Role of Chronic Use of Tolvaptan in Patients with Heart Failure Undergoing Peritoneal Dialysis

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In the present study, we assessed the effect of chronic tolvaptan treatment and compared it with the effect of conventional treatment without tolvaptan. In addition, changes in cardiac load and body fluid composition were compared.

The study enrolled 22 patients undergoing peritoneal dialysis who had been receiving tolvaptan for more than 1 year and 10 patients undergoing peritoneal dialysis who had been treated with conventional diuretics. Left ventricular mass index (LVMI), left ventricular ejection fraction (LVEF), and E/e' index were measured by echocardiography at baseline and after 12 months of tolvaptan treatment (or an equivalent period). Body composition was analyzed by bioimpedance monitoring (BIM).

In the tolvaptan group, LVMI was significantly reduced after 12 months of treatment; in the conventional-treatment group, it was significantly increased. The measured LVEF did not change in the tolvaptan group, but it increased significantly in the conventional-treatment group. The E/e' index was not altered in either group; however, it was reduced in patients receiving tolvaptan whose initial E/e' was greater than 15. Although urine volume was not significantly increased in either group, renal creatinine clearance increased significantly in tolvaptan group; no change was observed in the conventional-treatment group. Renal and peritoneal Kt/V did not significantly change during the study. In both groups, β_2-microglobulin was significantly and similarly increased. Extracellular water (ECW) and intracellular water (ICW) as determined by BIM were both reduced after 12 months of tolvaptan treatment. We observed a significant correlation between the ratio of ECW to total body water at the initiation of tolvaptan and the reduction in ECW after 12 months.

Our results indicate that chronic tolvaptan treatment has a beneficial role in body fluid control without a reduction in cardiac and renal function. Volume control depends on an equal reduction in ECW and ICW, which can also have a benefit in avoiding hyponatremia.

Key words
Left ventricular mass index, body composition, bioimpedance

Introduction

Volume overload is a major concern for heart failure patients undergoing peritoneal dialysis (PD), affecting both morbidity and mortality (1). Loop diuretics have been widely used for the reduction of body fluid. However, several concerns—such as enhancement of the renin–angiotensin system, reduced renal flow, renal injury, hypokalemia, and hypocalcemia—have been associated with the use of loop diuretics, especially furosemide (2).

Tolvaptan is now being used for body fluid control in patients with heart failure. The benefits of tolvaptan in heart failure have been postulated as better maintenance of the renin–angiotensin system, vasopressin, catecholamine, circulation such as renal flow and blood pressure, and electrolytes (3,4). Tolvaptan has been shown to have a beneficial role for body fluid control in heart failure patients undergoing PD. Tolvaptan significantly increased urine volume in 8 of 12 such patients for up to 3 months. Renal function improved after tolvaptan treatment, without alteration

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of peritoneal function. Although tolvaptan is a water diuretic, an increase in urinary excretion of Na was observed (5). However, the mechanism by which chronic tolvaptan treatment plays a beneficial role in body fluid control in heart failure patients has not been fully elucidated. In the present study, we therefore examined the effects of tolvaptan treatment and compared them with the effects of conventional treatment without tolvaptan. In addition, changes in cardiac load and body fluid composition were compared.

Methods

This retrospective observational study enrolled 22 patients undergoing PD who had received tolvaptan for more than 1 year and 11 patients undergoing PD who had been treated with conventional diuretics.

All patients agreed to, and gave written informed consent for, echocardiography and body composition measurement by bioimpedance monitoring [BIM (InBody S10: InBody, Seoul, Korea)]. The study protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine, Sendai, Japan. Solutions for PD contained either 1.5% or 2.5% D-glucose or icodextrin as the osmotic agent. Patients used 1500 mL – 2000 mL of dialysis solution per exchange.

Clinical parameters

Once monthly, samples of blood and urine were collected from the patients and body composition was measured by BIM. Brain natriuretic peptide, blood urea nitrogen, creatinine, and Na were measured in serum, and urinary creatinine and urine volume were measured using the 24-hour urine samples.

Echocardiography

A 2-dimensional M-mode transthoracic color Doppler echocardiographic examination was performed at baseline and after 12 months of tolvaptan treatment (or an equivalent period) by a sonographer who was not involved in the study. Left ventricular mass (LVM) was calculated using the method reported by Devereux and Reichek (6):

$$\text{LVM (in grams)} = 1.04 \times [(\text{LVDd} + \text{PWTd} + \text{IVSTd})^3 - \text{LVDd}^3] - 13.6.$$

where LVDd is the left ventricular end-diastolic dimension, PWTd is the posterior wall thickness at end diastole, and IVSTd is the interventricular septal thickness at end-diastole.

The LVM index (LVMI) was calculated as the LVM divided by body surface area, which was calculated using the equation set out by Du Bois and Du Bois (7):

$$\text{Body surface area} = W^{0.425} \times H^{0.725} \times 0.007184.$$

In addition, the left ventricular ejection fraction (LVEF) and the ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e′) were also determined by echocardiography.

Bioimpedance measurement

Body composition analysis was performed using BIM, and the volume change at each measurement was determined. Measurements were made with PD fluid in place. The PD fluid volume at the time of BIM measurement was constant for all patients. Using multiple broadband frequencies in the range 1 kHz – 1000 kHz, ICW, ECW, and total body water (TBW) were determined.

Statistical analysis

Data were analyzed using the JMP statistical software (pro version 11 for Windows: SAS Institute, Cary, NC, U.S.A.). Data are presented as mean ± standard deviation. The Student t-test or a correlation test was used to compare the means of the continuous variables with normal distribution. Values of p less than 0.05 were considered statistically significant.

Results

Table I shows the characteristics of the patients. The 22 patients who received tolvaptan consisted of 14 men and 8 women (21 on continuous ambulatory PD, 1 on automated PD). The 10 patients receiving conventional treatment without tolvaptan consisted of 6 men and 4 women (9 on continuous ambulatory PD, 1 on automated PD). Average age in the groups was 64 ± 19 years and 62 ± 19 years respectively, and dialysis vintage was 5.2 ± 7.5 months and 10.4 ± 2.0 months respectively. Of the 22 patients in the tolvaptan group, 17 (77%) had diabetes; 4 of the 10 patients in the conventional-treatment group (40%) were diabetic. Before starting tolvaptan treatment, all patients in the latter group had received Na-sparing diuretics. Icodextrin dialysate was being used by

3 patients in the tolvaptan group and 2 patients in the conventional-treatment group.

We first analyzed cardiac function as measured by echocardiography. As Figure 1(A) shows, LVMI was significantly reduced in the tolvaptan group after 12 months of treatment; in the conventional-treatment group, LVMI was significantly increased. In the tolvaptan group, LVEF did not change; however, it increased significantly in the conventional-treatment group [Figure 1(B)]. The E/e′ index was not altered in either group overall [Figure 1(C)]; however, it was reduced in patients of the tolvaptan group who had a baseline E/e′ greater than 15 [Figure 1(D)]. Although neither group showed a significant increase in urine volume [Figure 2(A)], renal creatinine clearance increased significantly in the tolvaptan group; no change was observed in the conventional-treatment group [Figure 2(B)]. Renal [Figure 2(C)] and peritoneal [Figure 2(D)] Kt/V did not significantly change during the study. In both groups, serum β_2-microglobulin increased significantly and similarly [Figure 2(E)]. During the study, neither serum Na nor systolic blood pressure changed in the two groups [Figure 2(F,G)].

As determined by BIM, ECW and ICW were both reduced after 12 months of tolvaptan treatment [Figure 3(A,B)]. Those results suggest that tolvaptan decreases both ICW and ECW. Dividing the ICW or ECW by TBW yields a ratio that indicates water

TABLE I Characteristics of the study patients

Variable	*Treatment group*	
	Tolvaptan	*Conventional*
Patients (*n*)	22	10
Mean age (years)	64±19	62±19
Sex (*n* men:women)	14:8	4:6
Mean PD vintage (months)	5.2±7.5	10.4±2.0
With diabetes (*n*)	17	4
Receiving furosemide (*n*)	20	10
Receiving spironolactone (*n*)	16	6

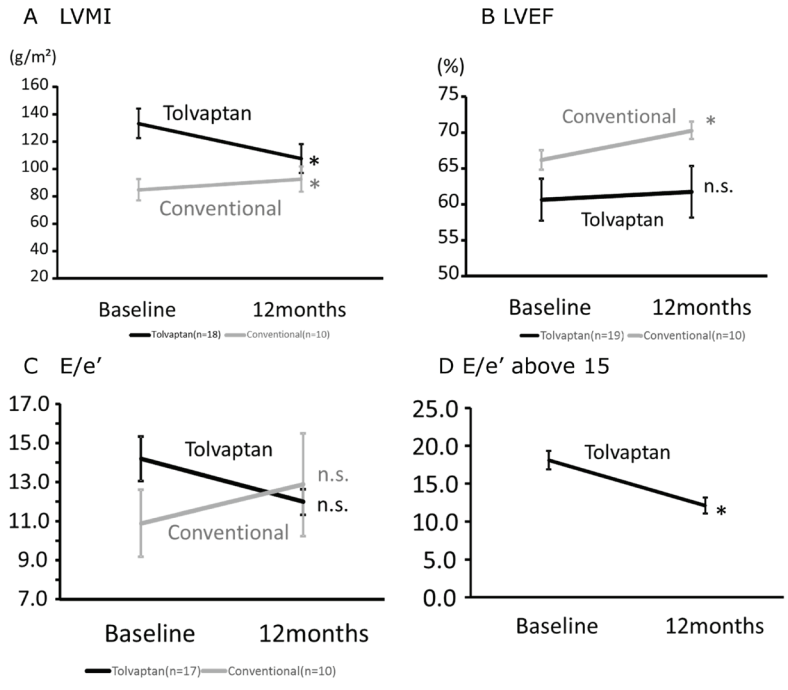

FIGURE 1 Cardiac function determined by echocardiography at baseline and at 12 months after tolvaptan treatment: (A) left ventricular mass index (LVMI), (B) left ventricular ejection fraction (LVEF), (C) ratio of early mitral inflow velocity to mitral annular early diastolic velocity (E/e′), and (D) E/e′ > 15. Results are presented as mean ± standard error. *$p < 0.05$.

balance, and dividing the TBW by height squared (TBW/height^2) yields the adjusted TBW. The ratio ECW/TBW is widely used as an indicator of edema. The ICW/ECW ratio was calculated to determine the balance of water composition and movement between the intracellular and extracellular spaces. An increase in the ICW/ECW ratio indicates movement of water from the ECW to either the ICW or outside the body. In contrast, a decline in the ICW/ECW ratio indicates water movement from the ICW

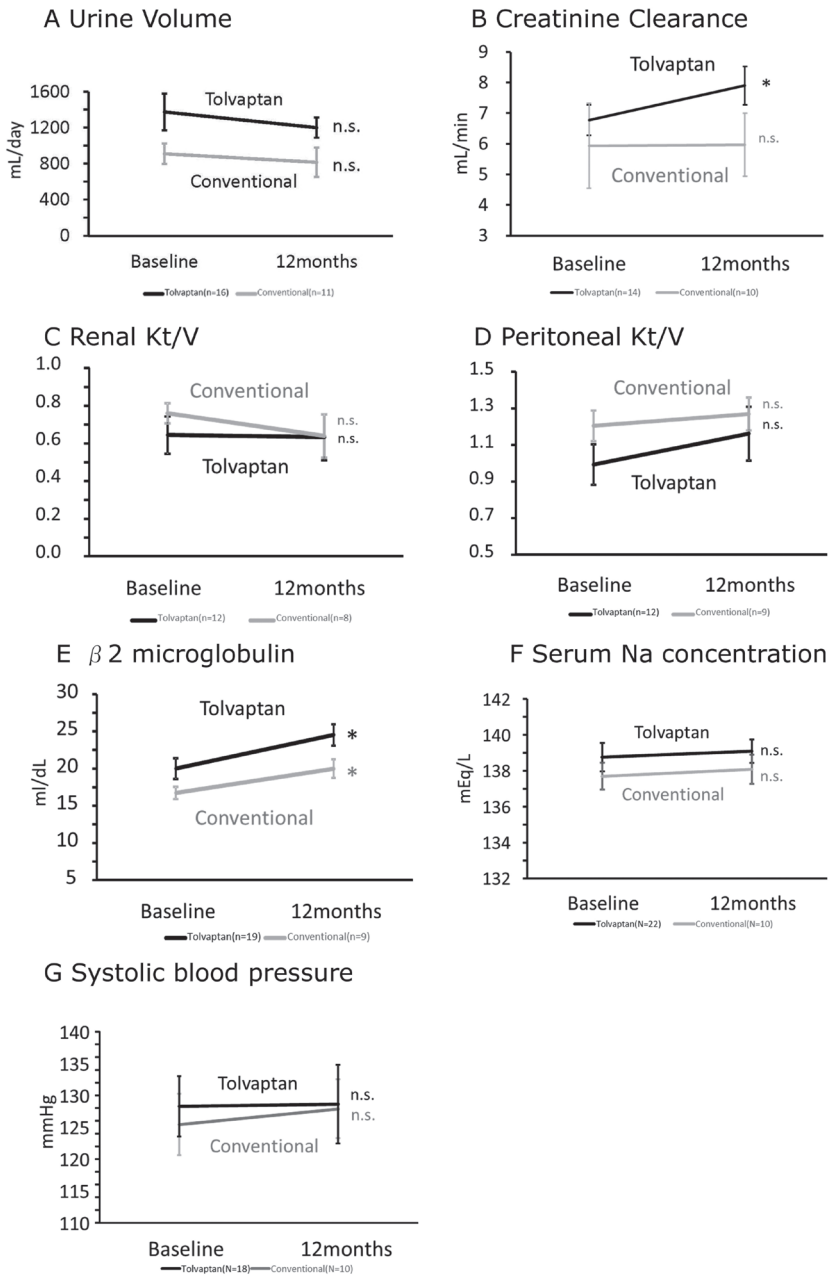

FIGURE 2 Renal parameters at baseline and at 12 months after tolvaptan treatment. Results are presented as mean ± standard error. *$p < 0.05$.

to the ECW. We observed a significant correlation between ECW/TBW at the initiation of tolvaptan and a reduction in TBW/height^2 and ECW after 12 months of treatment [Figure 3(C,D)], indicating that TBW and ECW decreased in patients with volume overload (edema) in the extracellular space. Baseline ECW/TBW correlated with an increase in ICW/ECW [Figure 3(E)], suggesting that tolvaptan decreases ECW in patients who have extracellular volume overload. In contrast, a significant correlation was observed between baseline ICW/TBW and reduction in ICW/ECW [Figure 3(F)], indicating that patients with intracellular volume overload experienced a higher incidence of ICW-to-ECW movement.

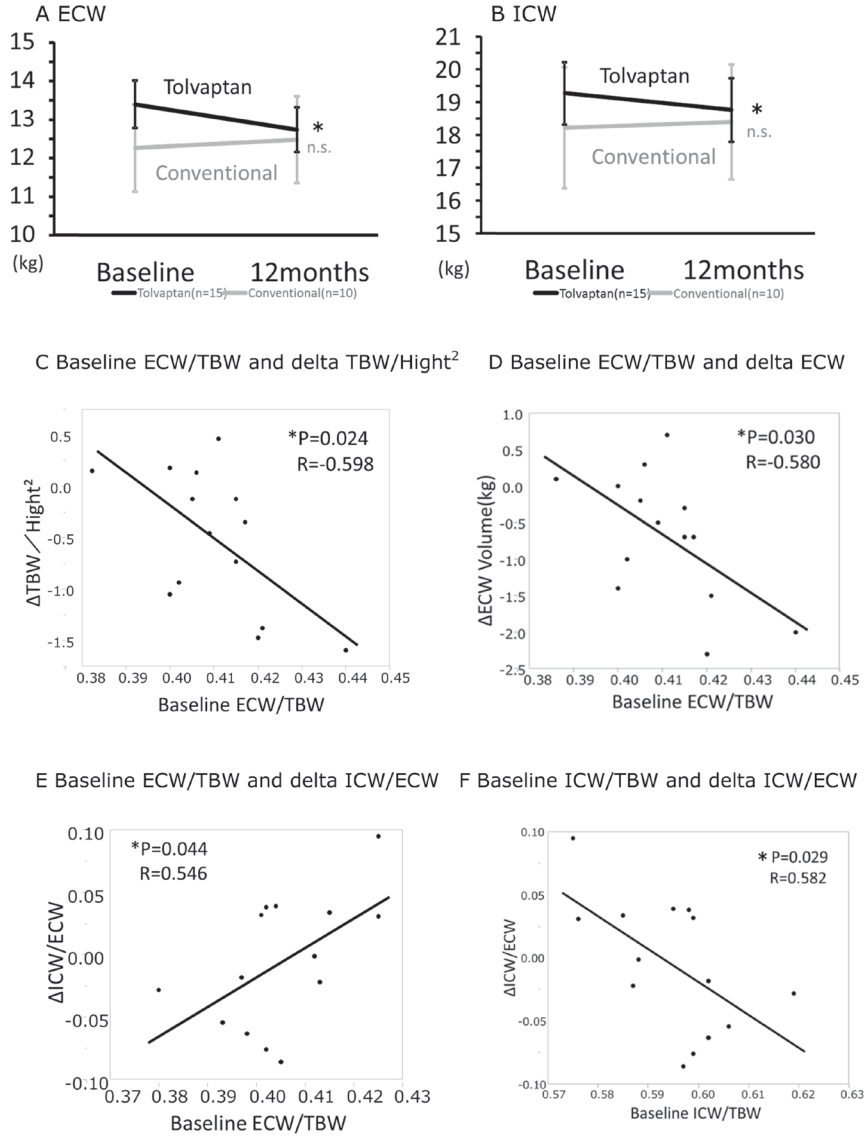

FIGURE 3 Bioimpedance monitoring of body composition at baseline and at 12 months after tolvaptan treatment: (A) extracellular water (ECW), (B) intracellular water (ICW), (C) association between baseline ECW/TBW and ΔECW volume, (D) association between baseline ECW/TBW and ΔICW/TBW, (E) association between baseline ICW/TBW and ΔICW/ECW. Results are presented as mean ± standard error of the mean. *$p < 0.05$.

Discussion

Results from the present study demonstrate that LVMI is reduced with chronic tolvaptan treatment and that no change is observed after conventional therapy without tolvaptan. Tolvaptan also improved left ventricular diastolic dysfunction, as indicated by the E/e′ index, in patients with a worse E/e′ index at baseline. In patients treated with tolvaptan, ICW and ECW were both decreased, without a reduction in residual renal function or peritoneal function. No significant changes in serum Na were observed during the study. Those results indicate a beneficial role for chronic tolvaptan treatment in body fluid control. The novel finding in the present study was the movement of body water with tolvaptan treatment, which was demonstrated by BIM in patients undergoing PD.

Chronic tolvaptan treatment and cardiac function

Higher cardiovascular mortality has been reported in patients with end-stage renal disease (8). Left ventricular hypertrophy has been used as a predictor for cardiovascular death in end-stage renal disease (9). Compared with patients on hemodialysis or on PD for less than 5 years, those on PD for more than 5 years have been reported to have a higher LVMI and higher blood pressure (10). We previously reported that, in PD patients, morning blood pressure is associated both with TBW by BIM and with LVMI (11). Given that blood pressure was not significantly altered in the present study (data not shown), body water might have been involved in the changes of LVMI. Body fluid control by PD has also been shown to be beneficial for the reduction of LVMI without altering residual renal function. Oba *et al.* (12) showed that patients using icodextrin PD solution experienced a reduced LVMI over 12 months; no change was observed in patients not using icodextrin. Ultrafiltration by icodextrin correlated with changes in LVMI, indicating that ultrafiltration is responsible for improving cardiac function. Interestingly, in the latter study, the changes in LVMI were almost identical to those associated with tolvaptan in the present study, which also suggests the role of volume control in regulating LVMI.

Assessment of body fluid by BIM during tolvaptan treatment

Assessment by BIM is a beneficial tool for maintaining body fluid control and nutrition status in PD (11,13,14). Reductions in ICW and ECW were successfully achieved with tolvaptan in the present study. The ICW/ECW ratio by BIM has been shown to be useful for the differential diagnosis of hyponatremia in nondiabetic patients undergoing PD (15). Hyponatremia is a predictor for cardiovascular events and mortality in PD (16,17). Extracellular water decreases because of Na loss with ultrafiltration and increases because of loss of residual renal function or ultrafiltration failure (15). Results in the present study demonstrate that tolvaptan moves water from the intracellular to the extracellular compartment when the ICW volume is high. On the other hand, TBW declined when tolvaptan was applied in patients with a high ECW volume. Malnutrition and chronic inflammation lower ICW. Changes in ECW or ICW can result in hyponatremia. Tolvaptan increases excretion mostly of free water, which could increase crystalloid osmolality in the blood vessels and absorb water from the intracellular compartment. Thus, its use is expected to reduce both ICW and ECW and to avoid hyponatremia, which accords with the results of the present study. Thus, tolvaptan also avoids the collapse of vascular fluid and maintains renal flow (3), which could result in better-maintained residual renal function, as was also observed in the present study.

Limitations of the study

This report describes a single-facility retrospective observational study. The comparison groups were not fully matched, and some of the observations for the groups differ because of missing data. Also, the number of the subjects was not large enough to exclude the possibility of selection bias. Multicenter randomized controlled studies are required in future.

Conclusions

The present study suggests that chronic treatment with tolvaptan could have a beneficial role in body fluid control without a reduction in cardiac and renal function. Volume control depends on an equal ECW and ICW reduction, which has the additional benefit of avoiding hyponatremia and adverse effects on residual renal function.

Disclosures

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