N-Terminal Pro–Brain Natriuretic Peptide in Prevalent Peritoneal Dialysis Patients

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Previous reports have shown that N-terminal pro–brain natriuretic peptide (NT-Pro-BNP) is a predictive marker for mortality in both peritoneal dialysis (PD) and hemodialysis (HD) patients. The aim of the present study was to clarify whether NT-Pro-BNP reflects a specific status in PD patients.

We analyzed 40 stable PD patients, allocating them to one of two groups (20 each) according to the median value of NT-Pro-BNP: group A below and group B above 5423 pg/mL. In group B as compared with group A, red blood cell (RBC) counts, hemoglobin, hematocrit, sodium, chlorine, albumin, and daily urinary volume were significantly lower, and cardiothoracic ratio (CTR) and daily ultrafiltration volume were significantly higher. Patients using icodextrin and diabetic patients showed significantly higher NT-Pro-BNP values. We observed significant correlations between NT-Pro-BNP and RBC count, hematocrit, hemoglobin, sodium, chlorine, albumin, lactate dehydrogenase, CTR, daily urinary volume, and ultrafiltration volume. Multiple regression analysis revealed that increasing CTR and hyponatremia were significant predictors of an increase in NT-Pro-BNP.

Our results indicate that increased serum NT-Pro-BNP well reflects anemia status, water balance, hyponatremia, and hypoalbuminemia in prevalent PD patients.

Key words

N-Terminal pro–brain natriuretic peptide, cardiothoracic ratio, hydration status, anemia

Introduction

In cardiac tissue, brain natriuretic peptide (BNP) is synthesized as 134–amino acid precursor (pre pro-BNP), which is cleaved by proteases to form a 26–amino acid signal peptide and a 108–amino acid pro-BNP. Proteolytic digestion of pro-BNP results in formation of 76–amino acid N-terminal pro-BNP (NT-Pro-BNP) and biologically active 32–amino acid BNP hormone molecule (1).

Compared with BNP, NT-Pro-BNP has the advantage of having a longer plasma half-life and lower biologic variation (2). The proBNP and NT-Pro-BNP both circulate in human plasma and have been proposed as excellent markers for early diagnosis of left ventricular (LV) dysfunction and of possible cardiac complications in patients with heart failure. Moreover, increased levels of NT-Pro-BNP are recognized as a new and useful biochemical marker that is predictive of clinical outcomes in patients with congestive heart failure (3). Previous reports also have shown that NT-Pro-BNP is a predictive marker for mortality in both peritoneal dialysis (PD) and hemodialysis (HD) patients (4,5). We therefore used cross-sectional observation to investigate whether NT-Pro-BNP reflects a specific status in PD patients.

Patients and methods

We analyzed 40 stable PD patients who we allocated to one of two groups (20 patients each) according to the median value of their serum NT-Pro-BNP concentration: group A, below 5423 pg/mL (range: 194 – 5357 pg/mL), and group B, above 5423 pg/mL (range: 5489 – 35,000 pg/mL). Table I shows the characteristics of the patients in the two groups.

Intergroup comparisons were performed for patient demographic, hematologic, biochemical, and PD-related parameters and for cardiothoracic ratio (CTR) calculated from a chest radiograph, daily ultrafiltration (UF) volume, daily urinary volume (UV), systolic and diastolic blood pressure (BP), and body weight (BW). Clotted blood samples were collected for measurement of NT-Pro-BNP, β_2-microglobulin (β2MG),

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blood urea nitrogen (BUN), serum creatinine, Na, K, Cl, Ca, phosphate (IP), total protein (TP), albumin, total cholesterol (Tcho), intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin, hematocrit, and blood glucose on study enrollment. Total Ca was corrected relative to the patient's albumin level. Serum NT-Pro-BNP was quantified by electro-chemiluminescence immunoassay on the EClusys 2010 analyzer (Roche Diagnostics K.K., Tokyo, Japan). The cut-off used was 125 pg/mL (taken from the manufacturer's package insert). The detection limit is 5 – 35,000 pg/mL. For samples with NT-Pro-BNP concentrations above the measuring range, the final concentrations were taken as 35,000 pg/mL.

Statistics

All data with a normal distribution are presented as mean ± standard deviation. Differences between

TABLE 1 Background of the patients in groups A and B

Characteristic	*N-Terminal pro–brain natriuretic peptide*		p *Value*	
	Group A (<5423 pg/dL)	*Group B (>5423 pg/dL)*		
Age (years)	56.3±11.5	59.5±13.5	0.424	NS
Male sex (%)	50	50	0.755	NS
Body weight (kg)	54.5±10.5	52.2±11.2	0.576	NS
PD duration (days)	1287±1438	1694±1275	0.35	NS
Complementary HD (%)	5	25	0.08	NS
Extraneal[a] use (%)	40	85	0.004	
Diabetes mellitus (%)	15	50	0.02	
Cardiothoracic ratio (%)	42.0±3.1	49.3±4.9	<0.001	
Daily ultrafiltration (mL)	479±312	814±501	0.029	
Daily urinary volume (mL)	643±467	290±298	0.029	
Systolic BP (mmHg)	126±21	137±27	0.187	NS
Diastolic BP (mmHg)	74±15	75±19	0.837	NS
WBC count (/μL)	6605±1839	6930±2442	0.637	NS
RBC (10^4/μL)	336±50	298±54	0.027	
Hemoglobin (g/dL)	10.4±1.5	9.3±1.6	0.027	
Hematocrit (%)	31.3±4.4	27.7±4.7	0.017	
Platelets (10^4/μL)	24.0±9.4	22.5±7.7	0.579	NS
BUN (mg/dL)	52.9±9.4	50.0±11.3	0.384	NS
Creatinine (mg/dL)	10.4±2.8	10.4±2.6	0.979	NS
Na (mEq/L)	139±3	135±5	0.012	
K (mEq/L)	4.2±0.5	3.8±0.7	0.079	NS
Cl (mEq/L)	101±5	97±4	0.011	
Ca (mg/dL)	9.3±1.1	8.8±0.8	0.695	NS
Corrected Ca (mg/dL)	9.8±1.0	9.7±0.8	0.695	NS
P (mg/dL)	5.3±1.2	5.2±1.5	0.688	NS
Total protein (g/dL)	6.4±0.8	6.2±0.8	0.388	NS
Albumin (g/dL)	3.4±0.5	3.1±0.5	0.037	
Total cholesterol (mg/dL)	183±28	184±42	0.906	NS
ALP (U/L)	313±166	484±337	0.05	NS
LDH (U/L)	226±91	263±90	0.203	NS
Blood glucose (mg/dL)	108±20	120±40	0.236	NS
β_2-Microglobulin (mg/L)	24.9±6.8	28.4±8.7	0.23	NS
Intact PTH (pg/mL)	333±321	169±125	0.064	NS
NT-Pro-BNP (pg/mL)	2327±1720	22 673±12 380	—	

[a] Baxter Healthcare, Tokyo, Japan.

HD = hemodialysis; BP = blood pressure; WBC = white blood cell; RBC = red blood cell; BUN = blood urea nitrogen; ALP = alkaline phosphatase; LDH = lactate dehydrogenase; PTH = parathyroid hormone; NT pro-BNP = N-Terminal pro–brain natriuretic peptide.

groups were examined using the Student *t*-test or Mann–Whitney *U*-test. The Pearson product-moment correlation coefficient was used to assess baseline correlation between NT-Pro-BNP and each parameter. Multiple regression analysis was also adopted to determine the important factors causing increased NT-Pro-BNP concentrations. A value of 0.05 was used to determine statistical significance.

Results

Table I summarized the clinical parameters and demographics of the patients. The groups allocated according to the median value of NT-Pro-BNP did not differ significantly in terms of age, sex, PD duration, systolic and diastolic BP, or BW. A higher presence of diabetes mellitus (DM) was seen in a group B. The use of icodextrin-containing solution (Extraneal: Baxter Healthcare, Tokyo, Japan) in group B was also higher than that in group A.

Patients using icodextrin showed remarkably high levels of NT-Pro-BNP [Figure 1(A)], and the presence of DM was also associated with a high value of NT-Pro-BNP [Figure 1(B)]. The percentage CTR and daily UF volume were remarkably higher in group B, but the daily UV was lower in group B.

With regard to blood results in group A as compared with group B, RBC counts and levels of hemoglobin, hematocrit, Na, Cl, and albumin were significantly lower in a group B than in group A. Counts of WBCs and platelets, and values of K, IP, Ca (and corrected Ca), BUN, creatinine, β2MG, TP, Tcho, and LDH showed no significant difference between the groups. Table II shows the correlation between NT-Pro-BNP and PD-related parameters. Corrected Ca had no relationship with NT-Pro-BNP. A multiple regression analysis revealed that CTR (standardized coefficient $\beta = 0.536$, $p = 0.002$) and sodium ($\beta = -0.402$, $p = 0.017$) were significant predictors for NT-Pro-BNP levels.

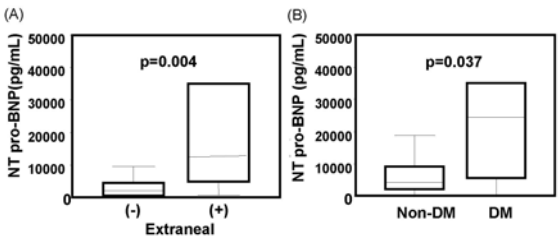

FIGURE 1 Concentrations of N-terminal pro–brain natriuretic peptide (NT-pro-BNP) in patients based on (A) icodextrin (Extraneal: Baxter Healthcare, Tokyo, Japan) use and (B) presence of diabetes (DM). Use of icodextrin and presence of DM was higher in group B than in group A. Patients using icodextrin showed remarkably high levels of NT-pro-BNP. The presence of DM resulted in high values of NT-pro-BNP.

Discussion

In patients with end-stage renal disease (ESRD), cardiovascular disease is recognized as the leading cause of mortality. Although traditional risk factors such as elevated low-density lipoprotein, hypertension, diabetes mellitus, and smoking account for a substantial percentage of the risk factor profile in the general population, in patients with ESRD, these traditional risk factors are limited in their ability to predict future events (6). Therefore, nontraditional risk factors such as BNP, C-reactive protein, serum albumin, and numerous others have been investigated.

Reasons other than impaired renal clearance are still not clear, but in ESRD patients undergoing dialysis therapy, levels of NT-Pro-BNP are almost always markedly raised (4,5). Importantly, despite the massive elevation of NT-Pro-BNP concentrations in HD patients, Madsen *et al.* showed that NT-Pro-BNP nevertheless correlated with LV hypertrophy (LVH) and reduced LV ejection fraction (5). Their results suggested that the massively elevated concentrations of NT-Pro-BNP were in part based on the same parameters seen in patients without renal insufficiency.

Lee *et al.* reported that NT-Pro-BNP levels also correlated with LV mass index and LV ejection fraction in CAPD patients (7). Although NT-Pro-BNP was

TABLE II Significant correlation in peritoneal dialysis–related parameters with N-terminal pro–brain natriuretic peptide

Parameter	*Coefficient*	p *Value*
RBCs	–0.435	0.005
Hemoglobin	–0.457	0.003
Hematocrit	–0.452	0.003
Na	–0.36	0.023
Cl	–0.33	0.037
Albumin	–0.443	0.004
LDH	0.353	0.026
Cardiothoracic ratio	0.738	<0.001
Daily urinary volume	–0.421	0.036
Daily ultrafiltration	0.408	0.018

RBCs = red blood cells; LDH = lactate dehydrogenase.

recognized as a good marker of cardiac impairment and a predictor for mortality, it has been subjected not been widely studied in PD patients. In chronic PD patients, few reports show NT-Pro-BNP as an important predictor of risk for cardiovascular congestion, mortality, and adverse cardiovascular outcomes or as adding important prognostic information beyond that contributed by LV hypertrophy, systolic dysfunction, and other conventional risk factors (4,5,7). We therefore investigated which patients statuses might be linked to serum concentration of NT-Pro-BNP in PD patients.

In our study, the presence of DM and of icodextrin use was associated with higher NT-Pro-BNP levels. To interpret this finding, we hypothesized that more patients with worse heart disease might be included in a group B and that additional use of icodextrin solution in PD patients with volume overload might be useful. Although our results indicated that hyponatremia could be a predictor for increased levels of NT-Pro-BNP, we believe that this association is at least partly a result of group B including more icodextrin users, because hyponatremia is a well-known effect of icodextrin use (8), naturally resulting from dilution by volume overload. In addition, CTR was also found to be a very likely predictor for NT-Pro-BNP. Thus, a CTR of more than 50% or hyponatremia may signify the presence of abnormal LV function.

Determination of a patient's NT-Pro-BNP concentration is not recommended as a routine part of the evaluation for structural heart disease. But a CTR of more than 50% or hyponatremia in patient undergoing PD might be a useful signal to examine the patient's NT-Pro-BNP levels, with a more careful diagnostic approach being taken with patients who have massively elevated NT-Pro-BNP levels.

Several limitations of our study should be considered. First, we did not ask patients detailed questions about episodes of cardiovascular congestion or cardiovascular disease. Second, fluid status was not fully assessed at the time of enrollment. Third, we did not evaluate cardiac disease or LV function by electrocardiography or echocardiography at the same time that other parameters were measured.

Conclusions

Our study revealed that serum concentrations of NT-Pro-BNP well reflect anemia, hyponatremia, hypoalbuminemia, and water removal in prevalent PD patients. In addition, we quantitatively proved by multiple regression analysis that CTR and hyponatremia might be useful as predictors for serum NT-Pro-BNP levels. Although NT-Pro-BNP has considerable prognostic potential, evaluation of its role in treatment and monitoring remains to be determined. Considering the limitations of our study, further investigation is needed.

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