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Brain natriuretic peptide: Can be used as prognostic marker in children with sepsis

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ABSTRACT

Objective: The prognostic importance of brain natriuretic peptide (BNP) in sepsis is controversial. We aimed to compare serum BNP levels in children with sepsis and the role of BNP as a marker of severity and mortality in those children.

Material and Methods: A prospective observational study was performed in our pediatric intensive care unit. Children were grouped as patients with sepsis and septic shock. Serial blood samples were collected at admission, 24th, 48th, 72th, and 96th h for BNP assay. Organ functions were evaluated according to Pediatric Logistic Organ Dysfunction (PELOD) score. Echocardiography was performed for all patients by the same pediatric cardiologist. The severity of sepsis and mortality risk was determined by calculating of Pediatric Risk of Mortality (PRISM) score within 24 h after the admission. The results were analyzed statistically.

Results: Twenty children with septic shock, 14 children with sepsis, and 26 healthy controls were recruited. The mean BNP level at admission was significantly higher in children with sepsis syndrome than healthy controls (242.13±929.6 vs. 2.61±1.26; p<0.001). Mean BNP level was significantly higher in septic shock group than sepsis group (384.88±1191.31 vs. 28±38.94; p<0.001). In septic shock group; BNP levels were significantly higher in non-survivors than those of survivors (p<0.01). BNP levels correlated with PRISM score and PELOD score in particular cardiac and neurologic dysfunction.

Conclusion: We can suggest that serum BNP level may be useful predictor of prognosis in critically ill children with sepsis..

Keywords: Brain natriuretic peptide; BNP; children; PELOD; PRISM; sepsis.

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Beyin natriüretik peptit: Sepsisli çocuklarda prognostik belirteç olarak kullanılabilir mi?

ÖZET

Amaç: Beyin natriüretik peptit (BNP), çocuklarda ve yetişkinlerde miyokardiyal disfonksiyon belirtecidir. BNP, konjenital kalp kusurlarından kaynaklanan kalp yetmezliği olan çocuklarda yükselir. Septik şoktaki hastalarda da miyokardiyal disfonksiyon nedeniyle yükseldiği gösterilmiştir. Sepsiste BNP'nin prognostik önemi tartışmalıdır. Bu çalışmada sepsisli çocuklardaki serum BNP düzeylerini karşılaştırmayı ve ağır sepsiste ve sepsise bağlı mortalitede bir belirteç olarak BNP'nin rolünü belirlemeyi amaçladık.

Gereç ve Yöntemler: Altı yataklı bir çocuk yoğun bakım ünitesinde prospektif gözlemsel bir çalışma gerçekleştirildi. Hastalar sepsis ve septik şok olarak gruplandırıldı. Başvuru anındaki, 24., 48., 72. ve 96. saatlerde klinik ve laboratuvar verileriyle birlikte BNP ölçümü için seri kan örnekleri alındı. Sağlıklı çocuklardan oluşan kontrol grubundan BNP testi için bir defa kan örneği alındı. Hastaların günlük laboratuvar ve klinik değişkenlere dayanan organ işlevlerinin değerlendirmesi, PELOD (Pediatrik Lojistik Organ Disfonksiyonu) skorlaması, başvuru sırasında ve dört gün boyunca her 24 saatte bir kaydedildi. Yatıştan sonraki 24 saat içinde PRISM (Pediatrik Mortalite Riski) skoru hesaplanarak sepsis ve mortalite riski belirlendi. Sonuçlar istatistiksel olarak analiz edildi.

Bulgular: 20 septik şoklu çocuk, 14 sepsisli çocuk ve 26 sağlıklı çocuk kontrol grubu olarak dahil edildi. Başvuru anındaki ortalama BNP düzeyi (BNP(0)), sepsis sendromlu çocuklarda sağlıklı kontrollere göre anlamlı olarak daha yüksekti (242.13±929.6'ya karşı 2.61±1.26; p<0.001). Ortalama BNP(0) düzeyi septik şok grubunda sepsis grubuna göre anlamlı olarak yüksek bulundu (384.88±1191.31'e karşı 28±38.94; p<0.001). Septik şok grubunda; kaybedilen hastalarda BNP(0) seviyeleri, sağ kalanlara göre anlamlı olarak daha yüksekti (p<0.01). Serum BNP düzeyleri, çoklu organ disfonksiyonu, PRISM skoru, PELOD skoru, PELOD'a göre kardiyak ve nörolojik disfonksiyon ile uyumlu bulundu.

Tartışma: Serum BNP düzeyinin sepsisli kritik hasta çocuklarda prognozu belirlemede güçlü bir belirteç olarak kullanılabileceğini düşünmekteyiz.

Anahtar Kelimeler: beyin natriüretik peptit, BNP, çocuk, PELOD, PRISM, sepsis

INTRODUCTION

Despite improvements in antibiotic therapy and fluid management, sepsis induced multi-organ failure and septic shock remain main causes of deaths in pediatric intensive care units (PICU) around the world (1, 2). Half of the children with sepsis are infants and majority of them at high risk for severe sepsis. The mortality rate of severe sepsis is high and increases in the presence of multi-organ failure and septic shock (3, 4). Particularly cardiac decompansation in sepsis is very important for mortality. According to surviving sepsis campaign guideline, sepsis with cardiac decompansation is defined as septic shock (2). We aimed to measure brain natriuretic peptide (BNP) levels in septic shock because of BNP is a reliable marker for cardiac failure and to determine the role of BNP as a prognostic marker for mortality in children. Many factors such as age, clinical signs, laboratory values, and sepsis-related organ failure assessment scores are used to predict mortality in sepsis (5–7).

BNP is a hormone synthesized and secreted by the ventricular myocardium in response to ventricular wall tension (8). BNP measurement is recommended and it is a useful cardiac biomarker for the diagnosis of decompensated heart failure in adults (9). BNP is also elevated in children with heart failure from various congenital heart defects. In the literature, the studies reported that elevated serum BNP levels were associated with mortality in critically ill patients (6, 10–12).

We also aimed to compare serum BNP levels in children with sepsis and septic shock and to determine the role of BNP as a marker of severity and mortality in those children.

MATERIAL AND METHODS

A prospective observational study was performed in a six-bed PICU. Children between the ages of 1-month and 14-year who were admitted to PICU with the diagnosis of sepsis or septic shock were enrolled. Thirty-four patients were categorized as two study groups as having sepsis or septic shock. Patients were grouped on the basis of the diagnostic criteria of the International Pediatric Sepsis Consensus Conference (IPSCC) in 2008 (1). Sepsis was defined as the systemic response to infection manifested by two or more of the following conditions: (1) Temperature of >38°C or <36°C, (2) heart rate of >90th percentile for age, (3) respiratory rate of >90th percentile for age, apnea for >15 s or mechanical ventilation, and (4) white blood cell count of >12,000 cells/mm^3 or <4000 cells/mm^3 or the presence of >10% bands. Septic shock was defined as sepsis with cardiovascular dysfunction. According to IPSCC, the criteria of cardiovascular dysfunction: (1) Hypotension persisting despite >40 mL/kg fluid resuscitation in 1 h or (2) needed vasoactive drugs such as dopamine, dobutamine, adrenaline, noradrenaline to provide normal blood pressure or (3) presence of two of the following: metabolic acidosis (base excess > 5 meq/L), more than two fold of normal serum lactate levels, oliguria (<0.5 mL kg/h), decreased capillary refill (>5 sn), difference >3°C between rectal and peripheral temperature. The control group was comprised 26 healthy children aged 1–14 years who came to pediatric outpatient clinic for routine control, they had no acute or chronic illness.

Serial blood samples of the children with sepsis syndrome were collected at admission, 24th, 48th, 72th, and 96th h. The blood

Table 1. Comparison of BNP (0) levels among patients with sepsis syndrome and healthy control group

	BNP (0) (pg/mL)		p
	Min–Max	Mean±SD	
Sepsis syndrome	2–5135	242.13±929.60	0.001*
Healthy control	1–7	2.61±1.26	

Mann–Whitney U-test; *: P<0.01. BNP: Brain natriuretic peptide; Min: Minimum; Max: Maximum; SD: Standard deviation.

samples of the healthy control group were taken only once. Samples were centrifuged at 3500 rpm for 15 min at 4°C. Supernatant was frozen at −80°C until to assay. BNP values were determined using the Triage BNP meter 98200 (Biosite, San Diego, CA). Serum BNP levels were expressed as pg/mL.

At the same hours, clinical, and laboratory data were recorded. Multi-organ functions were evaluated according to the Pediatric Logistic Organ Dysfunction (PELOD) score. PELOD scores were recorded for each of the six organ systems on admission and every 24 h for 4 days. The severity of sepsis and mortality risk was determined by calculating of the Pediatric Risk Of Mortality (PRISM) score within 24 h after the admission. Echocardiography was performed for all patients by pediatric cardiologist.

Patients were excluded from this study if they had congenital heart defects, congenital kidney diseases, chronic diseases, and malignancies.

Statistical analysis

All analyses were performed using Number Cruncher Statistical System 2007 and Power Analysis and Sample Size 2008 Statistical Software (Utah, USA). If data were normally distributed, the comparisons were performed using Student t-test; otherwise, Mann-Whitney U test was used. The Spearman rank test was used for correlations. The χ^2 test was used for categorical variables. p<0.05 with two tailed test was considered to be statistically significant.

RESULTS

Twenty children with septic shock, 14 children with sepsis, and 26 healthy controls were recruited. Mean age of children with sepsis and septic shock (n=34) was 2.87±3.22 years. Female (n=19)/male (n=15) ratio was 1.26. There was no difference in age and gender among groups (p<0.05). The mean hospitalization day in PICU was similar for both children with sepsis and septic shock (p>0.05). Echocardiography was normal in 31 patients, pathological signs were pericardial effusion with pericardial tamponade (n=1) and pericardial effusion with myocarditis (n=2). Blood cultures revealed *Neisseria meningitidis* (n=1), *Streptococcus pneumoniae* (n=1), coagulase-negative *Staphylococcus* (n=2), *Staphylococcus aureus* (n=1), H1N1 (n=1), *Escherichia coli* (n=1), *Klebsiella pneumoniae* (n= 1), *Pseudomonas aeruginosa* (n=3), and urine culture revealed *K. pneumoniae* (n=1). No infectious etiology could be detected in blood and urine cultures of 23 patients.

The mean BNP levels at admission (BNP [0]) significantly higher in children with sepsis syndrome than those of the healthy controls (242.13±929.6 vs. 2.61±1.26; p<0.001, Table 1). Mean BNP (0) level was significantly higher in septic shock group than sepsis group (384.88±1191.31 vs. 28±38.94; p<0.001, Table 2). BNP levels at the time of admission to PICU, at 24th and 48th h were significantly elevated in septic shock patients compared with sepsis group (p=0.008, p=0.001, and p=0.001), respectively, Table 3). The highest values were found in septic shock group (p<0.001, Table 3).

Of the 34 children with sepsis or septic shock, 13 (38.2%) were died. All of non-survivors were presented with septic shock. The BNP (0) levels were significantly elevated in non-survivors compared with survivors in children with sepsis syndrome (p<0.01, Table 4). The serial measurements of serum BNP levels at admission, 24th h, 48th h, 72th h, and 96th h were significantly difference between survivors and non-survivors in children with sepsis syndrome (p=0.003, p=0.001, p=0.001, p=0.05, and p=0.008, respectively, Table 4).

BNP (0) values correlated with positively with number of organ dysfunction in particular cardiac and neurological, PRISM score, PELOD score, prothrombin time, internalized normalized ratio, partial thromboplastin time, and 24th h inotropic score. BNP (0) values also correlated with platelet count and serum calcium levels, negatively (Table 5).

DISCUSSION

The present study showed that BNP levels were elevated in children with sepsis syndrome. There are few published studies

Table 2. Comparison of BNP (0) levels among sepsis, septic shock, and control groups

	BNP (0) (pg/mL)		p
	Min–Max	Mean±SD	
Control group (healthy children)	1–7	2.61±1.26	Control-Sepsis P=0.001*
Sepsis group	2–145	28±38.94	Control-Septic shock P=0.001*
Septic shock group	8–5135	384.88±1191.31	Sepsis-Septic shock P=0.008*

Mann–Whitney U-test; *: P<0.01. BNP: Brain natriuretic peptide; Min: Minimum; Max: Maximum; SD: Standard deviation.

Table 3. Comparison of serial BNP measurements between sepsis and septic shock groups

P (pg/mL)	Sepsis			Septic shock			p
	Min–Max	Mean±SD	Median	Min–Max	Mean±SD	Median	
0th h	2–145	28±38.94	14	8–5135	384.88±1191.31	63	0.008**
24th h	2–45	17.45±14.06	12	7–2642	423±767.66	108	0.001**
48th h	3–43	10.33±13.04	6	16–1835	247.38±496.49	65	0.001**
72th h	2–17	9.25±6.94	9	2–344	84.5±116.41	32.5	0.148
96th h	2–23	9.66±8.40	7	5–467	91.5±139.41	54.5	0.034*

Mann–Whitney U-test; *: P<0.05; **: P<0.01. BNP: Brain natriuretic peptide; Min: Minimum; Max: Maximum; SD: Standard deviation.

Table 4. Serial BNP measurements between survivors and non-survivors

BNP (pg/mL)	Survivors			Non-survivors			p
	Min–Max	Mean±SD	Median	Min–Max	Mean±SD	Median	
0th h	2–255	47.33±73.09	14	13–5135	534.3±1454.15	69	0.003**
24th h	2–108	28.83±28.61	20	33–2642	752.25±954.96	33	0.001**
48th h	3–141	24.5±35.2	16.5	25–1835	486.16±679.66	212	0.001**
72th h	2–144	26.6±42.76	12.5	103–344	223.5±170.4	223.5	0.050*
96th h	2–69	19.16±23.17	10	44–467	185.75±192.55	116	0.008**

Mann–Whitney U-test; *: P<0.05; **: P<0.01. BNP: Brain natriuretic peptide; Min: Minimum; Max: Maximum; SD: Standard deviation.

about BNP levels in children with septic shock. Elevated BNP levels have been shown in septic shock patients and they have been attributed to myocardial dysfunction in those (6, 7, 10, 12). However, some researchers reported that BNP levels were increased in septic patients regardless of cardiac dysfunction (7, 11). Endotoxins and inflammatory mediators can also induce the BNP synthesis, the mechanisms leading to elevated BNP levels in patients with sepsis remain unclear (13–15). We also found high BNP levels in patients with sepsis without cardiac involvement, it is suggested that the peptide could be secreted due to inflammatory mediators in sepsis.

Most of the previous studies show that BNP levels are elevated in children with congenital cardiac defects or heart failure (16–21). Nowadays, less clear is its clinical relevance in children with sepsis syndrome. Recently published studies showed that BNP levels elevated in children with both sepsis and septic shock, otherwise some of the studies reported that NT-proBNP was not associated with the prognosis of pediatric severe sepsis (22–24). Zhang et al. (23) reported that the levels of plasma BNP and troponin-I were associated with the severity of sepsis in pediatric patients, and were positively correlated with CRP and TNF-a levels, which provides a novel strategy for the early diagnosis and evaluation of sepsis in pediatric patients. The results of our study confirm previous studies indicating elevated BNP levels in patients with sepsis syndrome (6, 12, 15, 22, 23). The limitation of all published manuscripts is the small patient volume.

Domico et al. (6) reported that BNP levels were elevated in 13 children with septic shock compared with 12 healthy and 5 PICU controls. As known septic shock is defined as sepsis with cardiac dysfunction, the elevation of BNP in patients with septic shock can be attributed to cardiac involvement. We also investigated BNP levels in 34 children with sepsis syndrome, those of 20 with septic shock and those of 14 with sepsis. We found elevated BNP levels in children with sepsis regardless of cardiac involvement. In addition, the highest BNP levels were measured in non-survivors with septic shock. Fried et al. (25) reported that serum BNP levels in children with sepsis and impaired systolic function were not different from those of children with sepsis and normal systolic function.

We compared BNP levels with organ dysfunctions according to PELOD scores. Cardiac and neurological dysfunctions in sepsis syndrome were associated with high BNP levels. BNP levels were also correlated with number of organ dysfunction and scores of prognostic scoring systems (PRISM and PELOD). Therefore, results of our study suggest that BNP can be used for prediction of severity of sepsis and prognosis in children with sepsis syndrome at admission to the PICU.

Domico et al. (6) measured serum BNP level at admission to PICU and the median value of BNP level in children with septic shock was 115 pg/mL. It was over 10 times that of their controls (9 pg/mL in healthy controls and 10 pg/mL PICU controls). We also found similar results that the median BNP levels were 384 pg/mL in septic shock group, 28 pg/mL in sepsis group, and 2.6

Table 5. The relationship of serum BNP levels with mortality scores, organ dysfunctions, and laboratory parameters

	Serum BNP level at admission (BNP [0])	
	r	p
PRISM score	0.385	0.039*
Total PELOD score	0.483	0.007**
PELOD cardiologic	0.447	0.015*
PELOD neurologic	0.423	0.022*
PELOD pulmonary	0.303	0.110
PELOD hepatic	0.332	0.078
PELOD renal	−0.087	0.655
PELOD hematologic	0.302	0.111
Number of organ dysfunction	0.498	0.005**
WBC	−0.146	0.442
Platelet count	−0.459	0.012*
C-reactive protein	−0.113	0.551
Prothrombin time	0.531	0.004**
aPTT	0.558	0.002**
Serum calcium level	−0.399	0.032*

r: Spearman's correlation coefficient; *: P<0.05; **: P<0.01; BNP: Brain natriuretic peptide; PELOD: Pediatric logistic organ dysfunction; PRISM: Pediatric risk of mortality; WBC: White blood cell count; aPTT: Activated partial thromboplastin time.

pg/mL in health controls. Charpentier et al. (12) also found BNP levels were significantly elevated on days 2 and 3 in adults who expired during their intensive care unit stay. Ueda et al. (26) reported similar finding in adults on day 2, predicted mortality with a sensitivity of 92% and specificity of 80%. In our study, the BNP levels at 24th and 48th h were significantly higher than at admission and the highest values were found in non-survivors and patients with septic shock. Because of most of non-survivors were died on day 2 or 3 during their PICU stays, number of our patients with sepsis syndrome on day 4 and 5 were less, so the results of BNP levels on 72th and 96th h were less significant statistically.

PRISM and PELOD scoring systems are used for determine risk of mortality and severity of illness in PICU. Domico et al. (6) reported that BNP level at 12 h after admission was highly associated with severity of illness and correlated with PRISM III score. Reel et al. (27) also found that BNP levels were correlated with PRISM and PELOD scores in children with acute lung injury. In our study, BNP levels at admission to PICU were correlated with PRISM score and PELOD score. Kollef and Sherman (28) reported that among critically ill patients, neurological and cardiac dysfunctions are the acquired organ system derangements most closely associated with mortality. According to our results, in particular cardiac and neurological involvements were correlated with the BNP levels at admission. According to this finding, it suggests that BNP levels may be associated with mortality.

Bilevicius et al. (29) reported that multi-organ failure due to sepsis is associated with high mortality related to the number of failing organs. We also found that the BNP levels at admission were correlated with the number of failing organs. We suggest that BNP may be used for predict of mortality and severity of the sepsis.

CONCLUSION

Serum BNP level may be useful predictor of prognosis in critically ill children with sepsis. We recommend to measure serum BNP level in children with sepsis at admission, because of early identification of septic shock can help to perform early therapeutic interventions and to decrease mortality risk. Further studies are needed to confirm our findings.

Ethics Committee Approval: The Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 18.06.2009, number: 96).

Informed Consent: Written informed consent was obtained from the families of the patients who participated in this study.

Conflict of Interest: No conflict of interest was declared by the authors.

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Authorship Contributions: Concept – BŞK, EŞ; Design – BŞK, EŞ, AG; Supervision – BŞK; Fundings – EŞ, AG; Materials – BŞK, YD; Data collection and/or processing – BŞK, YD; Analysis and/or interpretation – BŞK, EŞ; Literature review – BŞK; Writing – BŞK; Critical review – BŞK, EŞ.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastaların ailelerinden alınmıştır.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

Yazarlık Katkıları: Fikir – BŞK, EŞ; Tasarım – BŞK, EŞ, AG; Denetmele – BŞK; Kaynaklar – EŞ, AG; Malzemeler – BŞK, YD; Veri Toplanması ve/veya İşlemesi – BŞK, YD; Analiz ve/veya Yorum – BŞK, EŞ; Literatür Taraması – BŞK; Yazıyı Yazan – BŞK; Eleştirel İnceleme – BŞK, EŞ.

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