Tolvaptan for Fluid Management in Living Donor Liver Transplant Recipients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Tolvaptan, an antagonist of the vasopressin V2 receptor is a novel oral diuretic that promotes water excretion selectively. We have used furosemide as a primary diuretic and added human atrial natriuretic peptide (hANP) if necessary for fluid management postoperatively in living-donor liver transplantation (LDLT) recipients. Recently we introduced tolvaptan and used both tolvaptan and furosemide as primary diuretics.

Material/Methods: Clinical outcomes were compared between LDLT recipients whose postoperative fluid management was performed before (control group, n=10) and after (tolvaptan group, n=16) introduction of tolvaptan.

Results: Preoperative and intraoperative demographic data did not differ significantly between the groups except for the period of post-surgical follow-up and total ischemic time. Urine volume was 1,242±692, 2,240±1307, and 2,268±1262 mL on postoperative day 1, 3, and 7, respectively, in the tolvaptan group. These volumes did not significantly differ from those in control group (1,027±462, 1,788±909, and 2,057±1216 mL on day 1, 3, and 7 postoperatively, respectively). Body weight gain and fluid volume from abdominal drainage tubes postoperatively did not differ significantly between groups. The time from hANP initiation to discontinuation and the time to removal of central vein catheters were significantly reduced in tolvaptan-treated patients. No severe side effects directly related to tolvaptan were observed. The survival rate at month 6 was 90.0% in control patients versus 93.8% in tolvaptan-treated patients.

Conclusions: The outcomes of this investigation indicate that tolvaptan in combination with furosemide provides an adequate diuretic for fluid management subsequent to LDLT without causing adverse effects.

MeSH Keywords: Diuretics • Liver Transplantation • Living Donors • Postoperative Care

Abbreviations: **hANP** – human atrial natriuretic peptide; **LDLT** – living-donor liver transplantation; **CNI** – calcineurin inhibitor; **eGFR** – estimated glomerular filtration rate; **AST** – aspartate transaminase; **MELD** – model for end-stage liver disease

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Background

Tolvaptan, a novel oral active vasopressin V2 receptor antagonist, was approved for the treatment of fluid retention in patients with cardiac failure in Japan in 2010 [1]. Tolvaptan received an additional indication in September 2013 for the treatment of fluid retention in patients with liver cirrhosis, a condition that is not adequately responsive to other diuretics such as loop diuretics [2–4]. A growing number of studies in Japan have reported the efficacy of tolvaptan for severe cirrhosis [5–9]. The drug has become an important therapeutic option for the treatment of cirrhosis patients and is now widely used in many hospitals in Japan.

Optimal management of fluid balance is important for and sometimes determines the success of liver transplantation [10]. Living-donor liver transplantation (LDLT) in adults is sometimes performed using small-sized grafts, which can lead to increased portal venous pressure and persistent ascites [11,12]. Furthermore, in ABO blood type-incompatible LDLT, recipients are subjected to high levels of calcineurin inhibitor (CNI) in the acute phase after transplantation and are at high risk of developing acute kidney injury [13]. It is very important to maintain a sufficient urine volume immediately after LDLT. However, use of conventional diuretics alone, such as furosemide or potassium canrenoate, is sometimes insufficient to maintain urine volume. Synthetic human atrial natriuretic peptide (hANP) is another effective diuretic [14], but it is an injectable drug that has to be delivered by continuous intravenous infusion.

We have used furosemide as our primary diuretic and added hANP if the diuretic effect was inadequate with furosemide only in the management of fluid balance following adult LDLT. Since the approval of tolvaptan for severe cirrhosis, we have used both tolvaptan and furosemide as first-line diuretics for adult LDLT. In this study, we describe our experience with tolvaptan usage during the postoperative phase after LDLT.

Material and Methods

Patients

Between January 2015 and July 2016, we performed 16 cases of LDLT in adults with end-stage liver disease who were treated with tolvaptan for postoperative fluid balance management (tolvaptan group, n=16). As a control group, we employed 10 additional adult LDLT patients who underwent transplantation in 2014 and were treated using diuretics other than tolvaptan (control group, n=10). All procedures were carried out in conformity with the Declaration of Helsinki following approval from the Institutional Review Board (authorization number 20120443) at our hospital. The surgical procedures employed for LDLT were based on previously published methods [15,16]. Splenectomies were performed intraoperatively in ABO-incompatible and in patients positive for hepatitis C virus. A catheter was intraoperatively inserted in the portal vein for portal infusion therapy. Different immunosuppressive regimens were used based upon ABO blood-type compatibility [13,17]. In all cases, the regimen comprised a CNI, steroid, and anti-metabolite, and at week 1 post-LDLT the CNI target trough concentration was greater in cases that were ABO blood-type incompatible cases versus identical and blood-type compatible cases (tacrolimus cases, 15–18 mg/dL versus 10–15 mg/dL; cyclosporine A cases, 400–500 mg/dL versus 300–400 mg/dL). Administration of prostaglandin E1 was carried out via the portal vein for 1 week post-LDLT in both ABO blood-type identical and compatible cases. Prostaglandin E1, steroid, and gabexate mesilate were injected into the portal vein for two weeks post-LDLT in cases who were ABO blood-type incompatible. For cases who were ABO blood-type incompatible, treatment included CNI, steroid, and anti-metabolite preoperatively; plasma exchange preoperatively; and rituximab preoperatively and postoperatively for depletion of B cells. A jejunostomy tube was intraoperatively inserted into the jejunum for early enteral nutrition [12].

Therapeutic policies for postoperative diuretics and fluid management

Until January 2015, we used furosemide as a primary diuretic and hANP was used as an add-on diuretic when necessary for the management of postoperative fluid balance after LDLT. Furosemide was intravenously administered at a dose of 20 mg/day immediately after transplantation and the dose was increased to 60 mg/day depending on the fluid balance at that time. Furosemide was given orally as soon as oral intake became possible. When urine volume became less than 0.5 mL/kg/hour for three hours or fluid volume was considered overloaded based on hemodynamic parameters, hANP was immediately administered via a central venous catheter at a dose of 0.0125 to 0.05 µg/kg/minute in addition to furosemide. When daily urine volume was greater than 1,000 mL and the volume-overload status had ended, hANP was gradually decreased and discontinued. Since January 2015, we introduced tolvaptan and used both furosemide and tolvaptan as first-line diuretics. Tolvaptan was administered via jejunostomy tube or orally at a half or full dose (3.75 or 7.5 mg/day) in all recipients within 24 hours after transplantation. The indication to add hANP along with the first-line diuretics of furosemide and tolvaptan was the same as before the introduction of tolvaptan. When the indication (urine volume <0.5 mL/kg/hour for three hours or volume-overload status) could not be resolved with the use of the two diuretics, hANP was added to the regiment as the third diuretic. Similarly, when daily urine volume was greater than 1,000 mL and the recipient was no longer volume-overloaded, hANP was the first drug discontinued and then tolvaptan administration was stopped. The central venous catheter was removed when

injectable drugs such as hANP were discontinued and oral intake became stable. Abdominal drainage tubes were removed when the drainage amount was 1,000 mL or less.

Analysis of postoperative outcomes in the tolvaptan and control groups

We retrospectively examined medical records of recipients in the tolvaptan group and control groups and assessed the following parameters: urine volume (mL/day), change in body weight (%), abdominal fluid volume from drainage tubes (mL/day), and mean arterial pressure (mm Hg) on postoperative day 1, 2, 3, 7, and 14. The percentage change in body weight was defined by the following equation: ([body weight on postoperative days]-[body weight immediately prior to transplantation])/ [body weight immediately prior to transplantation] ×100. To evaluate changes in diuretic usage after introduction of tolvaptan, we assessed the following parameters for furosemide and hANP intravenously administered for 21 days postoperatively: ratio of patients treated with the diuretic (%), period from initiation to discontinuation (days), and daily and total amount of the diuretic (mg/kg for furosemide, μg/kg for hANP). To compare postoperative short-term outcomes between the groups, we assessed the number of days from operation to discharge from the intensive care unit, from operation to central venous catheter removal, from operation to abdominal drainage tube removal, and from operation to discharge from the hospital. To compare adverse events between the groups, we assessed the estimated glomerular filtration rate (eGFR) as well as postoperative blood levels of creatinine, aspartate transaminase (AST), and sodium immediately prior to surgery and on postoperative days 7, 14, and 28 in both groups. Postoperative complications occurring within six months after surgery were recorded without any judgment about causality or relationship to tolvaptan usage. We also assessed six-month survival in both groups.

Adverse events of grade 2 to 5 (Common Terminology Criteria for Adverse Events (CTCAE) version 4) were recorded [18]. Renal dysfunction was defined as the need for temporary or permanent hemodialysis. Hepatic dysfunction was defined as an increase in AST levels by more than twice the normal limit. Acute cellular rejection was diagnosed based on the Banff criteria [19], and mild, moderate, and severe grades of acute cellular rejection were included. Fungal infection was defined as plasma β-D glucan positivity (turbidimetric time assay). Cytomegalovirus infection was defined as plasma CMV antigenemia test positivity (indirect enzyme immunoassay, SRL, Inc., Tokyo, Japan).

Statistical analysis

Student's *t*-test was used for comparisons between continuous data in the groups. Chi-square test was used for categorical data comparisons between groups. Kaplan-Meier analysis

was used to calculate survival rates. IBM SPSS 19 software was used for all statistical analyses. Results are presented as mean ±SD. All statistical tests were two-sided and results were deemed statistically significant if the *p*-value exceeded 0.05.

Results

Patient characteristics in the tolvaptan and control groups

Patient characteristics in the tolvaptan and control groups are shown in Table 1. Demographic data preoperatively and intraoperatively did not differ significantly between groups except for the time of follow-up following surgery and total ischemic time.

Postoperative urine volume, body weight gain, drainage volume from abdominal drainage tubes, and mean arterial pressure

Daily urine volume (mL) was 1,242±692, 2,240±1,307, 2,268±1262, and 1,950±754 on postoperative day 1, 3, 7, and 14, respectively, in the tolvaptan group. These volumes did not significantly differ from the respective values in the control group (1,027±462, 1,788±909, 2,057±1216, and 1,550±918 mL) (Figure 1A). Body weight gain postoperatively, fluid volume from abdominal drainage tubes, and mean arterial pressure did not differ significantly between groups (Figure 1B–1D).

Usage of hANP and furosemide after operation

Changes in furosemide and hANP usage after the introduction of tolvaptan are shown in Figure 2A–2H. As for furosemide usage, the period from initiation to discontinuation (4.5±2.8 versus 8.1±4.9 days, *p*=0.026; Figure 2C) and the total amount administered for 21 days postoperatively (3.0±2.0 versus 9.2±7.3 mg/kg, *p*=0.003; Figure 2G) were significantly lower in the tolvaptan group compared with the control group. The daily amount of furosemide was significantly lower from postoperative day 3 to 12 in the tolvaptan group than in the control group (Figure 2E). As for hANP usage, the period from initiation to discontinuation was significantly shorter in the tolvaptan group compared with the control group (3.4±2.7 versus 9.3±6.5 days, *p*=0.004; Figure 2D). The daily amount of hANP was significantly lower from postoperative day 9 to 14 in the tolvaptan group than in the control group (Figure 2E). Notably, no patients used hANP after postoperative day 10 in the tolvaptan group.

Number of days from operation to intensive care unit discharge, removal of central venous catheters, abdominal drainage tubes, and hospital discharge

The time from operation to intensive care unit discharge, removal of central venous catheters, and drainage tube removal were

**Table 1.** Characteristics of patients in the tolvaptan and control groups.

	Control group (n=10)	Tolvaptan group (n=16)	p-Value
Recipient sex, male/female	6/4	8/8	0.701
Recipient age, years	57 (51–67)	56.5 (43–68)	0.412
Recipient body weight, kg	58.6±24.4	62.9±11.4	0.540
Recipient body mass index, kg/m^2	23.5±4.0	23.7±3.4	0.894
Donor age, years	26.5 (20–56)	32 (20–62)	0.293
Follow up period after surgery, months	69.0±22.2	29.4±16.7	<0.001
Diseases			
Hepatitis C	4	6	1.000
Primary biliary cirrhosis	2	4	1.000
Alcohol	1	4	0.617
Hepatocellular carcinoma, +/−	2/8	5/11	0.668
MELD score	17.8±8.3	17.9±7.1	0.981
Child-Pugh Score	11.5±4.9	11.1±1.4	0.790
ABO identical and compatible/incompatible	7/3	10/6	1.000
Preoperative tolvaptan usage, +/−	2/8	9/7	0.109
Preoperative eGFR, mL/min/1.73 m^2	58.9±17.9	65.5±26.4	0.492
Preoperative blood parameters			
Creatinine, mg/dL	1.05±0.48	1.01±0.60	0.882
Total bilirubin, mg/dL	7.9±7.8	5.7±5.7	0.410
Albumin, g/dL	2.9±0.5	2.7±0.5	0.366
Sodium, mEq/L	135.9±6.4	135.8±4.5	0.957
Graft weight recipient body weight ratio,%	0.74±0.92	0.80±0.10	0.118
Graft, left lobe/right lobe	6/4	9/7	1.000
Warm ischemic time, minutes	56.0±15.5	58.7±26.2	0.773
Total ischemic time, minutes	142.7±32.7	191.9±77.6	0.036
Blood loss, g	7398±7204	7669±17593	0.964

MELD – model for end-stage liver disease; eGFR – estimated glomerular filtration rate.

significantly shorter in patients in the tolvaptan group than in the control group (6.3±3.0 versus 9.2±2.7 days, *p*=0.022; 8.3±4.5 versus 13.3±7.2 days, *p*=0.041; 12.0±5.6 versus 19.6±10.7 days, *p*=0.029; Figure 3A–3C). The number of days to hospital discharge was also lower in the tolvaptan group (56.2±37.2 days) than in the control group (69.9±32.9 days), but the difference was not statistically significant (Figure 3D).

Postoperative adverse events and six-month survival

Postoperative changes in eGFR, creatinine, aspartate transaminase, and sodium are shown in Figure 4. There were no significant between-groups differences in these parameters postoperatively. Postoperative complications observed within six months after surgery are shown in Table 2. No recipients presented with severe hypernatremia exceeding the normal limit. In the control group, two recipients developed chronic renal failure permanently requiring hemodialysis and one recipient
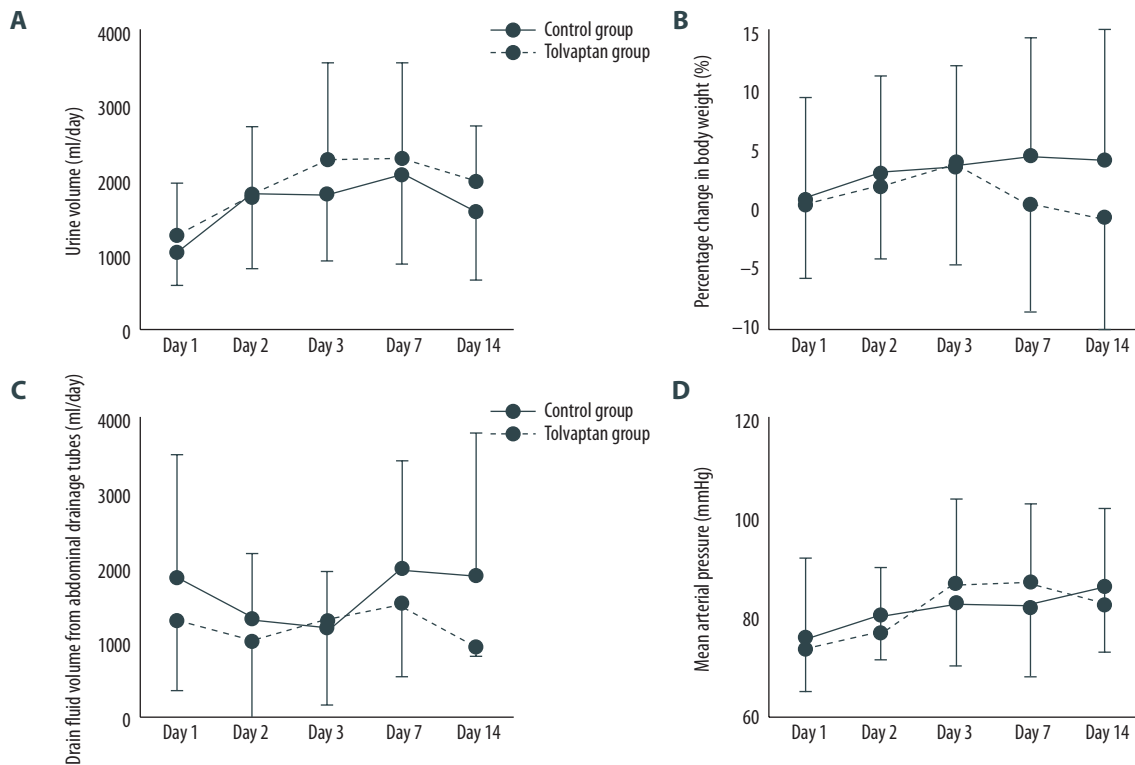
Figure 1. Changes in (**A**) urine volume, (**B**) percentage change in body weight, (**C**) drainage volume from abdominal drainage tubes, and (**D**) mean arterial pressure in control and tolvaptan groups. The solid and broken lines indicate parameters in control and tolvaptan groups, respectively. The percentage change in body weight is defined by the following equation: ([body weight on postoperative 1, 2, 3, 7, or 14 days]-[body weight immediately prior to transplantation])/[body weight immediately prior to transplantation] ×100.

developed acute kidney injury transiently requiring hemodialysis, while in the tolvaptan group, two recipients developed acute kidney injury requiring transient hemodialysis. There was no difference in the incidence of hemodialysis between the groups. Elevation of AST exceeding twice the normal limit was observed in five recipients in the tolvaptan group and seven recipients in the control group. The elevation of AST was caused by acute cellular rejection, graft liver failure, or other causes but not by tolvaptan usage. No complications were associated with tolvaptan usage. Survival rates at month 6 in the control and tolvaptan-treated patients were 90.0% and 93.8%, respectively. One recipient in the tolvaptan group died of subarachnoid bleeding on postoperative day 13, and a recipient in the control group died of fungal infection on postoperative day 112. Both causes of death were unrelated to tolvaptan usage.

Discussion

Careful and meticulous postoperative management is necessary for the success of liver transplantation. Fluid balance management is one of the most important postoperative concerns after LDLT. Positive fluid balance can cause pulmonary complications, prolong intubation time, and is associated with poor outcomes after LDLT [20,21]. To maintain proper body fluid balance, securing reliable urine volume is indispensable. We introduced tolvaptan for postoperative fluid balance management in 2015 and have used both furosemide and tolvaptan as first-line diuretics and utilized hANP as an additional option in 16 recipients. The resultant outcomes of daily urine volume, percentage change in body weight, and fluid volume from abdominal drainage tubes suggest that postoperative fluid management can be achieved by the combination of furosemide, tolvaptan, and hANP. Tolvaptan is used for the treatment of fluid retention in patients with liver cirrhosis but could also be effective for postoperative fluid management in patients with liver cirrhosis who have undergone LDLT.

It has been reported that the continuous infusion of hANP is effective for maintaining urine volume after LDLT [14], and we have also used hANP for the purpose of maintaining urine volume in the acute phase after LDLT. However, hANP is an injectable drug and postoperative administration of multiple injectable drugs requires that a catheter be maintained in the central
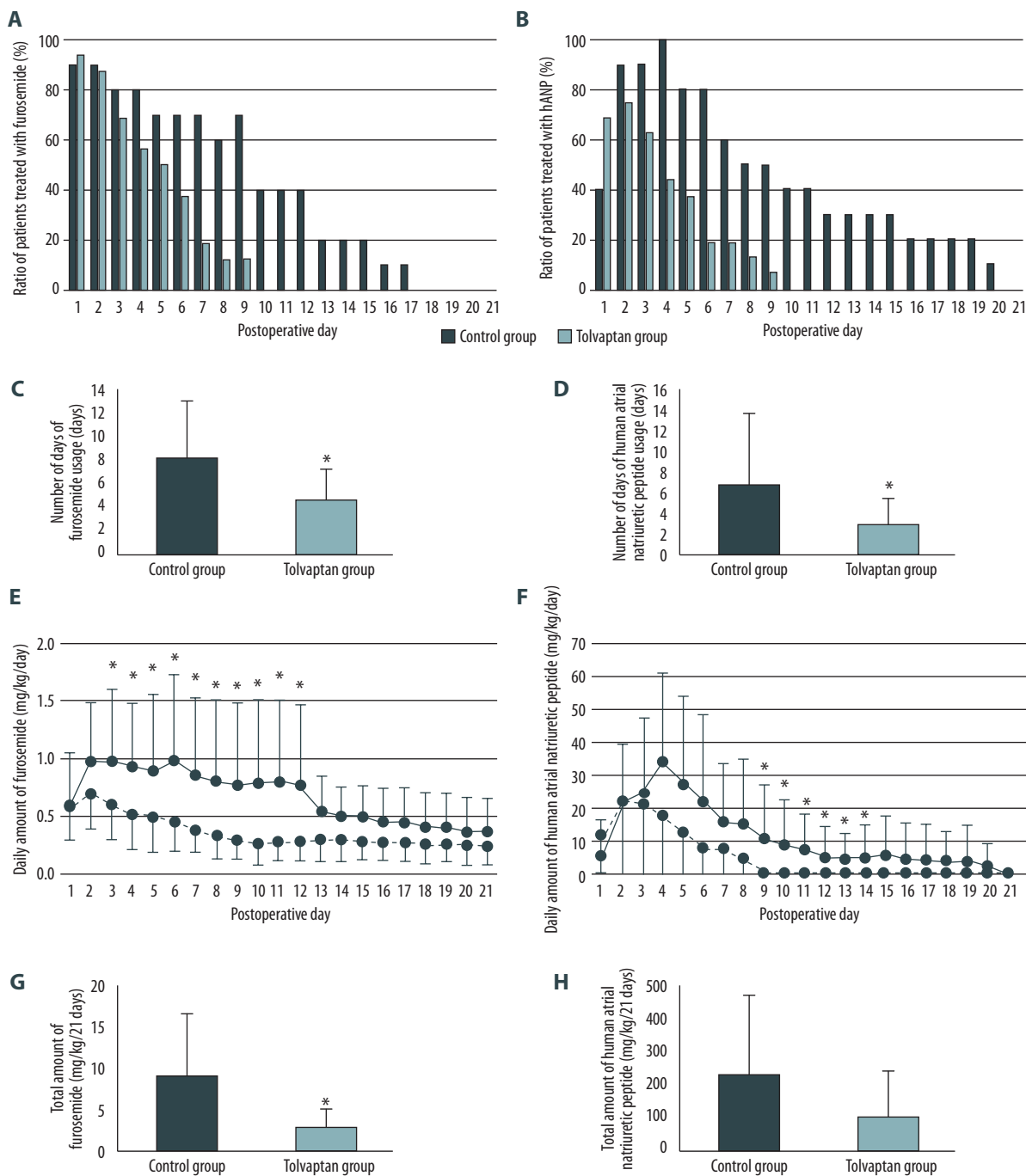
Figure 2. Changes in diuretic usage after introduction of tolvaptan. Ratio of patients treated with (**A**) furosemide and (**B**) hANP, period from initiation to discontinuation of (**C**) furosemide and (**D**) hANP (days), daily amount of (**E**) furosemide and (**F**) hANP, and total amount of the (**G**) furosemide and (**H**) hANP (mg/kg for furosemide, μg/kg for hANP). Furosemide and hANP administered intravenously for 21 days postoperatively were assessed. Asterisk (*) indicates a statistically significant difference versus the control group ($p < 0.05$).
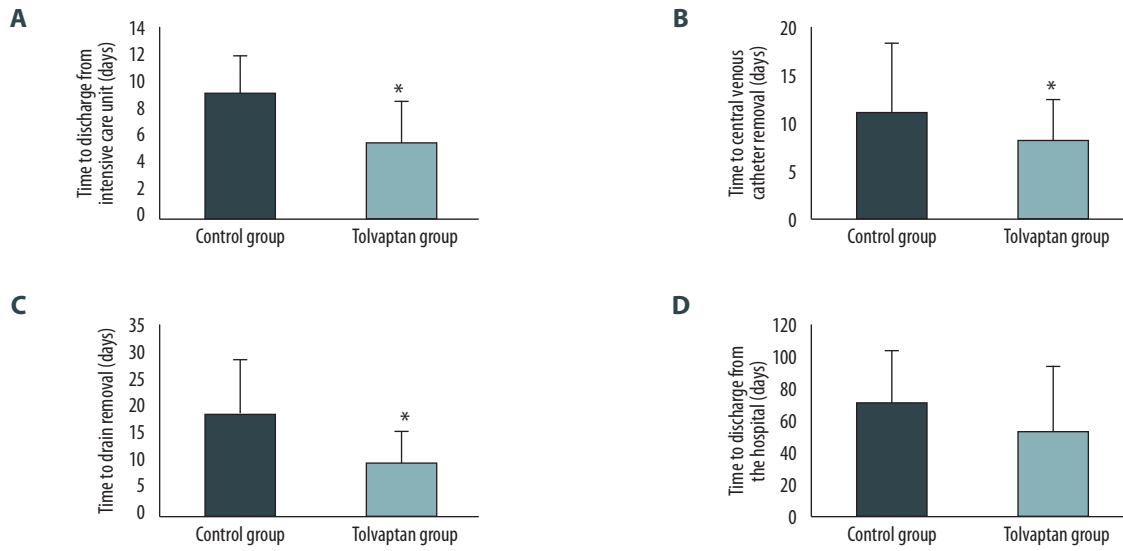
Figure 3. Number of days to (**A**) discharge from intensive care unit, (**B**) central venous catheter removal, (**C**) drain removal, and (**D**) discharge from hospital in control and tolvaptan groups.
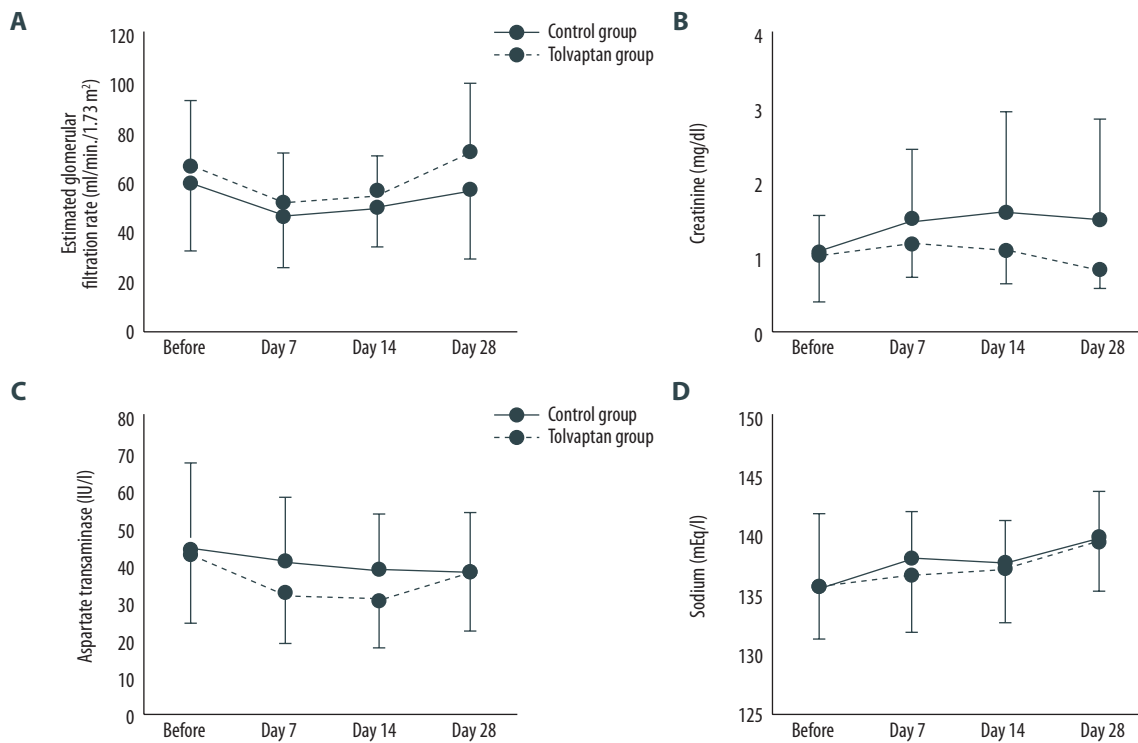
Figure 4. Changes in (**A**) estimated glomerular filtration rate, (**B**) creatinine, (**C**) aspartate transaminase, and (**D**) sodium in control and tolvaptan groups. The solid and broken lines indicate parameters in control and tolvaptan groups, respectively. Asterisk (*) indicates a statistically significant difference versus the control group ($p<0.05$).

Table 2. Postoperative adverse events.

	Control group (n=10)	Tolvaptan group (n=16)	p-Value
Postoperative bleeding	3	4	1.000
Hepatic artery thrombosis	2	0	0.138
Portal vein thrombosis	1	2	1.000
Bile leakage	1	0	0.385
Biliary stenosis	1	1	1.000
Cytomegalovirus infection	6	8	0.701
Bacterial or fungal infection	5	2	0.069
Central nervous disturbance	2	2	0.625
Brain hemorrhage	0	1	1.000
Renal dysfunction	3	2	0.340
Hepatic dysfunction	5	7	0.756
Acute cellular rejection	1	5	0.352
Hypernatremia	0	0	

vein following LDLT. We favor removal of central vein catheters as soon as possible after LDLT to reduce the risk of infection in immunosuppressed recipients and, therefore, have attempted to terminate injectable drugs after discharge of patients from intensive care. It has also been reported that hANP can cause severe hypotension because of its vasodilatory effect [22] and, therefore, careful monitoring of hemodynamics during hANP infusion is needed. Tolvaptan is an oral vasopressin V2 receptor antagonist that does not require intravenous administration and has minimal effect on blood pressure. We observed that the use of furosemide and hANP decreased both quantitatively and periodically after the introduction of tolvaptan. In particular, periodic reduction of the intravenous diuretics seemed to contribute to the early removal of central venous catheters in tolvaptan-treated patients. We did not observe any substantial changes in blood pressure during treatment with tolvaptan. It is noteworthy that postoperative fluid management after LDLT was performed with reduced usage of intravenous diuretics.

It is of great interest to determine whether tolvaptan is advantageous for protecting renal function. Intravenous furosemide is a fundamental diuretic therapy for several diseases and clinical situations including postoperative management after LDLT. However, volume reduction by loop diuretics leads to a decrease in renal blood flow in patients with renal dysfunction. Furthermore, loop diuretics activate the renin-angiotensin-aldosterone system (RAAS), which can lead to a deterioration of renal function [23,24]. In contrast, tolvaptan acts as a diuretic without activating the RAAS [25]. It has been shown to increase renal blood flow and reduce renal vascular resistance in patients with heart failure [26]. Many other studies

have shown favorable effects of tolvaptan on renal function when used in volume-overload diseases such as heart failure and liver cirrhosis [27–30]. In patients who undergo LDLT, continuous infusion of hANP has been reported to be beneficial for preventing acute renal failure postoperatively [14], but there have been no reports on the effect of tolvaptan in liver transplant recipients. In this study, the creatinine and eGFR levels showed a trend for improvement until postoperative day 28 in tolvaptan-treated patients versus controls. We are greatly encouraged to investigate in the future whether usage of tolvaptan can protect renal function after LDLT in a study involving a larger number of patients.

It has been reported that tolvaptan can cause adverse events such as hypernatremia and hepatic dysfunction [1]. Therefore, we carefully monitored serum sodium levels and hepatic function parameters. As shown in Table 2, there were some adverse events in both groups, none of which were related to tolvaptan usage. In our experience, tolvaptan has been safely used for postoperative management after LDLT. However, a large scale post-marketing surveillance study recently reported that tolvaptan can produce various adverse effects in liver cirrhosis patients, albeit at a low rate [31]. Therefore, onset of potential adverse effects should be closely monitored during postoperative management.

There are several limitations associated with the present study. It was not a prospective study, and two separate cohorts were employed whose operations were performed sequentially. Although postoperative management was consistent throughout this study, the two cohorts showed a difference in follow-up period and total

ischemic time. Moreover, the study was conducted with results from a single institution, and included a limited number of patients. A prospective randomized study employing larger number of patients is needed to clarify the efficacy of tolvaptan after LDLT.

Conclusions

While the present investigation was limited by the small number of patients studied and its retrospective design, the experience at our clinical center yielded valuable findings with respect to tolvaptan usage for postoperative fluid management in the acute phase after LDLT. Our results suggest that tolvaptan reduces the use of injectable diuretics, such as hANP and furosemide, with respect to both quantity and frequency, and is also beneficial in promoting early removal of central venous catheters. Further investigation is needed employing a larger number of recipients over a longer time period to confirm the effects of tolvaptan on other long-term outcomes including renal function and patient survival.

Conflicts of interest

None.

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