TIPS for prevention of recurrent bleeding in patients with cirrhosis: meta-analysis of randomized clinical trials

Authors' objectives
To compare the effects of transjugular intrahepatic portosystemic shunt (TIPS) creation with those of endoscopic treatment with or without propranolol administration (i.e. conventional treatment) on recurrent bleeding, encephalopathy and mortality.

Searching
MEDLINE (Jan 1991 to Feb 1998) was searched using the terms: 'TIPS', 'sclerotherapy', 'variceal band ligation', and 'beta blockers', and by limiting the search to reports of clinical trials and studies with human patients. In addition a manual search was performed by checking the reference lists from articles or reviews to identify further studies. Finally, the abstracts from international congresses on liver disease underwent peer review to identify trials still in progress.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) which assessed two or more of the above outcomes. Results had to be published in English as abstracts or full reports

Specific interventions included in the review
Transjugular intrahepatic portosystemic shunt (TIPS). The comparison groups were endoscopic treatment (sclerotherapy or banding ligation) with or without propranolol administration.

Participants included in the review
Patients with cirrhosis and previous variceal bleeding. Where stated, the mean age ranged from 46-60 years, and the percentage of male patients ranged from 52-79%. In addition, the percentage (where stated) with alcoholic cirrhosis ranged from 24-77%; the percentage with Child-Pugh class A, B or C ranged from 12-56%, and 32-90% had ascites. The bleeding interval ranged from 1 day to 180 days.

Outcomes assessed in the review
Recurrence of gastrointestinal bleeding due to any cause, portosystemic encephalopathy, mortality due to any cause and mortality due to recurrent bleeding.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
A previously reported quality assessment system (see Other Publications of Related Interest no.1) was partially modified according to the treatment under study. The system was based on the following criteria: clearly defined inclusion and exclusion criteria, blinded treatment assignment, baseline comparability of treatment groups, clearly defined outcome variables, treatment for acute bleeding equal in the two groups and assessment of treatment side effects and complications. The quality of the reports was assessed by two independent observers. Any discrepancies between the two observers was discussed, and a consensus was achieved.

Data extraction
Two independent reviewers extracted data from each trial. For each study and type of treatment, the following data were extracted: number of patients, mean age, sex, prevalence of alcoholic cirrhosis, Child-Pugh score, presence of ascites, time between index bleeding and random assignment to treatment, type and modality of control treatment, rate of technical success of the procedures, portocaval pressure gradient before and after TIPS creation, mean length of follow-up, incidence of TIPS dysfunction, and definition and number of each outcome. Numeric discrepancies between the two independent data extractions were resolved after discussion.

Methods of synthesis
How were the studies combined?
Data were extracted on the basis of the intention-to-treat principle, and treatment effects were measured as risk differences between TIPS creation and conventional treatment. For all outcomes, the pooled risk difference was computed using the methods of DerSimonian and Laird (see Other Publications of Related Interest no.2). The control treatments, variceal endoscopic sclerotherapy and banding ligation were considered as equivalent.

How were differences between studies investigated?
Due to differences in clinical characteristics among study groups, varying sample sizes and different control treatments, it was assumed that heterogeneity was present even when not statistically significant and data were combined using a random-effects model. The chi-squared statistic for heterogeneity were computed and reported. In addition, sensitivity analyses were performed for type of publication (full report or abstract), and type of conventional treatment.

Results of the review
A total of 750 patients were included in 11 trials.

Quality of the trials:
The quality score for the seven trials published as full articles ranged from 51% to 88%, which was deemed to be fair or good quality.

Treatment effects:
No significant heterogeneity was found for any of the outcomes. The pooled risk difference for recurrent bleeding was -31% (95% CI, -39%, -23%) based on 750 patients in 11 trials; for encephalopathy +16% (95% CI, +10%, +22%) based on 685 patients in 10 trials; for death due to all causes +2% (95% CI, -4%, +9%) based on 750 patients in 11 trials; and for death due to bleeding -5% (95% CI, -11%, +6%) based on 593 patients in 8 trials. Clinically important complications occurred in 22% of patients and were associated with both treatments. TIPS dysfunction occurred in 55% of patients.

Sensitivity analyses:
Sensitivity analyses showed consistency of results for type of publication (full report or abstract), and type of conventional treatment (sclerotherapy, sclerotherapy plus propranolol, or endoscopic band ligation). However, the increased risk of encephalopathy after TIPS creation was not statistically significant in abstract reports, and in trials in which banding ligation was the conventional treatment.

Authors’ conclusions
TIPS creation markedly reduces risk of rebleeding but increases risk of encephalopathy without affecting survival. Therefore, TIPS creation may not be the best first-choice therapy for prevention of recurrent variceal bleeding.

CRD commentary
This is a thorough and well-written review. The review's objectives, inclusion/exclusion criteria, presentation of details of primary studies and methods of pooling were clearly presented. The search strategy involved a single database, was limited to English language only, and did not include an extensive search for unpublished data, so publication bias...
cannot be excluded. The quality of the included trials was assessed and sensitivity analysis was performed. The author's conclusions appear to follow on from the results of the review.

**Implications of the review for practice and research**

**Practice:** The authors state that, because of the significant increased risk of encephalopathy, TIPS creation is far from the ideal therapy for prevention or recurrent bleeding and, in their opinion, cannot be considered a first choice treatment.

**Research:** The authors state that the frequency of encephalopathy should probably be reassessed in further randomised clinical trials that have been more specifically designed to tailor portal venous pressure reduction to achieve the best decrease in risk of bleeding with the lowest frequency of encephalopathy. Criteria for selection of candidates for TIPS creation should be assessed in future prospective studies.

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the reliability of the review and the conclusions drawn.