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Original Contribution

Plasma copeptin levels in the patients with gastrointestinal bleeding

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ABSTRACT

Introduction: Gastrointestinal bleeding is a significant cause of morbidity and mortality worldwide. In addition, it constitutes an important part of health expenditures.
In this study, we aimed to determine whether there is a relationship between plasma copeptin levels and the etiology, location and severity of gastrointestinal bleeding.
Materials and methods: This study was performed prospectively in 104 consecutive patients who were admitted to an emergency department with complaints of bloody vomiting or bloody or black stool. To evaluate the level of biochemical parameters such as Full Blood Count (FBC), serum biochemistry, bleeding parameters and copeptin, blood samples were obtained at admission. For the copeptin levels, 2 more blood samples were obtained at the 12th and 24th hours after admission.
The values obtained were compared using statistical methods.
Results: In terms of the etiology of bleeding, the copeptin levels in the patients with peptic ulcer were higher than the levels in patients with other gastrointestinal bleeding. However, the difference was not statistically significant.
There were no significant differences among all groups' 0th, 12th and 24th hour levels of copeptin.
Discussion: We conclude that copeptin cannot be effectively used as a biochemical parameter in an emergency department to determine the etiology and location of gastrointestinal bleeding. It can, however, be used to make decisions on endoscopy and the hospitalization of patients with suspected gastrointestinal bleeding.

1. Introduction

Acute gastrointestinal bleeding can vary in clinical manifestation from obscure to abundant bleeding. It can involve the whole gastrointestinal system, including the pancreas, liver and bile ducts [1]. The incidence in adults is approximately 170 cases per 100.000 population, and is higher in elders. It is more common in males than in females [2]. Early diagnosis of the disease and especially timely endoscopic intervention should positively influence the mortality and morbidity rates and help to avoid the complications observed in the follow-up of the disease [1]. Traditional diagnostic tools such as nasogastric drainage, physical examination and medical history are important in the diagnosis of gastrointestinal bleeding. However, the diagnosis of gastrointestinal bleeding is complicated by the fact that 16% of patients with active gastrointestinal bleeding might have clear nasogastric drainage [3]. Despite all modern diagnostic and therapeutic modalities, gastrointestinal bleeding still has average mortality rates as high as 10% [4]. It has been considered that the use of new markers in addition to conventional diagnostic approaches might help the physician in both the diagnosis and follow-up of gastrointestinal bleeding.

Arginine-vasopressin (AVP), also known as antidiuretic hormone (ADH), is a nanopeptide structured protein with endocrine, hemodynamic and osmoregulator effects [5,6]. It is produced in the hypothalamus and carried by neurophysin 2 to the posterior hypophysis, where it is released into circulation after hemodynamic and osmotic stimuli. It shows peripheral effects on receptors V1a, V1b and V2 [7,8]. Copeptin, located on the C terminal end of AVP, is a long glycosylated peptide consisting of 39 amino acids with a core that abounds in leucine [9]. It is more stable in circulation than AVP, and thus, quantifying or preserving it is easier [10].

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This study aimed to investigate any relationship between plasma copeptin level and the etiology, localization or severity of bleeding in patients with gastrointestinal bleeding.

2. Materials and methods

This study was performed in the Erciyes University School of Medicine Emergency Medicine Department with assistance from the Gastroenterology Department and support by the Erciyes University Research Fund (Project code: TSU-12-3867), pursuant to approval by the research ethics committee (Approval number: 07–2011/136). 104 patients referred to the emergency room with gastrointestinal bleeding symptoms were consecutively and prospectively enrolled into the study, and a voluntary informed consent form (ICF) signature was obtained from each patient and/or relative.

All patients referred to the emergency room who were diagnosed with gastrointestinal bleeding were closely monitored and urgently treated. The onset time and characteristics of bleeding were carefully determined through questioning by an emergency medicine resident. Patients' data (medical history, risk factors, past medical history, physical examination, laboratory, endoscopic findings) were recorded by an emergency medicine resident. Thirty healthy volunteers over 18 years old with no pathological findings on a physical exam who had not experienced gastrointestinal bleeding, surgical operation or any chronic disease were enrolled in the control group. At the time of referral, blood samples were obtained to check blood parameters such as FBC, biochemistry, bleeding parameters and copeptin.

Subsequent blood samples were taken at 12th and 24th hours to quantify the copeptin levels by the sandwich ELISA method. The human copeptin kit (Copeptin human EIA kit, number: EK-065-032, Phoenix Pharmaceuticals Inc.®, Burlingame, USA) used to evaluate the plasma levels of copeptin had a normal reference interval of 0.3–0.6 ng/mL.

Patients who were diagnosed with gastrointestinal bleeding underwent upper or lower gastrointestinal system endoscopy.

Patients who met the following criteria were excluded from the study:

-Patients younger than 18 years old.
-Patients with renal failure.
-Patients with congestive heart failure.
-Patients with myocardial infarction.

2.1. Statistical analysis

Data were processed using the statistical packages IBM SPSS Statistics 20 and Sigma Stat 3.5. The normal distribution of the data was calculated by the Shapiro-Wilk test. The summary statistics of numerical variables were defined as the mean ± standard deviation (SD). In two-group comparisons, the Mann-Whitney *U* test was applied; for more than two groups, One-way Analysis of Variance for normally distributed variables and Kruskal-Wallis Analysis for non-normally distributed variables were applied. Spearman's correlation test was used to compare numerical variables, and the chi-square test was applied to compare categorical variables. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

A total of 134 patients and healthy volunteers were enrolled in the study. Of these patients, 104 suffered from gastrointestinal bleeding, and 30 healthy volunteers constituted the control group. All of the 104 patients were diagnosed with gastrointestinal bleeding, both endoscopically and clinically. Ten of them died during follow up, after emergency treatment. Sixty-seven (64.4%) of the 104 patients were male, while 37 (35.6%) were female. In the control group; 19 (63.3%) of them were male, and 11 (36.7%) were female. The average age was calculated as 65.64 ± 15.56 years in the patient group and 34.27 ± 11.43 in the healthy volunteer group.

Among the 104 enrolled patients, 55 (52.9%) had a history of peptic ulcer disease, 15 (14.4%) had esophageal varicosis, 20 (19.2%) had alcohol intake, 19 (18.3%) had liver cirrhosis, 12 (11.5%) had malignancy, 14 (13.4%) had prior episodes of gastrointestinal bleeding, 44 (42.3%) had gastroprotective agent usage (H_2 receptor blocker or proton-pump inhibitor (PPI)) and 44 (42.3%) had a history of smoking.

The approximate time between patients' observation of bleeding and referral was 9.6 ± 7.16 h. The average systolic and diastolic blood pressure of patients was 103.13 ± 40.21 mmHg and 64.81 ± 11.4 mmHg, respectively. The complete blood count and bleeding parameter averages of patients with gastrointestinal bleeding at referral are presented in Table 1.

The biochemical parameter averages of patients with gastrointestinal bleeding are presented in Table 2.

Initial rectal examination findings revealed solid melena in 47 (45.2%), watery melena in 36 (34.6%), normal feces in 17 (16.3%) and hematochezia in 4 (3.8%) of all patients.

Thirty healthy volunteers were enrolled in the study's control group to establish plasma copeptin levels in healthy adults and to investigate any statistically significant difference between healthy individuals and patients with gastrointestinal bleeding. Thus, for plasma copeptin level analysis, only one blood sample was obtained from each healthy volunteer. The mean copeptin level was found to be 0.48 ± 0.09 ng/mL (mean ± SD) in healthy volunteers and 0.88 ± 0.50 ng/mL (mean ± SD) at hour 0 in the gastrointestinal bleeding group. Comparison of these two values revealed a statistically significant difference ($p < 0.05$).

The mean copeptin levels of the 104 patients at 0th, 12th and 24th hours were 0.88 ± 0.50 ng / dL, 0.92 ± 0.43 ng / dL, and 0.89 ± 0.36 ng / dL (mean ± SD), respectively. There were no statistically significant differences between these three values, which are presented in Table 3.

To compare patients' endoscopic results and copeptin levels, the Kruskal-Wallis test was performed, and no statistically significant difference was found ($p > 0.05$). These findings are presented in Table 4.

Comparison of the 0th, 12th and 24th hour copeptin levels within each endoscopic group revealed no statistically significant difference ($p > 0.05$). There was also no statistically significant inter-group difference in the 0th, 12th and 24th hour copeptin levels ($p > 0.05$).

Patients were endoscopically divided into subgroups in terms of bleeding etiology, and there were no statistically significant inter-group differences in vital parameters such as arterial blood pressure, heart rate, minute respiratory rate and temperature ($p > 0.05$).

4. Discussion

Gastrointestinal system bleeding is still a prominent referral reason in emergency rooms. Despite the decrease in the incidence of gastrointestinal bleeding over the years, gastrointestinal system bleeding-related mortality rates are still 5–10% [11]. In the study by Laine et al. [12], it was reported that 5 million patients with gastrointestinal bleeding were admitted and treated annually in the USA, and despite all modern diagnostic approaches, it was impossible to reveal the origin of bleeding in 10% of patients. In our study, patients with an obscure origin for bleeding occurred at a rate of 4.8%, which is low compared to the literature data.

Gastrointestinal bleeding is possible in any age group but is more frequent between the ages of 40 and 70 (59 as average). Gastrointestinal bleeding-related mortality mostly occurs at ages over 60 years;

Table 1
Referral full blood count and bleeding parameters averages of patients.

Parameter	Hb (g/dL)	Hct(%)	WBC (/mm^3)	Plt ($\times 10^3$/mm^3)
Mean ± SD.	9.88 ± 2.15	30.7 ± 6.18	9.04 ± 4.19 × 10^3	204.59 ± 105.45