Is Brain Natriuretic Peptide a Reliable Biomarker of Hydration Status in All Peritoneal Dialysis Patients?

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Key Words

Hydration status · Brain natriuretic peptide · Bioimpedance spectroscopy · Peritoneal dialysis

Abstract

Background: Achievement of euvolemia is a fundamental challenge in the peritoneal dialysis (PD) population. Bioimpedance spectroscopy (BIS) is one of the best techniques for routine assessment of hydration status (HS) in PD, but in recent years, the role of brain natriuretic peptides (BNP) in the assessment of volume status has gained interest. The aim of this study was to investigate the relation between BNP and volume status as measured by BIS in PD patients and to assess how these variables correlate according to the time that a patient has been on PD. **Methods:** We prospectively studied 68 PD patients from whom measurements of BNP and assessments of HS by BIS were performed every 3 months. Three groups were defined based on HS: group A, measurements of HS <−1.1 liters (underhydrated); group B, measurements of HS between −1.1 and +1.1 liters (normohydrated), and group C, measurements of HS >+1.1 liters (overhydrated). Measurements were also separated according to

the time on PD (<6 vs. ≥6 months). Correlation between HS and BNP was performed using Spearman's correlation. **Results:** We performed a total of 478 measurements of HS and BNP. There was a statistically significant difference in BNP ($p < 0.001$) among three HS groups, with higher levels of BNP detected in overhydrated patients. We found a positive correlation between HS and BNP ($r_s = 0.28$; $p < 0.001$) that seemed stronger in the first 6 months on PD ($r_s = 0.42$; $p = 0.006$). **Conclusions:** BNP correlated positively with fluid overload measured by HS, and this correlation was stronger in the first 6 months on PD.

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Introduction

The assessment and achievement of an optimal body volume status ('dry weight') in peritoneal dialysis (PD) patients is extremely complex. A validated definition of 'dry' or ideal body weight for PD patients does not exist. Krediet [1] suggested to define optimal volume status as the weight associated with a normal extracellular water (ECW), however this complex determination depends on

the specific methods utilized that are costly and not readily available. An alternative, effective technique to assess extracellular, intracellular and total body water (TBW) is bioelectrical impedance analysis (BIA) [2]. BIA is a non-expensive and non-invasive technique that has shown to be reproducible, easy to perform and accurate [3, 4]. At the present, bioelectrical impedance vector analysis (BIVA) or bioelectrical impedance spectroscopy (BIS) are probably among the best tools to perform an 'everyday' assessment of hydration status (HS) on PD patients [2, 5]. However, this measurement does require training and time to perform. Ideally, serum biomarkers of volume status could supplement this measurement.

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-pro-BNP) provide strong prognostic information in patients with heart failure, stable coronary artery disease and acute coronary syndrome [6]. In chronic kidney disease (CKD), their concentrations are often elevated due to high prevalence of ventricular dysfunction and hypertrophy, but also because of impaired renal clearance [7]. These molecules have been extensively associated with increased cardiovascular and overall mortality in hemodialysis and PD patients [8–12]. Their association with fluid overload was also studied in the last decade [13–16], but many questions regarding their usefulness for assessment of dry weight remain [17].

The aim of the present study was to investigate the relationship between BNP levels and volume status measured by BIS in a PD population and to assess how these variables might change and correlate with the time that a patient has been performing PD.

Methods

Study Design and Data Collection

We prospectively collected data on PD patients from a single North-East Italian Center between January 2009 and January 2012. All adult, prevalent and incident PD patients were eligible. Exclusion criteria included the presence of any class of heart failure defined by the New York Heart Association classification, history of major cardiovascular events, limb amputation and pacemaker or defibrillator implantation. Evaluation of HS by BIS and blood sampling for determination of the serum BNP levels were performed every 3 months, during scheduled routine visits. Measurements of HS were performed by BIS with Body Composition Monitor® (BCM) (Fresenius Medical Care, Bad Homburg, Germany): patients were in a supine position and after appropriate skin cleaning, electrodes were placed on ipsilateral foot, ankle, hand and wrist. BNP analysis was performed by chemiluminescence immunoassay with Siemens Centaur XP® device (Diamond Diagnostics, Holliston, Mass., USA). Both HS and BNP measurements were performed in the same day, with dialysate dwelling in the abdomen.

Additional data was collected, including demographics, etiology of CKD, duration of renal replacement therapy and PD, PD modality and use/dose of furosemide. The institutional review board waived the need for informed consent due to the non-interventional nature of the study and the normal application of the methods in the clinical routine for patient care.

Definitions

The HS was determined by BCM and expressed as HS in liters. According to BIS HS, three groups of hydration were defined based on the reference ranges for human body composition from previous studies [18]: group A (underhydration) included measurements with HS <−1.1 liters, group B (euvolemia) included measurements with HS between −1.1 and +1.1 liters, and group C (overhydration) included measurements with HS >+1.1 liters. We also performed a separate analysis according to the time on PD: for this purpose we separated the measurements performed in patients on PD for <6 months from the ones performed in patients on PD for a period ≥6 months.

Statistical Analysis

The normality of data was assessed by the Kolmogorov-Smirnov test. Continuous variables are expressed as mean ± SD or median (interquartile range) and compared between any two groups using a t test or Mann-Whitney U test, and among three groups using analysis of variance or Kruskal-Wallis H test, as appropriate. Categorical variables are expressed as number of cases and proportion and compared with the Mantel-Haenszel χ^2 test or Fisher's exact test. A Spearman's rank order correlation was run to determine the relationship between BNP and HS. All statistical analyses were performed using the SPSS 17.0 software package (SPSS, Inc., Chicago, Ill., USA), with a two-sided p value <0.05 considered as statistically significant.

Results

During the study period, 175 patients were treated with PD and 68 of them were eligible and enrolled in the study. A total of 478 measurements of BNP and HS were performed, representing a mean of 7 measurements per patients (minimum of 2 and maximum of 12). Patient characteristics are shown in table 1. The median age was 63 years (43–71) and 52.9% were male. The median duration of PD in non-incident patients was 25 (14–46) months. The modality of treatment was automated PD in 33.8% and continuous ambulatory PD in 66.2%.

Of the 478 measurements performed, 270 (56.5%) indicated HS >+1.1 liters, while 177 (37.0%) were found between −1.1 and +1.1 liters, and 31 (6.5%) had values of HS <−1.1 liters.

There was a statistically significant difference in BNP levels between HS groups ($p < 0.001$) with a mean rank of 178.9 pg/ml for group A, 215.2 pg/ml for group B, and 262.4 pg/ml for group C (fig. 1).

Fig. 1. Mean BNP levels obtained at each assessment.

The median HS measured during the first 6 months on PD was higher than the median HS after 6 months of treatment. The difference of HS between these two groups was statistically significant with a mean rank of 288.3 pg/ml for the former and of 234.8 pg/ml for the last ($p = 0.016$), while no statistically significant difference in BNP levels was found ($p = 0.663$) (table 2).

Using Spearman's rank order correlation, we found a significant positive correlation between BNP levels and HS considering the entire sample ($p < 0.001$) and also when separate analysis was performed for the subgroups and according to time on PD. The correlation was much stronger in the group with shorter PD duration <6 months (table 3).

Discussion

The achievement of euvolemia in PD patients is a fundamental measure of care since volume overload is an independent predictor of mortality in this population [10]. However, the measurement of volume status is not easy in PD patients, despite the availability of several methods that have been developed to help clinicians [19].

In the cohort studied, for more than 50% of the BIS measurements, the HS was higher than +1.1 liters. Simi-

Table 1. Baseline characteristics of the population at the time of the first assessment

Age, years	63 (43–71)
Male gender	36 (52.9%)
Caucasian	63 (92.6%)
Incident patients <3 months	19 (27.9%)
Duration of RRT, months	17 (2–45)
Duration of PD, months	17 (2–40)
Duration of PD on non-incident patients, months	25 (14–46)
Patients on PD ≥ 24 months	25 (36.8%)
Urine volume/24 h, ml	900 (325–1,575)
Anuric	12 (17.6%)
Cause of CKD	
Diabetic nephropathy	14 (20.6%)
Nephrosclerosis	20 (29.4%)
Glomerulonephritis	10 (14.7%)
ADPKD	12 (17.6%)
Others	5 (7.4%)
Unidentified	7 (10.3%)

PD characteristics

Predominant PD modality	
APD	23 (33.8%)
CAPD	45 (66.2%)
Use of furosemide	53 (77.9%)
Daily dose of furosemide (mg) for patients who used furosemide	312.5 (200–500)

RRT = Renal replacement therapy; ADPKD = autosomal dominant polycystic kidney disease; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis.

larly, the median HS defined by BIS was always >+1.1 liters, regardless if the measurements were performed before 6 months or after a period of 6 months on PD, indicating that more than half of these patients had fluid overload during the study (table 2). This is not surprising as a high prevalence of fluid overload in PD patients was also found by other authors [20, 21]. Importantly, this finding is associated with increased mortality [10].

After the division of the groups by HS, we found that BNP levels were higher in HS group C (overhydrated) and lower in HS group A (underhydrated) and the difference between the three HS groups was statistically significant ($p < 0.001$). This observation seems to confirm that higher levels of BNP are present in overhydrated patients independently of their cardiac status. In the Spearman's rank order correlation, BNP levels and HS positively correlated. Other authors have also established a positive correlation between natriuretic peptides and HS in PD patients. Gangji et al. [14], in a cross-sectional

Table 2. Comparison between HS and BNP levels according to the time on PD on the day of the assessment

	Median HS, liter		p	Median BNP, pg/ml		p
<6 months (n = 42)	1.9	288.3	0.016	75	248.4	0.663
≥6 months (n = 436)	1.4	234.8		87.5	238.7	

Table 3. Spearman's rank order correlation between HS and BNP according to the time on PD on the day of the assessment

	All measurements BNP	Measurements performed on PD	
		BNP, <6 months	BNP, ≥6 months
HS	$r_s = 0.28$; $p < 0.001$	$r_s = 0.42$; $p = 0.006$	$r_s = 0.26$; $p < 0.001$

study of 22 PD patients, showed that NT-pro-BNP levels positively correlate with ECW/TBW ratio ($r_s = 0.45$; $p = 0.04$). More recently, in a larger cohort, Papakrivopoulou et al. [16] demonstrated that the patients in the highest NT-pro-BNP quartile had increased ECW/TBW ratio. An interesting finding of the present study is the fact the correlation between BNP and HS was less robust when all the assessments were included, but its strength increased if the data of the first 6 months of treatment was considered separately (from $r_s = 0.28$ to $r_s = 0.42$). This may be related to the fact that during the early period after the initiation of PD, patients tend to be more overhydrated and over time, their volume status improves. An alternative explanation would be that over time, overhydrated PD patients develop cardiac changes that render BNP a less effective biomarker for volume status. Serial echocardiographic findings are needed to assess this possibility. Finally, changes in peritoneal transport characteristics or decreases in residual renal function may account for these time-dependent changes in the operational characteristics of BNP measures.

The usefulness of natriuretic peptides in the diagnosis of volume status and cardiovascular risk has been studied in recent years and debate still exists on whether they represent reliable biomarkers in the assessment of volume status in CKD patients. For PD in particular, some authors found a positive correlation between natriuretic peptides and HS [14, 16], while others could not establish a relationship, but instead found a positive correlation with left ventricle mass index and a negative correlation

with left ventricle ejection fraction [22]. Furthermore, NT-pro-BNP has shown to have a high negative predictive value for the presence of systolic dysfunction [23] and to be associated with overall and cardiovascular mortality [9–11]. A limitation is that most of the studies that established correlations are cross-sectional and with relative small populations. Furthermore, the time patients were on PD was highly variable in those cohorts and the same is true for ours, representing a limitation of the study due to heterogeneity of the studied population. Possibilities to test a more homogeneous population are either to use only incident patients or to divide the studied population based on treatment duration. With time, peritoneal transport characteristics change [24] contributing to changes in ultrafiltration that can be detected in the follow-up. Additionally, residual renal function deteriorates over time and is accompanied by more adverse cardiovascular, inflammatory, nutritional and metabolic profiles with increased mortality [25]. Because of these changes that occur in PD patients over time, we analyzed the correlation between BNP and HS considering PD duration and we concluded that this correlation is stronger in the first months of treatment. As follow-up duration increases, BNP concentration may be elevated mainly due to higher prevalence of cardiovascular disease and less because of fluid overload.

Our study has several strengths, including a large number of measurements and prospective analysis. Considering the possible changes in PD patients over time, the separate analysis according to time on PD increased the strength of our results. We also recognize some limitations in our study, namely the lack of information on cardiovascular indexes. We did exclude patients with symptoms of heart failure, but we cannot rule out the possibility that they have structural alterations in the myocardium that may contribute to BNP elevations. Since our exclusion criteria were only based on clinical symptoms and without measured cardiovascular indexes, we must consider our results as hypothesis-generating concepts. Multiple factors influence BNP levels among dialysis patients, including fluid overload,

hypertension and left ventricular hypertrophy. Additionally, BNP tends to accumulate with decreased renal clearance and renal replacement therapies, including PD, contribute to the removal of these molecules, adding more complexity to this issue and complicating the interpretation of BNP levels in this population. The lack of knowledge of BNP clearance by PD is a limitation of our work, similarly to other authors that have studied BNP in PD patients.

In conclusion, this study demonstrates that BNP correlates positively with fluid overload and this correlation seems to be stronger in the first months of treatment. Larger cohorts and analysis by more homogeneous subgroups are still required to better establish the real impact of BNP as a marker of fluid overload. However, in circumstances where the volume status may be uncertain, BNP measurements may serve as additional clinical information to make change in the PD prescription.

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