N-Terminal-Pro-Brain Natriuretic Peptide for The Differential Diagnosis of Hypovolemia vs. Euvolemia in Hyponatremic Patients

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Background: *Hyponatremia (serum sodium < 135 mEq/L) is the most common electrolyte abnormality in hospital and has impact on patient morbidity and mortality. The accuracy of volume status assessment is a major problem for the treatment planning especially to discriminate mild hypovolemic from euvolemic patients.*

Objective: *To examine the relationship between plasma N-Terminal-pro-Brain Natriuretic Peptide (NT-pro-BNP) level and extracellular water (ECW) status during the treatment of hyponatremia, as well as the cut-off value of plasma NT-pro-BNP in the differential diagnosis of volume status in hypovolemic vs. euvolemic hyponatremic patients.*

Material and Method: *Hyponatremic patients without clinical hypervolemia in Rajavithi Hospital were divided into the hypovolemic group and the euvolemic group according to ECW volume determined by bioimpedance analysis (BIA). Serum sodium, plasma NT-pro-BNP and ECW were assessed at the beginning, at the half correction of hyponatremia and at the end of treatment.*

Results: *Of the 26 patients, 18 (69.2%) were hypovolemic and 8 (30.8%) were euvolemic. Before treatment, NT-pro-BNP levels of the patients with hypovolemia was significantly lower than the patients with euvolemia [median (min, max)] (pg/mL) of hypovolemic vs. euvolemic group [114 (21, 6,803) vs. 1,509 (538, 8,541)] respectively (p < 0.001) and NT-pro-BNP levels change in the similar direction as ECW volume during the treatment. The best cut-off value of plasma NT-pro-BNP level to distinguish hypovolemic from euvolemic hyponatremia was 518 pg/ml with the sensitivity of 94.4% and the specificity of 100%.*

Conclusion: *Plasma NT-pro-BNP levels provide objective information with respection to volume status in hyponatremia patients and can be used in clinical diagnosis of hypovolemic vs. euvolemic hyponatremic hyponatremia.*

Keywords: *N-terminal-pro brain natriuretic peptide, Volume status, Hyponatremia*

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Hyponatremia (serum sodium < 135 mEq/L) is among the most common electrolyte abnormalities in clinical practice[1]. Both the disorder itself and its treatment can be associated with morbidity and mortality[2]. Accurate assessment of the volume status is a major problem and has a significant impact in the decision making for the treatment of hyponatremia.

Several different clinical assessment techniques have been used to assess volume status but none of those techniques is generally accepted and used. Bioimpedance analysis (BIA) has been recognized as a non-invasive and simple technique for the determination of body compositions including volume status but expensive[3].

Brain natriuretic peptide (BNP) is a natriuretic hormone initially identified in the brain but released primarily from the heart, particularly the ventricles in response to the high ventricular filling pressures[4]. BNP serves as an effective volume regulator and potentially be a biomarker reflecting volume status. BNP are elevated in disease stages which are associated with volume overload, such as heart failure[4, 5].

BNP is produced by cleavage of pro-BNP into BNP and the biologically inactive N-terminal pro-BNP (NT-pro-BNP), in normal subjects, the plasma concentrations of BNP and NT-pro-BNP are similar. However, in patients with LV dysfunction or heart failure, plasma NT-pro-BNP rises more than BNP, with NT-pro-BNP concentrations are approximately four-fold higher than BNP concentrations[6]. Plasma

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concentrations of NT-pro-BNP increase with renal failure[7] and are higher in women than men as well as older individuals[8] and NT-pro-BNP levels are lower in obese individuals[9].

Up to the present, no published studies have demonstrated the relationship of BNP or NT-pro-BNP level in hypovolemic or euvolemic patients. The purpose of the present study was to examine the relationship between plasma NT-pro-BNP level and extracellular water (ECW) status during the treatment of hyponatremia, as well as the cut-off value of plasma NT-pro-BNP in the differential diagnosis of volume status in hypovolemic vs. euvolemic hyponatremic patients.

Material and Method

The institutional ethical committee approved the present study and all patients gave written informed consent after reviewing a written summary of the present study plan. Hyponatremic patients who were admitted in Rajavithi Hospital were recruited from March 2009 to August 2009. Inclusion criteria were (1) serum sodium < 135 mEq/L (2) age > 18 years (3) stable vital sign and no sign of sepsis. The authors excluded the patients with (1) age > 80 years (2) glomerular filtration rate < 15 mL/min/1.73 m^2 according to the calculation formula of Cockcroft-Gault (3) pulmonary infection or (4) clinical hypervolemia (patients with generalized edema, ascites or heart failure).

After enrollment, the patients were divided into hypovolemic and euvolemic group according to the result of BIA. The patients with extracellular water (ECW) volume less than the lower limit of normal range were defined as hypovolemia, whereas, the patients with ECW volume higher than the lower limit were defined as euvolemia. The normal range of ECW volume of each patient was calculated by BIA program using patient's age, gender and body weight as inputs. For the purpose of comparison between the patients, ECW volume of each patient was expressed as normalized ECW (nECW) which defined as ECW/the lower limit of normal range of ECW of each patient. All the patients received standard treatment of hyponatremia including cause corrections, volume replacement for hypovolemic patients, free water restriction for euvolemic patients etc. Serum sodium levels, plasma NT-pro-BNP levels and ECW volume were measured at the study entry, at the half way of serum sodium correction and after the correction of serum sodium was completed. Blood samples were obtained from the patients in supine position and were carried in tubes containing EDTA for NT-pro-BNP analysis. Plasma NT-pro-BNP were determined by electrochemiluminescence immunoassay on the Elecsys 2010 analyzer (Roche diagnostics Corp, Hitachi) with an interassay coefficient of variation of 2.6% at 1,068 pg/mL and a measuring range from 5 to 35,000 pg/mL. The BIA data was obtained by a trained nurse using the Inbody S20 (Biospace, Thanes Development Co. Ltd). Impedance measurements were performed at the bedside in the supine position according to standard.

Statistical analysis

All analyses were performed using the SPSS statistical package, version 17.0 (SPSS Inc, Chicago, Illinois, USA). Variables those distributed normally were expressed as mean $\pm$ SD and the group comparisons were assessed by independent sample t-test. Variables which did not distribute normally were expressed as median (min, max) and the group comparisons were assessed by the Mann-Whitney U test and Chi-square test. Values of $p < 0.05$ were considered statistically significant. The diagnostic accuracy of plasma NT-pro-BNP level was analyzed using receiver operating characteristic (ROC) curve, sensitivity and specificity.

Results

Table 1 shows the demographics of the present study population. Of the 26 patients who were enrolled in the present study, 18 (69.2%) were considered hypovolemic and 8 (30.8%) were euvolemic according to bioimpedance and clinical assessment.

Mean serum sodium at the beginning of the present study in the hypovolemic and euvolemic group were 127.4 $\pm$ 3.6 mEq/L and 128.8 $\pm$ 4.1 mEq/L, respectively. Whereas mean serum sodium at the end of the present study in the hypovolemic and euvolemic group were 136.4 $\pm$ 3.3 mEq/L and 135.8 $\pm$ 2.5 mEq/L, respectively (Fig. 1).

Table 1. Baseline patient demographics that potentially effect on plasma NT-pro-BNP levels

Characteristics	Hypovolumic (n = 18)	Euvolumic (n = 8)	p-value
Age (years)	46.3 $\pm$ 22.0	54.0 $\pm$ 10.4	0.240
Gender (Male)	15 (83.3)	4 (50.0)	0.020
BW (Kg)	50.0 $\pm$ 10.0	53.4 $\pm$ 14.0	0.580
eGFR (mL/min/1.73 m^2)	78.2 $\pm$ 22.0	90.0 $\pm$ 32.3	0.370

Values are represented as n (%), Means $\pm$ SD

Before treatment, nECW of the patients with hypovolemia was significantly lower than the patients with euvolemia (median (min,max) nECW of hypovolemic vs. euvolemic group: 0.96 (0.72, 0.99) vs. 1.17 (1.07, 1.35) respectively ($p < 0.001$)). During the treatment, nECW of the patients with hypovolemia were increased, whereas nECW of the patients with euvolemia were decreased (Fig. 2).

Before treatment, NT-pro-BNP levels of the patients with hypovolemia were significantly lower than the patients with euvolemia (median (min,max) (pg/mL) NT-pro-BNP levels of hypovolemic vs. euvolemic group: 114 (21, 6,803) vs. 1,509.5 (538, 8,541) respectively ($p < 0.001$)). During the treatment NT-pro-BNP levels of the patients with hypovolemia were increased, whereas NT-pro-BNP levels of the patients with euvolemichypovolemia were decreased (Fig. 3).

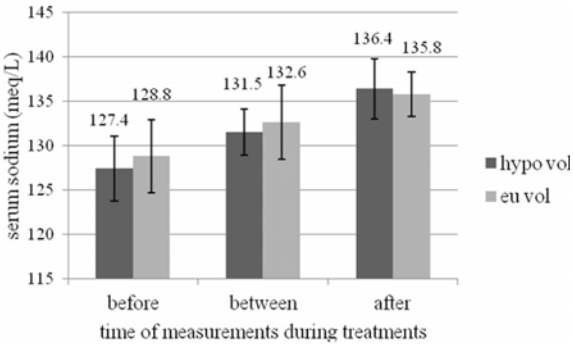

Fig. 1 Change in serum sodium levels (mEq/L) in hypovolemic vs. euvolemic hyponatremic patients before, between and after treatment. Bars represent means of serum sodium levels and the error bars represent 1 SD of serum sodium levels (hypovol = hypovolemic patients, euvol = euvolemic patients)

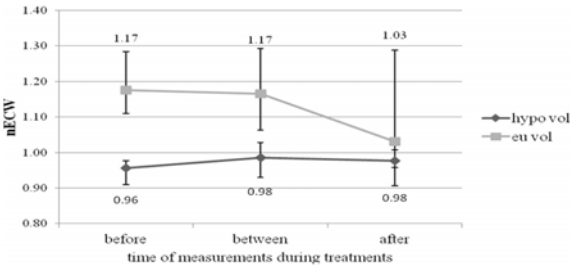

Fig. 2 Change in normalized extracellular water volume (nECW) in hypovolemic vs. euvolemic hyponatremic patients before, between and after treatment. Lines represent medians of nECW and the error bars represent 75 and 25 percentiles of nECV (hypovol = hypovolemic patients, euvol = euvolemic patients)

Therefore, NT-pro-BNP levels change in the similar direction as extracellular fluid volume during the treatment.

The best cut off value of plasma NT-pro-BNP level to distinguish hypovolemic from euvolemic hyponatremia was 518 pg/mL with the sensitivity of 94.4% and the specificity of 100% (Fig. 4).

Discussion

The presented is the pioneer study which demonstrates the association between plasma NT-pro-BNP level and volume status in the hyponatremic

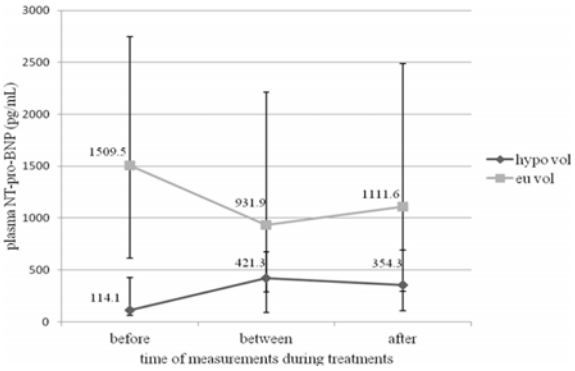

Fig. 3 Change in NT-pro-BNP levels (pg/mL) in hypovolemic vs. euvolemic hyponatremic patients before, between and after treatment. Lines represent medians of NT-pro-BNP levels and the error bars represent 75 and 25 percentiles of NT-pro-BNP levels (hypovol = hypovolemic patients, euvol = euvolemic patients)

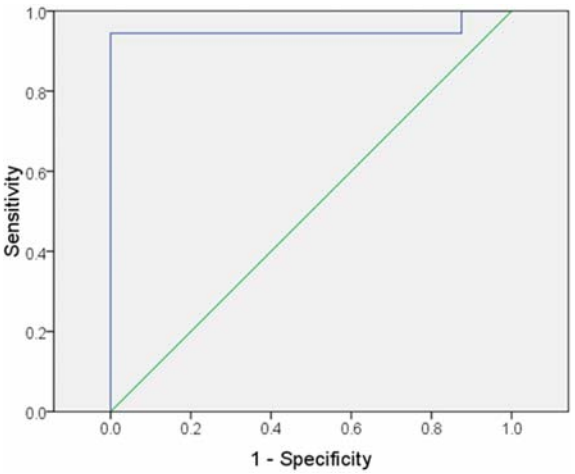

Fig. 4 Diagnostic accuracy of plasma NT-pro-BNP levels for discriminating hypovolemic vs. euvolemic hyponatremia by the ROC curve. Area under the ROC curve = 0.95

patients with hypovolemia or euvolemia. The authors founded that plasma NT-pro-BNP level changed in parallel to the extracellular fluid volume during the treatment of hyponatremia and also showed the best cut-off value of plasma NT-pro-BNP level to distinguish hypovolemic from euvolemic hyponatremia was 518 pg/mL with the sensitivity of 94.4% and the specificity of 100%.

Previous studies suggested that NT-pro-BNP level is elevated and could be used as an accurate tool to assess volume status of the patients with congestive heart failure and decreases significantly after the treatment of congestive heart failure condition[10-12], implying that plasma NT-pro-BNP level changes in parallel to the direction of patients' volume status similar to the finding in the present study even although there were the differences in volume status between the present study and previous studies.

As a results, plasma NT-pro-BNP can be used in diagnosis and assessments of volume status. However, the clinical application seems to be limited in some situations such as in the patients with extremely young or old age[8], severe renal failure[7,13,14], morbid obesity or pulmonary disease[9]. Therefore, the authors suggest using the plasma NT-pro-BNP level as the additional tool together with other assessments to reach the maximum accuracy. A recent study in the patients with congestive heart failure demonstrated that there was a high variability in the serial NT-proBNP measurement results[15]. But, such information in the patients with hypovolemic or euvolemic hyponatremia is not available yet. Finally, no consensus has yet been reached concerning the definition of "normal" NT-pro-BNP concentration in hyponatremia patients. The issue requires further investigation.

Some limitations of the present study should be mentioned. First, the present study had a small sample size. Secondly, there is no generally accepted cut-off value of body water volume for the diagnosis of hypovolemia vs. euvolemia.

Conclusion

Plasma NT-pro-BNP levels provide objective information with respection to volume status in hyponatremia patients and can be used in clinical diagnosis of hypovolemic vs. euvolemic hyponatremic hyponatremia.

Acknowledgement

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Potential conflicts of interest

None.

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การใช้ระดับ N-Terminal-Pro-Brain Natriuretic Peptide ในเลือดเพื่อจำแนกภาวะขาดสารน้ำออกจากภาวะสารน้ำในร่างกายปกติในผู้ป่วยที่มีภาวะโซเดียมในเลือดต่ำ

สกานต์ บุนนาค, กัมพล พัฒนสมบัติสกุล

ภูมิหลัง: *ภาวะโซเดียมในเลือดต่ำ (ซีรัมโซเดียม < 135 mEq/L) เป็นความผิดปกติของเกลือแร่ในเลือดที่พบบ่อยที่สุดในผู้ป่วยที่รักษาตัว ในโรงพยาบาลและมีความสัมพันธ์กับการเพิ่มอัตราการเจ็บป่วยและเสียชีวิต การประเมินภาวะสารน้ำในร่างกายให้ถูกต้องมีส่วนสำคัญในการวางแผนการรักษาโดยเฉพาะอย่างยิ่งระหว่างผู้ป่วยที่ขาดสารน้ำไม่รุนแรงกับผู้ป่วยที่มีภาวะสารน้ำปกติซึ่งทำได้ยากและมีโอกาสผิดพลาดสูงแต่มีแนวทางในการรักษาแตกต่างกัน*

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ระหว่างระดับ N-Terminal-pro-Brain Natriuretic Peptide (NT-pro-BNP) ในเลือดและปริมาณสารน้ำในร่างกายระหว่างการรักษาภาวะโซเดียมในเลือดต่ำ และหาระดับของ NT-pro-BNP ที่เหมาะสมใช้ในการจำแนกผู้ป่วยที่ภาวะขาดสารน้ำออกจากผู้ป่วยที่ภาวะสารน้ำในร่างกายปกติ*

วัสดุและวิธีการ: *ทำการศึกษาในผู้ป่วยที่รับการรักษาแบบผู้ป่วยใน ในโรงพยาบาลราชวิถีที่มีภาวะโซเดียมในเลือดต่ำและไม่มีภาวะน้ำในร่างกายเกินจากการตรวจร่างกาย โดยผู้ป่วยจะถูกแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มที่มีภาวะขาดสารน้ำและกลุ่มที่มีสารน้ำปกติโดยพิจารณาจากปริมาณสารน้ำนอกเซลล์ ซึ่งวัดและจำแนกโดย bioimpedance analysis (BIA) หลังจากนั้นผู้ป่วยจะได้รับการตรวจระดับโซเดียมและ NT-pro-BNP ในเลือด และปริมาณสารน้ำนอกเซลล์ ทันทีก่อนเริ่มการรักษา ระหว่างครึ่งทางของการรักษา และหลังการรักษาภาวะโซเดียมในเลือดต่ำ*

ผลการศึกษา: *ผู้ป่วยที่ทำการศึกษาทั้งหมด 26 คน แบ่งออกเป็นผู้ที่มีภาวะขาดสารน้ำ 18 คน (69.2%) และผู้ป่วยที่มีภาวะสารน้ำปกติ 8 คน (30.8%) ก่อนการรักษาผู้ป่วยที่มีภาวะขาดสารน้ำมีระดับ NT-pro-BNP ต่ำกว่าผู้ป่วยที่มีภาวะสารน้ำปกติอย่างมีนัยสำคัญทางสถิติ โดย median(min, max) ของระดับ NT-pro-BNP (pg/mL) ในผู้ป่วยที่มีภาวะขาดสารน้ำและผู้ป่วยที่มีภาวะสารน้ำปกติเท่ากับ 114 (21, 6803) และ 1509.5 (538, 8541) ตามลำดับ ($p < 0.001$) และการเปลี่ยนแปลงของระดับ NT-pro-BNP ในเลือดมีความสัมพันธ์ไปในทิศทางเดียวกันกับปริมาณสารน้ำนอกเซลล์ พบว่าระดับของ NT-pro-BNP ที่เหมาะสมใช้ในการแยกผู้ป่วยที่ภาวะขาดสารน้ำออกจากผู้ป่วยที่ภาวะสารน้ำในร่างกายปกติคือ 518 pg/mL โดยมี sensitivity เท่ากับ 94.4% และมี specificity เท่ากับ 100%*

สรุป: *ในผู้ป่วยที่มีภาวะโซเดียมในเลือดต่ำ ระดับ N-Terminal-pro-Brain Natriuretic Peptide (NT-pro-BNP) ในเลือดมีความสัมพันธ์ไปในทิศทางเดียวกันกับปริมาณสารน้ำนอกเซลล์ในร่างกายและสามารถนำมาใช้ช่วยจำแนกผู้ป่วยที่ภาวะขาดสารน้ำออกจากผู้ป่วยที่ภาวะสารน้ำในร่างกายปกติ*