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【 ORIGINAL ARTICLE 】

Tolvaptan Reduces Extracellular Fluid per Amount of Body Fluid Reduction Less Markedly than Conventional Diuretics

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Abstract:

Objective Tolvaptan, a vasopressin V2 receptor antagonist, is a water diuretic, removing electrolyte-free water from the kidneys and affecting the water balance between the intracellular and extracellular fluid. We previously reported that tolvaptan efficiently reduced the intracellular fluid volume, suggesting its utility for treating cellular edema. Furthermore, tolvaptan is known for its low incidence of worsening the renal function, with conventional diuretics use associated with worsening of the renal function

Methods In this retrospective observational study, five chronic kidney disease (CKD) patients with fluid retention were assessed by the bioelectrical impedance (BIA) method twice (before and after tolvaptan therapy). Tolvaptan was used with conventional diuretics. The post/pre ratio of extracellular water (ECW)/total body water (TBW) in the tolvaptan group was compared with that in 18 CKD patients undergoing body fluid reduction with conventional diuretics alone (conventional diuretics groups), taking the reduced amount of body fluid into consideration.

Results Removing body fluid, either by tolvaptan or by conventional diuretics alone, decreased the ECW/TBW ratio. Of note, the reduction in extracellular fluid was milder in the tolvaptan group than in the conventional diuretics group.

Conclusion Tolvaptan reduces the extracellular fluid per amount of body fluid reduction less markedly than conventional diuretics.

Key words: tolvaptan, conventional diuretics, intracellular fluid (ICF), extracellular fluid (ECF), bioimpedance, worsening of renal function

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Introduction

Arginine vasopressin regulates water balance. Tolvaptan, a vasopressin V2 receptor antagonist, belongs to the water diuretics class, removing electrolyte-free water from the kidneys and reducing body fluid. We previously reported that whether or not tolvaptan can reduce the body weight by ≥5% in one week can be predicted based on the urine osmolarity before use (1). Tolvaptan also affects the water balance between the intracellular fluid (ICF) and extracellular fluid (ECF) (2, 3). We previously reported that tolvaptan was able to efficiently reduce intracellular water (ICW) in reducing the amount of body fluid, suggesting that tolvaptan might be a good treatment option for cellular edema (4).

Furthermore, tolvaptan is known for its low incidence of worsening the renal function, with conventional diuretics use associated with worsening of the renal function (5-7). This difference is mainly explained by the notion that the intravessel volume is better preserved and intravessel hypovolemia less likely to occur when using tolvaptan than when using conventional diuretics. However, supporting evidence remains scarce, although a few reports have investigated the ECF by a bioelectrical impedance analysis (BIA) (8-11).

We therefore investigated the effect of tolvaptan on the ECF, taking the amount of reduced body fluid into consideration, and compared the findings with those achieved with conventional diuretics.

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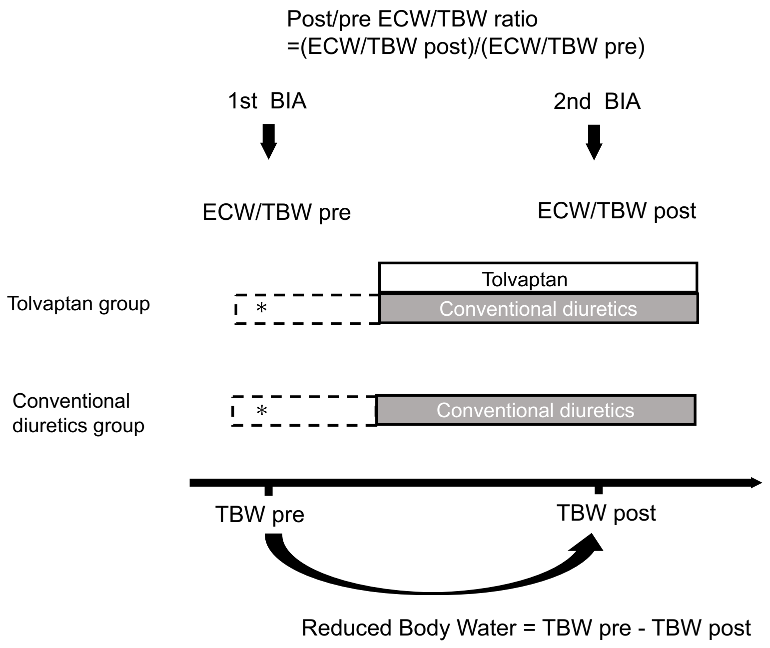

Figure 1. The protocol of the present study. *It does not matter whether or not conventional diuretics were used at the first BIA in the tolvaptan group and conventional diuretics group.

Materials and Methods

We performed a retrospective observational study to non-invasively investigate the change in the ECF by a BIA (12, 13). When assessing the ECF by a BIA in general, assessing the parameter "extracellular water (ECW)" in the BIA instrument is usual, so we used the parameter "ECW" to monitor the ECF.

We enrolled chronic kidney disease (CKD) inpatients with fluid retention in the Department of Nephrology of Osaka National Hospital who underwent a bioimpedance measurement at least twice between July 2016 and July 2018. Patients in whom a BIA had been conducted immediately after a meal, those in whom a BIA had been conducted immediately after albumin fraction solution had been administered intravenously, and those with systemic traumatic injury were excluded. Finally, five patients who started tolvaptan administration between the first and second BIA were enrolled as the tolvaptan group. In addition, 18 patients who underwent the second BIA measurement under the prescription of conventional diuretics and who had not been administered tolvaptan at the first or second BIA measurements constituted the conventional diuretics group. In the tolvaptan group, tolvaptan was used together with conventional diuretics to remove overhydrated water. In the present study, some patients changed their conventional diuretics prescription after the first BIA measurement. Therefore, the conventional diuretics at the first BIA measurement and those at the second BIA measurement were not identical in some patients.

Fig. 1 shows the protocol of the present study. Reduced body water was defined as the total body water at the 1st BIA - the total body water at the 2nd BIA. We focused on the post/pre ECW/total body water (TBW) ratio, defined as (ECW/TBW post)/(ECW/TBW pre), and used it to investigate the differences in the distributional change in the amount of body fluid when the body fluid was reduced between the tolvaptan group and conventional diuretics group. Bioelectrical impedance was measured using an InBody 720 (Biospace, Tokyo, Japan).

Statistical analyses were performed using the JMP software program (ver. 14; SAS Institute Japan, Tokyo, Japan). To discern a difference in the slopes of regression lines, we performed a covariance analysis.

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). All patients were allowed to opt out of participation. The need for informed consent was waived via the opt-out method of our hospital website. The institutional review board (IRB) of National Hospital Organization Osaka National Hospital approved this study, and the opt-out method was adopted instead of obtaining informed consent (IRB Number 18053).

Results

The patients' characteristics [age (years), sex, estimated glomeruler filtration rate (GFR) (mL/min/1.73 m^2)] at the first BIA were as follows: median 83 [interquartile range 75-85], 3 women and 2 men, and 13 [12-17] for the tolvaptan group and 75 [64-81], 6 women and 12 men, and 17 [11-24] for the conventional diuretics group, respectively (Table 1). Changes in the use of diuretics and in the clinical parameters in the tolvaptan group and conventional diuretics group are shown in Tables 2 and 3, respectively.

When data were plotted with the body water reduction on

Table 1. Patient Characteristics of Tolvaptan Group and Conventional Diuretics Group.

	Tolvaptan group	Conventional diuretics group	p value
n	5	18	
Age, yo	83 (75, 85)	75 (64, 81)	0.1674
F/M	3/2	6/12	0.2798
eGFR, mL/min/1.73m^2	13 (12, 17)	17 (11, 24)	0.4777
Na, mEq/L	143 (141, 145)	142 (140, 144)	0.5982
Alb, g/dL	2.1 (1.8, 2.7)	3.3 (2.4, 3.8)	0.0438
Underlying disease			
Heart failure	2 (40)	2 (11)	0.1316
Diabetes mellitus	2 (40)	9 (50)	0.6921
Nephrotic syndrome	2 (40)	4 (22)	0.4232
Unknown	0 (0)	6 (33)	0.1332

Median (interquartile range), number (%), Alb: albumin

Table 2. Summary of Diuretics Used in Tolvaptan Group and Conventional Diuretics Group.

	Tolvaptan group	Conventional diuretics group	p value
Tolvaptan dose at 1st BIA (mg)	Zero	Zero	1.0000
Tolvaptan dose at 2nd BIA (mg)	15 (11, 15)	Zero	<0.0001
Conventional diuretics at 1st BIA			
Furosemide	2 (40)	8 (44)	0.8592
Azosemide	3 (60)	11 (61)	0.9641
Trichlormethiazide	0 (0)	3 (17)	0.3276
Spironolactone	0 (0)	4 (22)	0.2461
Conventional diuretics at 2nd BIA			
Furosemide	3 (60)	9 (50)	0.6921
Azosemide	3 (60)	11 (61)	0.9641
Trichlormethiazide	1 (20)	4 (22)	0.9151
Spironolactone	2 (40)	4 (22)	0.4232

Median (interquartile range), number (%). BIA: bioelectrical impedance analysis

Table 3. Changes in the Clinical Parameters in Tolvaptan Group and Conventional Diuretics Group.

	Tolvaptan group	Conventional diuretics group	p value
BW at 1st BIA (kg)	61.5 (51.8, 76.1)	58.0 (48.8, 69.3)	0.6818
BW at 2nd BIA (kg)	50.8 (46.5, 73.2)	59.8 (49.0, 68.8)	0.6547
TBW at 1st BIA (L)	38.3 (30.9, 42.4)	34.3 (29.4, 42.1)	0.5022
TBW at 2nd BIA (L)	32.1 (29.4, 38.5)	34.4 (28.7, 39.9)	0.9703
ECW/TBW at 1st BIA	0.438 (0.418, 0.445)	0.413 (0.405, 0.428)	0.0622
ECW/TBW at 2nd BIA	0.424 (0.416, 0.438)	0.411 (0.402, 0.416)	0.0401
Reduced TBW (L)	2.9 (-0.05, 7.2)	1.4 (0.1, 2.3)	0.2634
Reduced BW (kg)	3.1 (2.8, 9.15)	1.35 (0.275, 2.325)	0.0058
Post/pre ratio of ECW/TBW	0.988 (0.972, 0.995)	0.986 (0.978, 1.001)	0.8521
Days between the two BIA measurements (days)	8 (7-30)	8 (7-11)	0.6495

Median (interquartile range). BW: body weight, BIA: bioelectrical impedance analysis, ECW: extracellular water, TBW: total body water

the x-axis and post/pre ECW/TBW ratio on the y-axis, the slope was negative in both groups (Fig. 2). However, the slope was shallowed in the tolvaptan group (-0.003393) than in the conventional diuretics group (-0.007085) with statistical significance (p=0.0427).

Discussion

The present study clearly indicates two important novel findings. First, the more the total body water is reduced, the

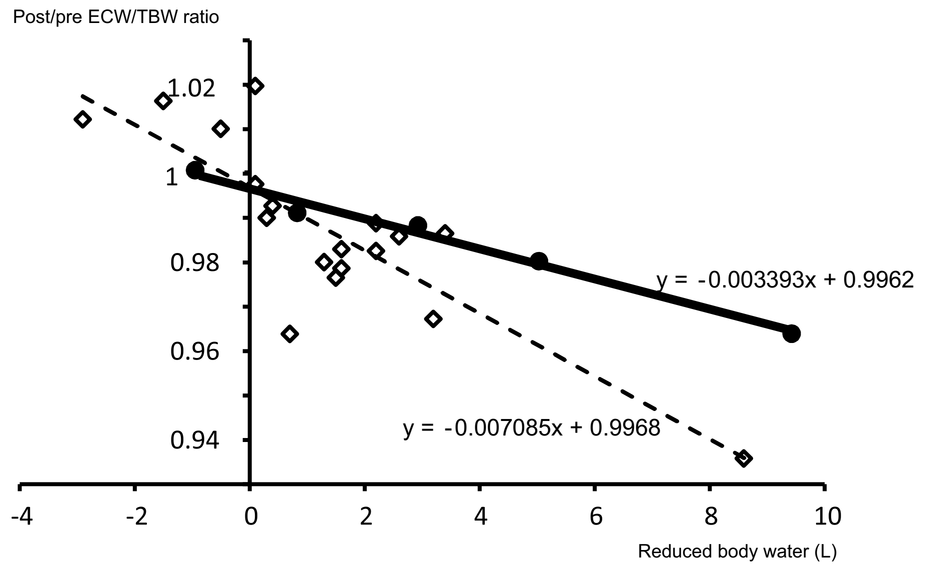

Figure 2. The relationship between the post/pre ECW/TBW ratio and reduced body water in the tolvaptan and conventional diuretics groups. Tolvaptan group (●), Conventional diuretics group (◇). A regression analysis demonstrated a linear relationship between the post/pre ECW/TBW ratio and body water reduction in each group. The regression lines and R^2 values were as follows: Y=-0.003393X+0.9962, R^2=0.985 for the tolvaptan group (solid line) and Y=-0.007085X+0.9968, R^2=0.700 for the conventional diuretics group (dotted line). There was a significant difference in the slopes of the regression lines between the groups (p=0.0427). The body water reduction in the tolvaptan group resulted in a milder decrease in the post/pre ECW/TBW ratio than in the conventional diuretics group.

more the ECF rate (ECF/TBW) decreases. This held true in both the tolvaptan group and the conventional diuretics group. Second, in reducing body water, the ECF reduction rate per the reduction in body water was milder in the tolvaptan group than in the conventional diuretics group. Our considering the reduced body water when analyzing the ECF rate is a novel point of this study.

The present study investigated the relationship between the post/pre ECW/TBW ratio [(ECW/TBW post)/(ECW/TBW pre)] and reduced body water while comparing the tolvaptan and conventional diuretics groups.

(1) We did not focus on the change rate of ECW(%)=ECW post/ECW pre but instead focused on the change rate of ECW/TBW=(ECW/TBW post)/(ECW/TBW pre).

(2) We focused on the factor of "reduced body water." We found that the more the body water was reduced, the more the post/pre ECW/TBW ratio decreased. This held true in both the tolvaptan and conventional diuretics groups.

(3) We compared a tolvaptan group and a conventional diuretics group.

(4) The slope for the post/pre ECW/TBW ratio per amount of body water reduction was significantly shallower in the tolvaptan group than in the conventional diuretics group.

These 4 points, especially (2) and (4) in our analysis, are novel points that have not been addressed in previous reports (4, 8-11).

Compared with conventional diuretics that actively remove sodium from the ECF for excretion and are less likely to shift water from the ICF to the ECF in terms of osmolality, the electrolyte free-water diuretic tolvaptan tries to upregulate the plasma sodium concentration, is more likely to shift water from the ICF to ECF via slightly upregulated osmolarity in the ECF, and tries to maintain the ECF volume. However, *in vivo*, each event happens in series, so separating these events is difficult. This would be the mechanism underlying the milder ECF reduction with tolvaptan than with conventional diuretics.

According to a recent report (10) that investigated tolvaptan as a single-arm study, the serum albumin level was positively and significantly correlated with the changes in the ECW (%) when tolvaptan was used. Furthermore, the serum albumin levels were lower in high responders [defined as those whose change in TBW <-6.02% (median) of the tolvaptan arm] than low responders (change in TBW ≥ -6.02% of the tolvaptan arm). In that report, high responders of tolvaptan were patients who attained a greater decline in ECW% with tolvaptan than low responders. When we focused on the association between the post/pre ECW/TBW ratio and the serum albumin concentration, we found that the higher the albumin concentration, the higher the post/pre ECW/TBW ratio in both groups. This result seems to be compatible with the previous report (10).

In our present study, the serum albumin concentration in the tolvaptan group was much lower than that in the conventional diuretics group. To analyze the effect of serum albumin, we further compared the tolvaptan group with patients with a low serum albumin level (≤3 g/dL) in the conventional diuretics group (low-Alb conventional diuretics group; n=8). The serum albumin concentration in the low-Alb conventional diuretics group was a median of 2.4 (interquartile range 1.8-2.9) g/dL, showing no significant difference from that in the tolvaptan group. Plotting the body water reduction (x-axis) versus the post/pre ECW/TBW ratio (y-axis) suggested a mild difference in the slopes of the regression lines at a glance, but the difference was not statistically significant (Supplementary material, p=0.167). This may be due to the lack of statistical power because of the small number of patients analyzed. However, the significant difference in slopes between the tolvaptan group and the conventional diuretics group was lost after excluding patients with a serum albumin concentration >3 g/dL in the conventional diuretics group. Therefore, the possibility that the lower serum albumin level in the tolvaptan group than in the conventional diuretics group might have been a confounding factor for the results (significant difference in the slopes of the regression lines between the tolvaptan group and conventional diuretics group in Fig. 2) cannot be denied.

Several limitations associated with the present study warrant mention. First, the study subjects were small in number. A larger number of participants will be necessary in the future. Second, which conventional diuretic affected the post/pre ECW/TBW ratio in the conventional diuretics was unclear.

In short, the milder ECF-reducing capacity of tolvaptan for reducing body water may be due to the accompanying efficient water shift from the ICF to ECF, as we previously reported (4). The present study clearly explains why tolvaptan is known for its low incidence of worsening the renal function compared with conventional diuretics (5-7). In conclusion, tolvaptan reduces the ECF per amount of body fluid reduction less markedly than conventional diuretics.

Author's disclosure of potential Conflicts of Interest (COI).
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