Safety and Efficacy of Tolvaptan for the Prevention of Contrast-Induced Acute Kidney Injury in Patients with Heart Failure and Chronic Kidney Disease

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Keywords

Tolvaptan · Contrast-induced acute kidney injury · Heart failure · Chronic kidney disease

Abstract

Background: Tolvaptan is a promising drug for the prevention of contrast-induced acute kidney injury (CI-AKI) because it induces aquaresis without adversely affecting renal hemodynamics. CI-AKI is a major cause of acute renal failure associated with increased morbidity and mortality. **Objective:** To investigate the effectiveness of different doses of tolvaptan for the prevention of CI-AKI. **Method:** Ninety-one consecutive patients with congestive heart failure (CHF) and chronic kidney disease (CKD) were prospectively enrolled as the tolvaptan group in this study (T-group; 7.5-mg: $n = 42$, 15-mg: $n = 49$). In addition, 91 consecutive patients with CHF and CKD were collected retrospectively as a control group (C-group, $n = 91$). All patients received continuous intravenous infusion of isotonic saline, and tolvaptan was administered to the T-group. **Results:** One patient developed CI-AKI in the T-group versus 3 in the C-group (1.1 vs. 3.3%, $p = 0.61$). On the other hand, the change of serum creatinine in the

T-group was lower than that in the C-group. Additionally, in the 7.5-mg group, serum creatinine was unchanged up to 72 h after contrast administration, showing a significant difference from the 15-mg group (-0.00 ± 0.09 vs. 0.05 ± 0.12 mg/dL, $p = 0.009$). Similarly, the change of eGFR was significantly smaller in the 7.5-mg group than that in the 15-mg group (0.7 ± 5.4 vs. -2.8 ± 5.1 mL/min/1.73 m², $p = 0.002$). No patient required hemodialysis and there was no prolongation of hospitalization due to exacerbation of heart failure. **Conclusions:** Compared to hydration alone, tolvaptan combined with hydration could be a safer method for preventing CI-AKI while avoiding exacerbation of heart failure, and a dosage of 7.5-mg might be safer than 15-mg.

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Introduction

Contrast-induced acute kidney injury (CI-AKI) is a major complication of coronary angiography and interventional procedures that is associated with various unfavorable outcomes [1, 2]. Congestive heart failure (CHF) and chronic kidney disease (CKD) are well-known risk

factors for CI-AKI [3]. Although periprocedural intravenous hydration with saline is a widely accepted method of prophylaxis [4, 5], in patients with CHF, hydration is usually restricted to a level below that which has been demonstrated to provide protection against CI-AKI because of the risk of overhydration and exacerbation of heart failure [6]. Several studies have demonstrated that combining the administration of diuretics with intravenous infusion of fluid can increase urine output and avoid overhydration [7]. In addition to increasing urine output and thus diluting the contrast medium within the renal tubules to reduce direct toxicity, diuretics may have a protective effect against renal medullary ischemia, which is a possible mechanism of CI-AKI [8].

Tolvaptan is a selective nonpeptide vasopressin V2 receptor antagonist that increases electrolyte-free excretion of water [9]. Some studies have shown a beneficial effect of tolvaptan on renal function in heart failure [10], and tolvaptan has also been reported to decrease the pulmonary capillary wedge pressure and dose-dependently increase urine output in patients with heart failure [11].

To investigate the effectiveness of different doses of tolvaptan for the prevention of CI-AKI, we conducted a prospective dose comparison study in patients undergoing cardiac catheterization who received intravenous hydration combined with 7.5 mg or 15 mg of tolvaptan.

Methods

Subjects

We prospectively screened consecutive patients with CKD and CHF scheduled for coronary angiography/angioplasty at Showa University Northern Yokohama Hospital (Yokohama, Japan) from October 2012 to April 2013. The estimated glomerular filtration rate (eGFR) was assessed on admission by the modified formula of Matsuo et al. [12]. CKD was defined as eGFR <60 mL/min/1.73 m², based on the recommendations of the National Kidney Foundation [13]. CHF was established in two ways. First, it was defined by a cardiologist on the basis of a history of CHF of at least 6 months' duration as defined by at least one prior episode of symptomatic heart failure, characterized by dyspnea at rest or on exertion and radiographic evidence of cardiomegaly and pulmonary congestion. Another definition was that continued dyspnea (New York Heart Association [NYHA] class II–IV) despite optimal medical therapy. The other inclusion criteria were the ability to take oral medication, patients of either sex aged over 20 years, and the ability to provide written informed consent. Patients with any of the following conditions were excluded from this study: (i) a history of allergy to tolvaptan or similar compounds, (ii) anuria (urine output <100 mL/day), (iii) inability to feel thirsty or difficulty in drinking, (iv) serum sodium >147 mEq/L, (v) pregnancy or possible pregnancy (female patients), (vi) prior use of tolvaptan, and (vii) acute coronary syndrome.

A total of 93 patients were not included for the following reasons: hemodialysis ($n = 89$) and refusal of consent ($n = 4$). The remaining 91 patients were enrolled as the tolvaptan group in this study (T-group, $n = 91$). To establish matched pairs, we also collected 91 consecutive patients retrospectively with CKD and CHF who experienced hydration before coronary procedure from August 2011 to September 2012 as the control group (C-group, $n = 91$).

Study Protocol

Baseline values of the following parameters were recorded: demographic data, medical history, current medications, eGFR, CI-AKI risk score, and left ventricular ejection fraction. The preprocedural serum creatinine level was measured before initiation of prophylaxis for CI-AKI. The CI-AKI risk score was calculated according to the algorithm of Mehran et al. [14]: hypotension (score = 5), intra-aortic balloon pump support [5], CHF [4], age >75 years [4], diabetes mellitus [3], eGFR <60 mL/min/1.73 m² [2–6], pre-existing anemia [3], and volume of contrast medium administered (1 for each 100 cm³). All patients received continuous intravenous infusion of isotonic saline at 1 mL/kg/h via a standard 22-gauge catheter inserted into an antecubital vein from at least 12 h before the procedure to 18–24 h after it (Fig. 1). The total volume of intravenous hydration administered for CI-AKI prophylaxis and the total urine volume were recorded. The C-group patients ($n = 91$) received only hydration without tolvaptan administration as described. Among the 91 patients in T-group, 42 patients received 7.5 mg of tolvaptan (low-dose group) during the period from October to December 2012, while 49 patients received 15 mg of tolvaptan (high-dose group) during the period from January to April 2013. The first dose of tolvaptan was administered before the coronary procedure and the same dose was given again after 24 h. A standard Foley catheter was inserted into the bladder for urine collection precisely before the procedure and was removed 24 h after the procedure. Blood samples were collected before the procedure and at 4, 8, 24, and 72 h after the administration of contrast medium. Urine samples were also collected before the procedure and at 0, 4, 8, and 24 h after the administration of contrast medium. Chest X-ray films were obtained at least 24 h before and 48–72 h after the procedure. Periprocedural medical management, angioplasty techniques, and the contrast medium dose were decided by each patient's cardiologist and the interventional cardiologist on the basis of current guidelines.

Study Endpoints

The primary endpoint was the frequency of CI-AKI, which was defined as an increase of $\geq 25\%$ or ≥ 0.5 mg/dL in the serum creatinine level within 72 h after the administration of contrast medium [15]. Secondary endpoints were (i) the actual or percent (%) change of serum creatinine, eGFR, sodium, and brain natriuretic peptide within 72 h after the administration of contrast medium, and (ii) major postprocedural in-hospital adverse events, including cardiogenic shock, clinically important arrhythmia, CI-AKI requiring renal replacement therapy (hemofiltration or hemodiafiltration), pulmonary edema, and death.

Drugs

Nonionic iodinated contrast medium (Iopamiron 370) was obtained from Nihon Schering (Osaka, Japan) for use in all patients, and tolvaptan was obtained from Otsuka Pharmaceutical Co. (Tokyo, Japan).

Fig. 1. Time course of change in urine osmolality in the 7.5-mg and 15-mg groups * $p < 0.05$ versus baseline (mean $\pm$ standard deviation, paired t test).

Statistical Analysis

Continuous variables are presented as the mean $\pm$ standard deviation and were compared using Student's t test or analysis of variance (ANOVA). Categorical data are expressed as frequencies and were compared using Pearson's χ^2 test. Primary and secondary endpoints were analyzed according to the intention-to-treat principle. Multiple regression analysis was used to evaluate the relationship between the change of creatinine and other factors. All the independent variables with a univariate p value < 0.25 were included in the model. The beta coefficient (β) and 95% confidence interval were calculated. A probability (p) value < 0.05 (two-tailed) was accepted as indicating statistical significance. All analyses were performed with JMP® 12 software (SAS Institute Inc., Cary, NC, USA).

Ethical Considerations

The ethics committee of our institution approved the study protocol. All patients gave written informed consent to participate in this study. The trial was registered at <http://www.umin.ac.jp/ctr/index-j.htm> (trial identifier: UMIN000009924).

Results

Baseline characteristics and laboratory findings of the all groups are displayed in Table 1. There were no significant differences between the T-group and the C-group in terms of age, gender, body mass index, and left ventricular ejection fraction. Although hypertension was less frequent in the 15-mg group than that in the 7.5-mg group (77.6 vs. 90.5%, $p = 0.09$), there was no significant

difference between the groups. The serum eGFR level was similar in both the T-group and the C-group (50.4 ± 9.7 and 48.8 ± 8.6 mL/min/1.73 m²) and also similar within the T-group (49.9 ± 8.0 vs. 50.9 ± 8.2 mL/min/1.73 m² in the 7.5-mg and 15-mg group, respectively).

Table 2 summarizes the fluid balance including the contrast media volume in the procedure. There was no significant difference in hydration volume but oral water intake on the second day was significantly greater in the T-group than that in the C-group. Also, urine output was significantly greater in the T-group on the first and second days after the procedure. Moreover, Table 2 shows the fluid balance of both the 7.5-mg and 15-mg groups. Similarly, there were no significant differences in oral water intake, hydration volume, and contrast medium volume between the two groups. However, the mean urine volume was significantly greater in the 15-mg group than in the 7.5-mg group during the period from 24 to 48 h after the procedure ($2,523 \pm 950$ vs. $2,075 \pm 950$ mL, $p = 0.04$). Moreover, urine osmolality of the 7.5-mg and 15-mg groups was measured before and after the administration of contrast medium (Fig. 1). The urine osmolality at 0 h after the administration of contrast medium was the smallest and significantly decreased from baseline. The osmolality at 4 h still indicated smaller data but that recovered at 8 h after administration. Urine osmolality after taking tolvaptan in the 15-mg group was smaller than that in the 7.5-mg group until 24 h after administration,

Table 1. Baseline clinical characteristics of all groups

	T-group (n = 91)	C-group (n = 91)	p value	7.5-mg group (n = 42)	15-mg group (n = 49)	p value
Age, years	73.0±8.2	73.3±8.1	0.33	73.6±7.4	72.5±8.8	0.53
Male	73 (80.2)	67 (73.6)	0.29	34 (81.0)	39 (79.6)	0.87
Height, cm	161.8±8.1	162.3±8.9	0.42	161.6±7.9	161.9±8.4	0.86
Body mass index, kg/m ²	24.4±2.8	24.4±2.4	0.82	24.4±2.4	24.4±3.1	0.89
Ejection fraction, %	45.4±8.1	43.8±6.5	0.31	42.8±7.8	42.1±7.8	0.52
Systolic BP, mm Hg	126.2±16.8	120.6±18.2	0.24	123.8±15.9	128.3±17.4	0.21
Diastolic BP, mm Hg	69.6±10.1	70.3±9.3	0.35	68.0±10.4	71.0±9.7	0.16
CI-AKI risk score	13 (5–21)	12 (5–18)	0.20	13 (6–21)	14 (5–20)	0.18
Hypertension	76 (83.5)	73 (80.2)	0.56	38 (90.5)	38 (77.6)	0.09
Diabetes	52 (57.1)	48 (52.7)	0.55	27 (64.3)	25 (51.0)	0.20
Dyslipidemia	52 (57.1)	58 (63.7)	0.36	28 (66.7)	24 (49.0)	0.09
Albumin, g/dL	3.7±0.4	3.8±0.3	0.23	3.6±0.3	3.7±0.3	0.16
Uric acid, mg/dL	6.2±1.5	6.3±1.7	0.58	6.1±1.4	6.3±1.6	0.60
Urea nitrogen, mg/dL	19.7±6.3	18.1±5.3	0.12	17.3±4.3	17.7±4.0	0.23
Creatinine, mg/dL	1.1±0.3	1.2±0.3	0.84	1.1±0.2	1.1±0.3	0.78
eGFR, mL/min/1.73 m ²	50.4±9.7	48.8±8.6	0.71	49.9±8.0	50.9±8.2	0.63
Hemoglobin A _{1c} , %	6.4±1.1	6.5±1.2	0.48	6.6±1.0	6.3±1.1	0.26
Serum sodium, mEq/L	140.5±2.5	140.5±1.6	0.89	141.5±1.9	140.9±1.8	0.22
Serum potassium, mEq/L	4.4±0.4	4.5±0.4	0.34	4.4±0.3	4.4±0.4	0.73
Serum BNP, pg/mL	266.9±75.4	236.4±84.9	0.19	257.9±77.8	270.2±60.2	0.13

Data are expressed as *n* (%), mean ± standard deviation, or median (min–max). BP, blood pressure; CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

Table 2. Fluid balance of all groups

	T-group (n = 91)	C-group (n = 91)	p value	7.5-mg group (n = 42)	15-mg group (n = 49)	p value
Urine output, mL/day						
0–24 h after the procedure	3,461±1,142	1,886±658	0.02	3,593±997	3,348±1,250	0.31
24–48 h after the procedure	2,282±1,016	1,163±350	0.01	2,075±1,033	2,523±950	0.04
Water intake, mL/day						
0–24 h after the procedure	1,060±567	724±331	0.14	984±478	1,124±631	0.24
24–48 h after the procedure	1,025±576	610±287	0.08	921±566	1,114±575	0.11
Dose of contrast medium, mL	128.4±58.0	131.6±59.3	0.44	132.9±60.9	124.5±55.8	0.50
Hydration volume, mL	986±238	963±216	0.41	967±244	1,014±232	0.22

Data are expressed as mean ± standard deviation.

but not significantly. With regard to the primary end-point, CI-AKI only developed in 1 patient from the T-group and in 3 patients from the C-group during the present study (Table 3), but it was not statistically significant. There were no major postprocedural adverse events in this study. On the other hand, the postprocedural change (increase) of creatinine was significantly larger in the C-group (0.18 ± 0.13 vs. 0.03 ± 0.11 mg/dL, $p = 0.002$) and

the percent change of creatinine was also significantly greater in the C-group than that in the T-group (14.7 ± 12.2 vs. $2.9 \pm 9.8\%$, $p = 0.001$). Similarly, the eGFR showed a significant decrease in the C-group compared with the T-group (-6.8 ± 6.0 vs. -1.2 ± 5.5 mL/min/1.73m², $p < 0.001$). When serum sodium levels were measured at 4, 8, 24, and 48–72 h after the procedure, the change of serum sodium was significantly greater in the T-group than that

Table 3. Primary and secondary outcomes in the two groups

	T-group (n = 91)	C-group (n = 91)	p value	7.5-mg group (n = 42)	15-mg group (n = 49)	p value
CI-AKI	1 (1.1)	3 (3.3)	0.61	0 (0)	1 (2.0)	0.35
Major in-hospital adverse events	0 (0)	1 (1)	1	0 (0)	0 (0)	–
Cardiogenic shock	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Clinically important arrhythmia	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Renal replacement therapy	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Pulmonary edema	0 (0)	1 (1)	–	0 (0)	0 (0)	–
Death	0 (0)	0 (0)	–	0 (0)	0 (0)	–
Change of creatinine, %	2.9±9.8	14.7±12.2	0.001	–0.5±8.8	5.7±9.8	0.002
Change of creatinine, mg/dL	0.03±0.11	0.18±0.13	0.002	–0.00±0.09	0.05±0.12	0.009
Change of eGFR, mL/min/1.73 m ²	–1.2±5.5	–6.8±6.0	<0.001	0.7±5.4	–2.8±5.1	0.002
Change of BNP, pg/mL	–20.3±79.1	57.4±88.6	0.01	–35.5±92.7	–7.3±63.5	0.09
Change of Na, mEq/L						
0–4 h	0.6±2.0	–0.2±1.4	0.04	–0.2±1.6	1.2±2.0	0.001
0–8 h	1.0±2.3	0.4±1.0	0.01	–0.2±1.7	1.9±2.3	<0.001
0–24 h	2.3±2.2	0.3±0.9	<0.001	1.4±1.7	3.1±2.3	<0.001
0–72 h	2.5±2.2	0.3±0.8	<0.001	1.7±1.8	3.2±2.2	0.001

Data are expressed as *n* (%) or mean ± standard deviation. CI-AKI, contrast-induced acute kidney injury; eGFR, estimated glomerular filtration rate; BNP, brain natriuretic peptide.

in C-group throughout the postprocedural period (Table 3). Moreover, we also compared those data between the 7.5-mg and the 15-mg group. As a result, the change of creatinine level and eGFR was statistically significantly greater in the 15-mg group. Also, the change of serum sodium levels was greater in the 15-mg group, but nobody experienced severe hyponatremia in this study.

Multivariate analysis of variables related to the change of serum creatinine demonstrated that use of tolvaptan and older age were significant predictors of worsening kidney function ($\beta = 0.16$, $p = 0.001$ and $\beta = 0.10$, $p = 0.04$, respectively) (Table 4).

Discussion

The main findings of this study were as follows: first, CI-AKI only occurred in 1 patient in the T-group despite 3 patients in the C-group experiencing CI-AKI; there was a low incidence of this outcome and no significant difference between the two T-groups. Second, urine output was significantly greater in the 15-mg group and serum Na also increased significantly in this group. Third, the change of eGFR was significantly greater in the C-group than that in the T-group. Moreover, the 15-mg group experienced a significantly greater decrease of kidney function than the 7.5-mg group. According to multivariate

Table 4. Multivariate logistic analysis of the relation between the change of creatinine and clinical factors in all patients

	β -coefficient	p value
Age	0.10	0.04
Baseline serum creatinine level	0.12	0.09
Ejection fraction	–0.09	0.20
Contrast medium volume	–0.03	0.19
Tolvaptan use	0.16	0.001

analysis, use of tolvaptan showed a negative correlation with the deterioration of eGFR.

Two mechanisms of CI-AKI have been suggested [16, 17]. One is that contrast medium directly damages epithelial cells of the proximal tubules, while the second is that osmotic diuresis due to the administration of contrast medium leads to a reduction of renal blood flow and causes renal medullary ischemia. Based on this mechanism, hydration with 0.9% sodium chloride has become widely used as the standard method for the prevention of CI-AKI [18]. However, standard hydration can lead to volume overload in patients with heart failure and may result in renal dysfunction, making hydration a difficult option in these patients. It is possible to perform hydration with 0.45% sodium chloride as an alternative, but a

randomized clinical trial demonstrated that this was less effective than 0.9% sodium chloride [6].

The CI-AKI risk score was developed to predict the risk of CI-AKI in patients receiving contrast medium, with a total score of ≤ 5 , 6–10, 11–16, and ≥ 16 predicting a risk of 7.5, 14, 26.1, and 57.3%, respectively [19]. The CARE study targeted similar patients to those in the present study with an eGFR of 20–59 mL/min/1.73 m², but the incidence of CI-AKI was higher in the CARE study at 5–6% [20]. Considering the median CI-AKI risk score of the patients in the present study, the frequency of CI-AKI was quite low at 1.1% (1/91 patients). This may have been related to rapid removal of water by the administration of tolvaptan which prevented exacerbation of heart failure by volume overload.

Unlike conventional diuretics, tolvaptan is an oral vasopressin V2 receptor antagonist that blocks the action of arginine vasopressin on the collecting ducts of the kidney and inhibits retention of free water, thereby having a diuretic effect while ameliorating hyponatremia [21]. This means that tolvaptan increases renal blood flow without reducing the serum sodium level and could prevent renal medullary ischemia/hypoxia as a result of increased renal blood flow without aggravating heart failure if used for the prophylaxis of CI-AKI. Despite reports that diuretics can prevent CI-AKI, the effect of these drugs remains controversial [22]. Majumdar et al. [23] found that forced euvolemic diuresis with saline, mannitol, and furosemide was associated with a significantly higher incidence of CI-AKI than saline hydration (50 vs. 28%, $p = 0.03$). However, Stevens et al. [24] performed a randomized trial in 98 patients with CKD who received forced diuresis with intravenous crystalloid, furosemide, mannitol, and low-dose dopamine or intravenous crystalloid and matching placebos, and they reported a lower incidence of CI-AKI with forced diuresis (21.6 vs. 45.9%).

In the present study, multivariate analysis suggested that tolvaptan had a negative correlation with the change of serum creatinine level. On the other hand, the creatinine and eGFR levels became significantly worse in the 15-mg group than in the 7.5 mg group. Urine output was comparable between groups, but the urine osmolality level in the 15-mg group was lower from 0 to 24 h after administration. The blood concentration of tolvaptan could be different in two groups and it may affect the total urine output in 24–48 h. Therefore, combining 7.5 mg of tolvaptan with hydration may be a promising method of preventing CI-AKI without volume overload.

The present study had several limitations. The sample size of this study was relatively small. Therefore, no sig-

nificant difference was observed regarding the primary endpoint. However, the incidence of CI-AKI was smaller than that in the CARE study with similar subjects. Moreover, it was a single-center, nonrandomized trial. In the future, a comparison of hydration using 0.9% saline with or without 7.5 mg of tolvaptan should be considered prospectively. Another limitation is that there was no data concerning the serum concentration of tolvaptan in this study. Kim et al. [25] concluded that the mean peak serum concentrations occurred between 1 and 4 h after dosing. It was unclear whether all of the cases received the maximum effect of tolvaptan. However, we investigated urine osmolality at several time points. In that analysis, the urine osmolality showed a minimum result at 0 h after contrast administration. That means the serum concentration of tolvaptan existed in an effective concentration. On the other hand, in contrast to CT angiography, contrast medium was administered several times during coronary angioplasty. As a result, it was a bit difficult to match the timing of the maximum concentration of tolvaptan and the administration of contrast medium consistently.

In conclusion, hydration by infusion of 0.9% saline combined with oral tolvaptan could be effective in preventing CI-AKI in CHF patients with CKD undergoing cardiac catheterization, and a dosage of 7.5-mg might be better than 15-mg for preventing renal injury while avoiding exacerbation of heart failure.

Statement of Ethics

The ethics committee of our institution approved the study protocol. All patients gave written informed consent to participate in this study.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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