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Plasma copeptin level predicts acute traumatic coagulopathy and progressive hemorrhagic injury after traumatic brain injury

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ABSTRACT

Higher plasma copeptin levels correlate with poor clinical outcomes after traumatic brain injury. Nevertheless, their links with acute traumatic coagulopathy and progressive hemorrhagic injury are unknown. Therefore, we aimed to investigate the relationship between plasma copeptin levels, acute traumatic coagulopathy and progressive hemorrhagic injury in patients with severe traumatic brain injury. We prospectively studied 100 consecutive patients presenting within 6 h from head trauma. Progressive hemorrhagic injury was present when the follow-up computerized tomography scan reported any increase in size or number of the hemorrhagic lesion, including newly developed ones. Acute traumatic coagulopathy was defined as an activated partial thromboplastic time greater than 40 s and/or international normalized ratio greater than 1.2 and/or a platelet count less than 120×10^9/L. We measured plasma copeptin levels on admission using an enzyme-linked immunosorbent assay in a blinded fashion. In multivariate logistic regression analysis, plasma copeptin level emerged as an independent predictor of progressive hemorrhagic injury and acute traumatic coagulopathy. Using receiver operating characteristic curves, we calculated areas under the curve for progressive hemorrhagic injury and acute traumatic coagulopathy. The predictive performance of copeptin was similar to that of Glasgow Coma Scale score. However, copeptin did not obviously improve the predictive value of Glasgow Coma Scale score. Thus, copeptin may help in the prediction of progressive hemorrhagic injury and acute traumatic coagulopathy after traumatic brain injury.

Introduction

Severe traumatic brain injury (STBI) is a frequent pathology and is associated with high morbidity and mortality [19]. Acute traumatic coagulopathy (ATC) and progressive hemorrhagic injury (PHI) has been verified to be an independent determinant of death and disability after STBI [3,7,14,18]. Copeptin, which is the C-terminal part of the arginine vasopressin (AVP) precursor, is secreted stoichiometrically with AVP from the neurohypophysis [4]. AVP is a marker of endogenous stress but routine measurement of AVP is limited due to its instability and difficulty of the assay [2]. Copeptin now appears to be an attractive alternative to AVP because of its stability and development of automated technique for reliable and reproducible dosage [9,22,24]. Copeptin is associated with poor clinical outcomes in patients with critical illness [6,17,22]. Although higher copeptin levels have been shown to increase risk of poor outcome and death after STBI in several studies [5,13,16,23], the link between copeptin levels, ATC, and PHI in patients with acute STBI remains largely unknown. The aim of the present study was to investigate the relationship between copeptin levels and ATC in patients with STBI and their impact on PHI.

Materials and methods

Study population

A prospective observatory study over period of 3 years from September 2010 to September 2013 at the Hangzhou First People's Hospital, Hangzhou, China was conducted. This study included the patients with isolated head trauma, postresuscitation Glasgow Coma Scale (GCS) score of 8 or less and two or more head computed tomography (CT) scans in the first 72 h. Isolated head trauma was defined as CT scan – confirmed brain injury without other

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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 less than 3. Exclusion criteria included less than 18 years of age, admission time >6 h, previous head trauma, neurological disease including ischemic or hemorrhagic stroke, use of antiplatelet or anticoagulant medication, diabetes mellitus, hypertension or presence of other prior systemic diseases including uremia, liver cirrhosis, malignancy, chronic heart or lung disease. Written consent to participate in the study was obtained from study population or their relatives. This protocol was approved by the Ethics Committee of the Hangzhou First People's Hospital before implementation.

Clinical and radiological assessment

Head trauma severity was assessed using initial postresuscitation GCS score. Abnormal cisterns, midline shift >5 mm and traumatic subarachnoid hemorrhage were recorded on initial computerized tomography (CT) scan. PHI was present when the follow-up CT scan reported any increase in size or number of the hemorrhagic lesion, including newly developed ones [1]. All CT scans were performed according to the neuroradiology department protocol. Investigators who read them were blinded to clinical information.

Immunoassay methods

Venous blood was drawn from patients on admission. Coagulation test or blood routine test were completed using the routine laboratory assay. Coagulopathy was defined as an activated partial thromboplastic time greater than 40 s and/or international normalized ratio greater than 1.2 and/or a platelet count less than 120×10^9/L [8,10]. The blood samples for the determination of copeptin were immediately placed into sterile EDTA test tubes and centrifuged at $3000 \times g$ for 30 min at 4 °C to collect plasma. Plasma was stored at −70 °C until assayed. The plasma concentrations of copeptin were analyzed by enzyme-linked immunosorbent assay using commercial kits (Phoenix Pharmaceuticals, Belmont, CA) in accordance with the manufactures' instructions. The person carrying out the assays was completely blinded to the clinical information.

Statistical analysis

Statistical analysis was done using the SPSS 10.0 statistical package (SPSS Inc., Chicago, IL, USA) and MedCalc 9.6.4.0. (MedCalc Software, Mariakerke, Belgium). The categorical variables are presented as counts (percentage), and the continuous variables are presented as mean ± standard deviation. Statistical significance for intergroup differences was assessed by chi-square for categorical variables, and by Student t for continuous variables. Receiver operating characteristic (ROC) curves were configured to establish cutoff points of plasma copeptin level that optimally predicted the ATC and PHI with calculated area under curve (AUC). Multivariable logistic regression analyses were performed to determine factors that could be considered as independent predictors of the ATC and PHI, adjusted by confounding variables according to the results of the univariate analysis. Variables showing $P < 0.1$ in univariate analysis were included in the multivariate model. The logistic regression results are presented as odds ratio (OR) and 95% confidence interval (CI). In a combined logistic-regression model, we estimated the additive benefit of copeptin to GCS score. A P value <0.05 was considered significant.

Table 1
The factors associated with acute traumatic coagulopathy.

	Acute traumatic coagulopathy		*P* value
	Positive	Negative	
Number	45 (45.0%)	55 (55.0%)	
Sex (male/female)	30/15	36/19	0.899
Age (y)	44.0 ± 14.5	36.9 ± 14.9	0.018
Glasgow Coma Scale score	3.7 ± 0.9	5.8 ± 1.5	<0.001
Unreactive pupils	30 (66.7%)	21 (38.2%)	0.005
Abnormal cisterns	29 (64.4%)	19 (34.6%)	0.003
Midline shift >5 mm	31 (68.9%)	22 (40.0%)	0.004
Traumatic subarachnoid hemorrhage	31 (68.9%)	25 (45.5%)	0.019
Admission time (h)	2.0 ± 1.2	2.2 ± 1.3	0.529
Plasma-sampling time (h)	3.9 ± 1.9	4.6 ± 2.5	0.111
Time from trauma to the first CT scan (hr)	2.3 ± 0.8	3.3 ± 2.2	0.002
Blood glucose level (mmol/L)	12.8 ± 3.8	11.2 ± 3.4	0.031
Plasma C-reactive protein level (mg/L)	18.5 ± 7.1	15.2 ± 5.3	0.012
Plasma fibrinogen level (g/L)	2.3 ± 0.9	2.8 ± 0.9	0.007
plasma D-dimer level (mg/L)	4.0 ± 1.5	3.2 ± 1.1	0.002
Plasma copeptin level (pg/mL)	2798.8 ± 839.0	1767.3 ± 579.2	<0.001

Numerical variables were presented as mean ± standard deviation and analyzed by student *t* test. Categorical variables were expressed as counts (percentage) and analyzed by chi-square test. CT indicates computerized tomography.

Results

Study population's characteristics

One hundred patients were enrolled, including 66 men and 34 women. The mean age was 40.1 ± 15.1 years (range, 18–78 years). The mean initial postresuscitation GCS score was 4.8 ± 1.6 (range, 3–8). 51 patients (51.0%) suffered from unreactive pupils on admission; 48 patients (48.0%), abnormal cisterns on initial CT scan; 53 patients (53.0%), midline shift >5 mm on initial CT scan; 56 patients (56.0%), presence of traumatic subarachnoid hemorrhage on initial CT scan. The mean admission time was 2.1 ± 1.2 h (range, 0.5–6 h). The mean plasma-sampling time was 4.3 ± 2.3 h (range, 1.0–9.0 h). The mean time from trauma to the first CT scan was 2.9 ± 1.8 h (range, 1.2–9.5 h). The mean blood glucose level was 11.9 ± 3.7 mmol/L (range, 7.0–22.6 mmol/L). The mean plasma C-reactive protein level was 16.7 ± 6.3 mg/L (range, 7.6–33.4 mg/L). The mean Plasma fibrinogen level was 2.6 ± 0.9 g/L (range, 1.1–4.2 g/L). The mean plasma D-dimer level was 3.5 ± 1.4 mg/L (range, 1.9–7.4 mg/L). The mean plasma copeptin level was 2231.5 ± 872.8 pg/mL (range, 1192.0–5374.6 pg/mL).

Association of copeptin with ATC

45 patients (45.0%) had ATC. Higher baseline plasma copeptin level was associated with ATC, as well as other variables shown in Table 1. A multivariate analyse selected GCS score (OR, 0.318; 95% CI, 0.164–0.671; $P = 0.001$) and baseline plasma copeptin level (OR, 1.002; 95% CI, 1.001–1.004; $P = 0.004$) as the independent predictors for ATC. When plasma copeptin levels were bifurcated at mean value of 2231.5 pg/mL, a multivariate analyse selected GCS score (OR, 0.312; 95% CI, 0.168–0.579; $P < 0.001$) and plasma copeptin level (OR, 11.081; 95% CI, 1.703–72.121; $P = 0.012$) as the independent predictors for ATC.

A ROC curve showed that the plasma copeptin level predicted ATC of patients with high predictive value (AUC, 0.853; 95% CI, 0.769–0.916) (Fig. 1). The predictive value of the copeptin concentration was similar to that of GCS score (AUC, 0.870; 95% CI, 0.788–0.929) ($P = 0.737$). In a combined logistic-regression model, copeptin improved the AUC of GCS score to 0.920