Original Article

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A selective oral vasopressin V2-receptor antagonist for patients with end-stage liver disease awaiting liver transplantation: a preliminary study

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Summary **Administration of the selective arginine vasopressin V2 receptor antagonist tolvaptan to cirrhotic patients is controversial. There are no reports of tolvaptan use for patients with far-advanced end-stage liver disease (ESLD) and refractory ascites awaiting liver transplantation. Between 2013 and 2016, 64 patients awaiting adult-to-adult living donor liver transplantation (LDLT) were screened for enrollment. Patients with refractory ascites and on dual conventional diuretics (≥ 50 mg/day of spironolactone and ≥ 20 mg/day of a loop diuretic) were enrolled and assigned to the tolvaptan (TOL) group (n = 10), and low-dose tolvaptan, 3.75 mg/day, was started. The remaining patients who had no or little ascites on conventional diuretic therapy (CDT) were assigned to the CDT group (n = 23). The median model for end-stage liver disease and Child-Pugh scores were 16 (range 7-41) and 10 (7-15), respectively. The median dose of spironolactone in the TOL group was 88 mg (range 50-200) *vs*. 50 (0-100) in the CDT group ($p < 0.01$). The median dose of loop diuretics in the TOL group was 70 mg (20-120) *vs*. 20 (0-80) in the CDT group ($p = 0.03$). No significant liver damage was detected during tolvaptan therapy. Tolvaptan demonstrated favorable effects in 60% (6/10) of the patients, decreasing the body weight by at least 1.5 kg during the 7 day treatment. These findings suggest that low-dose of tolvaptan may be safe for patients having far-advanced ESLD patients with apparent and refractory ascites taking dual conventional diuretics for a short period before LDLT.**

Keywords: Tolvaptan, liver transplantation, end-stage liver disease

1. Introduction

Liver transplantation is a definitive treatment option for patients with end-stage liver disease (ESLD). A potentially serious major complication of cirrhosis is ascites, which occurs in 50% of patients over a 10-year observation period (*1*) and in approximately 90% of patients with ESLD (*2*). Management of ascites related to ESLD is a major challenge during the waiting period for liver transplantation.

Spironolactone and loop diuretics are key drugs used to manage cirrhotic patients with ascites (*3,4*). A new, recently approved diuretic, the selective arginine vasopressin V2 receptor antagonist tolvaptan, which acts at the V2 receptors in the renal collecting duct to inhibit water resorption, increases urine output volume, decreases body weight, increases serum sodium values (*5*), and helps to maintain renal function in patients with liver cirrhosis and ascites (*6,7*).

Tolvaptan was approved in the United States in 2009 for use in patients with hyponatremia due to heart failure, syndrome of inappropriate antidiuretic hormone secretion, and liver cirrhosis. In a randomized

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controlled trial of tolvaptan for patients with autosomal dominant polycystic kidney disease, however, 1.2% of patients in the tolvaptan group discontinued the trial due to liver-function abnormalities (*8*). In 2013, the United States Food and Drug Administration raised concerns regarding the potential risk of liver injury in patients taking tolvaptan (*9*). Therefore, tolvaptan is not yet approved for patients with liver cirrhosis in the United States. Sakaida and colleagues reported favorable results of a clinical trial of low-dose tolvaptan in cirrhotic patients with ascites without liver injury (*10*) , leading to its approval for cirrhotic patients by the Ministry of Health, Labour, and Welfare in Japan in 2013. A recent post-marketing surveillance report showed encouraging results for ascites control; three patients (0.7%, 3/473) had liver failure, however, and discontinued treatment.

Worldwide, tolvaptan administration for cirrhotic patients remains controversial. Currently, the American Association for the Study of Liver Diseases does not recommend tolvaptan for patients with cirrhosis (*11,12*). The clinical practice guidelines of the European Association for the Study of the Liver mention tolvaptan and its expected effects for cirrhotic patients with ascites and severe hypervolemic hyponatremia (*13*).

Despite the increasing number of studies of tolvaptan for patients with cirrhosis, there are no reports of tolvaptan for far-advanced ESLD patients with refractory ascites awaiting liver transplantation. In this preliminary study, we report the short-term results of tolvaptan use for patients scheduled to undergo living donor liver transplantation (LDLT).

2. Methods

Between May 2013 and January 2016, 64 consecutive adult-to-adult LDLTs were performed at the Tokyo University Hospital. The present preliminary, prospective study protocol was approved by the University of Tokyo Ethics Committee. The protocol was registered to the clinical trials registry managed by the university hospital medical information network in Japan (UMIN000027096, *http://www.umin.ac.jp/ctr/index.htm*).

Inclusion criteria were as follows: over 18 years of age, cirrhotic patients awaiting adult-to-adult LDLT, refractory ascites (*14*), and taking dual conventional diuretics (≥ 50 mg/day of spironolactone and ≥ 20 mg/day of a loop diuretic). The patients were enrolled and assigned to the tolvaptan (TOL) group during the preoperative evaluation period. The remaining patients who had no or little ascites on conventional diuretic therapy (CDT) were assigned to the CDT group, and the pre-and postoperative factors were compared between the TOL and CDT groups. Exclusion criteria were no apparent ascites without diuretics, patient already on tolvaptan, and acute liver failure. Preoperative factors, including Child-Pugh score, model for end-stage liver disease (MELD) score, total bilirubin, prothrombin time-international normalized ratio (PT-INR), serum creatinine, aspartate aminotransferase, alanine aminotransferase, serum albumin, serum sodium, and platelet counts, were recorded. Operation time, estimated blood loss, actual amount of ascites (all ascites was drained and measured just after starting the operation), amount of blood transfused, and Clavien-Dindo classification were compared between the TOL and CDT groups. Informed consent was obtained from all recipients.

In the TOL group, low-dose tolvaptan (Samsca; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan), 3.75 mg /day, was started. The dose was based on half the starting dose and clinical trial recommendation for hepatic edema (*10*) and the Japanese guidelines (*15*). If the patient's symptoms did not improve, the dose was increased to 7.5 mg. Tolvaptan administration was continued until the day before LDLT and discontinued immediately after LDLT. Body weight, daily urine output volume, total bilirubin, serum albumin, serum creatinine, sodium levels, PT-INR, Child-Pugh score, and MELD score were monitored on days 0, 1, 3, 7 after tolvaptan initiation. The serum creatinine level was also monitored on days 0, 1, 3, 7, and 30 after LDLT.

The primary endpoint was change in body weight: a 1.5-kg decrease from baseline to 7 days after tolvaptan initiation. The secondary endpoints were urine output volume on days 1, 3 and 7; whether or not the urine output volume was greater than that before tolvaptan initiation; and use of additional diuretics other than tolvaptan. Liver damage was defined as a two-fold increase in the levels of aspartate aminotransferase and alanine aminotransferase compared with the levels before tolvaptan initiation. Patients for whom tolvaptan was effective, defined as a greater than 1.5-kg decrease in body weight during the 7 days after tolvaptan initiation, were classified into the tolvaptan-effective group. The remaining patients were classified into the tolvaptan-ineffective group. Preoperative and postoperative factors were compared between the groups.

Statistical analysis The Mann-Whitney *U* test was used to compare the patient characteristics between groups. After tolvaptan initiation, variables were compared by the Wilcoxon signed-rank test. Changes in body weight and daily urine output volume in both groups were compared by two-way repeated measures analysis of variance using the JMP pro 12.2 statistical software package (SAS Institute Inc., Cary, NC, USA). Data are expressed as median and range. A $p < 0.05$ was considered statistically significant.

3. Results

A total of 64 patients were screened for enrollment. Of the 64, 31 patients were excluded from the study

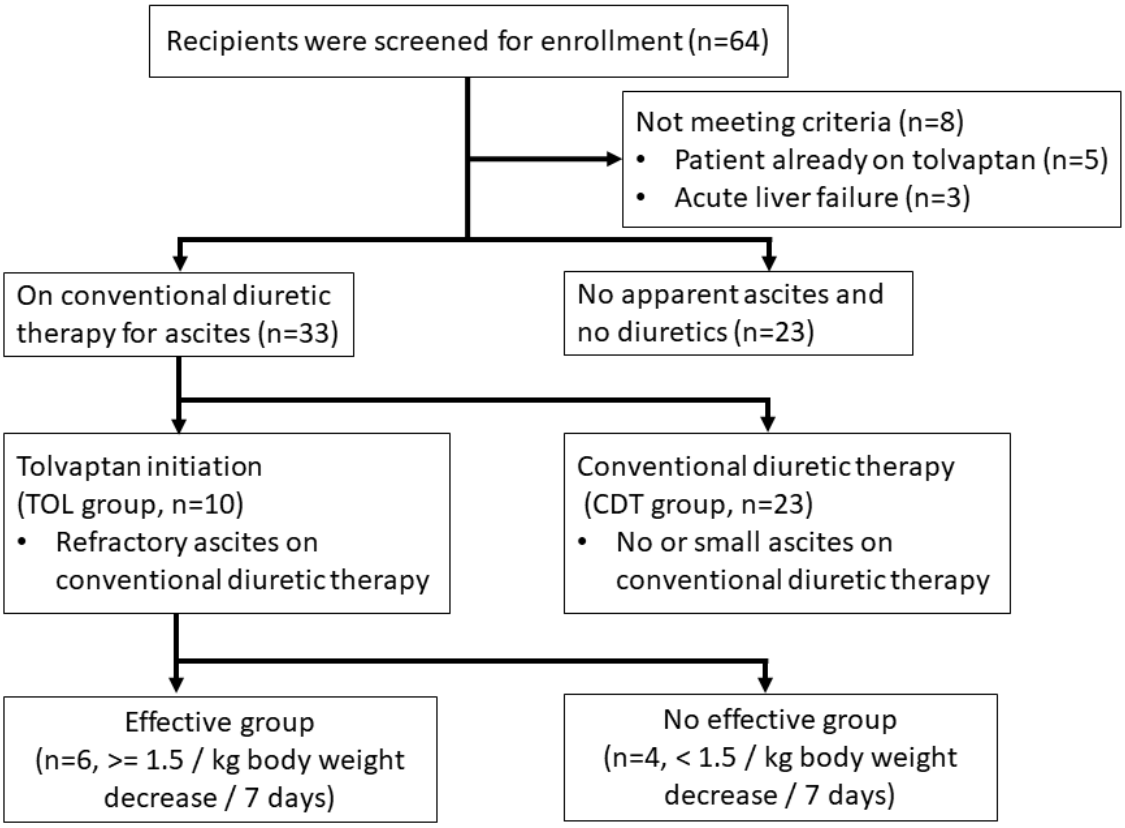

Figure 1. Flow chart summarizing subject enrollment for the present study.

because they did not meet the criteria, including no apparent ascites and no diuretics (n = 23), currently on tolvaptan prescribed during a previous hospital visit (n = 5), and acute liver failure (n = 3). Ten patients were assigned to the TOL group and tolvaptan was started. The remaining 23 patients, having no or little ascites on CDT, were assigned to the CDT group (Figure 1).

The subjects comprised 18 men and 15 women with a median age of 50 (range 18-67) years. Indications for transplantation included hepatitis B or C-related cirrhosis (n = 14), primary biliary cirrhosis (n = 6), alcoholic liver cirrhosis (n = 3), cryptogenic liver cirrhosis (n = 3), Budd-Chiari syndrome (n = 3), primary sclerosing cholangitis (n = 2), non-alcoholic steatohepatitis (n = 1), and Wilson's disease (n = 1). The median MELD and Child-Pugh scores were 16 (range 7-41) and 10 (7-15), respectively.

Characteristics of patients in the TOL and CDT groups are shown in Table 1. There was no significant difference between groups with respect to the Child-Pugh score, MELD score, total bilirubin, PT-INR, and serum creatinine, serum alanine transaminase, serum aspartate transaminase, or serum albumin levels. The median serum sodium concentration differed significantly between the TOL and CDT groups (130 mmol/L [122-139] *vs*. 136 [131-140], $p < 0.01$). The median dose of spironolactone in the TOL group was 88 mg (range 50-200) *vs*. 50 (0-100) in the CDT group ($p < 0.01$). The median dose of loop diuretics in the TOL group was 70 mg (20-120) *vs*. 20 (0-80) in the CDT group ($p = 0.03$).

In the TOL group, the median tolvaptan administration period was 18 (range 7-16) days before LDLT. Tolvaptan administration could continue for all patients. Changes in body weight, daily urine output volume, serum sodium concentration, and MELD score are shown in Figures 2A-D. The TOL and CDT groups differed significantly with respect to body weight between preadministration and 1 day after tolvaptan initiation (-1.1 kg, p = 0.02, 2A) and in daily urine output volume between preadministration (1475 mL/day) and 7 days (2675 mL/day, $p < 0.01$, 2B) after tolvaptan initiation. The change in the serum sodium concentration was not significant between preadministration and 1, 3, and 7 days after tolvaptan initiation (Figure 2C). The MELD score was relatively stable during the 7 days of treatment (Figure 2D). The change in the serum creatinine level was not significant between preadministration and 1, 3, and 7 days after tolvaptan initiation (Figure 2E). The remaining factors, including serum albumin level, PT-INR, and Child-Pugh score, did not change during the 7 days of treatment (data not shown).

The changes in the serum aspartate transaminase and alanine transaminase levels in the TOL group are shown in Figure 3. The median serum aspartate transaminase and alanine transaminase levels preadministration and 7 days after tolvaptan initiation were 57.5 and 58.0 U/L,

Table 1. Characteristics of patients in the tolvaptan (TOL) and conventional diuretic therapy (CDT) groups

Patient characteristics	TOL (n = 10)	CDT (n = 23)	P value
Age	58 (41-64)	57 (23-67)	0.75
Male/female	4/6	14/9	0.45
Liver disease			
Hepatitis B or C	2	12	0.09
Primary biliary cirrhosis	3	3	0.25
Alcoholic	1	2	0.9
Cryptogenic	2	1	0.15
Budd-Chiari syndrome	0	3	0.23
Primary sclerosing cholangitis	1	1	0.53
Non-alcoholic steatohepatitis	1	0	0.12
Wilson's disease	0	1	0.50
Preoperative factors			
Child-Pugh score	11 (8-13)	10 (8-13)	0.13
Model for end-stage liver disease score	16 (10-21)	14 (8-13)	1.00
Total bilirubin (mg/dL)	5.2 (1.7-19.3)	4.1 (0.8-27.1)	0.43
Prothrombin time-international normalized ratio	1.32 (1.15-1.78)	1.37 (1.12-1.92)	0.78
Serum creatinine (mg/dL)	0.83 (0.50-1.62)	0.75 (0.54-1.33)	0.35
Alanine transaminase (U/L)	58 (29-173)	49 (9-163)	0.47
Aspartate transaminase (U/L)	28 (12-63)	31 (6-89)	0.84
Serum albumin (g/dL)	2.9 (2.4-3.6)	2.7 (2.0-3.6)	0.13
Serum sodium (mEq/L)	130 (122-139)	136 (131-140)	< 0.01*
Platelet count (*10^4μL)	7.1 (4.0-32.2)	7.7 (2.6-18.5)	0.67
Conventional diuretics			
Spironolactone (mg)	88 (50-200)	50 (0-100)	< 0.01*
Loop diuretics (mg)	70 (20-120)	20 (0-80)	0.03*

The median serum sodium concentration differed significantly between the TOL and CDT groups (130 mmol/L [range 122-139] *vs*. 136 [131-140], $p < 0.01$). The dose of spironolactone was 88 mg (50-200) in the TOL group *vs*. 50 (0-100) in the CDT group ($p < 0.01$). The dose of loop diuretics was 70 mg (20-120) in the TOL group *vs*. 20 (0-80) in the CDT group ($p < 0.05$).

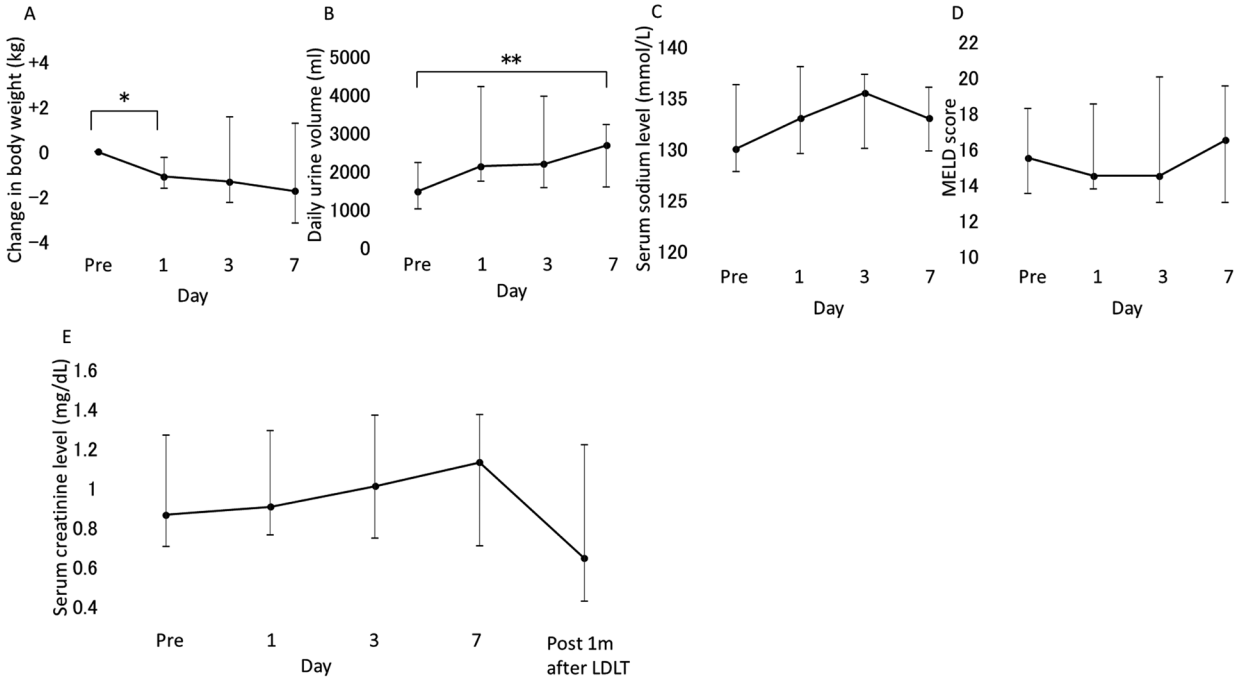

Figure 2. Changes in body weight (A), daily urine output volume (B), serum sodium concentration (C), model for end-stage liver disease (MELD) score (D) , and serum creatinine level (E) in the tolvaptan (TOL) group are shown. The groups differed significantly with respect to body weight between preadministration and 1 day after tolvaptan initiation (-1.1 kg, $p = 0.02$, **A**) and daily urine volume between preadministration and 7 days after tolvaptan initiation (1475 mL/day *vs*. 2675 mL/day, $p < 0.01$, **B**). The serum sodium concentration increased up to day 3, but the difference was not significant (**C**). The MELD score remained relatively stable over the 7 days (**D**). The serum creatinine level gradually increased up to day 7 and decreased within 1 month after LDLT. The difference, however, was not significant (**E**).

28 and 32 U/L, respectively. There was no significant difference between these values (Figure 3A, $p = 1.00$ and Figure 3B, $p = 0.89$) and no two-fold increase in the values.

A 1.5-kg body weight decrease during the 7 days of tolvaptan administration occurred in 60% (6/10) of the TOL patients in whom the drug was considered effective. The body weight did not decrease in 40% (4/10) of the TOL patients in whom the drug was considered ineffective. The median Child-Pugh score in the tolvaptan-effective and tolvaptan-ineffective groups was 10.5 (8-11) and 12.5 (11-13), respectively ($p < 0.01$; Table 2). The amount of ascites in the tolvaptan-effective and tolvaptan-ineffective groups was 1,450 mL (500-4,100) and 7,050 mL (4,000-13,550), respectively ($p = 0.04$). There were no significant differences between groups in the other related factors (Table 3). The change in body weight differed significantly ($p < 0.01$) between groups (Figure 4A). The groups did not differ significantly in the change in the daily urine output volume ($p = 0.88$, Figure 4B).

Operative factors of the TOL and CDT groups are shown in Table 3. The median amount of ascites was higher in the TOL group (3,450 mL [500-13,550]) than in the CDT group (250 mL [0-4,750], $p < 0.01$). There were no significant differences between groups in operation time, estimated blood loss, blood transfusion, or Clavien-Dindo classification. Changes in serum creatinine levels were not significant between preadministration of tolvaptan and 1 month after liver transplantation.

4. Discussion

The findings of this preliminary study demonstrated the safety of a low dose of tolvaptan for far-advanced ESLD patients with apparent and refractory ascites taking dual conventional diuretics for a short period before LDLT. Tolvaptan administration could be

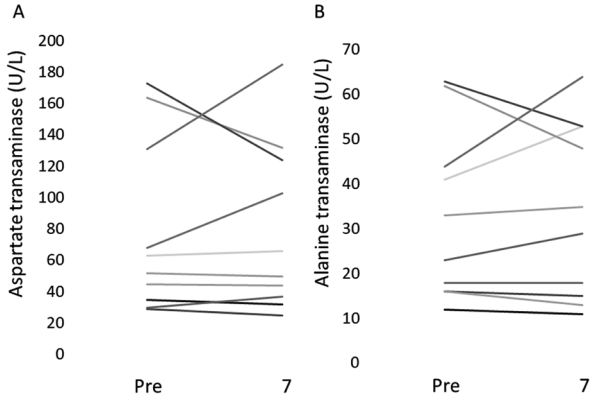

Figure 3. Changes in the serum aspartate transaminase (A) and alanine transaminase (B) levels in the tolvaptan (TOL) group are shown. There was no significant difference between preadministration and tolvaptan initiation ($p = 1.00$ and $p = 0.89$), and no 2-fold increase in the serum aspartate transaminase and serum alanine transaminase levels.

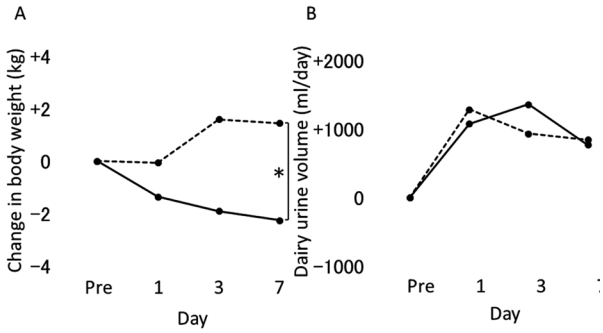

Figure 4. (A) Change in body weight in both groups. There was a significant difference between groups ($p < 0.01$). (B) Change in daily urine output volume in both groups. There was no significant difference between groups ($p = 0.88$).

Table 2. Tolvaptan was considered effective in 60% (6/10) of the patients

Relative factors	Effective ($n = 6$)	No effective ($n = 4$)	P value
Child-Pugh score	10.5 (8-11)	12.5 (11-13)	< 0.01*
Model for end-stage liver disease score	14.5 (10-19)	17 (14-21)	0.24
Total bilirubin (mg/dL)	3.7 (1.7-19.3)	7.9 (4.3-14.4)	0.39
Prothrombin time-international normalized ratio	1.20 (1.15-1.63)	1.59 (1.26-1.78)	0.05
Serum creatinine (mg/dL)	1.01 (0.50-1.62)	0.76 (0.75-0.98)	0.52
Serum sodium (mEq/L)	135 (122-139)	129 (127-131)	0.16
Operative factors			
Operation time (min)	657 (634-854)	639 (584-732)	0.39
Estimated blood loss (mL)	4,323 (1,640-6,690)	6,565 (4,770-7,740)	0.10
Amount of ascites (mL)	1,450 (500-4,100)	7,050 (4,000-13,550)	0.04*
Blood transfusion			
Red blood cells (unit)	8 (4-14)	10 (8-20)	0.26
Fresh frozen plasma (unit)	16 (12-28)	12 (12-28)	0.60
Platelet concentrate (unit)	15 (10-20)	20 (10-40)	0.61
Clavien-Dindo classification (> III)	3	4	0.09

The median Child-Pugh score in the tolvaptan-effective and tolvaptan-ineffective groups was 10.5 (range 8-11) and 12.5 (11-13), respectively ($p < 0.01$). The median amount of ascites in the tolvaptan-effective and tolvaptan-ineffective groups was 1,450 mL (500-4,100) and 7,050 mL (4,000-13,550), respectively ($p = 0.03$).

Table 3. Operative factors in the tolvaptan (TOL) and conventional diuretic therapy (CDT) groups

Operative factors	TOL (n = 10)	CDT (n = 23)	P value
Operation time (min)	657 (584-854)	697 (605-949)	0.18
Estimated blood loss (mL)	5,660 (1,640-7,740)	3,530 (1,520-13,520)	0.08
Amount of ascites (mL)	3,450 (500-13,550)	250 (0-4,750)	< 0.01*
Blood transfusion			
Red blood cells (unit)	10 (4-20)	6 (0-28)	0.20
Fresh frozen plasma (unit)	14 (12-28)	14 (8-28)	0.46
Platelet concentrate (unit)	20 (10-40)	20 (0-40)	0.61
Clavien-Dindo classification (>III)	6	12	0.40
Clavien-Dindo classification V	0	1	0.50

The median amount of ascites was significantly higher in the TOL group (3450 mL, range 500-13,550 than in the CDT group (250 mL, range 0-4,750; $p < 0.01$).

continued for all patients without a significant change in liver function, and discontinued immediately after LDLT without affecting renal function. Tolvaptan demonstrated favorable effects in 60% (6/10) of the patients, decreasing the body weight by at least 1.5 kg during the 7 day treatment.

Ascites is a crucial manifestation that occurs as a result of portal hypertension, the most common manifestation of decompensated cirrhosis and usually considered an important first sign (*16*). Proper treatment of ascites is thought to relate to an overall better outcome by reducing the likelihood of renal and electrolyte complications, decreasing hospital admissions, and providing a better quality of life for ESLD patients (*17*). Somsouk and colleagues reported that among patients awaiting liver transplantation, those with moderate ascites had a significantly higher mortality rate than those with little or no ascites (*18*). D'Amico and colleagues reported that mortality increases from 3% to 20% per year in the presence of ascites, and 5% to 7% of patients with compensated cirrhosis annually progress to a decompensated status (*19*). Ascites control is important for the management of ESLD patients awaiting liver transplantation.

To control ascites, spironolactone, an aldosterone antagonist, is started either alone or in combination with a loop diuretic, furosemide. Nevertheless, ascites may become refractory before LDLT. The International Ascites Club defines refractory ascites as ascites that cannot be mobilized or recurs early and cannot be satisfactorily prevented by medical therapy (*14*). Therapeutic abdominal paracentesis and a transjugular intrahepatic portosystemic shunt are recommended when these diuretics are not sufficiently effective or are poorly tolerated (*3*), but post-paracentesis circulatory dysfunction is a critical side effect (*20*). Tolvaptan, a new diuretic with a different mechanism of action (*5*), may have a role in the treatment of ESLD patients with refractory ascites who are on the waiting list for liver transplantation, but there have been no reports. The present study is the first report of the use of tolvaptan for ESLD patients awaiting liver transplantation.

Severe liver dysfunction is reported to be an adverse effect of tolvaptan (*12,21*). Safety remains a concern. According to one report published in 2015, tolvaptan was evaluated in a clinical trial of autosomal dominant polycystic kidney disease patients. A total of 1,445 subjects were randomized 2:1 (tolvaptan vs. placebo) (*12*). Significant increases in serum aminotransferase were detected in 16 patients on tolvaptan and in only 1 on placebo. The onset of hepatocellular injury occurred between 3 and 18 months after starting tolvaptan and gradually improved over the subsequent 1 to 4 months. Although hepatocellular injury was infrequent and reversible, there is a potential for serious irreversible injury. The authors recommended that transaminase levels be monitored regularly (*12*). Notably, however, in their study, the dose of tolvaptan was high, 60 mg to 120 mg/day. In the present study, a low dose tolvaptan was administered without significant alterations in liver function. The dose used in the present study was selected on the basis of a tolvaptan phase III trial in Japan (*10*).

In a Japanese clinical trial of cirrhotic patients, a dose of tolvaptan of 7.5 to 15 mg/day was selected as the optimal dose for liver cirrhosis patients (*22*). The details of that study are unknown, but there was no tolvaptan withdrawal from the study due to aminotransferase elevation and/or hepatocellular injury. In the present study, we selected a dose of 3.75 to 7.5 mg/day. No significant liver damage was detected during close follow-up after the initiation of tolvaptan therapy before liver transplantation. Thus, a low dose of tolvaptan may be safe for ESLD patients for a short period before LDLT.

In the non-transplant setting, a similar targeted patient population was reported (*23*). According to a report of post-marketing surveillance of tolvaptan for cirrhotic patients with edema or ascites, the mean decrease in body weight from baseline was -2.4 kg on day 7 (*23*). Surveillance focused on patients with better liver function. In their report, half of the cohort was classified as Child-Pugh A to B and the remaining patients were classified as Child-Pugh C. The total bilirubin level and mean platelet count were 2.4 mg/dl and 12.1 × 10^4 μL, resepctively. In the present

study, patients had far-advanced liver function. The median Child-Pugh score, total bilirubin level, and platelet count were 11, 5.2 mg/dL, and 7.1×10^4 μL, respectively. In the surveillance report, many details of changes in liver function remained to be clarified. The present study is the first to detail the changes in liver function during tolvaptan administration. Further studies are needed to clarify the effects of longer term use of tolvaptan in those patients.

On the basis of previous reports, we defined the tolvaptan-effective group as those patients on tolvaptan who lost more than 1.5 kg body weight within 7 days (*22*). Patients in the tolvaptan-ineffective group showed an increase in body weight despite an increase in the daily urine output volume. Although a low dose of tolvaptan was used, thirst was another problem for those in the tolvaptan-ineffective group, which led to difficulties in controlling their body weight. In the present study, the median Child-Pugh score of the tolvaptan-effective group was lower than that in the tolvaptan-ineffective group (10.5 *vs*. 12.5). The small number of patients and short administration period are limitations of the present study. In addition, the disease severity of patients in the TOL and CDT groups differed, resulting in a selection bias. Further, because the cohort size was not sufficient, there was also a statistical bias. The Child-Pugh score may be useful for selecting patients for tolvaptan administration, but studies of a larger patient cohort are needed to confirm this speculation. The findings of the present study demonstrate that tolvaptan administration may be a promising strategy for ESLD patients awaiting liver transplantation, but further evaluation is necessary.

In conclusion, administration of a low dose of tolvaptan may be safe for far-advanced ESLD patients for a short period before LDLT.

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