Successful Transjugular Portosystemic Shunt Treatment of Pediatric Sinusoidal Obstruction

Case Report and Review of Literature

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Background: In adults with medically refractory sinusoidal obstruction syndrome (SOS), a transjugular intrahepatic portosystemic shunt (TIPS) has been used successfully to improve portal hypertension and symptoms such as ascites. There is limited data on the use of TIPS for SOS in pediatric patients. **Methods:** The index case was reviewed retrospectively. PubMed and Medline databases were searched to identify other cases.

Results: A 4-year-old male with high-risk neuroblastoma, developed SOS after tandem autologous stem cell transplant. He was medically managed with defibrotide, diuretics, and peritoneal drainage, but, due to refractoriness, he underwent TIPS day +54 following bone marrow transplant. Hepatic venous pressure gradient improved from 17 to 8 mm Hg following TIPS placement with significant improvement in the patient's clinical status and ascites. However, 15 months later, his shunt remained patent, and he remains clinically well with stable liver enzymes. A literature review identified 13 pediatric cases of TIPS for SOS due to varied causes. TIPS caused a median hepatic venous pressure gradient of 9 mmHg (range, 2–38 mm Hg). The mortality following the procedure was 15%, with 2 cases who died at 2- and 11-days post-TIPS. At the time of the last follow-up (range 8–25 months), 5 patients were alive, and 8 were lost to follow-up.

Conclusion: We present here a pediatric case of SOS due to stem cell transplant treated successfully with TIPS with a review of the literature. A timely, individualized application of TIPS can be effective in treating children with medication-refractory SOS.

Key Words: SOS, TIPS, portal hypertension, pediatric

INTRODUCTION

Hepatic sinusoidal obstruction syndrome (SOS) is a distinctive and potentially fatal complication of hematopoietic stem cell transplant (SCT) (1). Patients with SOS present with ascites, weight

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What Is Known

- Sinusoidal obstruction syndrome (SOS) can be treated medically, or in refractory cases with transjugular intrahepatic portosystemic shunt (TIPS) in adults.
- TIPS for SOS in pediatrics is uncommon and controversial, with evidence of early mortality in some cases.

What Is New

- We present the first pediatric case of successful TIPS for SOS after a stem cell transplant. It is also the youngest child with a documented follow-up history.
- A total of 13 cases of TIPS used in pediatrics for SOS have been reported, with most of these cases being lost to follow-up with uncertain outcomes.

Translational Impact

•The use of TIPS should be considered as an option in medically refractory SOS in children.

gain, hepatomegaly, and jaundice (1,2). SOS and the subsequent portal hypertension can lead to multi-organ failure and are characterized by a very poor prognosis and a high mortality rate (2). In a pediatric study, survival rates were 62% at 5 years, and 5 out of 6 patients (83%) with severe SOS who had progressed to multi-organ failure died within 61 days of their diagnosis (3).

The medical treatment for SOS involves defibrotide and supportive measures such as diuretics and paracentesis, but in rare instances, it becomes resistant to medical treatment (3,4). Transjugular intrahepatic portosystemic shunt (TIPS) can be used to decompress the portal system to ameliorate portal hypertension and are typically used to treat refractory variceal bleeding and refractory ascites (5–7).TIPS remains a controversial therapy for SOS due to a high mortality rate following the procedure and insufficient evidence that the prognosis is improved by lowering portal pressures (8,9). Recent adult literature suggests favorable outcomes following TIPS for adults with SOS post-SCT (10,11). There is a paucity of data about the clinical course post-TIPS for SOS and long-term follow-up in the pediatric population. We present the case of a 4-year-old boy with high-risk neuroblastoma who underwent successful TIPS for "very severe" SOS (12) in the setting of autologous SCT, along with a review of the literature.

METHODS

A retrospective review of the index case was completed for care received at the Children's Hospital of Eastern Ontario in Ottawa, Ontario, and The Hospital for Sick Children (Sick Kids) in Toronto, Ontario. No research ethics board approval was required; however, written consent from the parents was obtained.

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For the literature review, Pubmed and Medline databases were searched using the terms: "Transjugular Intrahepatic Portosystemic Shunt", and "Sinusoidal Obstruction Syndrome" or "Veno-occlusive disease", and "pediatric". Reference lists of articles obtained were also searched to identify additional relevant articles. Only full-text and English-language articles were included in the analysis. Inclusion criteria were evidence of SOS with TIPS procedure performed in a pediatric patient (age under 18 years). Demographic information, details about the TIPS procedure, and outcomes were retrieved from the studies.

RESULTS—CASE REPORT

A 4-year-old male presented to the emergency department with acute abdominal pain. A large left suprarenal mass was identified with compression of the inferior vena cava and inferior mesenteric vein. Additionally, metastases to supraclavicular lymph nodes as well as sub-pleural nodules in bilateral lungs were found. Urine catecholamines were not elevated, but the iodine 123-metaiodobenzylguanidine scan was positive. Following a biopsy of the abdominal mass, he was diagnosed with high-risk neuroblastoma. After 4 cycles of induction chemotherapy, he underwent resection of the primary mass and proceeded to consolidation therapy with tandem autologous SCT.

His conditioning regimen for his second SCT consisted of carboplatin, etoposide, and melphalan. On day +6, he began to develop signs and symptoms of SOS. He developed a mildly elevated unconjugated bilirubin (10 µmol/L [normal <7µmol/l]; peak value pre-TIPS 17 µmol/L) and was started on ursodiol. His liver enzymes were mildly elevated and proceeded to rise (alanine transaminase [ALT]: 65 U/L [normal <33 U/l], aspartate aminotransferase [AST]: 96 U/L [normal <39 U/L]; peak values pre-TIPS ALT: 283 U/L, AST: 879 U/L). He had a prolonged international normalized ratio for which he received vitamin K starting at day +3 (1.8, peak value pre-TIPS 3.9, normal 0.8–1.2). Persistent thrombocytopenia $(24 \times 10^9/L)$, nadir pre-TIPS 6×10⁹L, normal 150-450) was managed with platelet transfusion at day +3 and +6 as well as Granulocyte colony stimulating factor at day +5. On day +11 he was started on defibrotide for increasing abdominal distension with SOS concern. SOS was confirmed by a Doppler ultrasound of the abdomen on day +12 which revealed hepatomegaly and ascites accompanied by a reversal of flow in the portal veins, marked attenuation of the hepatic veins, and elevated hepatic artery indexes in the intraparenchymal arteries (0.84, normal 0.5–0.8).

His weight increased from his baseline of 19.2–21.6 kg by day +18 despite diuretic administration with furosemide and spironolactone alongside albumin drop to a nadir of 29 at day +17. His creatinine became elevated at 42 µmol/L (normal 16-35µmol/L) on day +6 rising to a peak value of 112 µmol/L on day+19, this rise was accompanied by a drop in glomerular filtration to 37 mL/min/1.73m² consistent with stage 2 acute kidney injury. He had increased work of breathing with a tracheal tug and grunting while on high-flow oxygen and crackles on auscultation. On day +18, 7 days after SOS diagnosis, he was transferred to the pediatric intensive care unit for management of acute kidney injury and clinical deterioration secondary to SOS. He was given blood products, including red blood cell transfusion, platelet transfusion, and 25% albumin, for supportive management. To control his significant ascites, which were refractory to medical management, a peritoneal drain was placed. Following placement, the peritoneal drain evacuated between 2300 and 2900 mL per day, and multiple attempts to clamp the drain led to fluid re-accumulation. He developed an oxygen requirement (up to 2L by nasal prongs), and at day + 49, he developed oliguria with urine output at 0.2 mL/kg/hr. In an attempt to reverse his clinical deterioration secondary to "very severe SOS" (AST/ALT >5 times the upper limit of normal, persistent thrombocytopenia, ascites needing paracentesis, impaired coagulation), the TIPS procedure was performed on day +54.

During the procedure, the right jugular and portal veins were accessed. A guide wire was introduced into the portal system (Fig. 1) to provide a target for puncture from the hepatic vein with a TIPS set (Gore). To limit blood flow and decrease encephalopathy risk in this small patient, a constrained insertion technique was used. After dilatation of the parenchymal tract, a 6 cm Express LD balloon expandable stent (Boston Scientific, Galway, Ireland) was expanded to 6 mm. A 5 cm Gore Viatorr TIPS endoprosthesis with a controlled expansion stent (Gore) was inserted, and the ends expanded to 8 mm (Fig. 2). Right atrial, free, and wedged hepatic pressures were recorded but were not scanned or included in the dictation. The reported hepatic venous pressure gradient improved from 17 mm Hg to 8 mm Hg (normal <5mm Hg) after TIPS placement.

His clinical status improved significantly following the procedure, and the peritoneal drain was removed 10 days post-TIPS (day +64). The serum ammonia concentration was noted to increase to 70 μ mol/L (normal <41 μ mol/L) by day 20 after TIPS without symptoms of hepatic encephalopathy but returned to normal within 7 days after lactulose administration. His last follow-up was at 15 months postprocedure, and he continued to have normal conjugated bilirubin value (3 μ mol/L) and total bilirubin value (8 μ mol/L), albumin of 43 g/L, ammonia of 41 μ mol/L, international normalized ratio of 1.21, AST of 60 U/L, and ALT of 50 U/L (Fig. 3) with no overt features of hepatic encephalopathy.

LITERATURE REVIEW

Our review of the literature revealed 13 pediatric cases in which TIPS was used to manage SOS (Table 1). The median age of patients was 11 years (range, 3.59–16 years), with 4 male, 6



FIGURE 1. Successful puncture into the portal system. A tract has been created from the right hepatic vein to the right portal vein. A guide wire was inserted through the left lobe of the liver into the portal vein to act as a target for the needle puncture through the hepatic parenchyma.



FIGURE 2. Final TIPS Appearance. A balloon expandable stent (black arrow) narrows the central portion of the TIPS stent to limit the portosystemic blood flow in this small patient. If higher flow rates are required in the future, the narrowed area can be dilated to a larger size. TIPS = transjugular intrahepatic portosystemic shunt.

female, and 3 cases with biological sex unreported. The causes of SOS included SCT/bone marrow transplant, malignancy, congenital hepatic fibrosis, thrombosis, and consumption of herbal medicine. Indications for TIPS included significant portal hypertension presenting with acute variceal bleeding and refractory ascites. Before the placement of TIPS, patients had failed to respond to therapy with diuretics, ursodeoxycholic acid, defibrotide, and/or albumin. Time to TIPS insertion was only indicated in 2 cases (13), at 6 and 48 days post-SOS diagnosis. No technical complications were reported in any case. The median hepatic venous pressure gradient before and after TIPS treatment was 12.5 mm Hg (range, 5-40 mm Hg) and 3 mm Hg (range, 2-27 mm Hg), respectively, with a median drop of 9 mm Hg (range, 2-38 mm Hg). The mortality rate following the procedure was 15% (2 cases) with fatality due to multi-organ failure (at 2 days post-TIPS) and acute respiratory distress syndrome (at 11 days post-TIPS). A very limited amount of information about long-term follow-up is available. In the last follow-up, 5 patients were alive at 8, 9, and 25 months (with 2 alive at an unknown follow-up duration), and 6 patients (46%) have been lost to follow-up. In 2 cases following TIPS, the ascites worsened (6,14) necessitating balloon dilation followed by additional stent placement, with 1 case requiring a liver transplant following TIPS (14).

DISCUSSION

Herein, we present a successful use of TIPS in pediatrics for a patient with "very severe SOS" due to SCT. During the previous 2 attempts for TIPS in SOS in the context of a SCT, both patients died (13). In our patient, the TIPS procedure performed 43 days after SOS diagnosis led to an improved hepatic venous pressure gradient, decreased fluid retention, and improved clinical status. There are 13 other published pediatric cases, with 5 alive at the time of follow-up, 2 patients that died within 2 weeks, and 6 had an unknown postprocedure course (6, 7, 13–18, 19) with a patent shunt and clinically well, our patient remains alive at 15 months of follow-up.

SOS is an obliterative venulitis of the terminal hepatic venules and can cause centrolobular congestion leading to portal hypertension and ascites (20). TIPS has primarily been used for the control of variceal bleeding or medically refractory ascites. Despite the limited data regarding TIPS usage in children (in comparison to adults), it has been found to be effective in treating medically refractory variceal hemorrhage, ascites secondary to biliary atresia, cryptogenic cirrhosis, congenital hepatic fibrosis, portal vein thrombosis, and autosomal recessive polycystic kidney disease (15,21). In 1993, TIPS treatment for bleeding stomal varices in children was first described (22). The first case reports of TIPS use for medical-refractory SOS were presented in adults in 1994 and 1996 (23,24). Both of these cases had favorable outcomes post-TIPS and were alive at followup (4 and 9 months, respectively). Despite this initial success, 14 deaths in adults were reported within 26 days after TIPS between 1999 and 2000, and the indication of TIPS in this setting became more controversial (13,25-27). In 2000, the first cases of TIPS for SOS were reported in children, and both died within 11 days (13). It was not until 2008 when the first successful report of TIPS for SOS was reported in children (14).

TIPS has shown to universally decrease the hepatic venous pressure gradient, at a median decrease of 9 mm Hg, similar to the index case. Decreasing portal hypertension with TIPS leads to improvement in ascites and can prevent renal failure in SOS patients (8), however, TIPS does not address the underlying pathophysiology of SOS. A reduction in the pressure gradient of <12 mm Hg or at least 50% compared to pre-TIPS levels has been associated with the near-complete elimination of portal hypertensive bleeding in adults (28). In the setting of medically refractory ascites, it is not clear what is the optimal level of a decrease in hepatic venous pressure gradient, and further research is needed in this area. In our literature review of previously reported cases, a median decrease of 9 mm Hg has been shown to improve the clinical status, liver enzymes, and decrease fluid overload.

Our case is the second-youngest case of TIPS use for SOS in the literature, as well as the youngest case described after SCT. Further, this is the youngest case with a follow-up described in the literature. The diagnosis of SOS occurred on day +11, which is consistent with 1 of 2 other cases (12 and 28 days), though the other cases did not describe the time to diagnosis (13). This patient met the criteria for "very severe" SOS based on the persistent need for peritoneal drainage according to the European Bone Marrow Transplant Society guidelines (12). In our case, TIPS was performed 43 days post-SOS diagnosis, similar to another pediatric case where it was performed at 48 days (13). Considering the lack of supporting literature for this indication in pediatric patients, it is likely that TIPS is performed as a last resort, explaining the delayed time to procedure in our case.

Of the 13 presented cases in the literature, the causes of SOS varied widely. Six cases were due to malignancy (4 cases of acute lymphoblastic leukemia) (7,17) or malignancy-related bone marrow transplant (lymphoma and medulloblastoma) (13). All 6 were additionally completing regimens with chemotherapy. The underlying clinical status and severity of these 2 patients completing bone marrow transplant may have contributed to their outcome, as both died within 11 days of the procedure. Other children with SOS resulting



Key laboratory values

FIGURE 3. Graph depicting key laboratory values at the onset of SOS, peak and at last follow-up. AST = aspartate aminotransferase; ALT= alanine transaminase; INR = international normalized ratio; SOS = stem cell transplant.

from herbal medicine ingestion or thrombosis (15,16) may have had a better clinical state before TIPS, and this may have contributed to their prognosis after TIPS. Children undergoing TIPS were generally older than the index case (4 years), as the median age was 11 years. Only 1 case is described in a younger individual, at 3.59 years, though the outcome of the procedure was not reported. The impact of age on TIPS outcomes remains uncertain; nevertheless, technical challenges can arise in younger patients (29).

Since 2000, the cases of TIPS used in children for the treatment of SOS have not been frequently reported in the literature, and follow-up is sparse. Long-term follow-up after TIPS has been described by Woerner et al. (18) and included 1 patient with SOS who developed hepatic nodules. In their cohort of 18 patients post-TIPS, 50% developed hepatic nodules after a mean follow-up of 4.4 years. Many of the cases of TIPS for SOS have been reported as cases within a series, so it is not possible to discern if complications such as hepatic encephalopathy occurred in those patients. However, in all pediatric patients undergoing TIPS, rates of hepatic encephalopathy range up to 50% of cases reported (18). It is important to note that studies describing TIPS often do not have large sample sizes, and the largest retrospective review found hepatic encephalopathy occurring 9.8% of the time postprocedure (with a sample size of 61) (7). In the

index case, there was no evidence of hepatic encephalopathy following the procedure, and the patient remains in good health to the date of the last follow-up. There is a general lack of data in the literature about follow-up after the TIPS procedure in children. Due to the rare nature of TIPS being used for SOS in pediatrics, it is necessary to conduct multicenter studies with long-term follow-up, as currently, most cases do not present data on follow-up.

Due to limited data availability, there is currently no standardized protocol or guideline to guide the decision-making process about using TIPS in cases of SOS. The decision to use TIPS as a temporary measure until liver transplantation or as a final treatment option depends on factors such as the patient's clinical condition, response to TIPS treatment, and the availability of a suitable liver donor. TIPS can serve as a bridge to transplantation in critical cases, stabilizing the patient until a suitable liver becomes available. Alternatively, it can be a final treatment option when the patient's condition is stable and TIPS effectively manages complications. The ultimate decision is reached through careful evaluation and discussion among the patient's family, treating physicians, and the transplant team.

When performing the TIPS procedure, several technical considerations come into play. Patient selection is crucial, involving the evaluation of overall health, liver function, and the severity of portal

| Study | Patient age (years), sex | Etiology | Reduction in hepatic venous pressure gradient (mm Hg) | Outcome | Time of death (days after TIPS) | Last living fol- low-up (months after TIPS) |
|------------------------------|-----------------------------|-----------------------------|---|-----------|---------------------------------------|---|
| Azoulay et al. (2000) (13) | 13, Male | BMT/SCT | Yes (6 mm Hg) | Death | 2 | |
| | 11, Male | BMT/SCT | Yes (38 mm Hg) | Death | 11 | |
| Mermuys et al. (2007) (14) | 8, Male | (Unknown) | Yes (7 mm Hg) | Alive | | 9 |
| Nagral et al. (2010) (16) | 7, Female | Herbal medicine ingestion | Yes | (Unknown) | | |
| Di Giorgio et al. (2012) (6) | 11, Female | Congenital hepatic fibrosis | Yes (8 mm Hg) | Alive | | 8 |
| Vo et al. (2012) (17) | 14, Female | ALL | Yes (10 mm Hg) | Alive | | 25 |
| Ghannam et al. (2018) (15) | 13, Female | Thrombosis | Yes | (Unknown) | | |
| Johansen et al. (2018) (19) | 3.59 | (Unknown) | (Unknown) | (Unknown) | | |
| Bertino et al. (2019) (7) | 10, Male | ALL | Yes (10 mm Hg) | (Unknown) | | |
| | 14, Female | ALL | Yes (10 mm Hg) | (Unknown) | | |
| | 16, Female | ALL | Yes (2 mm Hg) | (Unknown) | | |
| Woerner et al. (2021) (18) | (Unknown) | (Unknown) | (Unknown) | Alive | | |
| | (Unknown) | (Unknown) | (Unknown) | Alive | | |
| Index | 4, Male | SCT | Yes | Alive | | 15 |

TABLE 1. Literature review of pediatric TIPS cases with SOS

hypertension, along with age and weight considerations, particularly in younger patients. Although TIPS has been feasible in children, it has rarely been reported in infants weighing less than 22 pounds (10kg), except for a recent successful case in a 3-month-old infant with rapidly progressive refractory ascites of unknown origin due to portal fibrosis (30).

Another important factor is the expertise of the interventional radiologist. Having skilled practitioners available is vital for ensuring the success and safety of the procedure. Additionally, it is necessary to evaluate the patency of the portal vein before TIPS placement. A thorough assessment is conducted to ensure sufficient blood flow and the viability of the procedure. Considering these technical aspects contributes to the effective implementation of TIPS and the overall patient outcomes.

In summary, we report the first successful cases of TIPS used for "very severe SOS" after SCT in pediatrics. Despite previous controversy in the use of TIPS for SOS, recent cases suggest TIPS can improve symptoms and have favorable outcomes at follow-up. We believe that TIPS for select patients with "very severe SOS" can be considered based on the demonstrated success of the procedure with this patient. Further studies are warranted to establish whether TIPS achieves long-term control of portal hypertension as well as overall survival for pediatric patients with "very severe SOS" who undergo this procedure.

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