Transjugular intrahepatic portosystemic shunt versus endoscopic therapy in the secondary prophylaxis of variceal rebleeding in cirrhotic patients: meta-analysis update

CRD summary
The authors concluded that transjugular intrahepatic portosystemic shunts therapy compared to endoscopic therapy significantly reduced variceal bleeding, but with higher incidence of post-treatment encephalopathy. The number of deaths due to all causes was similar in both groups. Given the potential for error and bias and unclear blinding in the included studies, the reliability of the authors’ conclusions is unclear.

Authors’ objectives
To conduct an up-to-date review of the effectiveness of transjugular intrahepatic portosystemic shunts (TIPS) in reducing variceal bleeding in patients with cirrhosis (see Other Publications of Related Interest).

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Chinese Biological Medicine Database were searched across various dates that spanned January 1966 to December 2006. Search terms were reported. Reference lists of relevant reviews and retrieved articles were handsearched for further studies. Only full publications published in peer-reviewed journals were eligible for the review.

Study selection
Randomised Controlled Trials (RCT) that compared TIPS with endoscopic therapy (sclerotherapy or variceal band ligation) with or without propranolol in adults (at least 18 years old) with cirrhosis and a prior history of variceal bleeding were eligible for inclusion. Eligible studies had to assess two or more of the following outcomes: variceal rebleeding; post-treatment encephalopathy; survival; and hospitalisation days.

Most included RCTs were of TIPS monitored by Doppler ultrasonography or angiography compared to sclerotherapy or ligation (alone or in combination with propranolol) in cirrhotic adults (mean age range 47 years to 59 years). Where stated, the interval between randomisation and the intervention ranged from within 48 hours to a mean of 3.4 days. The indications for crossover from endoscopic therapy to TIPS were: uncontrolled variceal bleeding; variceal bleeding that did not respond to sclerotherapy; rebleeding by gastric varices; more than two or three episodes of variceal bleeding in a specified period of time; treatment failure; or physician recommendation. Patients with alcoholic cirrhosis ranged from 24% to 88% and those with ascites ranged from 26% to 90%. Where reported, all studies included patients across the range of Child-Pugh classification of the severity of liver disease. Definitions of clinical outcomes varied between studies. Follow-up ranged from 420 days to 1,476 days. Most studies were conducted in Europe and North America.

Two reviewers independently selected the studies for review. Disagreements were resolved through discussion.

Assessment of study quality
Validity was assessed using the Jadad scale. Studies were awarded a score between 0 and 5 points. Studies that scored less than 3 points were described as poor quality; those that scored at least 3 points were described as high quality.

The authors did not state how many reviewers carried out the assessment of study quality.

Data extraction
For dichotomous outcomes, the number of events in each group was extracted and used to calculate odds ratios (OR) with 95% confidence intervals (CIs). In 2x2 tables where there were no events in a cell, a correction factor of 0.5 was added to each cell. The number of days in hospital was extracted for each group and the mean and standard deviation (SD) were calculated.
The authors did not state how the data were extracted for the review.

**Methods of synthesis**
Pooled ORs or weighted mean differences (WMD) with corresponding 95% CIs were calculated using the general inverse variance fixed-effect model. Heterogeneity was assessed using the Der Simonian and Laird Q statistic. Where significant heterogeneity was found, a random-effect model was used. Sensitivity analyses were performed according to methodological quality and type of control treatment. Publication bias was assessed using Begg and Mazumdar’s adjusted rank correlation test and Egger's test of funnel asymmetry.

**Results of the review**
Twelve RCTs were included for the review (n=883). Nine studies scored 3 on the Jadad scale and three studies scored 2. Blinding was unclear in all studies.

The use of TIPS was associated with a significantly reduced risk of variceal bleeding (OR 0.32, 95% CI 0.24 to 0.43, \(p<0.00001\)) and death due to rebleeding (OR 0.35, 95% CI 0.18 to 0.67, \(p=0.002\)) compared to endoscopic therapy. However, the risk of post-treatment encephalopathy was significantly higher in those patients treated with TIPS compared to those treated with endoscopic therapy (OR 2.21, 95% CI 1.61 to 3.03, \(p<0.00001\)). There was no evidence of significant statistical heterogeneity for these outcomes. Neither deaths due to all causes nor the number of days of hospitalisation differed significantly between TIPS and endoscopic therapy groups. The main causes of death in the TIPS groups were liver failure (10.2%), sepsis (3.2%) and variceal bleeding (3.0%); in the endoscopic therapy group they were variceal bleeding (7.9%), liver failure (7.0%), sepsis (1.8%) and carcinoma (1.8%).

Sensitivity analyses did not significantly alter the findings. However, there was no evidence of increased risk of encephalopathy with TIPS in trials of low quality (Jadad score ≤2) or when compared to ligation. Nor did TIPS significantly reduce the risk of variceal bleeding when compared to ligation plus propranolol. There was no evidence of significant publication bias.

**Authors' conclusions**
TIPS therapy compared to endoscopic therapy significantly reduced variceal bleeding at the cost of a higher incidence of post-treatment encephalopathy. The number of deaths due to all causes was similar in both groups, but there were significantly fewer deaths due to rebleeding in patients treated with TIPS.

**CRD commentary**
The review addressed a clear question, inclusion criteria were well-defined and several relevant databases were searched. The review was restricted to published articles. Publication bias was assessed and no evidence of it found; given the small number of included studies, these findings may not be reliable. It was unclear whether language restrictions were applied to the search, so language bias could not be ruled out. Appropriate steps were taken in the study selection process in order to minimise the risk of reviewer error and bias; it was unclear whether similar steps were taken in the validity assessment and data extraction stages, so error and bias could not be ruled out. A well-established tool was used to assess the methodological quality of included studies. Statistical heterogeneity was assessed and ruled out, but there was considerable clinical heterogeneity between the included studies. Given the potential for error and bias in the review process and wide variation between included studies, the reliability of the authors conclusions is unclear.

**Implications of the review for practice and research**
**Practice**: The authors stated that active surveillance was needed to ensure early detection and treatment of TIPS dysfunction.

**Research**: The authors stated that in light of the risk of post-treatment encephalopathy associated with TIPS, alternative interventions for variceal bleeding should be investigated.

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