A Safety and Efficacy Study of Tolvaptan Following Open Heart Surgery in 109 Cases

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SUMMARY

This study was conducted to evaluate the safety and efficacy of tolvaptan following open heart surgery.

We retrospectively reviewed 109 patients who were administered tolvaptan following open heart surgery between August 2011 and July 2014. We divided the patients according to their urine output index (amount of urine output/body surface area) into tertiles as follows: T1 (low responders; $n = 36$), T2 (intermediate responders; $n = 36$), and T3 (high responders; $n = 37$). No fatal adverse events were observed following tolvaptan administration. The factors that showed a significant difference among the 3 groups were body surface area (BSA) and preoperative body weight. Body weight rapidly decreased and a greater increase in the serum sodium level was observed on day 1 in the T3 group than in the other 2 groups. No decrease in blood pressure and no significant differences in the occurrence of atrial fibrillation were observed among the 3 groups during tolvaptan administration.

Tolvaptan can be safely and effectively administered to increase the urine output without adversely affecting the cardiovascular system or renal function following open heart surgery. However, careful attention is required regarding the possibility of a rapid increase in the serum sodium level so it is important to monitor changes in serum Na levels. (Int Heart J 2016; 57: 496-502)

Key words: Vasopressin V2-receptor antagonist, Volume control, Postoperative congestive heart failure

Despite remarkable advances in perioperative care for open heart surgery in recent years, volume control is one of the most important factors in the perioperative management of open heart surgery. Tolvaptan, a vasopressin V2-receptor antagonist, is available as a diuretic drug that can be used in the treatment of fluid accumulation in heart failure. Several studies have reported the efficacy of tolvaptan in patients with chronic congestive heart failure and acute heart failure.[1-5] According to previous reports, the use of tolvaptan for acute heart failure at an early stage of hospitalization prevents exacerbation of acute kidney injury, improves patient prognosis,[6] is superior to carperitide in terms of treatment cost of acute heart failure,[7] and is effective for correcting hyponatremia.[8-10] Although there are case reports indicating the efficacy of tolvaptan after open heart surgery, the number of patients reported is small.[11-14] Open heart surgery using cardiopulmonary bypass is often followed by symptoms such as circulatory inflammatory response, capillary hyperpermeability due to low body temperature, decreased intravascular colloid oncotic pressure due to hemodilution, and stromal edema as a result of decreased lymph flow.[15] Blood vasopressin concentration also increases after cardiac surgery because of hypotension during cardiopulmonary bypass and sympathetic nerve activation caused by operative stress.[16] Therefore, it is believed that reabsorption of water in the collecting tubules is excessive following open heart surgery. Because the diuretic effect of tolvaptan reduces the accumulation of intercellular fluid through an increase in the serum Na level or a difference in osmotic pressure, tolvaptan is expected to be clinically effective in this setting. In the present study, we report our findings with 109 patients who received tolvaptan following open heart surgery and discuss the safety and efficacy of this treatment.

METHODS

At our hospital, tolvaptan treatment was provided when oral medication became possible following open heart surgery and when adequate diuresis and weight loss could not be achieved with conventional diuretic agents, such as furosemide, spironolactone, and trichlormethiazide. Depending on the case, tolvaptan was occasionally administered together with catecholamine or carperitide. With minor exceptions, we used tolvaptan for patients who were preoperatively overweight and whose urinary volume was less than 1 mL/kg/hour despite the use of conventional therapy for 24–48 hours.

Tolvaptan was initiated at 7.5 or 15 mg/day, with a maximum dose of 15 mg/day. A total of 139 patients were adminis-

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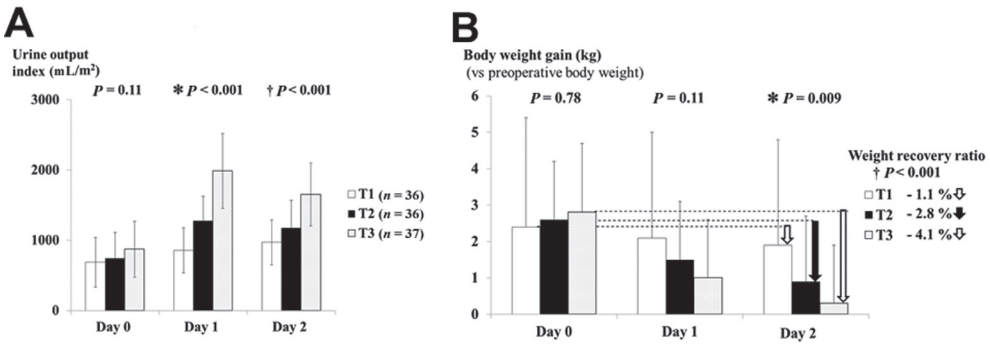

Figure 1. **A:** Urine output index on days 0, 1, and 2 after the start of tolvaptan administration in the 3 groups. **B:** Body weight gain (versus preoperative body weight) in the 3 groups on days 0, 1, and 2 after the start of tolvaptan administration. Weight recovery ratio: (body weight on day 0 – body weight on day 2)/body weight on day 0. T1: low responders; T2: intermediate responders; and T3: high responders. Day 0 is the start of tolvaptan administration. *P*-value is based on the analysis of variance. *,† $P < 0.05$.

tered tolvaptan following open heart surgery from August 2011 to July 2014. Of these, 20 patients were excluded, for whom precise data on urine volume before and after tolvaptan administration were not available. In addition, 7 patients who were treated with continuous hemodiafiltration (CHDF) during tolvaptan administration, 2 patients who experienced shock caused by cardiac tamponade, and 1 patient who experienced shock caused by sick sinus syndrome were also excluded. Finally, a total of 109 patients were examined.

It was not clear if the amount of the post-open heart surgery urine output was sufficient. Thus, we defined the urine output index as the [amount of urine output/BSA] and the subjects were divided according to their urine output index into tertiles. The average amount of urine output index on days 1 and 2 following tolvaptan administration was measured, and we divided the subjects depending on the urine output index into tertiles as follows: T1 (low responders; $n = 36$), T2 (intermediate responders, $n = 36$), and T3 (high responders; $n = 37$). Following this, we proceeded with the examination.

We defined weight recovery ratio as [(Body weight on day 1-body weight on day 2)/body weight on day 0] and show the data in Figure 1B.

The following parameters were examined among the 3 groups: preoperative patient background, surgical time, and cardiopulmonary bypass time (off-pump coronary artery bypass graft was used in 1 case each in groups T1 and T2; these cases were treated as missing values). The other parameters examined were concomitant diuretics at the time of tolvaptan administration; timing, duration, and dose of tolvaptan; change in the urine volume and body weight before and after tolvaptan administration; preoperative body weight recovery rate; duration until preoperative body weight recovery (cases who did not return to preoperative body weight were treated as missing values); hypotension and presence of atrial fibrillation during tolvaptan administration; serum sodium (Na), serum potassium (K), serum blood urea nitrogen (BUN), serum creatinine (Cr), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels; and urine osmolality (U-OSM) before and after tolvaptan administration.

Statistical analysis: Mantel–Haenszel chi-square tests were used for the evaluation of categorical parameters. In the comparison of continuous parameters among the 3 groups, analysis of variance (ANOVA) was used to compare the means of variables, stratified by the tertiles of the amount of urine. Analyses of covariance (ANCOVAs) were performed to evaluate age and sex adjusted mean levels of the amount of urine in the 3 groups. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using the SPSS (Ver. 21, Chicago, IL, USA) software system.

Results

Table I shows the background data of the patients. No significant differences in sex, age, height, hypertension, diabetes, liver function abnormalities, emergency operations, or valvular disease ratios were observed among the 3 groups. Cardiopulmonary bypass time and aorta clamp time significantly differed among the 3 groups and were longer in the order of T3 group > T2 group > T1 group. No significant differences were observed in preoperative serum BUN, Na, and K levels; estimated glomerular filtration rate (eGFR); pre and postoperative ejection fraction (EF); pre and postoperative tricuspid regurgitation; amount of diuretics at the time of tolvaptan administration; or combination infusion ratio of carperitide and catecholamine. Preoperative severe mitral regurgitation significantly differed among the 3 groups. However, no significant differences were observed for none, mild, and moderate mitral regurgitation, postoperative mitral regurgitation, and postoperative tricuspid regurgitation.

Urine output index increased after tolvaptan administration in all 3 groups, with a significant intergroup difference in the urine output index on days 1 and 2 after tolvaptan administration (Figure 1A). Preoperative body weight was greater in the order of T1 < T2 < T3, and this order did not change following tolvaptan administration.

Figure 1B depicts the change in body weight. Weight gain (versus preoperative body weight) on day 0 (T1: 2.4 ± 3.0 kg, T2: 2.6 ± 1.6 kg, and T3: 2.8 ± 1.9 kg) did not show a significant difference among the 3 groups ($P = 0.78$), but there were significant weight gain differences on day 2 (T1: 1.9 ± 2.9 kg, T2: 0.9 ± 1.9 kg, and T3: 0.3 ± 1.6 kg; $P = 0.009$). Weight recovery ratio and difference in body weight before and after tolvaptan administration as a percentage of preoperative body

Table I. Patient Backgrounds

	T1 (n = 36) Low responders	T2 (n = 36) Intermediate responders	T3 (n = 37) High responders	P
Males, n (%)	12 (33.3)	20 (55.7)	21 (56.8)	0.08
Age (years)	75.4 ± 9.3	74.1 ± 8.6	70.6 ± 12.3	0.12
Height (cm)	154.6 ± 10.8	158.3 ± 9.1	159.9 ± 10.7	0.08
Body surface area (m^2)	1.50 ± 0.20	1.58 ± 0.18	1.63 ± 0.20	0.02*
Preoperative body weight (kg)	52.6 ± 11.7	56.8 ± 10.3	60.2 ± 12.6	0.02*
Hypertension, n (%)	28 (77.8)	28 (77.9)	30 (81.1)	0.92
Diabetes mellitus, n (%)	15 (41.7)	11 (30.6)	13 (35.1)	0.61
Liver function abnormality, n (%)	1 (2.8)	0	1 (2.7)	0.44
Emergency, n (%)	5 (13.9)	1 (2.8)	6 (16.2)	0.10
Valve operation, n (%)	24 (63.9)	22 (63.9)	26 (70.3)	0.80
Operative time (minutes)	451 ± 133	496 ± 115	465 ± 125	0.30
Cardiopulmonary bypass time (minutes)	168 ± 77	206 ± 66	206 ± 64	0.03*
Aorta clamp time (minutes)	100 ± 45	124 ± 46	127 ± 54	0.04*
Preoperative serum BUN (mg/dL)	23.3 ± 13.1	21.3 ± 7.1	20.2 ± 9.0	0.39
Preoperative serum Cr (mg/dL)	1.00 ± 0.65	1.01 ± 0.50	0.92 ± 0.36	0.74
Preoperative eGFR (mL·minute^{-1}·1.73 m^{-2})	60.4 ± 23.5	57.0 ± 18.8	63.3 ± 21.8	0.46
Preoperative eGFR < 60 mL·minute^{-1}·1.73 m^{-2}, n (%)	16 (44.4)	20 (55.6)	14 (37.8)	0.31
Preoperative serum Na (mEq/L)	139.1 ± 3.9	139.2 ± 3.1	139.8 ± 2.9	0.59
Preoperative serum K (mEq/L)	4.2 ± 0.5	4.4 ± 0.5	4.2 ± 0.9	0.27
Preoperative left ventricular ejection fraction (%)	64.2 ± 13.7	58.7 ± 12.0	63.4 ± 11.0	0.12
Preoperative left ventricular end-diastolic diameter (mm)	49.6 ± 9.3	54.0 ± 7.9	51.2 ± 7.4	0.08
Preoperative left ventricular end-systole diameter (mm)	32.5 ± 10.2	36.7 ± 8.8	33.4 ± 7.1	0.09
Preoperative mitral regurgitation				
none, n (%)	16 (44.4)	14 (38.9)	11 (29.7)	0.42
mild, n (%)	12 (33.3)	11 (30.6)	16 (43.2)	0.49
moderate, n (%)	6 (16.7)	3 (8.3)	1 (2.7)	0.10
severe, n (%)	2 (5.6)	8 (22.2)	9 (24.3)	0.04*
Preoperative tricuspid regurgitation				
none, n (%)	18 (50.0)	21 (58.3)	21 (56.8)	0.75
mild, n (%)	10 (27.8)	11 (30.6)	8 (21.6)	0.67
moderate, n (%)	7 (19.4)	2 (5.6)	7 (18.9)	0.13
severe, n (%)	1 (2.8)	2 (5.6)	1 (2.7)	0.78
Postoperative left ventricular ejection fraction (%)	61.4 ± 12.9	59.4 ± 10.9	63.6 ± 9.7	0.28
Preoperative left ventricular end-diastolic diameter (mm)	45.3 ± 8.1	48.2 ± 9.1	46.9 ± 6.9	0.33
Preoperative left ventricular end-systole diameter (mm)	30.6 ± 8.6	33.3 ± 9.1	30.9 ± 6.4	0.29
Postoperative mitral regurgitation				
none, n (%)	24 (66.7)	24 (77.9)	33 (89.2)	0.06
mild, n (%)	10 (27.8)	8 (22.2)	4 (10.8)	0.16
moderate, n (%)	2 (5.6)	0	0	0.11
severe, n (%)	0	0	0	-
Postoperative tricuspid regurgitation				
none, n (%)	21 (58.3)	24 (66.7)	27 (73.0)	0.42
mild, n (%)	14 (38.9)	12 (33.3)	10 (27.0)	0.56
moderate, n (%)	1 (2.8)	0	0	0.33
severe, n (%)	0	0	0	-
Dose of furosemide at administration of tolvaptan (mg/day)	36.7 ± 8.9	37.2 ± 8.5	34.9 ± 8.7	0.48
Dose of spironolactone at administration of tolvaptan (mg/day)	31.2 ± 23.4	26.4 ± 16.8	31.8 ± 20.1	0.47
Dose of trichlormethiazide at administration of tolvaptan (mg/day)	0.8 ± 1.0	0.7 ± 1.0	0.8 ± 1.0	0.88
Carperitide infusion, n (%)	14 (38.9)	8 (22.2)	11 (29.7)	0.40
Dopamine infusion, n (%)	5 (13.9)	4 (11.1)	6 (16.2)	0.82
Dose of dopamine infusion (γ)	2.6 ± 0.2	3.0 ± 0.3	2.4 ± 0.2	0.27
Dobutamine infusion, n (%)	2 (5.6)	1 (2.8)	3 (8.1)	0.59
Dose of dobutamine infusion (γ)	2.3 ± 1.1	3.0	2.5 ± 0.9	0.82

Unless marked otherwise, data are expressed as the mean unit ± standard deviation. BUN indicates blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration ratio; Na, serum sodium; and K, serum potassium. *$P < 0.05$.

weight were significantly different among the 3 groups (T1: decreased by 1.1%; T2: decreased by 2.8%; and T3: decreased by 4.1%; $P < 0.001$).

Table II shows the clinical courses and laboratory parameters during tolvaptan administration. There were also significant differences in duration until preoperative body weight recovery, and body weight decrease per day among the 3 groups. There were no differences in the timing of treatment initiation, dose of tolvaptan on day 1 and day 2, or the maximum dose of tolvaptan between the groups. Tolvaptan administration time and hospitalization period tended to be shorter in the T3 group, but no significant difference was observed among the 3 groups.

Figure 2 shows serum Na levels after tolvaptan administration. There was no significant difference in serum Na levels

Table II. Clinical Course and Laboratory Parameters During Tolvaptan Administration

	T1 (n = 36) Low responders	T2 (n = 36) Intermediate responders	T3 (n = 37) High responders	P
Preoperative body weight recovery, n (%)	27 (75.0)	33 (91.7)	33 (89.2)	0.11
Duration until preoperative body weight recovery (days)	6.3 ± 4.5	5.2 ± 3.9	3.5 ± 2.3	0.01*
Body weight decrease (kg/day)	0.5 ± 0.4	0.7 ± 0.5	0.9 ± 0.6	0.0005*
Postoperative day of tolvaptan initiation (days)	4.2 ± 2.5	4.1 ± 2.1	4.0 ± 1.7	0.90
Tolvaptan maximum dose (mg/day)	10.4 ± 3.7	11.5 ± 3.8	10.3 ± 3.7	0.37
Dose of tolvaptan on day 1	9.2 ± 3.2	10.6 ± 3.8	9.1 ± 3.1	0.10
Dose of tolvaptan on day 2	9.3 ± 3.2	10.8 ± 3.8	9.2 ± 3.2	0.09
Tolvaptan dosing period (days)	6.7 ± 6.0	5.7 ± 4.0	4.2 ± 2.2	0.06
Total hospitalization (days)	35.7 ± 13.9	35.2 ± 11.8	31.2 ± 8.6	0.18
Minimum systolic blood pressure during tolvaptan administration (mmHg)	98.4 ± 12.8	99.8 ± 10.3	100.8 ± 12.0	0.68
Minimum diastolic blood pressure during tolvaptan administration (mmHg)	56.3 ± 11.2	57.8 ± 9.7	56.2 ± 7.5	0.74
Paroxysmal atrial fibrillation during tolvaptan administration, n (%)	8/29 (22.2)	13/32 (36.1)	4/31 (10.8)	0.12
Postoperative paroxysmal atrial fibrillation, n (%)	14/29 (38.9)	14/32 (38.9)	8/31 (21.6)	0.32
Serum K, day 0 (mEq/L)	3.8 ± 0.4	3.7 ± 0.4	3.8 ± 0.3	0.78
Serum K, day 1 (mEq/L)	3.8 ± 0.4	3.8 ± 0.4	3.9 ± 0.5	0.67
Serum K, day 2 (mEq/L)	3.8 ± 0.4	3.8 ± 0.4	3.9 ± 0.5	0.74
Serum K, on the last day of tolvaptan (mEq/L)	4.1 ± 0.5	4.3 ± 0.5	4.2 ± 0.5	0.14
Serum BUN, day 0 (mg/dL)	28.8 ± 11.3	27.1 ± 9.7	28.3 ± 14.7	0.83
Serum BUN, day 1 (mg/dL)	27.3 ± 12.6	25.2 ± 12.2	23.1 ± 11.9	0.42
Serum BUN, day 2 (mg/dL)	30.5 ± 14.7	24.7 ± 10.6	24.9 ± 16.0	0.30
Serum BUN, on the last day of tolvaptan (mg/dL)	27.2 ± 12.2	26.8 ± 12.8	24.8 ± 13.2	0.69
Serum Cr, day 0 (mg/dL)	1.07 ± 0.72	1.16 ± 0.78	1.13 ± 0.70	0.85
Serum Cr, day 1 (mg/dL)	1.11 ± 0.96	1.19 ± 0.96	1.01 ± 0.55	0.74
Serum Cr, day 2 (mg/dL)	1.19 ± 1.19	1.06 ± 0.93	1.02 ± 0.68	0.84
Serum Cr, on the last day of tolvaptan (mg/dL)	1.03 ± 0.76	1.12 ± 0.62	1.04 ± 0.55	0.74
Postoperative maximum serum Cr (mg/dL)	1.44 ± 1.09	1.45 ± 0.81	1.38 ± 0.70	0.82
Serum AST, day 0 (IU/L)	38.7 ± 31.2	41.3 ± 38.1	40.1 ± 21.4	0.94
Maximum serum AST during tolvaptan administration (IU/L)	40.6 ± 30.8	46.7 ± 41.9	51.4 ± 44.0	0.50
Serum ALT, day 0 (IU/L)	32.4 ± 25.7	30.8 ± 26.4	33.6 ± 19.7	0.88
Maximum serum ALT during tolvaptan administration (IU/L)	42.6 ± 38.2	44.6 ± 37.5	56.1 ± 53.5	0.37
U-OSM, day 0 (mOsm/L)	566 ± 183	453 ± 162	486 ± 148	0.48
U-OSM, day 2 (mOsm/L)	444 ± 199	428 ± 138	348 ± 135	0.22

Unless marked otherwise, data are expressed as the mean unit ± standard deviation. Tolvaptan administration began on day 0. K indicates serum potassium; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; and U-OSM, urine osmolality. *$P < 0.05$.

Table III. Analysis of Covariance Adjusted for Age and Sex

	T1 (n = 36) Low responders	T2 (n = 36) Intermediate responders	T3 (n = 37) High responders	P
Urine output index day 1 (mL/m^2)	897 ± 450	1269 ± 444	1956 ± 448	< 0.001*
Urine output index day 2 (mL/m^2)	887 ± 374	1273 ± 369	1637 ± 372	< 0.001*
Change in serum Na on day 1 (mEq/L)	1.0 ± 3.0	2.4 ± 3.3	3.2 ± 3.1	0.008*
Duration until preoperative body weight recovery (days)	5.5 ± 4.2	6.0 ± 4.1	3.6 ± 3.9	0.03*
Body weight decrease (kg/day)	0.5 ± 0.4	0.7 ± 0.5	0.9 ± 0.6	0.006*

Data are expressed as mean ± standard deviation. Na indicates serum sodium. *$P < 0.05$.

on days 0, 1, or 2 among the 3 groups. However, there was a significant difference among the 3 groups in the amount of change of serum Na levels on postadministration day 1 (T1: 0.9 ± 2.5 mEq/L, T2: 2.1 ± 3.1 mEq/L, and T3: 3.7 ± 2.5 mEq/L; $P = 0.003$) and maximum change in serum Na levels during tolvaptan administration (T1: 2.8 ± 2.4 mEq/L, T2: 3.2 ± 2.4 mEq/L, and T3: 4.3 ± 2.7 mEq/L; $P = 0.03$). There was no significant difference in the maximum amount of serum Na levels during the treatment (T3: 142.8 ± 3.0 mEq/L, T2: 142.7 ± 3.0 mEq/L, and T1: 142.1 ± 4.0 mEq/L; $P = 0.63$). There was 1 patient in the T3 group whose serum Na level increased to > 10 mEq/L on day 1 after tolvaptan administration. In contrast, no patients in the T1 and T2 groups experienced a rapid increase in serum Na levels. One patient was found to have a serum Na level of ≥ 150 mEq/L during tolvaptan administration (group T2); however, his serum Na level was already elevated (149 mEq/L) before tolvaptan administration.

There were no significant differences in minimum systolic and diastolic blood pressure at the time of tolvaptan administration among the 3 groups. Moreover, no patients had to discontinue the medication because of a circulatory failure, such as hypotension, during treatment. The incidence of paroxysmal atrial fibrillation during the period of tolvaptan administration was 22.2%, 36.1%, and 10.8% in the T1, T2, and T3 groups, respectively. The incidence was the lowest in the T3 group, but there were no significant differences among the 3 groups.

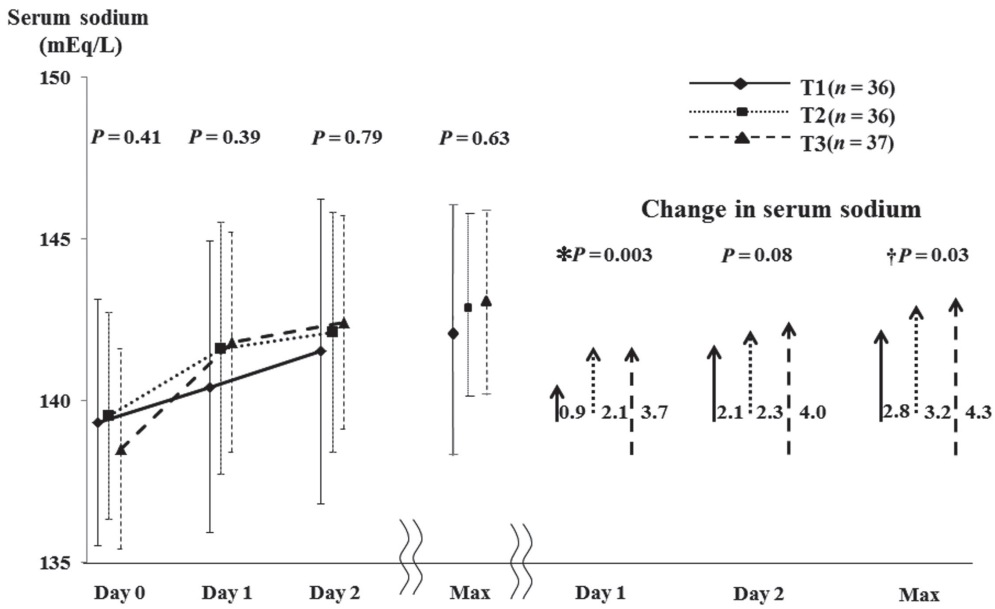

Figure 2. Serum Na levels in the 3 groups on days 0, 1, and 2 after the start of tolvaptan administration; maximum serum Na levels; change in serum Na on days 1 and 2; and maximum change in serum Na (maximum serum Na during tolvaptan administration − minimum serum sodium during tolvaptan administration). T1: low responders; T2: intermediate responders; and T3: high responders. Day 0 is the start of tolvaptan administration. *P*-value is based on the analysis of variance. *,† $P < 0.05$.

There were also no significant differences in serum K or BUN levels among the 3 groups. At the time of tolvaptan discontinuation, all groups exhibited an improvement in serum Cr levels, but the differences were not significant. U-OSM was similar across all groups before the tolvaptan treatment and decreased from day 0 to day 2 after administration in each group (T1: 12.8 ± 12.1%, T2: 8.6 ± 11.2%, and T3: 11.9 ± 11.6 ; $P = 0.96$).

Analysis of covariance adjusted for age and sex was conducted to investigate the differences among the groups. Table III shows that significant differences were found in the urine output index, change in serum Na levels on day 1, duration until preoperative body weight recovery, and body weight decrease during the period of tolvaptan administration. There were no other significant intergroup differences.

Discussion

In evaluating the efficacy of tolvaptan, a cutoff line between low responders and high responders is difficult because of various interacting factors, such as patient background and drug dose. Therefore, in the present study, we proceeded with the analysis using the urine output index on days 1 and 2 following tolvaptan administration. The urine output index increased following tolvaptan administration in all 3 groups, with their reaction differing in the order T1 < T2 < T3. Significant differences in preoperative factors among the 3 groups were observed for physique (greater body weight and larger BSA). However, there were significant differences in not only the amount of urine output but also the urine output index. We showed that the effect of tolvaptan, in terms of urine output, increased in the order T1 < T2 < T3, even after adjusting for differences in physique. It should be noted that the dosage of tolvaptan was the same among the 3 groups regardless of differences in physique. Furthermore, as shown in Table 3, the significant difference in physique between the 3 groups disappeared when analysis of covariance was performed with adjustment for age and sex, but there were significant differences in the urine output index.

Imamura, *et al*[17] reported that age > 69 years predicted nonresponsiveness. In the present study, the T3 group had a slightly higher ratio of males and the average age was younger than T1 or T2, but there were no significant differences.

There were significant differences in cardiopulmonary bypass times and aorta clamp time among the 3 groups. However, because there was no consistent trend in the order of T1 < T2 < T3 and because no significant difference was found in the analysis of covariance, we concluded that these differences were not significant. We did not find any other factor predictive of a response other than those mentioned above. Further studies examining a larger number of cases are required.

Imamura, *et al*[17] compared tolvaptan responders and nonresponders using the amount of urine output at 24 hours after administration as an index. They identified U-OSM before the administration of > 352 mOsm/L and a decrease in U-OSM of > 26% at 4–6 hours after administration as predictors of a response and Cr > 1.3 mg/dL, serum BUN > 44 mg/dL, and age > 69 years as predictors of no response.[17] In the present study, mean U-OSM was > 352 mOsm/L in all 3 groups, and there was no significant difference in U-OSM either before or 2 days after tolvaptan administration in all 3 groups. This finding suggested that U-OSM is not necessarily appropriate as a prognostic index for tolvaptan following open heart surgery because U-OSM tends to be higher than usual following open heart surgery, even without tolvaptan. The per-

cent decreases in U-OSM for the T1, T2, and T3 groups were 12.8%, 8.6%, and 11.9%, respectively. Thus, each group showed a decrease in U-OSM although the difference was not significant.

The main mechanism of tolvaptan-induced water diuresis is reflected by the fact that U-OSM decreased as reactive urine volume increased. No significant group difference in serum BUN and serum Cr any time before or after tolvaptan administration was observed among the 3 groups in this study. This finding was unexpected because a response to conventional diuretics generally depends on the original level of renal function. Frequent use, high doses, and long-term administration of conventional diuretics tend to cause a deterioration in renal function. In addition, the serum Cr level at the time of tolvaptan discontinuation slightly improved in all 3 groups compared with preadministration. This finding suggests that tolvaptan can be used at an acute phase following open heart surgery without concern for potential worsening of renal function.

Serum Na levels increase with water diuresis during tolvaptan administration, and this response has been utilized as a treatment for hyponatremia. In the present study, an increase in serum Na level was observed in all groups. Hyponatremic patients may often be asymptomatic or have only mild symptoms (fatigue, nausea, and anorexia), and there are reports that clinical symptoms improve following the correction of hyponatremia.[8-10)]

We often found cases of patients whose general malaise improved following the correction of hyponatremia, although we did not investigate it in this study because the clinical effect was difficult to quantify. The improvement in serum Na levels with tolvaptan treatment appeared to have a favorable influence on management following open heart surgery. However, we must be cautious with regard to hypernatremia associated with excessive water diuresis during tolvaptan administration because a rapid increase in serum Na level may lead to central pontine myelinolysis. Kinugawa, *et al* reported that hypernatremia (serum Na ≥ 150 mEq/L) was observed in 3.31% of patients, and they defined the following indices as factors predictive of hypernatremia: serum Na > 142 mEq/L and serum K > 3.8 mEq/L at the time of tolvaptan administration and 15 mg for the initial tolvaptan dose.[18)]

In the present study, only 1 patient had serum Na levels exceeding 150 mEq/L, and the serum Na level of this patient on day 0 was already 149 mEq/L. In another patient, the serum Na level increased by 10 mEq on day 1. This patient showed a good response to tolvaptan (urine output on day 0 was 800 mL, which increased to 3786 mL on day 1). In these cases, the tolvaptan dose was 15 mg, which was consistent with the findings of Kinugawa, *et al*, where a starting dose of 15 mg/day was an independent predictor for hypernatremia. An increase in serum Na level was more remarkable in high responders (T1 < T2 < T3), and an increase of 3.7 ± 2.5 was observed in the T3 group. We must be cautious following open heart surgery, particularly for hypernatremia patients with high preadministration serum Na levels (serum Na ≥ 145 mEq/L) who respond well to tolvaptan (urine output > 3500 mL/day after administration). It is recommended that serum Na levels should be checked 6 or 8 hours following tolvaptan administration. When we first started using tolvaptan, we also checked serum Na levels at 6 hours following administration. Fortunately, there were no cases in which the serum Na level rapidly increased (10 mEq/L/6 hours). The risk of hypernatremia is unlikely to be high in patients with smaller volumes of post-treatment urine output, and we suggest that evaluating the serum Na level after 24 hours should be sufficient. We also think that the initial tolvaptan dose should be at least 7.5 mg; it is safer to decide whether to increase the tolvaptan dose after considering the initial response.

Considering that the serum K (< 3.8 mEq/L) level was identified as a predictive factor for hypernatremia, Kinugawa, *et al* hypothesized that secondary aldosteronism could be caused by the long-term use of loop diuretics.[18)] In the present study, we found no significant intergroup differences in serum K levels, either before or after tolvaptan administration. The upward trend of serum K levels in all 3 groups after tolvaptan administration was not considered to be due to the action of tolvaptan but rather was the result of aggressive correction and supplementation to raise serum K levels above 4 mEq/L; this was in consideration of the fact that low serum K levels following open heart surgery increase the incidence of atrial fibrillation.[19,20)] We do not consider the serum K level as a good predictor of hypernatremia following open heart surgery.

With regard to AST/ALT, the TEMPO study[21)] reported that AST/ALT was 4.9% in patients with hepatic dysfunction, whereas Kinugawa, *et al*[18)] reported that it was < 1%. This difference was probably related to the difference in tolvaptan dose (15 mg/day versus 60–120 mg/day). In the present study, AST/ALT increased compared with preadministration levels, with values crossing 100 IU/L in 5 cases (4.6%). However, the possible influence of surgical procedures, including the use of cardiopulmonary bypass as well as various drugs, such as antibiotics, could not be neglected. The patient who had the largest increase in the AST/ALT (IU/L) ratio experienced an upsurge from 101/100 (IU/L) to 272/274 (IU/L). However, no patient had critical liver damage and all patients recovered to an approximately normal AST/ALT ratio by the time of discharge.

One report has stated that the frequency of atrial fibrillation following tolvaptan treatment ranges from 10% to 65%,[22)] with the largest series reporting an incidence of around 30%.[23)] While the frequency of atrial fibrillation caused by the rapid increase in urine output because of tolvaptan is of some concern, the incidence was low at 10.8% in the T3 group, and there were no significant differences in the incidence of paroxysmal atrial fibrillation among the 3 groups. The frequency of paroxysmal atrial fibrillation did not increase even among high responders; therefore, we consider it unlikely that tolvaptan will increase the incidence of atrial fibrillation in treated patients. No problematic decrease in blood pressure was observed among any of the 3 groups during tolvaptan administration.

The present study reconfirmed that tolvaptan administration for the control of body fluid can increase the amount of urine output and serum Na levels without adversely affecting the cardiovascular system or renal function because of its diuretic effect, even in the perioperative period following open heart surgery. The present study encourages a more proactive approach to the administration of tolvaptan.

We found that it is difficult to predict the effect of tolvaptan on the basis of U-OSM, serum BUN, serum Cr, or electrolyte levels measured prior to administration. However, tolvaptan is an oral medication with few side effects and may

contribute to the early improvement of activities of daily life (ADL) in the perioperative period, for example, by the promotion of ambulation. Therefore, we suggest that the most practical approach may be to administer tolvaptan in small dosages from an early stage and to closely observe the reaction. While using such a protocol, careful observation of the serum Na level changes is important, particularly in the case of high responders with initially higher serum Na levels.

There are some limitations to this study. First, it was a retrospective study, and the number of patients from each facility was not very large. Second, there were no clear criteria regarding the timing of tolvaptan administration. Third, underlying diseases, preoperative use of existing diuretics, and operative methods were not standardized. Fourth, patients who had started artificial dialysis and CHDF and whose precise urine amount could not be measured were excluded. We cannot rule out the possibility that these factors could have influenced the efficacy evaluation of tolvaptan in this study. Future studies that involve more cases should be conducted to verify these results.

Conclusion: Following open heart surgery, we used tolvaptan in patients who could not obtain an effective diuresis using conventional diuretics. This study reconfirmed that the use of tolvaptan could increase the amount of urine output and serum Na level without adversely affecting the cardiovascular system or renal function. On the basis of the findings of this study, we consider tolvaptan to be relatively safe and effective for the management of fluid accumulation following open heart surgery. However, it is important to monitor changes in serum Na levels, particularly in patients with a larger treatment response.

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Disclosures

Disclosure Statement: The authors declare that they have no conflicts of interest to disclose.

Ethical approval: All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional research committee.

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