European Review for Medical and Pharmacological Sciences 2017; 21: 3277-3281

Assessment of obestatin and arginine vasopressin (AVP) levels in acute renal failure and acute heart failure

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Abstract. – OBJECTIVE: We conducted this study to assess the clinical application of obestatin and arginine vasopressin (AVP) levels in cases of acute renal failure (ARF) and acute heart failure (AHF).

PATIENTS AND METHODS: 30 cases of ARF, 30 cases of AHF, 30 cases of ARF complicated with AHF, and 30 cases of healthy subjects (control group) were successively selected. An ELISA test was conducted to detect levels of obestatin and AVP. Routine biochemistry testing was applied to detect the levels of serum creatinine and calculate the glomerular filtration rate (GFR). Electrochemiluminescence double antibody sandwich fluorescence immune testing was applied to detect NT-proBNP and color Doppler ultrasound diagnostic apparatus was applied to detect renal arterial resistive index (RI) and left ventricular ejection fraction (LVEF). The 30-day mortality was documented.

RESULTS: Compared to other groups, the group of patients suffering from ARF complicated with AHF had significantly higher levels of obestatin and AVP, and significantly higher levels of serum creatinine, NT-proBNP and RI; however, their GFR and LVEF levels were the lowest. Differences were statistically significant ($p < 0.05$). Levels of obestatin and AVP are positively correlated with serum creatinine, NT-proBNP and RI levels, but negatively correlated with GFR and LVEF levels. The mortality rate of the group suffering from ARF complicated with AHF was markedly increased ($p = 0.035$). The obestatin and AVP levels of the death group were significantly higher than that of the survival group. However, the comparison among levels of serum creatinine, GFR, NT-proBNP, RI and LVEF revealed no statistical significance ($p > 0.05$).

CONCLUSIONS: Obestatin and AVP levels were closely related to the severity of ARF and AHF and survival prognosis, which could be a sensitive indicator for diagnoses and prognoses.

Key Words:
Obestatin, Arginine vasopressin, Acute renal failure, Acute heart failure.

Introduction

Obestatin and ghrelin are generated from the same gene; they demonstrate antagonistic effects against each other regarding ingestion[1]. Notably, obestatin can inhibit thirst and regulate water metabolism[2]. It is a protein that is expressed in various organs and tissues, such as the stomach and kidney[3]. Intraventricular exogenous supplements of obestatin can inhibit the release of action of vasopressin (AVP)[4] in a dose-dependent manner. It should be noted that obestatin could be involved in water metabolism by affecting AVP or local autocrine and paracrine effects of the kidney[5]. Some studies[6] have confirmed that obestatin and AVP levels play an important role in the occurrence of "cardiorenal syndrome". This study aims to analyze whether obestatin and AVP are equally important in both acute renal failure (ARF) and acute heart failure (AHF), as well as their clinical value in diagnoses and prognosis assessment.

Patients and Methods

Patients

30 cases of ARF, 30 cases of AHF, 30 cases of ARF complicated with AHF, and 30 healthy subjects (control group) were selected successively. ARF indicates renal failure; cases of prerenal failure and postrenal failure were excluded. AHF indicates primary cardiogenic failure, pul-

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Table I. Comparison of baseline data among groups.

Group	ARF (n=30)	AHF (n=30)	ARF Complicated with AHF (n=30)	Control (n=30)	F/χ2	p
Male/Female	16/14	15/15	17/13	14/16	0.667	0.881
Age (y)	52.6±8.3	53.7±9.2	55.4±7.7	53.3±8.4	0.324	0.857
Occurrence time (h)	10.3±3.6	11.2±3.7	12.5±3.8	11.7±3.5	0.246	0.927
mSBP (mmHg)	156.4±5.7	152.7±5.8	162.3±6.3	152.4±5.4	0.385	0.769
mDBP (mmHg)	86.3±3.4	85.7±3.5	84.9±3.7	87.5±3.6	0.352	0.823
FBP (mmol/L)	5.2±1.3	5.3±1.2	5.4±1.3	5.3±1.4	0.524	0.638
HbA1C (%)	5.8±0.9	5.9±1.2	6.0±1.3	5.7±0.8	0.357	0.862
TC (mmol/L)	5.6±1.3	5.7±1.2	5.8±1.4	5.6±1.3	0.624	0.537
LDL-C (mmol/L)	4.2±0.9	4.3±0.8	4.4±1.0	4.5±1.3	0.267	0.835

monary, nephrogenic or hepatogenic heart failure; cases of heart failure caused by infection, infusion and other inducements were excluded. Also, patients with sapremia, autoimmune diseases, severe organ dysfunction of liver, lung and brain, and incomplete clinical data were excluded. This study was approved by the Ethics Committee of our hospital, and informed consent was obtained from patients and their families. The baseline data among groups was comparable (Table I).

Research Methods

Diagnosis and treatment of acute renal failure and acute heart failure were carried out according to the standard medical procedure. Basic diseases and cause of disease were identified. Blood pressure, blood glucose, water homeostasis, acid-base balance, and electrolytes were reasonably controlled. Continuous hemofiltration and left ventricular assist devices such as an intra-aortic balloon pump were applied when necessary. The detection of all indicators was completed within 24 hours after hospitalization. ELISA testing was applied to detect levels of obestatin and AVP. Routine biochemistry testing was applied to detect the levels of serum creatinine, and the glomerular filtration rate (GFR) was calculated. Electrochemiluminescence double antibody sandwich fluorescence immune testing was applied to detect NT-proBNP. Color Doppler ultrasound diagnostic apparatus was applied to detect renal arterial resistive index (RI) and left ventricular ejection fraction (LVEF). The 30-day mortality was documented. Kits for obestatin and AVP were bought from the Sigma-Aldrich (St. Louis, MO, USA). The microplate reader was bought from Bio-Rad Co. (Hercules, CA, USA). The fully automatic biochemical detector was purchased from Beijing Liuyi Instrument Factory. The fully automatic NT-proBNP detector and supplementary reagents were purchased from BioMerieux Company (Marcy l'Étoile, France). Procedures were performed strictly according to the manufacturer's instructions.

Color Doppler ultrasonic diagnosis apparatus (iU22, 3.5 MHz probe frequency) was purchased from the Philips Co. (Andover, MA, USA). Echocardiography examination was performed at the left lateral position. Apical four chamber views were collected by a Simpson single plane testing. Left ventricular endocardial outline and left ventricular length diastole (LvLD) was read. LVEF was automatically calculated using the machine. Renal arterial resistive index (RI) of left and right renal artery were detected respectively when the patient was in a supine position. When the color blood flow signal was stable, patients were asked to hold their breath. Then, the Doppler spectrum was used to detect peak systolic velocity and end-diastolic velocity. RI was automatically calculated using the machine. Above detections were performed three times by the same sonographer to get an average value.

Statistical Analysis

The SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was utilized to conduct statistical analysis. Measurement data were expressed by average ± standard deviation. Single factor ANOVA analysis was applied for comparison among groups. LSD *t*-test was applied to pair comparison. Independent sample *t*-testing was applied to the comparison between two groups. Pearson test was applied to relative analysis after normality test. Enumeration data were expressed by case number or (%). Comparison among groups (correction) adopted χ^2 or Fisher's exact test. $p<0.05$ was regarded as being statistically significant.

Table II. Comparison of obestatin and AVP levels among groups (pg/ml).

Group	ARF	AHF	ARF Complicated with AHF	Control	F	p
Obestatin	367.8±42.6	372.8±52.3	564.9±75.4	153.6±32.5	15.328	0.000
AVP	75.3±12.3	84.2±15.8	123.6±23.2	32.5±10.4	12.305	0.000

Note: AVP, arginine vasopressin.

Results

Comparison of Obestatin and AVP Levels Among Groups

Concerning obestatin and AVP levels, the group suffering ARF complicated with AHF had significantly higher levels of these proteins than the ARF and AHF groups; the control group had the lowest levels. Differences were statistically significant ($p<0.05$) (Table II).

Levels of Serum Creatinine, GFR, NT-proBNP, RI and LVEF Among Different Groups

The levels of serum creatinine, NT-proBNP and RI were significantly higher in the group suffering ARF complicated with AHF than the ARF and AHF groups; the control groups had the lowest levels. However, the group suffering ARF complicated with AHF had the lowest GFR and LVEF levels. Differences were statistically significant ($p<0.05$) (Table III).

Correlation Analysis between Obestatin and AVP Levels and Other Indicators

Plasma obestatin and AVP levels positively correlated with serum creatinine, NT-proBNP, and RI levels, but negatively correlated with plasma GFR and LVEF levels (Table IV).

30-Day Mortality Comparison

The mortality rate of the group suffering ARF complicated with AHF was 23.33% (7 cases), the ARF group was 3.33% (1 case), and the AHF group was 6.67% (2 cases). The mortality rate of the group suffering ARF complicated with AHF was signifi-

Table III. Comparison of levels of serum creatinine, GFR, NT-proBNP, RI and LVEF among groups.

Group	ARF	AHF	ARF Complicated with AHF	Control	F	p
Creatinine (μmol/L)	562.3±43.5	345.2±32.5	675.8±65.7	65.2±12.3	12.534	0.000
GFR (ml/min)	65.3±5.6	85.7±7.3	46.3±4.5	95.6±10.2	13.627	0.000
NT-proBNP (pg/ml)	356.4±32.6	763.2±52.7	1653.5±123.5	52.7±12.4	15.428	0.000
RI (%)	0.75±0.12	0.63±0.16	0.86±0.17	0.35±0.10	10.320	0.000
LVEF (%)	48.6±3.5	44.2±3.2	41.3±3.0	55.2±5.2	9.635	0.000

Note: GFR, glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide; RI, resistance index; LVEF, left ventricular ejection fraction.

Table IV. Correlation analysis between obestatin and AVP levels and other indicators.

	Obestatin		AVP	
	Determination coefficient	p	Determination coefficient	p
Creatinine	0.326	0.035	0.367	0.032
GFR	-0.425	0.030	-0.458	0.026
NT-proBNP	0.421	0.031	0.463	0.024
RI	0.321	0.034	0.352	0.033
LVEF	-0.362	0.033	-0.389	0.028

Table V. Indicator comparison between death group and survival group.

Group	Case No.	Obestatin (pg/ml)	AVP (pg/ml)	Creatinine (μmol/L)	GFR (ml/min)	NT-proBNP (pg/ml)	RI (%)	LVEF (%)
Death	10	732.4±77.6	165.7±25.6	743.2±72.3	35.2±4.2	1865.2±324.5	0.89±0.21	39.5±2.5
Survival	80	332.6±45.3	56.9±16.4	312.5±33.5	89.3±6.3	324.5±35.7	0.58±0.16	49.6±4.3
t		8.627	9.325	8.462	7.535	12.306	7.658	7.329
p		0.000	0.000	0.000	0.000	0.000	0.000	0.000

cantly increased (χ^2=6.729, p=0.035). The obestatin and AVP levels of the death group were significantly higher than that of the survival group. However, comparison among groups in the levels of serum creatinine, GFR, NT-proBNP, RI, and LVEF were not statistically significant (p>0.05) (Table V).

Discussion

The occurrence of heart failure can activate the sympathetic nerve, renin-angiotensin-aldosterone system (RAAS) and the AVP system, which increases reabsorption of sodium and water and results in fluid retention and aggravation of renal filtration and reabsorption[7]. Meanwhile, the AVP system may be further activated due to the inadequate hemoperfusion of the kidney to promote water reabsorption, and AVP in circulating blood was significantly increased[8]. AVP can affect aquaporin 2 (AQP2) by activating kidney vasopressin receptor 2 (V2R) receptor, enhancing the water permeability of the collecting duct, increasing water reabsorption rate and volume load, all of which finally leads to hyponatremia[9]. AVP can increase cardiac preload by promoting water reabsorption and increasing intracellular Ca^{2+} level by the inositol triphosphate pathway, which raises the peripheral vascular resistance and further increases cardiac after-load. AVP also increases the synthesis of myocardial cell contractile proteins to promote ventricular remodeling. Meanwhile, AVP allows hyponatremia to serve as an independent predictive factor of heart failure fatality rate by further activating the sympathetic nerve and RAAS system, which results in aggravated heart failure and increased insulin resistance, etc.[10]. AVP receptors have three subtypes, including V1a, V1b and V2. V2R antagonist, represented by lixivaptan and tolvaptan, is different from traditional diuretics as it allows excretion of water without sodium and potassium. Therefore, it has evident clinic efficacy for normovolemic and hypervolemic hyponatremia[11].

Obestatin, a type of polypeptide with 23 amino acids, plays an important role in various pathological and physiological activities, such as substance and energy metabolism, gastrointestinal motility, pancreatic secretion, cell proliferation, memory and sleep, etc.[12]. The release of AVP in basic conditions is increased after the administration of obestatin antiserum; the release of AVP is further increased after water deprivation[2]. It should be noted that obestatin-AVP can regulate body water metabolism. Previous studies have confirmed that[13,14] the secretion of obestatin is abnormally high in patient with chronic heart failure, chronic renal failure and chronic cardiorenal syndrome. Compared to other groups, we discovered that the group of patients suffering ARF complicated with AHF have significantly higher levels of obestatin and AVP, and significantly higher levels of serum creatinine, NT-proBNP, and RI. However, their GFR and LVEF levels were the lowest; differences were statistically significant. Levels of obestatin and AVP were positively correlated with serum creatinine, NT-proBNP, and RI levels, but negatively correlated with GFR and LVEF levels. It should be noted that obestatin and AVP levels were closely related to the occurrence and severity of ARF and AHF[15]. The obestatin and AVP levels of the patients that died that suffered ARF complicated with AHF were significantly higher than that of the survival group. However, the comparison among levels of serum creatinine, GFR, NT-proBNP, RI and LVEF revealed no statistical significance. It should be noted that obestatin and AVP levels were closely related to the severity of ARF, AHF and survival prognosis[16]; therefore, it may be a sensitive indicator of diagnosis and prognosis.

Conclusions

Further research should be conducted in which animal models can be used to verify the secretory pathway and mechanism of obestatin and AVP

levels in ARF, AHF and cell signaling pathway that is involved in disease occurrence and progression. Besides, the improvement of a patient's condition after pharmacological intervention may also be verified. At the same time, we can set up a model to describe the sensitivity, specificity and accuracy of diagnosing ARF and AHF by plasma obestatin and AVP levels in order to provide a reference for the early diagnosis of disease.

Conflict of interest

The authors declare no conflicts of interest.

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