sciendo

Journal of Cardiovascular Emergencies 2021;7(4):107-115
DOI: 10.2478/jce-2021-0016

ORIGINAL RESEARCH

Possible Option for Treatment of Severe Congestive Heart Failure Under Mechanical Ventilation Using Tolvaptan via Nasogastric Tube: A Single-Center Analysis

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ABSTRACT

Background: The oral vasopressin-2 receptor antagonist tolvaptan causes aquaresis, and its effect on heart failure is proven. However, it is not recommended in patients who are unable to appropriately respond to thirst because of possible severe hypernatremia. Aim: To assess the safety and efficacy of tolvaptan treatment via nasogastric tube in patients who are unable to respond to thirst by fluid ingestion. **Methods:** We analyzed 70 consecutive patients with severe congestive heart failure (CHF) who were resistant to loop diuretics and treated with tolvaptan. From the 70 patients, 12 required endotracheal intubation under sedation (Group Tube; GT) and 58 did not (Group Oral; GO). We administered tolvaptan orally in GO; however, in GT, we had to administer tolvaptan via nasogastric tube to achieve pulmonary decongestion quickly. In GT, serum sodium level was monitored closely, and intravenous fluid infusion volume was controlled in the intensive care unit (ICU). Outcomes, including safety and efficacy parameters, were evaluated. **Results:** In both groups, tolvaptan treatment did not develop a significant rise in serum sodium level compared with baseline, and the incidence of worsening renal failure was comparable, despite greater net fluid loss and higher doses of loop diuretics used in patients of GT compared to GO. In GT, all patients achieved pulmonary decongestion and were weaned from mechanical ventilation. **Conclusions:** In sedated patients with severe CHF who are unable to respond to thirst by fluid ingestion, tolvaptan can be used without clinically significant hypernatremia under close monitoring in the ICU.

Keywords: tolvaptan, diuretics, hypernatremia, nasogastric tube, severe congestive heart failure

ARTICLE HISTORY

Received: September 29, 2021
Accepted: October 21, 2021

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INTRODUCTION

Tolvaptan, an oral vasopressin V2 receptor antagonist that has been approved in Japan, induces aquaresis and is effective in patients with congestive heart failure (CHF).[1,2] However, patients who are unable to sense or appropriately respond to thirst stimulation, should not take tolvaptan because this increases the risk of severe hypernatremia and subsequent neurological complications such as central pontine myelinolysis.[3] In patients suffering from

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severe CHF who require invasive mechanical ventilation under sedation, intravenous loop diuretics have been conventionally used for the purpose of decongestive therapy. Undoubtedly, high-dose diuretic therapy using loop diuretics has improved pulmonary congestion in patients with severe CHF; however, higher loop diuretic dosages have been shown to be associated with an increased risk of worsening renal function (WRF) and hyponatremia, both of them having been reported as negative prognostic factors for heart failure.[4,5] Therefore, a more safe and efficacious decongestive therapy, other than loop diuretics, is required in sedated patients with severe CHF. To solve this dilemma, we have incorporated tolvaptan administration via nasogastric tube (NGT), to achieve pulmonary decongestion and weaning from mechanical ventilation quickly without WRF and hyponatremia.

We have previously reported the case of a patient with severe CHF who required invasive mechanical ventilation with endotracheal intubation and in whom tolvaptan was administered via NGT.[6] In the present study, we aimed to further demonstrate the safety and efficacy of tolvaptan administration via NGT in sedated patients who are unable to respond to thirst by fluid ingestion. This therapeutic option was analyzed in comparison to oral tolvaptan administration in conscious patients who are able to respond to thirst by fluid ingestion.

MATERIALS AND METHODS

STUDY PATIENTS

This is a single-center retrospective observational study. We analyzed 70 consecutive patients admitted with New York Heart Association (NYHA) class III to IV CHF, who received tolvaptan between January 2014 and December 2017. The attending physician diagnosed heart failure according to the Framingham criteria.[7] Patients who met the following criteria did not receive tolvaptan: cardiogenic shock, hypovolemia, dependence on hemodialysis, active systemic infection, severe aortic stenosis, hypernatremia with serum sodium (s-Na) concentration ≥146 mEq/L. Patients were administered an initial tolvaptan dose of 7.5 or 15 mg/day orally (Group Oral; GO) in 58 patients who were able to take fluid orally, and via NGT (Group Tube; GT) in 12 sedated patients who required invasive mechanical ventilation with endotracheal intubation in the intensive care unit (ICU). The use of invasive mechanical ventilation with endotracheal intubation was started according to the Japanese guidelines for the treatment of acute heart failure.[8] We considered that sedated patients represent a challenging group for tolvaptan treatment, as they are unable to respond to thirst themselves by fluid ingestion. However, in the ICU, there is a closer monitoring of the urine output and s-Na level, and there is a possibility to counter steer quickly against a massive diuresis and a rapid rise of s-Na. The likelihood of side effects of tolvaptan, especially hypernatremia, was explained to all patients' families, and informed consent was obtained for subjects in the GT group. This study complied with the Declaration of Helsinki, and the institutional review board approved the research protocol.

DATA COLLECTION AND TREATMENT

Demographic data were obtained from the patients' medical records. Echocardiography was performed at least once from the day of admission until tolvaptan administration. Usage of intravenous carperitide and inotropes was at the discretion of the attending physician. For patients in the GT, to prevent possible hypernatremia induced by tolvaptan, an intra-arterial cannula was inserted in the radial artery for frequent blood sampling. Vital signs, including blood pressure and heart rate, were checked continuously in patients in GT or twice a day in GO. In patients from GT, serum electrolytes were measured and fluid balance was calculated every six hours with intravenous fluid infusion volume control. In patients from GO, blood tests were performed at the time before tolvaptan administration (day 0) and every morning before breakfast until day 7 after starting tolvaptan administration. In each group, based on the calculated fluid balance, attending physicians determined fluid infusion or restriction at their discretion. The choice of conventional therapy, i.e., standard heart failure medicine including renin-angiotensin-aldosterone antagonists, vasodilators, and beta-blockers, was left to the attending physician. We considered weaning from invasive mechanical ventilation and extubation in patients who met the following criteria: a tidal volume of more than 200 mL, an arterial pressure of oxygen more than 80 mmHg with positive end-expiratory pressure 0 and 50% oxygen, improved physical findings and chest X-ray.[8]

EFFICACY AND SAFETY OF TOLVAPTAN TREATMENT

We evaluated daily urine volume, s-Na and serum creatinine (s-Cr) levels, and adverse events including hypernatremia and WRF from day 0 to 7 in both groups. We also evaluated body weight and brain-type natriuretic peptide (BNP) level before starting tolvaptan administration (day

0) and at day 7 after tolvaptan administration. Hypernatremia was defined as s-Na concentration ≥146 mEq/L, and WRF was defined as increases in s-Cr ≥0.3 mg/dL from baseline.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS statistical software (SPSS Inc, Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (SD) and categorical data as percentage. Continuous variables were compared using the unpaired Student's t-test or Mann-Whitney test. Categorical data were compared using the Chi-square or Fisher's exact test, as appropriate. Time course data were analyzed by repeated-measures analysis of variance (ANOVA). In all analyses, p values of <0.05 were considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

As shown in Figure 1, the time from admission to tolvaptan administration was 13.1 ± 23.0 days in GO and 7.6 ± 7.1 days in GT, and the difference was not significant. Comparison of baseline characteristics of the two groups is summarized in Table 1. The rate of intravenous carperitide/inotropes usage was significantly higher in patients from GT than GO (p = 0.042 vs. p = 0.001, respectively), and the dose of loop diuretics before tolvaptan administration was significantly higher in GT than in GO (p = 0.024). A summary of the patients' backgrounds before tolvaptan administration in GT is shown in Table 2. S-Na concentration was below 135 mEq/L in 4 from 12 patients before tolvaptan administration. Both carperitide and inotropes were used in 8 out of 11 patients.

EFFECTS OF TOLVAPTAN ADMINISTRATION ON CLINICAL AND LABORATORY PARAMETERS

The time-course changes in systolic blood pressure, daily urine output, and s-Na levels are shown in Figure 2A, 2B, and 3A, respectively. There was no significant difference in the serial change of each parameter between the two groups during the 7 days after tolvaptan administration. The daily urine volumes from day 1 to 3 were significantly increased in GO, as well as from day 1 to 5 in GT, compared with baseline levels (Figure 2B). In both groups, tolvaptan administration did not result in a significant rise in s-Na levels (Figure 3A). Figure 3B shows the daily changes of s-Na levels in each patient in GT. During the 7 days after initial tolvaptan administration, 4 patients' sodium concentration was raised to 145 mEq/L; however, it did not continue for more than 48 hours, and the sodium concentration did not exceed 146 mEq/L in any of the included patients. Furthermore, from the 4 patients with hyponatremia (<135 mEq/L) before tolvaptan administration (Case 1, 3, 4, and 5 in Table 2), in 3 cases the sodium concentration was corrected within normal range on day 7 (Case 1, 4, and 5).

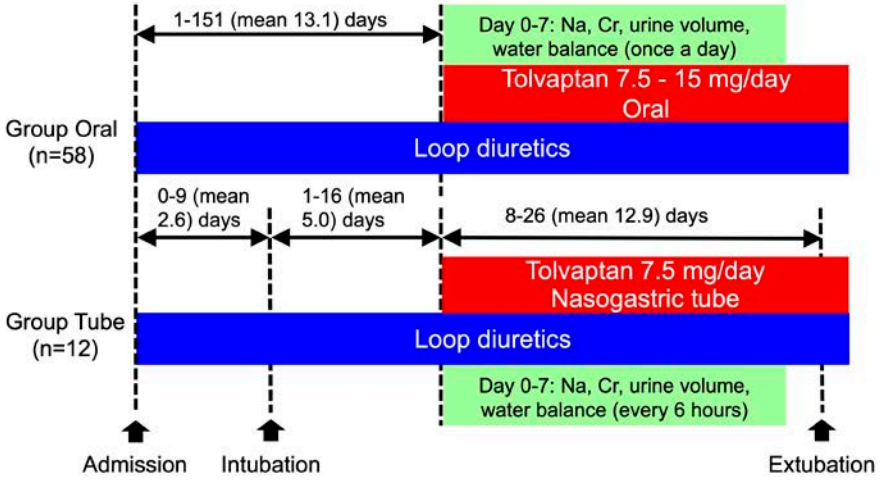

FIGURE 1. Schematic representation of two groups. Seventy consecutively hospitalized patients with severe heart failure were retrospectively divided in two groups. "Group Oral" or "Group Tube" represents patients who were administered tolvaptan orally or via nasogastric tube, respectively.

TABLE 1. Baseline characteristics of patients

	Group Oral (n = 58)	Group Tube (n = 12)	p value
Age (years)	78.0 ± 12.4	74.3 ± 8.0	0.3
Male (%)	27 (47)	8 (67)	0.1
BMI	23.9 ± 5.3	24.7 ± 4.7	0.4
History of heart failure hospitalization (%)	14 (24)	3 (25)	0.6
NYHA class IV (%)	32 (55)	12 (100)	0.005
Etiology of heart failure			0.2
IHD (%)	25 (43)	7 (58)	
HHD (%)	10 (17)	2 (17)	
VHD (%)	11 (19)	1 (8)	
DCM (%)	7 (12)	2 (17)	
Others (%)	5 (9)	0 (0)	
Hypertension (%)	36 (62)	7 (58)	0.9
Diabetes mellitus (%)	27 (47)	5 (42)	0.9
Chronic AF (%)	15 (26)	2 (17)	0.5
Medications at admission			
Loop diuretics (%)	32 (55)	6 (50)	0.7
ACEI/ARB (%)	33 (57)	4 (33)	0.3
Beta blockers (%)	14 (24)	3 (25)	0.9
Aldosterone antagonist (%)	4 (7)	2 (17)	0.7
CCB (%)	28 (48)	6 (50)	0.8
Serum BUN (mg/dL)	29.1 ± 16.3	23.8 ± 12.2	0.2
Serum creatinine (mg/dL)	1.3 ± 0.7	1.3 ± 1.2	0.9
Sodium (mEq/L)	138.0 ± 4.9	136.8 ± 5.2	0.4
Potassium (mEq/L)	4.4 ± 0.5	4.5 ± 0.7	0.2
BNP (pg/mL)	1069 ± 1450	962 ± 636	0.8
LVEF (%)	44 ± 19	40 ± 18	0.6
LVEF <50% (%)	33 (57)	9 (75)	0.5
Systolic blood pressure (mmHg)	117 ± 19	112 ± 14	0.5
Diastolic blood pressure (mmHg)	64 ± 12	60 ± 9	0.07
Heart rate (bpm)	80 ± 22	88 ± 20	0.1
HbA1c (%)	6.4 ± 1.3	6.8 ± 1.1	0.3
Furosemide-equivalent loop diuretics (mg per day)	32.1 ± 19.6	46.7 ± 23.1	0.02
Carperitide (%)	20 (34)	9 (75)	0.04
Inotropes (%)	9 (16)	10 (83)	0.001
IVC diameter (mm)	17.6 ± 5.1	20.9 ± 5.2	0.06
TR-PG (mmHg)	34.8 ± 11.1	44.0 ± 14.3	0.1
Tolvaptan start day from admission (days)	13.1 ± 23.4	7.6 ± 6.8	0.4
Tolvaptan starting dose			0.9
7.5 mg (%)	56 (97)	12 (100)	
15 mg (%)	2 (3)	0 (0)	

Data are presented as number (%) or mean ± SD. BMI, body mass index; NYHA, New York Heart Association; IHD, ischemic heart disease; HHD, hypertensive heart disease; VHD, valvular heart disease; DCM, dilated cardiomyopathy; AF, atrial fibrillation; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BUN, blood urea nitrogen; BNP, brain-type natriuretic peptide; LVEF, left ventricular ejection fraction; IVC, inferior vena cava; TR-PG, tricuspid regurgitation pressure gradient.

LABORATORY DATA AND CLINICAL COURSE

Tolvaptan treatment significantly decreased plasma BNP levels in both groups from day 0 to 7 (p = 0.0133 and 0.0025 for GT and GO, respectively) (Figure 4A), and there was no significant difference in reduction of BNP levels after tolvaptan administration between the groups

TABLE 2. Patient profiles of Group Tube before tolvaptan administration

No.	Age	Gender	Etiology of heart failure	LVEF (%)	AF	Furosemide-equivalent loop diuretics (mg per day)	Na (mEq/L)	Cre-atinine (mg/dL)	SBP (mmHg)	BNP (pg/mL)	Inotropes	Car-perit-ide	Admis-sion to tolvaptan start (days)	Intuba-tion to tolvaptan start (days)
1	76	M	VHD	69	+	60	133	1.3	103	384	+ (DA)	+	1	1
2	59	M	IHD	39	–	40	142	0.54	128	1617	+ (DA/DB)	+	22	16
3	60	M	IHD	23	–	60	131	0.58	104	639	+ (DA/DB)	+	5	4
4	81	F	IHD	30	–	40	126	0.25	110	2061	+ (DA/DB)	+	21	12
5	74	M	IHD	27	–	40	134	1.04	122	1552	+ (DA/DB)	+	8	8
6	80	F	DCM	30	–	40	136	0.71	92	531	+ (DB)	+	7	1
7	72	M	HHD	63	+	40	141	1.03	122	1120	–	+	4	2
8	79	M	IHD	40	–	20	141	3.64	118	289	+ (DB)	–	2	2
9	79	M	HHD	69	–	60	144	1.16	138	224	–	–	4	0
10	71	F	IHD	34	–	20	136	0.72	104	998	+ (DB)	+	7	6
11	75	F	DCM	22	–	60	139	1.3	102	431	+ (DA/DB)	+	4	4
12	85	M	IHD	30	–	100	139	3.81	100	1696	+ (DA/DB)	-	6	4

LVEF, left ventricular ejection fraction; AF, atrial fibrillation; SBP, systolic blood pressure; BNP, brain-type natriuretic peptide; VHD, valvular heart disease; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; HHD, hypertensive heart disease; DA, dopamine; DB, dobutamine

(p = 0.610). We also compared the changes in s-Cr levels from day 0 to 7 between the groups. As shown in Figure 4B, s-Cr levels increased slightly in GO, whereas a slight decrease in s-Cr levels was apparent in GT from day 0 to 7. Consequently, the changes in s-Cr levels from day 0 to 7 were significantly different between groups (p = 0.028). Clinical outcomes of the two groups are shown in Table 3. There were no significant differences in the incidence rate of hypernatremia, WRF, in-hospital death, and in the length of hospital stay between groups. In GT,

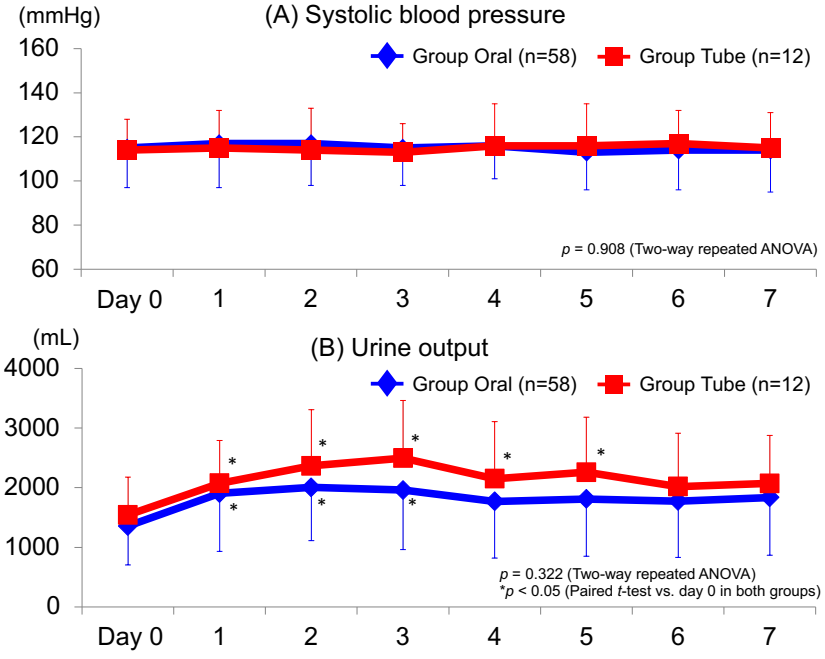

FIGURE 2. The time-course change in systolic blood pressure (**A**) and urine output (**B**) in Group Oral and Group Tube from day 0 (pre-tolvaptan administration) to 7 after tolvaptan administration. Data are presented as mean ± SD.

TABLE 3. In-hospital clinical outcomes of Group Oral and Group Tube

Outcome	Group Oral (n = 58)	Group Tube (n = 12)	p value
Hypernatremia (Na ≥146 mEq/L) within 7 days after tolvaptan administration (%)	5 (9)	0 (0)	0.3
Worsening of renal function (%)	17 (29)	2 (17)	0.4
7-day total urine volume after tolvaptan administration (mL)	14,422 ± 5,197	16,978 ± 8,204	0.5
7-day net water in-out balance after tolvaptan administration (mL)	−2,380 ± 2,517	−4,128 ± 2,845	0.03
Dose of furosemide-equivalent loop diuretics within 7days after tolvaptan administration (mg)	224 ± 125	294 ± 97	0.03
Change in body weight from baseline to 7 days after tolvaptan administration (kg)	−3.3 ± 2.7	−6.3 ± 3.2	0.03
Length of hospital stay after tolvaptan administration (days)	50.7 ± 40.9	75.1 ± 53.5	0.08
In-hospital death (%)	6 (10)	0 (0)	0.3

Data are presented as number (%) or mean ± SD

tolvaptan therapy yielded a higher 7-day total urine volume compared with GO (16,978 ± 8,204 mL vs. 14,422 ± 5,197 mL, respectively; p = 0.557). The net water balance was calculated by subtracting the total urine volume from the total fluid intake plus infusion within 7 days from initial tolvaptan administration, which was compared between groups. GT showed a significantly greater fluid loss than GO (−4,128 ± 2,845 mL vs. −2,380 ± 2,517 mL, respectively; p = 0.028). The amount of loop diuretics used from day 0 to 7 was significantly greater in GT than in GO (294 ± 97 mg vs. 224 ± 125 mg, respectively; p = 0.032). A significant reduction in body weight from day 0 was observed on day 7 in both groups, but the extent of weight loss was significantly greater in GT compared to GO (−6.3 ± 3.2 kg vs. −3.3 ± 2.7 kg, respectively; p = 0.031). During the 7 days after initial tolvaptan administration, 5 patients' sodium levels exceeded 145 mEq/L in GO and no patients showed hypernatremia in GT. In GT, all patients weaned from mechanical ventilation and recovered from CHF. No severe hypernatremia (≥150 mEq/L) was observed, and therefore we did not reduce the tolvaptan dose in both groups.

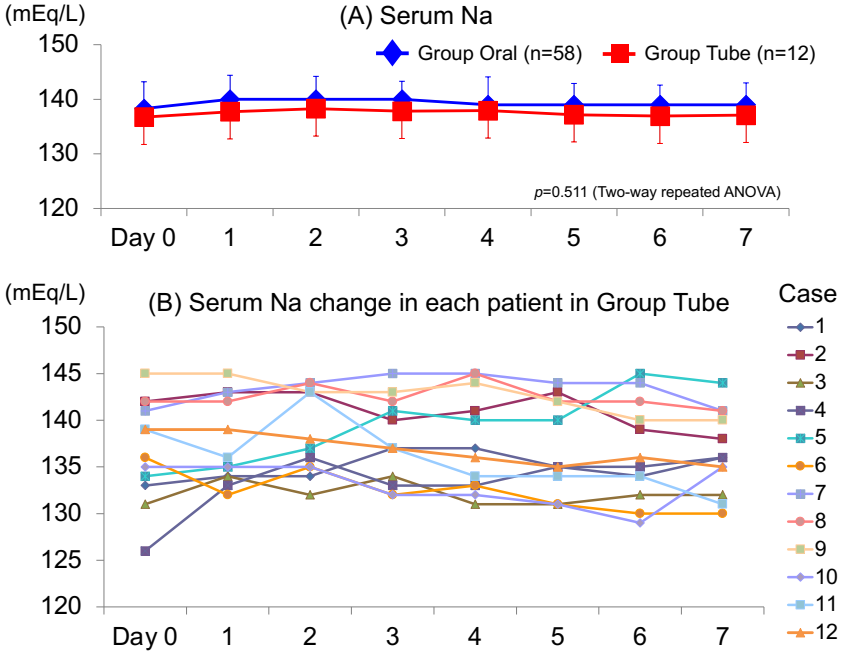

FIGURE 3. **A** – The time-course change in serum sodium in Group Oral and Group Tube from day 0 (pre-tolvaptan administration) to 7 after tolvaptan administration. Data are presented as mean ± SD. **B** – The time-course changes in serum sodium from day 0 to 7 in each patient in Group Tube.

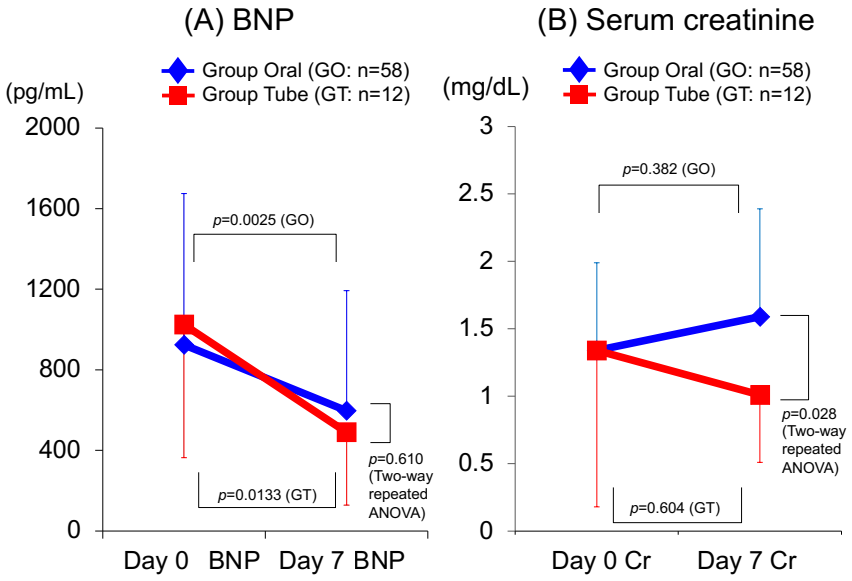

FIGURE 4. Comparison of the BNP (**A**) and serum creatinine (**B**) levels between on day 0 (pre-tolvaptan administration) and 7 after tolvaptan administration in Group Oral and Group Tube. Data are presented as mean ± SD.

DISCUSSIONS

The present study demonstrates the safety and efficacy of tolvaptan treatment in patients with severe CHF under invasive mechanical ventilation with endotracheal intubation who are unable to respond to thirst by fluid ingestion. Tolvaptan has potent aquaretic effects[9] and has been shown to ameliorate symptomatic congestion,[10] but sometimes this results in marked increases in s-Na levels.[11] In the Samsca post-Marketing surveillance In heart faiLurE (SMILE) study, which investigated the use of tolvaptan in 3,349 patients with heart failure, hypernatremia was reported in 4.4% patients, and of the reported cases, 0.4% were assessed as serious.[12] Furthermore, it has been reported that among over 8,000 patients who were admitted to the ICU, a mortality rate of 46.2% was observed in patients with severe hypernatremia,[13] suggesting that it is a predictor for poor prognosis. Therefore, initiation of tolvaptan in an inpatient setting with close monitoring of s-Na is recommended. Especially, in patients who are unable to appropriately respond to thirst stimulation, we should be vigilant against hypernatremia. However, many patients with severe CHF are unable to respond to thirst by fluid ingestion if they need a respiration support by invasive mechanical ventilation. In such cases, adequate diuresis cannot be obtained quickly by conventional therapy of high-dose loop diuretics, and this might result in a delayed recovery from pulmonary congestion, increased susceptibility of WRF, hyponatremia, opportunistic infection, malnutrition, and disuse syndrome. In cases who are refractory to loop diuretics, extracorporeal ultrafiltration has been an effective method to remove fluid from congested patients. However, extracorporeal ultrafiltration therapy is not a cost-saving method compared to tolvaptan administration. In this study, we challenged tolvaptan administration via NGT and demonstrated that tolvaptan treatment in sedated patients could be safely performed under close monitoring in the ICU. In our study, there were 5 cases of asymptomatic hypernatremia, which may indicate temporal hemoconcentration, in GO, whereas no cases in GT. This suggests that safe fluid management was achieved in GT. Furthermore, as shown in the results, in patients from the GT group, s-Cr level was significantly lower and the incidence of WRF tended to be less frequent after 7 days of tolvaptan treatment compared to patients from the GO group, despite greater net fluid loss and higher doses of loop diuretics. These findings are noteworthy, because the use of high-dose loop diuretics has been reported to correlate with increased mortality and deterioration of renal function in patients with CHF.[14-17] Loop diuretics have been shown to decrease renal blood flow and activate the renin-angiotensin and sympathetic nervous systems, which might explain their adverse effects on renal function and poor outcome in patients with CHF.[18,19] Unlike loop diuretics, tolvaptan produces aquaresis and an increase in serum osmolality, which have beneficial effects on the oncotic forces leading to tissue

congestion. These effects produce a sustained movement of fluid from the extravascular to the vascular space without hemodynamic instability.[10] Therefore, tolvaptan does not affect renal hemodynamics or neurohormonal activation.[20] In this study, tolvaptan treatment did not affect blood pressure, it significantly increased urine output, as well as reduced body weight in both groups. Furthermore, tolvaptan combined with conventional diuretic therapy was shown to achieve fluid removal while preserving renal function in patients from GT, more than in GO. In patients from GT, we strictly controlled fluid in-out balance not to fall in excess dehydration under monitoring in the ICU. Intensive therapies could prevent the deterioration of renal function due to hyperdiuresis induced by high doses of loop diuretics, as well as prevent hypernatremia due to aquaresis induced by tolvaptan, in patients from GT. On the other hand, in patients from GO, we could not strictly control fluid in-out balance because these patients were hospitalized in a general ward, and water intake had to be self-controlled unless the attending physician controlled the fluid balance by intravenous infusion. The difference in the levels of patient care intensity might be one of the explanations of preserving renal function and avoiding hypernatremia in patients from GT compared to GO.

The findings of this study suggest that tolvaptan could be a strong option for the treatment of patients with severe CHF who are unable to respond to thirst by fluid ingestion. The early administration of tolvaptan was reported to be associated with a shorter hospital stay and reduced incidence of WRF in patients with heart failure.[21,22] In high-risk populations, such as GT in this study, the early administration of tolvaptan via NGT and the appropriate management of fluid balance could offset the potential renal dysfunction induced by high-dose loop diuretics. Our study also supports the future perspective of intravenous vasopressin V2 receptor antagonists for patients with severe CHF who are unable to intake water orally. Although it is not indicated currently for the indication of heart failure, it may be a promising therapeutic agent for the treatment of severe CHF in the near future.

The present study has several limitations. (i) It was a single-center, retrospective, observational study with a small sample size. (ii) The use of tolvaptan, conventional diuretics, and other drugs were dependent on the judgement of the attending physician. (iii) The severity of the disease was higher, and the use of intravenous inotropes and carperitide was significantly more frequent in GT patients compared to GO. To further clarify the safety and efficacy of tolvaptan treatment in sedated patients with severe CHF, prospective randomized trials comparing added tolvaptan and increasing doses of loop diuretics via NGT should be performed. However, randomized trials using tolvaptan may be difficult since the advantage of tolvaptan therapy over conventional diuretics in the acute phase of heart failure was already demonstrated in other trials.[23,24]

CONCLUSIONS

Early tolvaptan administration via NGT is a possible option under close monitoring in the ICU, in patients without significant hypernatremia, who are unable to respond to thirst by fluid ingestion.

CONFLICT OF INTEREST

Nothing to declare.

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