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Diagnostic Value of Bedside Brain Natriuretic Peptide Measurement in Patients with Head Trauma

Kafa Travmalı Hastalarda Yatak Başı Brain Natriüretik Peptit (BNP) Ölçümünün Tanısal Değeri

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ABSTRACT

BACKGROUND: Brain natriuretic peptide (BNP) is secreted by cardiac ventricles in response to increased wall stress and intraventricular volume but it was showed that there was some immunoreactivity of BNP in the human brain including cerebral cortex, thalamus, pons, and cerebellum.

AIM: The aim of this study is to investigate the diagnostic value of bedside measurement of BNP that is used in order to predict the presence of intracranial pathologies in patients with head trauma.

MATERIALS AND METHODS: This study was performed prospectively with head trauma patients. Bedside BNP measurements and cranial computed tomography (CT) scans were performed in these patients.

RESULTS: The mean BNP level of 23 patients with pathologic cranial CT scan was 16.16±15.8 pg/mL and the mean BNP level of 17 patients with normal cranial CT scan was 5.78±3.0 pg/mL. It was 6.91±3.2 pg/mL in the control group. The mean BNP level of patients with pathological cranial CT was significantly higher than mean BNP levels of patients with normal cranial CT and patients in the control group ($p<0.01$)

CONCLUSION: We think that BNP levels over 10 pg/mL values without known causes of BNP increase may be effective and specific to detect intracranial pathologies in head trauma patients.

Key words: Brain natriuretic peptide, head trauma, cranial CT, emergency department

ÖZET

GIRIŞ: Brain natriüretik peptit (BNP) kalpte artmış duvar gerilimi, duvar basıncı ve intraventriküler volüme sekonder olarak kardiyak ventriküllerden salınır. Ancak, insan beyninde serebral korteks, hipotalamus, talamus, pons ve serebellumda da immünreaktif yöntemle tespit edilmiştir.

AMAÇ: Bu çalışmanın amacı, kafa travmalı hastalarda kafa içi yaralanmaların belirlenmesinde yatak başı BNP ölçümünün tanısal değerini araştırmaktır.

GEREÇ VE YÖNTEMLER: Çalışma kafa travmalı hastalarla prospektif olarak yapıldı. Bu hastalara bilgisayarlı beyin tomografisi (BBT) çekildi ve yatak başı BNP ölçümü yapıldı.

BULGULAR: BBT'sinde intrakraniyal lezyon olan 23 hastanın ortalama BNP düzeyi 16.16±15.8 pg/mL, intrakraniyal lezyon olmayan 17 hastanın ortalama BNP düzeyi 5.78±3.0 pg/mL olarak bulundu. Kontrol grubunda ortalama BNP düzeyi ise 6.91±3.2 pg/mL idi. Yapılan istatistiksel analiz sonucu intrakraniyal patoloji tespit edilen grubun BNP düzeyi diğer iki gruba göre anlamlı derecede yüksek bulundu ($p<0.01$)

SONUÇ: BNP'yi arttırdığı bilinen diğer nedenler olmaksızın, 10 pg/mL üzerindeki BNP değerlerinin kafa travmalı hastalarda kafa içi yaralanmaları belirlemede etkili ve spesifik olabileceğini düşünüyoruz.

Anahtar Kelimeler: Brain natriüretik peptit, kafa travması, beyin BT, acil servis

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INTRODUCTION

Brain natriuretic peptide (BNP) which was first isolated from porcine brain in 1988 is a 3472-dalton polypeptide and it consists of 32 amino acids [1]. The half-life of BNP in plasma is approximately 20 minutes. BNP level can be measured by using ethylene diamine tetraacetic acid (EDTA) anticoagulated whole blood or plasma within 15 minutes. The detectable level of BNP is 5-1300 pg/mL. It is secreted by the cardiac ventricles in response to increased wall stress and intraventricular volume. It provides balanced vasodilatation and increased urinary sodium excretion. It also inhibits the sympathetic nervous system and the activities of several other hormone systems including the renin-angiotensin-aldosterone system [2, 3]**.** It was showed that there was some immunoreactivity of BNP in the human brain including the cerebral cortex, hypothalamus, thalamus, pons, and cerebellum [4]. It was reported that BNP plasma concentrations were significantly higher in patients with subarachnoid hemorrhage (SAH) and BNP stimulated diuresis and natriuresis [4-6]**.** It was also reported that BNP levels were elevated after epileptic seizure, hypertension, acute coronary syndrome, ischemic stroke, acute lung injury, and cardiac syncope [7-13]**.** There were limited numbers of studies about elevated BNP levels that were measured after severe traumatic brain injuries [14, 15]. The aim of this prospective study is to investigate the diagnostic value of bedside measurement of BNP that is used in order to predict the presence of intracranial pathologies in patients with head trauma (minor, mild, major).

MATERIALS AND METHODS

This prospective study was performed with head trauma patients who met the inclusion criteria and were admitted to our Emergency Department (ED) between January 01, 2004 and April 01, 2004. The study was approved by the local ethical committee, and informed consents were collected from the patients. We excluded patients with thorax trauma, congestive heart failure, hypertension, acute coronary syndrome, ischemic stroke, no indication for cranial CT scan and admission after the first 24 hour.

Bedside BNP measurements were performed by using the BNP triage kit (Biosite Incorporated, San Diego, CA, USA) within 15 minutes. Cranial computed tomography (CT) scans were performed in patients with head trauma according to Canadian CT Head Rule (CCHR) [16]. Cranial CT scans which were performed on a HITACHI W1000 X-Ray CT System were obtained at 5 and 10 mm intervals and they were reviewed by the same radiologist. Patients were divided into two groups based on the presence (cerebral edema, epidural hematoma, subdural hematoma, SAH, cerebral contusion, intraparenchymal hematoma, basal skull fracture, and depressed fracture) and absence of intracranial lesions (normal cranial CT and linear fracture) that were shown by cranial CT scans. Then the diagnostic value of BNP plasma concentrations in patients with intracranial lesions was investigated.

Twenty patients who did not have a history of head trauma and met the inclusion criteria were included into the study as the control group. Cranial CT scan was not performed on this group.

Statistical Analysis

The statistical analysis was performed by using SPSS 11.0 for Windows software package program (SPSS Inc., Chicago, IL, USA). Demographic and clinical features of patients were recorded and the basic descriptive statistics were calculated (frequencies and percentage for qualitative variables; mean, median and standard deviation for quantitative variables). The Kolmogorov-Smirnov test was applied in order to evaluate the normal distribution. As the data followed a continuous distribution, the Mann-Whitney U test was applied in order to perform a meaningful comparison of two groups of patients. Kruskal-Wallis Test was used in order to compare quantitative variables including Glasgow Coma Scale (GCS) and plasma BNP levels. Pearson correlation test was performed in order to evaluate the correlation between parametric and nonparametric groups. To evaluate the diagnostic value of BNP for presence of intracranial pathologies in patients with head trauma, a receiver-operating characteristic (ROC) curve was created and the area under the curve (AUC) was calculated. The sensitivity, the specificity, negative predictive values and positive predictive values were determined for BNP in the head trauma patients with diagnosis for intracranial pathologies.

RESULTS

3214 patients were admitted to our ED between January 01, 2004 and April 01, 2004 and 103 patients had a history of head trauma (3.2%). 40 patients were included into the study. 20 patients who had neither a head injury nor a chest injury were chosen as control group.

Demographic and Clinical Features

There were 28 male (70%) and 12 female (%30) patients with head trauma, ranging ages from 2 to 74 years with a mean of 26.78±20.7 years. There were 16 male (80%) and 4 female (20%) patients, ranging ages from 3 to 56 years with a mean of 25.05±16.4 years in the control group. Of 40 patients, 29 (72.5%) had isolated head trauma, 7 (17.5%) had multiple extremity fractures, 1 (2.5%) had pelvic fracture, 1 (2.5%) had vertebral fracture, and 1 (2.5%) had clavicle fracture. In the control group; 15 (75%) had extremity injuries, 2 (10%) had abdominal trauma, 1 (5%) had pelvic trauma, 1 (5%) had extremity and abdominal trauma, and 1 (5%) had vertebrae trauma.

The most common symptoms at admission were nausea (42.5%), headache (42.5%), drowsiness (42.5%), and vomiting (32.5). The mean delay in admission to the hospital was 163,38±158,5 minutes in patients with head trauma and 123,50±97,4 minutes in the control group. There was no statistically significant difference in admission delay between two groups (p=0,428).

Brain natriuretic peptide

Cranial CT scans were evaluated and patients with head trauma were divided into two groups. One group was consisting of patients with intracranial lesions (pathological cranial CT) and other group was patients who had no intracranial lesion (normal cranial CT). 13 patients with isolated linear fracture were included into the normal cranial CT group. Of 40 patients with head trauma 17 (42.5%) had normal cranial CT scan and 23 (57.5%) had pathologic cranial CT scan. The mean BNP level of 17 patients with normal cranial CT scan was 5.78±3.0 pg/mL (ranging 5 to 17.2). The mean BNP level of 23 patients with pathologic cranial CT scan was 16.16±15.8 pg/mL (ranging 5 to 72.2). A statistically significantly difference was observed in BNP levels between these two groups ($p<0.01$). It was observed that BNP levels were significantly raised in patients with depressed fracture, basal skull fracture, cerebral contusion, and intracerebral hematoma (respectively; $p<0.01$, $p<0.01$, $p<0.05$, $p<0.01$). The relationship between cranial CT findings and BNP levels was shown in *Table 1*.

The mean BNP level of patients with head trauma was 11.75±13.1 pg/mL. It was 6.91±3.2 pg/mL in the control group. There was no statistically significant difference in BNP levels between these two groups ($p>0.05$).

BNP levels of patients with normal cranial CT and pathological cranial CT were compared separately to the BNP levels of the control group. The mean BNP level of patients with pathological cranial CT was significantly higher in comparing mean BNP levels of patients with normal cranial CT and patients in the control group ($p<0.01$). There was no significant difference in the mean BNP level of patients with normal cranial CT comparing mean BNP level of patients in the control group ($p=0.099$). The distribution of BNP levels among the groups was shown in figure.1.

The ROC curve was formed to determine the diagnostic value of BNP for intracranial pathologies in patients with head trauma (figure 2) and the AUC was calculated. AUC was 0.797 and $p=0.002$ for BNP. When various cut-off points were evaluated, potentially useful value for predicting intracranial injury was 10 pg/mL for BNP. The sensitivity of the test was 61%, the specificity was 94%, the positive predictive value was 93%, and the negative predictive value was 64% for the diagnosis of intracranial pathologies in patients with head trauma.

There was no significant difference in BNP levels according to age and gender (respectively $p=0.644$, $p=0.686$). There was no significant relationship between BNP levels and symptoms of patients. BNP levels were significantly higher in patients with scalp hematoma and depressed fracture (respectively $p<0.05$, $p<0.01$).

There was a significant relationship between the delay in admission to the hospital (total delay after the trauma) and BNP levels ($p<0.01$). It showed that there was a positive correlation between the admission time and BNP levels.

Patients with head trauma were evaluated according to GCS and three subgroups were formed as follows: Minor head trauma with a GCS of 14-15, mild head trauma with a GCS of 9-13 and major head trauma with a GCS smaller than 8. There was no significant difference with respect to BNP levels of these three subgroups ($p=0.829$). Except a patient with a GCS of 13, all other patients (GCS≤13) had pathological cranial CT findings (%85.7). Cranial CT scans of 12 patients with a GCS of 14 were evaluated and it was observed that 9 patients (75%) had pathological cranial CT. Cranial CT scans of 21 patients with a GCS of 15 were evaluated and it was observed that 9 patients (38.1%) had pathological cranial CT. GCS and BNP levels of patients were shown in *Table 2*.

Table 1. *The relationship between cranial CT findings and BNP levels*

Finding	Number of patient (n)	(%)	BNP (pg/ml±SD)	P value
Linear fracture	13	32,5	10,93±6.5	0.788
Depressed fracture	2	5	38.6±47.5	**0.002**
Basal skull fracture	2	5	38.6±47.5	**0.002**
Cerebral edema	9	22,5	15.41±22.3	0.347
Epidural hematoma	2	5	21.85±1.2	0.269
Subdural hematoma	4	10	10.33±4.4	0.822
SAH	3	7,5	11.63±6.3	0.988
Cerebral contusion	5	12,5	23.6±13.7	**0.029**
Intraparenchymal hematoma	1	2,5	46.8±0	**0.005**

Table 2. *GCS and BNP levels of patients*

GCS	Number and %	BNP level
≤ 8	3 (%7.5)	10.23±5.4
9-13	4(%10)	12.38±9.4
14-15	33 (%82.5)	11.81±14.1

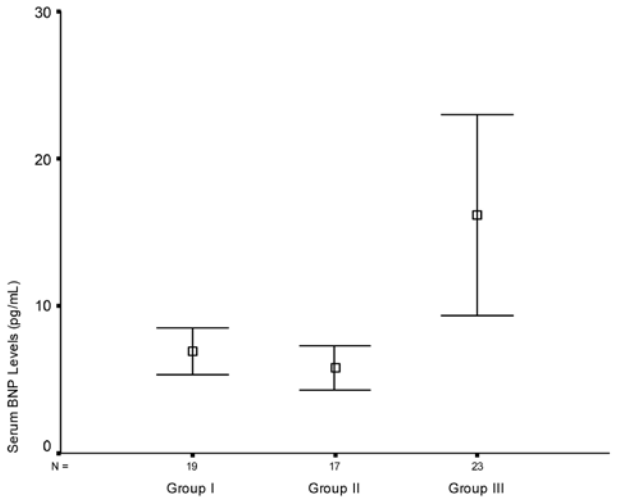

Figure. 1*. The distribution of BNP levels among the groups (Group I= Control group, Group II= Patients with head trauma and normal cranial CT), Group III= Patients with head trauma and pathological cranial CT)*

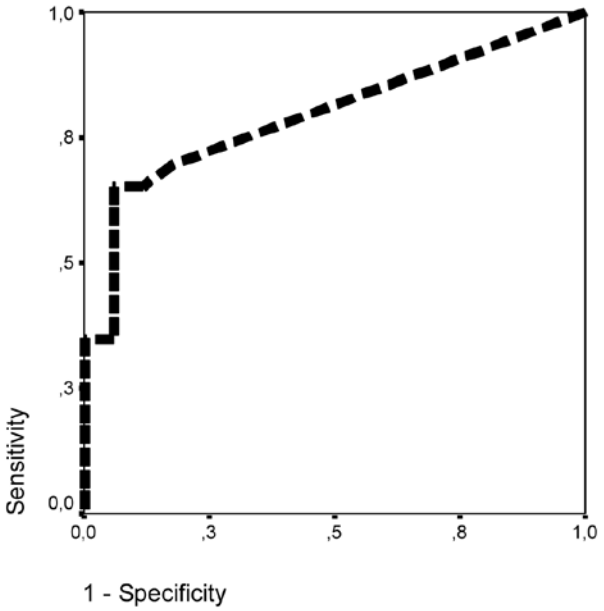

***Figure 2**. Receiver operating characteristic curve for BNP (AUC=0.797, p=0.002)*

DISCUSSION

Head traumas and traumatic brain injuries (TBI) are the leading causes of mortality and long term disabilities especially among male adolescents and young adults [17]. There are a lot of studies about biochemical markers including endothelin-1, CK-BB, glial fibrillary acidic protein, interleukie-8, myelin basic protein, NSE, S-100β, serum cleaved Tau protein in order to investigate the severity of TBI [18]. There was limited number of studies about BNP levels after severe head traumas [14, 15].

BNP which is a 32-amino acid natriuretic peptide was first isolated from porcine brain. It is secreted primarily by the cardiac ventricles. BNP plays an important role in the diagnosis of cardiovascular diseases including congestive heart failure and ischemic heart disease. It is commonly used for the estimation of the degree of heart failure and is used as a determining factor of left ventricular systolic and diastolic functions. Besides it is used for determining the prognosis after acute myocardial infarction. BNP is also a predictor of mortality and cardiovascular events in older adults [1, 3, 19, 20, 21, 22].

In our study we found that BNP levels of patients with intracranial lesion on cranial CT scan were significantly higher in comparing BNP levels of patients who had no intracranial lesion ($p<0.01$). When we took 10 pg/mL as cut-off value for BNP, we determined that it had high specificity and positive decisiveness (94% and 93% respectively). The AUC value (0.797) of the test showed that it was valuable as a diagnostic tool.

BNP levels of patients with intracranial lesion were also significantly higher in comparing BNP levels of patients with other kind of traumas except acute lung injury which showed significant positive correlations with head trauma and BNP levels ($p<0.01$) [13]. These findings suggest that BNP could be secreted primarily from the areas of neuronal injury. Besides we think that BNP levels could be also higher because of trauma stress-induced release of cardiac catecholamine.

BNP is found in the human brain including the hypothalamus, cerebral cortex, thalamus, pons, and cerebellum [4]. Sviri et al found that BNP plasma concentrations were significantly higher in patients with severe traumatic brain injury as compared to the control group and BNP plasma concentrations were progressively elevated in head trauma patients with elevated intracranial pressure (ICP) as compared to head trauma patients without ICP. They reported that BNP plasma concentrations were elevated shortly after head injury and were continuously elevated during the acute phase in patients with elevated ICP but BNP levels decreased significantly in patients with lower ICP [14]. In our study we also found that there was a significant relationship between the delay in admission to the hospital and BNP levels ($p<0.01$). Plasma BNP concentration might be elevated continuously after head trauma. As the half-life of BNP in plasma is approximately 20 minutes, BNP might be released either continuously or periodically. The significant relationship between the delay in admission to the hospital and BNP levels could be an important factor for determining the presence of intracranial lesions in patients who admitted to the hospital later.

GCS is commonly used as a clinical instrument to assess the head trauma patients. Although there is a general consensus about the predictive value of GCS in patients with mild and major head trauma, there are different approaches about radiological assessment of patients with minor head trauma. For this reason there were lots of studies conducted in order to determine either indications of cranial CT scanning by using biochemical markers and clinical features or indications for hospital admission [23-25]. In our study no statistically significant relationship was found between GCS scores and BNP levels of patients with head trauma ($p>0.05$) and its' reason could be the presence of intracranial lesions in most of patients with minor head trauma. We think that plasma BNP concentration could be a useful determining factor if there is a doubt about cranial CT scanning in patients with minor head trauma.

Berenders et al found that patients with aneurysmal SAH had significantly much higher plasma concentrations of BNP than patients with cerebral tumor and the control group. They reported that there was a significant relationship between the elevated plasma BNP concentration and elevated ICP and urinary excretion of sodium [6]. It was suggested that BNP might be part of a central mechanism for control of blood volume, blood pressure, and electrolyte composition. We found that there was a positive relationship between urinary sodium excretion and BNP levels ($p<0.05$, $r=0.384$). It was reported that increased secretion of BNP resulted in an osmotic diuresis which large amounts of sodium was excreted from the kidney along with "osmotically" free water. The reason was the reduction in the efficacy of aldosterone and hence a reduction in the ability to reabsorb sodium in the kidney [26]. Our study consisted of patients who admitted to

the emergency department within the first 24 hour after the trauma. We concluded that plasma BNP concentrations were progressively elevated during the acute phase following TBI and BNP was responsible for the hyponatremia that resulted from the natriuresis. It was found that TBI-induced severe hyponatremia was associated with high mortality rate and neurological deficits [14, 27]. For this reason plasma sodium concentration should be monitored carefully in patients with TBI in order to avoid hyponatremia and BNP level could potentially be used in the management of patients with ICP following head trauma.

CONCLUSION

We think that BNP levels over 10 pg/mL values without known causes of BNP increase may be effective and specific to detect intracranial pathologies in head trauma patients. We think that bedside BNP measurement might be useful in determining the indication of cranial CT scan in patients with head trauma but we need more studies consisting of large number of patients.

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