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Original Scientific Paper

THE ROLE OF PLASMA COPEPTIN LEVEL IN DETERMINING THE SEVERITY AND MORTALITY OF SUBARACHNOID HEMORRHAGE

Seda Ozkan[1], Necmi Baykan[2], Omer Salt[2], Sule Yakar[2], Ahmet Sen[3] and Polat Durukan[4]

[1]Department of Emergency Medicine, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey;
[2]Department of Emergency Medicine, Kayseri City Hospital, Kayseri, Turkey;
[3]Department of Biochemistry, Van Training and Research Hospital, Van, Turkey;
[4]Department of Emergency Medicine, Faculty of Medicine, Erciyes University, Kayseri, Turkey

SUMMARY – The study aimed to investigate the role of plasma copeptin level in setting the diagnosis, severity and mortality of patients with subarachnoid hemorrhage (SAH) admitted to the emergency department. We included patients aged ≥18 years who were diagnosed with SAH. Blood samples were collected from patients at the time of admission to the emergency department for assessment of plasma copeptin levels. The Glasgow Coma Scale (GCS), World Federation of Neurological Surgeons (WFNS), modified Fisher score, in-hospital mortality and one-year mortality rates were determined in patients. There was a statistically significant difference in plasma copeptin levels between the patients (mean: 0.78±0.41 ng/mL) and healthy controls (mean: 0.48±0.27 ng/mL) (p=0.001). There was no significant correlation of plasma copeptin levels with the GCS, WFNS, and modified Fisher scores. There was no significant difference in copeptin levels between the patients who died in the hospital (mean: 0.73±0.42 ng/mL) and those who did not (mean: 0.80±0.41 ng/mL) (p=0.41). Although plasma copeptin level may be used in the diagnosis of SAH, it does not have a role in determining the patient condition severity and mortality.

Key words: *Copeptin; Emergency department; Mortality; Subarachnoid hemorrhage*

Introduction

Subarachnoid hemorrhage (SAH) is a disruptive cerebrovascular condition associated with long-term morbidity and mortality[1-5]. Death and disability following SAH occur either directly due to hemorrhage or due to ischemic cerebral infarction that develops following vasospasm or aneurysmal rebleeding[2]. Furthermore, conditions that lead to secondary cerebral damage after SAH, such as hypoxia, hypotension, and hyperglycemia, play an important role in mortality and morbidity[1].

The gradual improvement in the understanding of the pathophysiology of SAH has prompted efforts aimed at identifying biomarkers that can predict outcomes in patients with SAH[6]. Suitable laboratory biomarkers are likely to become an appealing solution for the accurate diagnosis and timely identification of delayed cerebral ischemia (DCI) in patients with SAH. Clinical values relating to various laboratory parameters have been evaluated for nearly half a century in patients with SAH[7]. However, in contrast to other

Correspondence to: *Prof. Seda Ozkan, MD*, Department of Emergency Medicine, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Cerrahpaşa Mah. Kocamustafapaşa Cad. No: 34/E Fatih, Istanbul, Turkey
E-mail: sedacil@gmail.com

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diseases, laboratory biomarkers are still not routinely used as predictors of DCI in patients with SAH[7].

Vasopressin is a hypothalamic hormone that is stimulated by different stressors. Vasopressin enhances the effect of corticotropin-releasing hormone and triggers the release of adrenocorticotropic hormone and production of cortisol further downstream[8-10]. Copeptin is the C-terminal portion of provasopressin and a novel neurohormone of the arginine–vasopressin system[11,12]. Copeptin is a stable peptide of the vasopressin precursor, and it is synthesized in the hypothalamus together with arginine vasopressin and released into the portal circulation of the pituitary gland. Copeptin is secreted in equimolar ratio as arginine vasopressin, and the concentration of copeptin reflects the concentration of arginine vasopressin[12,13]. Copeptin thus reflects the individual stress response at the hypothalamic level[14]. Copeptin is a 39 amino acid-long glycoprotein that is stable at room temperature. It can therefore be readily detected using automatic assays that provide results within 30 minutes[9,15]. Previous studies report that copeptin can be used in the diagnosis and prognosis of several diseases[12,15-18]. Copeptin has been associated with poor prognosis for ischemic strokes, head traumas, and intracerebral hemorrhages[18-23].

Several clinical studies have been performed in recent years to investigate the relationship of SAHs, and especially aneurysmal SAHs, with plasma copeptin levels[8,19,24-26]. There are limited studies on isolated traumatic SAHs, and the majority of these studies report a consistent correlation between copeptin and the severity and prognosis of SAH. However, it is unclear whether copeptin release is specific to SAH or a general stress response.

Thus, we investigated the role of plasma copeptin level in the diagnosis, severity and mortality of patients diagnosed with SAH.

Materials and Methods

Study design and setting

This prospective study was carried out in line with research regulations, including approval of the Ethics Committee of our institute (No. 2018/04) and according to the principles of the World Medical Association Helsinki Declaration.

We included patients aged >18 years who developed spontaneous SAH or experienced SAH secondary to an isolated head trauma, and were brought to the emergency department within 72 hours of the onset of hemorrhage. We excluded patients aged <18 years; those who arrived in the emergency department more than 72 hours after the onset of hemorrhage; who had previous head trauma or cerebral infarction; who had hemorrhagic or ischemic stroke; who used antiplatelet or anticoagulant medication; and those with malignancies, cardiac insufficiency, and chronic liver disease. The healthy control group was selected from volunteer patients' relatives and emergency department staff who did not have any disease. In total, 53 patients and 30 healthy subjects were included in the study.

All participants were informed about the study. There was no intervention in the follow-up and treatment of patients. In addition to the routine blood tests performed in the patients, 3 mL of blood was collected from the patients to determine the plasma copeptin level. Age, gender, and vital signs of the patients were recorded in addition to the time between the onset of SAH and admission to the emergency department. The Glasgow Coma Scale (GCS) and World Federation of Neurological Surgeons (WFNS) scores were calculated in the patients. The modified Fisher scores were determined using computerized tomography images of the brain. The patients were followed-up to determine the in-hospital and 1-year mortality rates.

Measurement of copeptin

To measure copeptin, 3 mL of venous blood was collected in EDTA tubes. After shaking the tube, the blood was transferred to a centrifuge tube and centrifuged at 3500 rpm for 10 min. The plasma was separated from the centrifuged samples, and the samples were stored at -70 °C until further analysis. The sandwich ELISA method was performed using the EK-065-32 Human Copeptin EIA test kit (Phoenix Pharmaceuticals Inc., Burlingame, USA) and blood levels were quantitatively measured.

Statistical analysis

Data were statistically analyzed using the Statistics Program for Social Scientists (SPSS) 24.0 software (SPSS Inc., Chicago, IL, USA). The normality analysis of data was performed using the Kolmogorov-Smirnov test. The Shapiro-Wilk test was used for the normality analysis of data for which there were less than 30 patients in the group. The Mann-Whitney U test was used for comparison of two groups without normal distribution, whereas Student's t test was used for comparison of two groups showing normal distribution. Comparison of three or more groups without normal distribution was performed using the Krus-

Table 1. Comparison of copeptin levels according to characteristics of study patients

	n (%)	Copeptin (ng/mL) Mean ± SD (min-max)	p-value
Gender			
Female	22 (41.5)	0.89±0.51 (0.30-2.32)	
Male	31 (58.5)	0.71±0.31 (0.24±1.53)	p=0.26
Blood sample collection time			
0-3 hour	34 (64.2)	0.74±0.38 (0.24-1.73)	
3-6 hour	10 (18.9)	0.96±0.59 (0.34-2.32)	
6-12 hour	2 (3.8)	0.71±0.17 (0.59-0.83)	
12-24 hour	2 (3.8)	0.69±0.36 (0.43-0.95)	
24-72 hour	5 (9.4)	0.82±0.29 (0.57-1.33)	p=0.72
Mechanism of occurrence			
Spontaneous	30 (57)	0.87±0.46 (0.34-2.32)	
Trauma	23 (43)	0.67±0.46 (0.24-1.53)	p=0.12
SAH types			
Aneurysmal	23 (43.4)	0.91±0.51 (0.34-2.32)	
Arteriovenous malformation-related	2 (3.8)	0.98±0.01 (0.97-0.99)	
Traumatic	23 (43.4)	0.67±0.46 (0.24-1.53)	
Others-unknown	5 (9.4)	0.68±0.23 (0.41-1.01)	p=0.30
GCS (points)			
14-15	23 (43.4)	0.77±0.31 (0.43-1.52)	
9-13	21 (39.6)	0.84±0.50 (0.30-2.32)	
3-8	9 (17)	0.68±0.44 (0.24-1.69)	p=0.59
WFNS Score			
Grade 1	21 (39.6)	0.79±0.32 (0.43-1.52)	
Grade 2	2 (3.8)	0.66±0.04 (0.63-0.70)	
Grade 3	4 (7.5)	1.13±0.82 (0.41-2.32)	
Grade 4	21 (39.6)	0.76±0.37 (0.30-1.73)	
Grade 5	5 (9.4)	0.64±0.59 (0.24-1.69)	p=0.49
Modified Fisher Score			
Grade 1	28 (52.8)	0.72±0.31 (0.31-1.52)	
Grade 2	6 (11.3)	0.60±0.08 (0.45-0.70)	
Grade 3	9 (17)	0.97±0.68 (0.24-2.32)	
Grade 4	10 (18.9)	0.92±0.43 (0.34-1.69)	p=0.43
Intraventricular hemorrhage			
Yes	13 (24.5)	0.77±0.35 (0.34-1.69)	
No	40 (75.5)	0.79±0.43 (0.24-2.32)	p=0.88
Intracerebral hemorrhage			
Yes	18 (34)	0.92±0.57 (0.30-2.32)	
No	35 (66)	0.72±0.29 (0.24-1.52)	p=0.42
Acute hydrocephalus			
Yes	12 (22.6)	0.59±0.22 (0.24-0.99)	
No	41 (77.4)	0.84±0.44 (0.30-2.32)	p=0.05
Rebleeding			
Yes	2 (3.8)	0.47±0.06 (0.43-0.52)	
No	49 (96.2)	0.80±0.42 (0.24-2.32)	p=0.10
In-hospital mortality			
Yes	12 (22.6)	0.73±0.42 (0.24-1.69)	
No	41 (77.4)	0.80±0.41 (0.30-2.32)	p=0.41
One-year mortality			
Yes	20 (37.7)	0.85±0.44 (0.24-1.73)	
No	33 (62.3)	0.75±0.40 (0.30-2.32)	p=0.42

p<0.05 statistically significant; SAH = subarachnoid hemorrhage; GCS = Glasgow Coma Score; WFNS = World Federation of Neurological Surgeons

kal-Wallis test. Spearman's correlation test was used for correlation analysis of study data. A p value <0.05 was considered to be statistically significant.

Results

In the study period, the number of patients diagnosed with SAH was 53, and their mean age was 53±20 (18-90) years. Of these, 57% (n=30) had spontaneous SAH, and 58% were male. The mean age of the healthy control group (n=30) was 42±17 (24-67) years. The mean time between the incident and admission to the emergency department was 6±8 (0.5-24) hours. The mean systolic blood pressure of the patients was 141±30 (90-240) mm Hg, whereas their mean diastolic blood pressure was 83±14 (57-110) mm Hg, mean GCS was 12±3 (3-15), mean WFNS was 3±1 (1-5), and mean modified Fisher score was 2±1 (1-4). The mean copeptin level in the patient and healthy control groups was 0.78±0.41 (0.24-2.32) ng/mL and 0.48±0.27 (0.09-0.97) ng/mL, respectively. Significant difference was observed in copeptin levels between the patient and healthy control groups (p=0.001) (Fig. 1). In the patient group, 23 (43.4%), 23 (43.4%), 2 (3.8%), and 5 (9.4%) patients had aneurysmal SAH, traumatic SAH, arteriovenous malformation-related SAH, and SAH related to other causes, respectively. No significant relationship was observed between the patient copeptin levels and gender, time of blood col-

Table 2. Relationship between copeptin levels and severity of SAH patients at the time of admission

Spearman's rho		GCS	WFNS Score	Modified Fisher score
Copeptin	rho	0.143	-0.160	0.194
	p	0.306	0.253	0.165

Spearman correlation test, p<0.05 statistically significant; SAH = subarachnoid hemorrhage; GCS = Glasgow Coma Score; WFNS = World Federation of Neurological Surgeons

Table 3. Comparison of plasma copeptin levels for mortality according to SAH types

	Non-survival Copeptin ng/mL Mean ± SD (min-max)	Survival Copeptin ng/mL mean ± SD (min-max)	p-value
In-hospital mortality			
All patients (N=53)	0.73±0.42 (0.24-1.69)	0.80±0.41 (0.30-2.32)	0.41
Spontaneous SAH (n=30)	0.92±0.46 (0.34-1.69)	0.86±0.47 (0.41-2.32)	0.63
Aneurysmal (n=23)	0.92±0.46 (0.34-1.69)	0.90±0.55 (0.43-2.32)	0.72
Arteriovenous malformation-related (n=2)	-	0.98±0.01 (0.97-0.99)	
Unknown-other reasons (n=5)	-	0.68±0.23 (0.41-1.01)	
Traumatic SAH (n=23)	0.46±0.14 (0.24-0.60)	0.73±0.32 (0.30-1.53)	0.09
One-year mortality			
All patients (n=53)	0.85±0.44 (0.24-1.73)	0.75±0.40 (0.30-2.32)	0.42
Spontaneous SAH (n=30)	0.93±0.43 (0.34-1.73)	0.83±0.49 (0.41-2.32)	0.32
Aneurysmal SAH (n=23)	0.92±0.45 (0.34-1.73)	0.89±0.59 (0.43-2.32)	0.46
Arteriovenous malformation-related (n=2)	0.97	0.99	-
Unknown-other reasons (n=5)	-	0.68±0.23 (0.41-1.01)	
Traumatic SAH (n=23)	0.70±0.44 (0.24-1.53)	0.66±0.25 (0.30-1.25)	0.76

p<0.05 statistically significant; SAH = subarachnoid hemorrhage

lection, mechanism of occurrence, GCS and WFNS scores at the time of admission, and modified Fisher scores (Table 1). Plasma copeptin levels did not vary in the presence of intraventricular bleeding, intracerebral bleeding, and acute hydrocephaly. No statistically significant difference was noted (Table 1). Rebleeding was identified in two patients with aneurysmal SAH. The copeptin levels in these patients were not significantly different in comparison with those without rebleeding (Table 1). There was no significant correla-

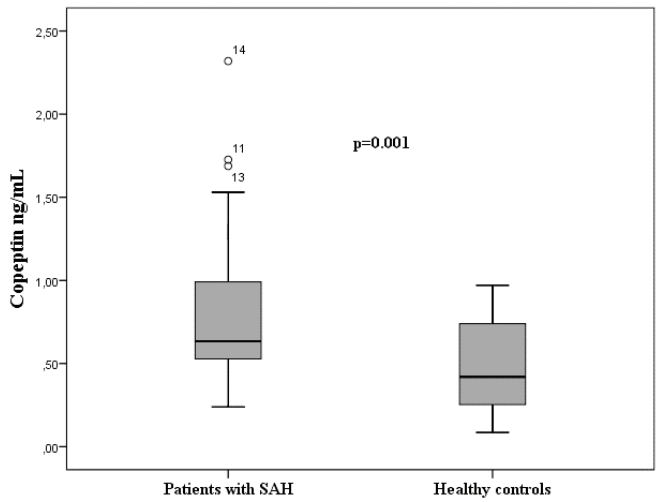

Fig. 1. Comparison of plasma copeptin levels in SAH patients and healthy controls.

SAH = subarachnoid hemorrhage

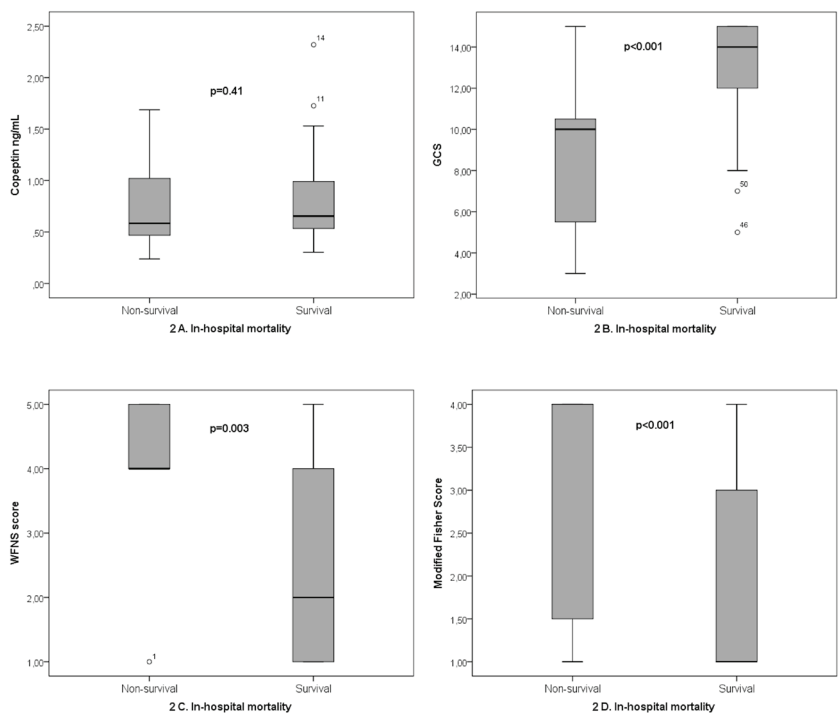

Fig. 2. Comparison of copeptin levels, GCS, WFNS and modified Fisher scores relative to in-hospital mortality.

GCS = Glasgow Coma Score; WFNS = World Federation of Neurological Surgeons

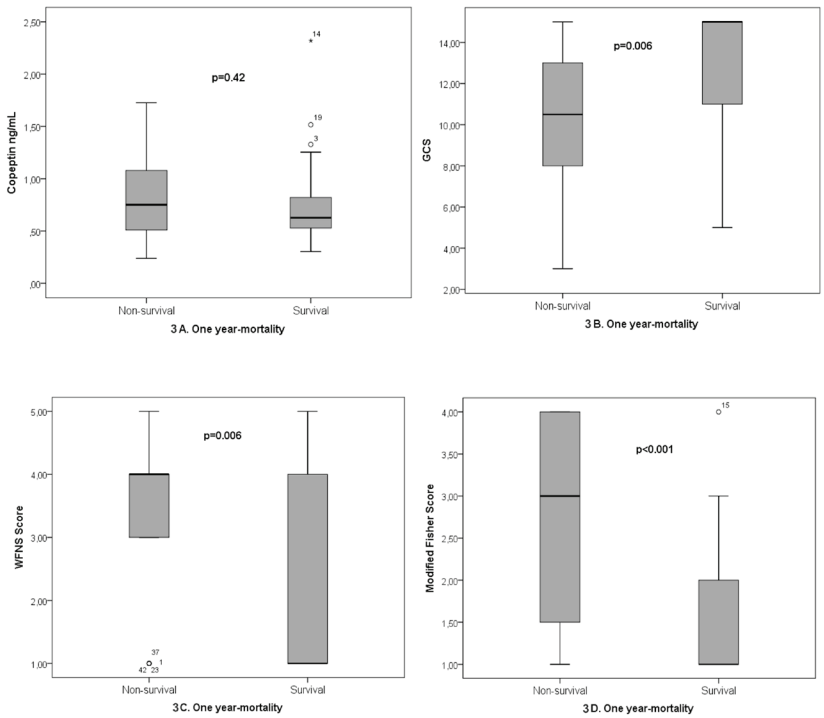

Fig. 3. Comparison of copeptin levels, GCS, WFNS and modified Fisher scores relative to one-year mortality.

GCS = Glasgow Coma Score; WFNS = World Federation of Neurological Surgeons

tion of plasma copeptin levels with the GCS, WFNS, and modified Fisher scores (Table 2).

The rate of in-hospital mortality was 22.6% (n=12), and the mean copeptin level of patients without in-hospital mortality was 0.73±0.42 (0.24-1.69) ng/mL. No significant difference was observed in copeptin levels between the patients with and without in-hospital mortality [0.80±0.41 (0.30-2.32) ng/mL] (p=0.41) (Fig. 2A). There was a significant difference in the GCS scores between the patients with in-hospital mortality [median: 10; 5.5 (3-15)] and those without in-hospital mortality [median: 14; 3.5 (5-15)] (p<0.001) (Fig. 2B). Furthermore, there was a significant difference in the WFNS scores between the patients with in-hospital mortality [median: 4; 1 (1-5)] and those without it [median: 2; 3 (1-5)] (p<0.001) (Fig. 2C). In addition, there was a significant difference in the modified Fisher score between the patients with in-hospital mortality [median: 4; 2.75 (1-4)] and those without it [median: 1; 2 (1-4); median: 4; 2.75 (1-4); p=0.003) (Fig. 2D].

The one-year mortality of patients was 37.7% (n=20). The copeptin levels of patients with 1-year mortality [mean: 0.85±0.44 (0.24-1.73) ng/mL] were not significantly different from the copeptin levels of those without 1-year mortality [mean: 0.75±0.40 (0.30–2.32) ng/mL] (p=0.42) (Fig. 3A). The GCS scores of patients with one-year mortality [median: 10; 5 (3-15)] were significantly different from the GCS scores of those without it [median: 15; 4 (5-15)] (p=0.006) (Fig. 3B). Moreover, the WFNS scores of patients with one-year mortality [median: 4; 1 (1-5)] were significantly different from the WFNS score of those without it [median: 1; 3 (1-5)] (p=0.006) (Fig. 3C). The modified Fisher scores of patients with one-year mortality [median: 3; 2.75 (1-4)] were significantly different from the modified Fisher scores of those without it [median: 1; 1 (1-4)] (p<0.001) (Fig. 3D).

In patients with spontaneous SAH, no statistically significant difference was observed in copeptin levels between the patients with in-hospital mortality and those without in-hospital mortality (p=0.63). There was no difference in copeptin values between the patients with and without in-hospital mortality among the SAH subgroups (aneurysmal, arteriovenous malformation, etc.) (p>0.05). There was no significant

difference in one-year mortality between spontaneous SAH and its subgroups (p>0.05) (Table 3).

In traumatic SAH cases, no significant difference was observed in copeptin levels between the patients with and without in-hospital mortality, or between those with and without one-year mortality (p>0.05) (Table 3).

Discussion

The plasma copeptin levels are significantly higher in patients with subarachnoid bleeding at the time of admission as compared with healthy controls[24-26]. The present study also revealed that plasma copeptin levels in patients diagnosed with SAH at the emergency department were significantly higher than those in healthy controls. Any stressor that activates the hypothalamic-pituitary-adrenal (HPA) axis leads to an increase in cortisol concentration, an adrenal stress hormone. Vasopressin is one of the hypothalamic stress hormones that is stimulated by different stressors. Copeptin is released in equal concentrations as vasopressin, and therefore reflects the levels of vasopressin. Therefore, it was expected that copeptin would increase in patients with SAH because it is a hormone that shows the individual stress response at the hypothalamic level. Particularly in recent years, several studies have evaluated diagnostic value of copeptin as a biochemical parameter for different diseases. These studies have demonstrated that copeptin can be used for the diagnosis of different diseases[12,15-18].

Despite advances in the treatment, mortality rates in SAH continue to remain very high. Baydın *et al.*[27] have previously reported that the rate of in-hospital mortality of spontaneous SAH is 48.3%. A study on aneurysmal SAH determined the in-hospital mortality rate as 10.6% and the one-year mortality rate as 13.9%[24]. Zuo and Ji[26] report on the 3-month mortality rate of 10.3%, whereas Fung *et al.*[8] report on the 6-month mortality rate of 22.2%. In the present study, the rates of in-hospital mortality and one-year mortality were 22.6% and 37.7%, respectively. Differences in these mortality rates might be associated with the fact that we included patients with SAH without aneurysmal SAH. Although the trauma patients included in the present study had isolated head trauma, they may have played a role in causing this difference.

Several clinical studies in recent years have determined the applicability of copeptin as an indicator of prognosis in aneurysmal patients with SAH[18,19,24,26]. The results of these studies have shown that there is a consistent correlation between copeptin and the severity and prognosis of SAH[19,24,26].

The first study we identified in the literature regarding aneurysmal SAH was the study by Zhu *et al.*[24]. This retrospective study found a significant difference in the copeptin levels between patients with and without in-hospital mortality and one-year mortality. The authors report that high copeptin levels are associated with in-hospital mortality and one-year mortality. The predictive value of copeptin was found to be similar to that of the WFNS and modified Fisher score[24]. The study by Zhu *et al.* found the copeptin level to be useful and complementary in predicting poor function outcome and mortality following aneurysmal SAH[24]. The prospective study by Zheng *et al.* identified a significant difference in copeptin levels according to 6-month poor and good outcomes[19]. For 6-month poor outcome, the study by Zheng *et al.* reports on the area under the receiver operating characteristic (ROC) curve (AUC) values of 0.824 and 0.940 for copeptin and copeptin + WFNS, respectively[19]. A recently conducted retrospective study reports a significant difference in copeptin levels between patients with and without 3-month mortality[26]. The AUC value, sensitivity, and specificity of the plasma copeptin level for poor outcomes are reported as 0.74, 70.5% and 69.6%, respectively[26]. The AUC value of the WFNS score for poor outcomes was determined as 0.72. Moreover, the AUC value of combined copeptin and WFNS was determined as 0.77[24]. According to the Glasgow Outcome Score, there was a significant high difference in copeptin levels between the patients with good and poor functional outcomes[26]. The study also demonstrated a correlation between the copeptin levels and WFNS score. Zuo and Ji report that copeptin levels can reliably predict short-term prognosis of patients with SAH at the beginning[26].

Fung *et al.* previously conducted a prospective study on plasma copeptin levels of 18 aneurysmal patients with SAH and found significant difference in copeptin levels between the patients with good and poor WFNS scores at the time of admission[8]. They also determined that patients with Fisher grade 3 had significantly higher blood copeptin levels than those with Fisher grade 4 and 5. Fung *et al.* also report in the same study that plasma copeptin levels significantly increased in the presence of intracerebral hemorrhage in patients with SAH[8]. On the other hand, they

found no significant difference in plasma copeptin levels between good and poor outcomes according to the Modified Rankin Score. With respect to mortality, they found no significant difference in copeptin levels between the patients with and without mortality. Furthermore, copeptin lacked any significant relationship with intraventricular hemorrhage, hydrocephaly, vasospasm, location of aneurysm, gender, delayed ischemia, or 6-month mortality[8]. Aksu *et al.* previously identified significant difference in plasma copeptin levels between 29 patients with SAH and healthy individuals[25]. However, no significant correlation was observed between copeptin and the intracerebral hemorrhage score. In general, the present study showed that the copeptin level in patients with SAH is not useful for their prognosis[25].

In the present study, no significant relationship was found between the plasma copeptin level in patients with spontaneous SAH and their mortality and prognosis. Our findings are in agreement with two of the aforementioned studies on aneurysmal SAH, but in disagreement with three of them[8,19,24-26]. Moreover, we did not identify any relationship between copeptin levels and the severity of patients with SAH at the time of admission/arrival because copeptin levels lacked correlation with the GCS, WFNS, and modified Fisher scores.

We did not find any study regarding traumatic SAH and copeptin levels. However, there are various studies on traumatic brain injury, which generally evaluate all traumatic brain injuries together[20,21,28-30]. Yu *et al.* report on a significant difference in copeptin levels between the patients who died and lived following traumatic SAHs[28]. Increased plasma copeptin levels have also been reported to be associated with one-year function outcomes and mortality following traumatic brain injury[28]. In this respect, the results of the present study are in disagreement with the findings by Yu *et al.*[28]. With respect to in-hospital mortality and one-year mortality, copeptin levels were not significantly different between patients with SAH who died and those who survived.

A study on patients admitted to the emergency department with slight head trauma found that copeptin levels in these patients were significantly higher than those in the control group[29]. However, the same study also found copeptin to have a low prognostic performance, and no significant difference was found between brain computed tomography images of patients with and without a pathology. Furthermore, there was no significant difference between 30-day good and poor functional outcomes[29]. In another study on isolated head trauma, no significant difference was found in copeptin levels (at admission to the emergency department and the sixth hour after admission) between the patients who survived and died within a one-month period (i.e., patients with different outcomes with respect to one-month mortality)[30]. The same study also found a difference in copeptin levels between the time of admission (hour 0) and the sixth hour following admission, and Δ-copeptin level was associated with mortality[30]. Cavus *et al.* report on the absence of any significant relationship between GCS and copeptin levels[30]. The prognosis and mortality-related findings of these two studies, which evaluated all head traumas except for isolated SAHs, are in agreement with the present study. Copeptin appears to have increased secondary to a trauma that is an acute stress factor.

A study on traumatic brain injuries determined that copeptin level began to increase in the first 6 hours, reaching a peak in the 24th hour and decreasing afterwards[20]. Zweifel *et al.* evaluated plasma copeptin levels within the 0-3-, 3-6-, 6-12-, 12-24-, and 24-72-hour periods in patients with intracerebral hemorrhage; no significant difference was observed among these levels[22]. Our study found no difference between copeptin levels observed during these different time periods either. The present study only investigated the copeptin levels in patients at the time of admission, which was a limitation of the study.

It is uncertain whether copeptin release is specific to SAH or it is a manifestation of a general stress response. Copeptin is released from the hypothalamus in equimolar ratio to vasopressin. Therefore, the copeptin increase in patients with SAH might stem from the activation of the HPA axis in response to stress[18,26]. This appears to be very likely because copeptin levels can be used for the prognosis of various conditions other than intracranial hemorrhage, such as respiratory tract infections, myocardial infarction, cardiac insufficiency, trauma, and shock. Plasma copeptin levels might be used for the prognosis of various diseases due to their close and repeatable relationship with the degree of activation of the stress axis.

Conclusion

Plasma copeptin level may be used for the diagnosis of SAH; however, it does not play a role in deter-

mining patient severity and mortality. Thus, there are insufficient studies on the use of copeptin for the prognosis of patients with SAH, and the results of these studies are contradictory. Therefore, there is a need for new prospective studies involving a larger number of patients.

Our study suffered from some limitations. The most important limitation was the low number of cases. We could not study copeptin level at different times in the same patient. Detection of differences in the level of copeptin studied in the series could increase the value of the study. In addition, the wide age range of patients may have affected the results.

References

1. Galea J, Ogungbenro K, Hulme S, Patel H, Scarth S, Hoadley M, *et al*. Reduction of inflammation after administration of interleukin-1 receptor antagonist following aneurysmal subarachnoid hemorrhage: results of the subcutaneous interleukin-1Ra in SAH (SCIL-SAH) study. J Neurosurg. 2018;128:515-23. doi: 10.3171/2016.9.JNS16615. Epub 2017 Feb 24.
2. Doerfler S, Faerber J, McKhann GM, Elliott JP, Winn HR, Kumar M, *et al*. The incidence and impact of secondary cerebral insults on outcome after aneurysmal subarachnoid hemorrhage. World Neurosurg. 2018;114:483-94. doi: 10.1016/j.wneu.2018.02.195. Epub 2018 Mar 21.
3. Hackman JL, Nelson AM, Ma OJ. Spontaneous subarachnoid and intracerebral hemorrhage. In: Tintinalli JE, Stapczynski JS, Ma OJ, Yealy DM, Meckler GD, Cline DM (eds). Emergency Medicine A Comprehensive Study Guide. 8th edn. New York: The Mc Graw Hill Companies, 2016; pp. 1137-41.
4. Novaković N, Lepić M, Minić L, Radenović K, Rotim A, Rasulić L. Combined treatment of ruptured middle cerebral artery aneurysm followed by subarachnoid hemorrhage and acute subdural hematoma in multiple aneurysm disease of cerebral blood vessels: case report. Acta Clin Croat. 2016;55:659-62. doi: 10.20471/acc.2016.55.04.19.
5. Pačić-Turk L, Jandrijević P, Havelka-Meštrović A. Recovery of memory after cerebral artery aneurysm surgery. Acta Clin Croat. 2019;58:229-39. doi: 10.20471/acc.2019.58.02.05.
6. Tamargo RJ. Copeptin in aneurysmal subarachnoid hemorrhage. Crit Care. 2012;16:103. doi: 10.1186/cc10594.
7. Jabbarli R, Pierscianek D, Oppong MD, Sato T, Dammann P, Wrede KH, *et al*. Laboratory biomarkers of delayed cerebral ischemia after subarachnoid hemorrhage: a systematic review. Neurosurg Rev. 2018;10. doi: 10.1007/s10143-018-1037-y.
8. Fung C, De Marchis GM, Katan M, Seiler M, Arnold M, Gralla J, *et al*. Copeptin as a marker for severity and prognosis of aneurysmal subarachnoid hemorrhage. PLoS One. 2013;8:e53191. doi: 10.1371/journal.pone.0053191.
9. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem. 2006;52:112-9. doi: 10.1373/clinchem.2005.060038. Epub 2005 Nov 3.
10. Volpi S, Rabadan-Diehl C, Aguilera G. Vasopressinergic regulation of the hypothalamic pituitary adrenal axis and stress adaptation. Stress. 2004;7:75-83. doi: 10.1080/10253890410001733535.
11. Bolignano D, Cabassi A, Fiaccadori E, Ghigo E, Pasquali R, Peracino A, *et al*. Copeptin (CTproAVP), a new tool for understanding the role of vasopressin in pathophysiology. Clin Chem Lab Med. 2014;52:1447-56. doi: 10.1515/cclm-2014-0379.
12. Katan M, Christ-Crain M. The stress hormone copeptin: a new prognostic biomarker in acute illness. Swiss Med Wkly. 2010;140:11-5. doi: 10.4414/smw.2010.13101. eCollection 2010.
13. Struck J, Morgenthaler NG, Bergmann A. Copeptin, a stable peptide derived from the vasopressin precursor, is elevated in serum of sepsis patients. Peptides. 2005;26:2500-4. doi: 10.1016/j.peptides.2005.04.019.
14. Katan M, Morgenthaler N, Widmer I, Puder JJ, Konig C, Muller B, *et al*. Copeptin, a stable peptide derived from the vasopressin precursor, correlates with the individual stress level. Neuro Endocrinol Lett. 2008;29:341-6.
15. Nickel CH, Bingisser R, Morgenthaler NG. The role of copeptin as a diagnostic and prognostic biomarker for risk stratification in the emergency department. BMC Med. 2012;10:7. doi: 10.1186/1741-7015-10-7.
16. Chai SB, Hui YM, Li XM, Xiao Y, Tang CS. Plasma levels of copeptin in patients with coronary heart disease. Heart Vessels. 2009;24:79-83. doi: 10.1007/s00380-008-1086-1. Epub 2009 Apr 1.
17. Ozkan S, Salt O, Durukan P, Sen A, Bulbul E, Duman A, *et al.* The relationship among plasma copeptin, carboxyhemoglobin, and lactate levels in carbon monoxide poisoning. Hum Exp Toxicol. 2020;39(3):311-318. doi:10.1177/0960327119886063
18. Katan M, Fluri F, Morgenthaler NG, Schuetz P, Zweifel C, Bingisser R, *et al*. Copeptin: a novel, independent prognostic marker in patients with ischemic stroke. Ann Neurol. 2009;66:799-808. doi: 10.1002/ana.21783.
19. Zheng YK, Dong XQ, Du Q, Wang H, Yang DB, Zhu Q, *et al*. Comparison of plasma copeptin and multiple biomarkers for assessing prognosis of patients with aneurysmal subarachnoid hemorrhage. Clin Chim Acta. 2017;475:64-9. doi: 10.1016/j.cca.2017.10.009. Epub 2017 Oct 13.
20. Dong XO, Huang M, Yang SB, Yu WH, Zhang ZY. Copeptin is associated with mortality in patients with traumatic brain injury. J Trauma. 2011;71:1194-8. doi: 10.1097/TA.0b013e31821283f2.
21. Choi KS, Cho Y, Jang BH, Kim W, Ahn C, Lim TH, *et al.* Prognostic role of copeptin after traumatic brain injury: a systematic review and meta-analysis of observational studies. Am J Emerg Med. 2017;35:1444-50. doi: 10.1016/j.ajem.2017.04.038. Epub 2017 Apr 19.
22. Zweifel C, Katan M, Schuetz P, Siegemund M, Morgenthaler NG, Merlo A, *et al*. Copeptin is associated with mortality and outcome in patients with acute intracerebral hemorrhage. BMC Neurol. 2010;10:34. doi: 10.1186/1471-2377-10-34.
23. Zhang R, Liu J, Zhang Y, Liu Q, Li T, Cheng L. Association between circulating copeptin level and mortality risk in pa-

tients with intracerebral hemorrhage: a systemic review and meta-analysis. Mol Neurobiol. 2017;54:169-74. doi: 10.1007/s12035-015-9626-z. Epub 2016 Jan 5.

24. Zhu XD, Chen JS, Zhou F, Liu QC, Chen G, Zhang JM. Detection of copeptin in peripheral blood of patients with aneurysmal subarachnoid hemorrhage. Crit Care. 2011;15(6):R288. doi: 10.1186/cc10575.
25. Aksu F, Gurger M, Yilmaz M, Atescelik M, Yildiz M, Ilhan N, *et al*. Copeptin levels in cerebral infarction, intracranial hemorrhage and subarachnoid hemorrhage. Clin Lab. 2016;62:2387-93. doi: 10.7754/Clin.Lab.2016.160532.
26. Zuo Z, Ji X. Prognostic value of copeptin in patients with aneurysmal subarachnoid hemorrhage. J Neuroimmunol. 2019;330:116-22. doi: 10.1016/j.jneuroim.2019.03.007. Epub 2019 Mar 8.
27. Baydin A, Amanvermez R, Tuncel ÖK, Ocak M, Meric M, Cokluk C. Ischemia-modified albumin is not better than creatine kinase-MB and cardiac troponin I in predicting a cardiac injury in nontraumatic subarachnoid hemorrhage. Am J Emerg Med. 2015;33:488-92. doi: 10.1016/j.ajem.2014.10.007. Epub 2014 Oct 12.
28. Yu GF, Huang Q, Dai WM, Jie YQ, Fan XF, Wu A, *et al*. Prognostic value of copeptin: one-year outcome in patients with traumatic brain injury. Peptides. 2012;33:164-9. doi: 10.1016/j.peptides.2011.11.017. Epub 2011 Nov 26.
29. Castello LM, Salmi L, Zanotti I, Gardino CA, Baldrighi M, Settanni F, *et al*. The increase in copeptin levels in mild head trauma does not predict the severity and the outcome of brain damage. Biomark Med. 2018;12:555-63. doi: 10.2217/bmm-2018-0041. Epub 2018 Apr 5.
30. Cavus UY, Yildirim S, Gurer B, Dibek K, Yilmaz D, Ozturk G, *et al*. The prognostic value of plasma Δ-copeptin levels in patients with isolated traumatic brain injury. Eur J Trauma Emerg Surg. 2014;40:373-8. doi: 10.1007/s00068-013-0357-4. Epub 2013 Dec 4.

Sažetak

ULOGA RAZINE KOPEPTINA U PLAZMI U ODREĐIVANJU TEŽINE I SMRTNOSTI SUBARAHNOIDNOG KRVARENJA

S. Ozkan, N. Baykan, O. Salt, S. Yakar, A. Sen i *P. Durukan*

Cilj istraživanja bio je ispitati ulogu razine kopeptina u plazmi u dijagnostici, težini i smrtnosti bolesnika sa subarahnoidnim krvarenjem (SAK) na odjelu hitne medicine. Uključeni su bolesnici u dobi od ≥18 godina kod kojih je dijagnosticiran SAK. Uzorci krvi za određivanje razine kopeptina u plazmi uzeti su kod prijma bolesnika na hitni odjel. Kod bolesnika su određeni Glasgowska ljestvica kome (*Glasgow Coma Scale*, GCS), *World Federation of Neurological Surgeons* (WFNS) zbroj, modificirani Fisherov zbroj, stopa smrtnosti u bolnici i jednogodišnja stopa smrtnosti. U razinama kopeptina zabilježena je statistički značajna razlika između bolesnika (srednja vrijednost: 0,78±0,41 ng/mL) i zdravih kontrolnih osoba (srednja vrijednost: 0,48±0,27 ng/mL) (p=0,001). Nije bilo nikakve značajne korelacije razina kopeptina u plazmi s GCS, WFNS i modificiranim Fisherovim zbrojem. Nije bilo statistički značajne razlike u razinama kopeptina između bolesnika koji su umrli u bolnici (srednja vrijednost: 0,73±0,42 ng/mL) i onih koji nisu umrli u bolnici (srednja vrijednost: 0,80±0,41 ng/mL (p=0,41). Iako bi se razina kopeptina u plazmi mogla rabiti u dijagnostici SAK ona ipak nema nikakvu ulogu u određivanju težine stanja bolesnika i smrtnosti.

Ključne riječi: *Kopeptin; Odjel hitne medicine; Smrtnost; Subarahnoidno krvarenje*