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Serum thioredoxin and in-hospital major adverse events after traumatic brain injury

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ABSTRACT

Background: In-hospital major adverse events (IMAEs), mainly including acute lung injury, acute traumatic coagulopathy, progressive hemorrhagic injury and posttraumatic cerebral infarction, are associated with poor prognosis after traumatic brain injury (TBI). Thioredoxin, a potent anti-oxidant, has been identified as an oxidative stress marker. This study was designed to explore the association of serum thioredoxin concentrations with IMAEs of patients with severe TBI.

Methods: This prospective, observational study recruited a total of 108 healthy controls and 108 patients with severe TBI. We investigated the possible relation of serum thioredoxin concentrations to IMAEs and trauma severity (reflected by Glasgow coma scale scores) following TBI using a multivariate analysis.

Results: Serum thioredoxin concentrations were higher in the patients than in the controls. Serum concentrations of thioredoxin significantly correlated with admission Glasgow coma scale scores. Thioredoxin in serum independently predicted any IMAEs. As compared to admission Glasgow coma scale scores, thioredoxin concentrations had similar areas under receiver operating characteristic curve for any IMAEs.

Conclusion: Increased serum thioredoxin concentrations are highly associated with trauma severity and IMAEs, indicating thioredoxin might be a potential prognostic biomarker after TBI.

1. Introduction

Severe traumatic brain injury (TBI) is a devastating form of trauma associated with a high rate of morbidity and mortality [1–4]. Acute lung injury (ALI), acute traumatic coagulopathy (ATC), progressive hemorrhagic injury (PHI) and posttraumatic cerebral infarction (PTCI) are some common in-hospital major adverse events (IMAEs) after severe TBI, which are associated with poor prognosis of patients with severe TBI [5–15]. It is now believed that secondary brain injury plays a crucial role in these IMAEs via a cascade of complex pathophysiologic pathways that continues to be investigated [14–18]. Increased concentrations of certain serum proteins have been identified as biomarkers that may reflect or directly participate in the oxidative stress, inflammation, blood brain barrier disruption, and neuronal and glial toxicity that occur during this secondary period of cerebral injury [19–22].

Thioredoxin (TRX), a ubiquitous, 12.5 kDa intracellular thiol protein, is a potent anti-oxidant [23,24]. It regulates inflammation, cell growth and apoptosis [25]. During oxidative stress and inflammation, TRX is released to the peripheral blood [26]. Its circulating concentrations are increased with the increasing severity in some diseases including sepsis, acute pancreatitis, post-cardiac arrest syndrome, acute myocardial infarction, child hydronephrosis and malignant neoplasms [27–32]. Recently, the close relation of increased serum TRX concentrations to the severity and clinical outcome has been confirmed in patients with acute ischemic stroke [33], spontaneous intracerebral hemorrhage [34], aneurysmal subarachnoid hemorrhage [35] and severe TBI [36], indicating TRX might be an oxidative stress marker in some neurological diseases. However, the relationship between circulating TRX concentrations and IMAEs in patients with severe TBI warrants to be established.

2. Methods

2.1. Study population

This prospective, observational study was performed at The

Abbreviations: TBI, traumatic brain injury; ALI, Acute lung injury; ATC, acute traumatic coagulopathy; PHI, progressive hemorrhagic injury; PTCI, posttraumatic cerebral infarction; IMAEs, in-hospital major adverse events

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Hangzhou First People's Hospital from May 2010 to November 2015. Study subjects comprised head trauma patients and controls. Inclusion criteria for the patients consisted of isolated head trauma, postresuscitation Glasgow coma scale (GCS) score of ≤ 8 or less, ≥ 2 head computed tomography (CT) scans in the first 72 h and at least four head CT scans in the first week after injury. Isolated head trauma was defined as CT scan - confirmed brain injury without other major extracranial injuries, such as pelvis or femur fractures, or severe abdominal or thoracic invasive injuries, as indicated by an extracranial abbreviated injury scale score < 3 [37]. Exclusion criteria for the patients were age of < 18 y, admission time of > 6 h since trauma, infection within recent a month, previous head trauma, neurological disease including ischemic and hemorrhagic stroke, use of antiplatelet or anticoagulant medication, and other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease, diabetes mellitus and hypertension. Alternatively, controls were composed of gender- and age-matched healthy individuals. This study was carried out in accordance with the ethical standards of the responsible committee on human experimentation in The Hangzhou First People's Hospital. Written informed consent was obtained from someone responsible for them.

2.2. Clinical and radiological assessment

Head trauma severity was evaluated in terms of GCS scores. Abnormal cisterns, midline shift > 5 mm and traumatic subarachnoid hemorrhage were recorded on initial CT scan. ALI was diagnosed according to the international consensus criteria, which include acute onset, the ratio of partial pressure of arterial oxygen to fractional inspired oxygen ≤ 300, bilateral infiltrates on chest radiograph, and no clinical evidence of left arterial hypertension [38]. Diagnosis of PHI and PTCI was made on the follow-up CT scan. PHI was defined as any increase in size or number of the hemorrhagic lesion, including newly developed ones [39]. Diagnosis of PTCI was made according to the following criteria: (1) distinctly hypodense lesions within a defined cerebral vascular territory; (2) hypodense lesions located in boundary zones between the defined cerebral vascular territories or situated in the terminal zones of perforating arteries within the deep white matter [40]. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information.

2.3. Immunoassay methods

Venous blood was drawn from patients on admission and from controls at study entry. Coagulation test or blood routine test were completed using the routine laboratory assay. ATC was defined as an activated partial thromboplastic time > 40 s and/or international normalized ratio > 1.2 and/or a platelet count < 120×10^9/L [41,42]. Serum was obtained by centrifugation at 3000 x *g* and then stored at − 80 °C before measuring. TRX were measured in duplicate samples with a commercially available sensitive enzyme-linked immunosorbent assay (Redox Biosciences). Patients exhibiting hemolysis were excluded due to the high intracellular concentration of TRX, which will bias assessment [23]. All determinations were done by the same laboratory technician having no access to all clinical data.

2.4. Statistical analysis

The categorical variables were reported as counts (percentage). Using Kolmogorov-Smirnov test or Shapiro-Wilk test, normality of data distribution was tested for all continuous variables. All continuous data in this study were non-normally distributed, and subsequently, were reported as median (interquartile range). Consequently, Mann-Whitney *U* test was performed to compare intergroup differences of these continuous variables. Bivariate correlation analysis was conducted using Spearman's correlation coefficient. Association of serum TRX concentrations with other variables was verified in a multivariate linear regression model, which included the significant parameters in the bivariate correlation analysis. Multivariate logistic regression analysis was performed to determine factors that could be considered as independent predictors for IMAEs (i.e., ALI, ATC, PHI and PTCI). The parameters, which were found to be significant in univariate logistic regression analysis, were entered into multivariate logistic regression model. Odds ratio (OR) and 95% confidence interval (CI) were estimated. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum TRX concentrations for the IMAEs. Subsequently, area under curve (AUC) and the corresponding 95% CI were calculated. In a combined logistic-regression model, we estimated the additive benefit of TRX concentrations to GCS scores. Statistical analysis was performed with SPSS 19.0 and MedCalc 9.6.4.0. Differences were considered to be significant at a $P < 0.05$.

3. Results

3.1. Participant characteristics

This study recruited a total of 108 patients and 108 gender- and age-matched healthy controls. The patients, consisting of 61 men and 47 women, had a median age of 34 (27) y (range, 18–76 y). The median postresuscitation GCS score was 5 (3) (range, 3–8). Unreactive pupils occurred among 44 patients (40.7%); abnormal cisterns, among 52 patients (48.2%); midline shift > 5 mm, among 47 patients (43.5%) and traumatic subarachnoid hemorrhage, among 61 patients (56.5%). Their median admission time, plasma-sampling time and time from trauma to the first CT scan were 2.3 (2.4) h (range, 0.5–6 h), 4.8 (4.7) h (range, 1.5–10.5 h) and 2.9 (2.0) h (range, 1.1–7.2 h) respectively. During stay in hospital, ALI, ATC, PHI and PTCI were found in 29 (26.9%), 44 (40.7%), 33 (30.6%) and 16 (14.8%) patients respectively.

3.2. Change of serum TRX concentrations

In Fig. 1, serum TRX concentrations were significantly higher in patients than in controls, in patients with ALI than in those without ALI, in patients with ATC than in those without ATC, in patients with PHI than in those without PHI and in patients with PTCI than in those without PTCI. Alternatively, using Spearman's correlation coefficient, serum TRX concentrations correlated with GCS scores (Fig. 2) and other parameters in Table 1. Moreover, even though multivariate linear regression analysis was performed, the close relation of serum TRX concentrations to GCS scores still existed ($t = -4.605$, $P < 0.001$).

3.3. ALI prediction

Table 2 shows that GCS scores, serum TRX concentrations and other variables were highly associated with ALI. A multivariate analysis chose GCS scores (OR, 0.333; 95% CI, 0.170–0.651; $P = 0.001$) and serum TRX concentrations (OR, 1.081; 95% CI, 1.003–1.165; $P = 0.043$) as the independent predictors for ALI of patients. Under ROC curve, serum TRX concentrations possessed high ability to discriminate patients at risk of ALI (AUC, 0.810; 95% CI, 0.724–0.879). Fig. 3 depicts an optimal cutoff value of serum TRX concentrations, which yielded the corresponding values of sensitivity and specificity. Moreover, compared with GCS scores (AUC, 0.831; 95% CI, 0.747–0.896), serum TRX concentrations had similar discriminatory ability reflected by AUC ($P = 0.713$). In a combined logistic-regression model, TRX concentrations numerically improved AUC of GCS scores to 0.878 (95% CI, 0.801–0.933; $P = 0.148$).

3.4. ATC prediction

In Table 2, univariate logistic regression analysis demonstrated that