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Review Article

Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: A systematic review and meta-analysis

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ABSTRACT

Background: Hepatorenal syndrome is a severe complication of advanced liver diseases with a dismal prognosis.
Aims: This systematic review and meta-analysis aims to explore the efficacy and safety of transjugular intrahepatic portosystemic shunt for the treatment of hepatorenal syndrome.
Method: Publications were searched via PubMed and EMBASE databases. The pooled proportion and mean difference were calculated by using a random-effect model.
Results: Nine publications were included, in which 128 patients with hepatorenal syndrome were treated with transjugular intrahepatic portosystemic shunt. The pooled short-term and 1-year survival rates were 72% and 47% in type 1 hepatorenal syndrome and 86% and 64% in type 2 hepatorenal syndrome. No lethal procedure-related complications were observed. The pooled rate of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt was 49%. The pooled rate of renal function improvement after transjugular intrahepatic portosystemic shunt was 93% in type 1 hepatorenal syndrome and 83% in any type of hepatorenal syndrome. After transjugular intrahepatic portosystemic shunt, serum creatinine, blood urea nitrogen, serum sodium, sodium excretion, and urine volume were significantly improved; by comparison, serum bilirubin slightly increased, but the difference was not statistically significant.
Conclusion: Limited evidence suggested a potential survival benefit of transjugular intrahepatic portosystemic shunt in patients with hepatorenal syndrome but with a high incidence of hepatic encephalopathy.

1. Introduction

Hepatorenal syndrome (HRS) is a functional kidney injury developing in advanced liver diseases [1]. It is characterized by a reduced glomerular filtration rate (GFR) together with circulatory dysfunction in the absence of obvious organic kidney diseases, nephrotoxic drugs, and shock [2,3]. There are 2 types of HRS. HRS-1 is a rapidly progressive acute renal failure that frequently develops in relationship with a precipitating factor, such as acute deterioration of hepatic function or infection [1]. It is characterized by a doubling of serum creatinine to greater than 2.5 mg/dl (221 μmol/l) in less than 2 weeks [3]. In contrary, HRS-2 is a more chronic form of HRS with a steady but moderate degree of functional renal failure, often occurring in patients with refractory ascites. The 3-month survival rate of cirrhotic patients with HRS is 15% [4]. The median survival time of HRS-1 and HRS-2 is about 2 weeks and 4–6 months, respectively.

Currently, liver transplantation is the best therapy for HRS [1]. However, the hepatic donor is often lacking, the cost is high, and many patients are being excluded due to age, comorbidity, or alcohol consumption. Vasoconstrictors combined with albumin are effective in the treatment of HRS. Several systematic reviews with meta-analyses showed the improvement or reversal of HRS by vasoconstrictors [5–9], but the survival benefit was mild or questionable [10,11], and the relapse could not be prevented [9]. The role of transjugular intrahepatic portosystemic shunt (TIPS) for the management of HRS remains controversial. The shunt reduces portal hypertension and ameliorates circulatory dysfunction [12]. The main adverse effects comprise hepatic encephalopathy (HE) and

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worsening of liver function. In experienced hands, the intervention is safe with a technical mortality approaching zero [13]. The Italian liver community suggests TIPS for HRS-2 associated with refractory/recidivate ascites, but not in unselected patients with HRS-1 [14]. Similarly, the German guideline recommends TIPS as the first-line treatment in patients with refractory ascites with or without HRS [15]. The practice guideline of the European Association for the Study of the Liver Diseases states that TIPS may improve the renal function but data is insufficient to recommend TIPS for both HRS-1 and HRS-2 [1]. The practice guideline of the American Association for the Study of Liver Diseases recommends that TIPS is of investigatory use for the treatment of HRS and that further studies are required [16].

HRS-1 is a relatively rare disease. Only few studies on TIPS for HRS-1 including few patients are available [1]. In contrast, HRS-2 is rather common [1]. Most of patients with tense or refractory ascites may have HRS-2 [1]. As demonstrated previously and summarized recently, renal function improves after TIPS [17]. However, the primary endpoints of the majority of these studies were ascites and survival, but not reversal of HRS. Patients are not defined according to renal function and, therefore, the samples may be mixed up including patients with normal renal function, HRS-2, and even HRS-1. In addition, a false diagnosis of HRS is relatively common and a proper diagnosis may not be guaranteed in these studies [2]. This is why studies devoted to the treatment of refractory ascites are not sufficiently appropriate to assess the effect of TIPS on HRS.

The purpose of this systematic review and meta-analysis is to explore the efficacy and safety of TIPS for the treatment of HRS.

2. Methods

2.1. Registration

The registration number of PROSPERO was CRD42016051386.

2.2. Literature search

The relevant publications were searched via PubMed and EMBASE databases. The search items were as follows: ("hepatorenal syndrome" [All Fields]) AND ("transjugular intrahepatic portosystemic stent-shunt" [All Fields]) OR ("tips" [All Fields]). The date of last search was November 9, 2016.

2.3. Selection of papers

There was no language limitation. The eligibility criteria were the patients diagnosed with liver cirrhosis and HRS who underwent TIPS with and without other therapy. Exclusion criteria were as follows: (1) duplicate articles; (2) review articles; (3) comments and correspondences; (4) meta-analyses; (5) irrelevant topics; (6) case reports; (7) unable to extract the data regarding patients with HRS; and (8) overlapping data.

2.4. Data extraction

Data extraction from the included studies was performed by two authors. The following data were extracted: characteristics of included studies, baseline characteristics of patients, and outcome variables.

2.5. Study quality

The quality of studies is assessed by the following 6 criteria. Thereby, a score of 6 represents the highest quality.

1. Description of study design including patient enrollment (prospective, retrospective, and consecutive) and inclusion and exclusion criteria.
2. Completeness of biomedical characteristics of patients.
3. Quality of statistical analysis.
4. Study duration and follow-up of patients.
5. Description of other interventions, such as vasoactive agents, albumin, antibiotics, and paracentesis.
6. Description of outcome parameters, such as survival, causes of death, efficacy, and adverse events.

2.6. Endpoints

The primary endpoints were: 1) survival, including short-term and 1-year survival, of patients with HRS-1 and HRS-2 after TIPS; and 2) renal function improvement in patients with HRS-1 and any type of HRS after TIPS. The secondary endpoints were the differences in the liver and renal function parameters before and after TIPS (changes) and the frequency of severe complications.

2.7. Statistical analysis

The results of each eligible article were extracted as either dichotomous or continuous data. The meta-analyses were performed by the StatsDirect Statistical Package software version 2.7.8 (StatsDirect Ltd., Sale, Cheshire, UK). Data were expressed as the frequencies, means ± SD, or median and ranges, as indicated. As for the proportion data, we calculated the pooled proportion with 95% confidence interval (CI) as the effect size. As for the difference in continuous data between two groups, we calculated the weighted mean difference (WMD) with 95%CI as the effect size. $P < 0.05$ was considered as a statistically significant difference. We employed the random-effect model alone. Heterogeneity was assessed by the Cochrane Q test and the I^2 statistics. $P < 0.1$ or I^2 >50% was considered as a statistically significant heterogeneity. Publication bias was assessed by the Begg–Mazumdar and Egger tests. $P < 0.1$ was considered as a statistically significant publication bias.

3. Results

3.1. Articles

The electronic search in PubMed and EMBASE databases detected a total of 636 articles. Nine of them were included in this meta-analysis (Fig. 1) [18–26].

Characteristics of studies are summarized in Table 1. A total of 128 patients were included. The sample size ranged from 5 to 31 among studies. Seven of them were published as original articles [18–22,24,26], 1 as a letter to the editor [23], and 1 as an abstract [25]. Articles were published between 1998 and 2012 and most of them came from Italy and Germany. All articles employed the diagnostic criteria of HRS published by the International Club of Ascites [3]. Five studies included only patients with HRS-1, 2 studies included only patients with HRS-2, and 2 studies included patients with HRS-1 and HRS-2 as well. Altogether, 77 patients had HRS-1 and 51 patients had HRS-2. Three studies were of prospective and 2 of retrospective nature. Four studies stated that patients were enrolled consecutively. In most studies, additional interventions, such as vasoactive drugs, albumin, hemodialysis, and paracentesis, were administered before TIPS procedures. Exclusion criteria were given in 7 studies. A bilirubin concentration of >5 mg/dl [22] or >15 mg/dl [19], a Child–Pugh score of >12, active infection, hepatocellular carcinoma, severe cardiac or respiratory disease, and overt HE exceeding stage 2 were considered as the contraindications for TIPS [18–20,22,23,26].

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