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Chromogranin A levels and mortality in patients with severe sepsis

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Abstract

Context—Chromogranin A (CgA) is a novel biomarker with potential to assess mortality risk of patients with severe sepsis.

Objective—Assess association of CgA levels and mortality risk of severely septic patients.

Methods—Serum CgA levels were measured in 50 hospitalized, severely septic patients with organ failure <48 hours.

Results—Higher CgA levels trended towards higher ICU and hospital mortality. Patients without cardiovascular disease who died in the ICU had higher median (IQR) CgA levels 602.3 (343.3, 1134.3) ng/ml vs. 205.5 (130.7, 325.9) ng/ml, $p=0.01$.

Conclusions—High CgA levels predict ICU mortality in severely septic patients without prior cardiovascular disease.

Keywords

Chromogranin A; sepsis; biological marker; mortality; cardiovascular diseases

Introduction

Sepsis has a worldwide incidence of approximately 19 million cases per year (Adhikari NK et al., 2010, Jawad I et al., 2012). In the United States, more than 750,000 new cases of severe sepsis occur yearly with a mortality rate up to 40%. (Angus DC and Wax RS, 2001, Gaieski DF et al., 2013, Annane D et al., 2003) Both the incidence and hospital costs of severe sepsis have been raising with total hospital costs in the United States estimated to be \$24.3 billion in 2007 (Lagu T et al., 2012, Linde-Zwirble WT and Angus DC, 2004). There are several promising biomarkers with potential to guide management of patients with sepsis. However, there is not yet a biomarker that is reliable and has been validated to accurately identify patients with high risk of mortality in sepsis (Suberviola B et al., 2013, Donadello K et al., 2014, Arora S et al., 2014). Therefore, identification of a new biomarker with therapeutic and prognostic utility could fundamentally change clinical care and potentially impact millions of lives.

Chromogranin A (CgA), a novel protein associated with both adrenergic and cardiovascular systems, has emerged as a promising sepsis biomarker (D'amico M A et al., 2014). Prior

studies have shown a correlation between plasma CgA levels and inflammatory markers and risk assessment indices of sepsis. More important, plasma CgA levels may predict prognosis and mortality (Zhang D et al., 2008, Zhang D et al., 2009). Although CgA was originally thought to be released by the adrenal medulla and neuroendocrine system (D'amico M A et al., 2014), CgA has since been isolated in rat and human hearts (Angelone T et al., 2012). The CgA is a pro-hormone and its cleaved peptides have cardiovascular effects, including vasodilatation, inhibition of cardiac contraction, and counteraction of cardiac adrenergic stimulation. High CgA level has been associated with poor prognosis with increased mortality in patients with myocardial infarction (MI), acute coronary syndrome (ACS), or acute decompensated heart failure (ADHF) (Angelone T et al., 2012). However, data about the utility of CgA in sepsis is limited. Whether CgA is associated with increased mortality risk in patients with severe sepsis and whether its prognostic utility is affected by prior cardiovascular disease is unknown. Our aim was to assess the association of CgA levels with ICU and hospital mortality in severely septic patients with and without prior cardiovascular disease.

Methods

Study design

A cohort study of patients admitted with severe sepsis at two academic institutions (South Texas Veterans Health Care System and University Hospital, San Antonio, TX) from November 2007 to October 2012 was performed. Subjects were previously enrolled in a double-blind placebo controlled trial assessing the impact of macrolides as immunomodulators. All patients had a blood sample obtained between 24–48 hours of developing organ failure in the presence of sepsis as defined by the American College of Chest Physician/Society of Critical Care Medicine (Bone RC et al., 1992). All the patients received standard therapy including antibiotics at the time of presentation and while in ICU (Dellinger RP et al., 2013). All participants signed a consent form. The study was approved by the local Institutional Review Board (HSC20070713H) and is posted on clinical trials.gov (NCT00708799). Because the trial did not show any significant effects of macrolide therapy on the end-points studied, it was considered valid to combine the intervention and placebo groups for this cohort study.

Inclusion criteria included: age ≥ 18 years, written informed consent obtained either from the patient or patient's legal representative, meeting SIRS criteria (two or more of the following conditions: Temperature $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$; heart rate > 90 beats/min; respiratory rate > 20 breaths/min or $\text{PaCO}_2 < 32\text{mmHg}$; white blood cell count $> 12,000/\text{mm}^3$, $< 4000/\text{mm}^3$ or $> 10\%$ immature (band) forms, presence of suspected or proven infection, and presence of one or more sepsis-associated organ failure. Exclusion criteria included: evidence of current treatment with medications that could potentially affect the inflammatory response, such as macrolides and corticosteroids; immunosuppressive states; and pregnancy or lactating. In addition, patients were excluded for prolonged QT syndrome, major arrhythmias, or medications associated with an increased risk of QT prolongation (Mortensen EM et al., 2014).

Enrollment and Follow-up

All patients were screened for eligibility at the time of admission to the ICU. Patients were followed daily during hospitalization until time of hospital discharge. After discharge, patients were followed for up to one year post-discharge. Patients were followed either at an outpatient clinic, by chart review, or by phone to assess their survival status. We calculated an Acute Physiology And Chronic Health Evaluation (APACHE II) score during the first 24 hours following ICU admission (Knaus WA et al., 1985).

Outcomes

The primary outcome was ICU mortality. Secondary outcomes included hospital mortality and need for vasopressors.

Subgroup analysis

Analysis was conducted in patients with and without prior cardiovascular disease, as we expected that patients with prior cardiovascular disease would have increased levels of CgA on admission (Schneider F et al., 2012). Conditions considered as prior cardiovascular diseases included: atrial fibrillation (or other chronic arrhythmia), non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), stroke, chronic heart failure (CHF), or coronary artery disease (CAD). These cardiovascular conditions were identified by medical records.

CgA assay

Venous blood was drawn between 24–48 hours of developing organ failure in the presence of sepsis. Serum CgA levels were measured using a commercially available Human Chromogranin A ELISA Assay Kit by Eagle Biosciences, Inc. (Nashua, New Hampshire, United States), which utilizes a “sandwich” technique with two antibodies binding to two epitopes of CgA. According to Eagle Biosciences, Inc., the normal serum CgA level in healthy adults is less than 100 ng/mL.

Statistical analysis

Fischer exact tests were used to test the associations of demographics and clinical characteristics between both groups. To evaluate the CgA levels, we used median values (IQR) and to compare the differences in concentration we used a non-parametric test (Mann-Whitney U Test). Statistical significance was defined as $p\text{-value} < 0.05$. A receiver operating characteristic (ROC) curve was developed to assess the accuracy of CgA to predict the outcomes. A subgroup analysis was performed stratifying patients according to the presence or absence of prior cardiovascular diseases at the time of admission. All statistical analyses were performed with SPSS, version 22.0 for Windows (IBM) statistical software.

Results

Patient Characteristics

Fifty patients met the inclusion criteria. Six subjects (12%) died in the ICU and 1 subject (2%) died outside of the ICU during hospitalization. Table 1 shows patient's characteristics

stratified by survival status. Survivors had lower APACHE II scores compared to non-survivors, but there were no other statistically significant differences between the groups. The mean (SD) serum CgA level on study inclusion was 389.45 ng/ml (272.74 ng/ml) and the median (IQR) was 304.29 ng/ml (163.73, 582.42). There were no significant differences in CgA levels between patients randomized to macrolide therapy or placebo.

Outcomes

Figure 1A demonstrates that patients with severe sepsis that did not survive while in the ICU had higher median (IQR) CgA levels (483.9 (394.1, 843.2) ng/ml vs. 237.8 (151.1, 567.4) ng/ml, $p=0.06$). Further, patients with severe sepsis that did not survive during hospitalization also had higher median (IQR) CgA levels (461.0 (288.8, 697.7) ng/ml vs. 241.0 (154.5, 576.4) ng/ml, $p=0.2$). Severely septic subjects who required vasopressors/inotropes had similar median (IQR) CgA levels compared to those who did not require vasopressors/inotropes at the time of inclusion (280.4 (148.9, 515.2) ng/ml vs. 330.3 (232.9, 615.1) ng/ml, $p=0.3$).

When we dichotomized all severely septic subjects into low or high CgA groups based on median values, we found the high CgA group had a trend towards higher ICU and hospital mortality (Figure 2). No difference in use of vasopressors/inotropes was seen in the high versus low groups, respectively (68.0% vs. 68.0%, $p = 0.9$).

In all severely septic subjects, the negative predictive values of CgA levels for ICU mortality and hospital mortality were high (96.0% and 92.0%, respectively). Other diagnostic characteristics of CgA were suboptimal, including sensitivity, specificity, positive predictive values, and AUC-ROC for ICU mortality, hospital mortality and the need for vasopressors/inotropes (Table 2).

Subgroup analysis

Figure 1B shows that subjects without prior cardiovascular disease who did not survive the ICU stay ($n=4$) secondary to severe sepsis had significantly higher median (IQR) serum CgA levels (602.3 (343.3, 1134.3) ng/ml vs. 205.5 (130.7, 325.9) ng/ml, $p=0.011$). Regarding hospital mortality, non-survivors without prior cardiovascular disease ($N=5$) also had higher median (IQR) CgA levels (506.9 (209.6, 988.8) ng/ml vs. 205.9 (131.8, 327.9) ng/ml, $p=0.09$). Severely septic subjects without prior cardiovascular disease ($N=33$) who required vasopressors/inotropes had similar median (IQR) CgA levels compared to those that did not require vasopressors/inotropes at the time of inclusion (200.7 (130.4, 447.2) ng/ml vs. 284.1 (219.2, 489.1) ng/ml, $p=0.3$).

When we dichotomized severely septic subjects without prior cardiovascular disease into low or high CgA groups based on the median values, we found that the high CgA group had a trend towards higher ICU and hospital mortality (Figure 2). No difference was seen regarding need for vasopressors/inotropes between the high versus low CgA groups, respectively (71.4% vs. 72.7%, $p = 0.9$).

In severely septic subjects without prior cardiovascular disease, the negative predictive values of CgA levels for ICU mortality and hospital mortality were 95.2% and 90.5%,

respectively. The AUC-ROC of CgA for ICU mortality was 0.884 in the severely septic subjects without prior cardiovascular disease. The other diagnostic characteristics of CgA for ICU and hospital mortality, including sensitivity, specificity and positive predictive values, were less than 80%. Similarly, all of the diagnostic characteristics of CgA regarding the need for vasopressors/inotropes were suboptimal (Table 2).

Discussion

Our study has two main findings. First, serum CgA levels were higher among all patients with severe sepsis who died during their ICU stay. Higher levels of CgA were also associated with ICU mortality in the subgroup of patients with severe sepsis without prior cardiovascular disease. Second, we observed high negative predictive values of CgA levels for ICU and hospital mortality in all patients with severe sepsis, including those without prior cardiovascular disease.

Our results support prior studies that have shown an association between higher CgA level and mortality (Zhang D et al., 2008, Rosjo H et al., 2012, Zhang D et al., 2009). In a study with 120 heterogeneous, critically ill nonsurgical patients, non-survivors were found to have higher median (IQR) plasma CgA levels compared to survivors (293.0 µg/L (163.5– 699.5 µg/L) vs. 86.0 µg/L (53.8–175.3 µg/L) (Zhang D et al., 2008). Another study comparing 53 heterogeneous critically ill patients to 14 healthy controls found that patients with plasma CgA levels greater than 71 µg/L had significantly shorter survival time (Zhang D et al., 2009). Data from the Finnsepsis study with 232 homogeneous patients with severe sepsis showed that patients who did not survive hospitalization had higher plasma CgA levels on study inclusion and after 72 hours (14.0 vs. 9.1 nmol/l, $P = 0.002$, and 16.2 vs. 9.8 nmol/l, $P = 0.001$, respectively) (Rosjo H et al., 2012). However, an important limitation of these studies is that not all patients were septic. Only the Finnsepsis study included a homogeneous population of patients with a diagnosis of severe sepsis. However, the Finnsepsis study did not distinguish between ICU and hospital mortality. Another study found sepsis to be more frequently associated with ICU death compared to death during the post-ICU period in the hospital wards (Braber A and Van Zanten AR, 2010). Thus, septic patients may die from causes other than sepsis after being transferred from the ICU to hospital wards. This raises the question of whether the Finnsepsis results can be extrapolated to predict increased ICU mortality with high plasma CgA levels. Our results demonstrate that both ICU non-survivors and hospital non-survivors with severe sepsis indeed had higher CgA levels, particularly among those without prior cardiovascular disease.

CgA is also a biomarker associated with a poor prognosis in acute coronary syndrome, myocardial infarction and acute decompensated heart failure (Angelone T et al., 2012). In the Finnsepsis study, a high plasma CgA level after 72 hours was associated with prior cardiovascular disease and cardiovascular Sequential Organ Failure Assessment (SOFA) scores on day 3 (Rosjo H et al., 2012). However, few studies have investigated whether the accuracy of CgA level to predict mortality secondary to severe sepsis is affected by pre-existing cardiovascular disease. By stratifying patients with and without prior cardiovascular disease, we demonstrated a marked increase in accuracy of CgA level to predict ICU mortality.

Little is known about the negative predictive values of CgA levels. Our study showed high negative predictive values of CgA levels to predict ICU and hospital mortality in patients with severe sepsis. Therefore, CgA has the potential to assist clinicians in prognostication of mortality at the time of admission of septic patients to an ICU. In other words, severely septic patients with low CgA levels measured within 24 to 48 hours of developing sepsis-related organ failure have a low likelihood of dying in the ICU or during hospitalization.

Our study has several limitations. First, the sample size is relatively small. Second, there were more male than female patients likely due to one of the two study sites being a Veterans Affairs hospital. It is unknown how serum CgA levels would have been affected if there had been more female subjects, but previous studies did not identify a major difference in serum CgA levels based on gender. Third, our study did not assess how serum CgA levels change with disease progression. However, our goal was to assess the properties of a biomarker that could potentially be used as a point-of-care test. Although this study was a secondary analysis of a randomized trial, no impact of the intervention was identified on serum CgA levels, and CgA measurements were made at the time of enrollment before any anti-inflammatory effect of macrolides could have confounded the results.

Conclusions

Our study demonstrates that serum CgA levels may play an important prognostic role in assessing ICU mortality, particularly in patients with severe sepsis without prior cardiovascular disease. As a next step, serum CgA needs to be tested as a biomarker on one or more validation cohorts, to further evaluate its potential prognostic utility in patients with sepsis.

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Figure 1.

Serum CgA levels comparing ICU and hospital survivors vs. non-survivors, and the need for vasopressors/inotropes vs. no need for vasopressors/inotropes. All patients with severe sepsis are shown in Panel A and patients without prior cardiovascular disease are shown in Panel B.

Figure 2. Proportion of patients with severe sepsis (Panel A) and those without prior cardiovascular disease (Panel B) who died during the ICU and hospital stratified by serum CgA levels.

Table 1

Patient characteristics of severe sepsis patients stratified according to survival status

Variables	ICU Survivors n=44	ICU Non-Survivors n=6
Age, median (IQR)	56.0 (45.3, 66.0)	61.5 (51.8, 79.5)
APACHE II *, median (IQR)	18.5 (14.0, 22.8)	29.5 (22.3, 32.8)
Male	39 (88.6)	5 (83.3)
Comorbid conditions		
Prior malignancy	9 (20.5)	1 (16.7)
Cardiovascular disease	10 (22.7)	2 (33.3)
Chronic heart failure	4 (9.1)	0 (0.0)
COPD	6 (13.6)	2 (33.3)
Chronic kidney disease	4 (9.1)	1 (16.7)
Depression	8 (18.2)	1 (16.7)
Diabetes mellitus	21 (47.7)	2 (33.3)
Hyperlipidemia	9 (20.5)	2 (33.3)
Liver disease	3 (6.8)	0 (0.0)
Tobacco use	11 (25.0)	3 (50.0)
Alcohol use	10 (22.7)	2 (33.3)
Asthma	4 (9.1)	0 (0.0)
Source of infection		
Pulmonary	15 (34.1)	2 (33.3)
Urinary tract	15 (34.1)	1 (16.7)
Gastrointestinal	4 (9.1)	2 (33.3)
Skin	7 (15.9)	1 (16.7)
Osteomyelitis	2 (4.5)	0 (0.0)
Endocarditis	1 (2.3)	0 (0.0)
Medications on admission		
Statin	3 (6.8)	1 (16.7)
ACE inhibitor	2 (4.5)	0 (0.0)
Oral corticosteroids	5 (11.4)	1 (16.7)
Chromogranin A levels		
• Mean (SD)	359.3 (250.0)	610.6 (353.6)
• Median (IQR)	237.7 (151.1, 567.4)	483.9 (394.1, 843.2)

* p < 0.05

All values are given in number of patients (percentages) unless indicated

COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; IQR, interquartile range; SD, standard deviation.

Table 2

Diagnostic characteristics of serum CgA levels among all patients included in the cohort with severe sepsis and among those without prior cardiovascular disease.

	Sensitivity	Specificity	PPV	NPV	AUC (95%CI)
All patients with severe sepsis					
ICU mortality	83.3	54.5	20.0	96.0	0.74 (0.58–0.90)
Hospital mortality	71.4	53.5	20.0	92.0	0.65 (0.44–0.86)
Need for vasopressors/inotropes	50.0	50.0	68.0	32.0	0.41 (0.24–0.58)
Severe sepsis without prior cardiovascular disease					
ICU mortality	75.0	71.4	27.3	95.2	0.88 (0.74–1.0)
Hospital mortality	60.0	70.4	27.3	90.5	0.74 (0.48–1.0)
Need for vasopressors/inotropes	34.8	66.7	72.7	28.6	0.37 (0.16–0.57)

PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.