Biomedical Research 2017; 28 (13): 5638-5641 *ISSN 0970-938X*
www.biomedres.info

Clinical significance of plasma levels of N-terminal brain natriuretic peptide and copeptin in patients with acute cerebral haemorrhage.

Niu Ruina*, Teng Junfang

Neural Severe Division, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, PR China

Abstract

Objective: To investigate the clinical significance of plasma levels of N-terminal Brain Natriuretic Peptide (NT-proBNP) and copeptin in patients with acute cerebral haemorrhage.
Methods: 126 patients with acute cerebral haemorrhage from June 2015 to August 2016 in our hospital were chosen as the observation group. In the same period, 60 health participants were included into the control group. The plasma levels of NT-proBNP and copeptin of the two groups were tested and compared. According to the different amount of bleeding, the observation group were divided into massive cerebral haemorrhage group (29 cases), medium cerebral haemorrhage group (57 cases) and a small cerebral haemorrhage group (40 cases). According to the prognosis of the patients, the observation group were divided into death group (24 cases) and survival group (102 cases). The plasma levels of NT-proBNP and copeptin in patients with different bleeding volume and prognosis were analysed.
Results: Plasma levels of NT-proBNP and copeptin of the observation group were significantly higher than that of the control group, with significant difference (t=34.21 P<0.05, t=34.85 P<0.05 respectively). Plasma levels of NT-proBNP and copeptin of the massive cerebral haemorrhage group (29 cases), the medium cerebral haemorrhage group and the small cerebral haemorrhage group were synchronously decreased, and there were significant differences among three groups (small group *vs.* mild group, q=6.36, P<0.05, small group *vs.* massive group, q=41.67, P<0.05, mild group *vs.* massive group, q=38.83, P<0.05). Compared with the death group, plasma levels of NT-proBNP and copeptin of the survival group were significantly reduced, the difference was statistically significant (t=26.86, P<0.05, t=6.98, P<0.05 respectively). There were a significant positive correlation between the plasma levels of NT-proBNP, copeptin and the amount of cerebral haemorrhage (r=0.54, P<0.05, r=0.48, P<0.05 respectively), GCS score (r=0.43, P<0.05, r=0.37, P<0.05 respectively).
Conclusion: Early combined detection of plasma levels of NT-proBNP and copeptin in patients with acute cerebral haemorrhage can reflect the severity of cerebral haemorrhage; assess the prognosis of patients, which have a certain clinical referential value.

Keywords: Acute cerebral haemorrhage, N-terminal brain natriuretic peptide, Copeptin, Clinical significance.

Accepted on December 30, 2016

Introduction

Acute Intracerebral Haemorrhage (AICH) is a common and frequently occurring disease in the neurology. It is also an acute and serious disease with high morbidity and mortality, becoming one of familiar diseases that threaten human health seriously [1]. In recent years, blood biochemical indicators of cardiovascular diseases in the clinical study gradually have increased, which also played an important clinical role in the risk stratification of patients with acute cerebral haemorrhage, and have an important meaning in the occurrence, development and prognosis of disease. Copeptin is the precursor of Arginine Vasopressin (Vasopressin, AVP), which is significantly increased in a variety of patients. Some studies have shown that the increased levels of copeptin had a correlation with poor prognosis of cerebrovascular disease and increased mortality, indicating it can help to optimize the prognosis stratification assessment of cerebrovascular disease [2,3]. Brain Natriuretic Peptide (BNP) is a kind of peptide neurohormone with sodium excretion and diuretic effect, which can effectively alleviate cerebral oedema. N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) is an N-terminal fragment of BNP-derived hormone, which has a long half-life, high sensitivity and easy detection, and is widely used in clinic [4,5]. In this study, the levels of plasma NT-proBNP and copeptin in patients with acute intracerebral haemorrhage were measured, and the relationship between plasma NT-proBNP, copeptin, the severity of the disease and prognosis were explored, which could provide scientific basis for clinical treatment of acute cerebral haemorrhage.

Materials and Methods

General information

A total of 126 patients with acute intracerebral haemorrhage in our hospital from June 2015 to August 2016, including 75 males and 51 females aged from 26 to 79 years (mean age of 63.80 ± 8.46 years), were enrolled as the observation group. All patients were in line with the relevant diagnostic criteria by the Fourth National Cerebrovascular Disease Conference [6]. They are in the first incidence with onset time within 24 h, excluding patients with the history of stroke and mental illness, heart, liver and kidney hematopoietic system. In addition, 60 healthy subjects were selected as the control group at the same time, including 40 males and 20 females aged 25-75 years (mean age of 63.52 ± 8.60 years). All participants gave their informed consent in the study, the trial was approved by the Ethics Committee in our hospital, and there was no significant difference between the general data of the two groups (P>0.05).

Method

According to the maximum diameter and thickness of the hematoma displayed by the CT scan of the patient, the hematoma size was calculated by the Tuo's formula (π/6 × length × width × number of CT layers) [4], and Glasgow Coma Scale (GCS) is used to evaluate neurological status. On the basis of the hematoma size, the observation group were divided into massive cerebral haemorrhage group (bleeding volume: >30 ml, 29 cases), moderate cerebral haemorrhage (bleeding volume: 10~30 ml, 57 cases) and small intracerebral haemorrhage (bleeding volume<10 ml, 40 cases). All patients were followed up for 6 months, and then were divided into survival group (102 cases) and death group (24 cases), the patients. Patients with acute cerebral haemorrhage within 24 h after admission and physical examinees in the morning of the day of examination were extracted for 5 ml fasting venous blood with Ethylenediaminetetraacetic Acid (EDTA) in the tube. NT-proBNP was detected with automatic electrochemiluminescence immunoassay analyser (Cobase4112010, Roche, Switzerland), using the instrument supporting the detection reagent. The Enzyme-Linked Immunosorbent Assay (ELISA) was used to determine copeptin. The kit was supplied by R & D (USA). All test procedures are carried out in accordance with the operating instructions.

Statistical analysis

The statistical analysis was conducted with SPSS 19.0 software, quantitative data was presented as mean ± standard deviation ($\bar{x} \pm s$). Comparison between the two groups was conducted with t test, while multiple groups with analysis of variance, comparison between any two groups using by SNK-q test. The correlation was analysed with Pearson correlation analysis, P<0.05 means the difference with statistical significance.

Results

Plasma levels of NT-proBNP and copeptin in the observation group and control group

As shown in Table 1, plasma NT-proBNP and copeptin levels in the observation group were significantly higher than that in the control group, with statistical significance (P<0.05).

Table 1. *Comparison of plasma levels of NT-proBNP and copeptin in the two groups ($\bar{x} \pm s$).*

Groups	Number of cases	NT-proBNP (pg/ml)	Copeptin (ng/ml)
Control group	60	87.65 ± 24.72	0.91 ± 0.15
Observation group	126	728.40 ± 143.86	3.52 ± 0.57
t-value		34.21	34.85
P-value		<0.001	<0.001

The plasma NT-proBNP, copeptin and GCS in the patients with different bleeding volume

Table 2 indicated the plasma levels of NT-proBNP, copeptin and GCS were decreased along with massive cerebral haemorrhage group, mild cerebral haemorrhage group and small haemorrhage group. There was statistically significant difference in the three groups (small group *vs.* mild group, q=6.36 P<0.05, small group *vs.* massive group, q=41.67, P<0.05, mild group *vs.* massive group, q=38.83, P<0.05).

Table 2. *Comparison of plasma levels of NT-proBNP and copeptin in patients with different bleeding volume and in control group ($\bar{x} \pm s$).*

Groups	Number of cases	NT-proBNP (pg/ml)	Copeptin (ng/ml)	GCS
small haemorrhage group	40	165.52 ± 58.36	3.12 ± 0.54	12.90 ± 1.23
mild haemorrhage group	57	417.28 ± 172.54	3.46 ± 0.55	7.95 ± 1.64
massive haemorrhage group	29	2116.30 ± 508.89	4.19 ± 0.58	4.17 ± 0.96
F-value		503.17	31.98	348.08
P-value				
	<0.001	<0.001	<0.001	

Comparison of plasma levels of NT-proBNP and copeptin in survivors and death patients with acute cerebral haemorrhage

As shown in Table 3, plasma levels of NT-proBNP and copeptin in survival group were significantly lower compared

with those in the death group, with statistical significance (P<0.05).

Table 3. *Comparison of plasma levels of NT-proBNP and copeptin in survival and death groups ($\bar{x} \pm s$).*

Groups	Number of cases	NT-proBNP (pg/ml)	Copeptin (ng/ml)
Survival group	102	432.38 ± 183.26	3.35 ± 0.56
Death group	24	1986.48 ± 450.73	4.24 ± 0.57
t-value		26.86	6.98
P-value		<0.001	<0.001

The correlation analysis of plasma NT-proBNP, copeptin, cerebral haemorrhage and GCS score

Pearson correlation analysis showed that plasma NT-proBNP and copeptin in patients with cerebral haemorrhage had significant positive correlation with cerebral bleeding volume and GCS score (P<0.05) (Table 4).

Table 4. *Correlation of Plasma NT-proBNP and copeptin with cerebral bleeding volume and GCS score.*

Item	Cerebral bleeding volume (ml)		GCS score	
	r-value	P-value	r-value	P-value
NT-proBNP (pg/ml)	0.54	0.000	0.43	0.001
Copeptin (ng/ml)	0.48	0.001	0.37	0.012

Discussion

Cerebrovascular disease, a kind of acute diseases with high incidence, is the second largest cause of human death. Within one year of the incidence, the mortality rate can be as high as 10.1% to 33%, even if the patient survived, about 15% to 38.4% would have a lifelong disability [7,8]. Due to increased acute intracranial pressure, brain herniation and pulmonary infection and other complications, cerebral haemorrhage has the higher mortality and makes patients with sequelaes of limb paralysis and vascular dementia, which has serious impact on the quality of life and brings a heavy burden to patients [9]. The causes of cerebral haemorrhage are more complicated, in addition, the early diagnosis and effective treatment can significantly improve the prognosis of cerebral haemorrhage. Therefore, the diagnosis of cerebral haemorrhage, the severity of the assessment and accurate prognosis is a hot clinical spot.

BNP is a member of the Natriuretic Peptide System stepping with Atrial Natriuretic Peptide (ANP). It can antagonize the vasoconstriction of the Renin-Angiotensin-Aldosterone System (RAAS) and inhibit Plasminogen Activator Inhibitor (PAI) effectively, which plays a role in sodium excretion, micturition, vasodilation and anti-thrombosis [10,11]. Huang Wei et al. [12] found that in 48 patients with hypertensive intracerebral haemorrhage, 18 patients were confirmed with delayed brain oedema by head CT, their BNP concentration was significantly increased, suggesting brain oedema may induce the release of BNP, or BNP may aggravate cerebral oedema. NT-proBNP and BNP are derived from the precursor proBNP, with homology [13], therefore, the metabolic processes of them are more synchronized, with close relationship. However, compared with BNP, NT-proBNP has a longer half-life, higher plasma concentration, and more stable biological properties, making its detection more convenient and more sensitive [14,15].

AVP is a bioactive peptide produced by the hypothalamus, with the function of osmotic pressure regulation, hemodynamic stability maintenance and regulation of the central nervous system. AVP can also effectively reflect the activation level of hypothalamic-pituitary-adrenal axis, as important indicators of critical disease severity and prognosis assessment [16,17]. Copeptin is a combined glycopeptide of AVP, with the same source as AVP, which can indirectly suggest AVP release levels, instead of AVP detection [18]. Studies have shown that copeptin level was significantly increased within 6 h after acute cerebral haemorrhage, and that reached a peak in 24 h, then it would gradually decrease. Within 7 days of the incidence, its average levels were significantly higher than that of normal population [19]. Recently, it is found that plasma copeptin concentration was significantly superior to MBP, GFAP, NSE, S100B, pNF-H, tau and UCH-L1 in the prediction of 6 months death of cerebral haemorrhage and functional prognosis [20].

In this study, the results indicated that plasma levels of NT-proBNP and copeptin in patients with acute cerebral haemorrhage were significantly higher than those of the healthy control group, and they were decreased along with massive cerebral haemorrhage group, mild cerebral haemorrhage group and small haemorrhage group. According to prognosis of diseases, the grouping results of the study showed that plasma levels of NT-proBNP and copeptin in patients of death group were significantly higher than those of the survival group. The correlation analysis showed that plasma levels of NT-proBNP and copeptin had significant positive correlation with bleeding volume and GCS score (P<0.05) in patients with acute cerebral haemorrhage. These results suggested that NT-proBNP and copeptin can participate in the pathophysiology of cerebral haemorrhage, and the higher the plasma levels of the two, the greater the amount of bleeding, the greater the severity of cerebral haemorrhage, which were consistent with others conclusions [15,21].

In summary, early combined detection of plasma levels of NT-proBNP and copeptin in patients with acute cerebral haemorrhage can reflect the severity of cerebral haemorrhage; assess the prognosis of patients, which have a certain clinical referential value. However, this study is a small sample control study, the specific mechanism and reliability remains to be further studied.

References

1. Tsivgoulis S, Zand R, Katsanos AH, Turc G, Nolte CH, Jung S, Cordonnier C, Fiebach JB, Scheitz JF, Klinger Gratz PP. Risk of symptomatic intracerebral haemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden: a meta-analysis. JAMA Neurol 2016; 73: 675-683.
2. Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol 2009; 66: 799-808.
3. Lewandowski K, Brabant G. Potential clinical utility of copeptin (c-terminal provasopressin) measurements in clinical medicine. Exp Clin Endocrinol Diab 2016; 124: 173.
4. Jickling GC. Relationship between the concentration of plasma N -terminal pro-brain natriuretic peptide and prognosis in patients with acute intracerebral haemorrhage. J Stroke Neurol Dis 2012; 29.
5. Tutarel O, Denecke A, Bodebger SM, Martens-Lobenhoffer J, Lovric S, Bauersachs J, Schieffer B, Westhoff BM, Kielstein JT. Asymmetrical dimethylarginine-more sensitive than Nt-Probnp to diagnose heart failure in adults with congenital heart disease. PLoS One 2012; 7: e33795.
6. Wu X. Epidemiological study on incidence and mortality of stroke in Chinese population. Chin J Infect Epidemiol 2003; 23: 236.
7. He M, Wang J, Gong L, Dong Q, Ji N. Community-based stroke system of care for Chinese rural areas. Stroke 2014; 45: 2385-2390.
8. Li M. Diagnosis of cerebrovascular diseases. J Clin Exp Med 2013; 559.
9. Morotti A, Goldstein JN. Diagnosis and management of acute intracerebral haemorrhage. Emerg Med Clin N Am 2016; 34: 883.
10. Akgun B, Erol FS, Yildirim H, Ilhan N, Kaplan M. The correlation of serum NT-proBNP levels of hemorrhagic and ischemic lesions detected with diffusion MRI in head traumas. Turk Neurosurg 2013; 23: 336-343.
11. Nyberg C, Karlsson T, Ronne EM. Predictors of increased cumulative serum levels of the n-terminal prohormone of brain natriuretic peptide 4 days after acute spontaneous subarachnoid haemorrhage. J Neurosurg 2014; 120: 599.
12. Changes of b-type natriuretic peptide in patients with delayed cerebral oedema after hypertensive intracerebral haemorrhage and its clinical significance. J Nanchang Univ 2010; 50: 56.
13. Weber M, Hamm C. Role of B-type natriuretic peptide (Bnp) and Nt-Probnp in clinical routine. Heart 2006; 92: 843.
14. Kara K, Lehmann N, Neumann T, Klsch H, Hlenkamp SM, Dykun I, Broecker-Preuss M, Pundt N, Moebus S, CKEL KH. Nt-Probnp is superior to Bnp for predicting first cardiovascular events in the general population: the Heinz Nixdorf recall study. Int J Cardiol 2015; 183: 155.
15. Detection of plasma n-terminal pro-brain natriuretic peptide and peptide in patients with acute cerebral haemorrhage and its clinical significance. Chongqing Med J 2015; 910.
16. Causey MW, Singh N.Clinical implications of B-type natriuretic peptide and N-terminal pro- B-type natriuretic peptide in the care of the vascular surgery patient. clinical implications of B-type natriuretic peptide and N-terminal pro- B-type natriuretic peptide in the care of the vascular surgery patient. Elsevier 2014; 143.
17. Zeynalov E, Jones SM. Recent advances and future directions in preclinical research of Arginine-Vasopressin (Avp) receptor blocker conivaptan in the context of stroke. Neur Regen Res 2016; 11: 392.
18. Advance of copeptin in clinical application of cerebrovascular diseases. Chin J Clin Phys Electr Vers 2015; 168.
19. Dong XQ, Huang M, Yu WH, Zhang ZY, Zhu Q, Che ZH, Du Q, Wang H. Change in plasma copeptin level after acute spontaneous basal ganglia haemorrhage. Peptides 2011; 32: 253.
20. Yu WH, Wang WH, Dong XQ, Du Q, Yang DB, Shen YF, Wang H, Zhang ZY, Zhu Q, Che ZH. Prognostic significance of plasma copeptin detection compared with multiple biomarkers in intracerebral haemorrhage. Clinica Chimica Acta 2014; 433: 174.
21. Garca D. Giralt T, Bustamante A, Etgen T, Jensen JK, Sharma JC, Shibazaki K, Saritas A, Chen X, Whiteley WN. B-type natriuretic peptides and mortality after stroke a systematic review and meta-analysis. Neurol 2013; 81: 1976.

*Correspondence to

Niu Ruina

Neural Severe Division

The First Affiliated Hospital of Zhengzhou University

Zhengzhou

PR China