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Copeptin: a diagnostic factor for critical patients

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Abstract. – Copeptin is important in determining the prognosis of the disease, assigning mortality, setting treatment modalities and increasing the patients' chances for survival in life threatening conditions. Any stress factor activating the hypothalamic-pituitary-adrenal (HPA) axis causes an increase in arginine vasopressin (AVP) plasma concentrations also known as antidiuretic hormone (ADH). Copeptin is derived from preprovasopressin along with neurophysin II and AVP. Copeptin is released in an equimolar ratio to AVP. Various studies have shown copeptin to be an independent indicator in determining the prognosis of the disease and assigning mortality. The purpose of this review was to analyze the advantages of copeptin in patients with life threatening illnesses by reviewing medical data bases.

Key Words:
Copeptin, Critical care, Emergency Department.

Introduction

Everything that disrupts the homeostatic balance of the body can be defined as stress. Both central nervous system and the peripheral nervous system respond to stress. Central components of the stress system are in hypothalamus and brain stem. Among these components are parvocellular neurons which produce corticoptorin releasing hormones (CRH) of hypothalamus, neurons of paraventricular nucleus which release arginine vasopressin (AVP), CRH neurons of paragigantocellular and parabranchial nucleus in medulla and locus coeruleus and mostly noradrenergic cells in medulla and pons[1].

Any stress factor that activates the hypothalamic-pituitary-adrenal (HPA) axis causes an increase in stress hormone concentrations released from adrenal gland[2]. AVP, also known as antidiuretic hormone (ADH), is one of the most important hypothalamic stress hormones. It reaches neurohypophysis by moving along axones along with neurophysine II in neurosecretory granules after being synthesized in supraoptic nucleus. Primary mechanisms which stimulate ADH secretion are osmotic and hemodynamic regulation. A decrease in blood pressure and blood volume stimulate the pressure receptors in the heart and carotid and cause ADH secretion[3]. ADH generally shows its effect via three types of receptors: V1a, V1b and V2. V1 receptor is related to arterial vasoconstriction while V2 receptor is related to the antidiuretic effect of ADH on kidney filtration tubules[4].

AVP has a potentializer effect on CRH. These two substances are considered to be the main adrenocorticotropic hormone (ACTH) releasing substances. ACTH stimulates the adrenal cortex for cortisol production[2]. In order to be able to make a direct analysis of stress on the level of perception, measurement of AVP or CRH's plasma levels will be important. However, it is difficult to measure levels of CRH or AVP in circulation. Both CRH and AVP are secreted pulsatile and they become unstable especially at ambient temperature and they are cleared off plasma in a few minutes[2,5]. Copeptin was defined by Holwerda DA (Eur J Biochem 1972; 28: 334-339) in 1972 for the first time and it was reported to be a glycosylated, 39-amino-acid long polypeptide with a weight of 5kDa molecular which had leucine-rich core segment[4,6,7]. The gene that controls copeptin secretion is located on the 20th chromosome p13 loculus. After its transcription, the copeptin will be derived from the third exon of the three exons encoding mRNA together with the last 17 amino acids of the C-terminus of neurophysin-II (NP-II). The other two exons will be translated into the signal peptide, AVP and the rest of NP-II. Following

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the translation of preprovasopressin mRNA, 168 amino acid long preprovasopressin, which is a major pre-peptide, will be produced. This 168 amino acids peptide will be segmented into 23 amino acid signal peptide, 9 amino acid AVP, 93 amino acid disulfide rich or cysteine rich NP-II and 39 amino acid copeptin. The process of preprovasopressin segmentation is a result of a cascade of four hydrolytic enzymatic reactions mediated by endopeptidase, exopeptidase, monooxygenase and lyase respectively during its axonal transport[8]. AVP is derived from preprovasopressin along with NP-II and copeptin[9,10]. Copeptin is released in an equimolar ratio to AVP, it is more stable in circulation and it is determined easily. Studies have reported that levels of copeptin reflect AVP production[2,5,6,11,12].

Plasma copeptin level was reported to be 4.2 pmol/l in average in healthy volunteers and plasma copeptin levels were found to differ across genders (M:5.2 W:3.7 pmol/l)[13]. The purpose of this review article was to analyze the advantages of copeptin in patients with life threatening illnesses by reviewing medical data bases.

Copeptin and Acute Coronary Syndrome

Increased copeptin values following acute myocardial infarction (MI) were defined for AVP a long time ago; however, they weren't used as diagnostic parameters because of complications in AVP measurements. Khan et al[7] in their Leicester Acute Myocardial Infarction Peptide (LAMP) study they conducted with 980 patients reported that plasma copeptin level reached the highest value in the first day after acute MI, later decreased to a stable level and when compared with healthy control group, the values were above normal levels during the second and fifth days. They also reported that STEMI patients had higher plasma copeptin levels when compared with non-STEMI patients and the patients who died or came to hospital again with a complaint of cardiac failure had higher plasma copeptin levels when compared with patients who did not have coronary ischemia.

Another study[14] which was conducted on 487 patients reported that plasma copeptin levels of patients who were diagnosed as acute MI were higher than the plasma copeptin levels of others. The same study reported that the patients who initially had low troponin T levels had significantly higher levels of plasma copeptin and a positive correlation was found between the time that passed since the beginning of their symptoms and troponin T levels while a negative correlation was found between the time that passed since the beginning of their symptoms and copeptin.

In their study with patients who came to hospital with a complaint of chest pain, Maisel et al[15] excluded MI in 58% of the patients who had negative plasma copeptin levels and cTnl levels which were checked when they first came to hospital and they stated that these had a negative predictive value with a rate of 99.2%. 10 of the 19 patients who were not diagnosed with the cTnI level when they first came to hospital were diagnosed with non-STEMI after having been found to have a serum copeptin level of > 14 pmol/l. Previous researches[14,16] showed that the use of a combination of copeptin and troponin T and troponin I was diagnostically moer useful than their being used alone.

Copeptin and Ischemic Stroke

Stroke is the second most common reason of death in the world following ischemic heart disease and it is the leading cause of serious functional dependence. It has been reported that, with early treatment and enough rehabilitation, functional dependence can be decreased to 6 months and long-term results can be improved[17]. Since stroke is the primary reason of long-term disabilities, people have begun to be more scared of the permanent results of stroke when compared with heart diseases[2]. In spite of the significant decrease in the mortality of congestive heart failure, there has been only a slight decrease in the mortality of stroke since 1990[17]. The activation of HPA axis is among the first physiological reactions of cerebral ischemia. Arginine vasopressin (AVP) plays an important role in the development of ishemic cerebral oedema and/or cerebral vasospasm. One study[18] showed that the serum AVP levels of patients diagnosed with ischemic stroke were higher when compared with the healthy control group and in patients diagnosed with stroke, those who had serious neurological deficit had higher AVP levels when compared with others.

One retrospective and empirical work[2] found out that copeptin was an independent and powerful new biomarker in the determination of mortality and functional results in the patients who had ischemic stroke and in addition, the article reported that besides clinical measures, patients with a stroke had higher copeptin prognostic accuracy than other commonly measured laborato-

ry parameters such as blood sugar, C-reactive protein (CRP) and white blood cell count. When compared with the use of clinical score or marker alone, the combination of biomarker and clinical score is more useful in the determination of functional result.

Copeptin and Intracerebral Hemorrhage

In case of intracerebral hemorrhage, the rate of mortality is higher when compared with ischemic stroke[19]. The prediction of the consequences of intracerebral hemorrhage is very important for optimal care and the decision for treatment. There are a great number of scales used for determining prognosis in patients with intracerebral hemorrhage. Dynamic factors such as the extension of the volume of hemorrhage, oedema formation or persistent high blood pressure are known to be associated with early neurological deterioration and poor prognosis[20]. High plasma copeptin levels were found to be associated with short-term bad consequences after intracerebral hemorrhage. In their study with patients who had intracerebral hemorrhage, Dong et al[21] measured the plasma copeptin levels at the time of coming to hospital and on the first, second, third, fifth and seventh days and found out that these levels increased in the first six hours and reached the peak level in 24 hours, after that they decreased gradually and were higher on the seventh day when compared with the healthy control group. This study also reported that plasma copeptin level was an independent marker for 1 week long mortality and it was reported to be associated with the volume of increasing hematom. In another study, Zhang et al[22] stated that the plasma copeptin levels of 89 patients who had basal ganglion hemorrhage measured at the time of coming to hospital were significantly higher than thıose of the healthy control group. Plasma copeptin levels were found to be an independent indicator of annual mortality, early phase neurological deterioration and annual consequences. Aimei et al[23] reported that plasma copeptin level was positively correlated with the volume of hemorrhage and when the 90 day long neurological conditions of the patients and mortality was considered, the copeptin level of patients who had nuerological deficit and who died had higher levels of copeptin than the other patients.

Copeptin and Subarachnoidal Hemorrhage

Subarachnoidal hemorrhage (SAH) mostly results from rupture of an aneurysm. The grading system of World Federation of Neurosurgical Societies (WFNS) is still a gold standard for the evaluation of the severity of aneurysmal SAH[24]. Plasma copeptin levels have been found to be high in patients with traumatic brain damage[25,26], intracerebral hemorrhage[21-23] and ischemic stroke[2,18] and high copeptin levels have been reported to have extremely predictive values for a bad result. In aneurysmal SAH patients, Fung et al[27] observed that according to WFNS grading, as the grade increased so did plasma copeptin levels and similarly, according to Fisher scale, as the grade increased in classificiation, so did plasma copeptin levels. The same study found out that the serum copeptin levels of patients who died were significantly higher than those of the patients who survived. Zhu et al[28] reported in 30 patients that the serum copeptin levels of SAH patients at the time of admission to hospital were statistically significantly higher than those of the control group and they found out that high serum copeptin levels were associated with one year long negative outcomes and mortality. WFNS score, modified Fisher score and plasma copeptin levels were stated to be independent risk factors for one-year mortality. Plasma copeptin level is a useful complementary tool in predicting the functional improvement and mortality following the aneurysmal SAH.

Copeptin and Trauma

Trauma is a very important public health issue which affects especially the productive young people and causes material and spiritual damages. Dong et al[25] in patients who had traumatic brain damage investigated post traumatic plasma copeptin levels and observed that copeptin increased within the first six hours following the trauma, it peaked within 2 hours and in the second day, it had plateau level and slowly decreased after that. They also found out that plasma copeptin levels of patients with trauma were significantly higher than those of the healthy control group within a period of 7 days. In the same work, Dong et al[25] reported that plasma copeptin levels were negatively correlated with Glasgow Coma Scale and plasma copeptin levels were reported to be an independent indicator of one month long mortalities. Westemann et al[29] compared the plasma copeptin levels of 87 patients at the time of their coming to the emergency service with healthy control and found out that the levels were significantly higher in patients with polytrauma when compared with

healthy controls and they stated that the copeptin levels of 24th hour were significantly lower than the initial level. Kleindienst et al[26] in 71 patients who had traumatic brain damage stated that the serum copeptin levels at the time of coming to hospital were the highest and the levels were stable between the third and seventh days and after this, the values became normal. The measurement of Copeptin/AVP excretion is a significant predictive factor for the determination of traumatic brain damage.

Copeptin and Sepsis

Sepsis is a condition that progresses severely and threatens life especially in old patients and patients with immune deficiency. It is characterized with early period of septic shock and a significant increase in the experimental endotoxemia plasma vasopressin levels[2]. Morgenthaler et al[30] reported that patients with sepsis had significantly higher copeptin levels when compared with healthy control group and serum copeptin levels checked at the time of coming to hopital increased in direct proportion to the seriousness of the infection. When the patients who died were compared to those who survived in the patient group, the patients who died had significantly higher serum copeptin levels. In their study, Jochberger et al[31] found out that the patients who had severe sepsis and who were in septic shock had significantly higher AVP levels than the patients who had only infection while no difference was found between the patients who had severe sepsis and those who were in septic shock. The same paper found no difference between the serum AVP levels of patients who died and those who survived. Unlike AVP, copeptin is higher in the patients who died. These results make us think that copeptin may be a prognostic indicator in sepsis.

Copeptin and Dyspnea

Acute dyspnea is a frequently encountered clinical situation in emergency services. More than 75% of all acute dyspnea cases are resulted from cardiac and pulmonary diseases[32,33]. Determining the mortality risks of patients with acute dyspnea and organizing their treatment protocols is still an issue. Copeptin is a new promising prognostic indicator for short term mortality independent of natriuretic peptid levels in patients who have acute dyspnea.

Cardiac Failure

Nowadays, there are a great number of neurohormones used as biomarkers in determining the diagnosis and prognosis of cardiac failure. Among these, BNP and NT-proBNP are the most frequently used ones. Serum AVP levels increase in patients who have chronic cardiac failure[34]. Cardiac failure is a clinical condition and a great number of neuorhormones play a role in its pathophysiology which has a complex structure. To date, a great number of biomarkers have been used in determining the diagnosis and prognosis of cardiac failure.

In a study conducted by Stoiser et al[35] with 268 patients who had heart failure, copeptin was stated to be an independent predictive factor for mortality. The same authors found out that along with renal dysfunction, age and BNP, copeptin was also a univariant determinant for hospitalization resulting from heart failure. Studies have shown copeptin levels to be a determinant of poor prognosis in the long term for patients with chronic heart failure[35,36]. In their report they investigated 287 patients who came to hospital with a complaint of acute dyspnoea, Potocki et al[37] found that patients who had dyspnoea resulting from acute decompensed heart failure had significantly high copeptin levels. A small relationship was found between copeptin and BNP or NT-proBNP concentrations. Whether or not they have acute decompensed heart failure, the patients who die have significantly higher serum copeptin levels than those who survive. It has been shown that, in dyspneic patients, whether the reason for dyspnoea is acute decompensed heart failure or not, it is a strong determinant of mortality and except for copeptin, NT-proBNP levels, glomerular filtration rate and systolic blood pressure are determinants for 30 day long mortality[37].

Chronic Obstructive Pulmonary Disease

Acute exacerbation of chronic obstructive pulmonary disease (COPD) continues to be the most important reason for morbidity and mortality associated with this disease. Since the diagnostic use of clinical criteria will be subjective, defining the biomarkers that can be used is important for standardization. Stolz et al[38] stated that along with CRP and procalcitonin, copeptin levels were significantly higher for patients who had acute exacerbation of COPD. They observed that regardless of their clinical condition, the patients'

serum copeptin levels at the time of coming to hospital predicted the patients' results in the hosptial and their time time in the hosptial and also reported that high copeptin levels were among the long term risk factors of pulmonary dysfunction. Zhao et al[39] in patients with COPD stated that there was a significant relationship between serum copeptin levels and COPD exacerbation that recurred in 6 months and that serum copeptin levels were an important indicator in determining mortality within a follow up period of more than 6 months.

Pulmonary embolism ecocardiography findings include right ventricular dilatation and increase in pulmonary artery pressure. Pulmonary arterial hypertension (PAH) is a syndrome which courses with increased pulmonary ventricular pressure resulting from pulmonary arterial emboli and right ventricular failure caused by this and the annual death rate of this syndrome is 15%[40]. There are not many reports in literature on the association between copeptin and pulmonary emboli. However, Nickel et al[41] found out that patients diagnosed with PAH had significantly higher copeptin levels than the patients who did not have a diagnosis of PAH and that increased levels of copeptin were an independent indicator of higher death risk and poor diagnosis.

Conclusions

Copeptin is a 39-amino-acid long peptide on the C-terminal portion of pro-AVP and it is released with AVP during the synthesis of AVP with the initial peptid. Copeptin is released in an equimolar ratio to AVP and serum copeptin levels reflect the production of AVP which is one of the most important of hypothalamic stress hormones. In life threatening emergency conditions, diagnosis and determining mortality is important for deciding on the treatment regimen and intervening the patient as soon as possible. In determining such patients, even if not alone, serum copeptin measurement is useful when combined with another diagnostic indicator. Especially the serum copeptin levels checked at the time of coming to the emergency service will be quite useful in determining and administrating critical patients. Although previous researches support the use of copeptin as a diagnostic factor, more detailed and more extensive studies are needed.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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