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Research Article

Neuromarkers as diagnostic adjuvant to cranial CT in closed traumatic brain injury patients admitted to ICU: A preliminary comparative study

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KEYWORDS

Neuromarkers;
Traumatic brain injury;
S100 protein;
NSE;
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Abstract *Objectives:* Evaluating the diagnostic and/or prognostic yield of serum levels of three neuromarkers, serum S100 protein, neuron-specific enolase (NSE) and Glial Fibrillary Acidic Protein (GFAP), in patients who were admitted to surgical intensive care unit (SICU) and had closed traumatic brain injury with suspicious presence of intracranial hematoma compared versus cranial CT (CCT) as a gold standard diagnostic modality.

Patients and methods: The study included 70 patients who had sustained a closed traumatic brain injury (TBI) requiring intensive care and/or surgical interference. All patients underwent clinical evaluation for all traumatized organs using Injury Severity Score (ISS) and concerning TBI Glasgow Coma Scale (GCS) score was recorded after non-surgical resuscitation. Then, all underwent CT scanning of the brain and patients with a surgically treatable mass underwent decompressive craniotomy, while patients free of hematoma or with minute-to-small hematoma not necessitating surgical interference were kept under observation. Venous blood samples were obtained from all enrolled patients at time of admission and patients who showed deterioration during conservative treatment gave second sample for ELISA estimation of serum S100 protein, NSE and GFAP.

Results: Forty-three patients had intracranial hematoma (Positive CCT); 26 patients underwent surgical interference, while the other 17 hematoma patients and 27 hematoma free patients (Negative CCT) were kept under observation. Of them 15 patients; 10 with hematoma and five who were

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hematoma free developed symptoms of increased ICP and follow-up CCT examination defined five cases required surgical interference with 66.7% rate for unnecessary follow-up CCT. Thirty-nine patients (55.7%) responded to conservative treatment and were discharged to the ward, while a total of 31 patients (44.3%) had surgical interference. Mean serum levels of studied parameters were significantly higher in all patients compared to controls with significantly higher levels in patients who had positive CCT compared to those who had negative CCT and in patients who required surgical interference compared to those managed conservatively. Patients who showed deterioration had significantly 2nd sample higher serum levels of S100 protein and GFAP, but non-significantly higher serum NSE levels compared to at admission levels. Percentage of increase of serum GFAP levels in follow-up sample obtained from patients who had positive CCT was significantly higher compared to the percentage of increase in serum S100 protein and NSE.

Conclusion: Estimation of serum levels of neuromarkers as adjuvant diagnostic and prognostic tools for closed TBI patients, but serum level of GFAP showed superior applicability and was more valid prognostic modality that could spare unnecessary CCT if applied as the percentage of change in comparison to at admission levels.

1. Introduction

At a surgical intensive care unit, the diagnosis, treatment, and prediction of outcome in traumatic brain injury present significant challenges to the treating clinician especially whenever, traumatic brain injury was a part of multiple trauma or associated with impaired or lost consciousness. Moreover, the neurological status can sometimes be difficult to evaluate because of sedation and despite radiology provides important information, but repeated investigations may not be feasible in critically ill patients [1–3].

However, clinical and radiological tools for assessing injury severity and predicting outcome, in particular, lack sensitivity and specificity. In patients with mild TBI, often there is uncertainty about which patients should undergo radiological imaging and who is at risk for long term neurological sequelae. In severe TBI, often there is uncertainty about which patients will experience secondary insults and what the outcome for individual patients will be [4,5].

These data point to the necessity for additional diagnostic and/or prognostic modalities to be combined with clinical and radiological data for evaluation and follow-up of patients especially in the extremes of traumatic closed brain injury; the mild that may be discharged home prior to manifesting full picture and the severe that could not cope with the need for frequent evaluation, and wherever CCT was not available.

Protein S100 is a dimeric acidic calcium-binding protein with a molecular mass of 10–12 kD and a biological half-life of about 1 h. It constitutes a major component of the cytosol of various cell types, but protein S100B is predominantly present in astrocytes and Schwann cells and can be both actively secreted into the extracellular space and passively released by cell death and the appearance of S100B in serum indicates both neuronal damage and increased permeability of the blood–brain barrier [6–8].

Enolase is a glycolytic enzyme that converts 2-phospho-D-glycerate to phosphoenolpyruvate, has a molecular weight of 70 kD and a biological half-life of 48 h. The encephalic NSE concentration ranges from 0.4% to 2.2%, and higher concentrations of NSE are found in the gray matter (e.g., neocortex) and lower levels in the white matter (e.g., pyramidal tract and corpus callosum). Besides being expressed selectively in neurons, NSE has a high stability in biological fluids and, as a free soluble cytoplasmic protein, can easily diffuse to the extracellular medium and cerebrospinal fluid (CSF) when neuronal membranes are injured [9–11].

The astrocytic Glial Fibrillary Acidic Protein (GFAP) is the principal intermediate filament protein found in the cytoskeleton of mature astroglia [12]. Previous studies showed a delayed release of the GFAP into the serum in patients with ischemic stroke, reaching maximum concentrations between days 2 and 4. Because of the more sudden disruption of the blood–brain barrier and the resulting brain damage, so it is hypothesised that GFAP would immediately be detectable in serum in the hyperacute phase of ICH [13–15].

Serum biomarkers were widely applicable for evaluation of patients who had various forms of acute illness especially those with misleading clinical and inconclusive radiological findings and for prognosis of patients with severe illness [16,17]. It is therefore imperative that inclusion of estimation of serum markers as a part of ICU workup could aid early diagnosis and adjustment of therapeutic planes for patients with closed traumatic brain injury and may greatly improve outcome. The present study aimed at evaluating the diagnostic and/or prognostic yield of serum levels of three neuromarkers in patients admitted to SICU and had closed traumatic brain injury with suspicious presence of intracranial hematoma compared versus cranial CT as a gold standard diagnostic modality.

2. Patients and methods

The present prospective double-blinded study was conducted at Departments of Anaesthesia and ICU, Neurosurgery Kasr AL-Eini Hospital in conjunction with Medical Biochemistry Department, Faculty of Medicine, Cairo University. After approval of the study protocol by the Local Ethical Committee and obtaining fully informed written consent from the nearest relative to the patient, 70 patients who had sustained a closed traumatic brain injury requiring intensive care and/or surgical interference were studied.

Patients with brain death, penetrating injury, infection and possible diseases that may alter the estimated parameters especially cerebrovascular accident, spinal injuries or spinal surgical procedures, Alzheimer or depressive psychosis was excluded. Twenty volunteers who passed the preliminary test for blood donation and within cross-matched age and sex were

included in the study to donate blood samples as control group for serum levels of estimated markers without undergoing other investigations conducted in the study.

All patients were admitted to surgical ICU and underwent clinical evaluation for all traumatized organs using Injury Severity Score (ISS) [18] and concerning TBI Glasgow Coma Scale (GCS) [19] was recorded after non-surgical resuscitation. Then, all underwent CT scanning of the brain and patients with a surgically treatable mass (subdural or epidural hematoma, large contusion with mass effect, and so on) were taken to the operating room for decompressive craniotomy. Patients free of hematoma or had minute-to-small hematoma not necessitating surgical interference were kept under observation for development of signs of or expansion of already present intracranial hematoma; and if occurred was assured by follow-up cranial CT.

Medical treatment was conducted according to patients' condition and consisted of sedation using (midazolam, fentanyl), intubation and ventilation to mild hypocapnia ($PaCO_2$ 26–30 mm Hg), and a muscle relaxant was administered if required.

Patients who had a surgically treatable lesion underwent ICP monitor insertion intraoperatively. The cerebral perfusion pressure (mean arterial pressure-intracranial pressure) was maintained >70 mm Hg with fluids and infusion of norepinephrine if required. Intracranial pressure levels >20 mm Hg were treated with mannitol, and moderate hyperventilation ($PaCO_2 > 35$ mm Hg) otherwise, barbiturate coma with burst suppression was induced. Patients who underwent conservative treatment were observed clinically and with repeated CCT on deterioration of neurological status, changes of GCS or appearance of manifestations of increased ICP.

Venous blood samples were obtained from all enrolled patients at time of admission and patients who showed deterioration during conservative treatment gave a second sample for comparison. Blood samples were allowed to clot then serum was separated by centrifugation at 3000 rpm for 10 min. Serum was removed, placed in pyrogen-free Eppendorf tubes and stored at -80 °C until ELISA assayed for estimation of serum S100 protein, NSE, and GFAP.

3. Statistical analysis

Obtained data were presented as mean ± SD, ranges, numbers and ratios. Results were analyzed using paired *t*-test and Chi-square test. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. p value <0.05 was considered statistically significant.

4. Results

The study included 70 patients; 52 males and 18 females with mean age of 40.8 ± 8; range: 22–64 years. There were 43 patients (61.4%) with CCT documented intracranial hematoma; 21 patients (27.1%) had epidural hematoma, 15 patients (8.6%) had subdural hematoma and seven patients (4.3%) had cerebral hematoma; the remaining 27 patients (38.6%) had CT free of hematoma collection. Twenty-six patients of those who had hematoma; 12 had epidural hematoma, nine had subdural hematoma and five had cerebral hematoma, underwent surgical hematoma evacuation, while the other 17 hematoma patients and the 27 hematoma free patients were kept under observation at surgical ICU. Throughout the observation period, 15 patients; 10 with hematoma and five of hematoma free developed symptoms of increased ICP and follow-up CCT examination defined four cases of expanding hematoma and one case of hematoma free developed hematoma and these five cases underwent surgical evacuation. Thirty-nine patients (55.7%) responded to conservative treatment and were discharged from the ICU to complete their follow-up at the surgical ward, while a total of 31 patients (44.3%) had surgical interference and completed their postoperative care at ICU. Thus, 15 patients required frequent CCT for establishment of the diagnosis of surgical intracranial hematoma in only five of them with 66.7% rate for unnecessary follow-up CCT (Table 1).

Mean ISS score of enrolled patients was 28.3 ± 8.8; range: 17–57 and mean GCS was 9.8 ± 2.6; range: 5–14. Mean ISS score of patients with intracranial hematoma (30.9 ± 11.2; range: 17–57) was non-significantly ($p > 0.05$) higher compared to hematoma free patients, (26.6 ± 6.4; range: 17–41), while had significantly ($p < 0.05$) lower GCS (7.2 ± 1.3; range: 5–10) compared to hematoma free patients, (11.5 ± 1.4; range: 9–14).

Mean serum levels of studied parameters were significantly higher in all patients, irrespective of the result of CCT, compared to controls with significantly higher levels in patients had hematoma (positive CCT) compared to those had negative CCT. Patients required surgical interference had significantly higher serum levels of the three parameters compared to patients managed conservatively. On contrary, patients who showed deterioration during conservation showed non-significantly higher GFAP, but non-significantly lower S100 and NSE serum levels compared to those responded to conservative treatment and discharged to the ward. Moreover, serum levels of the three markers showed non-significant difference between patients with positive follow-up CCT compared to those with negative follow-up CCT (Table 2).

Patients who showed deterioration during follow-up had significantly higher serum levels of S100 protein and GFAP, but non-significantly higher serum NSE levels compared to their levels estimated at time of admission. Moreover, patients with positive follow-up CCT showed significantly higher serum levels of the three parameters compared to their at-admission levels, while those with negative follow-up CCT showed non-significantly higher levels (Table 3).

The percentage of increase of serum GFAP levels in follow-up sample obtained from patients with positive follow-up CCT compared to at-admission levels was significantly higher compared to the percentage of increase in serum S100 protein and NSE with non-significant difference in the percentage of increase of S100 protein and NSE (Table 3, Fig. 1). However, the percentage of change of serum levels of studied parameters in cases showed deterioration during follow-up showed non-significant serum S100 and NSE levels compared to the change in serum GFAP levels (Table 3).

5. Discussion

Patients had significantly elevated serum markers compared to control group with significantly higher levels in patients who had intracranial hematoma and those who required surgical

Table 1 Patients' distribution according to CCT results and applied therapeutic modalities.

Management preliminary CCT		Surgical evacuation	Conservation and follow-up CCT			
			Total	Discharge	Deterioration	
					Positive CCT	Negative CCT
Positive	43	26	17	7	4	6
Negative	27	0	27	22	1	4
Total	70	26	44	29	5 (Surgical)	10 (Conservative)

Table 2 Mean (±SD) serum levels of estimated parameters in studied patients distributed according to therapeutic modality and outcome.

	S100 protein (μg/L)	NSE (μg/L)	GFAP (ng/L)
Control	0.239 ± 0.083	8.4 ± 2.8	1.5 ± 0.37
Preliminary CCT (n = 70)			
Positive (n = 43)	0.878 ± 0.377*	23.3 ± 7*	102.9 ± 47.1*
Negative (n = 27)	0.492 ± 0.35	19.4 ± 4.8	66.8 ± 22.4
Therapeutic modality (n = 70)			
Surgical (n = 26)	1.01 ± 0.31†	24.5 ± 5.8†	113.1 ± 46.2†
Conservative (n = 44)	0.562 ± 0.37	20.2 ± 6.4	74.8 ± 34.2
Outcome of conservative therapy (n = 44)			
Discharge (n = 29)	0.578 ± 0.416	21.2 ± 6.6	69.2 ± 27.2
Deterioration (n = 15)	0.517 ± 0.27	18.2 ± 5.8	86 ± 45.5
Follow-up CT of deteriorated cases (n = 15)			
Positive (n = 5)	0.547 ± 0.33	18 ± 4.8	92.2 ± 49.3
Negative (n = 10)	0.525 ± 0.25	17.8 ± 3.9	73.8 ± 31.4

* Significance versus patients had negative preliminary CCT.
† Significance versus patients received conservative treatment.

Table 3 Mean (±SD) serum levels of estimated parameters in patients showed deterioration during NICU stay and percentage of change compared to at-admission sample.

	S100 protein (μg/L)	NSE (μg/L)	GFAP (ng/L)
Patients had deterioration (n = 15)			
At admission	0.517 ± 0.27	18.2 ± 5.8	86 ± 45.5
At follow-up	0.606 ± 0.29*	19.7 ± 6.6	104.66 ± 55.9*
Patients had positive follow-up CCT (n = 5)			
At admission	0.547 ± 0.33	18 ± 4.8	92.2 ± 49.3
At follow-up	0.612 ± 0.35*	20.6 ± 9.4*	122.4 ± 50.4*
% of change	15.5 ± 8.9	15.9 ± 7.3	54.1 ± 25.3†‡
Patients had negative follow-up CCT (n = 10)			
At admission	0.525 ± 0.25	17.8 ± 3.9	73.8 ± 31.4
At follow-up	0.603 ± 0.284	20.6 ± 6.4	95.8 ± 29
% of change	14.7 ± 3.8	13.6 ± 12	10.3 ± 4.4

* Significance versus at-admission levels.
† Significance versus percentage of change in serum levels of S100 protein.
‡ Significance versus percentage of change in serum levels of NSE.

interference compared both to those free of hematoma and to patients managed conservatively, respectively. This finding indicated a fact that TBI is associated with release of these markers irrespective of the extent of brain trauma, but their levels increase with increased injury severity.

This finding indicated a fact that traumatic brain affection irrespective of the presence of bleeding or not and irrespective of the extent of trauma and its impact on consciousness results in injury of brain tissue with concomitant release of these markers and indicating their validity for diagnosis of brain tissue injury and reflecting its severity. The obtained data supported those previously reported in literature concerning the serum levels of neuromarkers after TBI; Berger et al. [20] found serum concentrations of S100 protein, NSE and myelin basic protein obtained at the time of pediatric TBI may be useful in predicting severity and outcome. Vajtr et al. [21] also, found serum values of NSE and protein S-100 overdrow the reference value in cases with negative findings on CT scan,

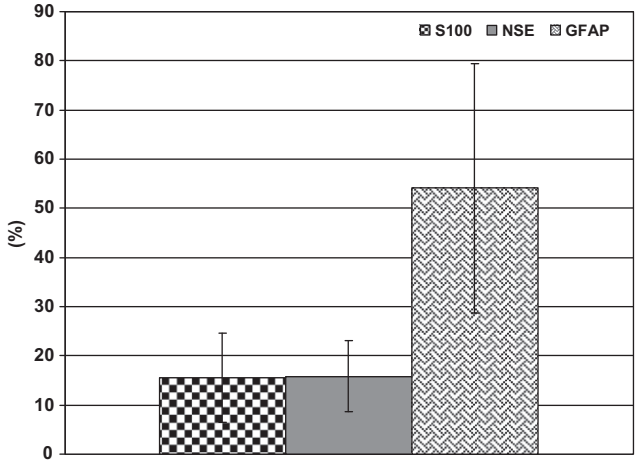

Figure 1 Percentage of change of serum levels of studied parameters estimated at deterioration versus at-admission levels in patients showed positive follow-up CCT.

mild or severe concussion. Lumpkins et al. [22] reported that at admission day, the mean GFAP level in non-TBI patients significantly lower compared with TBI patients and the significant difference extended to day 2 after trauma.

Fifteen patients out of 44 patients managed conservatively showed manifestations of neurological deterioration and estimation of serum markers at time of deterioration detected significant increase of serum S100 protein and GFAP with non-significant increase of serum NSE compared to their levels estimated at admission. However, such increase was more manifest in those proved to have increased hematoma size in four patients and new collection in one patient with previously free CCT, while no radiological abnormalities were detected in the other 10 patients and this was confirmed by new frequent CCT. Thus, CCT could be spared in about 67% of patients showed deterioration unless they had significantly increased serum neuromarkers. Such finding goes in hand with Korfias et al. [23] who found serum S100 alteration indicated neurological improvement or deterioration and surgical treatment reduced S100 levels and concluded that serum S100 protein reflects injury severity and improves prediction of outcome after severe TBI and may also have a role in assessing the efficacy of treatment after severe TBI.

The reported significantly elevated serum NSE in total patients, with non-significant increase in those showed deterioration points to a fact that no marker could be reliable by itself only. Another limitation was the non-significant elevation of serum neuromarkers in patients who showed deterioration and had negative CCT; both limitations indicated the necessity for the use of combined serum markers so as to cover the pitfalls of each and the better diagnostic yield of calculation of the percentage of change in serum levels instead of relying on the crude serum level. In support of this assumption, the percentage of change in serum GFAP was significantly higher compared to that calculated for both S100 and NSE in patients who required surgical interference after deterioration during conservative treatment, while showed non-significantly lower percentage of change compared to that calculated for both of S100 and NSE in patients did not require surgical interference.

These findings could be attributed to the data provided by Benneker et al. [24] who suggested that S100 serum levels might be useful for the diagnosis of acute vertebral body and spinal cord injury with a high negative predictive power especially if associated with fractured large bones and by Guzel et al. [25] who reported that there are several serious limitations of the use of NSE as a biomarker in TBI because hypoperfusion, extracranial trauma, bleeding, liver, or kidney damage also increase its level. On contrary, Honda et al. [26] reported that despite serum GFAP, S100, and NSE levels were significantly higher in TBI patients than in the non-TBI patients serum GFAP had the largest area under ROC curve (0.983), with 88.9% sensitivity and 100% specificity for TBI, defined by abnormal head CT findings, in prehospital-triaged patients with severe trauma. Wiesmann et al. [27] investigated the predictive value of early serum levels of S100 and GFAP in TBI and found blood levels of S100 and GFAP indicate the severity of brain damage and are correlated with neurological prognosis after trauma.

The better yield of estimation of serum GFAP could be attributed to its power for differentiation between hemorrhagic and non-hemorrhagic brain insults; Und et al. [28] found no differences in S100 and NSE levels between patients with ischemic stroke or intracranial hemorrhage; however, GFAP levels were significantly higher in intracranial hemorrhage patients. Dvorak et al. [29] found between 2 and 6 h of stroke onset, serum GFAP was significantly higher in intracranial hemorrhage patients than in ischemic stroke patients and serum GFAP values were significantly correlated with intracranial hematoma volume. Also, Lumpkins et al. [22] found at admission day, the mean GFAP level in non-TBI patients was significantly lower compared to TBI patients and the AUC for GFAP was 0.90.

These data illustrate the validity of estimation of serum levels of neuromarkers as adjuvant diagnostic and prognostic tools for closed TBI patients, but serum level of GFAP showed superior applicability and was more valid prognostic modality that could spare unnecessary CCT if applied as the percentage of change in comparison to at admission levels. However, wider scale studies are required for confirmation of the obtained results and identification of cutoff points for differentiation between surgical and non-surgical cases and for definition of deterioration.

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