Brief Report

Investigation of changes in brain natriuretic peptide serum levels and its diagnostic value in patients with mild and moderate head trauma, in patients referred to emergency department of Alzahra Hospital, Isfahan, 2013-2014

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Abstract

Background: Head trauma is one of the most common reasons for emergency department (ED) care. Over the past decade, initial management strategies in mild and moderate head trauma have become focused on selective computed tomography (CT) use based upon presence or absence of specific aspects of patient history and/or clinical examination which has received more attention following reports of increased cancer risk from CT scans. Recently changes in serum brain natriuretic peptide (BNP) levels following head trauma have been studied. We investigated the changes in serum levels of BNP in patients with mild and moderate head trauma, in whom the first brain CT scanning was normal.

Materials and Methods: This study is a cross-sectional, descriptive research. It was performed in patients with mild and moderate head trauma. Forty-one patients with isolated mild and moderate traumatic brain injury (Glasgow Coma Scale = 9–15) were included. First brain CT scans were obtained during 2 h after ED arrival and the second one after 24 h. Plasma BNP levels were determined using a specific immunoassay system.

Results: Twenty-three patients were in Group A (with normal first and second brain CT) and 18 patients in Group B (with normal first and abnormal second brain CT). With $P = 0.001$, serum BNP level = 9.04 was determined for differentiating two groups.

Conclusion: We concluded that serum BNP level is higher in patients with mild and moderate head trauma with delayed pathologic changes in second brain CT relative to patients with mild and moderate head trauma and with normal delayed brain CT.

Key Words: Brain computed tomography scan, brain natriuretic peptide, traumatic brain injury

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INTRODUCTION

Head trauma is one of the most common reasons for emergency department (ED) care. Cases of head trauma account for over 1 million visits/year in both the USA and the UK and are responsible for two-thirds of

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all trauma deaths. Only a small proportion of these are classed as severe head trauma, with a Glasgow Coma Scale (GCS) score of 3–8. The majority of patients is instead classed as minimal, mild and moderate head trauma and is generally conscious in the ED with varying degrees of neurological symptoms.[1] Overall, 80% of patients sustain minor head trauma (GCS score of 14 or 15), 10% have moderate head trauma (GCS score of 9–13), and 10% have severe head trauma (GCS score of 8 or less).[2]

Over the past decade, initial management strategies in mild and moderate head trauma have become focused on selective computed tomography (CT) use based upon presence or absence of specific aspects of patient history and/or clinical examination.[3] This selective management has received more attention following reports of increased cancer risk from CT scans, estimated at 1 in 5000–10,000 for a single brain CT scan in young adults. CT is also an expensive examination.[4] Following a normal CT scan after mild head trauma, the consensus is generally to discharge patients from the hospital, although subgroups of patients may still be at risk of developing delayed intracranial complications of varying significance.[5,6]

Brain natriuretic peptide (BNP) was isolated from the porcine brain, 1st time.[7] It has either 26 or 32 amino acid residues, porcine (p) BNP-26 and pBNP-32, respectively,[8] it has peripheral and central actions similar to those of atrial natriuretic peptide.[7,9,10] BNP is also synthesized in, and secreted into the circulation from the porcine heart.[11,12] It is secreted by the cardiac ventricles in response to increased wall stress and intra-ventricular 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.[13,14] By it systemic effect, BNP reduces blood pressure (BP) and plasma volume.[15]

In most patients with severe head trauma, brain CT scan shows pathologic lesions during few hours after the insult. In the majority of mild and moderate head trauma, the first brain CT scan is normal (85–95%). However, some of them find pathologic intracranial changes, subsequently.[16] These patients are hospitalized for observation and brain CT scanning is repeated for detecting subsequent lesions. It has additional charges for patient and country medical system, excessive exposure to radiation, occupies hospital beds, and is a time-consuming method. Establishing a new method for predicting intracranial injury-related lesions, presenting with time delay, is crucial. It can improve the prognosis of these patients. It can be also time-saving and cost-effective over traditional methods.

In recent years, changes in serum BNP levels following head trauma have been investigated by some researchers. There are evidences that show blood levels of BNP and N-terminal pro-BNP increases following traumatic brain injury (TBI).[17-19] Other studies have shown that it does not change.[20,21] It was also reported that BNP plasma concentrations were significantly higher in patients with subarachnoid hemorrhage (SAH).[22,23]

We arranged this research for further evaluation of the prognostic role of serum BNP in these patients. In this study, we investigated the changes in serum levels of BNP in patients with mild and moderate head trauma, in whom the first brain CT scanning was normal. We supposed that serum level of BNP in patients with mild and moderate brain injury is higher.

MATERIALS AND METHODS

This study is a cross-sectional, descriptive research which was designed for determining the prognostic role of serum BNP in patients with mild and moderate head trauma. The study was performed in ED of Al-Zahra Educational Hospital at Isfahan University of Medical Sciences between January 01, 2013 and August 01, 2014.

This study was performed in patients with mild and moderate head trauma. The severity of head trauma was determined by GCS. It is classified to severe (GCS ≤8), moderate (GCS = 9–13) and mild (GCS =14 and 15). Patients with isolated head trauma with GCS between 9 and 15 entered in this study. Patients with GCS = 15 but with the impaired content of consciousness entered in the study as mild head trauma.

The study population included 41 patients with isolated mild and moderate TBI (GCS = 9–15). Twenty-four patients had mild, and 17 patients had moderate head trauma. Patients with mild and moderate head trauma and with normal first brain CT scan were included. We studied patients with ages between 10 and 65 years (patients in extremes of age were excluded). Genders of patients were not important. Patients with thoracic injury, significant limb injuries and fractures, ischemic heart disease, congestive heart failure, pulmonary embolism, hypertension, and chronic renal failure were excluded, due to possibility of falsely elevated serum BNP level in these patients. Furthermore, patients with pathologic intracranial lesions in the first brain CTs were excluded.

Clinical data were collected prospectively. Neurological status was assessed by GCS for all patients at the time of ED arrival, after primary resuscitation, and at the time of discharge. The most common symptoms on admission were decreased the level of consciousness, nausea, headache, drowsiness, and vomiting.

First brain CT scans were obtained during 2 h after ED arrival and was interpreted by a radiologist and an emergency medicine specialist. If they had not any injury-related intracranial pathology, they could participate in the study. Pathologic changes which were significant in our study included: SAH, epidural hematoma, subdural hematoma, intracranial hemorrhage (ICH), brain edema, and brain contusions. Second brain CT scans obtained 24 h later for detecting delayed intracranial changes. Time for taking first and second brain CTs were according to hospital protocols.

All patients received standard therapeutic measures according to advanced trauma life support guideline (2012 edition). Standard neurosurgical measures also were done; surgical masses were evacuated by craniotomy as indicated. All patients with decreased level of consciousness were admitted to the neurosurgical Intensive Care Unit. Patients with elevated ICP were further treated by mild hyperventilation (target PCO_2 values between 30 and 35 mmHg) with mannitol 20% (0.5–1 g/kg/4 h).

We checked serum BNP levels 4 h after head trauma. Phlebotomy was performed for plasma sampling of BNP concentration. 2cc venous blood obtained for each patient. Blood samples were collected in chilled syringes and transferred into plastic tubes containing 7.5 mg potassium ethylenediaminetetraacetic acid at 2–8°C and centrifuged at 4000 RPM for 15 min at 4°C. Plasma was stored at −70°C and assayed for possible, necessary measurements. Plasma BNP levels were determined using a specific immunoassay system (ADVIA Centaur CP system, Siemens Healthcare GmbH Henkestr. 127 91052 Erlangen Germany), based on methods reported by its company manual.

Patients divided into two groups: Group A with normal first and second brain CT scans, and Group B with normal first and abnormal second brain CTs. Serum BNP levels in both groups measured and compared together using Mann–Whitney test, according to abnormal distribution of data. Differences were considered being significant when they had a $P < 0.05$. Confidence interval = 95% was determined. All calculations performed by SPSS software version 18, IBM Inc. 2010. In addition, patients divided into three groups, according to clinical course using GCS scoring at the ED presentation until discharge time: Patients with improved clinical course, patients with worsened clinical course and patients with no change. Mean serum BNP levels of these groups also determined and compared together by Mann–Whitney test. In this part of the study, differences were considered to be significant when they had $P < 0.05$. All data were interpreted and final results obtained.

Study was approved by local Ethical Committee of Isfahan University, and informed consents were collected from patients.

RESULTS

Among 41 studied patients, 35 (85.36%) patients were male and six (14.64%) were female, ranging in age from 12 to 64 years, with a mean of 28.45 years (standard deviation = 13.374 years).

Twenty-three patients were in Group A, and 18 patients in Group B. Mean of serum BNP levels in Group A was 11.83 pg/ml ± 20.47187 pg/ml, and in Group B was 37.65 pg/ml ± 47.38406 pg/ml. Comparison of two groups was performed by Mann–Whitney test, inattention to the abnormal distribution of data. $P = 0.001$ was obtained. It showed that mean of serum BNP levels in patients with abnormal second brain CT scans are significantly higher than patient with normal CT [Table 1].

We used receiver operating characteristic (ROC) curve for investigating this problem that whether measuring serum BNP level can differentiate patients with abnormal second brain CT scans from patients with normal CT. The area under the curve (AUC) = 0.804 was obtained. This means that serum BNP level is a good recognition value for differentiating two groups [Figure 1].

When different cut-off points were assessed, suitable BNP level for differentiating patients with normal second brain CT scan from patients with abnormal CT was 9.04 (≈9).

Sensitivity = 83.3%, specificity = 73.9%, positive predictive value = 71.4%, and negative predictive value = 85% were determined for test.

Table 1: Mean of serum BNP levels in patients with normal and abnormal second brain CTs

BNP	*n*	Mean	SD	SEM	Minimum	Maximum
Normal	23	11.8309	20.47187	4.26868	0.10	72.70
Abnormal	18	37.6478	47.38406	11.16853	1.42	163.00
Total	41	23.1651	36.78299	5.74454	0.10	163.00

SD: Standard deviation, SEM: Standard error of mean, BNP: Brain natriuretic peptide, CT: Computed tomography

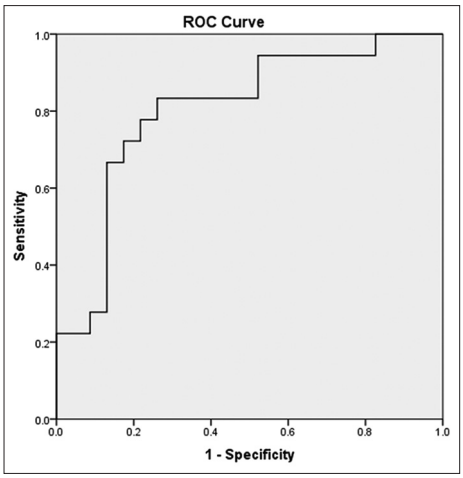

Figure 1: Receiver operating characteristic curve. Area under the curve = 0.804

DISCUSSION

Head trauma is the leading cause of mortality and long-term disability especially among male adolescents and young adults with motorized collisions.[24] There are a lot of studies about biochemical markers including endothelin-1, creatine kinase-BB, glial fibrillary acidic protein, interleukie-8, myelin basic protein, neuron-specific enolase, S-100β, serum cleaved tau protein in order to investigate the severity of TBI.[25] Changes in serum BNP level following head trauma also, have been investigated by some researchers in recent years. It is an interesting field for research. It seems to be an effective method for early diagnosis of pathologic changes after head trauma. However, its role is not clear especially after mild and moderate head injury.

In this study, we measured serum levels of BNP in patients with mild and moderate head trauma (GCS = 9–15), who had normal brain CT scans on ED arrival. Our aim was to know whether serum BNP level increases after such injuries or not. Patients were followed for their clinical changes until discharge time. Second brain CT scan obtained 24 h later for detecting subsequent injury-related intracranial pathologies. Finally, data analyzed and compared together.

We found that serum BNP level is significantly higher in victims of head trauma who have normal primary brain CT scan and abnormal delayed CT, rather than patients with normal delayed CT ($P < 0.01$). It means that they have a significant difference. Confidence interval = 95% was determined. When we defined cut-off point equal to 9 pg/ml for differentiating two groups, sensitivity = 83.3%, specificity = 73.9%, negative predictive value = 71.4%, and positive predictive value = 85% obtained for this test. Using ROC curve, the AUC = 0.804 was specified which was showed it is valuable as a diagnostic tool for differentiating two groups.

Sviri *et al*. in their research which was done in 2006, found that blood level of BNP increases following TBI. They evaluated BNP plasma concentration in 30 patients with severe isolated brain injury (GCS <8 on admission) in 4 time periods after the injury. BNP plasma concentrations were progressively elevated through days 7–8 after the injury in patients with diffused SAH as compared to patients with mild or no SAH ($P < 0.001$) and in patients with elevated ICP as compared to patients without elevated ICP ($P < 0.001$).[17] This was approved by Powner *et al*. in 2007 and Wu *et al*. researchers in 2011.[18,19]

In two other studies, it was seen that BNP plasma concentrations were significantly higher in patients with SAH.[22,23] Sviri *et al*. evaluate the relationship between BNP plasma concentration during the first 12 days following SAH and the development of cerebral vasospasm using 38 patients with spontaneous SAH. Results suggest that BNP secretion in SAH patients is closely related to the bleeding intensity and vasospasm severity as well as to development of delayed ischemic neurological deficit with a progressive and marked increase during the clinical course in patients who eventually develop cerebral ischemia. Berendes *et al*. investigated whether excess sodium secretion in patients with SAH is related to increased secretion of natriuretic peptides or to the presence of digoxin-like immunoreactive substances. They measured the plasma concentrations of digoxin-like immunoreactive substances and natriuretic peptides, aldosterone, renin, and antidiuretic hormone (by radioimmunoassay) in 10 patients with aneurysmal SAH, 10 patients undergoing elective craniotomy for cerebral tumors, and 40 healthy controls of similar age and sex distribution. According to findings salt-wasting of central origin may induce hypernatremia in patients with aneurysmal SAH, possibly as a result of increased secretion of BNP with subsequent suppression of aldosterone synthesis.

In opposite, Marx in 2010 suggested that serum BNP is not an adequate marker for determination of an ICH.[20] These authors measured serum BNP levels at presentation in 95 consecutive critically injured children (mean age, 6.4 years; 65% male) who presented to a single Level 1 pediatric trauma center in Los Angeles during 2008 and underwent brain CT. Patients with ICH had significantly higher rates of loss of consciousness than those without ICH (76% vs. 15%) and lower mean GCS scores (10.1 vs. 14.7). Mean BNP

levels did not differ significantly between patients with and without ICH.

Ali Demir in 2014 also reached to this result.[21] They investigate 162 patients who presented to the ED with minor brain injury were enrolled who were categorized into two groups as the cranial CT-negative and positive groups. There was no statistically significant difference between these two groups for serum BNP levels. This study suggested that serum BNP level was not used in defined of intracranial injury. Our results suggested that serum BNP was not an adequate marker for determination of an intracranial pathology in patients with minor head trauma.

Our study showed that after mild and moderate head trauma, even without obvious intracranial pathology apparent in brain CT scanning, serum BNP level can increase if the possibility of delayed pathologies be high. Taking second brain CT scans and comparing the mean of serum BNP levels in two groups with normal and abnormal second brain CT scans confirmed this theory.

BNP have a regulatory role in brain water and electrolyte content and were found in the different experimental animal model to reduce ICP and brain edema.[26,27] BNP can reduce systemic BP and decrease plasma volume. It can exacerbate cerebral blood flow reduction in patients with increased ICP. The exact mechanism of release of BNP and its role in the pathophysiology of brain injury is unknown. It can be the result of the cardiac release of BNP in response to sympathetic system-induced myocardial stress. However, the exact mechanism has not been defined. We were not able to determine the source of BNP release, and more researches should be done about this issue. Furthermore, the exact role of serum BNP increase after head trauma is not clear and more prospective studies should be done.

Cevik *et al*. in 2009 found that BNP levels more than 10 pg/ml may be effective and specific to detect intracranial pathologies in head trauma patients.[28] They investigated the diagnostic value of bedside measurement of BNP that is, used to predict the presence of intracranial pathologies in patients with head trauma. They used 3214 patients who were admitted to ED between January 01, 2004 and April 01, 2004 and 103 patients had a history of head trauma, and concluded 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 and BNP measurement might be useful in determining the indication of cranial CT scan in patients with head trauma.

We defined serum BNP level = 9 pg/ml as cut-off point for differentiating patients with head trauma and without intracranial pathologies in second brain CTs from patients with progressive lesions which is not apparent in the first brain CT.

Cevik *et al*. also has found that there is no statistically significant correlation 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. However, we proved the reverse; patients with improving clinical symptoms according to GCS level has lower levels of serum BNP.

We have some limitations in our study. There was not enough number of serum BNP kits in a hospital laboratory. We did not classify patients according to the type of pathologic findings in their brain CT. It is necessary to investigate the changes in serum BNP levels in each type of ICH in future studies. In addition, we studied mild and moderate head trauma patients, together. Studying each group of patients, separately, seems to be necessary.

CONCLUSION

We proved that serum BNP level is higher in patients with mild and moderate head trauma with delayed pathologic changes in second brain CT, relative to patients with mild and moderate head trauma and with normal delayed brain CT.

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Conflicts of interest
There are no conflicts of interest.

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