Somatostatin Therapy in Patients with Massive Ascites After Liver Transplantation

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Background: Patients with massive ascites (MA) after liver transplantation (LT, defined here as daily ascitic drainage more than 1000 ml per day for more than 7 days after liver transplantation) are at increased risks of infection, hypoalbuminemia, graft loss, and even mortality. The aim of this retrospective cohort study was to investigate the effects of somatostatin on patients with MA after LT.

Material/Methods: Twenty-eight patients with liver cirrhosis or hepatocellular carcinoma who underwent LT complicated by MA postoperatively were included. Ten participants were receiving somatostatin therapy. The postoperative course and adverse drug effects were investigated. Daily postoperative ascitic drainage and urine output were also recorded and compared to those in the non-somatostatin group.

Results: The somatostatin group had significantly less ascites drainage after LT compared to the non-somatostatin group (p=0.002). Urine output was significantly increased after somatostatin administration (p<0.001). No serious adverse effects influencing graft function or fatal complications occurred after somatostatin therapy.

Conclusions: Somatostatin treatment is beneficial for the management of MA after liver transplantation.

MeSH Keywords: Ascites • Liver Transplantation • Postoperative Complications • Somatostatin

Abbreviations: ABOi LDLT – ABO-incompatible living donor liver transplantation; MA – massive ascites; GRWR – graft-to-recipient weight ratio; HCC – hepatocellular carcinoma; ICU – intensive care unit; LDLT – living donor liver transplantation; MA – massive ascites; MELD score – Model for End Stage Liver Disease score; LT – liver transplantation; HBV – hepatitis B virus; HCV – hepatitis C virus; HCC – hepatocellular carcinoma; INR – international normalized ratio; POD – postoperative day; SD – standard deviation

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Background

Post-liver transplant ascites is common. It has received little attention because small to moderate amounts of ascitic fluid are often observed in the early postoperative period and usually disappear within a few days [1,2]. However, some patients develop massive ascites (MA), defined in the literature as the production of >500 mL of ascitic fluid per day for more than 10 days [1] or >1000 mL per day for more than 14 days [3]. Other studies have defined MA as postoperative ascitic drainage persisting for more than 7 days after liver transplantation (LT) in conjunction with diuretic treatments and sodium restriction [4,5]. In the present study, we defined MA as postoperative ascites drainage >1000 mL per day for more than 7 days. MA occurs in 5%–8% of patients after LT [1,3–5]. The causes of MA are multi-factorial and include previous hepatitis C virus infection, mechanical obstruction causing increased portal and hepatic vein outflow pressures, poor graft quality, small-for-size syndrome, prolonged operative times, preoperative refractory ascites, and hypoalbuminemia [4–10].

MA after LT may lead to complications such as peritoneal infection, impaired renal function, and prolonged intensive care unit (ICU) and hospital stays. Furthermore, patients with massive MA after LT can even experience graft loss and death [3]. Overcoming MA after LT is important to avoid fatal complications.

Management of MA after LDLT according to the literature includes modulating graft inflow and outflow and increasing the oncotic pressure and portal vein permeability until the graft matures [1,7]. The priority is to avoid hepatic vessel (including both portal and hepatic veins) anastomotic strictures, ensure adequate graft weight to prevent small-for-size syndrome, and to maintain the oncotic pressure with a supply of human albumin and the establishment of early nutrition [11]. Kim et al. [12] reported that 11 recipients underwent partial splenic arterial embolization to treat portal hypertension that developed after LT; 4 of the recipients experienced significant improvements in MA, but complications of abdominal pain and other gastrointestinal symptoms were observed. Reddy et al. [13] performed a double-blind controlled trial to investigate the routine administration of terlipressin to patients who underwent LDLT, reporting that perioperative administration significantly reduced ascitic drain output and increased urine output. Terlipressin is an octreotide analogue that induces splanchnic arteriolar vasoconstriction and reduces portal venous flow. It also shifts blood from the splanchnic to the systemic circulation, leading to improved renal blood flow. Additionally, it has also been used to treat type 1 hepatorenal syndrome.

Somatostatin is also an octreotide analogue that inhibits splanchnic vasodilatation, but it has no effect on renal perfusion [14,15]. It can modulate portal hypertension and increase urine output without adversely affecting liver function [16]. Angeli et al. reported on the use of somatostatin to treat type 1 hepatorenal syndrome [17], in which patients receiving somatostatin therapy had improved serum creatinine levels and urine outputs, more so than the patients in the control group, and portal venous pressure was also significantly decreased in the somatostatin-treated patients. Ijichi et al. also reported on a patient treated with somatostatin for post-LT chylous ascites [18]. Since somatostatin can modulate portal hypertension, we hypothesized that MA could be alleviated by the administration of somatostatin. Herein, we report our experience with somatostatin therapy in patients with MA after LT.

Material and Methods

We retrospectively reviewed the records of 439 patients who underwent LT at the Tri-Service General Hospital, Taipei, Taiwan from 1 Jan 2001 to 30 Jun 2017. No organs from executed prisoners were used. We included patients with daily ascitic drainage that exceeded 1000 mL per day in the first week after LT. Recipients who died or were transferred within the first week after LT, and who were younger than 20 years were excluded. The study protocol conformed to the ethics guidelines of the Declaration of Helsinki, received a priori approval from our Institutional Ethics Committee, and was registered with the Institutional Review Board of Tri-Service General Hospital (TSGH-IRB No: 1-107-05-079).

Graft vessel anastomosis techniques

The portal vein and hepatic artery were anastomosed end-to-end and hepatic artery anastomosis was performed under loop magnification (>2.5) using micro-instruments. The hepatic veins in LDLT were anastomosed to the inferior vena cava. Branches of the middle hepatic vein (V5, V8) and inferior accessory right hepatic vein were also anastomosed unless the vessel diameter was less than 0.5 cm. Piggy-back suture technique was used in the whole liver graft (orthotopic liver transplantation). All graft and recipient weights were measured, and our goal was to avoid GRWR <0.8. Portal venous pressure and inflow were measured after the anastomosis to avoid portal vein mechanical obstruction or hypertension. Splenectomy, varices branch ligations, or splenorenal shunt ligations were performed to adjust the graft inflow perfusion if portal hypertension or hypoperfusion was identified.

Immunosuppression protocols

Patients who underwent LT received postoperative corticosteroids, tacrolimus (FK-506) and mycophenolate mofetil for immunosuppression. For ABO-incompatible LT, Rituximab (anti-CD20...
antibody) 200 mg was prescribed 3 weeks before LT, and plasmapheresis was prescribed 1 week before the operation to avoid recipient ABO titer becoming greater than 1:64 preoperatively. Splenectomy was not regularly performed except to adjust the portal venous pressure or for future interferon therapy in patients with hepatitis C virus.

We monitored liver function of all participants and followed up patency of graft vessels via daily Doppler ultrasounds in the first week after LT to rule out stricture or obstruction of the graft inflow/outflow problems. The serum liver function testing frequency was decreased to twice weekly from the second week until the participant was discharged from the hospital. Liver biopsies were not routinely performed except in cases of unexpectedly elevated liver enzymes.

**MA management and data collection**

All recipients were managed with fluid and sodium restrictions. Human albumin (Buminate® 25%, 50 mL) plus furosemide were prescribed to maintain oncotic pressures until the daily ascitic drainage amount decreased to less than 1000 mL/day. Enteral nutrition was administered as soon as possible.

The decision to initiate or discontinue therapy with somatostatin was left to the discretion of the attending surgeons. Most of the patients treated with somatostatin had greater volumes of daily ascitic drainage (>2500 mL/day). Somatostatin (STILAMIN®) 6 mg in 500 mL normal saline was administered to the treatment group daily by infusion pump starting on postoperative day 7 (pre-intervention D1), and was discontinued after the daily ascites drainage decreased to less than 1000 mL/day.

Blood glucose levels were monitored every 4 h in the somatostatin group during the period of somatostatin administration to prevent hypoglycemia.

Variables of all participants were recorded, including ascitic drainage volume, urine output, length of hospital stay, length of ICU stay, post-LT complications, and viral or bacterial infections. All patients were followed until discharge.

**Statistical analysis**

Data on patient demographics, preoperative indicators of disease severity, and intraoperative variables were collected. Postoperative variables including daily urine output, drain output, complications, infections, need for intervention, and drug-related adverse effects were recorded.

Data management and statistical analyses were conducted using SPSS statistical software (version 22.0; IBM, Chicago, IL, USA). Continuous variables are presented as means and standard deviations (SD). Discrete variables are presented as percentages. Continuous variables were compared using the t test or the Mann-Whitney U test. Discrete variables were compared using the chi-square test with Fisher’s exact correction when necessary. If 20% of the cells had expected numbers <5, Fisher’s test was used instead of the chi-square test. Finally, the generalized estimating equation (GEE) was used to compare the daily ascitic drainage and urine output between the 2 groups to investigate the effects of the somatostatin therapy intervention. A statistically significant value was defined by \( p \leq 0.05 \).
Result

There were 28 recipients included in our study. The flow chart of the study participants is shown in Figure 1. Most of the recipients had liver cirrhosis and history of preoperative MA. The clinicopathological characteristics of all recipients are listed in Table 1A. There were no significant differences in age, sex, liver transplant indication (hepatitis B virus (HBV) or hepatitis C virus (HCV) infections, alcoholism, or hepatocellular carcinoma (HCC)). Most recipients underwent LDLT, and there were 6 patients who underwent ABO-incompatible LDLT (2 patients in the somatostatin group and 4 in the non-somatostatin group); however, there was no significant difference in type of transplantation (LDLT or ABO-incompatible LDLT) between the groups, preoperative ascites, or comorbidities, except for uremia ($p=0.04$). There were 3 patients in the somatostatin group that had a history of uremia and required regular hemodialysis, and no patients in the non-somatostatin group had uremia. There were also no significant differences in the laboratory test results, including serum sodium, albumin, creatinine, international normalized ratio (INR), total bilirubin, and the Model for End Stage Liver Disease (MELD) score, between the 2 groups.

### Table 1A. Patient characteristics.

|                        | Non somatostatin group | Somatostatin group | P value |
|------------------------|------------------------|--------------------|---------|
|                        | N=18 (64.3%)           | N=10 (35.7%)       |         |
| **Age (years old)**    | 55±15                  | 51±14.5            | N.S.    |
| **Sex**                |                        |                    |         |
| Men (%)                | 13 (72.2)              | 7 (70)             | N.S.*   |
| **LT indication**      |                        |                    |         |
| HBV                    | 8 (44.4)               | 5 (50)             | N.S.*   |
| HCV                    | 9 (50)                 | 3 (30)             | N.S.*   |
| Alcoholism             | 5 (27.8)               | 4 (40)             | N.S.*   |
| HCC                    | 6 (33.3)               | 1 (10)             | N.S.*   |
| **Type of transplantation** |                    |                    |         |
| LDLT                   | 15 (83.3)              | 8 (80)             | N.S.    |
| ABO incompatible LDLT   | 4 (22.2)               | 2 (20)             | N.S.*   |
| **Comorbidity**        |                        |                    |         |
| Diabetes Mellitus      | 6 (33.3)               | 6 (60)             | N.S.*   |
| Hypertension           | 2 (11.1)               | 3 (30)             | N.S.*   |
| Uremia                 | 0 (0)                  | 3 (30)             | 0.037** |
| History of preoperative massive ascites | 15 (83.3) | 10 (100) | N.S.* |
| **Preoperative serum laboratory test** | | | |
| Total bilirubin (mg/dL)| 8.0±9.3                | 9.2±11.4           | N.S.    |
| INR                    | 1.42±0.42              | 1.39±0.37          | N.S.    |
| Serum albumin (mg/dL)  | 2.96±6.4               | 2.89±0.47          | N.S.    |
| Creatinine (mg/dL)     | 1.2±0.73               | 1.3±0.31           | N.S.    |
| Serum sodium (mmol/L)  | 135±6.7                | 140±15             | N.S.    |
| MELD score             | 18.9±9.4               | 19.6±8.1           | N.S.    |

* P value <0.05, # Fisher test. Data are given as n (%) or mean ±SD. LT – liver transplantation; HBV – hepatitis B virus; HCV – hepatitis C virus; HCC – hepatocellular carcinoma; INR – international normalized ratio; MELD – model for end-stage liver disease; LDLT – living donor liver transplantation; SD – standard deviation; N.S. – not significant (P value >0.05)
With respect to the perioperative factor analysis (Table 1B), there were also no significant differences in the incidence of splenectomy, graft-to-recipient weight ratio (GRWR), proportion of small-for-size grafts, blood loss, or operative times. During postoperative follow-up, the daily ascitic drainage significantly increased in the somatostatin group on postoperative day (POD) 7 (p=0.018) and POD 14 (p=0.031). There was no significant difference in the amount of ascitic drainage between the 2 groups on POD 21.

The follow-up Doppler ultrasound showed no obstruction or stricture of venous anastomoses in any patients. In a comparison of the serum concentration of tacrolimus between the 2 groups, there were no significant differences on POD 7, POD 14, and POD 21. (Figure 2) The daily ascitic drainage decreased and most recipients in the somatostatin group discontinued somatostatin on D7. The ascitic drainage did not recur after discontinuation of the somatostatin. There was no significant difference in the amount of ascitic drainage between the 2 groups in the third week (POD 21, p=.96).

| Table 1B. Comparison of perioperative factors and post-operative follow up between two groups. |
|---------------------------------------------------------------|
| **Non somatostatin group** | **Somatostatin group** | **P value** |
| N=18 (64.3%) | N=10 (35.7%) | |
| **Perioperative factors** | | |
| Splenectomy | 5 (27.8) | 4 (40) | N.S.* |
| Graft weight (gm) | 580±257 | 577±296 | N.S. |
| GRWR (%) | 0.94±0.29 | 1.08±0.34 | N.S. |
| Small-for-size graft (GRWR < 0.8%) | 5 (27.8) | 2 (20) | N.S. |
| Operative time (mins) | 559±122 | 558±178 | N.S. |
| Blood loss (ml) | 1200±700 | 1555±987 | N.S. |
| **Post-operative follow-up** | | |
| Ascites in POD 7 (ml/day) | 1825±880 | 3085±1208 | 0.018* |
| Ascites in POD 14 | 1210±1121 | 1690±761 | 0.031* |
| Ascites in POD 21 | 1205±662 | 1140±251 | N.S. |
| Serum FK506 in POD7 (ng/mL) | 5.44±2.77 | 5.57±2.72 | N.S. |
| Serum FK506 in POD14 | 4.52±2.06 | 5.89±2.19 | N.S. |
| Serum FK506 in POD21 | 5.13±2.49 | 4.93±2.19 | N.S. |

* P value <0.05, * Fisher test. Data are given as n (%) or mean ±SD. GRWR – graft-to-recipient weight ratio; POD – postoperative day; FK506 – Tacrolimus; SD – standard deviation; N.S. – not significant (P value >0.05).

Outcomes

Regarding the primary outcomes, there were no drug-related adverse effects observed in the somatostatin group (such as hypoglycemia, gastrointestinal symptoms, or flushing) that necessitated withdrawal from the study. The amount of daily ascitic drainage after LT during the first week in the somatostatin group was significantly higher than in the non-somatostatin group (p=0.02). The daily ascitic drainage began to decrease in all recipients in the second postoperative week (D1). After administering somatostatin in D1, the somatostatin group experienced a significant decrease in ascitic drainage compared to the non-somatostatin group (p=.002). (Figure 2) The daily ascitic drainage decreased and most recipients in the somatostatin group discontinued somatostatin on D7. The ascitic drainage did not recur after discontinuation of the somatostatin. There was no significant difference in the amount of ascitic drainage between the 2 groups in the third week (POD 21, p=.96). Urine output significantly increased after somatostatin administration on D1 (p<.001) (Figure 3). One patient in the somatostatin group had tacrolimus intoxication and acute renal injury; after discontinuing somatostatin therapy, his daily urine output significantly increased.

Regarding the secondary outcomes, post-LT results revealed no significant difference in the incidence of biliary tract stricture or bilioma formation (Table 2). There were no differences in the incidence of acute rejection or acute antibody-mediated rejection (AMR) between the 2 groups, and no difference in infection rates (cytomegalovirus [CMV], fungus, herpes, or intra-abdominal bacterial infection). There was also no difference in acute or chronic kidney injury between the 2 groups. Two patients in the non-somatostatin group and 1 patient in the somatostatin group died within 1 year after LT. The 1-year overall survival rate was slightly higher in the somatostatin group than in the non-somatostatin group, but the difference was not significant (Table 2, p=.80).
Discussion

MA is commonly seen after LT and can be multi-factorial. Most postoperative ascites disappears within a few days [2]. In our case series, all patients were evaluated with intraoperative Doppler flow examination to check hepatic arterial flow, and portal venous flow. Portal venous pressure and central venous pressure were also recorded to evaluate the hemodynamic condition of the liver. After surgery, routine Doppler examinations of the portal vein, hepatic vein, and hepatic artery were also performed (at least once on POD1, prior to transfer from the ICU to a general ward, and prior to discharge). Confirmation

Table 2. Comparison of postoperative complications between the two groups.

|                          | Non somatostatin group | Somatostatin group | P value |
|--------------------------|------------------------|--------------------|---------|
| Biliary tract stricture  | 5 (27.8)               | 2 (20)             | N.S.*   |
| Biloma formation         | 3 (16.7)               | 2 (20)             | N.S.*   |
| Acute rejection          | 8 (44.4)               | 4 (40)             | N.S.*   |
| Antibody-mediated rejection | 1 (5.6)             | 2 (20)             | N.S.*   |
| Infection                |                        |                    |         |
| CMV                      | 0 (0)                  | 1 (10)             | N.S.*   |
| Herpes                   | 4 (22.2)               | 0 (0)              | N.S.*   |
| Bacteria                 | 6 (33.3)               | 3 (30)             | N.S.*   |
| Fungus                   | 1 (5.6)                | 1 (10)             | N.S.*   |
| Acute kidney injury      | 2 (11.1)               | 2 (20)             | N.S.*   |
| Chronic kidney injury    | 2 (11.1)               | 1 (10)             | N.S.*   |
| Mortality                | 2 (11)                 | 1 (10)             | N.S.    |
| 1-year-survival rate (%) | 89                     | 90                 | N.S.    |

* P value <0.05, * Fisher's exact test. Data are given as n (%) or mean ± standard deviation, N.S. – not significant (P value >0.05).

Figure 2. Comparison of daily ascites drainage after liver transplant. Somatostatin was administrated on D1 (POD7, black arrow). Most of the recipients discontinued somatostatin therapy on D7 (hollow arrow). * p=0.002. NS – non-somatostatin group; S – Somatostatin group.

Figure 3. Comparison of the daily urine output between the 2 groups. * p<0.001. Somatostatin administration began (black arrow). Discontinued somatostatin therapy (hollow arrow). NS – non-somatostatin group; S – somatostatin group.
of the patency of vessels is of paramount importance in these patients. In this study, we did not find significant vascular strictures that required intervention. There were also no obviously high incidences of rejection proportions of small-for-size grafts or ABOI LDLT between 2 groups. However, we found that recipients who had a previous history of MA were more likely to have MA after LT. Previous cirrhosis-related portal hypertension [7] increases the hydrostatic pressure within the hepatic sinusoids and favors transudation of fluid into the peritoneal cavity [19]. Portal hypertension leads to profound changes in the splanchic circulation. After LT, initial hemodynamic derangements resulting from liver cirrhosis are reversed, but the graft function and splanchic arterial vasodilation do not recover well [7]. Palmes et al. [20] reported that, in a rat model, portal hyperperfusion led to derangement of the sinusoidal microcirculation because of increased portal blood flow. The increased blood flow velocity following liver resection led to endothelial damage that exhibited morphological features of endothelial cell swelling, endothelial desquamation, loss of Disse’s space, and loss of endothelial cell fenestration. Furthermore, Kelly et al. [21] demonstrated that denudation of the portal vein and the perportal sinusoidal endothelium, as well as severe congestion with frank rupture and thrombosis of the periportal sinusoids, occurred as early as 5 min after porcine partial LT in grafts that were <30% of the expected liver volume. Portal venous hyperperfusion can lead to liver endothelial cell injury and influence recovery of graft function. Ascites after LT persists until the hydrostatic pressure and splanchic vessel distributions recover.

Traditionally, the management of MA after LT includes sodium and fluid restriction and maintenance of oncotic pressure [22]. Previously, we restricted sodium administration and prescribed human albumin (Buminate® 25%, 50ml) plus furosemide to modulate oncotic pressure. We discontinued all intervention until enteral nutrition was established until the graft began functioning well. However, these traditional management methods had low efficacy in patients with severe, massive ascites. Treating MA is challenging, and is made more difficult due to complications such as electrolyte imbalances, ileus, delay in initiation of enteral nutrition, and increased risk of intra-abdominal infections. Several studies have reported data indicating that modulation of the portal hypertension can improve MA after LT [1,23]. Gane et al. [23] reported successful treatment with propranolol (induction with 40 mg twice a day and increased to 80 mg 3 times a day 1 week later) in a patient with MA after LT. Kim et al. [12] also reported partial splenic artery embolization in 11 recipients, of which 5 had significant improvement in previously uncontrolled ascites after LT. In the present study, although there were 4 recipients in the somatostatin group and 7 recipients in the non-somatostatin group that underwent splenectomy perioperatively, there was no significant improvement of MA in the subgroup analysis.

Larger-scale studies and detailed portal hemodynamic investigations are necessary to determine the exact influence of portal inflow modulation.

In this study we did not constantly monitor the portal venous pressure after LT. However, the postoperative ascitic drainage was significantly decreased and urine output was significantly increased under somatostatin administration. This observation may indicate that somatostatin modulates portal venous pressure. MA did not recur, even though somatostatin interventions were discontinued in the somatostatin group on POD 14 and POD 21. There were no adverse effects on graft function noted during or after somatostatin therapy, and somatostatin is quite safe for portal venous perfusion modulation after LT. Additionally, it had no pharmaco-kinetic influence on tacrolimus, a main immunosuppressive drug used in our study. There were no significant differences in tacrolimus concentrations on POD7, POD14, or POD21 (Table 2).

Reddy [13] reported that a patient who underwent LDLT treated with terlipressin had significantly reduced ascitic drain output and increased urine output, consistent with our observations. However, terlipressin is associated with the significant adverse effect of bradycardia, and patients on this medication required constant cardiovascular monitoring. There was no significant adverse effect recorded in participants who were administered somatostatin postoperatively. As a consequence, somatostatin may be an effective, safe, and non-invasive therapy for MA after LT.

In our study, 1 patient with tacrolimus intoxication developed acute renal injury. We stopped tacrolimus administration and prescribed somatostatin therapy for his MA after LT. His urine output improved gradually and did not worsen even after discontinuing somatostatin. Somatostatin therapy may play a protective role in acute kidney injury; however, further studies on this are needed. MA after LT may result from portal venous hyperperfusion and graft injury in patients receiving partial graft transplantation. Fortunately, liver grafts regenerate rapidly within 3 months. Generally, most patients with ascites after liver transplantation can recover without intervention. However, longer periods of massive ascites can cause more complications, such as intra-abdominal infection, long hospital stay, electrolyte imbalance, postoperative ileus, and even graft failure or death. Early control of massive ascites after LT may avoid these complications. Somatostatin therapy can significantly decrease the ascitic drainage, and the periods of MA were short in our LT patients. Therefore, somatostatin may be a good choice for the management of MA after LT. Early perioperative administration of somatostatin in high-risk recipients, such as those with preoperative MA, could reduce the prevalence of massive ascites and protect renal function.
There were several limitations in our study, including its retrospective design and the small number of patients. The number of patients between 2001 and 2017 that received a transplant is shown in Figure 4. During this time, a long-term retrospective study occurred (2001–2017) and treatment strategies may thus have evolved. Such changes can affect the outcomes of a retrospective study. Randomized controlled trials are needed to confirm our observations.

Figure 4. The cumulative numbers of patients who received liver transplant in time at Tri-Service General Hospital from 2001 to 2017.

Conclusions

Somatostatin administration can significantly decrease massive MA after LT and increase urine output without negatively influencing graft function. Therefore, to avoid MA related complications in patients at high-risk of MA after LT, early administration of somatostatin should be considered a treatment of choice until the graft is functioning well.

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