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Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis (Review)

Brand M, Prodehl L, Ede CJ

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[Intervention Review]

Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Martin Brand[1], Leanne Prodehl[2], Chikwendu J Ede[2]

[1]Department of Surgery, University of Pretoria, Pretoria, South Africa. [2]Department of Surgery, University of the Witwatersrand, Johannesburg, South Africa

Contact address: Martin Brand, Department of Surgery, University of Pretoria, Pretoria, 0001, South Africa. martinbrand78@gmail.com.

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ABSTRACT

Background

Variceal haemorrhage that is refractory or recurs after pharmacologic and endoscopic therapy requires a portal decompression shunt (either surgical shunts or radiologic shunt, transjugular intrahepatic portosystemic shunt (TIPS)). TIPS has become the shunt of choice; however, is it the preferred option? This review assesses evidence for the comparisons of surgical portosystemic shunts versus TIPS for variceal haemorrhage in people with cirrhotic portal hypertension.

Objectives

To assess the benefits and harms of surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt (TIPS) for treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension.

Search methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, CENTRAL, MEDLINE, Embase, LILACS, Science Citation Index Expanded, and Conference Proceedings Citation Index - Science. We also searched on-line trial registries, reference lists of relevant articles, and proceedings of relevant associations for trials that met the inclusion criteria for this review (date of search 8 March 2018).

Selection criteria

Randomised clinical trials comparing surgical portosystemic shunts versus TIPS for the treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension.

Data collection and analysis

Two review authors independently assessed trials and extracted data using methodological standards expected by Cochrane. We assessed risk of bias according to domains and risk of random errors with Trial Sequential Analysis (TSA). We assessed the certainty of the evidence using the GRADE approach.

Main results

We found four randomised clinical trials including 496 adult participants diagnosed with variceal haemorrhage due to cirrhotic portal hypertension. The overall risk of bias in all the trials was judged at high risk. All the trials were conducted in the United States of America (USA). Two of the trials randomised participants to selective surgical shunts versus TIPS. The other two trials randomised participants to non-selective surgical shunts versus TIPS. The diagnosis of liver cirrhosis was by clinical and laboratory findings. We are uncertain whether there is a difference in all-cause mortality at 30 days between surgical portosystemic shunts compared with TIPS (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.44 to 1.99; participants = 496; studies = 4). We are uncertain whether there is a difference in encephalopathy between surgical shunts compared with TIPS (RR 0.56, 95% CI 0.27 to 1.16; participants = 496; studies = 4). We found evidence suggesting an increase in the occurrence of the following harms in the TIPS group compared with surgical shunts: all-cause mortality at five years (RR 0.61, 95% CI 0.42 to 0.90; participants = 496; studies = 4); variceal rebleeding (RR 0.18, 95% CI 0.07 to 0.49; participants = 496; studies = 4); reinterventions (RR 0.13, 95% CI 0.06 to 0.28; participants = 496; studies = 4); and shunt occlusion (RR 0.14, 95% CI 0.04 to 0.51; participants = 496; studies = 4). We could not perform an analysis of health-related quality of life but available evidence appear to suggest improved health-related quality of life in people who received surgical shunt compared with TIPS. We downgraded the certainty of the evidence for all-cause mortality at 30 days and five years, irreversible shunt occlusion, and encephalopathy to very low because of high risk of bias (due to lack of blinding); inconsistency (due to heterogeneity); imprecision (due to small sample sizes of the individual trials and few events); and publication bias (few trials reporting outcomes). We downgraded the certainty of the evidence for variceal rebleeding and reintervention to very low because of high risk of bias (due to lack of blinding); imprecision (due to small sample sizes of the individual trials and few events); and publication bias (few trials reporting outcomes). The small sample sizes and few events did not allow us to produce meaningful trial sequential monitoring boundaries, suggesting plausible random errors in our estimates.

Authors' conclusions

We found evidence suggesting that surgical portosystemic shunts may have benefit over TIPS for treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension. Given the very low-certainty of the available evidence and risks of random errors in our analyses, we have very little confidence in our review findings.

PLAIN LANGUAGE SUMMARY

Surgical shunts versus radiologic shunt for variceal haemorrhage in people with chronic disease of the liver

Background

Varices are enlarged thin walled vessels found in the walls of the oesophagus and stomach of people with high blood pressure in the portal circulation (blood vessels supplying the liver with blood from the bowels). Bleeding from varices are not uncommon and maybe life-threatening. The first-line treatment of this bleeding is with medications and endoscopy (use of a long tube fitted with camera to locate and occlude the varices with elastic bands). Most people will respond to the first-line treatment, but a few will continue to bleed or have repeat bleeding. This later group will require further treatments in the form of shunts (tubes that divert blood from portal circulation direct to the heart). There are two types of shunts; one that is created through a surgical operation and called surgical shunt, the other is created with the help of an ultrasound machine and called radiologic shunt. Both types of shunts have their benefits and harms. This review was done to determine whether surgical shunts are better than radiologic shunt in treating persistent and repeat bleeding due to varices in people with cirrhosis (chronic disease of the liver in which normal liver cells are replaced by hard scar).

Study characteristics

We found four randomised clinical trials in which 496 adult participants were allowed to receive either a surgical shunt or a radiologic shunt. There were problems with the design of the trials as they had small number of participants and used different shunt types. We judged all four trials at high risk of bias (trials may have overestimated the true effect of shunts treatment).

Key results

We found no difference in the number of participants who died within 30 days of treatment, and the number that developed encephalopathy (disease of the brain due to toxins bypassing the liver to reach the brain), when surgical shunts were compared with radiologic shunt. We found evidence suggesting more harms with radiologic shunt when we considered the number of participants that died five years after treatment; or had repeat bleeding; or required repeated treatment; or had shunt blockage; that appeared to be more in the radiologic shunt group.

Conclusions

Surgical shunts appear to be better than radiologic shunt for treating persistent and repeated bleeding due to varices in people with liver cirrhosis. Given the very low certainty of the evidence due to problems with design of the trials and inadequate number of participants, we are unsure if our conclusion is correct. Future trials with better design and adequate number of participants will likely produce results that are reliable.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Surgical portosystemic shunts compared to transjugular intrahepatic portosystemic shunt (TIPS) for variceal haemorrhage in people with cirrhotic portal hypertension

Patient or population: people with cirrhotic portal hypertension
Setting: health institutions in USA
Intervention: surgical portosystemic shunts
Comparison: transjugular intrahepatic portosystemic shunt (TIPS)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with TIPS	Risk with Surgical portosystemic shunts				
All-cause mortality at 30 days	Study population		RR 0.94 (0.44 to 1.99)	496 (4 RCTs)	⊕◯◯◯ Very low [abcd]	-
	178 per 1000	167 per 1000 (78 to 354)				
All-cause mortality at 5 years	Study population		RR 0.61 (0.42 to 0.90)	496 (4 RCTs)	⊕◯◯◯ Very low [abcd]	-
	551 per 1000	336 per 1000 (231 to 496)				
Number of participants with Variceal rebleeding episodes at 30 days	Study population		RR 0.18 (0.07 to 0.49)	496 (4 RCTs)	⊕◯◯◯ Very low [acd]	-
	117 per 1000	21 per 1000 (8 to 58)				
Number of participants with reintervention at 5 years	Study population		RR 0.13 (0.06 to 0.28)	496 (4 RCTs)	⊕◯◯◯ Very low [acd]	-
	518 per 1000	67 per 1000 (31 to 145)				
Irreversible shunt occlusion at 5 years	Study population		RR 0.14 (0.04 to 0.51)	496 (4 RCTs)	⊕◯◯◯ Very low [abcd]	-

	271 per 1000	38 per 1000 (11 to 138)				
Number of participants with encephalopathy at 5 years	Study population		RR 0.56 (0.27 to 1.16)	496 (4 RCTs)	⊕◯◯◯ Very low [abcd]	-
	385 per 1000	215 per 1000 (104 to 446)				
Health-related quality of life	See comment	See comment	-	210 (2 RCTs)	-	One trial provided data on health-related quality of life with median score, while the other trial provided data on health-related quality of life in a narrative way. Both studies appear to suggest improved health-related quality of life in people who received surgical shunts compared with TIPS

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RCT__: randomised clinical trial; __RR:__ risk ratio; __TIPS__: transjugular intrahepatic portosystemic shunt

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level for risk of bias due to lack of blinding.
[b] Downgraded one level for inconsistency due to significant heterogeneity.
[c] Downgraded two levels for imprecision due to small sample size and few events.

[d]Downgraded one level for publication bias due to few trials reporting outcome.

BACKGROUND

Description of the condition

Variceal haemorrhage is the most life-threatening complication of portal hypertension. By definition, there is a pathological increase in portal venous pressure that exceeds 8 mm mercury (Hg), and resulting in complications such as varices, encephalopathy, and new-onset, or worsening of pre-existing ascites (Goff 1993; Sanyal 2008). The pathogenesis of portal hypertension is complex, but involves an increase in portal outflow resistance as well as increased portal venous inflow. An imbalance in vasoactive mediators (endothelin-1, angiotensinogen, eicosanoids, and nitric oxide) that results in intrahepatic vasoconstriction has also been described (Sharara 2001; Moore 2004). Varices develop when natural portosystemic collateral vessels enlarge to decompress the elevated portal pressure. This develops commonly at the oesophagogastric junction in approximately half of people with liver cirrhosis, of these, 15% to 20% will bleed requiring an intervention to stop bleeding (Amitrano 2012). Oesophagogastric variceal haemorrhage occurs when portal venous pressure gradient is greater than 12 mm Hg (Garcia-Tsao 1985). An interplay between variceal pressure, variceal wall tension, and variceal size according to Laplace's law, explains how variceal rupture occurs when wall tension exceeds the elastic limit of the variceal wall (Rigau 1989). Due to the advancement in medical management of acute variceal haemorrhage, as well as primary prevention for high-risk varices (Jamal 2008a; Jamal 2008b), mortality from the first bleeding episode has reduced from approximately 50% to 15% (DeDombal 1986; Chalasani 2003; Carbonell 2004). Yet, the greatest morbidity is rebleeding, approaching 70% over two years without secondary prevention (D'Amico 2003). The risk of rebleeding is highest within the first few days after an index bleed (Smith 1982), with mortality similar to the first bleeding episode. Surveillance upper gastrointestinal endoscopy in people with liver cirrhosis can be used to establish diagnosis, and identify high-risk varices (i.e. medium to large size varices and red wale sign) (Garcia-Tsao 1985; de Franchis 2010). Mortality in portal hypertension is largely determined by the patient's underlying liver function (Graham 1981). Scoring systems such as the Child-Pugh and model for end-stage liver disease (MELD) scores are used to assess the degree of liver dysfunction and extrapolate this to predict survival (Child 1964; Pugh 1973). Patients with the best score of a Child-Pugh A5 have a predicted life expectancy of 15 years to 20 years as opposed to the worst score of a Child-Pugh C15, with a predicted life expectancy of one to three years (Kaplan 2015).

Description of the intervention

Variceal haemorrhage can be controlled effectively using a combination of pharmacologic as well as endoscopic therapy. However, about 20% to 30% of people treated with this modality will rebleed or have refractory bleeding despite the medical therapy (Sharara 2001). These people will require liver transplantation, or decompression shunting (either surgical shunts or radiologic shunt). As availability of donor organs is in short supply, transjugular intrahepatic portosystemic shunt (TIPS) is often proposed as an attractive option when medical therapy fails because it is less invasive and could serve as a bridge to transplantation (de Franchis 2010; Rosemurgy 2012). However, only 3% to 14% of people with cirrhosis who bleed from their varices eventually receive transplantation post-TIPS (Stanley 1996; Tripathi 2004; Rössle 2006; Rosemurgy 2012; Toomey 2013). When considering both methods of shunting, procedure-related mortality rates for elective surgical shunts are less than 10% (Cowgill 2006). Although TIPS is a less invasive procedure, it appears to have more complications and requires more reinterventions. The incidence of occlusion for TIPS is 17% compared to 9% for surgical shunts (Rosemurgy 2012); post-shunt encephalopathy is 18% to 45% for TIPS (Rössle 1994), compared to 25% for surgical shunts (Zervos 1998); and rebleeding occurs in 20% to 30% of patients who received TIPS compared with less than 10% in patients who received a surgical shunt. Median survival is 26 months in patients who received TIPS compared with 52 months in patients who received a surgical shunt (Rikkers 1998; Costa 2010; Rosemurgy 2012). In addition, TIPS requires more intensive long-term surveillance than surgical shunts due to the high likelihood for occlusion requiring reinterventions (up to 21% for TIPS compared to 6% for surgical shunts; Toomey 2013). This poses a significant burden on the healthcare system in terms of costs and resource utilisation. Another concern is that TIPS may divert nutrient-effective hepatic blood flow away from already compromised hepatocytes, potentially accelerating hepatic decompensation (Rosemurgy 2003). This contrasts with surgical shunts that may improve nutrient portal blood flow, thus resulting in less postprocedural liver failure (Rosemurgy 2004).

TIPS is created by an interventional radiologist using fluoroscopic guidance. Under conscious sedation or general anaesthesia, a jugular vein is cannulated and a guidewire is fed into the liver via a hepatic vein. A special needle known as a Colapinto is advanced over the guidewire, through the liver parenchyma into a portal vein. The tract is then dilated with an angioplasty balloon. A covered or uncovered metal stent is then placed through this tract creating an open channel between the hepatic vein and portal vein (LaBerge 1993).

Surgical portosystemic shunts are divided into non-selective and selective shunts. Non-selective shunts divert all portal circulation into the systemic circulation. This includes the portocaval shunts (either side-to-side or end-to-side) (Orloff 2007); central splenorenal shunts (constructed by anastomosing proximal splenic vein to left renal vein); and the large diameter H-graft shunts constructed with 16 mm polytetrafluoroethylene (PTFE) prosthesis (Sarfeh 1986). Selective shunts can maintain some hepatic perfusion while providing adequate portal decompression. Selective shunts include

the distal splenorenal shunt (DSRS) and the small diameter H-graft shunt constructed with 8 mm PTFE prosthesis (Sarfeh 1983; Rosemurgy 1994). The DSRS is constructed by anastomosing the distal splenic vein (portal venous system) to the left renal vein (systemic venous system) with or without splenopancreatic and gastric disconnection (Warren 1967). A review showed that there is no difference in overall survival and rebleeding between non-selective and selective surgical shunts (Wolff 2003).

The greatest concern with invasive (surgical) shunts are the perceived increased periprocedural morbidity and mortality rates of surgical procedures in patients with advanced liver cirrhosis (Garbuzenko 2016). Three months after a patient has survived their acute variceal bleed their expected survival returns to the survival rate of a comparable cirrhotic who has not bled (Carbonell 2004). Furthermore, acutely deteriorating liver function, which may be precipitated by a variceal bleed, is also associated with poorer surgical morbidity and mortality (Shalimar 2016). Hence the need for this review to determine whether or not surgical shunts compared with TIPS are safe as well as effective.

How the intervention might work

Surgical portosystemic shunts bypass blood flow from the portal venous circulation into the systemic venous circulation, thus decreasing the blood pressure within the portal system. This will ultimately reduce portal venous pressure gradient and consequently decrease the likelihood of variceal rebleeding.

Why it is important to do this review

An evidence-based approach should be developed to guide the treatment of people with hepatic cirrhosis complicated by potentially life-threatening refractory or recurrent variceal haemorrhage who require portal decompression. This review attempted to provide evidence for which type of shunting procedure to use in people with refractory or recurrent variceal haemorrhage due to cirrhotic portal hypertension.

OBJECTIVES

To assess the benefits and harms of surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt (TIPS) for the treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

We only considered randomised clinical trials in which surgical portosystemic shunts were compared with transjugular intrahepatic portosystemic shunt for treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension. For assessment of harms, we intended to include quasi-randomised studies and observational studies identified during our search for randomised clinical trials. We are aware that this approach increases the risk of overlooking harms of the interventions. We did not place any restrictions regarding language, year of publication, country of origin, or institution of publication in selecting studies for this review.

Types of participants

We included participants with cirrhotic portal hypertension diagnosed by clinical and laboratory data, irrespective of age and sex, that had documented refractory or recurrent variceal haemorrhage following pharmacologic and endoscopic interventions. We excluded participants with non-cirrhotic portal hypertension and participants who had non-shunt surgical interventions.

Types of interventions

We considered all types of surgical portosystemic shunt interventions as the experimental intervention. We divided the surgical shunt interventions into two groups as follows.

Surgical shunts

Selective shunts

Small diameter (8 mm) H-graft shunt (externally reinforced polytetrafluoroethylene (PTFE)) either as mesocaval or portocaval shunt); and distal splenorenal shunt (DSRS; connecting the distal splenic vein and left renal vein).

Non-selective shunts

Portocaval shunts (connecting the portal vein and vena cava); mesocaval shunts (connecting the mesenteric vein and vena cava); central splenorenal shunt (connecting proximal splenic vein and left renal vein); and 16 mm H-graft shunt (externally reinforced PTFE shunt either as mesocaval or portocaval shunt).

Non-surgical shunts

We considered the radiologic, transjugular intrahepatic portosystemic shunt (TIPS) as the control intervention.

Types of outcome measures

Primary outcomes

- All-cause mortality at 30 days, and five years
- Serious adverse events. We defined serious adverse events as any untoward medical occurrence that was life-threatening, resulted in death or persistent or significant disability, or any medical event that may have jeopardised the person or required intervention to prevent it (ICH-GCP 1997). We considered all other adverse events (i.e. any medical occurrence not necessarily having a causal relationship with the treatment, yet causing a dose reduction or discontinuation of treatment) as non-serious (see below).
- Health-related quality of life. We defined health-related quality of life as any deviation from a person's usual or expected physical, emotional, and social well-being that is due to an intervention.

Secondary outcomes

- Variceal rebleed-related mortality
- Number of participants with variceal rebleeding episodes at 30-days (diagnosed by endoscopy or identification of haematemesis, melena, or gastric aspirate containing blood)
- Non-serious adverse events

Exploratory outcomes

- Number of participants who were bridged to liver transplantation and were transplanted
- Number of participants with reintervention at five years
- Irreversible shunt occlusion at five years, identified by follow-up Doppler examination or abdominal computer tomography scan and failed reintervention
- Number of participants with encephalopathy (persistent or new-onset) at five years. Encephalopathy is defined by any of the following: classical signs detected on physical examination; signs unequivocally described by person's relatives; psychometric testing; and electroencephalogram
- Number of participants with clinically significant ascites at five years (new-onset or persistent) detected clinically or radiologically

Search methods for identification of studies

Electronic searches

We performed electronic searches for relevant trials in the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud 2018; 8 March 2018); Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 2); MEDLINE Ovid (1946 to 8 March 2018); Embase Ovid (1974 to 8 March 2018); LILACS (Latin American and Caribbean HealthSciences Literature) (BIREME; 1982 to 8 March 2018); Science Citation Index Expanded (Web of Science; 1900 to 8 March 2018); and Conference Proceedings Citation Index - Science (Web of Science; 1990 to 8 March 2018) (Royle 2003). The search strategies and the time spans of the searches are listed in Appendix 1.

Searching other resources

We handsearched reference lists of identified studies for further relevant trials.

We also searched conference/meeting proceedings and abstracts published by the International Hepato-Pancreato Biliary Association (IHPBA) (1994 to 8 March 2018); the American Association for the Study of Liver Diseases (AASLD) (1994 to 8 March 2018); and other relevant organisations.

We also searched on-line trial registries such as ClinicalTrials.gov (clinicaltrials.gov), the European Medicines Agency (EMA) (ema.europa.eu), the World Health Organization, International Clinical Trials Registry Platform (who.int/ictrp), and the Food and Drug Administration (FDA; fda.gov), for ongoing or unpublished trials on 8 March 2018.

Data collection and analysis

Selection of studies

Two review authors (CJE and LP) independently screened the list of titles and abstracts retrieved by the search in order to identify potentially eligible studies. We retrieved the full-text articles of those studies deemed potentially eligible, and two review authors (CJE and LP) reviewed the full-text articles for inclusion in the review. We resolved any areas of disagreement through discussion with MB. We planned to obtain unpublished data by writing to trial authors but we could not find any unpublished data through our database search. We used a flow diagram to summarise study selection according to the PRISMA statement (Liberati 2009)

Data extraction and management

Two review authors (CJE and LP) independently extracted the following data from included trials.

- Basic characteristics of each study including: name of first author; date of trial publication; country of trial; type of institution; time from bleeding episode to randomisation; duration of maximal follow-up; inclusion and exclusion criteria; number of participants randomised; number of participants excluded; and type of interventions.
- Participant information including: age; aetiology of cirrhosis, methods for diagnosis of cirrhosis; endoscopic findings and Child-Pugh criteria.

- Outcomes: proportion of participants with events for dichotomous outcome and the mean events with standard deviation for continuous outcomes.
- Assessment of risk of bias.

Assessment of risk of bias in included studies

Two review authors (CJE and LP) independently assessed the risk of bias of each included trial using the domains as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), the Cochrane Hepato-Biliary group Module (Gluud 2018), and methodological studies (Schulz 1995; Moher 1998; Kjaergard 2001; Wood 2008; Hrobjartsson 2012; Savović 2012a; Savović 2012b; Hrobjartsson 2013; Hrobjartsson 2014a; Hrobjartsson 2014b; Lundh 2017; Savović 2018). We judged trials to be at an overall low risk of bias if they were assessed at 'low risk of bias' in all 'Risk of bias' domains. We judged trials to be at an overall high risk of bias if they were assessed to be at 'unclear risk of bias' or 'high risk of bias' in one or more of the 'Risk of bias' domains. We used the following definitions to assess the risk of bias in included trials.

Allocation sequence generation

- Low risk of bias: sequence generation was achieved using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if performed by an independent person not otherwise involved in the trial.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random. We only used such studies for the assessment of harms.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. Allocation was controlled by a central and independent randomisation unit. The allocation sequence was unknown to the investigators (e.g. the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the method used to conceal the allocation was not described so that intervention allocations may have been foreseen in advance of, or during, enrolment.
- High risk of bias: the allocation sequence was likely to be known to the investigators who assigned the participants. These studies were only considered for the assessment of harms.

Blinding of participants and personnel

- Low risk of bias (any of the following): no blinding or incomplete blinding but the review authors judged that the outcome is not likely to be influenced by lack of blinding; or blinding of participants and key study personnel ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias (any of the following): insufficient information to permit judgement of 'low risk'; or 'high risk'; or the trial did not address this outcome.
- High risk of bias (any of the following): no blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; or blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias (any of the following): no blinding of outcome assessment, but the review authors judged that the outcome measurement is not likely to be influenced by lack of blinding; or blinding of outcome assessment ensured, and it is unlikely that the blinding could have been broken.
- Unclear risk of bias (any of the following): insufficient information to permit judgement of 'low risk'; or 'high risk'; or the trial did not address this outcome.
- High risk of bias (any of the following): no blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; or blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: no missing outcome data or missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputation, were employed to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk: the trial reported the predefined outcomes in the method section. If the original trial protocol was available; the outcomes should have been those called for in that protocol. If the trial protocol was obtained from a trial registry (e.g. www.clinicaltrials.gov), the outcomes sought should have been those enumerated in the original protocol if the trial protocol was registered before or at the time that the trial was begun. If the trial protocol was registered after the trial was begun, we will not consider those outcomes to be reliable.

- Unclear risk: the study authors did not report all predefined outcomes fully, or it is unclear whether the study authors recorded data on these outcomes.
- High risk: the study authors did not report one or more predefined outcomes.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that could manipulate the trial design, conductance, or results of the trial. (Industry-sponsored trials overestimate the efficacy by about 25%) (Lundh 2017).
- Unclear risk of bias: the trial may or may not be free of for-profit bias as the trial did not provide any information on clinical trial support or sponsorship.
- High risk of bias: the trial was sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other factors that could put it at risk of bias.
- Unclear risk of bias: the trials may or may not have been free of other factors that could put it at risk of bias.
- High risk of bias: there were other factors in the trial that could put it at risk of bias.

Overall risk of bias

We judged trials to be at an overall low risk of bias if they were assessed at 'low risk of bias' in all 'Risk of bias' domains. We judged trials to be at an overall high risk of bias if they were assessed to be at 'unclear risk of bias' or 'high risk of bias' in one or more of the 'Risk of bias' domains.

Measures of treatment effect

We measured intervention effects for dichotomous outcomes using risk ratio (RR) with 95% confidence intervals (CIs), and for continuous outcomes we planned to use mean difference (MD) with 95% CIs. We planned to report Trial Sequential Analysis-adjusted confidence intervals.

Unit of analysis issues

The unit of analysis was trial participants as randomised to the trial groups. We did not expect that cross-over trials or cohort, cluster-randomised trials were performed.

Dealing with missing data

We performed an intention-to-treat analysis.

Assessment of heterogeneity

We assessed heterogeneity between the trials using the Chi^2 test and I^2 test. The degree of heterogeneity observed was measured using the I^2 statistic (Higgins 2002; Sterne 2011). The values of the I^2 statistic were:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: represent considerable heterogeneity.

We considered an I^2 statistic above 50% as significant, and we explored the possible cause of heterogeneity further in a sensitivity analysis.

Assessment of reporting biases

We planned to investigate reporting bias by visual inspection of funnel plot asymmetry if we identified at least 10 trials. For dichotomous outcomes we planned to use the Harbord test for asymmetry (Harbord 2006). For continuous outcome we planned to use the regression asymmetry test (Egger 1997), and the adjusted rank correlation test (Begg 1994).

Data synthesis

Meta-analysis

We performed meta-analysis according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), and the Cochrane Hepato-Biliary Module (Gluud 2018). We meta-analysed data according to the eight-step procedure for validation of meta-analytic results in systematic reviews, as suggested by Jakobsen and colleagues (Jakobsen 2014). We used the software packages Review Manager 5 provided by Cochrane (Review Manager 2014), and Trial Sequential Analysis version 0.9.5.10 Beta provided by the Copenhagen Trial Unit for our data analysis (Thorlund 2011; TSA 2011). We used both the fixed-effect and the random-effects meta-analyses, and presented the data with the most conservative estimate of the two. The most conservative estimate of the two is the one closest to 1 for dichotomous outcomes or 0 (zero) for continuous outcomes (Jakobsen 2014). If the two point estimates were equal, we used the estimate with the widest CI as our main result of the two analyses (Jakobsen 2014). We presented heterogeneity using the I^2 statistic (Higgins 2002). Where data are only available from one trial, we planned to use Fischer's test for dichotomous data (Fisher 1922), and used Student's t-test for continuous data to present the results in a narrative way (Student 1908).

Trial Sequential Analysis

Cumulative meta-analysis can introduce random error because of sparse data and repetitive testing of accumulating data (Brok

2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Higgins 2011; Wetterslev 2017); hence we used Trial Sequential Analysis in this review to control for random errors (Thorlund 2011; TSA 2011). We calculated the diversity-adjusted required information size (DARIS) for all outcomes in order to control for random errors (Wetterslev 2008; Wetterslev 2009). The DARIS calculation took into account the following: control group event proportion observed in the meta-analysis; a plausible relative risk reduction of 20%; a risk of type I error of 2.5% due to three primary outcomes and three secondary outcomes; a risk of type II error of 10% (Castellini 2017; Wetterslev 2017); and the adjusted diversity from the meta-analysis (Wetterslev 2008; Wetterslev 2009; Jakobsen 2014; Wetterslev 2017). We also planned to calculate and report the Trial Sequential Analysis-adjusted CI (Thorlund 2011). We assumed that testing for statistical significance was performed with each new trial added to the trial sequential meta-analysis. On the basis of the calculated DARIS we planned to construct trial sequential monitoring boundaries. If the Z-curve crossed the trial sequential monitoring boundary for benefit or harm before the DARIS was reached, we planned to conclude evidence of benefit or harm of the intervention provided that bias could be excluded. In contrast, if the boundary was not surpassed, we planned to conclude the need to conduct further trials in order to attain the true intervention effect. However, where the Z-curve crossed the monitoring boundary for futility, we planned to conclude non-superiority, or non-inferiority of intervention, or both (Thorlund 2011; Wetterslev 2008; Wetterslev 2017).
A more detailed description of Trial Sequential Analysis can be found at www.ctu.dk/tsa/ (Thorlund 2011).

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.

- Trials at low risk of bias compared to trials at high risk of bias.
- Child-Pugh classes A compared to class B compared to class C (Child 1964); or model for end-stage liver disease score less than or equal to 18 compared to greater than 18 (Dhiman 2007).
- Selective shunts versus TIPS compared to non-selective shunts versus TIPS.
- Surgical shunts versus TIPS with bare stent compared to surgical shunts versus TIPS with covered stents.
- Surgical shunts by experienced surgeon compared to TIPS by experienced radiologist.

Sensitivity analysis

We planned sensitivity analysis of search methods for inclusion of trials; exclusion of trials; type of data analysed; process of data analysis; and measurement of intervention outcomes at six and 12 months. We also planned to compare our GRADE imprecision assessments to that conducted with Trial Sequential Analysis (Jakobsen 2014).

'Summary of findings' table

We designed one 'Summary of findings' table for our review comparison using GRADEpro software (community.cochrane.org/tools/review-production-tools/gradepro-gdt). Using GRADE (Balshem 2011; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c; Guyatt 2011d; Guyatt 2011e; Guyatt 2011f; Guyatt 2011g; Guyatt 2013a; Guyatt 2013b; Guyatt 2013c; Guyatt 2013d; Mustafa 2013; Guyatt 2017), we graded the certainty of evidence for our Primary outcomes: all-cause mortality; serious adverse events (reported individually as reintervention, irreversible shunt occlusion, and encephalopathy following ICH-GCP 1997 definition of serious adverse events); and health-related quality of life. We also graded the certainty of evidence for variceal rebleeding as Secondary outcomes. We based the grading of the certainty of evidence on five domains: risk of bias; indirectness of evidence (population, intervention, control, outcomes); unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses); imprecision of result, and a high probability of publication bias. We defined the levels of evidence as 'high', 'moderate', 'low', or 'very low'. We followed the recommendations of section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).
These grades are defined as follows.

- **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect
- **Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
- **Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
- **Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

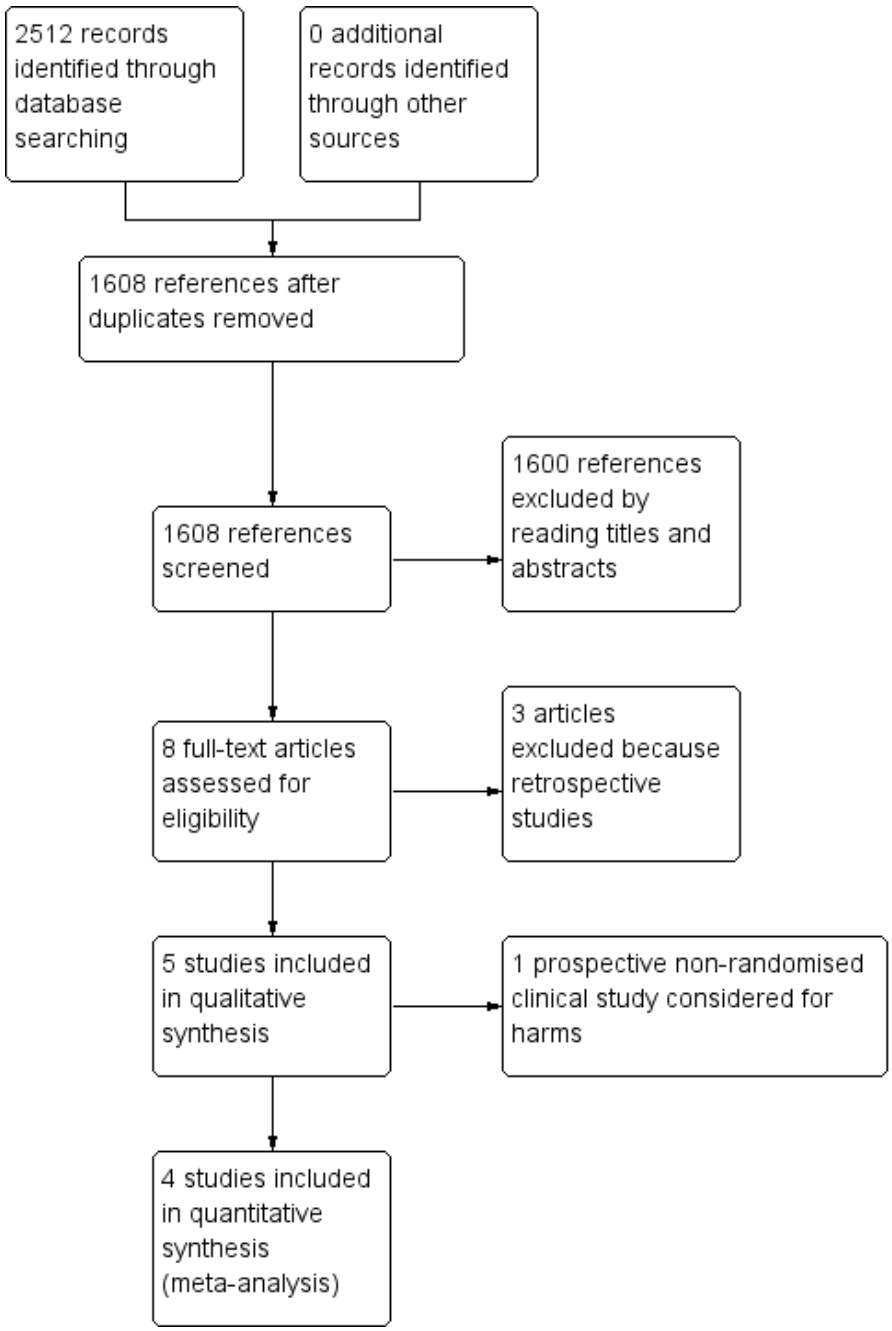
RESULTS

Description of studies

We identified 2512 references through the electronic database searches (Figure 1). After removing 904 duplicates, we were left with 1608 references that we screened by reading through their titles and abstracts, we excluded 1600 references. Of the remaining eight full-text articles, three were retrospective studies (Faust 1997; Zacks 1999; Helton 2001), and one was a prospective non-randomised study that we considered for harms (Khaitiyar 2000) (Characteristics of excluded studies). We selected four studies for meta-analysis (Henderson 2006; Orloff 2012; Rosemurgy 2012;

Orloff 2015). We identified no other references of interest through other sources or through screening the reference lists of the identified randomised clinical trials.

Figure 1. Study flow diagram. A total of 2512 records identified through electronic database search. After removing 904 duplicates, a total of 1608 references were screened for titles and abstracts, eight articles were selected for full-text review. Of these, three articles were retrospective studies and one article was a prospective non-randomised study. Four studies were selected for final meta-analysis.



Included studies

The four randomised clinical trials that we selected for meta-analysis are presented in Characteristics of included studies tables. Henderson 2006, Orloff 2012, Rosemurgy 2012, and Orloff 2015 randomised 496 participants, irrespective of sex, who were diagnosed with variceal haemorrhage secondary to liver cirrhosis into two interventions (surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt (TIPS)). In all the trials, diagnosis of liver cirrhosis was established by clinical and laboratory findings, then confirmed by liver biopsy at time of intervention. Participants in Henderson 2006 were Child-Pugh class A or B liver disease. Orloff 2012, Rosemurgy 2012, and Orloff 2015 included participants with Child-Pugh class A, B, or C liver disease. The predominant cause of variceal haemorrhage in all trials was alcohol-related liver cirrhosis. All the trials were conducted in the USA, and an intention-to-treat principle was used for data analyses. Henderson 2006 randomised 140 participants into a selective surgical shunt (distal splenorenal shunt; DSRS) versus TIPS. Orloff 2012 randomised 154 participants with oesophageal variceal haemorrhage into a non-selective surgical shunt (portocaval shunt) versus TIPS. Rosemurgy 2012 randomised 132 participants into a selective surgical shunt (8 mm H-graft shunt) versus TIPS, while Orloff 2015 randomised 70 participants with gastric variceal haemorrhage into a non-selective surgical shunt (portocaval shunt) versus TIPS. The mean age of the participants in Henderson 2006 was 53 ± 10 years, in Orloff 2012 it was 49 years, in Rosemurgy 2012 it was 55 ± 12 years, and in Orloff 2015 it was 50 years. Participants were followed up for a maximum period of eight years in Henderson 2006, 15 years in Orloff 2012, 18 years in Rosemurgy 2012, and 10 years in Orloff 2015. All the trials were funded by institutional grants.

Excluded studies

We excluded four studies from this meta-analysis with reasons (Faust 1997; Zacks 1999; Khaitiyar 2000; Helton 2001) (Characteristics of excluded studies). Of these, three were retrospective studies (Faust 1997; Zacks 1999; Helton 2001), while one was a prospective non-randomised study that grouped participants into distal splenorenal shunt compared to TIPS, that we considered only for harms (Khaitiyar 2000).

Risk of bias in included studies

The risks of bias in included trials have been summarised in Figure 2 and Figure 3. We considered all the trials to be at overall high risk of bias, due to lack of blinding of participants, personnel, or outcome assessors.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

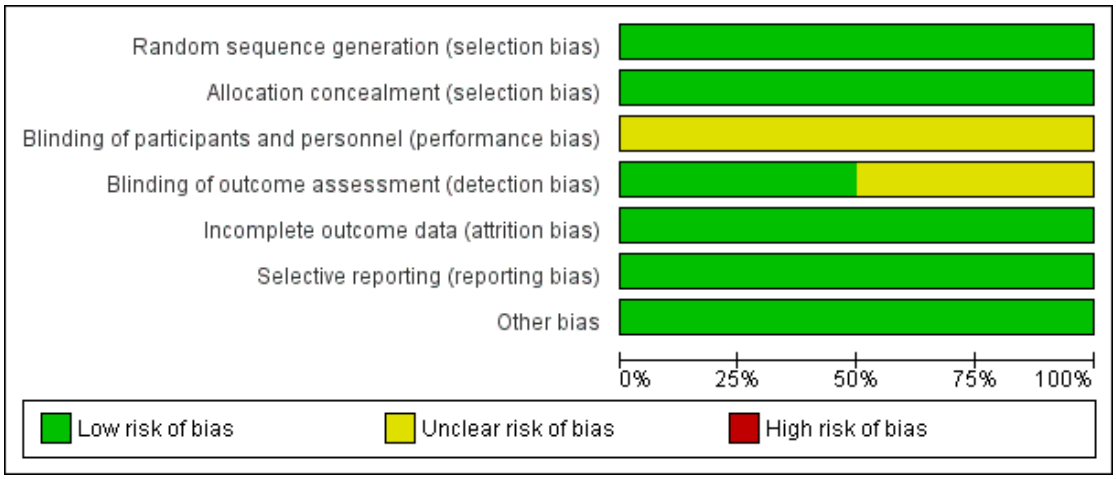
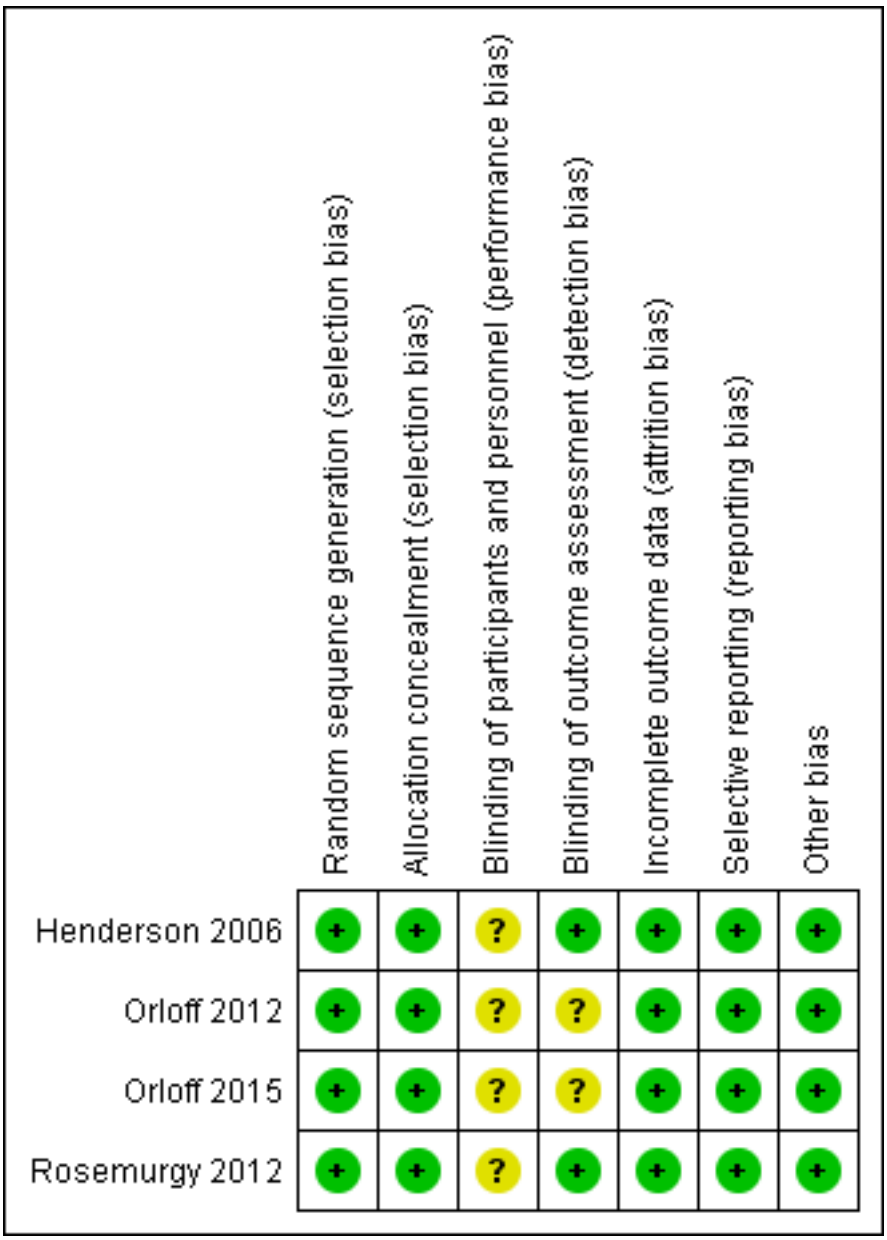


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation (selection bias)

We considered random sequence generation and allocation concealment to be adequate for all four trials included in our meta-analysis. So review authors judged all four trials at low risks of selection bias.

Blinding (Performance and detection bias)

Participants and personnel were not blinded in any of the four trials (Henderson 2006; Orloff 2012; Orloff 2015, Rosemurgy 2012). Given the nature of the interventions, it was unrealistic to blind participants and personnel to the interventions. Lack of blinding in randomised clinical trials could overestimate intervention effects (Savović 2018). Given that in all four trials most outcomes were objective we judged all four trials to be at unclear risk of performance bias. We judged two trials that blinded outcome assessors to be at low risk of detection bias (Henderson 2006; Rosemurgy 2012). We judged two other trials that did not specify blinding of outcome assessors to be at unclear risk of detection bias (Orloff 2012; Orloff 2015).

Incomplete outcome data (attrition bias)

We observed that data analyses in all four trials were performed using an intention-to-treat principle, so we judged all trials at low risk of attrition bias.

Selective reporting (reporting bias)

We found published protocols for three trials in the clinicaltrials.gov registry (Henderson 2006; Orloff 2012; Orloff 2015). We could not find a published protocol for one trial but all prespecified outcomes in the methods were reported (Rosemurgy 2012). Review authors judged all trials to be at low risk of reporting bias.

Other potential sources of bias

For-profit bias

We assessed all four trials for possible sources of funding and it was clear they were all funded by institutional grants. So we judged all trials at low risk for-profit bias.

Effects of interventions

See: **Summary of findings for the main comparison** Surgical portosystemic shunts compared to transjugular intrahepatic portosystemic shunt (TIPS) for variceal haemorrhage

Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt

All-cause mortality

Four trials provided data on all-cause mortality (Henderson 2006; Orloff 2012; Orloff 2015; Rosemurgy 2012). We have analysed all-cause mortality at 30 days and five years. We found no evidence of a difference in all-cause mortality at 30 days between surgical shunts (analysed together) versus TIPS (risk ratio (RR) 0.94, 95% confidence interval (CI) 0.44 to 1.99; participants = 496; studies = 4; I^2 = 64%; Analysis 1.1). We found evidence suggesting a difference in all-cause mortality at five years between surgical shunts (analysed together) versus TIPS (RR 0.61, 95% CI 0.42 to 0.90; participants = 496; studies = 4; I^2 = 64%; Analysis 1.2).

Serious adverse events

None of the trial authors reported adverse events as a composite outcome. Following the ICH-GCP 1997 definition of serious adverse events, we determined that, mortality, reinterventions, irreversible shunt occlusion, and encephalopathy were serious adverse events, and we presented data individually.

Health-related quality of life

Two trials provided data on health-related quality of life (Henderson 2006; Orloff 2015). Henderson 2006 used Short Form (SF)-36 questionnaire and reported no difference in the median score for health-related quality of life between surgical shunts versus TIPS. Orloff 2015 defined health-related quality of life as: freedom from encephalopathy, long-term shunt patency, abstinence from alcohol, improvement in liver function, improvement in Child-Pugh class, return to work or housekeeping, and avoidance of the need for liver transplantation. We could not perform a meta-analysis for this outcome. Based on these criteria, review authors concluded improved health-related quality of life in the surgical shunts group compared with the TIPS group.

Variceal rebleed-related mortality

Three trials provided data on variceal rebleed-related mortality (Henderson 2006; Orloff 2012; Rosemurgy 2012). We found evidence of a difference in variceal rebleed-related mortality at 30 days between surgical shunts (analysed together) versus TIPS (RR 0.18, 95% CI 0.04 to 0.82; participants = 426; studies = 3; I^2 = 0%; Analysis 1.3).

Number of participants with variceal rebleeding episodes

Four trials provided data on variceal rebleeding episodes (Henderson 2006; Orloff 2012; Rosemurgy 2012; Orloff 2015). We considered variceal rebleeding occurring within 30 days of intervention as related to failure of intervention rather than disease progression. We found evidence suggesting a difference in variceal rebleeding episodes at 30 days between surgical shunts (analysed together) versus TIPS (RR 0.18, 95% CI 0.07 to 0.49; participants = 496; studies = 4; I^2 = 0%; Analysis 1.4).

Non-serious adverse events

None of the four trials provided data on adverse events as a composite outcome.

Number of participants bridged to liver transplantation and were transplanted

We planned to report the number of participants who were bridged to liver transplantation and were transplanted. None of the trials bridged participants to liver transplantation.Two trials provided data only for participants who received liver transplantation as a definitive therapy (Henderson 2006; Rosemurgy 2012). We found no evidence of a difference in number of participants who received liver transplantation as a definitive therapy at 10 years between selective shunts versus TIPS (RR 0.46, 95% CI 0.13 to 1.65; participants = 272; studies = 2; I^2 = 33%; Analysis 1.5).

Number of participants with reintervention

All four trials provided data on number of participants who required reintervention at five years. We found evidence of a difference in number of participants with reintervention at five years between surgical shunts (analysed together) versus TIPS (RR 0.13, 95% CI 0.06 to 0.28; participants = 496; studies = 4; I^2 = 42%; Analysis 1.6).

Irreversible shunt occlusion

All four trials provided data on irreversible shunt occlusion at five years. We found evidence of a difference in number of participants with irreversible shunt occlusion at five years between surgical shunts (analysed together) versus TIPS (RR 0.14, 95% CI 0.04 to 0.51; participants = 496; studies = 4; I^2 = 59%; Analysis 1.7).

Number of participants with encephalopathy

All four trials provided data on persistent or new-onset encephalopathy at five years postintervention. We found no evidence of a difference in number of participants with persistent or new-onset encephalopathy at five years (RR 0.56, 95% CI 0.27 to 1.16; participants = 496; studies = 4; I^2 = 79%; Analysis 1.8).

Number of participants with clinically significant ascites

Two trials provided data on persistent or new-onset ascites at five years (Henderson 2006; Rosemurgy 2012). We found no evidence of a difference in persistent or new-onset ascites at five years between selective shunts versus TIPS (RR 0.93, 95% CI 0.60 to 1.44; participants = 272; studies = 2; I^2 = 12%; Analysis 1.9).

Subgroup analysis

We performed a subgroup analysis of selective shunts versus TIPS compared to non-selective shunts versus TIPS for all outcomes. We observed no change in our overall estimates of all-cause mortality at 30 days. The test for subgroup difference showed no difference for all-cause mortality at 30 days, P = 0.19 (Analysis 1.1). We also observed no subgroup difference in variceal rebleed-related mortality, P = 0.51 (Analysis 1.3); variceal rebleeding, P =0.72 (Analysis 1.4); reinterventions, P = 0.17 (Analysis 1.6); and irreversible shunt occlusion, P = 0.79 (Analysis 1.7). We observed a subgroup difference in estimates for all-cause mortality at five years, P = 0.01 (Analysis 1.2); and encephalopathy, P = 0.0003 when selective shunts versus TIPS analysed separately was compared to non-selective shunts versus TIPS analysed separately (Analysis 1.8). We observed that in performing subgroup analysis of selective shunts versus TIPS compared to non-selective shunts versus TIPS, the significant heterogeneity observed in estimates of all-cause mortality at 30 days and five years; irreversible shunt occlusion, and encephalopathy were eliminated. We also performed a subgroup analysis of survival at five years for Child-Pugh risk class A, versus class B, versus class C between surgical shunts compared with TIPS. Three trials provided data on survival based on Child-Pugh risk classes (Orloff 2012; Rosemurgy 2012; Orloff 2015). We found no evidence of a difference in survival at five years between surgical shunts versus TIPS for participants in Child-Pugh class A versus B or C from two trials (Orloff 2012; Orloff 2015; Analysis 1.10). We did not include Rosemurgy 2012 in our subgroup analysis of survival at five years for Child-Pugh risk class as the trial authors provided data as mean survival in months. Due to few trials we could not conduct the other prespecified subgroup analyses.

Sensitivity analysis

We investigated the source of significant heterogeneity in our estimates of all-cause mortality (at 30 days and 5 years), and encephalopathy by excluding from our analysis two trials from the same authors. We observed that by doing this, the significant heterogeneity that occurred in our effect estimates was eliminated. Due to only four included trials, we did not perform planned sensitivity analysis of search methods for inclusion of trials; exclusion of trials; type of data analysed; process of data analysis; and measurement of intervention outcomes at six and 12 months.

Trial Sequential Analysis

We performed Trial Sequential Analysis for all our review outcomes. Due to few included trials with small sample sizes, the alpha spending boundary could not be drawn for all-cause mortality at 30 days, variceal rebleed-related mortality, number of participants who received liver transplantation, encephalopathy, and ascites. We calculated diversity-adjusted required information size (DARIS) by taking into consideration the control group event proportion observed in the meta-analysis; a plausible relative risk reduction of 20%; a risk of type I error of 2.5% due to three primary outcomes and three secondary outcomes; a risk of type II error of 10%; and the adjusted diversity from the meta-analysis. We calculated a DARIS of 3400 participants for all-cause mortality at five years (Figure 4); 8304 participants for rebleeding episodes (Figure 5); 2594 for number of participants with reinterventions (Figure 6); and 7438 for irreversible shunt occlusion. Due to few trials with small sample sizes, the cumulative Z-curves did not cross the alpha spending boundaries for all-cause mortality, rebleeding, reinterventions, and shunt occlusion, suggesting the need to conduct further trials to attain the true intervention effect.

Figure 4. Trial Sequential Analysis for all-cause mortality at 5 years calculated based on control event rate of 55%; a RRR of 20%; a type I error of 2.5%, a type II error of 10%; and diversity of 70%. The DARIS of 3400 was not achieved and Z-curve did not cross the alpha spending boundary, (RR 0.61, alpha spending boundary adjusted CI 0.13 to 2.86).

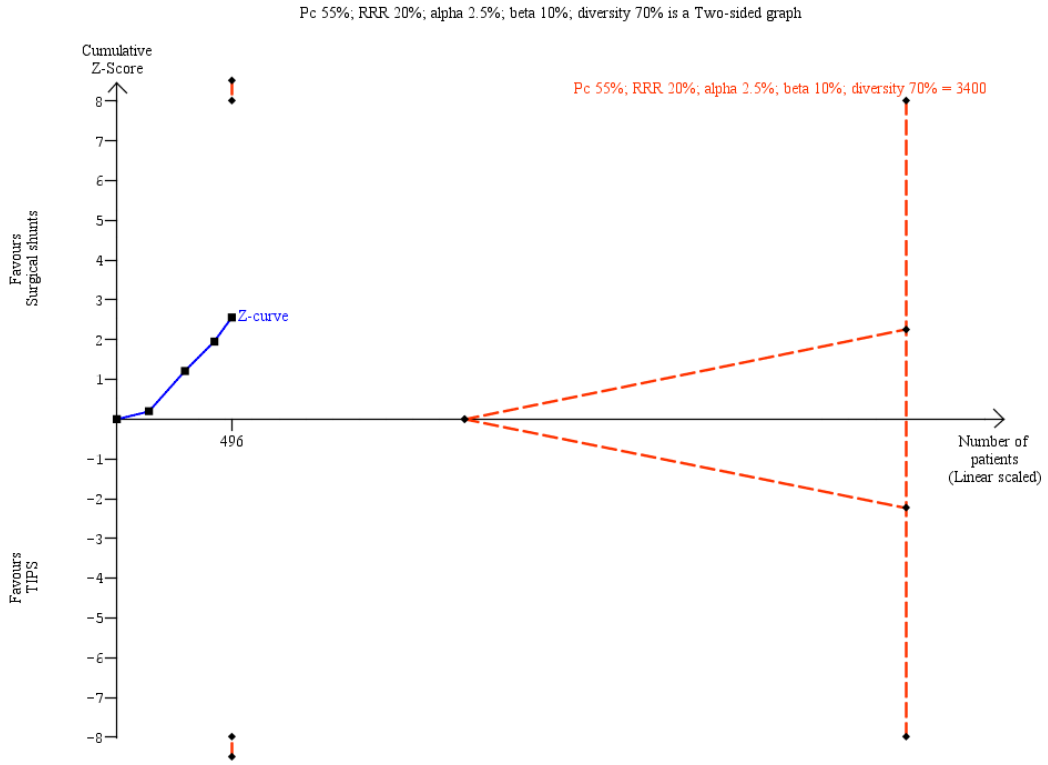


Figure 5. Trial Sequential Analysis for variceal rebleeding episodes at 30 days is calculated based on control event rate of 12%; a RRR of 20%; a type I error of 2.5%, a type II error of 10%; and diversity of 0%. The DARIS of 8304 was not achieved and Z-curve did not cross the alpha-spending boundary (RR 0.18, alpha-spending boundary-adjusted CI 0.00 to 10.31).

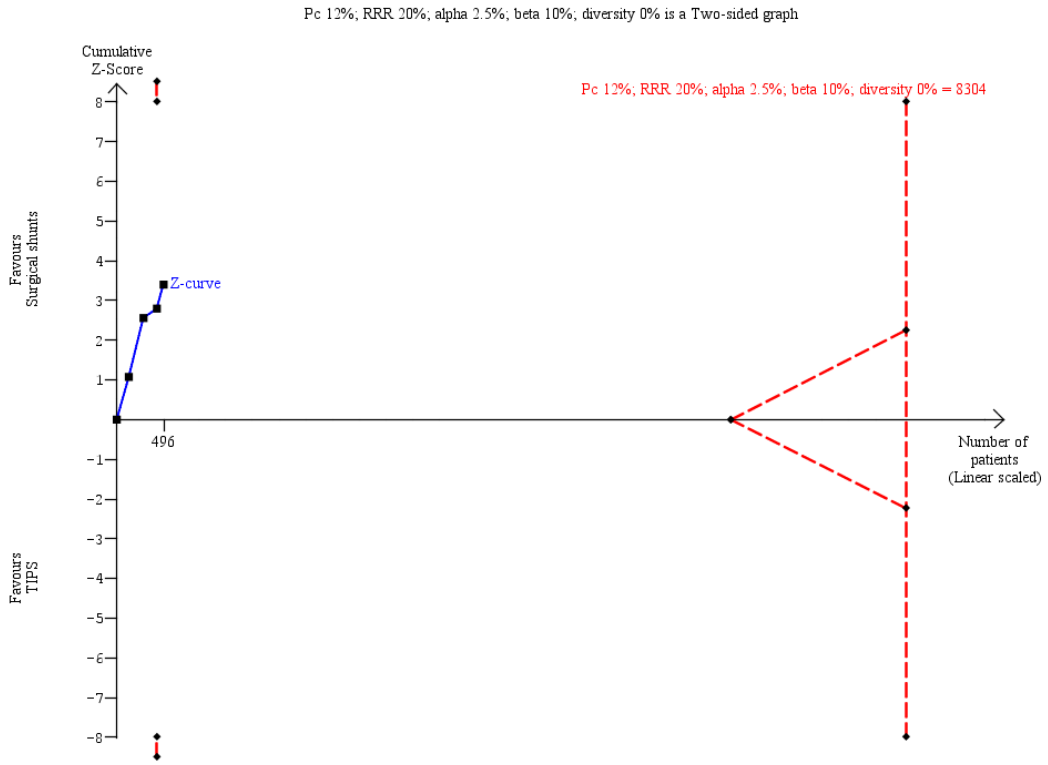
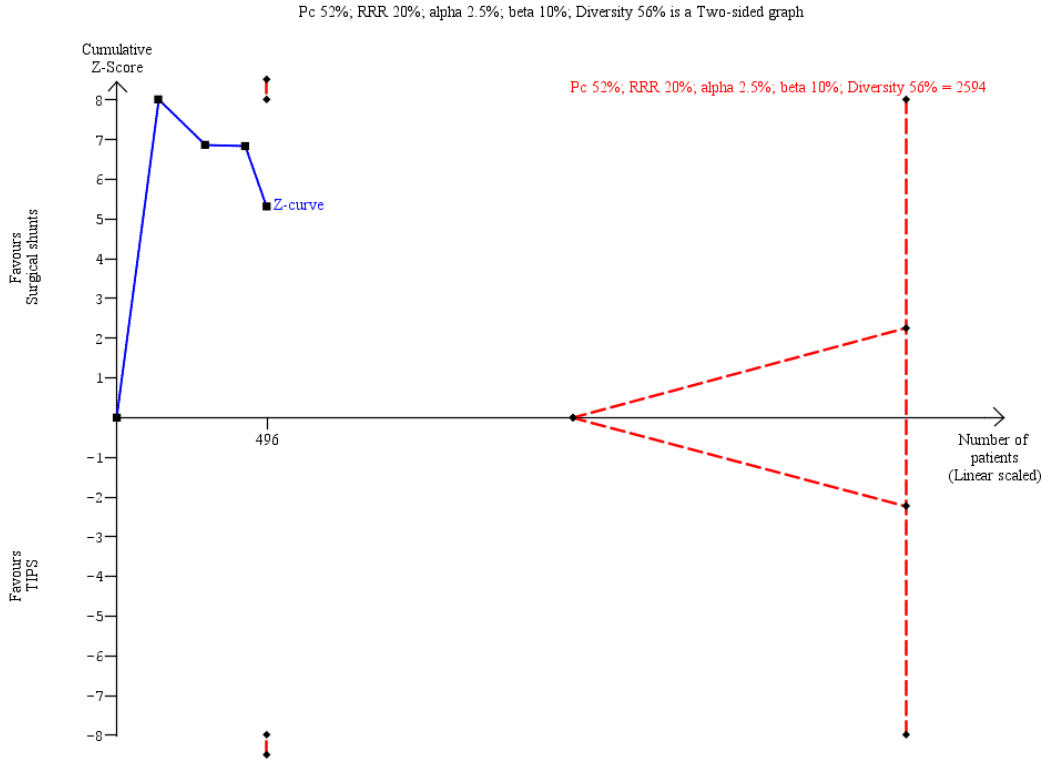


Figure 6. Trial Sequential Analysis for number of participants with reinterventions at 5 years is calculated based on control event rate of 52%; a RRR of 20%; a type I error of 2.5%, a type II error of 10%; and diversity of 56%. The DARIS of 2594 was not achieved and Z-curve did not cross the alpha-spending boundary (RR 0.13, alpha-spending boundary-adjusted CI 0.01 to 2.80).



Certainty of the evidence

We have presented the certainty of the evidence in Summary of findings for the main comparison. We judged the certainty of the evidence for all-cause mortality (at 30 days and 5 years), irreversible shunt occlusion, and encephalopathy as very low because of overall high risk of bias (downgraded one level due to lack of blinding), inconsistency (downgraded one level due to heterogeneity); imprecision (downgraded two levels due to small sample sizes and few events); and publication bias (downgraded one level due to few trials). We judged the certainty of the evidence for variceal rebleeding and reinterventions as very low because of overall high risk of bias (downgraded one level due to lack of blinding), imprecision (downgraded one level due to small sample sizes and few events), and publication bias (downgraded one level due to few trials).

DISCUSSION

Summary of main results

We identified only four small single-centre randomised clinical trials at high risk of bias that compared surgical portosystemic shunts with transjugular intrahepatic portosystemic shunt for treatment of refractory or recurrent variceal haemorrhage in 496 people with cirrhotic portal hypertension. The trials were all conducted in the USA. Two of the trials compared selective portosystemic shunts (distal splenorenal shunt (DSRS) and 8-mm H-graft stent) to TIPS in elective setting. The other two trials compared non-selective shunt (portocaval shunt) to TIPS in emergency setting. We found no evidence of a difference between surgical shunt versus TIPS for all-cause mortality at 30 days and encephalopathy at five years of follow-up. There appeared to be very low-certainty of evidence suggesting an increase in the development of all-cause mortality at five years; variceal-bleed related mortality; variceal rebleeding;

reintervention; and irreversible shunt occlusion in the TIPS group compared with surgical shunts (considered together). Two trials provided data on health-related quality of life that appeared to suggest better health-related quality of life after portocaval shunts compared with TIPS. We identified one small prospective non-randomised study from India, including 67 participants with cirrhotic portal hypertension that received DSRS (n = 32); and TIPS (n = 35). This study was considered for harms (Khaitiyar 2000; Table 1). The result from this study appears to suggest an increase in the development of adverse events with TIPS compared to surgical shunts. Our sensitivity analyses showed that significant heterogeneity observed in effect estimates for all-cause mortality (at 30 days and five years), and encephalopathy corrected when two trials conducted by the same authors were eliminated in the meta-analyses. This could be due to the type of surgical shunts used and the emergency setting that these shunts were placed. Because of the very low-certainty of the evidence for all outcomes encompassing high risk of bias (due to lack of blinding), inconsistency (due to heterogeneity), imprecision (due to small sample size and few events), and publication bias (due to few trials reporting outcomes), we are uncertain in our estimates of intervention effects. Furthermore, the small sample sizes and few events did not allow us to produce meaningful trial sequential monitoring boundaries, suggesting a plausible random error in our estimates.

Overall completeness and applicability of evidence

Our confidence in estimates of intervention effects is very low because of a small number of available trials including few participants, and risk of random error in our estimates. The participants included in all the trials had cirrhotic portal hypertension confirmed by histopathological investigation and so the findings of this review are applicable to people with variceal haemorrhage due to cirrhotic portal hypertension. Two of the trials included participants who received interventions in the emergency setting (the intervention was performed within 24 hours of contact with the trial team). It appeared that the results of these two trials introduced heterogeneity in our estimates. Considering that these trials were conducted by the same authors with vast experience in emergency portocaval shunts, their results may not be applicable in a different setting. All the trials were performed at the time when TIPS with polytetrafluoroethylene (PTFE)-covered stents were not common. So the findings of this review may not be applicable to TIPS with PTFE-covered stents which have been shown to improve patency and require less interventions than TIPS with bare metal stents (Clark 2011; Perarnau 2014).

Certainty of the evidence

We judged the four trials at high risk of bias. There was significant heterogeneity in the analysis of all-cause mortality and encephalopathy, mainly because of two trials from the same authors that compared non-selective surgical shunt versus TIPS in the emergency setting.

We downgraded the certainty of the evidence for all-cause mortality at 30 days and five years, irreversible shunt occlusion, and encephalopathy to very low because of high risk of bias (due to lack of blinding), inconsistency (due to heterogeneity), imprecision (due to small sample sizes of the individual trials and few events), and publication bias (few trials reporting outcomes). We graded the certainty of the evidence for variceal rebleeding and reintervention as very low because of high risk of bias (due to lack of blinding), imprecision (due to small sample sizes of the individual trials and few events), and publication bias (few trials reporting outcomes).

Potential biases in the review process

We performed an extensive search of databases according to the recommendation of Cochrane. We searched electronic databases for any randomised clinical trials that had included participants with variceal haemorrhage due to non-cirrhotic portal hypertension. We considered participants treated with surgical portosystemic shunts or TIPS either in the elective or emergency setting. Although our search strategies were very broad, we only retrieved four randomised clinical trials that fulfilled the inclusion criteria of our review. A reason for the paucity of the trials of interest to our review could be the wide availability and popularity of non-surgical interventions, such as endoscopy. Among the retrieved study references was one small size prospective non-randomised study that included the following harms: all-cause mortality, rebleed-related mortality, variceal rebleeding, shunt occlusion, reinterventions, encephalopathy, and ascites. The respective references to the included trials did not provide any further references to the topic of our review. We found no relevant observational studies reporting on harms among the search result for randomised clinical trials, and this is a known limitation for meta-analyses with randomised clinical trials alone. Because of the very small number of trials with small sizes, we could not produce meaningful Trial Sequential Analysis monitoring boundaries, and this underlines a high risk of random error in our review analysis. We could not construct funnel plots in order to look for publication bias. Thus, the risk of random errors because of paucity of trials and very low-certainty of the evidence contributed to the uncertainty in our review findings.

Agreements and disagreements with other studies or reviews

We found two systematic reviews that compared surgical portosystemic shunts versus TIPS for treatment of variceal haemorrhage

in people with cirrhotic portal hypertension (Clark 2010; Huang 2015). Clark 2010 included 314 participants of Child-Pugh risk class A and class B from four studies in their review. Two of the studies were randomised clinical trials while the other two were a prospective non-randomised study and a retrospective study. Although the authors reported their findings of two-year follow-up, there was no difference in all-cause mortality at 30 days between surgical shunts compared with TIPS. There was an increase in all-cause mortality at two years, and the number of shunt failures in the TIPS group compared with surgical shunts is very similar to our systematic review analysis. Huang 2015 included 493 participants, irrespective of Child-Pugh risk class, from four studies in their review. One of the studies was a prospective non-randomised study and the other three were randomised clinical trials included in our review. There was a significant heterogeneity in their analyses similar to our review, and the authors did not grade the quality of their evidence. The results of their meta-analyses showed there was no evidence of a difference in mortality at 30 days between surgical shunts and TIPS. There was evidence of an increase in occurrence of variceal rebleeding, shunt occlusion, and encephalopathy in the TIPS group compared with surgical shunt that is very similar to our review findings.

AUTHORS' CONCLUSIONS

Implications for practice

We found evidence suggesting that surgical portosystemic shunts may have benefits over transjugular intrahepatic portosystemic shunt (TIPS) for treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension. Given the very low-certainty of the available evidence and risk of random error in our analyses, we have very little confidence in our review findings.

Implications for research

Future randomised clinical trials including a large number of participants are required to address bias issues as well as play of chance due to random errors. Such trials should be multicentred in order to achieve sufficient statistical power to produce true intervention effects. TIPS intervention should include covered stents to assess benefit or harm of TIPS with covered stents compared to TIPS with bare metal stents in subgroup analyses. These trials should be registered and be given open access (Skoog 2015), with their protocols drafted according to the SPIRIT statement (Chan 2013), and their reporting according to the CONSORT statement (Schulz 2010).

ACKNOWLEDGEMENTS

S Khan et al. drafted a protocol in 1998 for this review title (Khan 1998). We used the original protocol as the starting point for the current review.

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Peer reviewers: Liu Fuquan, China; Jean-Marc Perarnau, France; Naimish Mehta, India.

Contact editors: Stefano Trastulli, Italy.

Sign-off editor: Christian Gluud, Denmark.

REFERENCES

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

Henderson 2006

Methods	Randomised clinical trial (DIVERT Study)
Participants	Country: USA Number randomised: 140 participants Analysis: intention-to-treat Age: mean age 53 ± 10 years for DSRS, and 52 ± 1 years for TIPS Initial endoscopic assessment, including therapy before randomisations Duration of follow-up: 8 years **Inclusion criteria** • Endoscopically proven variceal bleeding secondary to liver cirrhosis of any aetiology • Diagnosis of liver cirrhosis by clinical and laboratory data • Child-Pugh class A or B cirrhosis • Suitability for intervention confirmed by ultrasound and angiography • Failed endoscopic therapy (sclerotherapy or banding), defined as bleeding sufficient to produce hypotension, or transfusion requirement of three units per bleed, or recurrent bleeds not requiring transfusion, or participants who are not candidates for endoscopic therapy **Exclusion criteria** • Aetiology of varices other than cirrhosis • Bleeding from portal hypertensive gastropathy • Prior shunt procedure • Medically intractable ascites • Renal insufficiency with creatinine greater than 2 • Age less than 18 years • Portal vein thrombosis • Polycystic liver disease • Child-Pugh score greater than 9 • Right heart failure Prominent cause of liver cirrhosis: alcohol-related
Interventions	Distal splenorenal shunt (n = 73) versus TIPS (n = 67) Only uncovered stents of variable sizes from 8 mm to 12 mm used for TIPS Intervention performed within five days of randomisation
Outcomes	**Primary outcomes**: variceal rebleeding, and encephalopathy **Secondary outcomes**: mortality, ascites, shunt stenosis and thrombosis, need for liver transplantation, liver tests, quality of life, and cost
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Henderson 2006 (*Continued*)

Random sequence generation (selection bias)	Low risk	Patients were randomised. 'Randomisation' was controlled by a central data co-ordinating centre
Allocation concealment (selection bias)	Low risk	Treatment allocation achieved with use of "a variable 2 or 4 permuted block size design, stratifying by Child-Pugh class A and B, and alcoholic and nonalcoholic patients". By randomly varying the block sizes, treatment allocation could not be predicted towards the end of a block
Blinding of participants and personnel (performance bias) All-cause mortality; serious adverse events, variceal rebleed-related mortality, variceal rebleeding, non-serious adverse events	Unclear risk	Participants and personnel were not blinded to the interventions received. Given the nature of the interventions, it was unrealistic to blind participants and study personnel to the intervention received
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The Clinical Endpoint Review Committee received summary data on all outcomes in a blinded manner from the data co-ordinating centre. Blinding of outcome assessors judged as adequate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was by intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Trial protocol was published (NCT00006161). Reported all protocol predefined outcomes
Other bias	Low risk	Study sponsored by institutional grant

Rosemurgy 2012

Methods	Randomised clinical trials
Participants	Country: USA Number randomised: 132 participants Intention-to-treat analysis Mean age 54 ± 14 years for H-shunt and 55 ± 12 years for TIPS Maximal duration of follow-up: 18 years **Inclusion criteria** Child-Pugh A, B, C cirrhosis and portal hypertension with variceal or portal gastropathy bleeding who have failed or not candidates for endoscopic therapy. Median MELD score 13 **Exclusion criteria** Participants with unfavourable anatomy or unlikely to survive because of profound ill-

Rosemurgy 2012 (*Continued*)

	health or hepatic dysfunction were excluded
Interventions	TIPS (66), H-graft shunt 8mm (66) Intervention performed as a definitive procedure, never as a bridge to transplantation
Outcomes	Mortality, variceal rebleeding, shunt occlusion, liver failure requiring transplantation, inability to accomplish shunting, ascites, and encephalopathy
Notes	Shunt failure was referred to as mortality, variceal rebleeding, irreversible shunt occlusion, liver failure requiring transplantation, and inability to accomplish shunting

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerised randomisation by parallel allocation
Allocation concealment (selection bias)	Low risk	Computer generated sequential allocation
Blinding of participants and personnel (performance bias) All-cause mortality; serious adverse events, variceal rebleed-related mortality, variceal rebleeding, non-serious adverse events	Unclear risk	Participants were blinded to the intervention received. The surgeon was only blinded to the type of shunt to be assigned. Given the nature of the interventions, it was unrealistic to blind participants to the intervention received
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Personnel were blinded to the intervention received. "A senior faculty hepatologist/gastroenterologist was "blinded" to the intervention received and evaluated participants for encephalopathy during the clinic visits"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat principle used for data analysis
Selective reporting (reporting bias)	Low risk	Trial protocol was not found but predetermined outcomes in methods section were all reported
Other bias	Low risk	Trial supported by institutional grant

Orloff 2012

Methods	Randomised clinical trial
Participants	Country: USA Number randomised: 154 participants Analysis: intention-to-treat Age: mean age 49 years for both groups Initial combined endoscopic sclerotherapy and pharmacotherapy before randomisations

	Duration of follow-up: 15 years **Inclusion criteria** • All cirrhotic participants with acute (< 48 hours) bleeding from oesophageal varices or portal hypertensive gastropathy confirmed by upper endoscopy • Diagnosis of cirrhosis by clinical, and laboratory data • Child-Pugh class A, B, or C liver cirrhosis • Suitability for intervention confirmed by ultrasound • Requirement for two or more units of blood transfusion **Exclusion criteria** • Absence of cirrhosis and bleeding from sources other than oesophageal varices Prominent cause of liver cirrhosis: alcohol-related
Interventions	Emergency portocaval shunt (n = 76) versus emergency TIPS (n = 78) Either side-to-side or end-to-side portocaval shunt performed Only uncovered stents of variable sizes from 12 mm and above were used for TIPS Interventions performed within 24 hours of contact with study personnel Biopsy of liver performed during intervention
Outcomes	Survival, variceal rebleeding, encephalopathy, health-related quality of life, and economic costs
Notes	Treatment failure was defined as: variceal bleeding requiring six or more units of blood over and above normal transfusion requirements in first 8 days after study entry; variceal rebleeding that required eight units of blood transfusion during any 12-month period; or variceal rebleeding after participant deemed cured following endoscopy Rescue therapy was defined as use of alternative intervention when the primary therapy was declared a failure

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation achieved by a central computer-generated random blocks
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed to investigators by "drawing an instruction card from a serially numbered, opaque, sealed envelope"
Blinding of participants and personnel (performance bias) All-cause mortality; serious adverse events, variceal rebleed-related mortality, variceal rebleeding, non-serious adverse events	Unclear risk	Participants and personnel were not blinded to the intervention received. Given the nature of the interventions, it was unrealistic to blind participants and study personnel to the intervention received
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This information is not clear from the study.

Orloff 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat principle applied
Selective reporting (reporting bias)	Low risk	Trial protocol was published (NCT00734227). Reported protocol's predetermined outcomes
Other bias	Low risk	Study sponsored by institutional grant

Orloff 2015

Methods	Randomised clinical trial
Participants	Country: USA Number randomised:70 participants representing a subset in an extended trial Analysis: intention-to-treat Age: mean age 50 years for both groups Initial endoscopic therapy before randomisations Duration of follow-up: 10.5 years **Inclusion criteria** • All cirrhotic participants with acute bleeding (less than four hours) from gastric varices confirmed by endoscopy • Absence of bleeding from oesophageal varices or any other lesion that could account reasonably for the bleeding • Diagnosis of cirrhosis by clinical, and laboratory data, liver biopsy to confirm cirrhosis • Child-Pugh class A, B, or C liver cirrhosis • Suitability for intervention confirmed by ultrasound • Requirement for two or more units of blood transfusion **Exclusion criteria** • Absence of cirrhosis and bleeding from sources other than gastric varices Prominent cause of liver cirrhosis: alcohol-related
Interventions	Emergency portocaval shunt (n = 34) versus emergency TIPS (n = 36) Either side-to-side or end-to-side portocaval shunt performed Only uncovered stents of variable sizes from 10 mm and above were used for TIPS Interventions performed within 24 hours of contact with study personnel Biopsy of liver performed during intervention
Outcomes	Mortality, variceal rebleeding, encephalopathy, health-related quality of life, and economic costs
Notes	Treatment failure was defined as persistent or recurrent portal hypertension-related bleeding: requiring transfusion of 4 or more units of packed red blood cells or whole blood during the first 7 days after intervention; requiring transfusion of 8 or more units after the first 7 days; or requiring transfusion of 8 or more units of blood during any 12-month period; after the attending faculty endoscopist had previously declared the gastric varices obliterated or gone Crossover rescue therapy not included in protocol but, "whenever possible, every effort

Orloff 2015 (*Continued*)

	was made to facilitate rescue treatment"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation achieved by a central computer-generated random blocks
Allocation concealment (selection bias)	Low risk	Treatment allocation was concealed to investigators by "drawing an instruction card from a serially numbered, opaque, sealed envelope"
Blinding of participants and personnel (performance bias) All-cause mortality; serious adverse events, variceal rebleed-related mortality, variceal rebleeding, non-serious adverse events	Unclear risk	Participants and personnel were not blinded to the intervention received. Given the nature of the interventions, it was unrealistic to blind participants and study personnel to the intervention received
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This information is not clear from the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was by intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Trial protocol was published (NCT00820781). Reported protocol's predetermined outcomes
Other bias	Low risk	Study sponsored by institutional grant

DSRS - distal splenorenal shunt; MELD - model for end-stage liver disease; TIPS - transjugular intrahepatic portosystemic shunt

Characteristics of excluded studies *[author-defined order]*

Study	Reason for exclusion
Helton 2001	Retrospective case control study
Khaitiyar 2000	Prospective non-randomised study
Faust 1997	Retrospective case control study
Zacks 1999	Retrospective case control study

DATA AND ANALYSES

Comparison 1. Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at 30 days	4	496	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.44, 1.99]
1.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.62, 4.41]
1.2 Non-selective shunts versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.20, 1.86]
2 All-cause mortality at 5 years	4	496	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.42, 0.90]
2.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.60, 1.13]
2.2 Non-selective shunts versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.36, 0.63]
3 Variceal rebleed-related mortality at 30 days	3	426	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.04, 0.82]
3.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.03]
3.2 Non-selective shunts versus TIPS	1	154	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.01, 0.88]
4 Variceal rebleeding episodes at 30 days	4	496	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.07, 0.49]
4.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.24 [0.03, 2.19]
4.2 Non-selective shunts versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.64]
5 Number of participants transplanted at 10 years follow-up	2	272	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.13, 1.65]
5.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.13, 1.65]
6 Number of participants with reinterventions at 5 years	4	496	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.06, 0.28]
6.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.17 [0.09, 0.33]
6.2 Non-selective shunt versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.25]
7 Irreversible shunt occlusion at 5 years	4	496	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.04, 0.51]
7.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.06, 1.34]
7.2 Non-selective shunts versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.01, 0.36]
8 Encephalopathy (persistent or new-onset) at 5 years	4	496	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.27, 1.16]

8.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.33]
8.2 Non-selective shunts versus TIPS	2	224	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.23, 0.54]
9 Ascites (persistent and new-onset) at 5 years	2	272	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.44]
9.1 Selective shunts versus TIPS	2	272	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.60, 1.44]
10 Survival at 5 years by Child class	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Child-Pugh class A	2	224	Risk Ratio (M-H, Random, 95% CI)	9.06 [0.16, 521.82]
10.2 Child-Pugh class B	2	224	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.04, 13.80]
10.3 Child-Pugh class C	2	224	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.01, 96.10]

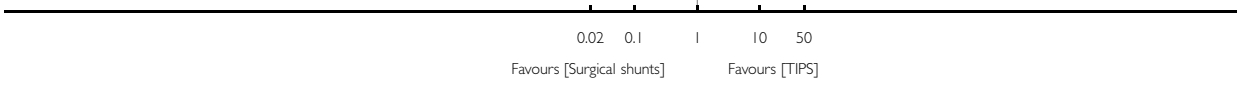
Analysis 1.1. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 1 All-cause mortality at 30 days.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 1 All-cause mortality at 30 days

Study or subgroup	Surgical shunts n/N	TIPS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Selective shunts versus TIPS					
Henderson 2006	5/73	1/67		9.7 %	4.59 [0.55, 38.28]
Rosemurgy 2012	13/66	10/66		29.9 %	1.30 [0.61, 2.75]
Subtotal (95% CI)	**139**	**133**		**39.6 %**	**1.65 [0.62, 4.41]**
Total events: 18 (Surgical shunts), 11 (TIPS)					
Heterogeneity: Tau^2 = 0.16; Chi^2 = 1.25, df = 1 (P = 0.26); I^2 =20%					
Test for overall effect: Z = 1.00 (P = 0.32)					
2 Non-selective shunts versus TIPS					
Orloff 2015	5/34	16/36		26.7 %	0.33 [0.14, 0.80]
Orloff 2012	17/76	17/78		33.7 %	1.03 [0.57, 1.86]
Subtotal (95% CI)	**110**	**114**		**60.4 %**	**0.61 [0.20, 1.86]**
Total events: 22 (Surgical shunts), 33 (TIPS)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 4.35, df = 1 (P = 0.04); I^2 =77%					
Test for overall effect: Z = 0.87 (P = 0.39)					
Total (95% CI)	**249**	**247**		**100.0 %**	**0.94 [0.44, 1.99]**
Total events: 40 (Surgical shunts), 44 (TIPS)					
Heterogeneity: Tau^2 = 0.34; Chi^2 = 8.25, df = 3 (P = 0.04); I^2 =64%					
Test for overall effect: Z = 0.16 (P = 0.87)					
Test for subgroup differences: Chi^2 = 1.71, df = 1 (P = 0.19), I^2 =42%					

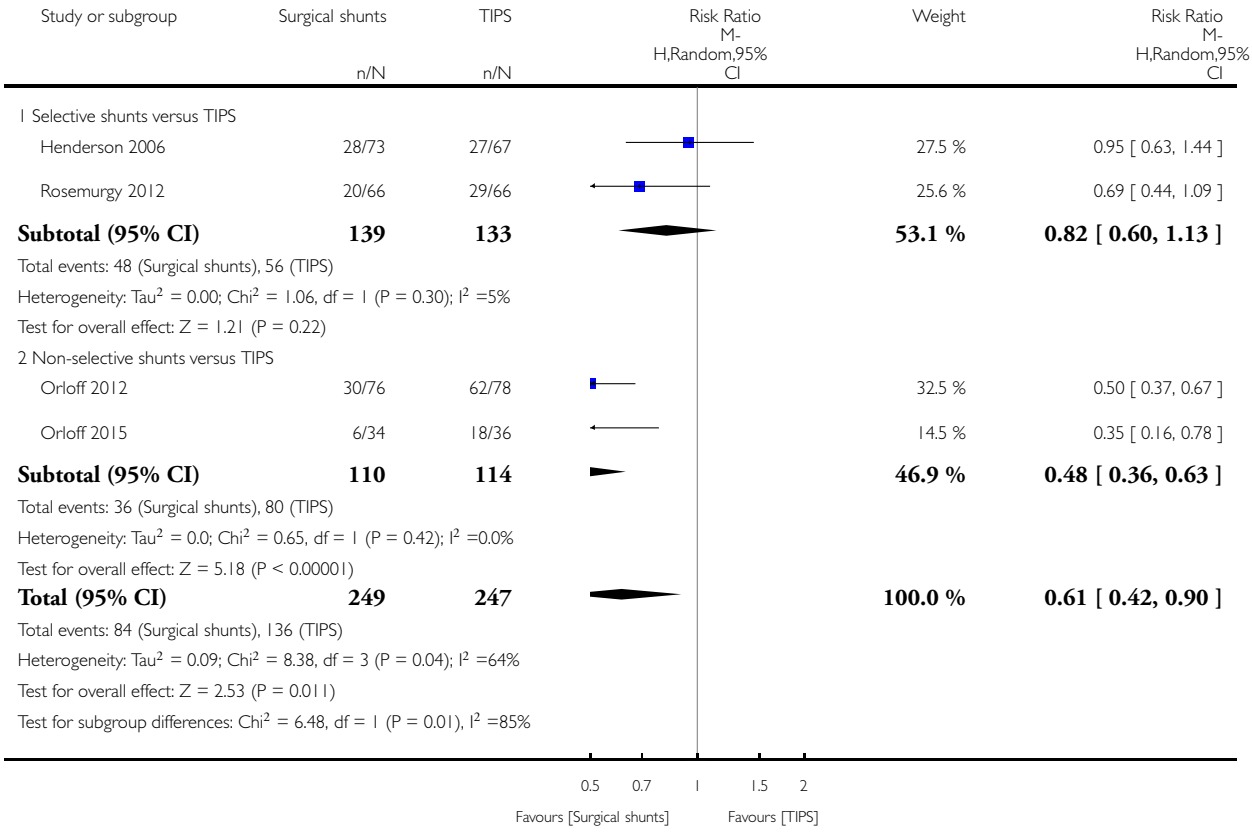


Analysis 1.2. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 2 All-cause mortality at 5 years.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 2 All-cause mortality at 5 years

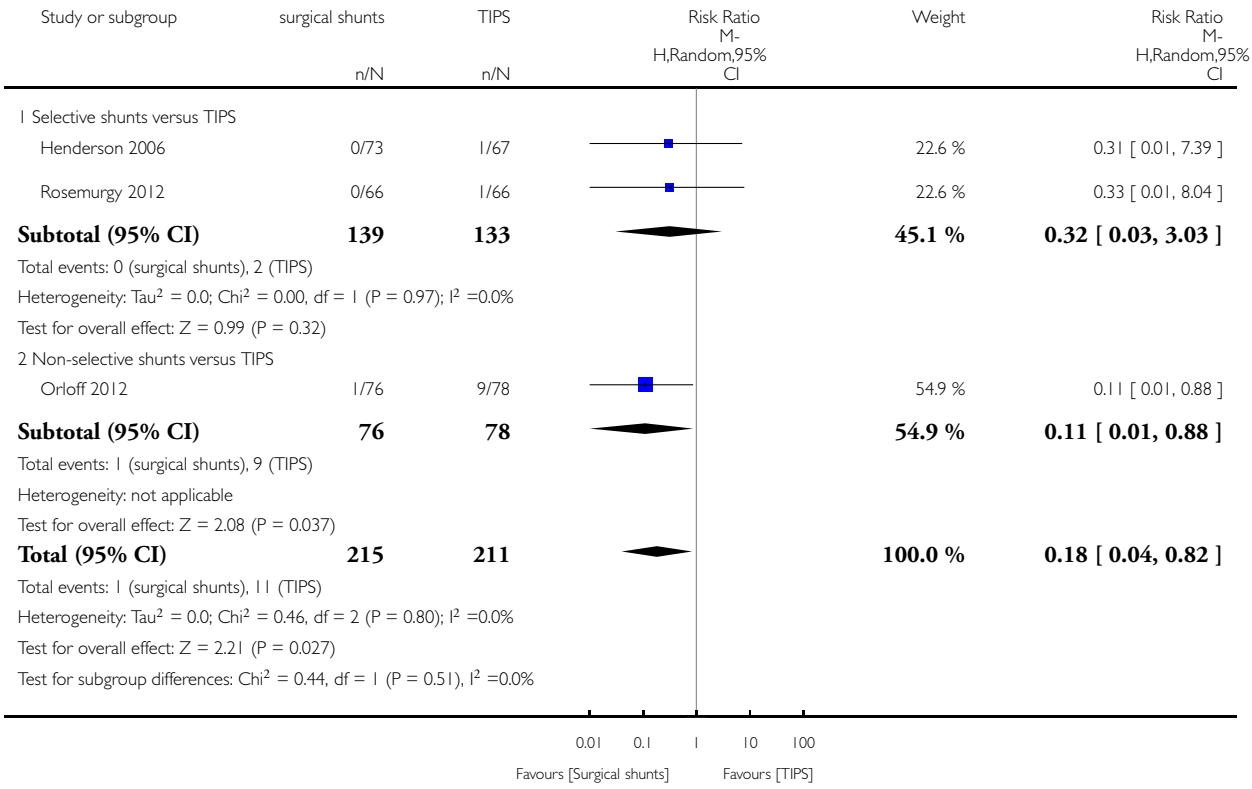


Analysis 1.3. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 3 Variceal rebleed-related mortality at 30 days.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 3 Variceal rebleed-related mortality at 30 days

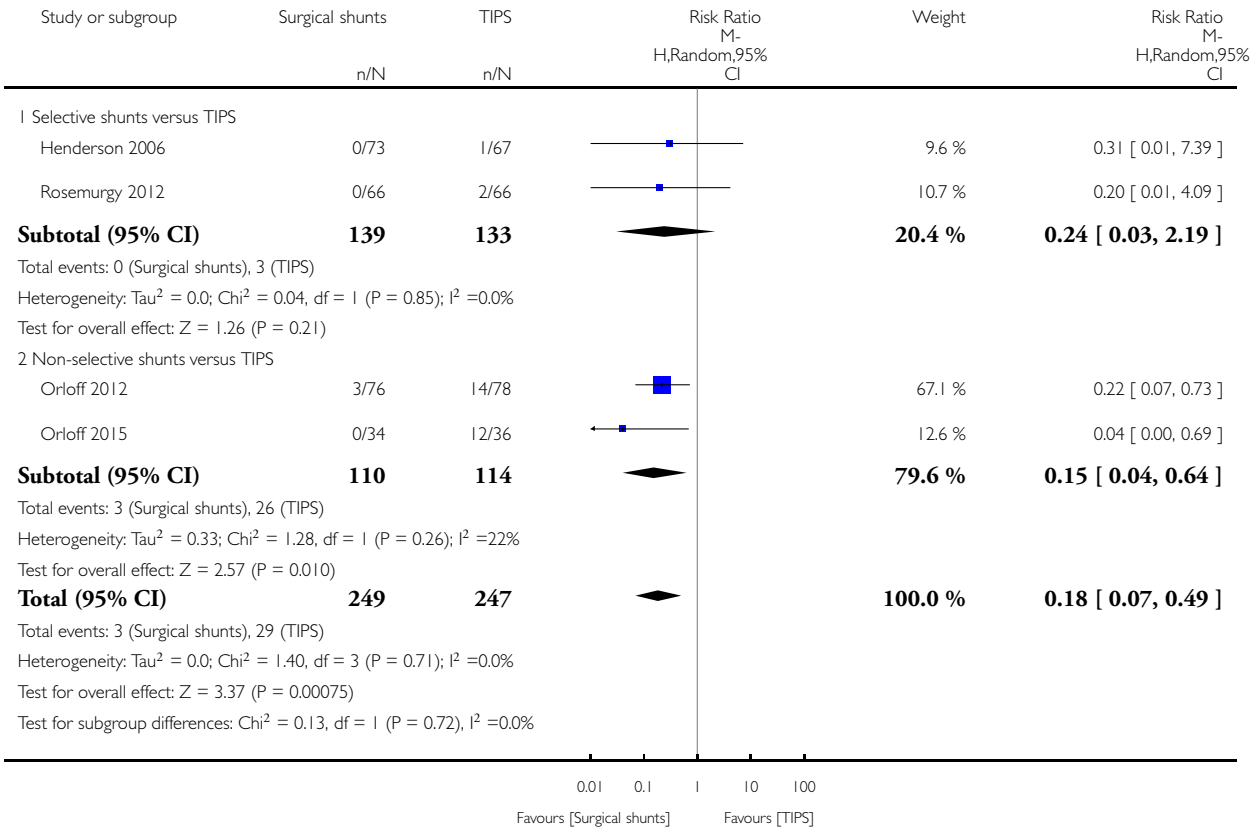


Analysis 1.4. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 4 Variceal rebleeding episodes at 30 days.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 4 Variceal rebleeding episodes at 30 days

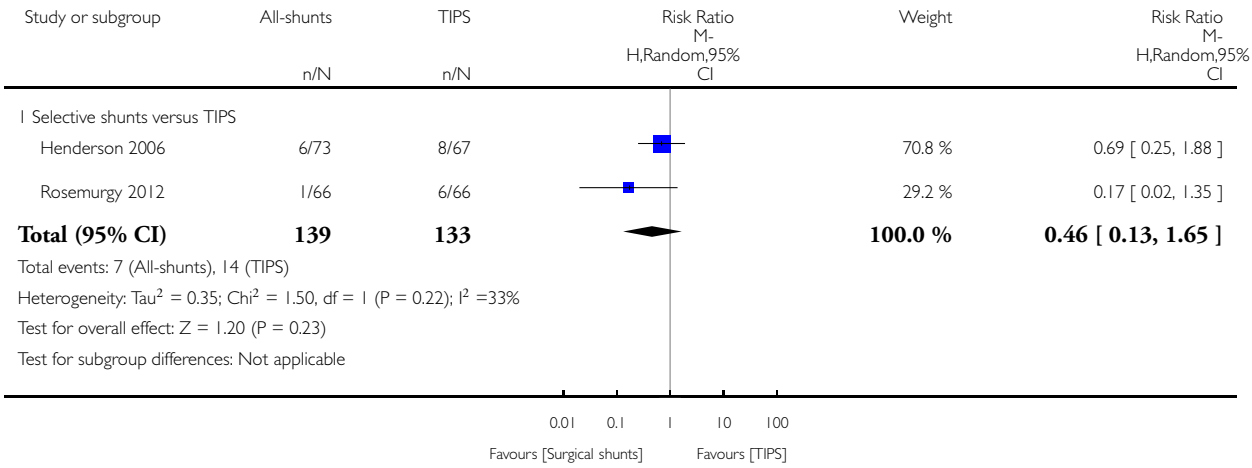


Analysis 1.5. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 5 Number of participants transplanted at 10 years follow-up.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 5 Number of participants transplanted at 10 years follow-up



Analysis 1.6. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 6 Number of participants with reinterventions at 5 years.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 6 Number of participants with reinterventions at 5 years

Study or subgroup	All-shunts n/N	TIPS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Selective shunts versus TIPS					
Henderson 2006	8/73	55/67		42.0 %	0.13 [0.07, 0.26]
Rosemurgy 2012	5/66	19/66		32.0 %	0.26 [0.10, 0.66]
Subtotal (95% CI)	**139**	**133**		**74.0 %**	**0.17 [0.09, 0.33]**
Total events: 13 (All-shunts), 74 (TIPS)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 1.37$, df = 1 (P = 0.24); $I^2 = 27\%$					
Test for overall effect: Z = 5.31 (P < 0.00001)					
2 Non-selective shunt versus TIPS					
Orloff 2012	2/76	24/78		19.4 %	0.09 [0.02, 0.35]
Orloff 2015	0/34	30/36		6.6 %	0.02 [0.00, 0.27]
Subtotal (95% CI)	**110**	**114**		**26.0 %**	**0.06 [0.01, 0.25]**
Total events: 2 (All-shunts), 54 (TIPS)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 1.18$, df = 1 (P = 0.28); $I^2 = 15\%$					
Test for overall effect: Z = 3.84 (P = 0.00012)					
Total (95% CI)	**249**	**247**		**100.0 %**	**0.13 [0.06, 0.28]**
Total events: 15 (All-shunts), 128 (TIPS)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 5.13$, df = 3 (P = 0.16); $I^2 = 42\%$					
Test for overall effect: Z = 5.30 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 1.85$, df = 1 (P = 0.17), $I^2 = 46\%$					

Analysis 1.7. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 7 Irreversible shunt occlusion at 5 years.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 7 Irreversible shunt occlusion at 5 years

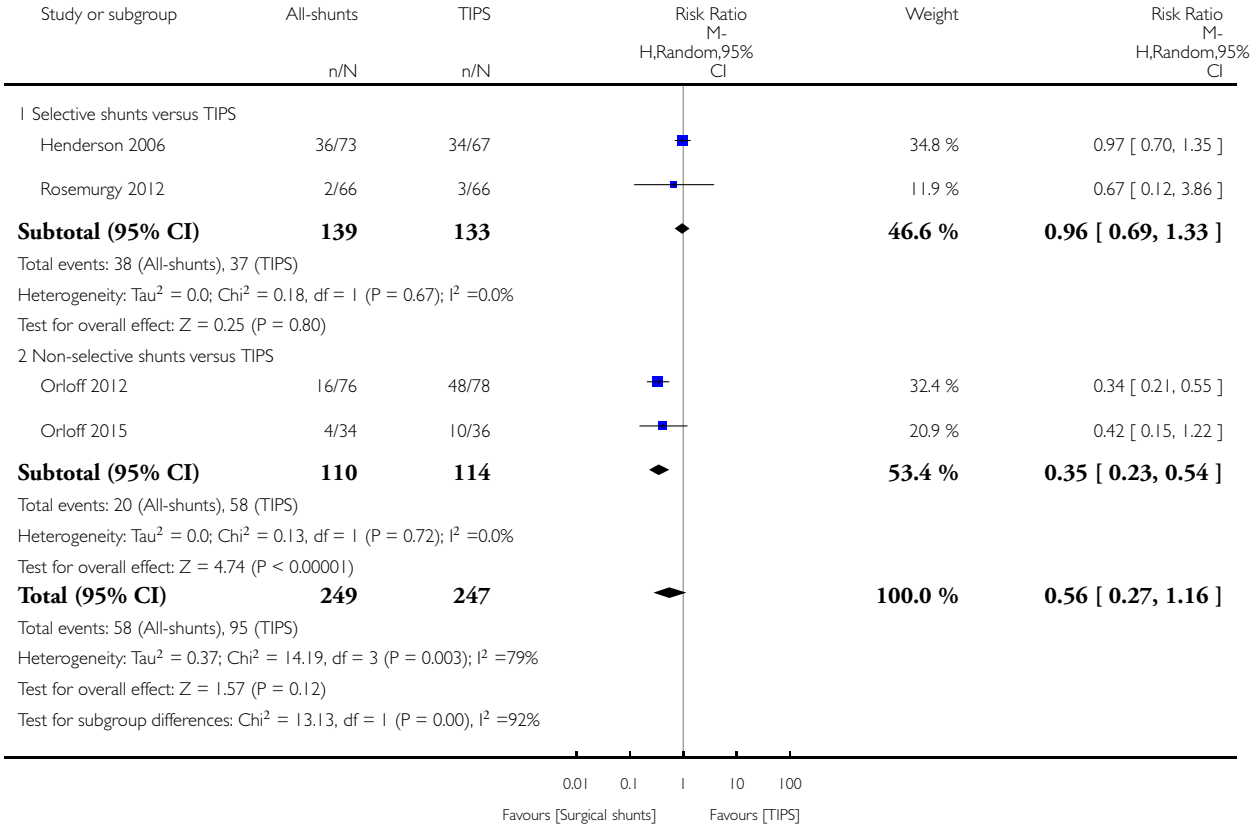
Study or subgroup	All-shunts n/N	TIPS n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Selective shunts versus TIPS					
Henderson 2006	2/73	15/67		28.2 %	0.12 [0.03, 0.52]
Rosemurgy 2012	3/66	5/66		28.9 %	0.60 [0.15, 2.41]
Subtotal (95% CI)	**139**	**133**		**57.1 %**	**0.27 [0.06, 1.34]**
Total events: 5 (All-shunts), 20 (TIPS)					
Heterogeneity: Tau^2 = 0.79; Chi^2 = 2.52, df = 1 (P = 0.11); I^2 =60%					
Test for overall effect: Z = 1.60 (P = 0.11)					
2 Non-selective shunts versus TIPS					
Orloff 2012	2/76	19/78		28.4 %	0.11 [0.03, 0.45]
Orloff 2015	0/34	28/36		14.4 %	0.02 [0.00, 0.29]
Subtotal (95% CI)	**110**	**114**		**42.9 %**	**0.06 [0.01, 0.36]**
Total events: 2 (All-shunts), 47 (TIPS)					
Heterogeneity: Tau^2 = 0.59; Chi^2 = 1.47, df = 1 (P = 0.23); I^2 =32%					
Test for overall effect: Z = 3.13 (P = 0.0018)					
Total (95% CI)	**249**	**247**		**100.0 %**	**0.14 [0.04, 0.51]**
Total events: 7 (All-shunts), 67 (TIPS)					
Heterogeneity: Tau^2 = 0.97; Chi^2 = 7.29, df = 3 (P = 0.06); I^2 =59%					
Test for overall effect: Z = 2.99 (P = 0.0028)					
Test for subgroup differences: Chi^2 = 1.49, df = 1 (P = 0.22), I^2 =33%					

Analysis 1.8. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 8 Encephalopathy (persistent or new-onset) at 5 years.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 8 Encephalopathy (persistent or new-onset) at 5 years

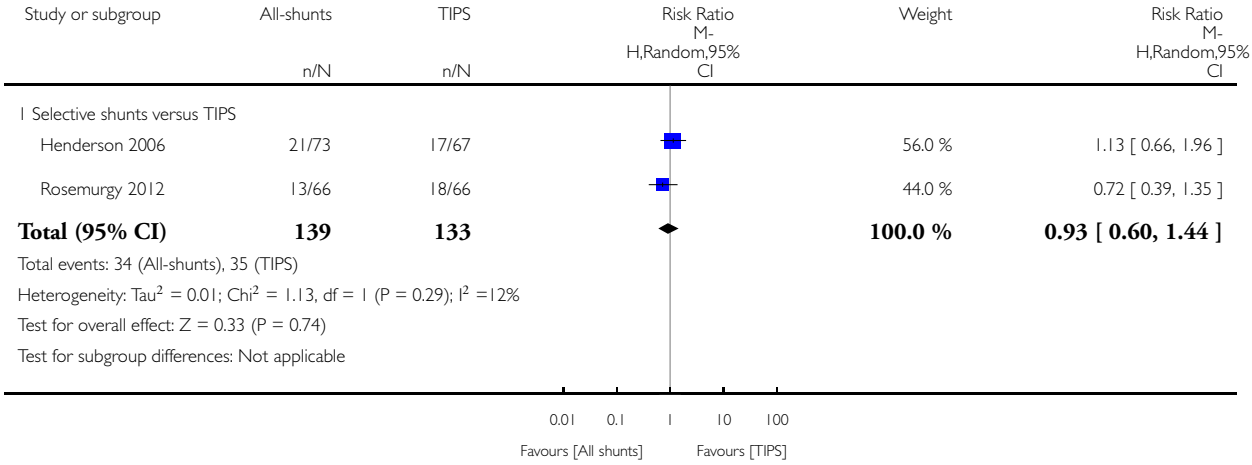


Analysis 1.9. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 9 Ascites (persistent and new-onset) at 5 years.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 9 Ascites (persistent and new-onset) at 5 years

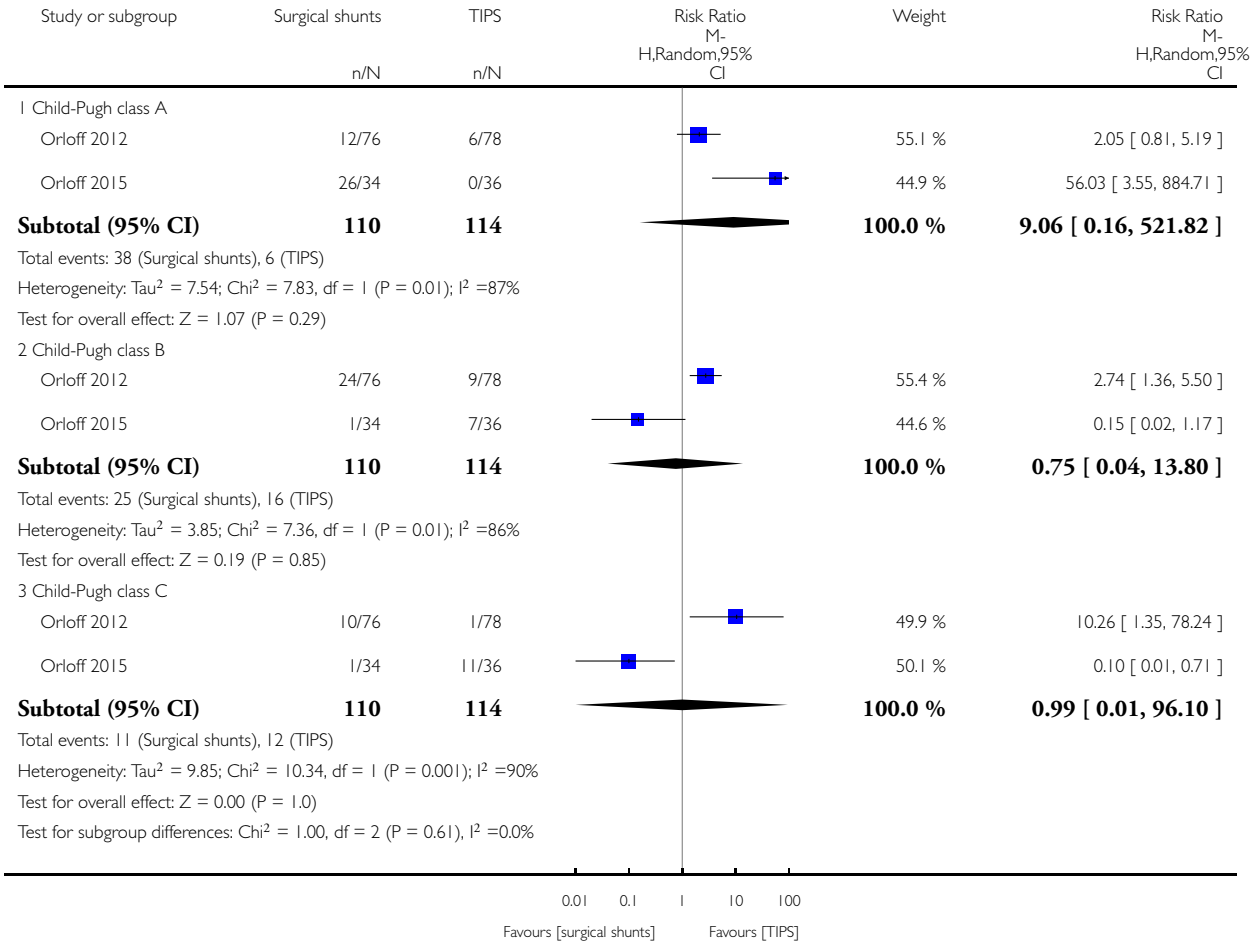


Analysis 1.10. Comparison 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS), Outcome 10 Survival at 5 years by Child class.

Review: Surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt for variceal haemorrhage in people with cirrhosis

Comparison: 1 Surgical shunts versus transjugular intrahepatic portosystemic shunt (TIPS)

Outcome: 10 Survival at 5 years by Child class



ADDITIONAL TABLES

Table 1. Harms of interventions from Khaitiyar 2000

No	Outcomes	DSRS (N = 32)	TIPS (N = 35)	Fisher exact test
1	All-cause mortality at 30 days	2	2	P = 1
2	All-cause mortality at 2 years	6	7	P = 1
2	Rebleed-related mortality at 2 years	2	9	P = 0.05
3	Variceal rebleeding episodes at 2 years	2	9	P = 0.05
4	Shunt occlusion at 2 years	2	24	P = 0.00001
5	Encephalopathy at 2 years	6	15	P = 0.04
6	Ascites at 2 years	4	13	P = 0.03

DSRS: distal splenorenal shunt; TIPS: transjugular intrahepatic portosystemic shunt

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	8 March 2018	((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intrahepatic or selective or non-selective or partial or total) and (shunt* or anastomos*)) AND (varic* and (hemorrhag* or Haemorrhage* or bleed* or rebleed*))
Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library	2018, Issue 2	#1 MeSH descriptor: [Portasystemic Shunt, Surgical] explode all trees #2 (portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intrahepatic or selective or non-selective or partial or total) and (shunt* or anastomos*) #3 'dean warren shunt*' or H-shunt* or TIPS or PSS

(*Continued*)

		#4 #1 or #2 or #3 #5 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees #6 MeSH descriptor: [Liver Cirrhosis] explode all trees #7 varic* and (h*emorrhag* or bleed* or rebleed*) #8 #5 or #6 or #7 #9 #4 and #8
MEDLINE Ovid	1946 to 8 March 2018	1. exp Portasystemic Shunt, Surgical/ 2. ((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intrahepatic or selective or non-selective or partial or total) and (shunt* or anastomos*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 3. ('dean warren shunt*' or H-shunt* or TIPS or PSS).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 4. 1 or 2 or 3 5. exp "Esophageal and Gastric Varices"/ 6. exp Liver Cirrhosis/ 7. (varic* and (h*emorrhag* or bleed* or rebleed*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 8. 5 or 6 or 7 9. 4 and 8 10. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] 11. 9 and 10
Embase Ovid	1974 to 8 March 2018	1. exp portosystemic anastomosis/ 2. ((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intrahepatic or selective or non-selective or partial or total) and (shunt* or anastomos*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 3. ('dean warren shunt*' or H-shunt* or TIPS or PSS).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

(*Continued*)

		4. 1 or 2 or 3 5. exp esophagus varices/ 6. exp liver cirrhosis/ 7. (varic* and (h*emorrhag* or bleed* or rebleed*)).mp. [mp= title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 8. 5 or 6 or 7 9. 4 and 8 10. (random* or blind* or placebo* or meta-analys*).mp. [mp= title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 11. 9 and 10
Science Citation Index Expanded (Web of Science)	1900 to 8 March 2018	#7 #6 AND #5 #6 TS=(random* or blind* or placebo* or meta-analys*) #5 #4 AND #3 #4 TS=(varic* and (h*emorrhag* or bleed* or rebleed*)) #3 #2 OR #1 #2 TS=('dean warren shunt*' or H-shunt* or TIPS or PSS) #1 TS=((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intra-hepatic or selective or non-selective or partial or total) and (shunt* or anastomos*))
Conference Proceedings Citation Index - Science (Web of Science)	1990 to 8 March 2018	#7 #6 AND #5 #6 TS=(random* or blind* or placebo* or meta-analys*) #5 #4 AND #3 #4 TS=(varic* and (h*emorrhag* or bleed* or rebleed*)) #3 #2 OR #1 #2 TS=('dean warren shunt*' or H-shunt* or TIPS or PSS) #1 TS=((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intra-hepatic or selective or non-selective or partial or total) and (shunt* or anastomos*))
LILACS (Bireme)	1982 to 8 March 2018	((portosystemic or portasystemic or portacaval or mesocaval or splenorenal or surgical or radiological or intrahepatic or selective or non-selective or partial or total) and (shunt$ or anastomos$)) [Words] and (dean warren shunt$ or H-shunt$ or TIPS or PSS) [Words] and (varic$ and (h$morrhag$ or bleed$ or rebleed$)) [Words]

CONTRIBUTIONS OF AUTHORS

MB and LP drafted the current protocol.

CJE and LP completed the trial selection.

CJE and LP completed the data extraction and entry into RevMan.

CJE performed the meta-analyses, Trial Sequential Analysis, and GRADE.

MB, CJE and LP agreed on the manuscript.

DECLARATIONS OF INTEREST

MB has on conflict of interest to declare

LP has no conflict of interest to declare

CJE has no conflict of interest to declare

SOURCES OF SUPPORT

Internal sources

- Department of Surgery, University of the Witwatersrand, South Africa.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- We improved the wording of the review objectives as follows: 'To assess the benefits and harms of surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt (TIPS) for the treatment of refractory or recurrent variceal haemorrhage in people with cirrhotic portal hypertension'. (The protocol objectives read: 'To compare the benefits and harms of surgical portosystemic shunts versus transjugular intrahepatic portosystemic shunt (TIPS) in the treatment of chronic variceal haemorrhage').

- We analysed outcomes at fixed time points instead of the protocol's prespecified maximal follow-up. This is because of wide variations in maximal follow-up in the trials.

- We added an exploratory outcome: 'irreversible shunt occlusion' to identify participants who had shunt failure despite reinterventions.

- We included emergency shunt procedures in the review, as one trial was specifically designed to investigate shunts in the management of acute variceal haemorrhage (Orloff 2012), and another trial included both elective and emergency shunt procedures and we were not able to differentiate the results of these two groups from their manuscript (Rosemurgy 2012).

- CJ Ede was added as an author for his contributions to this review

NOTES

CJ Ede joined the authors after the protocol was published.