

**Original
Article**

The Efficacy and Renal Protective Effect of Tolvaptan in Chronic Kidney Disease Patients after Open-Heart Surgery

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Purpose: Unlike loop diuretics, tolvaptan is reported to have a renal protective effect. The purpose of this study was to retrospectively assess the efficacy of tolvaptan administration in chronic kidney disease (CKD) patients following open-heart surgery.

Methods: From February 2017 to August 2020, 75 patients with preoperative CKD stages IIIb–V were enrolled in this study and were divided into two groups: the control group (n = 30) and the tolvaptan group (n = 45). All patients routinely received conventional diuretics starting from postoperative day (POD) 1. Tolvaptan at 7.5–15 mg/day was administered if the patients had persistent fluid retention or poor response to conventional diuretics.

Results: Tolvaptan administration was initiated at a mean of POD 2.9 ± 2.2 , and the mean dosing period was 4.1 ± 3.0 days. The mean time to return to the preoperative body weight in the control and tolvaptan groups was similar. However, estimated glomerular filtration rate (eGFR) was significantly increased at the time when body weight reached the preoperative level and at discharge in the tolvaptan group than in the control group.

Conclusion: This study demonstrated the renal protective effect of tolvaptan even in advanced CKD patients after open-heart surgery.

Keywords: open-heart surgery, tolvaptan, chronic kidney disease

Introduction

Renal dysfunction has been found to increase the risk of mortality in patients undergoing cardiac surgery, with the risk progressively increasing with the preoperative stage of chronic kidney disease (CKD).¹⁾ Therefore, perioperative

renal protection is considered one of the most important factors in the management after cardiac surgery. Postoperative fluid overload is associated with prolonged intensive care unit and hospital stays, subsequent cardiopulmonary dysfunction, and increased mortality.²⁾ There remains some clinical uncertainty, with several currently proposed pharmacological and non-surgical renal protective strategies following cardiac surgery.³⁾

Loop diuretics have been conventionally used as the first-line treatment to reduce excess volume overload after surgery. However, their high-dose requirement is associated with worsening of renal function,⁴⁾ since loop diuretics reduce the estimated glomerular filtration rate (eGFR) or renal blood flow.

Tolvaptan (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), which is an orally administered, selective vasopressin-2 receptor antagonist, has only been approved for the treatment of heart failure since 2010. Tolvaptan

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promotes an aquaretic effect without increasing electrolyte imbalance or causing renal impairment.⁵ The efficacy of tolvaptan after open-heart surgery has been reported in non-CKD patients,^{6,7} and recent reports have also demonstrated the renal protective effect of tolvaptan after cardiac surgery.⁸ We have used tolvaptan in the early stages and, on short-term basis, for postoperative fluid management even in advanced CKD patients. Little is known about the impact of tolvaptan in CKD patients in the perioperative management of open-heart surgery.⁹

In the present study, the purpose was to retrospectively assess the efficacy of tolvaptan administration in CKD patients in the early postoperative period, following open-heart surgery.

Methods and Materials

Study design

A single-center, observational, retrospective study was conducted in Aichi Medical University Hospital. There were a total of 500 patients who underwent cardiovascular surgery in our hospital from February 2017 to August 2020. Patients under 20 years of age, receiving regular dialysis, and with prolonged ventilation (>24 h) after surgery were excluded. Among these patients, 75 patients with preoperative CKD stages IIIb–V were enrolled in this study and were divided into two groups: the control group (n = 30) and the tolvaptan group (n = 45). All patients routinely received oral furosemide at 20–40 mg/day and oral spironolactone at 25–50 mg/day as conventional diuretics starting from postoperative day (POD) 1. The injection of diuretics was discontinued when patients could tolerate oral administration. Tolvaptan at 7.5–15 mg/day was administered despite conventional diuretics if the patients met any of the following criteria: significant body weight gain (≥ 3 kg) compared to the preoperative weight, no significant body weight loss, or no increase in urine volume. The administration of tolvaptan was stopped when the body weight reached the preoperative level. The daily body weight was recorded during hospitalization, and a blood test was performed to evaluate the serum sodium and creatinine levels and eGFR. These data were mainly recorded at admission, on the day when the body weight reached the preoperative level, and at discharge. The eGFR was calculated using a previously published equation¹⁰: $eGFR \text{ in mL/min/1.73 m}^2 = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$.

This study was conducted after receiving approval from the ethics committee of Aichi Medical University Hospital

(approval number: 2020-094), and written informed consent was obtained from each patient. The study was approved by the institutional review board and was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Values are expressed as means \pm standard deviation for continuous variables. Changes of continuous measurements between the two groups were performed by the unpaired Student's *t*-test or the Mann–Whitney *U* test. Categorical variables were compared by the χ^2 test or Fisher's exact test. A *p* value of <0.05 was considered statistically significant. All statistical analyses were conducted with the JMP Statistical Software v 14.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' baseline characteristics and operative parameters are shown in **Table 1**.

None of the patients exhibited hypernatremia (Na >145 mEq) when tolvaptan was initiated. The tolvaptan group tended to include a large number of patients with diabetes, low serum albumin level, and atrial fibrillation. Although there were no significant differences in the distribution of the CKD stages between the two groups, the tolvaptan group included significantly increased creatinine level and reduced eGFR, compared with the control group. There were no significant differences between the groups in surgical procedure, operation time, and operative water balance.

Tolvaptan administration was initiated at a mean of POD 2.9 ± 2.2 (range, POD 1–12). The majority of patients (41 of 45 patients) received tolvaptan by POD 4. The mean dosing period was 4.1 ± 3.0 days (range, 1–15 days).

The perioperative body weight changes are shown in **Fig. 1**. There were no significant differences in the body weight between the control and tolvaptan groups. The mean time to return to the preoperative body weight in the control and tolvaptan groups was similar (6.8 ± 0.6 and 6.7 ± 0.5 days, respectively) (*p* = 0.967). However, the serum creatinine level was significantly decreased, and the eGFR was simultaneously increased at the time when body weight reached the preoperative level and at discharge in the tolvaptan group than in the control group (**Figs. 2 and 3**).

Serum sodium level at the time when the body weight returned to the preoperative level was significantly higher in the tolvaptan group than in the control group

Table 1 Patients' baseline characteristics and operative parameters

	Control group: n = 30 (%)	Tolvaptan group: n = 45 (%)	p-value
Age (years)	74.1 ± 7.6	73.0 ± 7.8	0.536
Body weight (kg)	59.1 ± 12.3	59.8 ± 10.7	0.805
BMI (kg/m ³)	22.6 ± 3.3	23.5 ± 3.9	0.247
Sex (male)	23 (77)	31 (69)	0.459
Hypertension	21 (70)	36 (80)	0.324
Hyperlipidemia	17 (57)	28 (62)	0.631
Diabetes	7 (23)	20 (44)	0.058
LVEF (%)	58.4 ± 2.3	55.2 ± 2.3	0.378
LVEF <40%	2 (7)	10 (22)	0.158
Hemoglobin (mg/dl)	11.2 ± 0.3	11.7 ± 0.3	0.211
Albumin (mg/dl)	3.5 ± 0.1	3.7 ± 0.1	0.048
Atrial fibrillation	3 (10)	12 (27)	0.067
Serum sodium (mEq/L)	140.7 ± 4.5	139.5 ± 3.2	0.172
Serum creatinine (mg/dL)	1.46 ± 0.34	1.88 ± 0.96	0.025
eGFR (mL/min/1.73 m ²)	36.1 ± 1.5	30.5 ± 1.2	0.006
CKD stage			0.132
Stage IIIb	24 (80)	28 (62)	
Stage IV	6 (20)	13 (29)	
Stage V	0 (0)	4 (9)	
Operative procedure			0.646
CAD	7 (23)	13 (29)	
VHD	12 (40)	20 (44)	
Aortic surgery	11 (37)	12 (27)	
Emergency	7 (23)	9 (20)	0.730
Operation time (min)	397 ± 19	410 ± 15	0.583
OWB (ml)	2809 ± 217	2308 ± 177	0.078

BMI: body mass index; LVEF: left ventricular ejection fraction; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; CAD: coronary artery disease; VHD: valvular heart disease; OWB: operative water balance

(Fig. 4). However, serum sodium level at discharge was within normal range. There were no adverse events due to hypernatremia during the course of our study. Operative mortality was 0% in both groups. The duration of postoperative hospital stay in the control and tolvaptan groups was similar (20.9 ± 1.8 and 23.4 ± 1.4 days, respectively) ($p = 0.267$). No patients received new dialysis after surgery, despite being in advanced CKD stages. All patients were discharged without any postoperative complications such as bleeding, mediastinitis, pneumonia, myocardial infarction, and stroke.

Discussion

Perioperative fluid management following open-heart surgery is challenging in CKD patients because adequate body weight reduction cannot be achieved due to decreased urine volume. It is commonly accepted that preoperative CKD is a risk factor for acute kidney injury after cardiac surgery and is associated with the early and

long-term outcomes.¹¹ Therefore, the prevention of renal function deterioration in the early postoperative period is important.

Tolvaptan is reported to have advantageous effects for immediate body weight reduction in postoperative fluid overload patients.^{6,7} Unlike loop diuretics, tolvaptan does not cause hemodynamic instabilities, such as systematic hypotension or reduced cardiac output. As a result, the patients' renal blood flow does not decrease, and their renal function can be preserved.

A recent study has reported the safety and efficacy of long-term tolvaptan administration in heart failure patients with CKD.¹² Tubulointestinal functions were preserved to some degree even in advanced stage CKD patients, particularly in the collecting ducts of the medullary area.¹³

We hypothesized that earlier and short-term administration of tolvaptan could have a beneficial impact on the renal function even in CKD patients undergoing open-heart surgery. As a result, this retrospective study

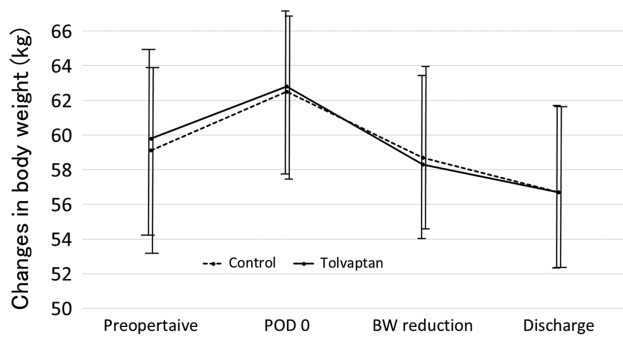


Fig. 1 Changes in BW in the tolvaptan and control groups. BW reduction signifies the time when the BW returned to the preoperative level. There were no significant differences in the BW between the control and tolvaptan groups. BW: body weight

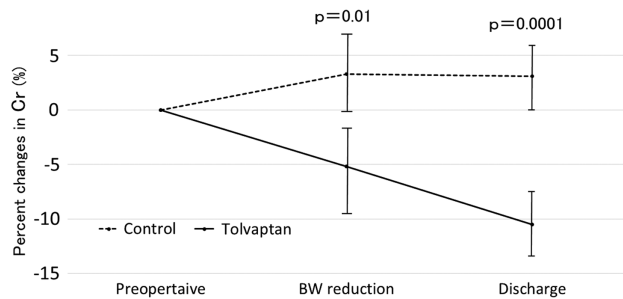


Fig. 2 Mean (SD) percent change from preoperative values in serum Cr, in the tolvaptan and control groups. The postoperative Cr change was significantly better in the tolvaptan group. Cr: creatinine

demonstrated that the use of tolvaptan in CKD patients could achieve body weight reduction without worsening renal function. The present study is one of a few to show the diuretic and renal protective effect of tolvaptan in patients with markedly deteriorated kidney disease following open-heart surgery. Tolvaptan administration was initiated at POD 2.9, and the mean dosing period was 4.1 days in the present study. Tolvaptan should be administered as early as possible when urine volume is not obtained despite conventional diuretics. In the majority of patients, the body weight can be returned to the preoperative level in a few days. Long-term administration of tolvaptan is not required.

On the other hand, in the present study, tolvaptan was not associated with shortness of the interval period return to the preoperative body weight. There may be an unfavorable bias that the tolvaptan group had patients with lower preoperative eGFRs. Moreover, there may be a disadvantageous bias in patient selection, although tolvaptan was administered only in patients with poor response to conventional diuretics. If tolvaptan had not

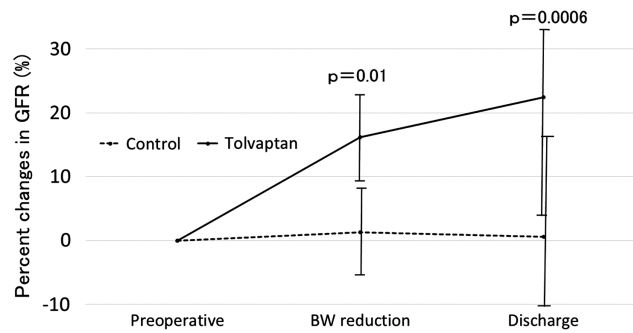


Fig. 3 Mean (SD) percent changes from preoperative values of the eGFR in the tolvaptan and control groups. The eGFR was significantly increased at the time when BW reached preoperative levels (BW reduction) and at discharge in the tolvaptan group. BW: body weight; eGFR: estimated glomerular filtration rate

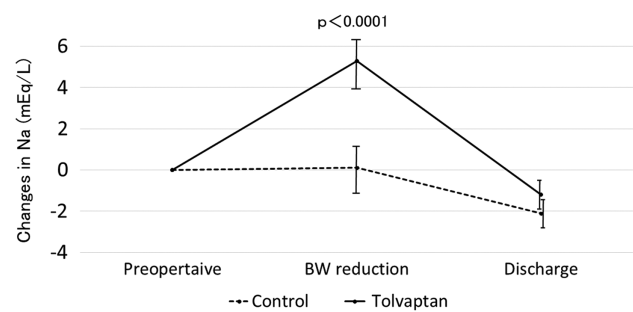


Fig. 4 Changes in serum sodium (Na) levels in the tolvaptan and control groups. Serum sodium level at the time when BW reached the preoperative level (BW reduction) was significantly higher in the tolvaptan than in the control group. BW: body weight

been used for those patients with persistent fluid retention, the time required to restore the preoperative body weight would have been further prolonged.

A recent report showed that aging or increased body mass index was a risk factor for progressive CKD after cardiac surgery.¹⁴⁾ Tolvaptan may be effective, especially in elderly or obese patients.

Among the several disadvantages associated with tolvaptan, the greatest concern associated with the use of tolvaptan is hypernatremia.⁷⁾ Little is known about the serum sodium level in CKD patients, although several studies have reported that marked hypernatremia does not cause any adverse effects.^{6,7)} Similarly, in the present study, there were no clinical adverse events in CKD patients, although significant hypernatremia occurred temporally after tolvaptan use.

The advantage of tolvaptan use is not simply to reduce the body weight by increasing urine volume. Appropriate volume reduction in the body in the early postoperative period can aid in early weaning from oxygen inhalation,

early recovery of respiratory dysfunction with reduced lung edema or pleural effusion, and immediate initiation of cardiac rehabilitation, ultimately leading to a shorter length of hospital stay.^{7,15} Moreover, tolvaptan was able to reduce the amount of loop diuretics and to prevent worsening of renal failure in CKD patients.

Our study has several limitations. First, this was an observational and retrospective study conducted at a single center with a small number of patients. Furthermore, our study included different types of cardiovascular surgery. Second, there was a bias that the decision of tolvaptan use was at the attending physician's discretion, although this study had some criteria for tolvaptan administration. Third, postoperative renal function may have varied depending on the postoperative cardiac function or hemodynamic variables, in addition to the preoperative CKD stage. These factors were not considered in the present study.

Conclusion

Our report demonstrated the renal protective effect of tolvaptan even in advanced CKD patients after open-heart surgery. We believe that aggressive and short-term use of tolvaptan in perioperative management can provide favorable long-term results in CKD patients following open-heart surgery. However, further studies are needed to confirm the long-term outcomes.

Disclosure Statement

The authors declare that they have no conflict of interest.

References

- 1) Yeo KK, Li Z, Yeun JY, et al. Severity of chronic kidney disease as a risk factor for operative mortality in nonemergent patients in the California coronary artery bypass graft surgery outcomes reporting program. *Am J Cardiol* 2008; **101**: 1269–74.
- 2) Tominaga N, Kida K, Matsumoto N, et al. Safety of add-on tolvaptan in patients with furosemide-resistant congestive heart failure complicated by advanced chronic kidney disease: a sub-analysis of a pharmacokinetics/pharmacodynamics study. *Clin Nephrol* 2015; **84**: 29–38.
- 3) Tan SI, Brewster DJ, Horrigan D, et al. Pharmacological and non-surgical renal protective strategies for cardiac surgery patients undergoing cardiopulmonary bypass: a systematic review. *ANZ J Surg* 2019; **89**: 296–302.
- 4) Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med* 2011; **364**: 797–805.
- 5) Onogawa T, Sakamoto Y, Nakamura S, et al. Effects of tolvaptan on systemic and renal hemodynamic function in dogs with congestive heart failure. *Cardiovasc Drugs Ther* 2011; **25**: 67–76.
- 6) Matsuyama K, Koizumi N, Nishibe T, et al. Effects of short-term administration of tolvaptan after open heart surgery. *Int J Cardiol* 2016; **220**: 192–5.
- 7) Nishi H, Toda K, Miyagawa S, et al. Effects of tolvaptan in the early postoperative stage after heart valve surgery: results of the STAR (Study of Tolvaptan for fluid retention After valve surgery) trial. *Surg Today* 2015; **45**: 1542–51.
- 8) Kishimoto Y, Nakamura Y, Harada S, et al. Can tolvaptan protect renal function in the early postoperative period of cardiac surgery? - results of a single-center randomized controlled study. *Circ J* 2018; **82**: 999–1007.
- 9) Yamada M, Nishi H, Sekiya N, et al. The efficacy of tolvaptan in the perioperative management of chronic kidney disease patients undergoing open-heart surgery. *Surg Today* 2017; **47**: 498–505.
- 10) Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis* 2009; **53**: 982–92.
- 11) Jiang W, Teng J, Xu J, et al. Dynamic predictive scores for cardiac surgery-associated acute kidney injury. *J Am Heart Assoc* 2016; **5**: e003754.
- 12) Uemura Y, Shibata R, Takemoto K, et al. Safety and efficacy of long-term use of Tolvaptan in patients with heart failure and chronic kidney disease. *Circ J* 2017; **81**: 1736–8.
- 13) Sato E, Nakamura T, Amaha M, et al. Effect of tolvaptan in patients with chronic kidney disease due to diabetic nephropathy with heart failure. *Int Heart J* 2014; **55**: 533–8.
- 14) Mårtensson J, Bellomo R. Prevention of renal dysfunction in postoperative elderly patients. *Curr Opin Crit Care* 2014; **20**: 451–9.
- 15) Noguchi K, Tanaka M, Katayama I, et al. Efficacy of Tolvaptan in patients with volume overload after cardiac surgery. *Heart Surg Forum* 2015; **18**: E232–6.