral etiology (n = 14)	
Pupil reaction on admission				
Normal	21 (50)	3 (18.7)	6 (42.8)	0.03*
Impaired	21 (50)	13 (81.3)	8 (57.2)	
GCS on admission	5.6±1.7	3.0±1.0	5.6±2.1	<0.001*
Final GCS	12.9±2.6	3.1±0.2	3.0±1.0	<0.001*
S100B on admission ($\mu U\ mL^{-1}$)	1.0±0.5	1.0±0.9	1.1±0.4	0.11
Fourty eight hour S100B ($\mu U\ mL^{-1}$)	1.0±0.5	2.4±1	1.5±0.5	0.001*
Final S100B ($\mu U\ mL^{-1}$)	0.8±0.4	1.5±0.0	1.1±0.4	0.09

Data are presented as mean±standard deviation and frequency (%), GCS: Glasgow Coma Scale, *p<0.05 is significant

Table 3: Serum levels of S100B protein in various grades of brain damage

Serum S100B ($\mu U\ mL^{-1}$)	Grade					p-value
	I	II	III	IV	V	
On admission	0.4±1.1	0.6±1.0	0.8±1.4	0.7±1.2	1.0±0.4	0.35
Forty-eight hour	0.4±1.0	0.6±0.6	0.9±1.6	1.2±2.0	1.4±0.6	0.02*
Final	0.5±0.9	0.4±0.8	0.6±1.1	0.8±1.3	1.0±0.5	0.34

Data are presented as mean±standard deviation, *p<0.05 is significant

According to the Marshall Grading System, the brain trauma was of grade I, II, III, IV and V in 18, 16, 13, 13 and 12 cases, respectively. The mean levels of the serum S100B at different occasions are compared between various grades of brain trauma on CT scan in Table 3. It was significantly higher in grade V only when it was measured 48 h after admission (p = 0.02).

DISCUSSION

In the present work, possible prognostic importance of the serum level of S100B protein (B dimer) was examined in patients with severe traumatic head injury. Based on these findings, the mean value of this marker was significantly higher in the cases expired due to the cerebral injury comparing with other patients (discharged or expired due to non cerebral causes) 48 h after admission. In addition, the mean serum level of S100B protein was significantly associated with more severe brain injury after 48 h of admission.

In line with these findings, Goncalves *et al.* (2008) suggested that S100B protein might be used as an accurate indicator of status of the brain glial cells in terms of their activity or death.

Similarly, Jang *et al.* (2006) reported that the mean serum level of this protein was significantly higher in expired patients due to severe head trauma two weeks after the primary insult.

In the present study, on admission and final (at discharge or at the time of expiration) values of serum S100B protein were not significantly associated with prognosis. Previously, it had been reported that the level of S100B protein in the cerebrospinal fluid of patients with head trauma rose instantly in the aftermath of trauma and decreased gradually thereafter. In this study a positive correlation between serum levels of this protein and intracranial pressure was documented and proposed as underlying cause of this trend (Hayakata *et al.*, 2004).

In another study in this regard by Raabe *et al.* (2004), the mean serum level of S100B protein was significantly higher in patients with poor prognosis after traumatic head injury. Furthermore, they showed that the normalization time of this parameter took significantly longer (6 days, on average) in the same group comparing with that in patients with good prognosis (3-4 days). They concluded that this difference might be due to progressive damage of the brain cells in cases with more sever insult and thus, poorer prognosis.

This may justify why the mean level of S100B was significantly associated with more severe brain damage in the present study.

Using a CT-based grading system, Saatman *et al.* (2008) in the present work connects laboratory and radiographic features of head trauma in predicting prognosis in such patients. Therefore in cases with uncertain findings on their CT scans or magnetic resonance images during early stay in emergency department, using a concomitant measurement of serum S100B could clarify the status of the patients with no much extra charge or expending precious time. This is an important step to facilitate and accelerate appropriate decision-making in patients with ambiguous traumatic head trauma (Oh *et al*., 2007).

A significant, negative correlation between the serum levels of S100B protein and GCS was also confirmed in a previous similar study (Townend *et al*., 2002). This correlation emphasizes on the importance of this factor as a prognostic agent in patients with severe head trauma.

According to the findings of the present work, 48 h after admission is the best time for reporting the serum level of S100B protein in severe head trauma as a prognostic indicator. The optimal time for was 6 h after admission in another study by Lomas and Dunning (2005). This heterogeneity may be due to different methodology used in two studies. In addition, expired cases due to cerebral and non-cerebral etiologies were separated in the present work, which increases the accuracy of report comparing with available data.

In the present study B dimer of S100 protein (S100B) was used. According to a preliminary study by the authors (unpublished data), this dimer of S100 is the cheapest one to be measured. Since there is no significant difference among various dimers of S100 protein for prognostic purposes (Sedaghat and Notopoulos, 2008) S100B was chosen.

Conducting future studies with larger sample sizes and measuring serum S100B protein in shorter intervals are recommended to reach more definite results.

CONCLUSION

Serum level of S100B protein 48 h after admission may accurately predict in-hospital outcome of patients with severe head trauma. This is also a significant indicator of severity brain injury in such cases according CT findings.

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