Efficacy of Tolvaptan on Fluid Management After Cardiovascular Surgery Using Cardiopulmonary Bypass

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Objective: **To investigate the efficacy of the selective vasopressin V_2-receptor antagonist tolvaptan in postoperative fluid management after cardiovascular surgery using cardiopulmonary bypass.**

Design: **A retrospective cohort study.**

Setting: **A tertiary care center.**

Participants: **The study comprised 99 patients undergoing cardiovascular surgery using cardiopulmonary bypass.**

Interventions: **Oral tolvaptan was administered after surgery.**

Measurements and Main Results: **Fifty-one patients treated with tolvaptan were compared with 48 patients treated with intravenous diuretics. Urine volume, the time interval until the patients' body weight returned to the preoperative value, and the length of oxygen dependency after extubation were assessed as surrogate markers for resolution of fluid overload. Urine output on postoperative days 1 and 2 was significantly higher in the tolvaptan-treated patients (29.2 *v* 20.1 mL/kg/day, $p = 0.001$; 43.0 *v* 27.4 mL/kg/day, $p < 0.001$, respectively). Postoperative body weight returned to baseline in 49 tolvaptan-treated patients compared with 33 patients treated with intravenous diuretics (96.1% *v* 68.8%, $p < 0.001$). Among those with successful body weight reduction, the time interval was shorter in the tolvaptan-treated patients (5 *v* 7 days, $p = 0.006$). The length of oxygen dependency after extubation also was shorter in the tolvaptan-treated patients (2 *v* 3 days, $p = 0.006$). The urine osmolarity reduction rate before and 4 hours after the first dose of tolvaptan emerged as a significant predictor of its efficacy with a cutoff point of 33.7%, sensitivity of 0.73, and specificity of 0.67 ($p = 0.030$).**

Conclusion: **Tolvaptan facilitated early improvement of postoperative fluid overload after cardiovascular surgery.**

KEY WORDS: cardiovascular surgery, cardiopulmonary bypass, postoperative care, diuresis

EFFICIENT REMOVAL OF excessive body fluid is one of the important objectives in postoperative treatment of patients undergoing cardiac surgery using cardiopulmonary bypass (CPB). CPB increases vascular permeability by inducing inflammatory cytokines, which results in fluid retention in the extravascular space. In addition, inappropriate elevation of serum arginine vasopressin caused by CPB during and until several days after surgery is considered to be another mechanism mediating water retention.[1,2] Fluid overload has been reported to be associated with increased mortality and incidence of postoperative complications, such as respiratory failure, renal impairment, and arrhythmia after cardiac surgery.[3,4]

To achieve effective diuresis, an intravenous bolus injection of loop diuretics is preferentially used in postoperative management, and continuous infusion of carperitide are used especially for patients with preoperative renal impairment and/or inadequate responses to intravenous loop diuretics[5]; however, intravenous loop diuretics have drawbacks, such as hypotension, electrolyte disturbances, renal dysfunction, and neurohormonal activation. In particular, activation of the renin-angiotensin-aldosterone system already induced by CPB during surgery could be upregulated further by loop diuretics.[6,7] Carperitide often is associated with hypotension, and continuous infusion imposes a physical restriction on patients and hinders early ambulation or rehabilitation.

To mitigate potential disadvantages of these intravenous diuretics, the authors sought to assess the efficacy of tolvaptan, which is an oral, nonpeptide, selective vasopressin V_2-receptor antagonist whose action on the collecting ducts of the kidneys causes loss of electrolyte-free water (ie, aquaresis).[8,9]

The effectiveness of tolvaptan (TLV) for congestive heart failure has been reported in many studies in the literature, in which it decreased body weight and edema and corrected hyponatremia for heart failure patients without adverse effects on heart rate, blood pressure, electrolytes, or renal function.[10] However, there have been a limited number of studies that described feasibility and efficacy of tolvaptan after cardiac surgery.[11]

The purpose of this study was to determine whether tolvaptan was safe and effective in fluid management after cardiovascular surgery using CPB. Surrogate markers for early resolution of fluid overload, such as decreases in postoperative body weight, the length of supplemental oxygen dependency after extubation, and pleural effusion requiring thoracentesis were evaluated, and potential adverse effects, such as worsening renal function, electrolyte disturbances, arrhythmias, or thromboembolic events, also were assessed. The authors also aimed to identify a predictor of efficacy of tolvaptan in the early postoperative period.

METHODS

This retrospective cohort study was approved by the institutional review board, and the need for written consent was waived. Data were collected from the electronic medical record.

Patients

Between December 2014 and September 2015, the cases of 55 consecutive patients undergoing cardiac surgery using CPB

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were managed with tolvaptan. The exclusion criteria for tolvaptan administration included off-pump cardiac surgery, preoperative hemofiltration or dialysis dependency, apparent intravascular volume depletion, and serum sodium concentration $\geq$145 mEq/L on postoperative day (POD) 1. Patients with preoperative chronic renal insufficiency with estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73m^2 were included in the study unless they were undergoing hemodialysis. Three tolvaptan-treated patients who had taken tolvaptan before surgery also were excluded from the study. In addition, between April and December 2014, 75 consecutive patients underwent cardiac surgery using CPB and from those, any emergency cases, patients dependent on hemodialysis, or those who did not receive any intravenous diuretics were excluded. Thus, 48 patients treated with intravenous loop diuretics and/or carperitide and oral diuretics comprised the control group (non-TLV group). The use of diuretics in the control group was at each surgeon's discretion. One patient in the tolvaptan-treated group (TLV group) required temporary hemodialysis postoperatively. Consequently, a total of 99 patients were enrolled in the 2 groups for comparison (TLV group, 51 patients; non-TLV group, 48 patients). Table 1 shows baseline characteristics of the study cohort, and they were well-balanced between groups other than left ventricular ejection fraction. Chronic lung disease was defined as a chronic lung condition with long-term use of bronchodilators or steroids aimed at lung disease and/or with forced expiratory volume 1.0% $<$70% on preoperative pulmonary function test.

Anesthesia, CPB, and Fluid Management

A pulmonary arterial catheter was placed in all patients to monitor pulmonary artery pressure, central venous pressure, mixed venous oxygen saturation (SvO_2), and cardiac index. General anesthesia was induced with a sleep dose of thiopental sodium and 50 μg of fentanyl. Rocuronium (0.6-1.0 mg/kg) was administered to facilitate endotracheal intubation. Anesthesia was maintained with continuous intravenous infusion of remifentanil (0.3 μg/kg/min) and target-controlled infusion of propofol using the bispectral index to monitor anesthetic depth. The target concentration of propofol was 1.0 to 2.0 μg/mL. Patients were mechanically ventilated with mixture of air and oxygen at a ratio of 2 to 1 to maintain an end-tidal carbon dioxide value of 35 mmHg.

Once activated clotting time $\geq$400 seconds was confirmed after systemic heparinization with 400 U/kg of heparin, CPB was initiated. The CPB priming volume was 1,000 mL (colloid and crystalloid solution in a 7:3 ratio). CPB was maintained to achieve a perfusion index $\geq$ 2.6 L/min/m^2, hematocrit $\geq$20%, and SvO_2 $\geq$75 %. Aortic surgery, especially total aortic arch replacement, was performed with the patient under moderate hypothermia (26-28°C), and other cardiac surgery was performed with the patient under normothermia (35°C). After aortic cross-clamping, cardioplegia (cold crystalloid solution and blood in a 1:4 ratio) was infused and repeated every 15 to 20 minutes. Terminal warm cardioplegia was infused immediately before aortic unclamping.

During the surgery and the early postoperative period, fluids, including crystalloid and colloid solutions, and blood transfusion were administered adequately to achieve cardiac index $\geq$2.2 L/min/m^2, SvO_2 $\geq$65%, central venous pressure around 8 mmHg, mean arterial pressure around 80 mmHg, hematocrit $\geq$30%, and urine output $\geq$1 mL/kg/hour. Inotropic agents and vasodilators also were adjusted to maintain these target values.

Table 1. Baseline Characteristics

Variables	TLV Group (n = 51)	Non-TLV Group (n = 48)	p Value
Age (years)	73.0 (66.0-79.0)	73.0 (67.0-79.3)	0.53
Female	20 (39.2%)	20 (41.7%)	0.84
Height (cm)	162.0 (151.8-165.0)	157.0 (150.0-165.0)	0.45
Weight (kg)	58.6 (51.3-65.7)	54.5 (46.7-63.6)	0.091
BSA (m^2)	1.59 (1.47-1.74)	1.53 (1.41-1.73)	0.30
CLD	10 (19.6%)	10 (20.8%)	0.88
BUN (IU/L)	19.0 (14.0-24.5)	17.0 (14.0-22.0)	0.51
Cr (mg/dL)	0.84 (0.69-1.05)	0.80 (0.66-1.03)	0.71
eGFR (mL/min/1.73m^2)	65.4 (46.4-73.5)	63.0 (45.5-77.2)	0.98
LVEF (%)*	62.4 (57.3-68.7)	57.1 (49.8-64.2)	0.010
CABG	2 (3.9%)	3 (6.3%)	0.74
Valve	29 (56.9%)	31 (64.6%)	
Aorta	16 (31.4%)	11 (22.9%)	
Others	4 (7.8%)	3 (6.3%)	

NOTE. Data are presented as median (interquartile range) or number (percentage).

Abbreviations: BSA, body surface area; BUN, blood urea nitrogen; CABG, coronary artery bypass grafting; CLD, chronic lung disease; Cr, serum creatinine; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; TLV, tolvaptan.

*Measured using transthoracic echocardiography.

Tolvaptan Administration Protocol

Tolvaptan was started at a dose of 7.5 mg on POD 1 with 20 mg of oral furosemide and continued until the day that body weight returned to the preoperative value. The dose of these oral diuretics was not changed throughout the postoperative period. If the serum sodium concentration exceeded 145 mEq/L, hemodialysis was required, or any other complications seemingly associated with tolvaptan occurred, it was discontinued. No fluid restriction was imposed on any patients while tolvaptan was given.

Efficacy Assessments

Cumulative 24-hour urine volume was measured on each postoperative day. The time interval during which the postoperative body weight returned to the preoperative value, the length of oxygen requirement after extubation, and pleural effusion requiring thoracentesis were assessed as surrogate markers for resolution of fluid retention. Net fluid balance until the first POD was measured, which was the subtraction of the total amount of volume output including urine and blood loss from that of volume input including intravenous fluid infusion and blood transfusion from during surgery to 12 hours after arrival in the intensive care unit (ICU).

Safety Assessments

Adverse events, such as hypernatremia (serum sodium concentration $>$145 mEq/L), new-onset postoperative atrial fibrillation (POAF), and cerebrovascular accident, were