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ORIGINAL ARTICLE

Efficacy and safety of tolvaptan after pediatric congenital heart disease surgery

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Abstract

It is not clear whether tolvaptan is safe and effective irrespective of various underlying clinical conditions including the functional ventricle morphology, chromosomal abnormalities, and renal function after complex pediatric congenital heart disease surgery. Also, the appropriate dose of tolvaptan in these patients has not been previously identified. We retrospectively assessed the urine volume, body weight, patient clinical characteristics, laboratory data, and vital signs before and on days 1 and 7 of the tolvaptan administration after congenital heart disease surgery. Also, we assessed the relationship between the tolvaptan dose and its effects. A total of 86 patients were included the study. The mean time from the surgery to the tolvaptan administration was 23.5 ± 3.7 days. After administering tolvaptan, the urine volume significantly increased and body weight significantly decreased from baseline by days 1 and 7 ($p < 0.0001$). The urine volume significantly increased more in the survivors than the deceased. Of the 22 patients who had low serum sodium concentrations at baseline, 20 had an increased serum sodium concentration on day 7. The clinical effect of tolvaptan was not affected by the functional ventricle morphology, chromosomal abnormalities, or renal function. There was a positive correlation between the tolvaptan dose and change in the urine volume until a tolvaptan dose of up to 0.3 mg/kg/day but not at more than 0.3 mg/kg/day. Tolvaptan administration is safe and effective after congenital heart disease surgery irrespective of various underlying clinical conditions. Though the urine volume tends to increase until a tolvaptan dose of up to 0.3 mg/kg/day in pediatric congenital heart disease patients, there was no further benefit with more than 0.3 mg/kg/day.

Keywords Tolvaptan · Urine volume · Body weight · Serum sodium concentration

Introduction

Appropriate fluid management is a key factor in the management of the early postoperative period after pediatric congenital heart disease surgery, because the procedure imposes an excessive volume overload mainly due to cardiopulmonary bypass [1, 2]. In that respect, diuretics play a pivotal role in the management of fluid retention after congenital heart disease surgery. At present, loop diuretics and thiazide diuretics are widely used after congenital heart disease surgery. However, there are many cases that cannot achieve an appropriate fluid management in spite of a sufficient dose of these diuretics. In cases with an excessive volume overload, an increase in the loop diuretic dosing is often performed at the expense of renal impairment and hyponatremia [3].

Tolvaptan is a selective vasopressin V_2-receptor antagonist [4]. The V_2 receptor mediates the effect of arginine vasopressin in water excretion. Tolvaptan selectively blocks the V_2-receptors of the renal collecting ducts and prevents the binding of vasopressin to the V_2 receptors, which leads to the prevention of water absorption in the renal collecting ducts. Tolvaptan administration results in an increased urinary volume, decreased body weight, normalization of the serum sodium, and amelioration of edema in acute and chronic heart failure patients [4–12]. Also, previous reports suggested that tolvaptan administration is effective and safe in adult patients who underwent open heart surgery [13], pediatric patients with heart failure [14] and patients who undergo relatively simple left-to-right shunt congenital heart disease surgery [15]. However, it is not clear whether tolvaptan is safe and effective irrespective of variable pediatric congenital heart disease patients including a difference in the

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morphology of the ventricles (functional single ventricle or two ventricles) or underlying patient characteristics including the renal function and presence or absence of chromosomal abnormalities. Also, it is not clear whether tolvaptan administration affects the patient outcome after pediatric congenital heart disease surgery. Moreover, an appropriate tolvaptan dose in pediatric patients after congenital heart disease surgery has not been previously identified. We hypothesized that the safety and efficacy of tolvaptan is applicable irrespective of the complexity of the disease or presence of chromosomal abnormalities and its effect depends on the tolvaptan dosage to some extent. Therefore, in this study, we aimed to assess the efficacy and safety of tolvaptan in the various clinical conditions after pediatric congenital heart disease surgery. Also, this study aimed to reveal the appropriate dose of tolvaptan in pediatric patients after congenital heart disease surgery.

Materials and methods

Study design

This retrospective study was approved by the Institutional Review Board of Saitama Medical University (No. 17-283) and all participants gave their informed consent. This study included pediatric patients who were administered tolvaptan after congenital heart disease surgery at the International Medical Center, Saitama Medical University between October 2014 and June 2019. All patients were admitted to the pediatric intensive care unit after the surgery and underwent circulatory support including inotropic agents and diuretics.

After enteral feeding had been established, we started prescribing oral medications and decreased the inotrope and diuretic infusions. We added tolvaptan if an adequate decrease in the body weight (less than 5–10% decrease in the body weight as compared to pre-operation or if there was an excessive weight gain compared to their enteral feeding) could not be achieved in the patient or if the urine output was not as much as we expected (less than 1–2 mL/kg/h). In addition to the patients with fluid retention, we added tolvaptan in patients with pleural effusions after surgery. The tolvaptan dose was decided depending on the patient's circulatory condition including the fluid retention (body weight, urine output, and pleural effusion) and serum sodium level. Especially, we took special note of the serum sodium level. If the serum sodium level was lower (< 134 mEq/L), then we prescribed a higher dose of tolvaptan (0.2–0.3 mg/kg/day). The tolvaptan dose was equivalent to a 10–15 mg/day dose in adult patients. If the serum sodium level was within normal range (≥ 135 mEq/L), then we prescribe a lower dose of tolvaptan (0.1–0.2 mg/kg/day). The tolvaptan dose was equivalent to a 5–10 mg/day dose in adult patients. The dose of tolvaptan was left to the discretion of the attending physician's clinical decision. In some cases, the attending physician preferred to prescribe a far higher dose of tolvaptan of more than 0.3 mg/kg/day (equivalent to a dose of more than 15 mg/day in adult patients). Once the tolvaptan administration was started, then we continued to monitor the effect of the medication until the discharge of the patient. The tolvaptan dose was decreased according to the condition of the patient by the attending physician during the follow-up in the outpatient clinic.

We retrospectively reviewed the patient characteristics including the preoperative diagnosis and medication use after the surgery. Also, information regarding the time from surgery, fluid intake, and intravenous administration of inotropes and vasodilator were assessed. The vital signs (heart rate and systolic blood pressure), laboratory data (serum sodium, serum potassium, serum creatinine, and aspartate aminotransferase) and echo cardiac data before and on day 7 of the tolvaptan administration were reviewed. The patients were classified into two groups according to the morphology of the ventricles (functional single ventricle and two ventricles). Also, the presence or absence of chromosomal abnormalities as an underlying condition was reviewed.

To assess the efficacy of tolvaptan, we compared the urine volume before, and on day 1 and day 7 of the tolvaptan administration. Similarly, we compared the body weight before, and on day 1 and day 7 of the tolvaptan administration. The tolvaptan dose (mg/kg/day) was calculated by using the body weight at the time of the tolvaptan administration.

Statistical analysis

All continuous data are expressed as the mean ± SD. Comparisons between the two groups were performed using an unpaired or paired *t* test. A Pearson's correlation analysis was used to assess the relationship between tolvaptan and each parameter. A $p < 0.05$ was considered statistically significant. All statistical analyses were performed using JMP version 13.0.0 (SAS, Cary, NC) and GraphPad PRISM version 7.02 (GraphPad Software, Inc., La Jolla, CA) software.

Results

Patient characteristics

Figure 1 shows the flow diagram of the participants and their tolvaptan dose. During the study period, a total of 103 patients were prescribed tolvaptan. Of the 103 patients, we excluded 17 patients whose tolvaptan dose was increased during the first 7 days after the administration, because we wanted to know the effect of a consistent dose of tolvaptan. Therefore, a total of 86 pediatric patients were included in

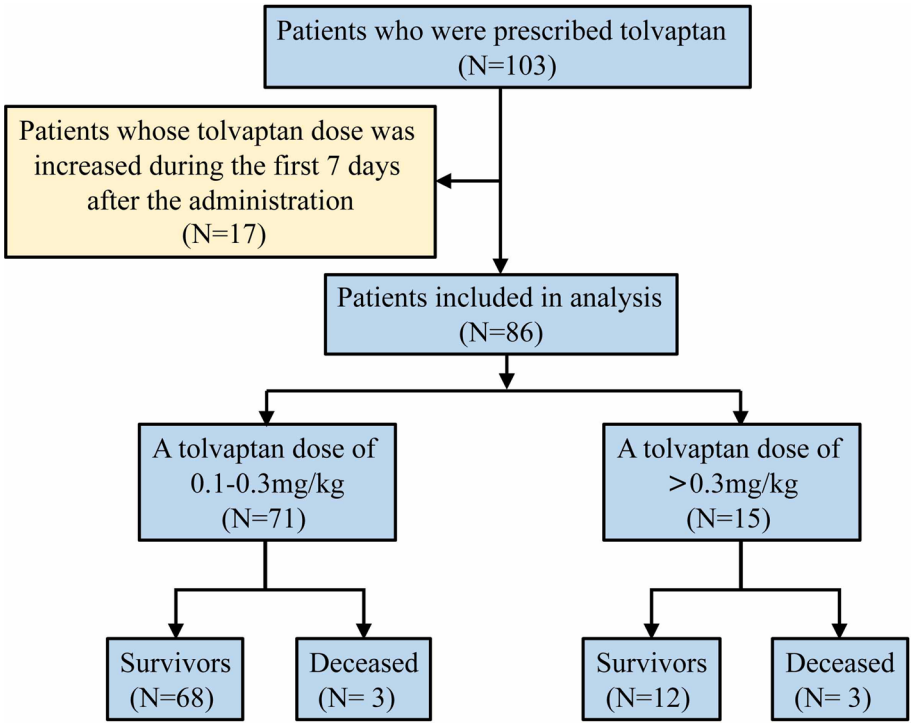

Fig. 1 Flow diagram and the results of the participants. Of the 103 patients who were prescribed tolvaptan, 17 were excluded because the tolvaptan dose was increased during the first 7 days after the administration. The tolvaptan dose was decided depending on the serum sodium level and requirements of the attending physician

this study. Of the 86 patients, 71 patients were prescribed tolvaptan dose of 0.1–0.3 mg/kg/day. On the other hand, 15 patients were prescribed tolvaptan dose of > 0.3 mg/kg/day.

The Table 1 demonstrates the basic patient characteristics. These patients consisted of those with a tetralogy of Fallot ($n = 14$), complete atrioventricular septal defect ($n = 10$), ventricular septal defect ($n = 9$), hypoplastic left heart syndrome ($n = 8$), double outlet right ventricle ($n = 7$), single right ventricle ($n = 7$), single left ventricle ($n = 4$), pulmonary atresia with ventricular septal defect ($n = 4$), persistent truncus arteriosus ($n = 3$), tricuspid valve atresia ($n = 3$), interruption of the aortic arch ($n = 3$), pulmonary atresia with intact ventricular septum ($n = 3$), and others ($n = 11$). Of the 86 patients, 19 (22%) had chromosomal abnormalities as an underlying feature. They included 21 trisomy ($n = 14$), deletion 22q11.2 syndrome ($n = 3$), Williams syndrome ($n = 1$), and 5p-syndrome ($n = 1$) patients. A total of six patients died after the surgery. They included those with a hypoplastic left heart syndrome ($n = 2$), complete atrioventricular septal defect ($n = 1$), single right ventricle ($n = 1$), total anomalous pulmonary venous return ($n = 1$), and transposition of the great arteries ($n = 1$). The time from surgery to tolvaptan administration was 23.5 ± 3.7 days. The serum sodium concentration at the time of tolvaptan administration was 136 ± 0.4 mEq/L. The doses of furosemide and

Table 1 Patient basic characteristics ($N = 86$)

Age (months)	14.5 ± 2.3
Male (*n*)	48
Body weight (kg)	6.69 ± 0.46
Morphology of the ventricles (*n*)	
Functional single ventricle	28
2 ventricles	58
Tolvaptan dose (mg/kg/day)	0.21 ± 0.01
Fluid intake (mL/kg/day)	95.0 ± 4.0
Intravenous administration (*n*)	
Olprinone	47
Dopamine	1
Dobutamine	14
Adrenaline	3
Carperitide	5
Medication (*n*)	
Furosemide	84
Spironolactone	84
ARB	18
ACEI	10
β-Blocker	4
None	2
Deceased (*n*)	6

ARB angiotensin receptor blocker, *ACEI* angiotensin converting enzyme inhibitor

spironolactone at the time of the tolvaptan administration were 2.93 ± 0.1 mg/kg/day and 2.94 ± 0.1 mg/kg/day, respectively.

Urine volume

After the tolvaptan administration, the urine volume significantly increased from baseline. On day 1, the urine volume increased to 141.2 ± 4.4% ($p < 0.0001$). Also, the urine volume was increased to 152.1 ± 6.1% on day 7 compared to baseline ($p < 0.0001$). The urine volume was significantly more increased in the survivors than the deceased both on day 1 and day 7 (day 1; 145.1 ± 4.4% and 89.9 ± 9.6%, respectively, $p = 0.001$, day 7; 156.8 ± 6.2% and 89.1 ± 14.7%, respectively, $p = 0.0042$) (Fig. 2). On the other hand, the change in the urine volume between the patients with chromosomal abnormalities and those without chromosomal abnormalities was equivalent (151.6 ± 8.5% and 138.3 ± 5.1%, respectively, $p = 0.21$). Similarly, the morphology of the ventricles did not affect the change in the urine volume. The increase in the urine volume was equivalent between the patients with a functional single ventricle and those with two ventricles (132.2 ± 7.7% and 145.6 ± 5.3%, respectively, $p = 0.15$).

Body weight

The tolvaptan administration resulted in a significant decrease in the body weight from baseline. On day 1, the body weight decreased to 1.62 ± 0.26% ($p < 0.0001$). Also, the body weight decreased to 1.54 ± 0.44% on day 7 ($p < 0.0001$) from baseline. The decrease in the body weight was equivalent between the survivors and deceased both on day 1 and day 7 (day 1; 1.61 ± 0.24% and 1.84 ± 2.11%, respectively, $p = 0.82$, day 7; 1.48 ± 0.43% and 2.29 ± 2.68%, respectively, $p = 0.64$). Similarly, the decrease in the body weight was equivalent between the patients with chromosomal abnormalities and those without chromosomal abnormalities on day 1 (2.17 ± 0.49% and 1.47 ± 0.31%, respectively, $p = 0.27$) and on day 7 (1.76 ± 0.7% and 1.48 ± 0.53%, respectively, $p = 0.79$). The patients with two ventricles had a greater decrease in the body weight than those with a functional single ventricle on day 1 (2.1 ± 0.35% and 0.64 ± 0.29%, respectively, $p = 0.008$), but this significance was lost on day 7 (2.0 ± 0.54% and 0.57 ± 0.73%, respectively, $p = 0.12$).

Serum sodium concentrations

After the tolvaptan administration, 51 patients (59%) had an increase in the serum sodium concentration on day 7 and its concentration remained within normal range in most patients. Only one patient had an increase in the serum sodium of up to 151 mEq/L after the tolvaptan administration. The hypernatremia normalized without any tolvaptan discontinuation. Twenty-two patients (26%) had a low serum sodium concentration ($Na^+ < 134$ mEq/L) at baseline. Of the 22 patients, the serum sodium concentration significantly increased in 20 patients (91%) and 16 patents (73%) had an increase in the serum sodium

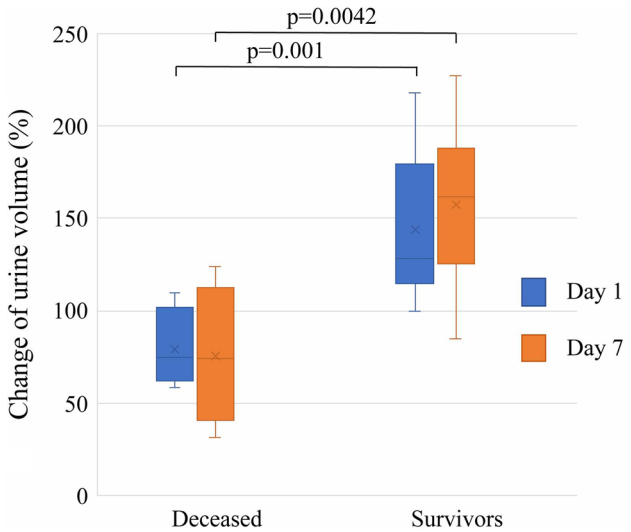

Fig. 2 Change in the urine volume after the tolvaptan administration. The urine volume was significantly more increased in the survivors than the deceased both on day 1 and day 7 after the tolvaptan administration

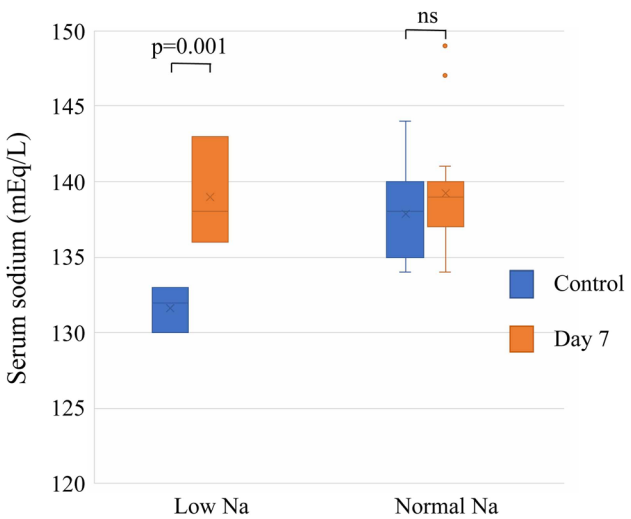

Fig. 3 Change in the serum sodium concentration after the tolvaptan administration. Of the 22 patients who had a low serum sodium concentration ($Na^+ < 134$ mEq/L) at baseline, 20 (91%) had a significant increase in the serum sodium concentration on day 7 ($p = 0.001$)

concentration to the normal range ($Na^+ \geq 135$ mEq/L) on day 7 ($p = 0.001$) (Fig. 3).

Other laboratory and clinical parameters

Before and after the tolvaptan administration there were no changes in the serum potassium concentration (4.1 ± 0.05 mEq/L and 4.3 ± 0.06 mEq/L, respectively, $p = 0.21$), serum creatinine concentration (0.24 ± 0.01 mg/dL and 0.23 mg/dL, respectively, $p = 0.48$), and aspartate aminotransferase concentration (35.2 ± 1.7U/L and 38.0 ± 2.5U/L, respectively, $p = 0.35$). Also, there was no relationship between the serum creatinine concentration and change in the urine volume after the tolvaptan administration (day 1; $p = 0.3$, day 7; $p = 0.89$). The ejection fraction by echo cardiogram before and on day 7 of tolvaptan administration did not change ($61.6 \pm 1.6\%$ and $62.1 \pm 1.4\%$, respectively, $p = 0.84$). Fluid intake before and on day 7 of tolvaptan administration was not significantly changed (95.0 ± 4.0 mL/kg/day and 98.0 ± 4.9 mL/kg/day, respectively, $p = 0.63$). Similarly, no changes in the heart rate (122.0 ± 2.0 bpm and 123.0 ± 2.0 bpm, respectively, $p = 0.97$) or systolic blood pressure (89.9 ± 1.3 mmHg and 90.8 ± 1.3 mmHg, respectively, $p = 0.42$) were observed before and after the tolvaptan administration.

Tolvaptan dose and urine volume

Finally, we assessed the relationship between the tolvaptan dose and change in the urine volume (Fig. 4). There was a positive correlation between the tolvaptan dose and change in the urine volume until a tolvaptan dose of up to 0.3 mg/kg/day ($r = 0.29$, $p = 0.04$) (Fig. 4a). However, there was no relationship between a tolvaptan dose of more than 0.3 mg/kg/day and the change in the urine volume ($p = 0.53$) (Fig. 4b).

Discussion

This study demonstrated that tolvaptan administration is safe and effective irrespective of the various clinical conditions after pediatric congenital heart disease surgery. Tolvaptan contributed to an increased urine volume, decreased body weight, and neutralization of the serum sodium, and its effect was applicable to variable patient conditions such as the underlying ventricular morphology, renal function, and chromosomal abnormalities. Also, we found that the urine volume was positively correlates with an initial tolvaptan dose of up to 0.3 mg/kg/day.

We showed that tolvaptan neutralized the serum sodium concentration in most patients without changes in the serum potassium and renal function. Especially, patients with hyponatremia had a much greater increase in the serum sodium level than normonatremic patients at baseline. This result was consistent with the previous reports [4, 6, 10, 16]. On the other hand, there was no change in the other laboratory parameters or vital signs such as the systolic blood pressure and heart rate after the tolvaptan administration. This indicated that tolvaptan can be used for the neutralization of hyponatremia without any major laboratory side effects after pediatric congenital heart disease surgery.

In the present study tolvaptan administration resulted in a significantly greater increase in the urine volume in survivors than the deceased. In other words, tolvaptan responders tended to show a better clinical outcome. However, there are several reports that tolvaptan administration did not achieve a better clinical outcome [5, 9, 17, 18]. In the present study, it was not clear whether tolvaptan administration led to a better clinical outcome after pediatric congenital heart disease

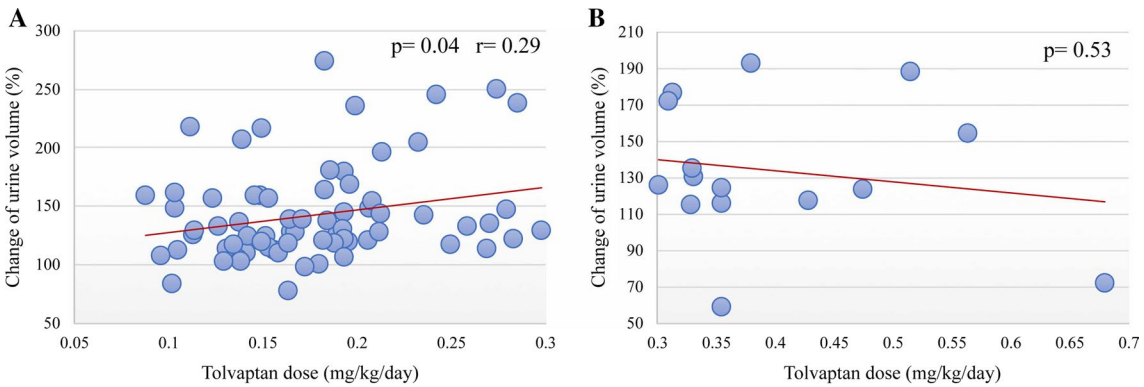

Fig. 4 Relationship between the dose of tolvaptan and change in the urine volume. There was a positive correlation between the tolvaptan dose and change in the urine volume until a tolvaptan dose of up to 0.3 mg/kg/day (**a**). However, there was no relationship between a tolvaptan dose of more than 0.3 mg/kg/day and the change in the urine volume (**b**)

surgery because its prognosis was often multifactorial and it depended on the severity of the underlying cardiac disease, type of cardiac surgery, and patient age.

There was no relationship between the tolvaptan administration and morphology of the ventricles, presence or absence of chromosomal abnormalities, and renal function. Underlying chromosomal abnormalities such as 21 trisomy, deletion 22q11.2 syndrome, Williams syndrome, and 5p-syndrome did not affect the safety and efficacy of tolvaptan. This suggested that tolvaptan had a stable effect irrespective of the various underlying clinical conditions in pediatric congenital heart disease patients. Also, we showed that these clinical characteristics were not additional risk factors in the tolvaptan administration. We recommend that the tolvaptan dose should not be arranged dependent on the morphology of the functional ventricle, presence of chromosomal anomalies, or serum creatinine concentration in these patients.

This study showed that there was no relationship between a tolvaptan dose of more than 0.3 mg/kg/day and the change in the urine volume. Katayama et al. showed that an add-on tolvaptan dose of 0.45 mg/kg/day was safe and effective after simple left-to-right shunt after pediatric congenital heart disease surgery [15]. Our study showed that the urine volume tends to increase until tolvaptan dose of up to 0.3 mg/kg/day in pediatric congenital heart disease patients and there were no further benefit in a urine volume with more than 0.3 mg/kg/day of tolvaptan. This dose was equivalent to a dose of about 15 mg/day in adult patients, which is the recommended dose by the manufacturer. The present study showed that tolvaptan was safe and effective not only in simple left-to-right shunt congenital heart diseases, but also in more complex biventricular diseases and those with a functional single ventricular circulation.

This study had some limitations to be noted. First, though previous reports suggest that the urinary osmolality is an independent predictor to assess the effectiveness of tolvaptan [14], we could not collect enough data on the urinary osmolality because of the retrospective study. Second, because the size of our study was small, the findings need to be confirmed in a larger, prospective study. Third, the patient population in the study was limited to Japanese pediatric patients. Because the tolvaptan dose may differ by the geographic region [19], this may need to be arranged dependent on the regions and races. Finally, because most patients in the study were neonates or infants, we could not assess the major side effects of tolvaptan such as a dry mouth and thirst [4, 6, 10].

In conclusion, this study demonstrated for the first time that tolvaptan was safe and effective irrespective of the various underlying clinical conditions after complex pediatric congenital heart disease surgery. Also, tolvaptan neutralized the serum sodium concentration in these patients without any laboratory and vital sign changes. Though the urine volume tends to increase until a tolvaptan dose of up to 0.3 mg/kg/day in pediatric congenital heart disease patients, there was no further benefit with more than 0.3 mg/kg/day.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interest.

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