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Efficacy of Tolvaptan in Patients with Volume Overload after Cardiac Surgery

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ABSTRACT

Background: The vasopressin type 2 receptor antagonist tolvaptan (TLV) has recently become available for treating congestion. However, there is no evidence confirming the efficacy of TLV for patients with volume overload after cardiac surgery. Here, we retrospectively studied the efficacy of TLV in patients with volume overload after cardiac surgery.

Methods: We enrolled a total of 39 patients who had volume overload after cardiac surgery and who were treated with our protocol of body fluid management. The primary endpoint of this study was to evaluate the hospitalization period, while the secondary endpoints were to estimate adverse events such as hypotension, electrolyte abnormality, presence or absence of renal dysfunction and liver damage, and the incidence of atrial fibrillation (AF).

Results: The hospitalization period of the T (TLV) and C (furosemide and spironolactone) groups was 12.3 ± 2.6 days and 14.7 ± 4.4 days, respectively (P = .044), the mean urine volume was 2761.5 ± 850.3 mL/day and 2205.2 ± 598.5 mL/day, respectively (P = .024), and the incidence of postoperative AF after diuretics administration was 2/19 (11%) and 9/17 (52%), respectively.

Conclusion: TLV successfully and rapidly improved organ congestion without causing hemodynamic abnormalities (hypotension, arrhythmia development), electrolyte abnormality, liver damage or renal dysfunction, thus significantly reducing the period of hospitalization.

INTRODUCTION

A patient under the influence of operative stress and cardiopulmonary bypass after open heart surgery often exhibits a clinical condition similar to transient acute heart failure where the body water balance is in excess. During a postoperative course, this excessive water effusion causes organ congestion and has a major influence on the final prognosis [Hirleman 2008]. Fluid adjustment utilizing diuretics (loop diuretics, aldosterone blockers, and carperitide) is the most common method for the management of postoperative body fluid.

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Arginine vasopressin (AVP) is secreted from the posterior pituitary in response to an elevation in plasma osmolality, decreases in arterial pressure, and stressors such as pain, hypoxia, and surgery. AVP is known to play an important role in water metabolism by facilitating water reabsorption at the renal collecting duct via the V2 receptor (V_2R). Tolvaptan (TLV), authorized in Japan in 2010, is a selective antagonist of the vasopressin V_2R that increases urine volume without increasing electrolyte excretion into the urine, as compared with existing diuretics, such as loop diuretics [Yamamura 1998]. In Japan, TLV has been approved for use in heart failure patients with volume overload when adequate responses are not obtained with other diuretics. This approval was based on results identifying the efficacy and safety of TLV in a cardiac edema study (QUEST) [Matsuzaki 2011]. More recently, the possibility that TLV also provides a positive influence for helping with the early prognosis of acute heart failure has been shown [Wuerz 1992; Peacock 2009]. Physiologically, following cardiac surgery, the water balance becomes superabundant due to an increase in the reabsorption of water caused by an increase in vasopressin. TLV, a vasopressin V_2R antagonist, therefore helps to improve this stromal edema by relieving the effusion of the interstitial fluid. In the current study, we analyzed the water diuresis effect of TLV, as compared to existing diuretics, and examined its efficacy for patients with volume overload after cardiac surgery.

MATERIALS AND METHODS

Standard Protocol in Our Institution (September 1, 2013)

The standard protocol of body fluid management used after cardiac surgery is described as follows: (1) All patients were initially treated with intravenous furosemide with or without carperitide administration when urine volume decreased after cardiac surgery. (We used carperitide for the patients more than systolic blood pressure 120 mmHg.); (2) After weaning from mechanical ventilation, the standard diuretics (furosemide: 20 mg and spironolactone: 25 mg) were used on patients whose weight gain from the first to the second day was more than 3 kg; (3) Diuretic administration was ended when the postoperative weight was 1 kg less than the preoperative weight. Patients with dialysis, unstable hemodynamics, and severe infection were excluded from the protocol. From December 1, 2013, when the standard protocol was resulting in a poor response (urine volume/day <1000 mL after intravenous furosemide with or without carperitide administration), we administered TLV at doses of 7.5 mg daily without using

furosemide and spironolactone until the postoperative weight was 1 kg less than the preoperative weight.

Study Design and Population

A retrospective and observational study was performed to determine the efficacy of TLV for patients with volume overload after cardiac surgery in a single center. A total of 104 cardiac surgeries were performed between September 1, 2013 and February 28, 2014; of these, 39 patients with volume overload after surgery who were subsequently treated by our protocol were enrolled. Inclusion criteria were: (1) successful weaning from mechanical ventilation by 0-3 days after surgery; (2) safe oral intake; (3) weight gain from the first to the second day following weaning from mechanical ventilation was more than 3 kg. Exclusion criteria were: (1) dialytic cases; (2) unstable hemodynamics; (3) severe infection; (4) hypernatremia (Na >145 mEq/L). The 39 patients were divided into 2 groups: a TLV group (December 1, 2013 to February 28, 2014; T group: n = 20) and a conventional group (September 1, 2013 to November 30, 2013; C group: n = 19). Conventional treatment included peroral loop diuretics (furosemide) and aldosterone blocker (spironolactone).

Within 1 or 2 days after weaning from mechanical ventilation, 20 patients were treated with oral TLV at doses of 7.5 mg daily without using furosemide and spironolactone until their postoperative weights were 1 kg less than their preoperative weight. Similarly, 19 patients were treated with oral furosemide and spironolactone (F/S) at doses 20/25 mg daily. The administration of existing diuretics (furosemide iv or carperitide civ: 0.025 γ) was discontinued when treatment with oral medicine, such as TLV or F/S, was initiated. This study protocol was approved by the Ethics Committee of the respective authority of our institution. Written informed consent was obtained from all patients in the T group before inclusion in the study.

Clinical Evaluation

We investigated patients' preoperative characteristics such as the baseline body weight and the presence or absence of diabetes mellitus, chronic kidney disease, hypertension, chronic obstructive pulmonary disease, and atrial fibrillation (AF). Echocardiography was performed to assess left ventricular ejection fraction, pleural effusion, and pericardial effusion. Levels of plasma human atrial natriuretic peptide, plasma B-type natriuretic peptide, plasma aldosterone concentration, plasma renin activity, serum sodium, potassium, alanine aminotransferase, aspartate aminotransferase, total bilirubin, and estimated glomerular filtration rate (eGFR) were measured before and after the administration of TLV or F/S. During the use of TLV or F/S, blood pressure, body weight, and daily urine volume were measured every day. The operative risk (mortality and morbidity) was estimated by the EuroSCORE Π method. The primary endpoint of this study was to evaluate the duration of the hospitalization stay. The discharge criteria of our institution is as follows: (1) There are no abnormal findings in postoperative examinations such as echocardiography, CT scan and blood test; (2) A prescribed rehabilitation menu is cleared (until stairs walk). When a discharge is postponed by social circumstances, we do not count the postponement period for length of stay. Secondary endpoints were adverse events, such as hypotension (<90 mmHg), hyper- and hyponatremia, hypokalemia, presence or absence of renal dysfunction and liver damage, incidence of the AF, pleural effusion puncture, and pericardial effusion.

Statistical Analysis

All statistical analyses were performed with the StatView-J software (version 5, SAS Institute, Cary, NC). Categorical

Table 1. Patients' Characteristics Preoperatively*

	T group (n =20)	C group (n = 19)	*P*
Age, y	69.4 ± 10.8	72.4 ± 6.5	.30
Sex, M/F	11/9	12/7	.84
Height, cm	161.8 ± 6.2	163.0 ± 6.7	.56
Weight, kg	60.9 ± 11.1	57.0 ± 10.1	.25
DM	7/20	8/19	.89
CKD	5/20	7/19	.64
HT	10/20	11/19	.85
COPD	2/20	1/19	.99
Sinus rhythm	19/20	17/19	.95
EF, %	62.1 ± 8.1	59.9 ± 12.4	.51

*Data are presented as the mean ± SD where indicated. DM indicates diabetes mellitus; CKD, chronic kidney disease; HT, hypertension; COPD, chronic obstructive pulmonary disease; EF, ejection fraction.
CKD: eGFR (estimated glomerular filtration) <60 ml/min/1.73 m^2.

Table 2. Patients' Serum Data before Administration*

	T group (n = 20)	C group (n = 19)	P
eGFR, mL/min/1.73 m^2	78.6 ± 22.8	66.9 ± 21.6	.10
Na, mEq/L	136.5 ± 3.0	135.8 ± 2.4	.46
K, mEq/L	4.1 ± 0.3	4.2 ± 0.4	.35
HANP, pg/mL	187.9 ± 287.1	515.7 ± 708.9	.07
BNP, pg/mL	237.8 ± 179.1	290.0 ± 162.2	.38
PAC, pg/mL	75.1 ± 40.2	97.8 ± 65.8	.22
PRA, ng/mL/h	3.9 ± 3.8	8.9 ± 14.0	.13
AST, IU/L	34.9 ± 22.3	36.0 ± 18.3	.86
ALT, IU/L	19.9 ± 10.6	17.9 ± 15.4	.63
T-Bil, mg/dL	1.1 ± 0.7	1.1 ± 1.1	.76

*Data are presented as the mean ± SD where indicated. eGFR indicates estimated glomerular filtration; HANP, human atrial natriuretic peptide; BNP, B-type natriuretic peptide; PAC, plasma aldosterone concentration; PRA, plasma renin activity; AST, aspartate aminotransferase; ALT, alanine aminotransferase; T-Bil, total bilirubin.

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Table 3. Medications Administered

	T group (n = 20)	C group (n = 19)	*P*
Furosemide (IV), mgl	26.0 ± 9.4	25.2 ± 9.0	.80
Carperitide(CIV:0.025γ), n	3	6	.39
ARB, n	5	5	.92
ACEI, n	1	1	.97
β blocker, n	4	5	.71
Statin, n	8	8	.89

ARB indicates angiotensin Π receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; IV, intravenous; CIV, continuous intravenous.

Table 4. Operative Procedure

T group (n = 20)		C group (n = 19)	
OPCAB, n	7	OPCAB	5
AVR, n	4	AAR (for DA)	3
MVP, n	2	MVR	2
AAR (for DA), n	2	TAR	2
Other, n	2	AVR	2
AVR+MAP, n	1	AVR+MVR	1
MVP+CABG, n	1	DVR	1
AVR+CABG, n	1	MVP	1
		MVP+CABG	1
		MVR+CABG	1

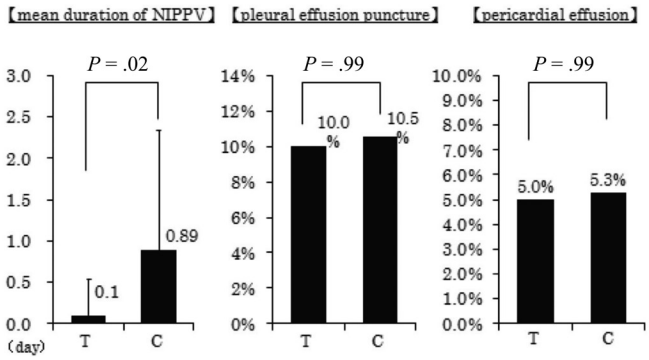
OPCAB indicates off-pump coronary artery bypass; AVR, aortic valve replacement; AAR, ascending aorta replacement; MVP, mitral valve plasty; MVR, mitral valve replacement; TAR, total arch replacement; DVR, double valve replacement; MAP, mitral annuloplasty; DA, dissected aorta.

variables were expressed as a percentage of the sample. Continuous variables were expressed as mean ± standard deviation. Significance between T group and C group was determined by unpaired Student t test for continuous variables and by χ^2 test for categorical variables. Blood sample data and echocardiographic data from the baseline in the same group were determined by paired t test. If data were not distributed normally, the Mann-Whitney U test was used. Missing data were excluded from analysis. We used Fisher exact probability test for the evaluation of adverse events. A *P* value less than .05 was considered statistically significant.

RESULTS

Comparisons of Baseline Clinical Characteristics between T and C Groups

The comparison of baseline clinical characteristics, including age, height, body weight, patient background, echocardiographic data, and laboratory data between the T and C groups are shown in Tables 1 and 2. There was no significant difference in the baseline clinical characteristics between the two groups. Transvenous administration of furosemide (20 mg iv, once or twice/day) was performed for all patients (26.0 ± 9.4 mg in the T group and 25.2 ± 9.0 mg in the C group, *P* = .80), but the frequency of carperitide (0.025 γ) use was 3/20 in the T group and 6/19 in the C group (*P* = .39). Concomitant medications, including β-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and statin were not significantly different between these two groups (Table 3). The precise operative method can be seen in Table 4. The number of mitral valve surgeries was 4/20 in the T group and 7/19 in the C group (*P* = .41). The evaluation of the operative risk via the EuroSCORE II showed no significance between the two groups (*P* = .30). The operative and postoperative data, including the number of off-pump coronary artery bypass, operating time, cardiopulmonary bypass time, blood loss, and postoperative δ body weight, are shown in Table 5. There were no significant differences in these parameters between the two groups. However, the mean administration duration of the respective drug showed a significant difference (3.8 ± 1.5 days in the T group and 5.8 ± 2.4 days in the C group, *P* = .004).



Mean duration of NIPPV and incidence of pleural effusion puncture, and pericardial effusion.

Clinical Effects

As shown in Table 5, average daily urine volume during the use of TLV or F/S was significantly higher in the T group than the C group (2761.5 ± 850.3 mL/day and 2205.2 ± 598.5 mL/day, respectively; *P* = .024). Moreover, the duration to regain weight was significantly shorter in the T group (3.8 ± 1.5 days and 5.8 ± 2.4 days, respectively; *P* = .004). Furthermore, the incidence of dyspnea as a sign of pulmonary congestion was 1/20 (5%) in the T group and 6/19 (31%) in the C group (*P* = .079). There was no significant difference between the two groups, but the duration of noninvasive positive pressure ventilation (NIPPV) use was significantly shorter in the T group than in the C group (0.1 ± 0.44 days and 0.89 ± 1.44 days, respectively; *P* = .024 (Figure). Finally, the hospitalization duration of the T and C groups was 12.3 ± 2.6 days and 14.7 ± 4.4 days, respectively (*P* = .044).

Table 5. Operative and Postoperative Data*

	T group (n = 20)	C group (n = 19)	*P*
EuroSCORE Π, %	4.2 ± 9.0	7.3 ± 9.8	.30
OPCAB, %	7/20 (35%)	5/19 (26%)	.99
Operating time, min	280.9 ± 59.1	297.5 ± 71.4	.43
CPB, min	97.2 ± 74.6	116.5 ± 79.3	.44
Blood loss, ml	1014.7 ± 776.0	843.8 ± 846.7	.51
Postoperative δBW, kg	5.2 ± 1.4	5.7 ± 2.1	.40
Starting date, ~POD	2.2 ± 0.5	2.6 ± 1.0	.06
Dose of diuretics, mg/day	all cases: 7.5	3/19 cases: 40/50	-
Duration, day	3.8 ± 1.5	5.8 ± 2.4	.004
Mean urine volume, mL	2761.5 ± 850.3	2205.2 ± 598.5	.024

*Data are presented as the mean ± SD or n (%) where indicated. CPB indicates cardiopulmonary bypass; POD, postoperative day.

Comparison of Adverse Events between T and C Groups

The adverse events following the administration of diuretics are shown in Table 6. In particular, electrolyte abnormalities such as hyponatremia (Na <135 mEq/L) and hypokalemia (K <3.5 mEq/L) occurred in the C group. The incidence of hyponatremia was 1/20 (5%) in the T group and 9/19 (47%) in the C group (*P* = .0076). The incidence of hypokalemia in the T and C groups was 0/20 and 4/19, respectively (*P* = .098). Hypernatremia is the most serious complication during the TLV treatment period.

Interestingly, if we defined hypernatremia as having a serum sodium level ≥150 mEq/L, hypernatremia did not occur in either group. However, as shown in Table 6, the plasma sodium concentrations were significantly higher in the T group than in the C group (143.7 ± 2.6 mEq/L and 139.2 ± 2.2 mEq/L, respectively; *P* = .0001). Cardiovascular events, such as worsening heart failure and hypotension (systolic blood pressure <90 mmHg), were not seen in either group (except in 1/19 in the C group: hypotension). Furthermore, renal dysfunction and liver damage were not found during the treatment period; a significant difference in eGFR was also absent (mL/min/1.73 m2) before and after diuretics administration (T group: 78.6 ± 22.8 versus 81.2 ± 19.5, *P* = .24; C group: 62.3 ± 23.4 versus 62.6 ± 22.7, *P* = .89). As shown in Table 6, after diuretics administration, the value of transaminase and total bilirubin were within the normal range for both groups. The number of patients who exhibited a sinus rhythm before cardiac surgery was 19/20 (95%) in the T group and 17/19 (89%) in the C group (*P* = .95). AF after cardiac surgery is a common complication. In this study, we defined an irregular supraventricular tachycardia that lasted more than 10 minutes as a postoperative AF. The incidence of postoperative AF after diuretics administration was 2/19 (11%) in the T group and 9/17 (52%) in the C group (*P* = .016).

Table 6. Patients' Data and Adverse Events after Administration*

	T group (n = 20)	C group (n = 19)	*P*
Max Na, mEq/L	143.7 ± 2.6	139.2 ± 2.2	.0001
Min K, mEq/L	3.7 ± 0.1	3.7 ± 0.3	.84
HANP, pg/mL	102.3 ± 83.2	99.5 ± 43.1	.90
BNP, pg/mL	179.6 ± 123.5	226 ± 111.6	.27
PAC, pg/mL	76.4 ± 37.6	86 ± 50.3	.52
PRA, ng/mL/h	2.1 ± 1.9	5.9 ± 9.0	.08
AST, IU/L	23.2 ± 7.1	25.9 ± 9.4	.32
ALT, IU/L	24.3 ± 16.2	22.7 ± 14.0	.75
T-Bil, mg/dL	0.9 ± 0.3	1.1 ± 1.0	.49
EF, %	59.8 ± 7.0	57.1 ± 10.0	.33
Hospitalization, day	12.3 ± 2.6	14.7 ± 4.4	.044
Hypernatremia, >150 mEq/L	0/20	0/19	.99
Hyponatremia, <135 mEq/L	1/20	9/19	.0076
Hypokalemia, <3.5 mEq/L	0/20	4/19	.098
Systolic BP, <90 mmHg	0/20	1/19	.95
Renal dysfunction	0/20	0/19	.99
Liver damage	0/20	0/19	.99
SR→AF	2/19	9/17	.016
PE puncture	2/20	2/19	.99

*Data are presented as the mean ± SD or n (%) where indicated.

DISCUSSION

The majority of patients with volume overload after cardiac surgery have signs and symptoms of pulmonary congestion followed by systemic congestion [Adams 2005]. As such, the early removal of excess fluid from either the pulmonary or systemic bed by properly managing the body fluid is an important factor for improving prognosis after cardiac surgery. Loop diuretics have high natriuretic potency by blocking the luminal Na-K-2Cl transporter in the thick ascending limb of the loop of Henle [Dohi 2014]. The symptomatic benefit exerted by loop diuretics has led to their wide clinical acceptance, even in the absence of efficacy and safety data from large randomized trials [Udelson 2011]. However, the observed improvement is often associated with electrolyte abnormalities, renal dysfunction, neurohormonal activation, and hypotension [Li 2011].

In this study, we observed the effects of the oral administration of the V2-receptor antagonist TLV in patients with volume overload after cardiac surgery. Importantly, we observed that the hospitalization time as the first end point significantly decreased in the T group, primarily due to the faster time for weight recovery. This fact suggests that the oral administration of TLV improves the postoperative hemostatic state more rapidly than that of F/S. As shown in

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the Figure, the improvement in pulmonary congestion was quite remarkable in the T group. Generally, after cardiac surgery, AVP concentrations increase due to various kinds of surgical stressors, such as pain and hypoxia. Therefore, our data suggests that TLV, which inhibits free water reabsorption in the kidney's collecting tubules via blocking the vasopressin V_2R, is very effective for managing fluid retention.

We did not observe electrolyte abnormalities, such as hypernatremia (>150 mEq/L), hyponatremia (<135 mEq/L), and hypokalemia in the T group due to the fact that TLV was able to increase the urine volume without increasing the electrolyte excretion into the urine. As shown in Table 2, plasma sodium concentrations after cardiac surgery were lower in both the T and C groups (136.5 ± 3.0 mEq/L and 135.8 ± 2.4 mEq/L, respectively; $P = .46$). This fact shows that AVP increases during surgery. In this regard, our data shows that treatment with TLV is beneficial for postoperative body fluid management.

There was little effect on hemodynamics. Between both groups, we only observed a single case of hypotension (BP <90 mmHg). However, we found that treatment with TLV significantly reduced the incidence of AF. The incidence of AF in the general population is approximately 1.8% [Almassi 1997], whereas the incidence after cardiac surgery is higher, with the average incidence being reported as approximately 30% [Hakala 2003]. Various pathophysiological mechanisms such as atrial factors, postoperative inflammation, autonomic imbalance, perioperative ischemia, and the presence of electrolyte imbalance are thought to have an important role in the occurrence of postoperative AF [Sahin 2014]. In this study, the incidence of postoperative AF after TLV administration was only 11%. A detailed explanation for the cause of postoperative AF is unknown. However, we speculate that TLV removes excess stromal fluid, thus maintaining the intravascular volume, due to the fact that the plasma sodium concentration does not decrease. Moreover, TLV does not induce the renin-angiotensin-aldosterone system (RAAS) or activate the sympathetic nervous system. Loop diuretics cause intravascular volume depletion as well as directly upregulate renin gene expression by blocking sodium chloride uptake at the maculadensa, thus activating the RAAS and sympathetic nervous system, both of which play fundamental roles in postoperative AF development. Therefore, we hypothesize that body fluid management by TLV administration may have a secondary effect of preventing postoperative AF. Further examination is necessary to elucidate a mechanism for this decrease in postoperative AF development.

Limitations

Our study had several possible limitations. First, it was retrospective and performed in a single center with a relatively small population size. Second, the patients were all relatively stable following cardiac surgery, thus reducing the occurrence of adverse events. Third, there is not a clear definition of volume overload. From experience, in this study we regarded volume overload as a weight gain of more than 3 kg from the first to the second day following weaning from mechanical ventilation. Finally, efficacy as measured in this study is underpowered especially as it is a retrospective analysis. Simply put, this is a pilot exploratory study that might be useful for hypothesis generation. Therefore, further prospective studies are needed to identify the efficacy of TLV in patients with volume overload after cardiac surgery.

Conclusion

In the current study, we determined that TLV helps manage body fluid after open heart surgery without causing hemodynamic abnormities (hypotension, arrhythmia development), electrolyte abnormality, and liver and renal dysfunction. Furthermore, TLV was able to rapidly improve organ congestion resulting in a significant shortening of the hospitalization period of the patients.

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