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# Effects of short-term administration of tolvaptan after open heart surgery☆·☆☆

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ABSTRACT

*Background:* Postoperative fluid overload following cardiac surgery is associated with increased morbidity and mortality. Unlike loop diuretics, tolvaptan (TLV) promotes aquaretic effect. Relatively little has been documented regarding the efficacy of TLV after cardiac surgery. The aim of the study was to investigate the effectiveness and safety of tolvaptan for the management of immediately postoperative fluid retention following cardiac surgery.
*Methods:* Between January to May 2014, patients undergoing cardiac surgery were randomly assigned to control or TLV group immediately after cardiac surgery. In control group, patients received 20 mg of furosemide and 25 mg of spironolactone as conventional diuretics. In the TLV group, 7.5 mg of TLV was administered in combination with conventional diuretics.
*Results:* TLV use was associated with increased urine output from postoperative day 1 to 3.Body weight reduction in the TLV group was significantly greater than the control group from postoperative day 2 to 4, and serum creatinine levels decreased to below preoperative values in the TLV group.
*Conclusions:* The combination of tolvaptan with conventional diuretics increases urine output without renal dysfunction and can be effective for postoperative fluid management and appropriate body weight reduction.


## 1. Introduction

Cardiac surgery, with or without cardiopulmonary bypass, causes a marked increase in total body water due to a heavy fluid load. Postoperative fluid overload following cardiac surgery is associated with increased morbidity and mortality [1]. Appropriate fluid management in the early postoperative period significantly improves prognosis. Loop diuretics, such as furosemide, are usually given as a first choice drug for diuresis immediately after surgery, but the effectiveness is sometimes limited, and high doses of loop diuretics leads to reduced sodium levels, increased renin-angiotensin-aldosterone system (RAAS) activity, and deterioration of renal function. Moreover, intravascular volume depletion due to natriuretic effects can lead to hypotension. Carpeptide, which is an intravenously administered diuretic and a recombinant of human atrial natriuretic peptide, has an anti-inflammatory effect and decreases RAAS activity, but produces hypotension due to vasodilation [2].

In Japan, tolvaptan (TLV) (Otsuka Pharmaceutical Co, Ltd., Tokyo, Japan), which is an orally administered selective vasopressin V2 antagonist, has only been approved for the treatment of heart failure since 2010. TLV promotes aquaretic effect without adverse effects, such as low blood pressure, electrolyte abnormalities, adverse impact on renal function, or increased RAAS activity [3]. The present study was designed to prospectively investigate the effectiveness and safety of TLV for the management of immediately postoperative fluid retention following cardiac surgery.

## 2. Methods

This study was conducted after approval by the ethics committee of Tokyo Medical University. All patients between 20 to 85 years of age who had undergone elective open heart surgery from January to May 2014 were included. Patients were randomly assigned to the control group or TLV group immediately following surgery. In the control group, patients received 20 mg of furosemide and 25 mg of spironolactone as conventional diuretics starting on postoperative day 1. In the TLV group, 7.5 mg of TLV was administered once daily in combination with conventional diuretics starting on postoperative day 1. However, TLV use was limited to 5 days. Inotropic agents were used when cardiac index was less than 2.2 L/min/mm$^2$, and carpeptide was used when urinary output decreased less than 0.5 ml/h/kg, but these

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agents were limited to the intensive care unit. The injection of diuretics was limited during intubation. The increase or discontinuation of conventional diuretics was permitted throughout the treatment period depending on the degree of fluid retention. Patients were excluded if they had an allergy to TLV, chronic kidney disease with an estimated glomerular filtration rate less than 15 ml/min/1.73 $m^2$, including dialysis patients, disturbance of consciousness, difficulty with water intake on postoperative day 1 or prolonged ventilation more than 24 h. Body weight (BW) was measured preoperatively and daily starting on postoperative day 1. Cumulative 24-h urine volume was measured and urine samples to determining urine osmolality were collected immediately after surgery and every morning just before TVP administration from postoperative day 1 to 5.

Changes were analyzed by Student t-test for continuous variables and chi-square test for categorical variables. Data were expressed as mean ± standard deviation. A p value less than 0.05 was considered significant.

## 3. Results

A total of 68 patients underwent cardiac surgery in our institution during the study period. Of those patients, 8 had chronic kidney disease, and 10 had prolonged ventilation more than 24 h. A total of 50 were enrolled in the study and 25 patients were randomized to each group. There were no postoperative complications such as bleeding, mediastinitis, pneumonia, myocardial infarction, or stroke. The baseline characteristics of the patients are listed in Table 1. The clinical parameters, including age, sex, BW, and serum creatinine level showed no significant differences between the two groups. The operative and postoperative outcomes are showed in Table 2. There were no significant differences in the cardiopulmonary time and operative water valance between the two groups. Urine output in the TLV group increased significantly compared to the control group from postoperative day 1 to 3 (Fig. 1). The changes from baseline BW are shown in Fig. 2. BW reduction in the TLV group was significantly greater than the control group from postoperative day 2 to 4, although BW was similar at discharge in both groups. The mean time to return to preoperative BW was significantly shorter in the TLV group than in the control group ($p < 0.0001$) (Table 2). However, there were no significant differences in ICU stay and hospital stay between the two groups. Serum sodium levels in the TLV group were significantly higher from postoperative day 3 to 6 but within the normal range, and then returned toward baseline at discharge (Fig. 3-A). There were no significant changes in serum potassium levels at any points between the two groups (Fig. 3-B). Serum creatinine levels decreased to below preoperative values in the TLV group and were significantly lower on postoperative day 3 in TLV group ($p < 0.05$) (Fig. 4-A). Similarly, blood urea nitrogen was significantly lower on postoperative day 3 in the TLV group ($p < 0.05$) (Fig. 4-B). Changes in urine osmolality, assessed before TVP administration, were similar between the two groups (Fig. 5).

**Table 1**
Preoperative Patient Characteristics.

| | Control (n = 25) | TLV (n = 25) | *p value* |
|---|---|---|---|
| Age (years) | 68.6 ± 10.0 | 71.4 ± 8.2 | 0.286 |
| Gender (Male) | 20 (80%) | 17 (68%) | 0.416 |
| Body weight | 61.7 ± 9.6 | 58.7 ± 11.9 | 0.320 |
| BSA ($m^2$) | 1.63 ± 0.2 | 1.61 ± 0.2 | 0.745 |
| BMI | 23.3 ± 2.8 | 21.9 ± 2.6 | 0.245 |
| Hypertension | 21 (84%) | 20 (80%) | 0.999 |
| Ischemic heart disease | 14 (56%) | 11 (44%) | 0.572 |
| Diabetes | 8 (32%) | 7 (28%) | 0.758 |
| Atrial fibrillation | 3 (12%) | 3 (12%) | 1.0 |
| Hyperlipidemia | 10 (40%) | 11 (44%) | 0.776 |
| Smoking | 11 (44%) | 11 (44%) | 1.0 |
| LVEF | | | 0.276 |
| > 60 | 19 (76%) | 21 (84%) | |
| 40–60 | 3 (12%) | 4 (16%) | |
| 40 < | 1 (4%) | 2 (8%) | |
| Creatinine | 0.87 ± 0.2 | 0.92 ± 0.2 | 0.363 |
| BUN | 15.9 ± 4.7 | 18.4 ± 5.2 | 0.095 |
| Na | 141.4 ± 3.4 | 141.8 ± 2.1 | 0.652 |
| K | 4.3 ± 0.4 | 4.2 ± 0.4 | 0.288 |
| Cardiac surgery | | | 0.565 |
| CABG (Isolated) | 9 (36%) | 9 (36%) | |
| Valvular (± CABG) | 10 (40%) | 9 (36%) | |
| Aortic (± CABG) | 6 (24%) | 7 (28%) | |

BSA = Body surface area, BMI = Body mass index, LVEF = Left ventricular ejection fraction, CABG = coronary artery bypass grafting.

**Table 2**
Operative and postoperative outcomes.

| | Control (n = 25) | TLV (n = 25) | *p value* |
|---|---|---|---|
| Operation time (min) | 395 ± 147 | 378 ± 115 | 0.718 |
| Cardiopulmonary bypass time (min) | 209 ± 95 | 207 ± 74 | 0.971 |
| Operative water balance (ml) | +2207 ± 1151 | +2498 ± 1256 | 0.316 |
| ICU stay (d) | 1.8 ± 0.5 | 1.9 ± 0.7 | 0.718 |
| New atrial fibrillation | 7 (28%) | 7 (28%) | 1.0 |
| Diuretic discontinuance | 3 (12%) | 6 (24%) | 0.365 |
| Mean time (d) to return to preoperative BW | 6.8 ± 1.9 | 4.7 ± 1.6 | 0.0001 |
| Hospital stay (d) | 20.2 ± 8.1 | 20.4 ± 7.1 | 0.715 |

ICU = Intensive care unit, BW = Body weight.

## 4. Discussion

This is a single center, randomized, parallel study of postoperative fluid management with or without TLV. To the best of our knowledge, reporting the efficacy of TLV in patients following cardiac surgery are rare [4]. Udelson JE et al. reported the efficacy of TLV in patients with uncontrollable heart failure with volume overload despite the use of loop diuretics [5]. Recent report has indicated that early administration of TLV reduces the amount of loop diuretics needed and improves the short- and mid-term patient outcomes [6]. We hypothesized that TLV would demonstrate greater effectiveness and safety over oral loop diuretics in patients following cardiac surgery. Slight RD et al. reported that patient BW approximated its pre-operative value at postoperative day 5 following cardiac surgery [7]. For this reason, TLV was administered for only 5 days postoperatively, to avoid the development of extreme dehydration, hypernatremia, and renal dysfunction. In the TLV group, the mean time to return to preoperative level of BW was 4.7 days, which was significantly shorter than the control group. TLV was useful for immediate BW reduction in patients with a positive postoperative water balance following cardiac surgery. However, the use of TLV did not lead to shortening of hospital stay. This may be due to other factors such as surgical procedures and differences in degree of

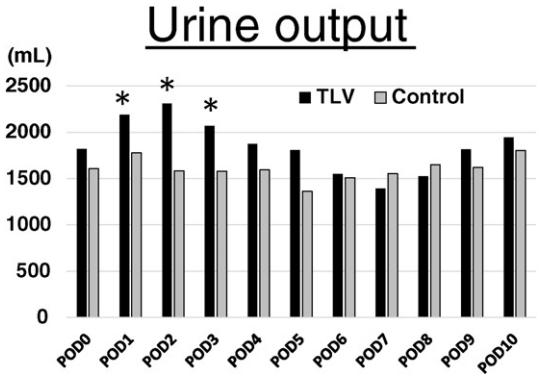


**Fig. 1.** Changes in postoperative urine output between the two groups. POD: postoperative day, *p < 0.05.