

The Role of Serum Beta-Trace Protein in the Diagnosis and Prognosis of Sepsis Patients in the Emergency Department

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Abstract

Aim: This study aimed to evaluate the diagnostic and prognostic significance of serum beta-trace protein (BTP) levels in patients diagnosed with sepsis in the emergency department.

Materials and Methods: This prospective, single-center, observational clinical study was conducted in the emergency department and intensive care unit of a tertiary hospital. A total of 104 sepsis patients and 48 healthy adult volunteers who presented to the emergency department between April 2015 and October 2015 were included. Blood samples were collected on days 1 and 3, and BTP levels were measured using the ELISA method. Statistical analyses were performed using SPSS 22.0.

Results: BTP levels were significantly higher in sepsis patients compared to the control group ($p=0.013$). However, no significant difference was observed between day 1 and day 3 BTP levels ($p=0.119$). When categorized by sepsis severity, BTP levels did not correlate with disease severity ($p>0.05$). Additionally, no significant association was found between BTP levels and mortality ($p=0.651$).

Conclusion: BTP may serve as a potential biomarker for sepsis diagnosis, but it is not a reliable indicator of disease severity or prognosis. Further large-scale studies are needed.

Keywords: Sepsis, beta-trace protein, biomarker, prognosis, emergency department

Introduction

Sepsis is a complex condition characterized by increasing incidence, high mortality, and challenging treatment (1). Despite advances in treatment strategies and a better understanding of the molecular pathophysiology of sepsis, the growing prevalence of multidrug-resistant microorganisms, the high frequency of infections in intensive care units (ICUs), and the increasing number of immunosuppressed patients due to transplantation, chemotherapy, and radiotherapy have contributed to the rising incidence of sepsis (2).

To improve the prognosis of critically ill patients admitted to ICUs, early recognition and intervention are essential. Various advanced diagnostic methods are routinely used to facilitate

early diagnosis, prevent septic shock or multiple organ failure, and enable prompt treatment, thereby increasing patient survival (3,4). The most crucial factors determining the prognosis of sepsis patients are early diagnosis and rapid treatment. Current diagnostic markers include clinical findings such as leukopenia or leukocytosis, as well as elevated C-reactive protein (CRP) and sedimentation rate. However, none of these biomarkers is specific to sepsis. Thus, there is an urgent need for novel biomarkers that can aid in the early diagnosis and treatment monitoring of sepsis, and ongoing research is focused on identifying such markers (3).

Beta-trace protein (BTP) was first identified in human cerebrospinal fluid in 1961 using immunoelectrophoresis. In 1985, a novel glycoprotein, lipocalin-type prostaglandin D2 synthase (L-PGDS),



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was isolated from mouse brains. Subsequent studies confirmed that BTP and L-PGDS are identical molecules (5). BTP plays a role in the induction of, inhibition of bronchoconstriction, and platelet aggregation. Hematopoietic prostaglandin D synthase (H-PGDS) is found in mast cells, helper T-cells, Kupffer cells, dendritic cells, and microglia and is known to be more active in allergic and inflammatory responses. As a mediator of allergic and inflammatory processes, BTP also exhibits a high affinity for various lipophilic compounds such as retinoic acid, bilirubin, biliverdin, thyroid hormones, amyloid β peptides, and gangliosides, functioning as an extracellular transporter. Additionally, by binding endogenous amyloid β , it prevents *in vivo* amyloid accumulation. BTP functions as a dual-purpose protein due to its role as an enzyme, producing prostaglandin D2 (PGD2) and as a lipophilic ligand-binding protein. It catalyzes the conversion of prostaglandin H2, an arachidonic acid derivative, to PGD2. Despite its multiple proposed functions, the exact physiological role of BTP remains unclear (6-8).

Recent studies have demonstrated that BTP serves as a PGD2 receptor for T-helper 2 cells, inducing the chemotaxis of eosinophils, basophils, and macrophages in response to PGD2 stimulation. In addition to its chemotactic effects, PGD2 has been shown to modulate the immune response by interacting with the prostaglandin D (PGD) receptor in inflammatory cells (9). These findings suggest that BTP may play a role in the pathophysiology of sepsis and could serve as a prognostic biomarker.

Materials and Methods

This prospective, single-center study was conducted in the emergency department and ICU a tertiary care hospital. Patients who presented to the emergency department between April 2015 and October 2015 were 18 years or older, not pregnant or breastfeeding, and provided informed consent were included in the study. A total of 104 patients diagnosed with sepsis and 48 healthy adult volunteers without any known diseases were enrolled. Blood samples were collected from the patients on day 1 and day 3. The study was designed as a controlled, open-label, observational, prospective clinical study. Ethical approval was obtained from the Necmettin Erbakan University Meram Faculty of Medicine Ethic Committee on (decision number: 2015/170, date: 18.09.2015), and the study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants before their inclusion in the study.

The human BTP levels were measured using an ELISA based on biotin and double-antibody sandwich technology. The assay was designed for research purposes and utilized 96-well plates pre-coated with BTP antibodies. BTP levels were measured using YH-BIOSEARCH Human BTP ELISA kits (catalog number: YHB3523Hu,

China). During the analysis, a BioTek EL50 microplate washer (USA) was used for washing steps, and absorbance readings were obtained using a BioTek ELx800 microplate reader (USA). All parameters were measured at a wavelength of 450 nm, and absorbance values were analyzed using a calibration curve to determine the BTP concentrations in the samples.

Statistical Analysis

All data were transferred to SPSS 22.0 (IBM, USA) statistical software for analysis. The normality of data distribution was assessed using the Shapiro-Wilk test and the Kolmogorov-Smirnov test. Numerical variables were presented as mean \pm standard deviation for normally distributed data, and as median (interquartile range) for non-normally distributed data, while categorical variables were expressed as percentages. Comparisons between groups were performed using the independent samples t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Changes within the same group over time were evaluated using the paired t-test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Comparisons among three or more groups were performed using the Kruskal-Wallis test for non-normally distributed data. Categorical variables were analyzed using the chi-square (χ^2) test or Fisher's exact test, depending on the sample size and distribution. A p value of <0.05 was considered statistically significant.

Results

In our study, a statistically significant difference was observed in the mean age between the patient and control groups ($p<0.001$), whereas no significant difference was found in gender distribution ($p=0.084$). When comparing blood BTP levels, patients in the sepsis group had significantly higher BTP levels than those in the control group ($p=0.013$) (Table 1).

Among sepsis patients, a comparison of laboratory parameters between day 1 and day 3 showed statistically significant changes in white blood cell count, neutrophil count, hemoglobin, platelet count, creatinine, sodium, potassium, calcium, CRP, and procalcitonin (PCT) levels. However, no significant difference was observed in BTP levels between day 1 and day 3 ($p=0.119$) (Table 2).

When sepsis patients were categorized into groups: sepsis, severe sepsis, and septic shock, no statistically significant association was found between BTP levels and sepsis severity on day 1 and day 3 ($p=0.520$, $p=0.217$) (Table 3).

Analysis of patients' medical history revealed a borderline significant relationship between stroke and BTP levels ($p=0.052$),

whereas no significant association was found between BTP levels and coronary artery disease (CAD), hypertension, chronic obstructive pulmonary disease, diabetes mellitus, chronic kidney disease (CKD), or cancer (Table 4).

Regarding patient outcomes, 48.1% (n=50) of sepsis patients died in the hospital, while 51.9% (n=54) were discharged. However, no statistically significant relationship was observed between BTP levels and mortality (p=0.651).

Variables	Sepsis group (n=104)	Control group (n=48)	p value*
Age, mean \pm SD	70.6 \pm 15.47	53.67 \pm 9.84	<0.001
Gender, n (%)			
Male	59 (56.7%)	20 (41.7%)	0.084
Female	45 (43.3%)	28 (58.3%)	
BTP, pg/mL, median (IQR)	72.6 (45.05)	66.07 (23.92)	0.013

*Statistically significant p values are highlighted in bold. BTP: Beta-trace protein, IQR: Interquartile range, SD: Standard deviation

Variable	Day 1	Day 3	p value*
Apache II score, mean \pm SD	18.6 \pm 7.249	18.96 \pm 8.235	0.378
GCS, median (IQR)	13 (5)	14 (4)	0.605
WBC, 10 ³ / μ L, median (IQR)	13.95 (12.11)	11.64 (8.38)	0.020
Neutrophil, 10 ³ / μ L, median (IQR)	11.45 (9.79)	9.69 (8.3)	0.009
Lymphocyte, 10 ³ / μ L, median (IQR)	0.84 (0.91)	1.12 (0.81)	0.053
Hemoglobin, g/dL, mean \pm SD	12.34 \pm 2.31	11.27 \pm 1.9	<0.001
Platelet, 10 ³ / μ L, median (IQR)	212 (169)	183 (173)	0.006
Creatinine, mg/dL, median (IQR)	1.81 (2.08)	1.13 (1.42)	<0.001
pH, mean \pm SD	7.39 \pm 0.11	7.39 \pm 0.09	0.890
pCO ₂ , mmHg, mean \pm SD	34.96 \pm 10.19	36.36 \pm 9.19	0.151
HCO ₃ , mmol/L, mean \pm SD	20.32 \pm 4.19	20.76 \pm 4.64	0.919
Lactate, mmol/L, median (IQR)	1.1 (1.05)	1.1 (1.07)	0.676
Sodium, mEq/L, mean \pm SD	135.84 \pm 9.08	137.88 \pm 6.49	0.011
Potassium, mEq/L, mean \pm SD	4.48 \pm 1.02	4.02 \pm 0.89	<0.001
Calcium, mEq/L, mean \pm SD	8.01 \pm 0.86	7.59 \pm 0.83	<0.001
Albumin, g/dL, mean \pm SD	2.67 \pm 0.6	2.48 \pm 0.41	0.057
Sedimentation rate, mm/h, median (IQR)	54 (49)	62 (51)	0.431
CRP, mg/L, median (IQR)	139 (90)	116 (105.6)	0.001
Procalcitonin, mg/dL, median (IQR)	6.75 (29.77)	4.79 (16.64)	<0.001
BTP, pg/mL, median (IQR)	72.6 (45.05)	69.1 (39.34)	0.119
Mechanical ventilation, n (%)	30 (%28.8)	21 (%25.3)	0.625
Vasopressor use, n (%)	53 (%51)	32 (%38.6)	0.118

*Statistically significant p values are highlighted in bold. APACHE: Acute physiology and chronic health evaluation, GCS: Glasgow coma scale, WBC: White blood cell, CRP: C-reactive protein, BTP: Beta-trace protein, IQR: Interquartile range, SD: Standard deviation

Sepsis severity	N (%)	BTP, pg/mL, median (IQR)	p value
Sepsis	53 (%51)	78.96 (36.27)	0.520*
Severe sepsis	27 (%26)	59.26 (51.31)	
Septic shock	24 (%23)	56.92 (89.62)	

*p values were calculated using the Kruskal-Wallis test. BTP: Beta-trace protein, IQR: Interquartile range

Table 4. Comparison of BTP levels based on patient history

Diagnosis	n (%)*	BTP, pg/mL, median (IQR)*	p value
CAD	20 (19.2%) / 84 (80.8%)	83.61 (66.83) / 68.87 (42.27)	0.466
Hypertension	44 (42.3%) / 60 (57.7%)	73.93 (99.85) / 67.32 (42.74)	0.177
Stroke	25 (24%) / 79 (76%)	81.52 (66.11) / 67.24 (40.22)	0.052
COPD	32 (30.8%) / 72 (69.2%)	71.63 (43.35) / 70.35 (50.76)	0.776
DM	29 (27.9%) / 75 (72.1%)	61.39 (52.56) / 70.81 (50.10)	0.821
CKD	30 (28.8%) / 74 (71.2%)	59.26 (45.22) / 74.50 (51.18)	0.249
Cancer	9 (8.7%) / 95 (91.3%)	67.86 (30.00) / 73.06 (53.21)	0.447

*Patients with/without the disease, BTP: Beta-trace protein, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CKD Chronic kidney disease, IQR: Interquartile range

Discussion

Sepsis is a critical syndrome with high mortality rates that arises from a dysregulated host response to infection (10). Early intervention in the diagnosis of sepsis is of vital importance; however, the sensitivity and specificity of existing biomarkers are still insufficient (11). In our study, BTP was found to be significantly elevated in septic patients, suggesting that this biomarker may play a role in the diagnosis of sepsis.

The pathophysiological mechanisms of sepsis remain complex and aren't fully understood. Traditionally, sepsis has been defined as a systemic inflammatory response to infection, yet in some cases, the source of infection cannot be identified (12). PGD, prostaglandin D synthase (PGDS), cyclooxygenase-1 and cyclooxygenase-2 play crucial roles in eicosanoid metabolism during infection. Since BTP, also known as L-PGDS, is linked to infection responses, it is hypothesized that it may play a role in the immune and inflammatory pathways of sepsis. Moreover, previous studies have demonstrated its involvement in thrombotic events, neurodegenerative diseases, kidney function, and inflammatory processes (5-8,13).

The current literature indicates that BTP plays a significant role in inflammatory processes and has important effects on vascular endothelium (14). Studies have reported that BTP actively participates in inflammatory processes, exhibiting pro-angiogenic and anti-inflammatory effects. BTP is produced by endothelial cells and contributes to the modulation of inflammatory responses. Similarly, the activation of PGD2 receptors has been shown to trigger strong inflammatory reactions in macrophages (5,15). Our findings support this, as BTP levels were significantly higher in sepsis patients compared to healthy controls. This suggests that BTP may contribute to inflammatory responses and could be useful as a diagnostic biomarker for sepsis.

The role of biomarkers in the diagnosis of sepsis has been investigated for a long time. In the existing literature, biomarkers

such as PCT and CRP have been frequently studied for sepsis diagnosis and prognosis. PCT has been reported to have better diagnostic value in the early diagnosis of sepsis compared to CRP. However, it has been shown that these biomarkers alone do not possess sufficient sensitivity and specificity (11,16).

The molecular and genetic differences among septic patients highlight the necessity of developing biomarker-based diagnostic systems. In recent years, it has been suggested that classifying septic patients into more specific subgroups through phenotyping and endotyping could improve treatment outcomes (17). In our study, the significantly elevated BTP levels in septic patients suggest that novel biomarkers, supported by molecular and genetic research, could contribute to the diagnostic process.

Moreover, considering the critical role of endothelial cells in the pathophysiology of sepsis, the role of BTP in vascular inflammation should be further investigated. Microvascular dysfunction and coagulation activation in sepsis are among the key factors that exacerbate disease severity (18). A study conducted by Bruegel et al. (19) demonstrated that arachidonic acid metabolism undergoes significant changes in sepsis and that these alterations may be associated with disease severity and clinical prognosis. Similarly, in the study by Kinoshita et al. (20), L-PGDS levels were found to be related to endothelial damage and identified as a potential diagnostic biomarker in preeclampsia. Given that similar mechanisms may be involved in septic patients, the contribution of BTP to vascular inflammation processes should be investigated in greater detail.

However, White et al. (6) demonstrated that BTP levels fluctuate during acute inflammatory conditions such as sepsis, limiting their usefulness in disease monitoring. Similarly, in our study, no significant difference was observed in BTP levels between day 1 and day 3, and BTP was not associated with mortality. This suggests that BTP may not be a reliable marker for disease progression or prognosis in sepsis.

Ahmad et al. (13) found that eicosanoid metabolites increase with sepsis severity but exhibit variability in prolonged inflammatory processes. In line with this, our study demonstrated that BTP levels were not correlated with disease severity, further suggesting that while BTP may assist in the diagnosis of sepsis, it may not be a reliable indicator.

Regarding kidney function, studies have shown that BTP is not cleared by hemodialysis and may serve as a biomarker for kidney injury in CKD patients (21,22). In addition, increased H-PGDS expression has been observed in skeletal, and cardiac muscle cells, although no significant association between BTP levels and CAD has been identified (7,23). Furthermore, BTP has been linked to neurodegenerative processes and has been suggested to have a protective role against cerebral ischemia (24). In our study, no significant relationship was found between BTP levels and CKD or CAD, whereas a borderline significant association was observed between BTP and stroke.

Study Limitations

Our study has several limitations. The sample size is relatively small, and the study was conducted at a single center. Larger, multicenter studies are needed to validate these findings. Since our control group consisted entirely of healthy individuals, it was not possible to compare the results with critically ill non-septic patients. To better understand the specificity of sepsis-related biomarkers, future studies should include non-septic critically ill patients. The case-control ratio in our study is unbalanced due to difficulties in recruiting healthy volunteers. Larger-scale studies are required to achieve more robust statistical analyses and generalizable results. The average age of individuals in the control group is lower than that of septic patients. There is no clear consensus in the literature regarding how BTP levels change with age. However, to better understand the impact of age on the results, future studies should include age-matched control groups. The data in our study were collected in 2015, and the effects of updated sepsis management protocols and new treatment approaches on BTP levels have not been evaluated. Therefore, further studies are needed to determine the diagnostic and prognostic value of BTP in current clinical practice.

Conclusion

Our study demonstrated that BTP levels are elevated in sepsis patients compared to healthy controls, suggesting their potential as a diagnostic biomarker. However, BTP was not associated with disease severity or mortality, limiting its use as a prognostic marker. Further large-scale, multicenter studies are required to better understand the diagnostic and clinical utility of BTP in sepsis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee on (decision number: 2015/170, date: 18.09.2015), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Informed consent was obtained from all participants before their inclusion in the study.

Footnotes

Author Contributions

Surgical and Medical Practices: M.Y., R.K., Concept: M.Y., R.K., B.Ç.Y., Design: M.Y., B.Ç.Y., B.C., Data Collection or Processing: M.Y., Ö.K., B.Ç.Y., Analysis or Interpretation: M.Y., R.K., Ö.K., B.Ç.Y., B.C., Literature Search: M.Y., R.K., Ö.K., B.Ç.Y., B.C., Writing: M.Y.

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