The Role of Plasma D-Dimer as Prognostic Marker in Traumatic Brain Injury

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Abstract: Objective: S-100 B, which is a calcium binding protein, is an attractive marker of primary and secondary brain insults. Coagulopathy is common in TBI with unique features; as the injured brain release tissue factor which triggers coagulopathy and hyperfibrinolysis marked by high levels of plasma D-dimer. The aim of the study was to investigate the value of D-dimer as a prognostic marker of severe traumatic brain injury (TBI) and compare it with serum S-100B. *Design and setting*: prospective study in general intensive care unit. **Patients and participants:** 50 adult patients with isolated non surgical traumatic brain injury. Admitted between September 2010 to August 2011. **Intervention:** serum S-100B and D-dimer levels were measured on admission, day 3 and day 14. **Results:** Initial and follow up S-100 B and D-dimer levels were significantly correlated with Glasgow outcome score (GOS) and also correlated with poor outcome in TBI patients.
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Key words: D-Dimer, Traumatic Brain Injury, TBI.

1. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability around the globe. And is the leading cause of brain damage in children and young adults. About 2% of all emergency department visits are due to head injury. (1)

Biochemical markers in TBI

S-100 B brain protein , is a calcium binding protein found in astroglial cells and in Schwann cells.(4,5) It has been shown that the concentration of this protein increases in CSF and serum after cerebral injuries such as: head injury, meningitis, subarachnoid haemorrhage and stroke.(6,7) However, increased levels of S-100B can also be detected after extra- cranial injuries (eg, coronary bypass surgery and of fractures of long bones).(8,9) S-100B is metabolized in the kidney and excreted in urine. The biological half-life of S-100B is estimated to be less than 30 min.(10,11) Nonetheless, other values for the half time have been reported.(12,13)**)** In the literature it was found that there is different half-times for S-100B, from less than 30 minutes to between 1.5 and 2 hours.(12)

S-100B is considered an attractive surrogate marker of primary severe brain injury and secondary insults. Even in moderate and mild brain injuries early S-100B measurements are indicative of outcome .(10,11)

Coagulopathy in TBI

The development of coagulation abnormalities following head trauma is recognized.(14,15) Brain tissue has a higher level of thromboplastin than any other part of the body(16,17) and it is believed that coagulopathy is initiated by the release of thromboplastin from damaged brain tissues activating the extrinsic clotting process. Endothelial injury reinforces the coagulation cascade by launching an intrinsic clotting factor and platelet aggregations. In the presence of cross-linked fibrin, D-dimer in the plasma is produced by the activation of thrombin and plasmin disintegrating cross-linked fibrin. If the D-dimer level is elevated, the hyper-coagulation process continues .

Aim of The Work

The aim of the study was to investigate the value of D-dimer as a prognostic marker of severe TBI and compare it with serum S-100B.

2. Patients and Methods

The study was done on 50 adult head trauma patients of both sexes, who were admitted to ER and ICU of Alexandria Main University Hospital. The patients had the following inclusion criteria , Isolated non surgical head trauma patients with CT findings of Brain contusion or laceration, Intra cerebral hemorrhage (ICH), Subarachnoid hemorrhage (SAH), Intra ventricular hemorrhage (IVH) and Patients with extradural (EDH) or subdural hematoma (SDH).

Exclusion criteria

Patients aged less than 16 years old, Isolated brain oedema**,** Patients who received any type of blood products during the first 24 hours of admission, Patients who were operated for hematoma evacuation, Pregnant females. Poly traumatized Patients.

Methods

Informed consent was taken from the patients or their legal guardians, and approval of the local ethical committee was obtained.

Examination and investigation

- Full history including time lapse since head injury till hospital admission.
- Complete physical & neurological examination
- Laboratory and radiological investigations ;
- Cranial CT scanning was done to all patients on admission and for regular follow up & when the patient's condition had sudden unpredictable changes in his Glasgow Coma Score (GCS) .

Venous sampling and processing ;

- S100B was processed using human S100B ELISA Kits manufactured by Biovendor research and diagnostics company, and ELISA testing device was used to analyze these kits.[35,36]
- D-dimer was processed using Pathfast D-dimer test kits manufactured by IVD for in vitro diagnostics company and the device used is chemiluminescent enzyme immunoassay (CLEIA).[2930]

The statistical analysis of the data obtained was carried out using SPSS version 15. comparison between the groups of normally distributed quantitative data will be analyzed using paired t-test, student t-test and F test (ANOVA) while not normally distributed quantitative data will be analyzed using non parametric test such as Wilcoxon signed ranks test, Mann Whitney test and Kruskal wallis test.

3. Results

All the patients' age ranged between 17-70 years of age with a mean of 36.96 ± 14.87 years while as regards their sex they were predominantly males, 40 male patients in the study group and 10 female patients. Patients were classified according to their final GOS into two groups:

Favorable outcome group

This included 22 patients with Glasgow Outcome Score of (GOS 4, 5).

Unfavorable outcome group

This included 28 patients with Glasgow Outcome Score (GOS 1, 2, 3).

In the favorable group GCS on admission had a mean of 10.27±2.16, It increased significantly after 3days and 14 days to reach mean values of 11.64±2.46 & 14.55±1.50 respectively.

In the unfavorable group GCS on admission had a mean value of 4.14±1.27. It increased significantly on day 3 to reach a mean of 4.40±1.14 but on day 14 it reached a mean of 5.0± – and this was non significant (Table 1).

Table 1. Comparison between the mean values of GCS in the two groups at the different time intervals.

		GCS on admission	GCS after 3 days	GCS after 14 days
Favorable (n = 22)	N	22	22	22
	Range	5.0 – 14.0	5.0 – 15.0	9.0 – 15.0
	Mean ± SD	10.27 ± 2.16	11.64 ± 2.46	14.55 ± 1.50
P_1	**Test of sig.**		$Z = 3.796^*$ $p < 0.001$	$Z = 4.121^*$ $p < 0.001$
Unfavorable (n = 28)	N	28	5	1
	Range	3.0 – 7.0	3.0 – 6.0	5.0 – 5.0
	Mean ± SD	4.14 ± 1.27	4.40 ± 1.14	5.0 ± -
P_1	**Test of sig.**		$Z = 2.00^*$ $p = 0.046$	-
P_2	**Test of sig.**	$Z = 5.632^*$ $p < 0.001$	$Z = 3.367^*$ $p = 0.001$	$Z = 2.832^*$ $p = 0.005$

P_1: is intragroup comparison. P_2: is inter group comparison. * : Statistically significant at $p \leq 0.05$

In the favorable group D-dimer value on admission had a mean value of 1980.0±2276.51 µ/L. It decreased significantly after 3 days and 14 days to reach mean values of 1073.45±810.86µ/L & 455.45±347.99µ/L respectively.

In the unfavorable group D-dimer value on admission had a mean of 5652.32±7916.04 µ/L. It decreased non significantly after 3 days and 14 days to reach mean values of 4529.0±5353.54µ/L &1150.0± – µ/L respectively (Table 2).

In the favorable group, S100-B had a mean value of 81.0±25.0 (pg/ml). It decreased significantly after 3 days and 14 days to reach mean values of 69.95±20.33 (pg/ml) & 55.36±15.59 (pg/ml), respectively.

In the unfavorable group S100B had a mean value of 125.43±30.94 (pg/ml). It increased non significantly after 3 days to reach a mean value of 142.40±6.19 (pg/ml), then after 14 days it decreased non significantly to reach a mean value of 96.0 (pg/ml) (Table3).

Table 2. Comparison between the mean values of the D-dimer in the two groups and the same group at the different time intervals.

		D-dimer on admission	D-dimer after 3 days	D-dimer after 14 days
Favorable (n = 22)	N	22	22	22
	Range	200.0 - 8964.0	110.0 -3200.0	200.0 – 1640.0
	Mean ± SD	1980.0 ± 2276.51	1073.45 ± 810.86	455.45 ± 347.99
p_1	**Test of sig.**		Z = 4.075* p <0.001	Z = 3.980* p <0.001
Unfavorable (n = 28)	N	28	5	1
	Range	920.0 – 46605.0	980.0 – 13765.0	1150.0 – 1150.0
	Mean ± SD	5652.32 ± 7916.04	4529.0 ± 5353.54	1150.0 ± -
p_1	**Test of sig.**		Z = 0.405 p = 0.686	-
p_2	**Test of sig.**	Z = 3.090* p = 0.002	Z = 2.282* p = 0.022	Z = 1.362 p = 0.173

P_1: is intragroup comparison. P_2: is inter group comparison. * : Statistically significant at $p \leq 0.05$

Table 3. Comparison between the mean values of S100B at the different time intervals.

		S100B on admission	S100B after 3 days	S100B after 14 days
Favorable (n = 22)	N	22	22	22
	Range	22.0–120.0	36.0–102.0	33.0–82.0
	Mean ± SD	81.0±25.04	69.95±20.33	55.36±15.59
P_1	**Test of sig.**		Z = 3.394* p <0.001	Z = 3.979* p <0.001
Unfavorable (n = 28)	N	28	5	1
	Range	75.0–190.0	136.0–150.0	96.0–96.0
	Mean ± SD	125.43±30.94	142.40±6.19	96.0±-
P_1	**Test of sig.**		Z = 0.944 p = 0.345	-
P_2	**Test of sig.**	Z = 4.409* p <0.001	Z = 3.436* p = 0.001	Z = 1.662 p = 0.097

P_1: is intragroup comparison. P_2: is inter group comparison. * : Statistically significant at $p \leq 0.05$.

When doing ROC curve to S100B we found that at a cut off value of 115pg/mL, S-100B had a sensitivity of 60.71% and specificity of 95.45% and a positive predictive value of 94.44 and a negative predictive value of 65.63 with an accuracy of 76.0 with statistical significance at this cut off value (Table 4, Figure 1).

D-dimer had a cut off value 1540 µ/L and with doing ROC curve we found statistical significance at this value and we found a sensitivity of 78.57 % and a specificity of 72.73 % and positive predictive value of 78.57 and negative predictive value of 76.0 and with an accuracy of 76.0 at this cut off value for D-dimer (Table 4, Figure 2).

Table 4. Cut off value for both D-dimer and S100 B.

Cut off value		Favorable	Unfavorable	Sensitivity	Specificity	PPV	NPV	Accuracy
D-dimer at 1540 µ/L	**-ve**	16	6	78.57	72.73	78.57	72.73	76.0
	+ve	6	22					
S100B at 115 pg/ml	**-ve**	21	11	60.71	95.45	94.44	65.63	76.0
	+ve	1	17					

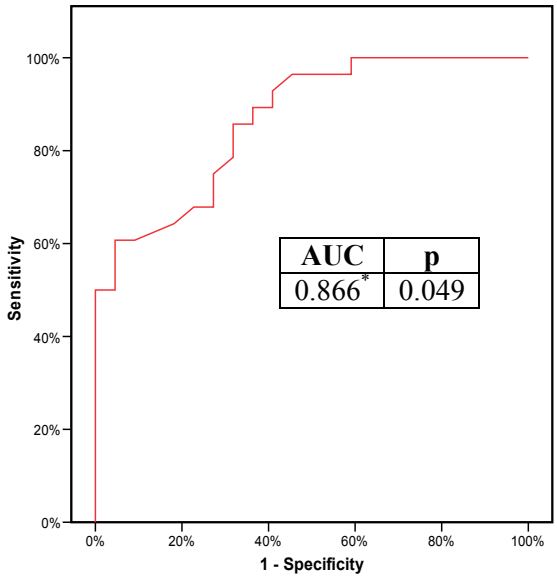

Figure 1: Sensitivity and specificity for S100 B at cut off value of 115pg/ml

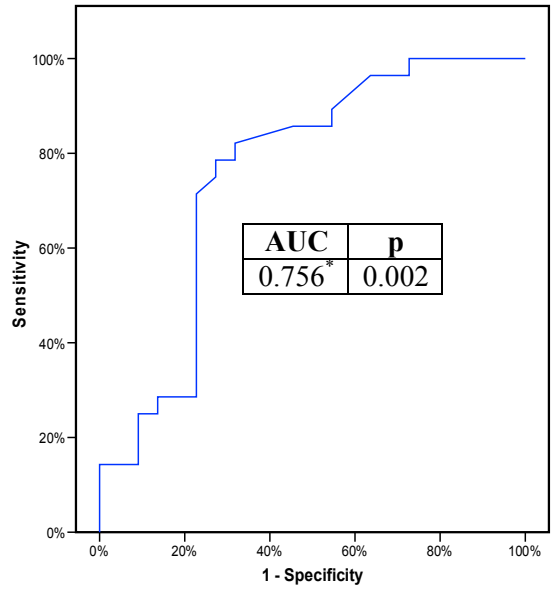

Figure 2: Sensitivity and specificity for D-dimer at cut off value of 1540 µ/L

Correlating the results of D- dimer and S100B on day of admission the r value (the pearson coefficient of correlation)was 0.047 and the p value was 0.748 with no statistical correlation found on the day of admission , while on day 3 we found a positive correlation between D- dimer and S100B and this correlation was statistically significant, while on day 14 it was not significant (Table 5).

When correlating D- dimer with the GCS on the day of admission it showed no statistically significant correlation but on day 3 and day 14 there was negative correlation with statistical significance. (Table 5).

When correlating D- dimer with GOS results we found that on admission it was not statistically significant at this time period, While on day 3 and day 14 there was negative correlation between D-dimer and GOS which was statistically significant. (Table 5)

Table 5. Correlation between the mean value of D-dimer with S100B, GCS and GOS in the two groups at different time intervals.

		D-dimer		
		On admission	**After 3 days**	**After 14 days**
S100B	**r**	0.047	0.470*	-0.050
	p	0.748	0.013	0.822
GCS	**r**	-0.195	-0.581*	-0.773*
	p	0.175	0.001	<0.001
GOS	**r**	-0.259	-0.552*	-0.556*
	p	0.070	0.003	0.006

r: Pearson coefficient

*: Statistically significant at $p \leq 0.05$

4. Discussion

The aim of this work was to investigate the potential of D-dimer as a prognostic marker in TBI patients and also to correlate D-dimer with S-100B and compare both markers in their ability to predict patient outcome.

As regards age and sex, No statistical significance was found. In the favorable group, GCS showed a significant successive increase throughout the period of the study. While in the unfavorable group GCS increased significantly at day 3 but yet did not affect the pateints outcome and stayed stationary till day 14.

The data found in this study regarding GCS matches the findings in the study done by Kue, et al,[18] who found that patients with GCS from 3 to 8 had poor outcome compared to those with GCS 9-12 and even better outcomes when GCS ranged between 12- 15.Also, Becker, et al,[38] found a significant association between GCS and clinical outcome in head trauma patients who developed disseminated intravascular coagulopathy (DIC).

In the current study the mean value of D-dimer was significantly higher in the unfavorable group than in the favorable group may be this was because patients in the unfavorable group were more severely injured and had a significantly lower GCS on admission While the mean values of D-dimer in the favorable group decreased from admission to day 3 to day 14 and this decrease was significant which means that the more D-dimer decreases in TBI patients the better they become clinically.

These results found in the study are in line with the study of Kuo, *et al.* [18] who studied 98 TBI patients and 59 non TBI patients with ICH and made a

correlation between D-dimer and GCS, pupillary light reflex, distance of midline shift on brain CT and the GOS. He excluded patients with pre existing venous thrombosis, recent surgery, drug use (asprin or Coumadin), or malignancy. They estimated the D-dimer levels within hours after acute insult and made the comparisons, they found a proportional inverse relation between initial GCS and D-dimer level in group of TBI patients, and they also found that D-dimer is correlated with poor patient outcome if D-dimer value is <1496 µ/L with sensitivity and specificity of 100% and 83% respectively.

The difference in our sensitivity and specificity values from those in the study done by Kue, *et al.* [18] may be attributed to the small number of patients in our study plus the high mortality in the unfavorable group in the study, which may have affected the statistical analysis of the current study.

D-dimer decreased significantly in the favorable group through all stages , this is concordant with the improvement in their GCS, but the decrease in the unfavorable group was noticed at day 3 and was not statistically significant which is also concordant with their GCS and it also goes with the results found on correlating D-dimer with GCS and GOS as one group in which there was inverse correlation between GCS,GOS and D-dimer in day 3 and day 14 which mean that the decrease in D-dimer values through the study was accompanied by improvement of the patients GCS and GOS. The same findings were recorded in previous studies done by Kuo, *et al.* and Bayir *et al.* [18,39]

As regards S-100B,It was found that S-100B rises with the primary insult and peaks around 48 to 72 hours then started falling down in the favorable group, which had good GCS, lower D-dimer value and better GOS, and this decrease gained statistical significance in the favorable group.

On the other hand in the unfavorable group the increased value of S-100B persisted throughout the study period, especially on day 3 where it peaked and this may be explained by the occurrence of secondary brain injury, leading to worse prognosis and finally eminent death.

ROC curve analysis of the mean values of S-100B was done whereby it was found that at a cut off value of 115 pg/ml, S-100B could predict poor prognosis in TBI patients and had a high accuracy of detecting such cases.

Correlation between S-100B, GCS and GOS whereby it was found that there is an inverse relation between S-100B ,GCS and with GOS, meaning that S-100B results could accurately give clues about which TBI patients may get worse or even die, according to its initial values, and its follow up. These results matched the study done by Korfias, *et al.* [44] who studied 102 patients with severe TBI adult patients where they measured the serum S-100B on admission and daily for the first 7 days. Their results showed that serum S-100B initial values were independent predictor of 1- month survival and subjects with initial levels higher than 100 pg/ml had a nearly threefold increased probability of death within one month, and the alteration in S-100B values indicated either improvement or deterioration, and finally they found that surgical intervention decreased the mean values of S-100B.

Raabe, *et al.* [40,41] concluded that S-100B is a promising serum marker for assessing the extent of primary injury (clinical and radiological factors) and the time course of secondary damage. Also Woertgen, *et al.* [45] found that serum S-100B above 200pg/ml measured within 6 hours after trauma has positive and negative predictive values of 87% and 77% for favorable and unfavorable outcome respectively.

Agian Mckeating, *et al.* [42] stressed the predictive value of S-100B in severe TBI. Petzold, *et al.* [43] described the ability of S-100B to predict increased ICP and unfavorable outcome in TBI patients.

So from the above mentioned studies we cannot overemphasis the new and widely proven and accepted role of S-100B as a reliable marker in predicting poor patient outcome in cases of TBI.

Conclusion

1- D-dimer is a good marker to predict outcome in TBI & It is widely available, cheap& reliable marker that can be easily done in most ICUs.

2- S-100B has definite role in prediction of poor patient outcome in TBI together with ability to mark the primary brain insult and its severity, the progression to secondary brain insult and ICH progression. It also can give us clues about which patient may die from his brain injury by reading its follow up results.

Recommendations

- D-dimer should be further studied to find the best time order to measure it whereby its results would much affect physician's orders and pateints management in TBI.
- S-100B is an excellent surrogate marker in TBI and it should be available in our ICUs and this would be a great opportunity to enhance TBI patient's management.

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