Transjugular intrahepatic portosystemic stent shunt for medically refractory hepatic hydrothorax: A systematic review and cumulative meta-analysis

Ivo C Ditah, Badr F Al Bawardy, Behnam Saberi, Chobufo Ditah, Patrick S Kamath

AIM: To assess the effectiveness of transjugular intrahepatic portosystemic stent shunt (TIPSS) in refractory hepatic hydrothorax (RHH) in a systematic review and cumulative meta-analysis.

METHODS: A comprehensive literature search was conducted on MEDLINE, EMBASE, and PubMed covering the period from January 1970 to August 2014. Two authors independently selected and abstracted data from eligible studies. Data were summarized using a random-effects model. Heterogeneity was assessed using the $I^2$ test.

RESULTS: Six studies involving a total of 198 patients were included in the analysis. The mean (SD) age of patients was 56 (1.8) years. Most patients (56.9%) had Child-Turcott-Pugh class C disease. The mean duration of follow-up was 10 mo (range, 5.7-16 mo). Response to TIPSS was complete in 55.8% (95%CI: 44.7%-66.9%), partial in 17.6% (95%CI: 10.9%-24.2%), and absent in 21.2% (95%CI: 14.2%-28.3%). The mean change in hepatic venous pressure gradient post-TIPSS was 12.7 mmHg. The incidence of TIPSS-related encephalopathy was 11.7% (95%CI: 6.3%-17.2%), and the 45-d mortality was 17.7% (95%CI: 11.3%-24.13%).

CONCLUSION: TIPSS is associated with a clinically relevant response in RHH. TIPSS should be considered early in these patients, given its poor prognosis.

Key words: Cirrhosis; Portal hypertension; Hepatic hydrothorax; Transjugular intrahepatic portosystemic stent shunt; Meta-analysis
INTRODUCTION

Hepatic hydrothorax (HH) is the accumulation of significant pleural effusion, usually in excess of 500 mL, in a patient with cirrhosis without coexisting primary cardiopulmonary disease[1-3]. It is a relatively uncommon complication of end-stage liver disease, with an estimated prevalence among cirrhotic patients of 5% to 10%[1-3,10-12]. Although the exact mechanisms involved in the development of HH have not been completely elucidated, the most widely accepted mechanism is the passage of fluid from the peritoneal to the pleural cavity through diaphragmatic defects, usually less than 1 cm in diameter[11-13]. The one way flow of the ascitic fluid into the pleural cavity is also thought to be influenced by the negative intrathoracic pressure. The effusion, typically a transudate, most commonly occurs in the right hemithorax (85%)[3,10]. Ascites can be absent in up to 20% of patients with HH[11-13]. A diagnostic thoracentesis often confirms diagnosis and excludes infection.

The initial management of HH is similar to that for ascites. Maximal sodium restriction (< 70-90 mmol/d) and optimal tolerated diuretics are the first-line therapy. Therapeutic thoracentesis is a safe and effective way to rapidly relieve symptoms of dyspnea in patients with large effusions (1.5-2.0 L)[13]. However, when thoracentesis is required more than once every 2 to 3 wk in patients on maximal sodium restriction and optimal diuretics, it is considered refractory, and alternative treatments should be considered. Pleurodesis and peritoneovenous shunts are surgical options that are usually associated with rapid fluid reaccumulation and procedure-related complications, and they are not generally recommended as treatments for HH[14,15]. In the absence of a large pneumothorax, hemothorax, or frank empyema, a chest tube should not be inserted in patients with HH[16,17].

Up to 25% of patients with HH will become refractory to treatment[18], compared to only 10%[17] of patients with cirrhotic ascites. Refractory HH (RHH) has traditionally been associated with poor prognosis. Patients with RHH should therefore be considered for liver transplantation. The treatment strategies for RHH are similar but not identical to those for refractory ascites. In patients with prerenal azotemia, therapeutic thoracentesis as a long-term regular treatment is not recommended because of the risk for bleeding and pneumothorax[19]. Transjugular intrahepatic portosystemic stent shunt (TIPSS) is a nonsurgical, angiographic technique of reducing hepatic sinusoidal pressure, which then results in a reduction in the accumulation of fluid in the peritoneal and pleural space. The procedure is often used as a bridge to liver transplantation in patients with end-stage liver disease. Since RHH is an uncommon complication of cirrhosis, most of the studies on the effectiveness of TIPSS have been limited to small numbers of patients, primarily in the form of case reports[19-22] or case series[3,14,23-28]. Findings from these studies have varied substantially. The purpose of this study was to evaluate the effectiveness of TIPSS in patients with RHH by pooling all available evidence in a systematic review with cumulative meta-analysis.

MATERIALS AND METHODS

Core tip: Evidence on the effectiveness of transjugular intrahepatic portosystemic stent shunt (TIPSS) in patients with refractory hepatic hydrothorax (RHH) is scarce and variable. This paper summarizes available data on the effectiveness of TIPSS in RHH in a cumulative meta-analysis. The sum total of the evidence shows that TIPSS is associated with a clinically relevant response in three-quarters of patients with medically RHH. We suggest that TIPSS be considered early in patients with RHH, given its impact on quality of life and prognosis. However, caution should be exercised in older patients and those with severe underlying liver or renal dysfunction.

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spreadsheets (Microsoft Corp, Redmond, Washington). The following information were abstracted from each study: author, time period of study, study methods and participants, outcome of interest (mortality/survival, response to TIPSS, TIPSS-related complications, incidence of hepatic encephalopathy (HE), mean change in hepatic venous pressure gradient (HVPG), and country of study). Differences between the 2 abstracting investigators were settled by reviewing the article together and seeking an independent input from a third investigator (BS).

**Definition of operational variables**

**Medically RHH:** Patients with underlying liver cirrhosis who underwent TIPSS because of symptomatic HH that had failed to respond to sodium (< 2 g/d) restriction, who had optimal diuretics dosing (maximal tolerated doses without electrolyte abnormalities or clinically significant side effects), and who required frequent (more than once every 2-3 wk) thoracentesis were classified as having medically RHH.

**Response to TIPSS**

Response to TIPSS was based on clinical or radiographic evidence of hydrothorax post-TIPSS. Response was categorized as complete, partial, or absent. Response was classified as complete if the patients’ symptoms of shortness of breath resolved or returned to baseline, with no evidence of pleural effusion requiring thoracentesis. Partial response was defined as improvement of shortness of breath but without complete symptomatic resolution; thoracentesis was required less frequently than pre-TIPSS. Absent response was defined as persistent or worsening symptoms of shortness of breath and/or persistent need for thoracentesis. Radiologically, complete response was defined as undetectable pleural effusion on chest radiographs, computed tomogram, or ultrasonogram; partial response if pleural effusion decreased compared to pre-TIPSS; and absent response if pleural effusion was unchanged or increased. The studies used either radiologic and/or clinical criteria to assess response to TIPSS.

**TIPSS-related complications:** (1) HE. TIPSS related HE was defined as new onset (i.e., never existed prior to TIPSS) or worsening (increased in frequency or severity of encephalopathy, compared to pre-TIPSS status). One study considered HE as TIPSS related if it occurred within 30 d of the procedure[24]; and (2) Mortality After TIPSS. Death was evaluated as early (i.e., occurred within 45 d of the procedure) and overall (death irrespective of when the event occurred throughout the follow-up period). The follow-up period varied across the studies, with the longest duration being 5 years.

**Statistical analysis**

Data from eligible studies were pooled using a random-effects model with Stata version 11 (Stata Corp LP, College Station, Texas). Outcomes are expressed as proportions (percentages) with 95% CIs. The pooled analyses are presented as forest plots. Since there were only 6 eligible studies, we determined a priori that subgroup analyses would not be performed. Statistical heterogeneity between studies was assessed using the Cochran Q test and the I² statistic. An I² value of greater than 50% or a P value of less than 0.05 for the Q statistic was taken to indicate significant heterogeneity. All analyses were performed in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines (Table 1)[25]. Since this was a cumulative meta-analysis, publication bias was not assessed.

**RESULTS**

**Literature search results**

Six studies involving a total of 198 patients were included in the analyses. Two studies were excluded because each had a small number of study subjects and were judged by 2 of the reviewing authors to be of poor quality[1,26]. Figure 1 summarizes the results of the literature search, including the reasons for the exclusion of studies, and Table 2 summarizes the characteristics of the 6 studies that were included in the analysis.

**Characteristics of study participants**

The mean (SD) age of the 198 patients was 56 years (1.8 years) and 52% were male. The majority of patients had Child class C disease (56.9%), while 40.7% and 0.8% were Child class B and A, respectively. The mean pre- and post-TIPSS HVPG values were 20.14 mmHg (range, 17.4-26.0 mmHg) and 7.37 mmHg (range, 5.7-10.0 mmHg), respectively. The mean duration of follow-up was 10 mo (5.7-16.0 mo). Table 3 shows the results of
There was no evidence of heterogeneity among the studies ($P = 0.86$ and $P = 0.81$, respectively).

The incidence of post-TIPSS encephalopathy was 11.7% (95%CI: 6.3%-17.2%) (Figure 4). On this outcome, however, there was evidence of significant heterogeneity among the studies ($P = 0.04$).

**DISCUSSION**

This study shows that TIPSS relieves symptoms in close to three-fourths (73%) of patients with RHH. The 45-d mortality and the 1-year survival in patients with RHH are comparable to those seen in patients with refractory ascites and variceal hemorrhage. The most important predictors of poor outcomes after TIPSS for RHH include older age and severe underlying liver disease and/or associated renal dysfunction.
Table 2 Characteristics of 6 studies evaluating the effectiveness of transjugular intrahepatic portosystemic stent shunt in patients with refractory hepatic hydrothorax

| Ref.          | Methods and patients                                                                 | Outcomes/complications                          | Remarks                                                                 |
|--------------|---------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------|
| Gordon et al | Retrospective chart review of 24 consecutive patients with medically RHH               | Post-TIPSS response was categorized as complete, partial, or absent | 11 patients had variceal bleeding > 4 wk before TIPSS                   |
|              | Post-TIPSS patients underwent Doppler US studies every 3 to 6 mo                        | Mean change in HVPG                              | Stent revision if decreased flow noted                                  |
|              | Mean follow-up was 7.2 mo (range, 0.25-49.0 mo)                                        | TIPS patency was assessed by change in CTP score, survival, and new or worsened HE | 5 failures were CTP C                                                   |
|              | Patients with infection were excluded                                                  |                                                | 12 patients had medially RHH; the rest of the 9 patients had TIPS and RHH as a secondary indication with the primary indication being intractable ascites (n = 7) and gastric varices (n = 2) |
| Jeffries et al | Retrospective chart review of 12 consecutive patients with medically RHH               | Post-TIPSS response at ≤ 1 or > 1 mows was categorized as complete, partial, or absent | Immediate pre- and post-TIPSS prophylactic antibiotics given           |
|              | Post-TIPSS; patients had Doppler US studies every 3 mo                                   | TIPS-related complications: ≤ 30 and > 30 d       | Shunt thrombosis or decreased velocities required angioplastic revision |
|              | Mean follow-up was 173 d (range, 7-926 d)                                              | New-onset or worsened HE survival                 | 4 patients had shunt revisions                                          |
|              | Patients with heart failure, HCC, alcoholic hepatitis, or intrinsic renal disease were excluded | Mean change in HVPG                              | Patients who died or underwent transplant ≤ 30 d after TIPS were classified as nonresponders to TIPS            |
| Siegerstetter et al | Retrospective chart review of 40 consecutive patients with medically RHH              | Post-TIPSS response was categorized as complete, partial, or absent | 8 patients had no ascites; RHH was diagnosed by intraperitoneal methylene blue injection or technetium-Tc-99 |
|              | Post-TIPSS; patients had Doppler US studies at 4 wk, then every 3 mo                   | Predictors of survival:                          | 2 stent size reductions due to chronic HE                               |
|              | Mean (SD) follow-up was 14 mo [14 (range, 1-54 mo)]                                     | Mean change in HVPG                              |                                                                         |
|              | Patients with infection were excluded                                                  | New-onset or worsened HE                         |                                                                         |
|              |                                                                                       | CTP score improvement                             |                                                                         |
| Spencer et al | Retrospective chart review of 21 consecutive patients with medically RHH               | Survival at 1 yr                                 | Prophylactic antibiotics administered                                   |
|              | Post-TIPSS; patients had Doppler US studies at 1, 3, and 6 mo, then every 6 mo         | Post-TIPSS complications: Early (< 30 d) or late (≥ 30 d) | Radiographic and clinical response                                     |
|              | Mean follow-up was 223 d                                                               | New-onset or worsened HE                         | TIPS placement 100% successful                                          |
|              | Patients with severe right-sided heart failure and patients with PVT with cavernous transformation were excluded | Post-TIPSS response was categorized as complete, partial, or absent | 1 patient with a partial response was weaned off oxygen due to decreased pleural fluid |
|              |                                                                                       | Mean change in HVPG                              |                                                                         |
|              |                                                                                       | Cumulative survival                              |                                                                         |
| Wilputte et al | Retrospective chart review of 28 consecutive patients with medically RHH               | Mean change in HVPG                              | Stent revised for stenosis, obstruction, or relapsing RHH              |
|              | Post-TIPSS; patients had Doppler US at 24 h and at 1, 2, 3, 6, 9, and 12 mo, then every 6 mo | 30-d mortality post-TIPSS                        | Patients who underwent transplant were censored at surgery date         |
|              | Mean (SD) follow-up was 358 d (121 d); 3 patients were excluded due to grade 3 HE, HCC, cardiopulmonary disease, and infection | Response to TIPSS was categorized as complete, partial, or absent | 6 patients required TIPS revision                                     |
|              |                                                                                       |                                                | 2 patients had TIPS reduction due to intractable HE                    |
|              |                                                                                       |                                                | Both covered and uncovered stents were used                            |
| Dhanasekaran et al | Retrospective chart review of 73 consecutive patients with medically RHH             | Post-TIPSS response at 1 mo and 6 mo was categorized as complete, partial, or absent | TIPS catheterization used if stenosis suspected or RHH reaccumulated   |
|              | Patients had Doppler US every 3 mo for 12 mo, then annually                            | Evaluated predictors of response to TIPSS        | Angioplasty performed, if needed                                       |
|              | Patients with heart failure, pulmonary disease, infection, severe HE, portal vein thrombosis, and multiple hepatic cysts were excluded | Assessed for new or worsening HE                  | Uncovered and covered stents used                                     |
|              |                                                                                       | Mean change in HVPG                              |                                                                         |
|              |                                                                                       | Overall and 30-d mortality                       |                                                                         |

CTP: Child-Turcotte-Pugh; HE: Hepatic encephalopathy; HCC: Hepatocellular carcinoma; HVPG: Hepatic venous pressure gradient; PVT: Portal vein thrombosis; RHH: Refractory hepatic hydrothorax; TIPSS: Transjugular intrahepatic portosystemic shunt; US: Ultrasound.
Table 3 Summary of studies included in the pooled analyses of transjugular intrahepatic portosystemic shunt in patients with refractory hepatic hydrothorax

| Ref.                        | No. of patients | Complete response (%) | Partial response (%) | 45-d mortality (%) | 1-yr survival (%) | Predictors of mortality |
|-----------------------------|-----------------|-----------------------|----------------------|-------------------|-------------------|-------------------------|
| Gordon et al[14]            | 24              | 58                    | 21                   | 21                | NA                | TIPSS nonresponse        |
| Jeffries et al[24]          | 12              | 42                    | 17                   | 25                | NA                | Age > 65 yr             |
| Siegerstetter et al[26]     | 40              | 53                    | 28                   | 13                | 64                | Age > 60 yr             |
| Spencer et al[27]           | 21              | 57                    | 28                   | 14                | NA                | Medical comorbidities    |
| Wilputte et al[28]          | 28              | 57                    | 11                   | 14                | 41                | CTP score > 10           |
| Dhanasekaran et al[23]      | 73              | 59                    | 21                   | 19                | 48                | Mayo score > 1.5        |

CTP: Child-Turcotte-Pugh; MELD: Model for end-stage liver disease; NA: Not applicable; TIPSS: Transjugular intrahepatic portosystemic stent shunt.

Figure 2 Response to transjugular intrahepatic portosystemic shunt. A: Forest plot shows that most [55.8% (95%CI: 44.7%-66.9%)] of the 198 patients in the 6 studies had a complete response (resolution of refractory hepatic hydrothorax without further need for thoracentesis) after TIPSS. There was no evidence of heterogeneity among studies (P = 0.99); B: About one-fifth [17.6% (10.9%-24.2%)] of the patients had only a partial response (defined as improvement in refractory hepatic hydrothorax symptoms and/or a decrease for the need for thoracentesis). There was no evidence of heterogeneity among studies (P = 0.65); C: Just over one-fifth (21.2%) of the patients had no improvement in refractory hepatic hydrothorax after TIPSS. There was no evidence of heterogeneity among studies (P = 0.76). TIPSS indicates transjugular intrahepatic portosystemic stent shunt.
HH remains a rare complication of liver cirrhosis, with limited therapeutic options. When symptomatic HH fails to respond to medical treatment, repeat thoracentesis is often undertaken. Although thoracentesis is less invasive than TIPSS and is effective in quickly relieving symptoms of dyspnea, it can be associated with complications such as re-expansion pulmonary edema, pneumothorax, and empyema[5,30]. Repeated thoracentesis is also associated with deteriorating clinical status and poor quality of life[1,6].

TIPSS is a nonsurgical approach that decompresses the portal system, thereby addressing the mechanism of fluid collection in the abdomen and/or chest[31]. TIPSS is superior to other treatment modalities in the prevention of rebleeding from varices, and its control of refractory ascites has been well studied in controlled trials[32-36]. In contrast, controlled studies on its use in patients with RHH are lacking, and comparative studies with other treatment options may not be feasible[37,38]. Consequently, evidence on the effectiveness of TIPSS in RHH has been limited to case series with often small numbers of study participants. Results from the 6 studies included in this pooled analysis found a wide range of responses and complication rates, perhaps due to the lack of statistical power. In this study, we combined data from all the small studies, which allowed us to provide the best evidence on TIPSS effectiveness in RHH.

One-fifth of the patients died in the first 45 d after TIPSS placement. This number is well within the range for mortality following TIPSS use in patients with refractory ascites and variceal bleeding[39-44]. Early mortality was observed in patients who developed progressive liver failure, sepsis, renal failure, bleeding,

| Study          | Period     | Proportion (95%CI)   |
|----------------|------------|---------------------|
| Dhanasekaran   | 1992-2008  | 19.18 (10.48, 32.18) |
| Gordon         | 1992-1995  | 21.00 (2.58, 36.53)  |
| Jeffries       | 1993-1997  | 25.00 (5.16, 73.06)  |
| Spencer        | 1995-2000  | 28.58 (10.49, 62.19) |
| Wilputte       | 1992-2001  | 14.29 (3.89, 36.58)  |
| Siegerstetter  | 1994-1998  | 12.50 (4.10, 29.20)  |
| Overall        |            | 17.74 (11.34, 24.13) |

Figure 3  Mortality after transjugular intrahepatic portosystemic stent shunt. A: Forest plot shows that about one-fifth [17.74% (95%CI: 11.34%-24.13%)] of the 198 patients in the 6 studies died within 45 d of undergoing TIPSS. There was no evidence of heterogeneity among studies (P = 0.86); B: Overall mortality after TIPSS was 50.17% (95%CI: 39.63%-60.71%) at a maximum follow-up of 5 years. There was no evidence of heterogeneity among studies (P = 0.81). TIPSS indicates transjugular intrahepatic portosystemic stent shunt.

| Study          | Period     | Proportion (95%CI)   |
|----------------|------------|---------------------|
| Dhanasekaran   | 1992-2008  | 52.05 (36.84, 71.45) |
| Gordon         | 1992-1995  | 54.17 (28.84, 92.63) |
| Jeffries       | 1993-1997  | 58.33 (23.45, 120.19) |
| Siegerstetter  | 1994-1998  | 37.50 (20.99, 61.85)  |
| Spencer        | 1995-2000  | 57.14 (29.53, 99.82)  |
| Wilputte       | 1992-2001  | 60.71 (35.37, 97.21)  |
| Overall        |            | 50.17 (39.63, 60.71)  |

Overall mortality post-TIPSS was 50.17% (95%CI: 39.63%-60.71%) at a maximum follow-up of 5 years. There was no evidence of heterogeneity among studies (P = 0.81). TIPSS indicates transjugular intrahepatic portosystemic stent shunt.

| Study          | Period     | Proportion (95%CI)   |
|----------------|------------|---------------------|
| Dhanasekaran   | 1992-2008  | 15.07 (7.52, 26.96)  |
| Gordon         | 1992-1995  | 37.50 (17.15, 71.19) |
| Jeffries       | 1993-1997  | 33.33 (9.08, 85.34)  |
| Siegerstetter  | 1994-1998  | 5.00 (0.61, 18.06)   |
| Spencer        | 1995-2000  | 42.86 (19.60, 81.36) |
| Wilputte       | 1992-2001  | 7.14 (0.87, 25.80)   |
| Overall        |            | 11.74 (6.25, 17.22)  |

Encephalopathy post-TIPSS was noted in 11.7% (95%CI: 6.3%-17.2%) of the 198 patients in the 6 studies. There was, however, evidence of heterogeneity among the studies (P = 0.04). TIPSS indicates transjugular intrahepatic portosystemic stent shunt.

Ditah IC et al. TIPSS in refractory hepatic hydrothorax
Hepatic hydrothorax (HH) which is the accumulation of "ascitic fluid" in the pleural cavity is an uncommon complication of cirrhosis with poor prognosis. When HH fails to respond to traditional medical management (salt restriction and diuretics), it is referred to as refractory HH (RHH).

**Research frontiers**

Therapeutic options for RHH are limited. Transjugular intrahepatic porto-systemic shunt (TIPSS) has been proposed as an option for RHH. Because HH is rare, studies on the effectiveness of TIPSS in RHH have been restricted to small numbers of patients and findings have varied substantially and are controversial.

**Innovations and breakthroughs**

The purpose of this study was to evaluate the effectiveness of TIPSS in patients with RHH by pooling all available evidence in a systematic review and cumulative meta-analysis. By combining data from all available studies, the authors generated enough statistical power to study the clinical effectiveness of TIPSS in RHH.

**Applications**

This study shows that TIPSS leads to a clinically relevant response in about three-fourths (73%) of patients with RHH. The 45-d mortality and the 1-year survival in patients with RHH are comparable to those seen in patients with refractory ascites and variceal hemorrhage. The most important predictors of poor outcomes after TIPSS for RHH include older age and severe underlying liver disease and/or associated renal dysfunction. The authors suggest that TIPSS should be considered early in patients with RHH.

**Terminology**

HH is the accumulation of fluid in the pleural cavity in patients with cirrhosis. The most widely accepted mechanism for HH is the passage of fluid from the peritoneal to the pleural cavity through a diaphragmatic defect. When HH fails to respond to medical management including salt restriction and maximal tolerated diuretics, it is considered refractory. Transjugular intrahepatic porto-systemic shunt decompresses the portal system, thereby addressing the mechanism of fluid collection in the abdomen and/or chest.

**Peer-review**

The manuscript is very well written.
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Ditah IC et al. TIPSS in refractory hepatic hydrothorax
