Prognostic value of the biomarker copeptin in critically ill patients with sepsis

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Received 19 July 2016
Accepted 5 October 2016

Kasr Al Ainy Medical Journal
2016, 22:123–128

Objective
The aim of this study was to evaluate copeptin as a predictor of short-term ICU mortality in patients with sepsis and its relation with disease severity.
Design
This study was an observational case–control one.
Methods
The study included 60 patients admitted to the ICU with sepsis: 20 patients with sepsis, 20 patients with severe sepsis, and 20 patients with septic shock. Baseline characteristics, serum copeptin, and APACHE II score were determined at the time of admission. They were prospectively followed up for 7 days to determine improvement, development of multiple organ failure, or death. Copeptin level in patients with sepsis was compared with its level in the control group comprising 10 patients with congestive heart failure, 10 patients with post-acute myocardial infarction, and 10 healthy individuals.
Results
The mean copeptin level was 48.4 (15.1) pmol/l in patients with sepsis, 69.2 (15.4) pmol/l in severe sepsis, and 120.9 (31.2) pmol/l in septic shock. It was significantly higher than its level in post-acute myocardial infarction [21.1 (8.0) pmol/l], congestive heart failure [20.6 (9.8) pmol/l], and healthy controls [8 (4.3) pmol/l] ($P<0.001$). Spearman correlation analysis showed a positive correlation between copeptin and total leukocytic count ($r=0.466$; $P<0.001$), urea ($r=0.496$; $P<0.001$), creatinine ($r=0.552$; $P<0.001$), alanine aminotransferase ($r=0.451$; $P<0.001$), and APACHII ($r=0.661$; $P<0.001$). Improved patients significantly had lower copeptin [43.5 (8.7) pmol/l] than those who died [103.8 (36.2) pmol/l] ($P<0.001$). Area under the curve of copeptin for predicting mortality was 0.880 ($P<0.001$). A cutoff value of 58.1 pmol/l had 96.6% sensitivity and 61.3% specificity.
Conclusion
Serum copeptin is a sensitive predictor of mortality in critically ill patients with sepsis. Moreover, it could be a promising biomarker for disease severity and development of multiple organ failure in this group of patients.

Keywords:
APACHE II score, copeptin, multiple organ failure, mortality, sepsis

Kasr Al Ainy Med J 22:123–128

1687-4625

Introduction

Sepsis is a major challenge in the ICU and it is associated with high mortality. Early diagnosis and quantification of its severity will allow the creation of appropriate management plan; hence, it may help in improving clinical outcome. Many researchers have focused on factors that predict mortality in sepsis. Furthermore, many biomarkers have been considered as predictors of sepsis outcomes.

Copeptin, the C-terminal fragment of arginine vasopressin (AVP), has been suggested as stress hormone and a stable surrogate marker for the unstable AVP [1]. Copeptin increases in heart failure, acute myocardial infarction (AMI), and pneumonia and its level is associated with adverse outcomes [2–4]. Moreover, copeptin level has been found elevated in sepsis, and recent studies showed that copeptin is independently associated with the degree of sepsis [5,6]. However, these studies did not compare copeptin level in sepsis and in other conditions – for example, in heart failure, which is associated with high copeptin values [6] – or did not exclude these diseases from their research [5].

Moreover, other research studies yielded conflicting results [7,8].

The aim of the present study was to evaluate copeptin as a predictor of short-term ICU mortality in patients with sepsis and its relation with disease severity.

 DOI: 10.4103/1687-4625.195893

Patients and methods

The studied patients were recruited from medical and surgical cases admitted in the medical ICU with diagnosis of sepsis from September 2013 to May 2014, and the study was approved by our ethical committee. Informed consent was obtained from the patients.

The study included 60 patients with sepsis who had at least two of the four criteria of Systemic Inflammatory Response Syndrome [9]. They were consecutively selected as follows: 20 patients with sepsis, 20 patients with severe sepsis, and 20 patients with septic shock. The patients were grouped according to the degree of sepsis, based on the classification of the American College of Chest Physicians/Society of Critical Care Medicine [10]. Thirty age and sex matched participants comprising 10 patients with destabilized heart failure, 10 post-AMI patients, and 10 normal individuals were selected as control groups.

Exclusion criteria for the sepsis group were as follows: previous diagnosis of AIDS; neutrophil count of 500 cells/ml or less; history of pituitary surgery; diabetes insipidus; anaphylactic shock, cardiogenic shock or hypovolemic shock; inflammatory response without a documented or suspected infection; destabilized heart failure; post-AMI; history of renal impairment; or previously documented kidney function.

Documented infection was defined as an infection confirmed by positive cultures of blood, or sterile body fluids, or a sample obtained from the site of suspected infection, or the presence of gross purulence or an abscess detected on physical examination, radiographic images, or histological examination. The patients were initially treated with an empirical antimicrobial regimen based on the surveillance data of the hospital infection control committee and suspected site of infection; antimicrobial therapy was then tailored as required according to the culture results.

Baseline characteristics, serum copeptin, and APACHE II score were determined at the time of admission. The patients were followed up for a week during their ICU stay. The endpoints were as follows: improvement, development of multiple organ failure (MOF), or death. Improvement was considered if the patient's mental status improved, urine output was at least 0·5 ml/kg/h, the amount of inotropes decreased or stopped, the patient was weaned from mechanical ventilation, or improvement in PaO_2/FiO_2 ratio with improvement in biochemical parameters.

MOF was defined as dysfunction of two or more of the following: renal dysfunction – serum creatinine of at least 2 mg/dl or urine output of less than 0.5 ml/kg/h despite adequate fluid resuscitation; hepatic dysfunction – serum bilirubin of more than 4.0 gm/dl or a three-fold increase in serum aminotransferases; disseminated intravascular coagulation – international normalized ratio of more than 1.5, platelet less than 100 000/mm^3; respiratory insufficiency – a PaO_2/FiO_2 ratio of 300 or less; hypotension – systolic blood pressure of up to 90 mmHg or the mean arterial blood pressure of up to 70 mmHg despite adequate fluid and vasopressor resuscitation; and central nervous system dysfunction – acute alteration of the mental status [11]. Deterioration was considered to be present if new signs of organ failure developed despite continuing proper management.

Sample collection

Blood samples were collected from the patients on admission to the ICU at the time of diagnosis, under complete aseptic precautions. The samples were collected in serum separator tubes and were allowed to clot for 30 min. Centrifugation was performed for 15 min at ~1000*g* and grossly hemolyzed samples were excluded. Serum was removed and stored at −80°C. Freeze-thaw cycles were avoided. At the time of the assay, samples were warmed up to room temperature slowly. Human Copeptin ELISA Kit (NovaTeinBio, Woburn, Massachusetts, USA) was used to quantify serum copeptin level in pmol/l. The test was performed according to manufacturers' instructions. We used a copeptin cutoff of 14 pmol/l.

Statistical analyses

Precoded data were entered on the computer using the statistical package of social science software program, version 15 (SPSS Inc., Chicago, Illinois, USA), to be statistically analyzed. Data were summarized using mean, SD, and median for quantitative variables and using frequency and percent for qualitative data. Analysis of variance with post-hoc Bonferroni test was used to compare quantitative normally distributed variables, whereas nonparametric Mann–Whitney test was used for quantitative variables that are not normally distributed. A *P* value of 0.05 or less was considered significant. Spearman's rank correlation coefficient analysis was used to correlate different parameters and copeptin. Receiver operator characteristic curve was used to find out the best cutoff and validity of certain variable.

Results

Patient characteristics

The mean age of the studied patients was 57 (14.2) years and 46.7% of them were male. The most common

underlying diseases were diabetes mellitus (53.3%) and hypertension (48.3%). Tables 1 and 2 show baseline characteristics and laboratory data of the study population.

Infection was documented in cultures in 42 patients (70%) of the sepsis group. The most common site of infection was the lung. *Escherichia coli* was the most commonly cultured gram negative organism

Table 1 Baseline characteristics of the study population

Variables	Sepsis (*n*=20)	Severe sepsis (*n*=20)	Septic shock (*n*=20)
Age (years) [mean (SD)]	60.80 (13.46)	59.85 (11.58)	50.3 (15.5)
Male/female (*n*)	8/12	9/11	11/9
Glasgow coma scale [mean (SD)]	12.75 (2.09)	12.60 (2.25)	13.2 (1.8)
APACHE II [mean (SD)]	14.20 (6.42)	20.80 (5.22)	25.2 (5.3)
Coexisting disease (*n*)			
Diabetes	12	12	8
Hypertension	14	11	4
Immunosuppression	2	2	3
Liver cirrhosis	1	3	1
Ischemic heart disease	9	2	1
Malignancy	0	1	1
COPD	1	1	1
Neurologica	4	4	3
Diagnosis (*n*)			
Pneumonia	11	9	7
Urosepsis	4	1	2
Peritonitis	3	2	5
Intra-abdominal sepsis	0	1	0
Skin/soft tissue infection	2	7	6

APACHE II, Acute Physiology and Chronic Health Evaluation score.

Table 2 Baseline systemic inflammatory response syndrome parameters and laboratory data of the study population

Variables	Mean (SD)		
	Sepsis (*n*=20)	Severe sepsis (*n*=20)	Septic shock (*n*=20)
SIRS criteria			
Heart rate/min	105.25 (12.76)	118.70 (9.59)	125.3 (10.4)
Mean arterial pressure (mean±SD)	88.10±20.01	60.45±9.90	57.2±9.0
Temperature (°C)	38.49 (0.53)	39.18 (0.75)	39.1 (0.4)
Respiratory rate/min	23.35 (4.39)	27.6 (4.2)	32.5 (4.2)
pCO_2 (mmHg)	33.65 (7.59)	33.2 (13.0)	32.3 (11.9)
TLC (10^3/mm^3)	16.5 (2.6)	19.9 (4.1)	23.8 (4.1)
Laboratory values on admission to ICU			
Hemoglobin (gm/dl)	10.8 (2.4)	10.1 (2.1)	7.9 (2.7)
Hematocrit (%)	38.4 (6.6)	39.8 (7.1)	27.9 (8.9)
Platelets (total/mm^3)	287.2 (161.5)	237.6 (100.6)	264.4 (114.9)
Urea (mg/dl)	65.8 (31.9)	133.3 (48.7)	163.7 (54.7)
Creatinine (mg/dl)	1.2 (0.5)	2.5 (0.8)	3.1 (0.8)
Sodium (meq/l)	132.3 (6.9)	134.2 (6.0)	132.9 (5.9)
Potassium (meq/l)	4.2 (0.8)	4.1 (0.9)	4.1 (0.7)
AST (IU/l)	32.3 (22.7)	48.9 (24.1)	67.8 (64)
ALT (IU/l)	29.5 (33)	36.8 (23.3)	79.0 (82.3)
Albumin (mg/dl)	3.7 (0.6)	3.3 (0.7)	3.2 (0.7)
Total bilirubin (mg/dl)	0.9 (0.5)	1.4 (0.9)	1.6 (0.9)
INR	1.44 (0.37)	1.4 (0.4)	1.4 (0.3)
pH	7.34 (0.13)	7.3 (0.1)	7.3 (0.1)
pO_2 (mmHg)	78.56 (21.62)	83.2 (17.4)	87.4 (24.1)
Bicarbonate (meq/l)	21.19 (5.51)	18.1 (7)	16.6 (7.6)
Oxygen saturation (%)	92.74 (3.21)	94.6 (4.6)	94.5 (4.4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; pCO_2, partial pressure of arterial CO_2; pO_2, partial pressure of oxygen; SIRS, systemic inflammatory response syndrome; TLC, total leukocytic count.

(17 patients), and MRSA was the most frequently cultured gram positive bacteria (eight patients).

Mortality increased from 35% in the sepsis group to 60% in the group of septic shock.

Copeptin levels among the different groups

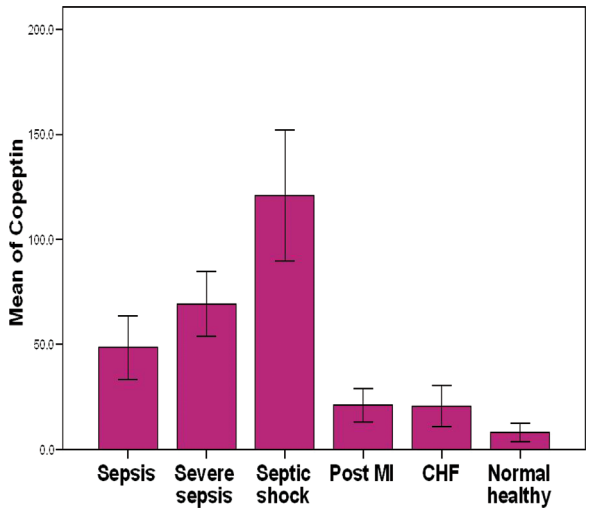
One-way analysis of variance showed that copeptin was significantly higher in all sepsis groups compared with all control groups. Pos-hoc analysis revealed that copeptin level in patients with sepsis [mean=48.4 (15.1) pmol/l] was significantly higher than that in patients with post-AMI [mean=21.1 (8.0) pmol/l], CHF [mean=20.6 (9.8) pmol/l], and healthy controls [mean=8.0 (4.3) pmol/l] ($P<0.001$). Patients with septic shock had the highest copeptin level [mean=120.9 (31.2) pmol/l], followed by patients with severe sepsis [mean=69.2 (15.4) pmol/l], and lastly patients with sepsis [mean=48.4 (15.1) pmol/l] ($P<0.001$). There was no statistically significant difference in copeptin level between patients with post-AMI and those with CHF (Fig. 1).

The highest copeptin level was in deceased patients [mean=103.8 (36.2) pmol/l], followed by patients with MOF [mean=65.2 (22.5) pmol/l], whereas the improved group had the lowest level [mean=43.5 (8.7) pmol/l] ($P<0.001$) (Fig. 2).

Correlations between copeptin and different parameters in patients with sepsis

Spearman's correlation analysis showed a significant positive correlation between serum copeptin and APACHII ($r=0.661$; $P<0.001$), urea ($r=0.496$; $P<0.001$), creatinine ($r=0.552$; $P<0.001$), and alanine aminotransferase ($r=0.451$; $P<0.001$), as shown in Table 3.

Figure 1



Comparison of mean copeptin level in different studied groups using one-way analysis of variance. The mean copeptin level was significantly higher in sepsis patients than in all control groups, but it was lower than that in severe sepsis and septic shock patients ($P<0.001$). CHF, congestive heart failure; MI, myocardial infarction.

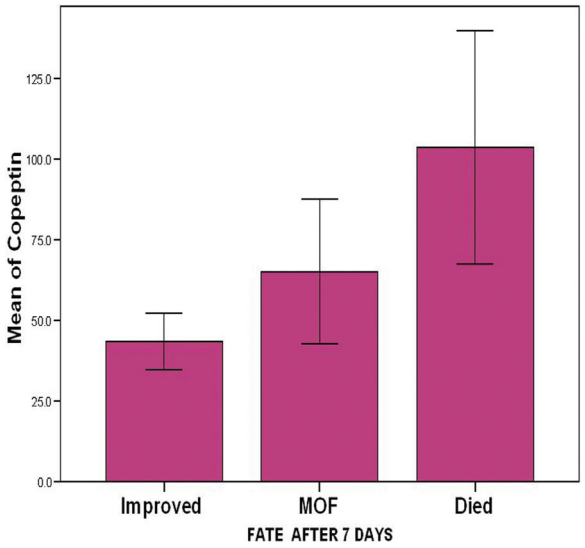
Copeptin as a predictor of mortality in sepsis

Area under the curve of receiver operator characteristic curve was 0.880 ($P<0.001$). Using a copeptin cutoff value of 58.1 pmol/l for predicting mortality, the sensitivity was 96.6% and the specificity was 61.3% (Fig. 3).

Discussion

AVP is the main hypothalamic hormone released by hypotension, hypoglycemia acidosis, infection, and

Figure 2



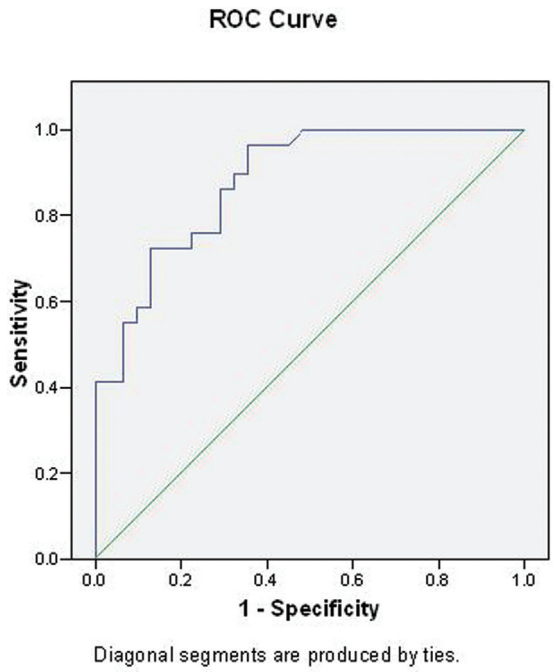
The mean copeptin level according to the outcome. Stepwise increase in the mean value of serum copeptin from patients who improved (43.5±8.7 pmol/l) to patients who developed multiple organ failure (MOF) (65.2±22.5 pmol/l) and deceased patients (103.8±36.2 pmol/l) ($P<0.001$).

Table 3 Correlations of copeptin levels with different variables

Variables	Copeptin	
	r	*P* value
TLC	0.476	<0.001
Urea	0.496	<0.001
Creatinine	0.552	<0.001
AST	0.412	0.001
ALT	0.451	<0.001
Albumin	–0.245	0.060
INR	0.068	0.604
pCO_2	–0.045	0.731
pO_2	0.122	0.353
APACHE II	0.661	<0.001

Spearman's rank correlation coefficient analysis. ALT, alanine aminotransferase; APACHE II, Acute Physiology and Chronic Health Evaluation score; AST, aspartate aminotransferase; INR, international normalized ratio; pCO_2, partial pressure of arterial CO_2; pO_2, partial pressure of oxygen; TLC, total leukocytic count.

Figure 3



Copeptin value for predicting mortality. Receiver operator characteristic (ROC) curve for copeptin level in predecting mortality at cutoff value 58.1 pmol/l had 96.6% sensitivity and 61.3% specificity. Copeptin area under the curve for predicting mortality was 0.880 and $P<0.001$.

many other stressful stimuli. Quantifying plasma AVP levels is difficult owing to its pulsatile secretion and its rapid washout from plasma. Pre-pro vasopressin is a large precursor peptide that releases equal amounts of AVP and copeptin. Copeptin has been found a good stable marker for quantification of secreted AVP [1].

Sepsis-related mortality is high and associated with disease severity; it can reach up to 30% in sepsis, 50% in severe sepsis, and 80% in septic shock [12]. Copeptin level was found to be elevated in sepsis in many previous studies [13,14]. In the current study, the mean copeptin level in nonsurvivors was significantly higher than that in survivors. In accordance with the current results, Jiang *et al.* [5] found that plasma copeptin was significantly higher in patients who died from sepsis than that in patients who survived. Moreover, we found that a copeptin cutoff of 58.1 pmol/l had better sensitivity and specificity compared with a previously reported value of 86.3 pg/ml in predicting mortality in sepsis [6]. In addition, this value is higher than the copeptin cutoff of 14 pmol/l used for the diagnosis of AMI in many previous studies [15].

The higher value of copeptin in sepsis could be explained by a higher degree of activation of hypothalamic pituitary axis in more severe disease [16].

The present study revealed an incremental increase in copeptin level with increased sepsis severity. In addition, copeptin was positively correlated with APACHE II score. In agreement with these findings, Jiang *et al.* [5] reported a positive correlation of copeptin with APACHE II scores in patients with sepsis. Moreover, Zhang *et al.* [6] found a stepwise increase in copeptin level with increase in sepsis severity. However, copeptin did not correlate with disease severity in a study of febrile neutropenic patients, which can be attributed to lack of mediators secreted by neutrophils in this group of patients [17].

The value of copeptin as a predictor of MOF was not previously evaluated. In the present study, copeptin correlated positively with urea, creatinine, aspartate aminotransferase, and alanine aminotransferase. These parameters may indicate MOF and are predictors of poor outcome [18,19]. AVP was found to have deleterious effect on the kidney, and acute administration of AVP in healthy humans was associated with an increase in urinary albumin excretion [20]. Furthermore, high plasma copeptin was associated with an increase in plasma creatinine and decline in renal function in patients with type 2 diabetes [21]. In the current study, correlation of copeptin level with creatinine concentration might help in predicting the development of renal impairment in patients with sepsis; however, further studies are needed.

To our knowledge, this is the first study that compares copeptin level in sepsis with that in cardiac patients. In the present study, mean copeptin levels in cardiac patients were similar to that previously reported in patients with heart failure [22,23] and AMI [19,24,25]. Copeptin level in patients with sepsis was significantly higher than that in cardiac patients. This might be attributed to factors other than stress, such as inflammatory mediators, which are related to sepsis. This observation could be promising in cardiac patients as they are common category in ICU and their condition can be complicated by sepsis.

Limitations in our study should be mentioned. It included limited number of patients. Single copeptin level was obtained at the time of admission; serial measurements during ICU admission might be useful. Because of the small number of cardiac patients, we were not able to determine whether there is copeptin cutoff could differentiate between cardiac patients and patients with sepsis. Further studies examining copeptin as a biomarker in sepsis complicating cardiac patients, which constitutes difficult challenge, may be valuable. We used short-term mortality as an outcome of sepsis, because sepsis

is an acute condition and its major complication is acute organ dysfunction that affects mainly short-term mortality. Hence, recent studies of sepsis investigated factors predicting death within 14 and within 7 days of ICU admission [26,27]. Further studies are needed to assess long-term outcome, which is highly related to cost-effectiveness.

Conclusion

In the present study, copeptin was a sensitive predictor of mortality in patients with sepsis and its level increased with disease severity. In addition, it could be a promising predictor of MOF development. The significant difference in copeptin level between patients with sepsis and cardiac groups provides support for examining copeptin level in cardiac patients with sepsis.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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