

## A PILOT STUDY EXAMINING THE EFFECTS OF TOLVAPTAN ON RESIDUAL RENAL FUNCTION IN PERITONEAL DIALYSIS FOR DIABETICS

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◆ **Background:** For patients with end-stage renal disease (ESRD), peritoneal dialysis (PD) serves as a possible renal replacement therapy. However, most PD patients, particularly those with ESRD and diabetes mellitus, reportedly discontinue PD early, resulting in shorter survival periods and poorer prognosis because of overhydration. Recently, the vasopressin-2 receptor antagonist tolvaptan was approved for volume control in patients with heart failure. The present study aimed to identify the effects of tolvaptan in diabetic PD patients.

◆ **Methods:** In this pilot study, the tolvaptan group ( $n = 12$ ) were treated with 15 mg/day of tolvaptan 2 weeks after PD initiation and were prospectively analyzed for 1 year, and patients in the control group ( $n = 12$ ) did not receive tolvaptan and were retrospectively analyzed for 1 year. In addition to the biochemical tests, echocardiograms, serum atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels, peritoneal Kt/V, and creatinine clearance (CCr) were examined at baseline and at 6 and 12 months after PD initiation.

◆ **Results:** In the control group, the urine volume, renal Kt/V, and renal CCr levels consistently decreased; however, these parameters were stably maintained during the study period in the tolvaptan group. Atrial natriuretic peptide, CRP levels and the left ventricular mass index of the tolvaptan-treated group were significantly lower than those in the control group, whereas total protein and albumin levels were significantly higher at 6 and 12 months in the tolvaptan group. There were no obvious adverse effects.

◆ **Conclusions:** These data suggest that tolvaptan may preserve residual renal function and improve volume control in PD patients with diabetes mellitus.

KEY WORDS: Peritoneal dialysis; end-stage renal disease; tolvaptan; vasopressin receptor; urine volume; ultrafiltration; Kt/V; creatinine clearance.

For end-stage renal disease patients (ESRD), peritoneal dialysis (PD) is a renal replacement therapy that has an advantage in preserving residual renal function (1–3), stabilizing blood pressure (1,4,5), and maintaining a better quality of life (QOL) by alleviating visits to the hospital (3,6) or allowing patients to return to work easily (6,7). According to the latest data from the Japanese Society for Dialysis Therapy, at the end of 2012, 44.1% of ESRD patients who underwent renal replacement therapy had a comorbidity of diabetes mellitus (DM) and 36.6% (745 out of 2,034) of patients initiated PD because of diabetic nephropathy. However, most of these PD patients with DM reportedly discontinued PD at an early stage, achieved worse survival rates, and had poorer prognoses than PD patients without DM because of uncontrollable fluid management (8–10). Therefore, it is important to adequately control fluid levels in PD patients with DM to maintain the highest possible QOL.

Recently, a novel aquaretic, tolvaptan, which has been indicated for use for congestive heart failure, was approved in Japan. Tolvaptan, a vasopressin antagonist, binds to the vasopressin V2 receptor at the collecting ducts, resulting in an inhibition of water uptake via a decrease in aquaporin-2 translocation at the epithelial basement membrane (11–15). A randomized controlled trial with 319 congestive heart failure patients with left ventricular ejection fractions less than 40% showed that compared with the placebo group, the urine volume was increased and the body weight was well controlled in the tolvaptan-treated group (16). However, there are limited data regarding the use of tolvaptan in PD patients. Therefore, we investigated the efficacy of short-term tolvaptan use for diabetic PD patients with congestive heart failure.

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## MATERIALS AND PATIENTS

### PATIENTS AND STUDY PROTOCOL

We analyzed 24 incident PD patients with ESRD and DM (mean age, 65 ± 15 years; mean DM duration, 15 ± 13 years), 6 of whom received continuous ambulatory PD and 18 automated PD (APD) (Table 1). For control and tolvaptan group, patients started PD during Jan. 1, 2010 to Oct. 31, 2011, and Nov. 1, 2011 to Nov. 31, 2012, respectively. The PD patients who had pulmonary congestion with a cardiothoracic ratio of more than 55% and whose heart functions were NYHA II, III, or IV regardless of the use of conventional diuretics were enrolled in the study. The dose of diuretics used is shown in Table 2. After regulatory approval of tolvaptan in Japan, patients who were introduced to PD and provided written consent on the use of tolvaptan were allocated to the tolvaptan group and were prospectively analyzed for a year. In contrast, patients who were introduced to PD before regulatory approval were allocated to the control group and were retrospectively analyzed for a year. All the patients in the present study demonstrated some level of pleural effusion, overt lower-limb edema, or dyspnea

at PD initiation, and the group allocation was not based on the extent of patients' symptom progression. In the tolvaptan group ( $n = 12$ ), the patients received 15 mg/day of tolvaptan 2 weeks after PD initiation, and in the control group ( $n = 12$ ), the patients did not receive tolvaptan. Initially, all the patients were administered 4 bags of 1.36% glucose-based dialysates. Thereafter, 1 bag of icodextrin per day was prescribed to 10 patients in each group 7 – 10 days after PD initiation because of overt edema or insufficient ultrafiltration volume (UF) (< 300 mL/day). Each group included nine APD patients. The biochemical parameters, urine volume, Kt/V, and creatinine clearance (CCr) were evaluated at baseline and 3 days, 6 months, and 12 months after PD initiation. Laboratory parameters were measured at the start of PD and at 6 and 12 months after PD initiation. Examined data included age, DM duration, gender, body weight, body mass index, and blood pressure. Blood samples were examined for C-reactive protein (CRP), total protein, serum hemoglobin A1c, blood urea nitrogen, creatinine (Cr),  $\beta_2$  microglobulin, Na, K, Ca, P, albumin, i-PTH, blood sugar, atrial natriuretic peptide (ANP), and brain natriuretic peptide (BNP) levels. Patients also collected 24-h urine and effluent samples at their house and carried

TABLE 1  
Baseline Characteristics

	Tolvaptan group ( $n=12$ )	Control group ( $n=12$ )	<i>p</i> value
Age (years)	63±12	67±18	0.60
DM duration (years)	12±12	19±15	0.25
Gender (male/female)	10/2	10/2	0.99
BMI (kg/m <sup>2</sup> )	25±4	23±4	0.17
Medication			
Peritoneal dialysis			
Dialysate (L/day)	6.9±1.3	6.5±0.9	0.40
Icodextrin use (case)	10	10	0.99
APD/CAPD (case)	9/3	9/3	0.99
Anti-diabetic agents			
Insulin use (case)	3	3	0.99
GLP-1 analogue use (case)	3	2	0.61
Oral anti-diabetic agent use (case)	4	4	0.99
Anti-hypertensive agents			
ARB (case)	11	9	0.27
CCB (case)	8	7	0.67
$\alpha$ -blocker (case)	3	2	0.62
$\beta$ -blocker (case)	1	2	0.54
no drugs (case)	1	2	0.54

DM = diabetes mellitus; BMI = body mass index; APD = automated peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; GLP-1 = glucagon-like peptide-1; ARB = Angiotensin II receptor blocker; CCB = calcium channel blocker. Age, DM duration, BMI, and dialysate are expressed as mean±SD.

them to the hospital; the volume and urea nitrogen, creatinine, protein, blood sugar, Na, K, Ca, and P levels were measured at baseline and at 6 and 12 months after PD initiation.

#### ECHOCARDIOGRAPHIC MEASUREMENT

Echocardiographic measurements were performed at the start of PD and every 6 months for 1 year. Two-dimensional echocardiography was performed using a standard imaging transducer with a linear probe frequency of 5 MHz. The analyzed parameters included the left ventricular mass index (LVMI) and left ventricular eccentric hypertrophy, which was calculated using the Devereux and Reichek formula (17):

$$LVM = 1.04 [(LVEDD + IVS - EDWT + PWT - EDWT)^3 - LVEDD^3] - 13.6$$

$$LVMI = LVM / \text{body surface area}$$

#### STATISTICAL ANALYSIS

Data were presented as means  $\pm$  standard deviations. The baseline characteristics of patients were appropriately analyzed by Student-*t*, Mann-Whitney *U*-test, or chi-square test. For repeated measured variables, we included treatment and times as main effects and treatment\*time as interaction, and analyzed by linear mixed model with compound symmetry covariance pattern. The *p* value of  $< 0.05$  was considered statistically significant.

TABLE 2  
The Doses of Diuretics Used at Baseline

	Tolvaptan group (case)	Control group (case)
Furosemide		
240 mg/day	2	0
160 mg/day	1	1
120 mg/day	1	2
80 mg/day	3	6
60 mg/day	1	1
40 mg/day	4	2
Trichloromechiazide		
4 mg/day	0	1
2 mg/day	7	5
0 mg/day	5	6
Spironolactone		
50 mg/day	1	0
25 mg/day	2	4
0 mg/day	9	8

Statistical analyses were performed using SPSS ver. 19 statistical software for Windows (SPSS, Inc., Chicago, Ill., USA).

The study protocol was approved by the ethics committees at Konan Kosei Hospital. The study was performed in accordance with the ethical principles stated in the Declaration of Helsinki and Japanese Ministry of Health, Labour and Welfare.

#### RESULTS

A total of 24 incident PD patients with DM were divided into 2 groups: those who received tolvaptan treatment (tolvaptan group; *n* = 12 patients) and those who did not (control group; *n* = 12 patients). No intergroup differences for age ( $63 \pm 12$  vs  $67 \pm 18$ ) or gender (17% women in each group) were observed. At baseline, the analyzed laboratory data, medications used (diuretics, antihypertensive agents and antidiabetic agents), and PD prescription or modality were similar between both groups (Table 1 and 2).

After 3 days of tolvaptan use, the urine volume, renal Kt/V ( $Kt/V_{RRF}$ ), and renal CCr ( $CCr_{RRF}$ ) values significantly increased over baseline (data not shown). During the study period, the urine volume consistently decreased after PD initiation in the control group, whereas it increased for 3 months and then gradually decreased in the tolvaptan group (Figure 1). The mixed model showed that the tolvaptan group had significantly higher urine volume during the study period (Figure 1). Peritoneal UF was stable in the control group (average peritoneal UF,  $509 \pm 195$  mL/day). In contrast, UF markedly decreased and showed significant differences in comparison with UF at baseline during the first 4 months (average peritoneal UF,  $340 \pm 297$  mL/day at 4 months,  $p < 0.05$  vs baseline)

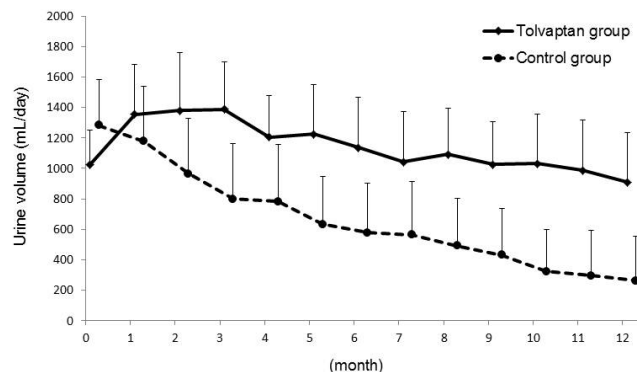


Figure 1 — Monthly urine volumes for 1 year. The *p* value for three factors: treatment, time and treatment\*time were analyzed by linear mixed model as  $p < 0.01$ ,  $p < 0.01$ , and  $p = 0.185$ , respectively.

in the tolvaptan group; it then gradually increased after 5 months, reaching the same level as UF in the control group resulting in no significant difference between groups (Figure 2).

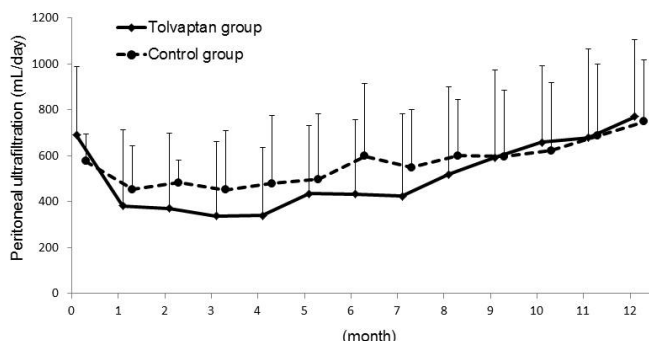


Figure 2 — Monthly peritoneal ultrafiltration volumes for 1 year. The *p* value for three factors: treatment, time and treatment\*time were analyzed by linear mixed model as *p*<0.4, *p*<0.01, and *p*=0.81, respectively.

Peritoneal Kt/V ( $Kt/V_{PM}$ ) and peritoneal CCr ( $CCr_{PM}$ ) values were stable in both the groups and showed no significant differences during the study period.  $Kt/V_{RRF}$  and  $CCr_{RRF}$  in the tolvaptan group were retained during the study period; however the control group showed gradual decrease over time.

CRP continued to increase from PD initiation in the control group, whereas CRP in the tolvaptan group constantly decreased.  $\beta_2$  microglobulin levels also increased in the control group, whereas they were stable in the tolvaptan group. Atrial natriuretic peptide and BNP levels, which indicate the body fluid status, were greatly decreased in the tolvaptan group with significant difference in ANP between groups. At baseline, LVMI was higher in the tolvaptan group than in the control group; however, it gradually decreased during the study period and showed significant difference between groups. There were no significant differences in body weight and diastolic blood pressure, but systolic blood pressure was significantly higher in the tolvaptan group during the study period (Table 3).

TABLE 3  
Changes in Laboratory Data Between the Tolvaptan and the Control Group Over Time

	Baseline		After 6 months		After 12 months		<i>p</i> value <sup>a</sup>		Interaction Treat*Time
	Tolvaptan ( <i>n</i> =12)	Control ( <i>n</i> =12)	Tolvaptan ( <i>n</i> =12)	Control ( <i>n</i> =12)	Tolvaptan ( <i>n</i> =12)	Control ( <i>n</i> =12)	Main effect Treatment	Time	
BW (kg)	66±13	63±14	64±12	62±12	65±11	65±11	0.32	0.07	0.41
BMI (kg/m <sup>2</sup> )	25±4	23±4	24±4	23±3	24±3	24±4	0.55	0.06	0.30
SBP (mmHg)	146±21	137±16	144±21	130±23	144±26	130±24	0.05	0.73	0.49
DBP (mmHg)	81±17	73±9	81±10	72±11	77±14	75±15	0.22	0.85	0.52
CRP (mg/dL)	0.41±0.59	0.35±0.53	0.10±0.11	0.53±0.51	0.07±0.09	0.55±0.50	<0.01	0.53	0.59
TP (g/dL)	5.7±0.8	6.0±0.6	6.2±0.4	5.9±0.4	6.4±0.8	5.9±0.6	0.17	0.09	0.01
Alb (g/dL)	3.1±0.5	3.2±0.6	3.3±0.3	2.9±0.4	3.5±0.4	3.0±0.6	0.05	0.36	0.07
$\beta_2$ MG (mg/dL)	23±5	20±4	20±4	26±6	21±4	28±7	0.05	0.25	0.85
BUN (mg/dL)	59±22	52±15	46±16	60±21	47±17	58±15	0.30	0.60	0.52
Cr (mg/dL)	8.0±2.3	7.1±2.2	7.3±2.3	8.7±3.5	8.0±2.6	9.2±3.9	0.01	0.03	0.34
i-PTH (pg/mL)	361±237	377±346	201±91	129±102	143±74	134±122	0.34	0.42	0.06
HbA <sub>1c</sub> (%)	5.4±0.6	5.9±0.7	5.7±0.9	5.6±0.4	5.5±0.5	5.9±1.0	0.59	0.64	0.56
ANP (pg/mL)	179±80	167±133	99±66	240±131	73±43	247±165	0.03	0.67	0.47
BNP (pg/mL)	394±235	273±251	228±207	529±479	144±83	545±636	0.18	0.74	0.82
Kt/V <sub>PM</sub>	1.12±0.30	1.31±0.18	1.22±0.34	1.41±0.38	1.37±0.18	1.37±0.35	0.34	0.48	0.24
Kt/V <sub>RRF</sub>	0.64±0.30	0.72±0.24	0.69±0.35	0.35±0.25	0.65±0.36	0.25±0.24	0.01	0.11	0.39
CCr <sub>PM</sub>	33±11	35±9	37±11	36±11	33±10	41±10	0.20	0.69	0.10
CCr <sub>RRF</sub>	46±20	42±16	45±18	21±10	48±14	12±13	0.01	0.20	0.03
LVMI (g/m <sup>2</sup> )	229±56	197±42	175±32	214±74	161±26	201±49	0.03	0.20	0.96
CTR (%)	55±6	56±8	51±7	53±6	50±4	54±8	0.19	0.66	0.17

BW = body weight; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; CRP = C-reactive protein; TP = total protein; Alb = albumin;  $\beta_2$ MG =  $\beta_2$  microglobulin; BUN = blood urea nitrogen; Cr = serum creatinine; i-PTH = intact parathyroid hormone; HbA<sub>1c</sub> = hemoglobin A<sub>1c</sub>; ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; Kt/V<sub>PM</sub> = peritoneal Kt/V; Kt/V<sub>RRF</sub> = renal Kt/V; CCr<sub>PM</sub> = peritoneal creatinine clearance; CCr<sub>RRF</sub> = renal creatinine clearance; LVMI = left ventricular mass index; CTR = cardio-thoracic ratio.

<sup>a</sup> Analyzed by linear mixed model analysis for three factors, treatment, time and treatment\*time.



The dialysate prescription of 3 patients in the control group was switched from 1.36% to 2.27% glucose at 1, 2, and 6 months after PD initiation. One of these 3 PD patients was transferred to combined therapy, in which 1 day of hemodialysis per week was added to the PD therapy because of unmanageable volume overload, and the diuretics dose was increased in 7 patients in the control group. In contrast, in the tolvaptan group, the prescription of diuretics as well as the PD prescription were not changed during the study period.

There were no specific adverse events during the study period, including hyponatremia.

## DISCUSSION

It is very important to achieve good fluid control in patients with chronic kidney disease to preserve residual renal function (RRF) and improve patient survival. Although loop, thiazide, and aldosterone diuretics are often used to control fluid levels, the efficacy of the newly launched aquaretic tolvaptan, which acts as a vasopressin receptor inhibitor, has not yet been reported in PD patients. In the present study, tolvaptan was administered to incident PD patients with DM and was found to increase the urine volume and preserve renal function, in comparison with those in the control group that were not prescribed tolvaptan.

Reportedly, PD provides a high QOL level to patients because it provides increased daily activity time. In contrast, more than half of the patients reportedly discontinued PD because of uncontrollable body fluid levels (18,19). In addition, PD patients with DM reportedly exhibit shorter survival times than patients without DM (19). Tolvaptan, an oral selective arginine vasopressin receptor antagonist, has been approved to treat hypervolemia in congestive heart failure patients (16,20–22). In the present study, diabetic PD patients with congestive heart failure who were refractory to diuretics were treated with 15 mg/day of tolvaptan 2 weeks after PD initiation for 12 months. Previous randomized, double-blind, placebo-controlled studies have shown that the 24-h urine volume and frequency increased in patients receiving tolvaptan (16,20–22). Consistent with these reports, in the present study, the urine volume in patients treated with tolvaptan increased at 1 month and continued to be higher than that in patients who were not treated with tolvaptan. The concentration of urine electrolytes such as Na, K, Ca, or P did not differ before and after the use of tolvaptan (data not shown), indicating that tolvaptan increased urine volume but not free water. In contrast, peritoneal UF in the tolvaptan group transiently decreased from 2 to 4 months, which

may have been due to a compensation effect because of the increased urine by tolvaptan treatment during this period. Furthermore, tolvaptan decreased ANP, BNP and LVMI. These results indicated that tolvaptan was effective for fluid management in diabetic PD patients with congestive heart failure.

Previous prospective studies, such as the CANUSA (23,24), ADEMEX (25), Hong Kong (26), and NECOSAD-2 studies (27), demonstrated that RRF is a useful prognostic factor for patient survival. A recent multivariate analysis of 383 stable PD patients found that in addition to age and log CRP and phosphate levels, RRF ( $\leq 4$  mL/min/1.73 m<sup>2</sup>) is a useful prognostic factor (28). Perl and Bargman reported that RRF could be preserved by PD selection and the utilization of renin-angiotensin-aldosterone system blockers and by the avoidance of nephrotoxic or nonsteroidal anti-inflammatory drugs (29). In addition, body fluid control is an important factor for RRF. Previous studies demonstrated that dehydration led to a decrease in RRF (30,31). An important issue of this research was the change in renal function in the tolvaptan group, which showed a higher urine volume and UF compared to the control group. Regardless of the higher fluid control during the 12-month study period in the tolvaptan group, renal Kt/V and CCr levels were preserved, indicating that tolvaptan could preserve renal function. A recent report that the daily CCr was increased in the tolvaptan-responder group also supports this evidence (32).

Hyponatremia is reportedly an adverse effect of tolvaptan (33,34); however, no patient exhibited obvious adverse events such as hyponatremia during the study period. This may be partly explained by the fact that patients were allowed to drink water when thirsty and the urine volume had not markedly increased in the tolvaptan group because the maximum urine volume was 2.5 L/day. In contrast, some patients exhibited mild hyponatremia.

There were several limitations to the present study, including the small sample size, lack of randomization, and the fact that the control and tolvaptan groups were analyzed retrospectively and prospectively. Therefore, a larger and long-term prospective study is required to illustrate the beneficial effects of tolvaptan in fluid management, RRF preservation, and improvement of patient survival.

In conclusion, we retrospectively investigated the short-term effects of the novel aquaretic tolvaptan in PD patients with DM who exhibited uncontrollable body fluid loss. The tolvaptan group showed significantly increased urine volume at day 3 of treatment and maintained RRF (i.e., renal Kt/V and CCr) during the observation period. Finally, we found that tolvaptan preserves RRF, increases urinary volume in PD patients with DM.

## DISCLOSURES

The authors declare no financial conflicts of interest.

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