

https://dspace.org/

Surgical portosystemic shunts versus devascularisation procedures for prevention of variceal rebleeding due to hepatosplenic schistosomiasis

Ede, Chikwendu Jeffrey

2017
http://hdl.handle.net/10539/23302

Downloaded from a DSpace repository. https://dspace.org/

Surgical portosystemic shunts versus devascularisation procedures for prevention of variceal rebleeding due to hepatosplenic schistosomiasis

Chikwendu Jeffrey Ede

Student Number 792063

Department of Surgery

Supervisor/ Co-reviewer

Martin Brand

FCS, Cert Gastroenterology, MRCS, PhD

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of

Master of Medicine in Surgery

Johannesburg, 2017

Table of Contents

Declaration	**iii**
Abstract	**iv**
Acknowledgements	**vi**
List of figures	**vii**
List of tables	**viii**
List of abbreviations	**ix**
Dedication	**x**
Section 1 –Literature review	**1**
Section 2 – Draft article to CDSR	**14**
Section 3 – Ethics Approval	**72**
Section 4 – Annexure - Proposal	**73**
Section 5 – Appendices	**94**

Declaration

I, Chikwendu Jeffrey Ede declare that this research report is entirely my own work. It is being submitted to the University of Witwatersrand in partial fulfilment of the requirement for the degree of Master of Medicine in General Surgery. It has never been submitted before for any degree or examination at this or any other university.

This review finding will be published in the Cochrane database of systematic reviews.

……

……day of……..20……

Abstract

Background: Surgical interventions such as shunts and devascularisation procedures are effective therapies to prevent variceal rebleeding in people with hepatosplenic schistosomiasis. As this disease is prevalent in low income countries, the impact of eco-social factors result in poor compliance with non-surgical therapies that require repeated sessions and long-term follow-up.

Objectives: To determine whether surgical portosystemic shunts have better outcomes compared with oesophagogastric devascularisation procedures in the prevention of variceal rebleeding due to schistosomal portal hypertension (SPH).

Methodology: This meta-analysis was conducted using standards expected by The Cochrane Collaboration. All randomised clinical trials comparing surgical portosystemic shunts with oesophagogastric devascularisation with or without splenectomy in the prevention of variceal rebleeding due to hepatosplenic schistosomiasis were selected. The risks of bias were assessed according to domains and risk of random errors with Trial Sequential Analysis. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group approach.

Results: Two trials met the inclusion criteria of this review and were selected. An analysis of 115 participants, 57 who received distal splenorenal shunt (DSRS) and 58 who received devascularisation procedure is presented. The trials were assessed at high risk of bias. There is no difference in overall mortality between DSRS versus devascularisation, risk ratio (RR) is 1.40, (95% confidence interval (CI) 0.32 to 6.15), downgraded to very low quality due to overall risk of bias, imprecision and publication bias. Variceal rebleeding following devascularisation is statistically significant higher than after DSRS (RR is 0.23, 95% CI 0.05 to 1.01), very low quality evidence due to bias, imprecision, and publication bias. The number of participants needed to treat with DSRS to achieve benefit (NNTB) is 8. Serious adverse events reported as procedure specific include: portal vein thrombosis, haemolysis, ascites and

shunt dysfunction. There was no report on quality of life. DSRS is associated with a statistically significant higher post procedure encephalopathy (RR 8.10, 95% CI 1.04 to 62.83), downgraded to very low quality due to overall risk of bias, imprecision, and publication bias. Trial sequential analysis shows no strong evidence to accept or reject the difference in variceal rebleeding and encephalopathy rate for both interventions because of bias and inadequate sample size. Outcomes of proximal splenorenal shunt (PSRS) compared to devascularisation were reported by a single trial, therefore no meta-analysis was computed for this comparison, nor subgroup of PSRS compared to DSRS.

Conclusion: Available evidence seems to suggest that DSRS is better than devascularisation for the prevention of variceal rebleeding due to hepatosplenic schistosomiasis, but this is at the cost of significant encephalopathy. The review authors are cautious to make this conclusion because overall evidence is very low quality and only few trials with small sample size are available. Further randomised clinical trials with adequate sample size and good methodological quality are needed.

Acknowledgements

I would like to express my gratitude to the following people and institutions for their invaluable assistance during the conduct of this research:

Martin Brand, co-reviewer

Dimitrinka Nikolova, the Managing Editor of the Cochrane Hepato-Biliary Group

Sarah L. Klingenberg who assisted with the search

Peer reviewers:

Dana Crisan, Romania

Amy Deipolyi, USA

Flora Zarate, Mexico

Contact Editors, the Cochrane Hepato-Biliary Group:

Saboor A'Khan, UK

Christian Gluud, Denmark

Institutions:

Cochrane South Africa, South African Medical Research Council

University of the Witwatersrand Medical Library

List of figures

Study flow diagram Page 42

Risk of bias graph Page 43

Risk of bias summary Page 43

Trial sequential graph (variceal rebleeding) Page 44

Trial sequential graph (encephalopathy) Page 45

List of Tables

Characteristics of included studies (Gawish 2000) Page 46

Characteristics of included studies (Raia 1994) Page 47

Characteristics of excluded studies Page 48

Summary of findings table 1 Page 49

Summary of findings table 2 Page 51

Serious adverse events table Page 53

Forest Plot: Analysis

All shunt versus devascularisation Page 54

Distal splenorenal shunt versus devascularisation Page 55

Proximal splenorenal shunt versus devascularisation Page 56

List of abbreviations

CDSR: Cochrane database of systematic review

CHBG: Cochrane Hepato-biliary Group

CI: Confidence interval

DSRS: Distal splenorenal shunt

OGDS: Oesophagogastric devascularisation and splenectomy

NNTB: Number needed to treat for benefit

OPSI: Overwhelming post splenectomy infection

PSRS: Proximal splenorenal shunt

RR: Relative risk

RRR: Relative risk reduction

SPH: Schistosomal portal hypertension

TIPS: Transjugular intrahepatic portosystemic shunt

Dedication

To Chioma, Chinemerem, Kenechukwu, and Golibe, your patience and support are highly appreciated.

Section 1: Literature Review

1.1 Background

Oesophagogastric varices occur in patients that suffer from portal hypertension either as sequelae of liver cirrhosis or with presinusoidal causes such as schistosomiasis. In portal hypertension there is a pathological increase in the portocaval pressure gradient (Sanyal *et al*, 2008) resulting in the development of varices, encephalopathy, hypersplenism and ascites (Goff *et al*, 1993). Portal Hypertension is defined as a portal venous pressure gradient greater than 8mmHg and clinically relevant variceal bleeding occur when the pressure gradient exceeds 12mmHg (Sanyal *et al.* 2008). Variceal bleeding is a significant cause of mortality in patients with portal hypertension (approximately 50% from the first bleed in liver cirrhosis) (Graham & Smith, 1981; de Dombal, *et al*. 1986). In survivors of the first episode, recurrent bleeding is not uncommon and the risk of rebleeding is greatest within the first thirty days that follow the initial bleed (Smith & Graham, 1982).

1.2 Treatment of Variceal Bleeding

The algorithm for the control of acute variceal bleeding is the same for both cirrhotic and non-cirrhotic portal hypertension, consisting of a combination of pharmacological (vasoactive agent) and endoscopic therapy. Using this management, bleeding will stop in 90% of people (D'Amico *et al*, 2003; Gonzalez *et al*, 2008; de Franchis, 2010). The remaining 10% are classified as people with refractory bleeding, and further management options include radiologically placed transjugular intrahepatic portosystemic shunt (TIPS) or surgical interventions (shunt, devascularisation procedures, or liver transplantation) (de Franchis, 2010). The risk of long-term rebleeding without further intervention following the control of acute variceal bleeding is approximately 80% (Kiire, 1989; D'Amico *et al,* 1995; Vleggaar *et*

al, 1998), hence secondary prevention is required in any person who has suffered a variceal bleed (de Franchis, 2010).

1.3 Prevention of variceal rebleeding

Medical treatment (combined endoscopic band ligation and non-selective beta-blockers) is an effective first-line modality to prevent variceal rebleeding (de Franchis 2010; Sarin *et al,* 2010). This requires repeated treatment sessions. However, approximately 20% to 30% of people who receive medical therapy will still have recurrent variceal bleeding while undergoing treatment (Kiire *et al*, 1989; Bhargava *et al* 1990; Vleggaar *et al*, 1998; Sarin *et al*, 2010).

TIPS has an efficacy of more than 90% rebleed-free rate and is recommended as rescue therapy following the failure of medical treatment in persons with cirrhosis (Rossle *et al,* 2006; Boyer & Haskal, 2010; de Franchis 2010). Although it is a less invasive procedure than a surgical procedure, it may have more complications and requires more re-interventions than surgical procedures. In the era of radiological shunt (TIPS), the use of surgical shunts and devascularisation procedures have decreased as TIPS offers a minimally invasive alternative and serve as a bridge to liver transplantation (John *et al*. 1996; Boyer & Haskal, 2010). Nonetheless, only 3% to14% of eligible cirrhotic patients eventually receive liver transplant (Rosemurgy *et al*. 2012; Toomey *et al*. 2013). However, people with schistosomal portal hypertension do not meet liver transplantation criteria as their liver function is preserved (Rosemurgy 2012).The long term patency of TIPS as well as long term survival rates are less than surgical shunts (Rosemurgy *et al.* 1996; Orloff *et al*, 2014). The 5-year patency and survival rate for a surgical shunt is 97% and 68% respectively (Gur *et al.* 2014). The median survival after TIPS is 26 months compared to 52 months after H-graft portocaval shunt (Rosemurgy *et al*. 2012). Early shunt occlusion occurred within 30 days in 17% of patient after TIPS compared to 9% after surgical shunt (Rosemurgy *et al.* 1996). This data is only

valid in cirrhotic patients. However, there is no literature to my knowledge supporting the use of TIPS in schistosomal portal hypertension (SPH) (Eesa & Clark, 2011).

In SPH hepatic venous pressure and hepatic function are largely preserved if there are no other concomitant liver diseases such as viral hepatitis infection (Denie *et al.* 1996; Bica *et al*. 2000). There is good data to support the use of surgical shunts for portal decompression in SPH as this subgroup of patients are young with preserved liver function (Henderson, 1988; Spina *et al*, 1992; Ferraz *et al,* 2001; Gur *et al*, 2014).

The aim of surgery is to reduce the high pressure in the portal circulation. This is achieved by diverting portal venous blood into the systemic circulation. Generally, two types of procedures are described, shunts and devascularisation (Da Silva & Carrilho, 1992). Surgical shunts are traditionally divided into selective and non-selective types. When compared to selective shunts, the non-selective shunts divert all portal blood away from the liver into the systemic circulation resulting in reduction in effective hepatic blood flow. The risk of encephalopathy after non-selective shunt in SPH approach 39%, hence selective shunts are advocated (Raia *et al*, 1994; Andersson & Chung, 2007). Perioperative mortality following shunt procedures is 6%, with 5-year survival rate of 68-75% (Paquet *et al.*1989; Rikker *et al*, 1992; Orloff *et al*. 2009; Gur *et al*, 2014).

On the other hand, devascularisation procedures have higher rebleeding rate of 7-40% (Henderson, 1988; Johnson *et al*. 2006), compared to surgical shunt with rates of 5-11% depending on the type of shunt (Rikkers *et al,* 1998). Also the risk of encephalopathy with devascularisation is rare and overall operative mortality higher at 13% (Suigura & Futagawa, 1984; Rikkers *et al,* 1998; Qazi *et al*, 2006). Hence, devascularisation procedures have higher mortality and a disappointing long term outcome because of high rate of rebleeding compared to selective surgical shunt.

1.4 Description of the condition

Schistosomiasis is a parasitic disease that is endemic in poor communities with inadequate sanitation and lack of access to portable water (Steinmann *et al,* 2006). The World Health Organisation estimates that the total number of people infected worldwide is over 200 million. More than 90% of these live in Africa (WHO, 2014). The hepatosplenic form of the disease is caused by two species of the blood fluke Schistosoma, namely S. *mansoni* found predominantly in Africa, Arabia and South America, and S. *japonicum* found in South-East Asia, especially mainland China.

1.4.1 Life cycle of Schistosoma spp

Human infestation starts with bite by the cercariae when there has been contact between the skin and infested water. These larvae are transformed into schistosomulae in bloodstream and subsequently mature into adult worms in the mesenteric veins. Mating between the male and female adult worms occurs within the mesenteric veins and results in release of eggs by the female worm. A granulomatous inflammatory reaction to the trapped eggs in portal vein radicles results in periportal fibrosis, also called Symmer's clay pipe stem fibrosis (Symmers, 1904). It is this fibrous occlusion of portal vein radicles that results in the development of presinusoidal portal hypertension (Ross *et al*. 2002).

1.5 Description of interventions

The two main categories of surgical procedures to prevent variceal rebleeding are portosystemic shunts and devascularisation procedures.

1.5.1 Surgical portosystemic shunt

These are surgically created conduits that divert some or all of portal venous blood away from the liver into the systemic circulation. These conduits may be autogenous vein graft or polytetrafluoroethylene prosthesis (PTFE). Commonly created surgical portosystemic shunts include the non-selective H-shunt and the selective DSRS (Warren, 1967). The H-shunt is created between the portal vein and the inferior vena cava using an 8 mm to 16 mm ringed PTFE prosthesis. The PTFE graft is non expansible and by diminishing its diameter from 16mm to 8mm a partial portal decompression is achieved (Sarfeh et al, 1986; Sarfeh et al, 1994).

The DSRS is created by anastomosing the distal splenic vein to the left renal vein and disconnecting the splenopancreatic and gastric venous connections to the portal system while preserving portal venous blood flow and hepatic function.

1.5.2 Oesophagogastric devascularisation procedures

This involves trans-hiatal devascularisation of the lower oesophagus and proximal half of the stomach, with ligation of branches of left gastric, short gastric, left gastroepiploic, and perforating oesophageal arteries and veins. This is combined with splenectomy (Hassab, 1967), or with oesophageal transection plus splenectomy in a two-stage operation (Sugiura & Futagawa, 1973). The original Sugiura procedure was subsequently modified into a one-stage abdominal procedure (Peracchia *et al*, 1980; Inokuchi, 1985), or without oesophageal transection (Jin & Rikkers, 1996; Johnson *et al,* 2006), or without truncal vagotomy (Ginsberg 1982), and without splenectomy (Orozco *et al*, 1998). One randomised clinical trial comparing devascularisation with splenectomy or without splenectomy showed no statistically significant difference in outcome between the two methods; however, there was a

significant increase in transfusion requirement in the splenectomy group. This trial demonstrates that splenectomy may not be mandatory in devascularisation procedure (Orozco *et al,* 1998).

1.6 How the interventions might work

Surgical portosystemic shunts and devascularisation procedures decrease portal venous pressure, and hence decrease portal hypertension, which consequently prevents variceal bleeding. Oesophagogastric devascularisation with or without splenectomy reduces portal hypertension by decreasing portal blood flow, but with a compensatory increase in hepatic artery flow. This maintains effective hepatic blood flow and preserves liver function. The procedure normalises the hyperdynamic circulatory state present in schistosomal portal hypertension (de Cleva *et al*, 2007; Zhang *et al*, 2009; Evangelista-Neto *et al*, 2012).

1.7 Why is this review important?

To date no meta-analysis or systematic review has compared surgical portosystemic shunts to devascularisation procedures in control of recurrent variceal bleeding due to schistosomal portal hypertension.

Yin et al in a meta-analysis of selective shunt, non-selective shunt, devascularisation, and a combined procedure (shunts plus devascularisation) in prevention of both cirrhotic and non-cirrhotic variceal bleeding, concluded that the combined procedure was the best choice for secondary prophylaxis of variceal rebleeding (Yin *et al*, 2013). They did not separate the results of people with and without cirrhosis in their review. Therefore this meta-analysis will compare the outcome of two surgical interventions (shunts and devascularisation) for the prevention of variceal rebleeding due to SPH.

References

Andersson K.L, Chung R.T. (2007), Hepatic schistosomiasis. *Curr Treat Options Gastroenterol* **10**:504-512.

Bica I, Hamer D.H, Stadecker M.J. (2000), Hepatic Schistosomiasis. *Infectious disease clinics of North America* **14**:583-604.

Bhargava DK, Dasarathy S, Atmakuri SP, Dwivedi M. (1990), Comparative efficacy of emergency endoscopic sclerotherapy for active variceal bleeding due to cirrhosis of the liver, non-cirrhotic portal fibrosis and extrahepatic portal venous obstruction. *Journal of Gastroenterology and Hepatology* **5**:432-437.

Boyer T.D, Haskal Z.J. (2010), American Association for the Study of Liver Diseases, The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* **51**(1):306

D'Amico G, De Franchis R. (2003), Upper digestive bleeding in cirrhosis, Post-therapeutic outcome and prognostic indicators. *Hepatology* **38**:599-612.

Da Silva L.C, Carrilho F.J. (1992), Hepatosplenic schistosomiasis: pathophysiology and treatment. *Gastroenterology clinics of North America* **21**:163-177.

de Dombal F T, Clarke J R, Clamp Susan E, Malizia G, Kotwal M R, Morgan A G.(1986) Prognostic Factors in Upper G.I. Bleeding. *Endoscopy* **18**:6-10.

de Franchis R. (2010), Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology* **53**:762-768.

Denié C, Vachiery F, Elman A, Soupison T, Gadano A, Moreau, R, *et al*. (1996), Systemic and splanchnic hemodynamic changes in patients with hepatic schistosomiasis. *Liver* **16**:309-312.

Eesa M, Clark T. (2011), Transjugular intrahepatic portosystemic shunt: state of the art. *Semin Roentgenol* **46**:125-132.

Evangelista-Neto J, Pereira FF, Franca ST, Amaral FJ, Brandt CT, Fonseca-Neto OC, et al. (2012), Splenectomy and gastric vein ligature in hepatosplenic schistosomiasis: effects upon esophageal variceal pressure and endoscopic risk factors of esophageal variceal bleeding. *Arquivos Brasileiros de Cirurgia Digestiva* **25**:41-48.

Ferraz A.A, Bacelar T.S, Silveira M.J, Coelho A.R, Camara N.R.D, de Araujo Junior J.G, et al.(2001), Surgical treatment of schistosomal portal hypertension. *Int Surg* **86**:1-8.

Ginsberg RJ, Waters PF, Zeldin RA, Spratt EH, Shandling B, Stone RM, et al. (1982), A modified Sugiura procedure. Annals of Thoracic Surgery **34**:258-264.

Goff J.S. (1993), Gastroesophageal varices: pathogenesis and therapy of acute bleeding. *Gastroenterol Clin North Am* **22**:779-800.

Gonzalez R, Zamora, J, Gomez-Camarero J, Molinero L M, Banares R, Albillos A. (2008), Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* **149**:109-122.

Graham D.Y, Smith J.L. (1981), The course of patients after variceal haemorrhage. *Gastroenterology* **80**:800-809.

Gur I, Diggs B.S, Orloff S.L. (2014), Surgical portosystemic shunts in the era of TIPS and liver transplantation are still relevant. *HPB* **16**:481-493.

Hassab MA. (1967), Gastroesophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: further studies with a report on 355 operations. *Surgery* **61**:169-176.

Hassab MA. (1998), Gastro-esophageal decongestion and splenectomy GEDS (Hassab), in the management of bleeding varices. Review of literature. *International Surgery* **83**(1):38-41.

Henderson, J.M. (1988), Surgical methods for the prevention of first and recurrent variceal bleeding. *Z Gastroenterol* **26(**Suppl 2):49-53.

Inokuchi K. (1985), Present status of surgical treatment of esophageal varices in Japan: a nationwide survey of 3,588 patients. *World Journal of Surgery* **9**:171-180.

John T G, Jalan R, Stanley A J, Redhead D N, Sanfey H A, Hayes P C, et al.(1996), Transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion as a prelude to orthotopic liver transplantation in patients with severe portal hypertension. *Eur J Gastroenterol Hepatol* **8**:1145-1149.

Johnson, M, Rajendran, S, Balachandar, T.G, Kannan, D, Jeswanth, S, Ravichandran, P, *et al.* (2006), Transabdominal modified devascularization procedure with or without esophageal stapler transection-an operation adequate for effective control of a variceal bleed. Is esophageal stapler transection necessary? *World J Surg* **30**:1507-1519.

Kiire CF. (1989), Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis. *BMJ (Clinical Research Ed.)* **298**:1363-1365.

Orloff, M.J, Isenberg, J.I, Wheeler, H.O, Haynes, K.S, Jinich-Brook, H, Rapier, R, et al.(2009), Randomized trial of emergency endoscopic sclerotherapy versus emergency portacaval shunt for acutely bleeding esophageal varices in cirrhosis. *J Am Coll Surg* **209**:25-40.

Orloff, M.J.(2014), Fifty-three years' experience with randomized clinical trials of emergency portacaval shunt for bleeding esophageal varices in Cirrhosis: 1958-2011. *JAMA Surg* **149**:155-169.

Orozco H, Mercado MA, Takahashi T, Hernandez-Ortiz J, Capellan JF, Garcia-Tsao G. (1992), Elective treatment of bleeding varices with the Sugiura operation over 10 years. *American Journal of Surgery* **163**:585-589.

Orozco H, Mercado MA, Martinez R, Tielve M, Chan C, Vasquez M, et al. (1998), Is splenectomy necessary in devascularization procedures for treatment of bleeding portal hypertension? *Archives of Surgery* **133**:36-38.

Paquet, K.J, Mercado, M.A, Koussouris, P, Kalk, J.F, Siemens, F, Cuan-Orozco, F.(1989), Improved results with selective distal splenorenal shunt in a highly selected patient population. A prospective study. *Ann Surg* **210**:184-189.

Peracchia A, Ancona E, Battaglia G. (1980), A new technique for the treatment of esophageal bleeding in portal hypertension. *International Surgery* **65**:401-404.

Qazi S A, Khalid K, Hameed A M, Al-Wahabi K, Galul R, Al-Salamah S M. (2006), Transabdominal gastro-esophageal devascularization and esophageal transection for bleeding esophageal varices after failed injection sclerotherapy: long-term follow-up report. *World J Surg* **30**:1329-1337

Raia S, da Silva L C, Gayotto L C, Forster S C, Fukushima J, Strauss E. (1994). Portal hypertension in schistosomiasis: a long-term follow-up of a randomized trial comparing three types of surgery. *Hepatology* **20**:398-403.

Rikkers L F, Sorrell W T, Jin G.(1992), Which portosystemic shunt is best? *Gastroenterology clinics of North America* **21**:179-96.

Rikkers L F. (1998), The changing spectrum of treatment for variceal bleeding. *Ann Surg* **228**:536-546.

Rosemurgy, A.S, Goode, S.E, Zwiebel, B.R, Black, T.J, Brady, P.G.(1996), A prospective trial of transjugular intrahepatic portasystemic stent shunts versus small-diameter prosthetic H-graft portacaval shunts in the treatment of bleeding varices. *Ann Surg* **224**:378-384.

Rosemurgy A S, Frohman H A, Teta A F, Luberice K, Ross S B. (2012), Prosthetic H-graft portacaval shunts vs transjugular intrahepatic portasystemic stent shunts: 18-year follow-up of a randomized trial. *J Am Coll Surg* **214**:445-453

Ross, A.G, Bartley, P.B, Sleigh, A.C, Olds, G.R, Li, Y, Williams, G.M, *et al*.(2002), Schistosomiasis. *N Engl J Med* **346:**1212-1220.

Rossle M, Haag K, Ochs A, Sellinger M, Noldge G, Perarnau JM, et al.(1994), The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. *New England Journal of Medicine* **330**:165-171.

Rossle M, Siegerstetter V, Euringer W, Olschewski M, Kromeier J, Kurz K, et al. (2006), The use of a polytetrafluoroethylene-covered stent graft for transjugular intrahepatic portosystemic shunt (TIPS): long-term follow-up of 100 patients. *Acta Radiologica* **47**:660-666.

Sanyal A J, Bosch J, Blei A, Arroyo V.(2008), Portal hypertension and its complications. *Gastroenterology* **134**:1715-1728.

Sarfeh IJ, Rypins EB, Mason GR.(1986), A systematic appraisal of portacaval H-graft diameters. Clinical and hemodynamic perspectives. *Annals of surgery* **204**(4):356-363.

Sarfeh IJ, Rypins EB.(1994), Partial versus total portacaval shunt in alcoholic cirrhosis. Results of a prospective, randomized clinical trial. *Annals of surgery* **219**(4):353-361.

Smith J.L, Graham D.Y.(1982), Variceal hemorrhage: a critical evaluation of survival analysis. *Gastroenterology* **82**:968-973.

Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. (2010), Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. *Gastroenterology* **139**:1238-1245.

Snady H (1987), The role of sclerotherapy in the treatment of esophageal varices: personal experience and a review of randomized trials. *Am J Gastroenterol* **82**:813-822.

Spina, G.P, Henderson, J.M, Rikkers, L.F, Teres, J, Burroughs, A.K, Conn, H.O, *et al*. (1992), Distal spleno-renal shunt versus endoscopic sclerotherapy in the prevention of variceal rebleeding. A meta-analysis of 4 randomized clinical trials. *J Hepatol* **16**:338-345.

Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J.(2006) Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis* **6**:411-425

Sugiura, M, Futagawa, S.(1973), A new technique for treating esophageal varices. *J Thorac Cardiovasc Surg* **66**:677-685.

Sugiura, M, Futagawa, S.(1984) Esophageal transection with paraesophagogastric devascularizations (the Sugiura procedure) in the treatment of esophageal varices. *World J Surg* **8:**673-679.

Symmers WSC.(1904), Note on a new form of Liver Cirrhosis due to the presence of the Ova of Bilharzia *Haematobia*. *J Pathol Bacteriol* **9**:237-239.

Toomey, P.G, Ross, S.B, Golkar, F.C, Hernandez, J.M, Clark W.C, Luberice, K, et al. (2013) Outcomes after transjugular intrahepatic portosystemic stent shunt: a "bridge" to nowhere. *Am J Surg* **205**:441-446.

Vleggaar FP, van Buuren HR, Schalm SW. (1998) Endoscopic sclerotherapy for bleeding oesophagogastric varices secondary to extrahepatic portal vein obstruction in an adult Caucasian population. *European Journal of Gastroenterology & Hepatology* **10**:81-85.

Warren, W.D, Zeppa, R, Fomon, J.J.(1967), Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. *Ann Surg* **166**:437-455

World Health Organization (2014), Schistosomiasis: number of people receiving preventive chemotherapy in 2012. *Wkly Epedemiol Rec* **89**(2): 21-28.

Yin L, Liu H, Zhang Y, Rong W. (2013), The surgical treatment for portal hypertension: a systematic review and meta-analysis. ISRN *Gastroenterology* 2013:464053.

Zhang Y, Wen T, Yan L, Chen Z, Yang H, Deng X, et al. (2009), The changes of hepatic hemodynamics and functional hepatic reserve after splenectomy with periesophagogastric devascularization. *Hepato-gastroenterology* **56**:835-839.

Section 2: Draft article to Cochrane Database of Systematic review

This review has been approved by the Cochrane hepatobiliary group (CHBG) and the protocol published in Cochrane Database of Systematic review. The protocol citation is as follows:

Ede CJ, Brand M. Surgical portosystemic shunts versus devascularisation procedures for variceal bleeding due to hepatosplenic schistosomiasis [Protocol]. Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD011717. DOI: 10.1002/14651858.CD011717.

The final review has been completed and submitted to the editorial team of CHBG on 17/8/2016

Abstract

Background

Surgical interventions such as shunts and devascularisation procedures are effective therapies to prevent variceal rebleeding in people with hepatosplenic schistosomiasis. As this disease is prevalent in low income countries, the impact of eco-social factors result in poor compliance with non-surgical therapies that require repeated sessions and long-term follow-up.

Objectives

To determine whether surgical portosystemic shunts have better outcomes compared with oesophagogastric devascularisation procedures in the prevention of variceal rebleeding due to schistosomal portal hypertension.

Search Methods

We searched the Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, Science Citation Index Expanded and reference lists and proceedings of relevant associations for relevant trials up until May 2016.

Selection criteria

All randomised clinical trials comparing surgical portosystemic shunts with oesophagogastric devascularisation with or without splenectomy in the prevention of variceal rebleeding due to hepatosplenic schistosomiasis were selected. Trials that included participants with concomitant cirrhosis or who had undergone TIPS were excluded.

Data collection and analysis

We conducted data extraction and assessment of methodological quality using standards expected by The Cochrane Collaboration. We assessed risk of bias according to domains and risk of random errors with Trial Sequential Analysis. The quality of evidence was assessed by the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group approach.

Main results

Two trials that met the inclusion criteria of this review were selected. An analysis of 115 participants, 57 who received distal splenorenal shunt and 58 who received devascularisation procedure is presented. The trials were assessed at high risk of bias. There is no difference in overall mortality between distal splenorenal shunt versus devascularisation, risk ratio (RR) is 1.40, (95% confidence interval (CI) 0.32 to 6.15), downgraded to very low quality due to

over-all risk of bias, imprecision and publication bias. Variceal rebleeding following devascularisation is statistically significant higher than after DSRS (RR is 0.23, 95% CI 0.05 to 1.01), very low quality evidence due to bias, imprecision, and publication bias. The NNTB is 8. Serious adverse events reported as procedure specific include: portal vein thrombosis, haemolysis, ascites and shunt dysfunction. There was no report on quality of life. DSRS is associated with a statistically significant higher post procedure encephalopathy (RR 8.10, 95% CI 1.04 to 62.83), downgraded to very low quality due to overall risk of bias, imprecision, and publication bias. Trial sequential analysis shows no strong evidence to accept or reject the difference in variceal rebleeding and encephalopathy rate for both interventions because of bias and inadequate sample size. Outcomes of PSRS compared to devascularisation were reported by a single trial, therefore no meta-analysis was computed for this comparison, nor subgroup of PSRS compared to DSRS.

Authors' conclusions

Available evidence seems to suggest that DSRS is better than devascularisation for the prevention of variceal rebleeding due to hepatosplenic schistosomiasis, but this is at the cost of significant encephalopathy. The review authors are cautious to make this conclusion because overall evidence is very low quality and only few trials with small sample size are available. We suggest further randomised clinical trials with adequate sample size and methodological quality.

Background

Portal hypertension refers to the pathological increase of the hepatic venous pressure gradient, in other words the pressure gradient between the portal vein and inferior vena cava is increased (Sanyal 2008). Manometrically, portal hypertension is defined as hepatic venous pressure gradient greater than 8 mmHg, and clinically obvious variceal bleeding occurs when the pressure gradient exceed 12 mmHg (Sanyal 2008). This is a hallmark of liver cirrhosis; however, bleeding may also be caused by non-cirrhotic conditions such as hepatosplenic schistosomiasis. The sequelae of portal hypertension include the development of varices, encephalopathy, hypersplenism, and ascites (Goff 1993).

Unlike liver cirrhosis in which there is destruction of liver architecture with concomitant loss of hepatocyte function, the hepatosplenic form of chronic schistosomiasis causes presinusoidal portal hypertension (Ross 2002) where hepatic architecture and function are preserved in the absence of concomitant liver disease such as viral hepatitis infection (De Cock 1986; Denié 1996; Bica 2000). Despite schistosomiasis control issues, current evidence suggest high prevalence of the disease in Africa and the burden of undiagnosed hepatosplenic form remains high (Payne 2013). An East African study demonstrated that isolated hepatosplenic schistosomiasis accounted for a third of oesophageal varices in their population (De Cock 1982).

Oesophagogastric variceal bleeding is the most lethal complication of portal hypertension as the mortality from the first bleeding episode is approximately 15% to 20% in cirrhotic portal hypertension (Chalasani 2003; Carbonell 2004; Villanueva 2006), and 10% in non-cirrhotic portal hypertension (Chofle 2014). Recurrent bleeding is not uncommon in survivors of the first episode and is also associated with a similar mortality. The greatest risk of rebleeding is during the first thirty days following the initial variceal bleeding (Smith 1982).

The algorithm for the control of acute variceal bleeding is the same for both cirrhotic and non-cirrhotic portal hypertension, consisting of a combination of pharmacological (vasoactive agent) and endoscopic therapy. Using this management, bleeding will stop in 90% of people (D'Amico 2003; Gonzalez 2008; de Franchis 2010). The remaining 10% are classified as people with refractory bleeding, and further management options include radiologically placed TIPS or surgical interventions (shunt, devascularisation procedures, or liver transplantation) (de Franchis 2010). The risk of long-term rebleeding without further intervention following the control of acute variceal bleeding is approximately 80% (Kiire

1989; D'Amico 1995; Vleggaar 1998), hence secondary prevention is considered required in any person who has suffered a variceal bleed (de Franchis 2010).

Medical treatment (combined endoscopic band ligation and non-selective beta-blockers) is an effective first-line modality to prevent variceal rebleeding (de Franchis 2010; Sarin 2010). However, approximately 20% to 30% of people will still have recurrent variceal bleeding while being treated with medical therapy (Kiire 1989; Bhargava 1990; Vleggaar 1998; Sarin 2010). Therefore, patients are usually offered repeated sessions of endoscopy with sclerotherapy or banding to obliterate the varices. This may have cost and travel implications for the person and health system, specifically in resource-poor areas where schistosomiasis is endemic. Although surgical options for preventing variceal rebleeding are only considered as an alternative strategy when medical therapy fails, they may well be a one-stop procedure which entails fewer hospital visits, and less intensive follow-up (Henderson 2005; Pal 2012). TIPS has an efficacy of more than 90% rebleed free rate and is recommended as rescue therapy following the failure of medical treatment (Rossle 2006; Boyer 2010; de Franchis 2010). Although it is a less invasive procedure than a surgical procedure, it may have more complications and requires more re-interventions than surgical procedures. The occlusion and stenosis rate for TIPS is 17% compared with 9% for surgical shunts (Rosemurgy 2012); rebleeding occurs in 20% to 30% of people compared with less than 10% for surgical shunts; a median survival of 26 months compared with 52 months for surgical shunts (Rikkers 1998; Costa 2010; Rosemurgy 2012), and post shunt encephalopathy rate ranges between 18% and 45% (Rossle 1994; Deng 2006). In addition, TIPS requires more intensive long-term surveillance than surgical shunts due to their higher occlusion rates and resulting more frequent need for re-intervention, up to 21% for TIPS versus 6% for surgical shunts (Toomey 2013). There is no literature to our knowledge supporting the use of TIPS in SPH (Conn 1993; Eesa 2011).

Liver transplantation is an effective treatment for the definitive control of variceal rebleeding in people with end-stage liver disease (de Franchis 2010; Rosemurgy 2012), yet only 3% to 14% of people with cirrhosis complicated by variceal bleeding eventually receive transplantation post TIPS (Stanley 1996; Tripathi 2004; Rossle 2006; Rosemurgy 2012; Toomey 2013). However, people with SPH do not meet liver transplantation criteria as their liver function is preserved (Rosemurgy 2012).

Surgical shunts are considered for people with good performance status and Child-Pugh class A or early B (Child 1964; Pugh 1973; Garcia-Tsao 2010; Orloff 2012; Gur 2014). On the basis of their haemodynamic effect on portal circulation, surgical shunts are divided into selective and non-selective types. Non-selective shunts totally bypass portal blood flow into the systemic circulation, as opposed to selective shunts which maintain nutrient hepatic blood flow. A recent meta-analysis concluded that the rebleeding rate, encephalopathy, and late mortality are comparable for selective and non-selective shunts (Yin 2013). However, it has been argued that total portal decompression may precipitate encephalopathy in up to 39% of people with preserved liver function, such as people with SPH (Raia 1994). Therefore, selective shunts are considered to be superior to non-selective shunts in this subgroup (Henderson 1988; Da Silva 1992; Conn 1994; Raia 1994; Andersson 2007). Overall perioperative mortality following shunt procedures is 6% to 15%, with five-year survival rates approaching 80% in cirrhotics in whom mortality occurs as a result of progressive hepatic decompression (Rosemurgy 2012; Gur 2014). The survival data for non-cirrhotics such as hepatosplenic schistosomiasis exceed cirrhotics (Raia 1994, Gawish 2000)

Devascularisation procedures are effective rescue options in people where vascular anatomy is unsuitable for shunt surgery, such as extensive splenoportal thrombosis. However, the further role of devascularisation procedures remains controversial due to the high morbidity and mortality when compared with shunts in certain patient series (Selzner 2001). Overall 30-day operative mortality following devascularisation procedures ranges from 13% to 24% (Rikkers 1998; Qazi 2006; Voros 2012), and variceal rebleed rates up to 40% have been reported (Henderson 1988; Orozco 1992; Johnson 2006). However, the risk of encephalopathy is rare (Conn 1994; Raia 1994), and there is no need for post-procedure surveillance of shunts. Overall five-year survival is approximately 75% and is comparable to shunt procedures (Ezzat 1990; Orozco 1992). A significant procedure-specific morbidity is oesophageal anastomotic leak, which may be as high as 10% (Voros 2012).

Yin 2013 in a meta-analysis of selective shunt, non-selective shunt, devascularisation, and shunts plus devascularisation in control of both cirrhotic and non-cirrhotic variceal bleeding, concluded that the combined procedure was the best choice for secondary prophylaxis of variceal rebleeding (Yin 2013). They did not separate the results of people with and without cirrhosis in their review.

Description of condition

Schistosomiasis is a parasitic disease that is endemic in poor communities with inadequate sanitation and lack of access to potable water (Steinmann 2006). The World Health Organization (WHO) estimates that the total number of people infected worldwide is over 200 million with more than 90% of total infected people living in Africa (WHO 2014). The life cycle of this parasite involves two hosts namely human (the definitive host) and snail (the intermediate host). Human host become infected by contact with infested water where cercariae released by infected snail of the genus *Bomphalaria* penetrate the skin or mucosa, or both. Further maturation takes place in the lungs and liver to produce adult worms that migrate to the mesenteric vein where they mate and deposit their eggs. There are several species of the blood fluke, *Schistomatidae* family, but the two species namely *Schistosoma mansoni* found predominantly in Africa, Arabia, and South America, and *Schistosoma japonicum* found in South-East Asia, especially mainland China, are responsible for the hepatosplenic form of the disease (Colley 2014a). Available evidence suggests an immune-mediated granulomatous inflammatory reaction to the trapped eggs in portal vein radicles results in periportal fibrosis also called Symmer's pipe-stem fibrosis (Symmers 1904; Burke 2009; Colley 2014). This fibrosis subsequently results in the development of pre-sinusoidal portal hypertension (Ross 2002).

The prevalence of portal hypertension in schistosomiasis endemic areas approaches 18% in the absence of a schistosomiasis control programme (Mudawi 2007), of these 30% to 60% will develop varices (De Cock 1982; Saad 1991).

Description of intervention

The two categories of surgical procedure that were compared are portosystemic shunts versus devascularisation procedures.

(i). Portosystemic shunts are surgically created conduits that divert some or all of portal venous blood away from the liver into the systemic circulation. These conduits may be autogenous vein graft or polytetrafluoroethylene prosthesis. Commonly created surgical portosystemic shunts include the non-selective H-shunt and the selective DSRS (Warren 1967).

The H-shunt is created between the portal vein and the inferior vena cava using an 8 mm to 16 mm ringed polytetrafluoroethylene prosthesis. The PTFE graft is non expansible and by

diminishing its diameter from 16mm to 8mm a partial portal decompression is achieved (Sarfeh 1986; Sarfeh 1994).

The DSRS is created by anastomosing the distal splenic vein to the left renal vein and disconnecting the splenopancreatic and gastric venous connections to the portal system while preserving portal venous blood flow and hepatic function.

(ii). Oesophagogastric devascularisation includes transhiatal devascularisation of the lower oesophagus and proximal half of the stomach, with ligation of branches of left gastric, short gastric, left gastroepiploic, and perforating oesophageal arteries and veins. This is combined with splenectomy (Hassab 1967), or with oesophageal transection plus splenectomy in a two-stage operation (Sugiura 1973). The original Suguira procedure was subsequently modified into a one-stage abdominal procedure (Peracchia 1980; Inokuchi 1985), or without oesophageal transection (Jin 1996; Johnson 2006), or without truncal vagotomy (Ginsberg 1982), and without splenectomy (Orozco 1998). One randomised clinical trial comparing devascularisation with splenectomy or without splenectomy showed no statistically significant difference in outcome between the two methods; however, there was a significant increase in transfusion requirement in the splenectomy group. This trial demonstrates that splenectomy may not be mandatory in devascularisation procedure (Orozco 1998).

How the intervention might work

Surgical portosystemic shunts and devascularisation procedures decrease portal venous pressure, and hence decrease portal hypertension, which consequently prevents variceal bleeding.

Oesophagogastric devascularisation with splenectomy reduces portal hypertension by decreasing portal blood flow, but with a compensatory increase in hepatic artery flow. This maintains effective hepatic blood flow and preserves liver function. The procedure normalises the hyperdynamic circulatory state present in schistosomal portal hypertension (de Cleva 2007; Zhang 2009; Evangelista-Neto 2012).

Why it is important to do this review

To date, no meta-analysis or systematic review has compared surgical portosystemic shunts versus devascularisation procedures to prevent variceal rebleeding due to schistosomal portal hypertension.

Objectives

To determine whether surgical portosystemic shunts have better outcomes compared with oesophagogastric devascularisation procedures in the prevention of variceal rebleeding due to schistosomal portal hypertension.

Methods

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) were identified in which surgical portosystemic shunts were compared with oesophagogastric devascularisation (with or without splenectomy) for the prevention of variceal rebleeding in people with hepatosplenic schistosomiasis. 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 reduces the risk of overlooking harms.

Types of participants

Inclusion

Participants with hepatosplenic schistosomiasis complicated by variceal bleeding (whether first episode or recurrent) were included.

Exclusion

Participants with concomitant cirrhosis from any cause or who have had TIPS were excluded.

Types of interventions

The following types of surgical shunt interventions were considered:

1. portacaval shunt (connecting the portal vein and the vena cava);
2. mesocaval shunt (connecting the mesenteric vein and the vena cava);
3. central (proximal) splenorenal shunt (connecting proximal splenic vein to left renal vein with or without splenopancreatic and gastric disconnection or splenectomy);
4. distal splenorenal shunt (connecting distal splenic vein to left renal vein with or without splenopancreatic and gastric disconnection);

5. large-diameter H-graft shunt (16 mm, externally reinforced polytetrafluorethylene either as mesocaval or portocaval shunt);
6. small diameter H-graft shunt (8 mm, externally reinforced polytetrafluorethylene either as mesocaval or portacaval shunt).

Oesophagogastric devascularisation with or without splenectomy, and with or without oesophageal transection was considered as the comparator.

Types of outcome measures

Primary outcomes

1. All-cause mortality:
    - immediate (30 days);
    - intermediate (one year); and
    - long-term (five years).
2. Variceal rebleeding rate (diagnosed clinically by haematemesis, melaena, or blood in gastric aspirate, or by endoscopy).
3. Serious adverse events (procedure-related complications). We used the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice's definition of a serious adverse event (ICH-GCP 1997), that is, any untoward medical occurrence that resulted in death, is life threatening, requires hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. We considered all other adverse events as non-serious.
4. Quality of life (QOL): We defined QOL as the extent to which a person's usual or expected physical, emotional, and social well-being has been affected by the intervention (Cella 1995). Since trial authors are likely to use different instrument to measure quality of life, the recommendation for choosing a statistical method to enhance interpretability (Thorlund 2011b) was used were possible to evaluate quality of life estimates in this meta-analysis.

Secondary outcomes

1. Number of people who developed encephalopathy, defined by any of the following:

a). classical signs detected on physical examination (change in mental status examination in association with elevated ammonia, and asterixis);

b). signs unequivocally described by person's relatives;

c). psychometric testing; or

d). electroencephalogram.

2. Development of new or worsening of pre-existing ascites detected clinically or radiologically.
3. Number of people requiring re-intervention.

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 2016 May 2016), Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4), MEDLINE (Ovid SP; 1946 to May 2016), EMBASE (Ovid SP; 1974 to May 2016), and Science Citation Index Expanded (Web of Science; 1900 to May 2016) (Royle 2003). The search strategies and the time spans of the searches are listed in Appendix 2.

Searching other resources

Reference list of identified studies were hand-searched for further relevant trials.

Conference/meeting proceedings and abstracts published by International Hepato-Pancreato Biliary Association (IHPBA) (1994 to May 2016), the American Association for the Study of Liver Diseases (AASLD) (1994 to May 2016), and other relevant organisations were also searched.

Data collection and analysis

Selection of studies

CJE and MB independently applied the inclusion criteria to select relevant studies. Areas of disagreement were resolved through discussion. Unpublished data were sort by writing to the authors.

Data extraction and management

The review authors (CJE and MB) independently extracted data from selected trials using a standardised data collection form Appendix 1, which included.

- Name of first author.
- The date of trial publication.
- Country of trial and duration of follow-up.
- Inclusion and exclusion criteria.
- Demographic data.
- Biochemical data.
- Method of diagnosis of schistosomiasis.
- Number of participants randomised, number excluded with reasons, and number of withdrawals.
- Methodological quality.
- Outcomes.

Assessment of risk of bias in included studies

Methodological quality was defined as the confidence that the trial design, conduct, analysis, and subsequent report have minimised or avoided biases in the intervention comparison (Schulz 1995; Moher 1998; Sterne 2002). In order to control for bias (Schulz 1995; Moher 1998; Kjaergard 2001; Verhagen 2001; Wood 2008; Lundh 2012; Savović 2012a; Savović 2012b), the risk of bias for included trials were assessed using the following domains as recommended in the *Cochrane Handbook for Systematic Reviews of interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2016). Where this information has not been provided in the trial report, trial authors were contacted.

Random sequence generation

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

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 used for the assessments of harms and not for benefits.

Blinding of participants and personnel

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.
- Unclear risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding and the assessment of outcomes were likely to be influenced by lack of blinding.

Blinding of outcome assessment

- Low risk of bias: blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding.

- Unclear risk of bias: there was insufficient information to assess whether blinding was likely to induce bias on the results.
- High risk of bias: no blinding or incomplete blinding and the assessment of outcomes were likely to be influenced by lack of blinding.

Incomplete outcome data

- Low risk of bias: missing data were unlikely to make treatment effects depart from plausible values. Sufficient methods, such as multiple imputations, 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 of bias: The original trial protocol is available and all predefined outcomes of interest in the review have been reported in the predefined pattern. If the trial protocol was obtained from a trial registry (e.g., www.clinicaltrials.gov), and the trial was run and published during the years when trial registration was not required, we would have scrutinised all publications reporting on the trial to identify the trial objectives, if all outcomes specified in the trial objectives are provided in the results section of the publication.
- Unclear risk of bias: not all pre-defined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more pre-defined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appeared to be free of industry sponsorship or other type of for-profit support that may manipulate the trial design, conductance, or results of the trial.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as no information on clinical trial support or sponsorship was provided.

- 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 bias domains that could put it at risk of bias.
- Unclear risk of bias: the trial may or may not have been free of other domains 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.

Trials were classified at low risk of bias if assessed with low risk of bias in all of the above domains and as high risk of bias if assessed as unclear or high risk in one or more of the above domains.

Measures of treatment effect

We measured intervention effects using risk ratios (RR) with 95% confidence interval (CI) for dichotomous variables, and continuous variables if identified were measured with a standardized mean difference. A pooled estimate of treatment effect was calculated using the random-effects model (DerSimonian 1986), and the fixed-effect model (DeMets 1987). In case of statistical differences between the two models, we report both results; otherwise, the results from the model with the most conservative findings (the analysis with the highest P-value) was reported (Jakobsen 2014). The degree of heterogeneity between trials was measured using the I^2 statistic (Higgins 2002; Sterne 2011).

Unit of analysis issues

The unit of analysis were the participants recruited into comparison groups of the trials.

Dealing with missing data

None of the trials used an intention-to-treat analysis, but we considered the impact of attrition bias in our review findings. Where the method of dealing with incomplete data was not clear the trial authors were contacted to provide clarification.

Assessment of heterogeneity

Heterogeneity was assessed using the Chi^2 test and I^2 statistic (Egger 1997; Sterne 2011), and the values interpreted as follows:

- 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.

An I^2 value above 50% was considered as significant, and subgroup analyses to investigate the possible cause of heterogeneity were attempted where possible.

Assessment of reporting biases

No published protocols were found for either trial; however, trial publications included outcomes of interest as stated in the method section. A funnel plot could not be drawn to assess reporting bias as there were only two trials (Begg 1994; Egger 1997; Harbord 2006).

Data synthesis

Recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and the Cochrane Hepato-Biliary Group Module (Gluud 2016) were followed while performing this meta-analysis. Intervention effect was calculated using risk ratio for dichotomous outcomes. The statistical packages Review Manager 5 (RevMan 2014) and Trial Sequential Analysis (Thorlund 2011a; TSA 2011) were used for data analysis. The Mantel-Haenszel method was also used for this meta-analysis (Mantel 1959).

Trial Sequential Analysis

Cumulative meta-analyses can introduce random errors because of sparse data and repetitive analyses; hence trial sequential analysis was used in this review (Thorlund 2011a; TSA 2011). In an attempt to reduce random errors, the diversity-adjusted required information size (i.e., the number of participants needed in a meta-analysis to detect or reject a certain intervention effect) was calculated by making the following assumption (Wetterslev 2008): a relative risk reduction of 20% or the relative risk reduction observed in the included trials

with low risk of bias, a risk of type I error of 5%, a risk of type II error of 20%, and assumed diversity present in the meta-analysis (Brok 2008; Wetterslev 2008; Brok 2009; Thorlund 2009; Wetterslev 2009; Thorlund 2010). A constant continuity correction of 1.0 was applied were trials recorded no event as required by trial sequential analysis software. 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 diversity-adjusted required information size, we constructed trial sequential monitoring boundaries. If the test statistics crossed the trial sequential monitoring boundary for benefit or harm before the required information size was reached, we concluded a statistically significant difference in estimate of effect exist. In contrast, if the boundary was not surpassed, we concluded that there is no difference in the estimate of effect as the test statistics were below the futility boundary. However, where the test statistic crossed the monitoring boundary for futility before the required information size was reached, it may not be necessary to continue conducting further trials (Wetterslev 2008; Thorlund 2011a).

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was performed to investigate the origin of significant heterogeneity in total rebleeding. Further subgroup analyses were not possible because of small sample or insufficient comparable groups. A funnel plot was not used as there were an insufficient number of trials for this meta-analysis.

Sensitivity analysis

Eligibility criteria for included and excluded trials were reviewed and none were found to be dubious. Data imputation for this review was reassessed; the results and conclusion were determined to be durable. Trial Sequential Analysis was used to reassess the imputed data for random errors.

'Summary of findings' table

Primary and secondary outcomes are listed in Summary of findings table 1 using GRADEpro software (GRADEpro), based on five domains: risk of bias, inconsistency, indirectness, imprecision, and risk of publication bias.

Assumed risk was determined from the literature. The corresponding risk (and its 95% credible interval) was based on the assumed risk in the comparison group and the relative effect of the intervention (and it's 95% CI).

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group grades of evidence were used:

- high quality: further research is very unlikely to change our confidence in the estimate of effect;
- moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- very low quality: we are very uncertain about the estimate.

Results

Description of studies

Results of the search

The database search identified 1846 references; no references were identified from other sources. Following exclusion of duplicates, 1144 references were screened for inclusion into this review. Seventeen references were selected for full manuscript review of which 12 studies were excluded with reasons (Characteristics of excluded studies). Five published reports of two randomised clinical trials (Da Silva 1992; Raia 1994; Strauss 1999; Gawish 2000, Conn 1994) met the eligibility criteria and were included for the meta-analysis (Characteristics of included studies), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher 2009; Figure 1).

Included studies

Two trials (Raia 1994; Gawish 2000) comprising 154 participants were analysed. Raia 1994 randomised 94 participants into three groups: 32 to proximal (central) splenorenal shunt, 30 to distal splenorenal shunt, and 32 to devascularisation. The age range of their participants was 18 years to 55 years, and 11 participants were excluded from their analysis. The study was conducted in Brazil. Gawish 2000 randomised 60 participants equally into two groups: distal splenorenal shunt versus devascularisation. The age range of their participants was 23

years to 65 years with a mean of 41 years. The participants excluded post randomisation were replaced and they conducted their study in Egypt. In both trials liver biopsy was performed to confirm features of periportal fibrosis and to exclude cirrhosis. However, Gawish 2000 included participants classified as Child-Pugh class A and B. This created the impression that some participants could be cirrhotic. The trial authors were contacted for clarity, but it appears that this could be problem of external validity (Characteristics of included studies).

Excluded studies

Twelve trials were excluded with reasons following the review of the full-text articles. Nine were excluded as they included cirrhotic participants. Two other articles were duplicate publications of excluded trials, while one (de Cleva 2007) is a quasi-randomised study which evaluated haemodynamic parameters before and after interventions in hepatosplenic schistosomiasis. This study was excluded because harms of intervention were not reported. (Characteristics of excluded studies).

Risk of bias in included studies

Methodological qualities in all predefined domains were evaluated; both included trials were at high risk of bias as more than one domain was either unclear or high risk (Figure 2; Figure 3).

Allocation (selection bias)

Allocation sequence was generated using random number table by (Raia 1994) but it was not clear the method used by (Gawish 2000). However in both trials sealed envelopes were used to conceal allocations and therefore are considered at low risk of selection bias.

Blinding (performance bias and detection bias)

It was not clear if blinding was used in either trial. However, blinding clinicians and trial participants for surgical procedures is difficult to impossible. Therefore, we considered this to have an unclear risk of performance and detection bias.

Incomplete outcome data (attrition bias)

Neither trial employed an intention-to-treat method in their analysis. Gawish 2000 excluded all participants whose procedure were regarded as not properly done and replaced them with others. The method of selection of neither these replacement participants nor the adverse events in the participants who were replaced was not clearly documented in their publication. The author was contacted to clarify this discrepancy but did not provide satisfactory explanation. Raia 1994 excluded all participants with missing data. Therefore, we assessed both trials as high risk of attrition bias.

Selective reporting (reporting bias)

Neither trial had published report of their protocol. However, it appears that all predefined outcomes in their method section were reported, but all potential adverse events were not reported. Therefore, we assessed both trials as unclear risk of reporting bias.

Other potential sources of bias

The impact of industry sponsorship was considered; however, it was unclear how Gawish 2000 funded their trial. Raia 1994 reported an institutional grant as source of funding. This was assessed as low risk of bias.

Effects of interventions

All shunts (proximal and distal splenorenal shunt) versus devascularisation

A total of 143 participants from two trials (Raia 1994; Gawish 2000) received one of three types of surgical procedures: 28 to proximal splenorenal shunt, 57 to distal splenorenal shunt, and 58 to oesophagogastric devascularisation with splenectomy. Raia 1994 randomised their participants into three surgical groups: proximal splenorenal shunt, distal splenorenal shunt and devascularisation, but Gawish 2000 randomised their participants into two groups: distal splenorenal shunt and devascularisation. We determined that a meta-analysis of 'all shunt' compared with devascularisation is not possible as both trials are not similar with regards to this comparison hence the occurrence of significant heterogeneity, I^2 =50% in the estimate of all-cause mortality and I^2 =78% in the estimate of total rebleeding rate (Analysis 1.1; Analysis 1.2).

Distal splenorenal shunt versus devascularisation

Both trials (Raia 1994; Gawish 2000) included data from 115 participants who received two types of procedures, distal splenorenal shunt or devascularisation. Raia 1994 reported their outcomes at different time points, two years, and ten years. Gawish 2000 reported five year outcomes.

All-cause mortality

There were a total of seven deaths out of 115 participants, four deaths occurred in the DSRS group versus three in the devascularisation group. The main cause of death was rebleeding in four out of seven deaths. There was no significant difference in all-cause mortality (RR 1.40, 95% CI 0.32 to 6.15) P = 0.66, I^2 = 3%; Analysis 2.1).

Variceal rebleeding

Both trials reported total rebleeding rate, and subgrouped participants into sources of rebleeding. This included two variceal, three non-variceal and two undetermined bleeders in the DSRS group; nine variceal and five non-variceal bleeders in devascularisation group. One variceal rebleed in DSRS group in Gawish 2000 was caused by shunt occlusion. There was no statistically significant difference for total rebleeding rate; however, substantial heterogeneity using random-effects meta-analysis was noted (RR 0.43, 95% CI 0.05 to 3.71, P = 0.44, I^2 = 74%; Analysis 2.2).

The meta-analysis of rebleeding sources (variceal or non-variceal) showed that the heterogeneity had disappeared. Random-effects meta-analysis of variceal rebleeding showed significantly less rebleeding with DSRS compared with devascularisation (RR 0.23, 95% CI 0.05 to 1.01, P = 0.05, I^2 = 0%). This was similar with fixed-effect model (RR 0.23, 95% CI 0.05 to 1.00, P = 0.05, I^2 = 0%; Analysis 2.3). The event rate in DSRS of two out of 57 compared to nine out of 58 in devascularisation gave a NNTB of 8.

However, Trial Sequential Analysis diversity-adjusted calculated required information size of 188 was not reached, and the cumulative Z-curve did not cross the trial sequential monitoring boundaries or the futility boundary. The trial sequential pooled effect is 0.23 with alpha-spending adjusted 95% confidence interval (CI) 0.03 to 1.69 (Figure 4).

Serious adverse events

The serious adverse events reported are shown in, Serious adverse event table. There was heterogeneity in the pattern of reporting and most events were procedure-specific. None of the studies reported on all types of serious adverse events, for example anastomotic leak and surgical site infections were not reported. The confidence interval for the reported serious adverse events was calculated using the Wilson method (Wilson 1927).

Quality of life

Neither trial reported on quality of life.

Encephalopathy

Seven out of 57 participant in DSRS group versus none in the devascularisation group developed post procedure encephalopathy. This difference is statistically significant using a random-effects meta-analysis (RR 8.10, 95% CI 1.04, to 62.83) P = 0.05, I^2 = 0%; Analysis 2.4). The same effect was observed using a fixed-effect meta-analysis (RR 8.15, 95% CI 1.05, to 63.07) P= 0.04, I^2 = 0%). Trial Sequential Analysis was used to compute diversity adjusted required information size of 157, based on assumed type I error of 5%, and type II error of 20%. The cumulative Z-curve did not cross the sequential monitoring boundary and the required information size was not reached. In addition futility boundary was not surpassed. The Trial sequential Analysis pooled effect is 8.1 and alpha-spending adjusted 95% CI 0.68 to 96.96 (Figure 5).

Re-intervention

One out of 30 participants (3%, 95% CI (1% to 17%) in the DSRS group required a re-intervention due to rebleeding caused by shunt occlusion (Gawish 2000).

Proximal splenorenal shunt versus distal splenorenal shunt

A meta-analysis of PSRS compared with DSRS could not be performed because only one trial (Raia 1994) could be identified. However the result from this study shows all-cause mortality (RR 2.89, 95% CI 1.06 to 7.87; Analysis 3.1), and encephalopathy (RR 2.65, 95% CI 0.96 to 7.32; Analysis 3.4), following PSRS is statistically significant higher than after

DSRS. There was no statistical difference in rate of variceal rebleeding (RR 2.89, 95% CI 0.32 to 26.12; Analysis 3.3), intravascular haemolysis (RR 0.55, 95% CI 0.28 to 1.10; Analysis 3.5), or shunt occlusion (RR 1.65, 95% CI 0.35 to 7.71; Analysis 3.6).

Discussion

Summary of main results

This systematic review was designed to compare all portosystemic shunts versus devascularisation in the prevention of variceal rebleeding due to hepatosplenic schistosomiasis. We identified only two randomised clinical trials which compared two types of procedures, namely distal splenorenal shunt and devascularisation with splenectomy suitable for this review. Hence the results of this comparison are presented in this review.

The meta-analysis demonstrated no mortality difference between both procedures based on very low quality evidence.

The risk of variceal rebleeding post procedure was more common with devascularisation compared to DSRS. There could be several reasons for the higher rate of rebleeding associated with devascularisation. Firstly, the various modifications of this procedure could result in incomplete devascularisation (Hassab 1998; Orozco 1998). Secondily, a high rate of portal vein thrombosis could follow splenectomy (Eguchi 1991); and lastly, recanalization of varices due to maintenance of azygos blood flow after devascularisation could play a role (Vons 1996). However, Trial Sequential Analysis showed no firm evidence to accept a significant difference in variceal rebleeding rate, but more trials are required in order to reach the required information size before a firm conclusion is drawn.

Encephlopathy was significantly more common following DSRS. This could be explained that a proportion of portal venous blood flow was diverted into the systemic circulation, thus bypassing the detoxifying liver as opposed to devascularisation were effective hepatic blood flow is maintained (Raia 1991; Vons 1996; Pereira 2013). A reversal of hepatopetal flow to hepatofugal flow which has been documented in cirrhotics treated with DSRS could play a role but none of the trials demonstrated this (Lacy 1992). Trial sequential analysis showed no firm evidence to accept the difference in encephalopathy because quality of evidence is very low due to imprecision, high risk of bias, and publication bias. Raia 1994 described a grading

system for encephalopathy in their method but did not grade their findings. Gawish 2000 reported a hepatopetal blood flow in all their participants, and all cases of encephalopathy were described as mild because they all resolved promptly with dietary modification. A meta-analysis of encephalopathy in PSRS compared with DSRS could not be undertaken as there were insufficient RCTs. Raia 1994 compared proximal splenorenal shunt versus distal splenorenal shunt and reported a significant difference in rate of encephalopathy in favour of DSRS (RR 2.65, 95% CI 0.96 to 7.32; Analysis 3.4).

Serious adverse events could not be analysed as an outcome; however, we report the individual trial adverse events in, (Serious adverse event table). The rate of portal vein thrombosis in Gawish 2000 is higher than published data (Eguchi 1991), which raises questions as the only modality for diagnosis as reported by the authors was use of duplex ultrasonography. These data are skewed by the number of asymptomatic partial portal thrombosis of 17 out of 30 participants compared to total portal vein thrombosis of one out of 30 participants, (Serious adverse events table). Infectious complications specifically overwhelming post splenectomy infection (OPSI) is a concern when devascularisation is associated with splenectomy. Both studies did not provide data for this adverse event; however evidence suggests a preservation of cellular and humoral immunity in hepatosplenic schistosomiasis that is protective against OPSI (Ma 1993; Ferreira 2007).

Quality of life following any healthcare intervention determines how patients accept such interventions, and has implication for healthcare policy decision-making (Vianello 2011; Roszell 2013). None of the studies measured this outcome and this adds to the limitations of this review.

Overall completeness and applicability of evidence

The two trials selected for this review consisted of a small number of participants; hence estimates of intervention effects varied between studies and were largely small. Neither of the trials evaluated all the predefined outcomes of our protocol; for example, we could not evaluate for quality of life and all adverse events. This has implication for acceptance of healthcare interventions. Although the correct participants were recruited, not all interventions were studied by both trials making comparison impossible. We intended to include quasi-randomised studies and observational studies for the assessment of harms of

interventions but no such studies that evaluated adverse events were found. This is limitation of this meta-analysis because of the risk of overlooking harms of interventions.

We could not investigate for heterogeneity using funnels plot because of inadequate number of trials. Subgroup analyses were not possible due to the small sample sizes. Therefore, available evidence is inconsistent, imprecise and of very low quality to adequately address the review question. Current guideline recommend endoscopic treatment as first-line for the prevention of variceal bleeding and surgery as rescue treatment when the former fails (de Franchis 2010; Sarin 2010). Nonetheless controversy remains as to what the best surgical procedure is. Trial sequential analysis demonstrated that more trials are needed to achieve the required information size in order to attain the true intervention effect for most outcomes.

Strauss 1999 studied 73 participant subsets of (Raia 1994) trial for changes in variceal size post intervention. Clinical assessment of variceal size is highly subjective. Moreover there was no correlation of variceal size to rebleeding in this study. Therefore this outcome was not included in this meta-analysis.

Quality of the evidence

The two trials selected for this review are at high risk of bias. Such trials have the potential to give false intervention effect estimates due to their inadequate design (Schulz 1995; Moher 1998; Kjaergard 2001; Verhagen 2001; Wood 2008; Lundh 2012; Savović 2012a; Savović 2012b). Both trials randomised 154 participants to three types of surgical procedure but only the data of 115 participants who received two types of surgical procedures (distal splenorenal shunt versus devascularisation) were available for the final analysis.

The quality of evidence for all-cause mortality, variceal rebleeding and encephalopathy is downgraded three levels to very low quality for risk of bias based on the over-all assessment, imprecision (very large confidence interval, few participants) heterogeneity; and reporting bias (few publications report the outcome).

There is significant heterogeneity between the trials. We performed a meta-analysisof variceal-rebleeding despite the small number of events. It is possible that the calculated effect size could have overestimated the benefit or underestimated the harm of the interventions. We applied Trial Sequential Analysis to evaluate for random error (Wetterslev 2008). It

appears that further trials are needed to draw a firm conclusion of an intervention effect. We could not perform a meta-analysis of PSRS versus DSRS, nor PSRS versus devascularisation due to insufficient number of trials. Moreover the impact of publication bias on this review could not be investigated using funnels plot because the number of trials required should be ten or more. This is also an important limitation of this review.

Potential biases in the review process

Analysis of the included studies (Raia 1994; Gawish 2000) showed that one trial (Raia 1994) used a random number table to generate sequence but the method used by Gawish 2000 was unclear. Both trials used sealed envelopes for allocation concealment. Neither of the trials was blinded to personnel, nor participants and outcome assessors, but we are not convinced that this could have introduced bias, because all were objective outcomes. There was risk of attrition bias in both trials as one study excluded incomplete data in their computation, while the other replaced all participants with incomplete data using a method that was unclear. Neither trials published protocol; one trial was funded by institutional grant while the source of funding was unclear for the other. We conclude that both trials were at high risk of bias based on the protocol predefined domains.

Sensitivity analysis was performed to evaluate the search process, method for selection of included studies and data extraction by the review authors. We also reviewed the decision made to exclude certain studies or resolve disagreement for potential sources of bias but found none.

Agreements and disagreements with other studies or reviews

To date there has been no systematic review that has compared surgical portosystemic shunts to devascularisation with or without splenectomy for prevention of variceal rebleeding due to hepatosplenic schistosomiasis. This review was designed to provide evidence for the best surgical procedure in terms of efficacy and adverse events. We found two surgical procedures (DSRS versus devascularisation) in two trials that fulfilled the requirements of our review protocol for this meta-analysis.

Yin 2013 published a meta-analysis that compared four types of interventions: non-selective shunt, selective shunt, devascularisation, and a procedure that combines shunt and

devascularisation. Their participants included cirrhotics and non-cirrhotics. The finding of their review is in agreement with this meta-analysis. However, they showed that the combined procedure was associated with significantly less rebleeding. Moreover, the encephalopathy rate for the combined procedure was comparable to that of devascularisation. They recommended the combined procedure in all type of variceal bleeding. Their review has similar limitations as the present review and they have not reported the adverse events associated with the combined procedure but one would expect it will be higher than the isolated procedures.

Zong 2015 published a meta-analysis of eleven studies comparing devascularisation to surgical shunts in both cirrhotic and non-cirrhotic portal hypertension. The conclusion of that meta-analysis agrees with our review. It would seem that people with hepatosplenic schistosomiasis behave the same as cirrhotics. This could be due to similar participant sets in both cirrhotic and non-cirrhotics. The current practice in the era of TIPS, and liver transplantation demand that these surgical procedures are performed in well-compensated cirrhotics (Gur 2014).

Authors' conclusions

Implications for practice

Given that available body of evidence is very low quality, we could not determine an overall outcome benefit or harm of DSRS compared with devascularisation in prevention of variceal rebleeding due to hepatosplenic schistosomiasis. There appears to be a tendency to less episodes of variceal rebleeding following a distal splenorenal shunt, and decreased incidence of encephalopathy following devascularisation.

Implications for research

Future randomised clinical trials evaluating the outcomes of surgical portosystemic shunts such as H-graft shunts and the DSRS compared with devascularisation with or without splenectomy and with or without oesophageal transection are required. In order to achieve sufficient statistical power, such trials should be conducted in multiple institutions located in schistosomiasis endemic areas. All outcomes of interests such as all-cause mortality, variceal rebleeding, serious adverse events, encephalopathy, cost, haemodynamic changes, and quality

of life should be evaluated. These trials should have their protocol drafted according to the SPIRIT statement (Chan 2013) and their reporting according to the CONSORT statement (Schulz 2010).

Differences between protocol and review

The title of the review was changed into: "Surgical portosystemic shunts versus devascularisation procedure for prevention of variceal rebleeding due to hepatosplenic schistosomiasis". This has been done to reflect the objective of the review as highlighted by the editors.

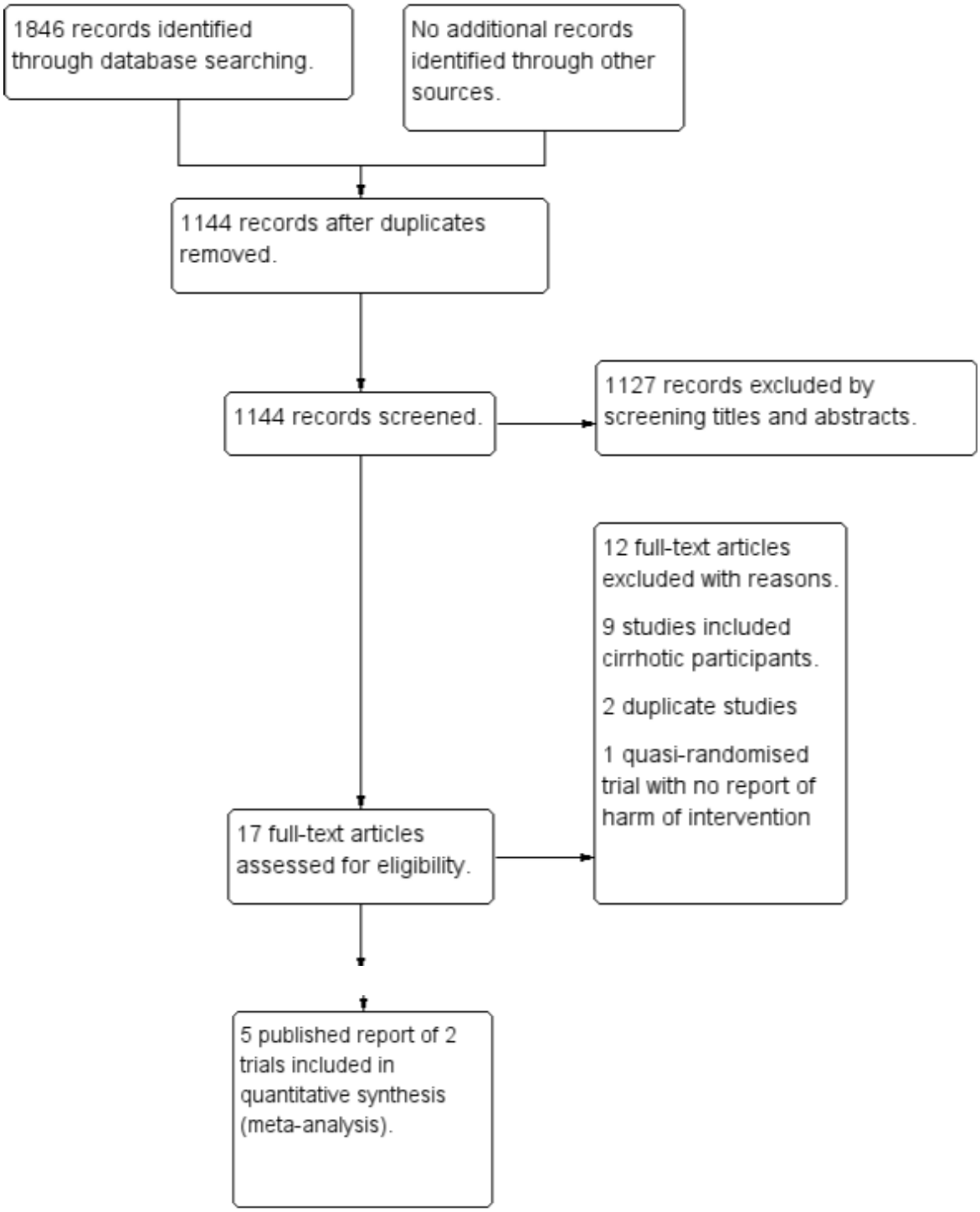
Contributions of authors

CJE drafted the review.
CJE and MB conducted the search and data extraction.
CJE entered the data into Revman, data analysis and interpretation.
CJE and MB discussed and approved this review.

Declarations of interest

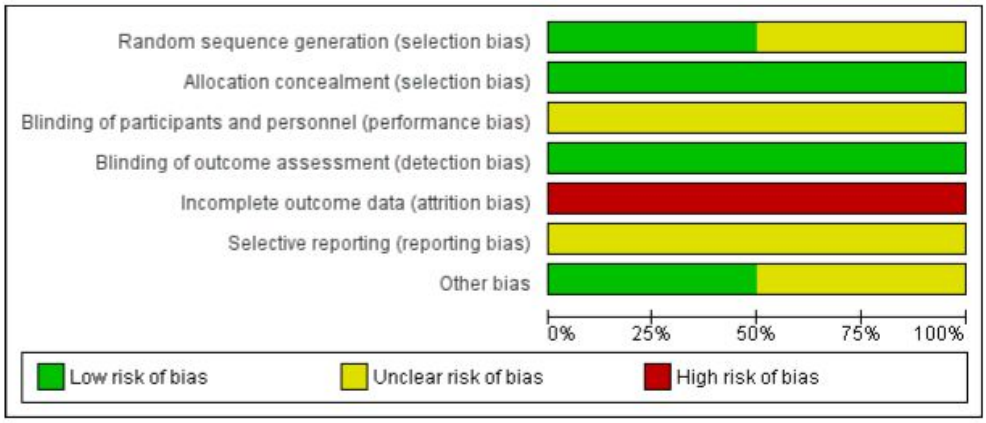
CJE has nothing to declare.
MB has nothing to declare.

Figure 1



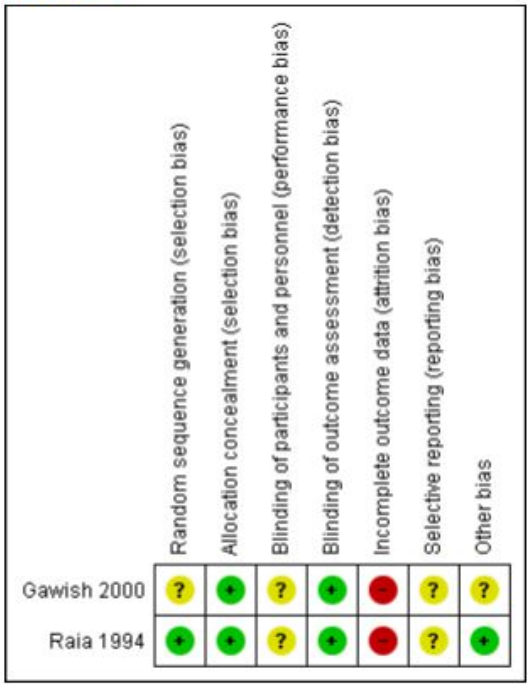
Study flow diagram.

Figure 2



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

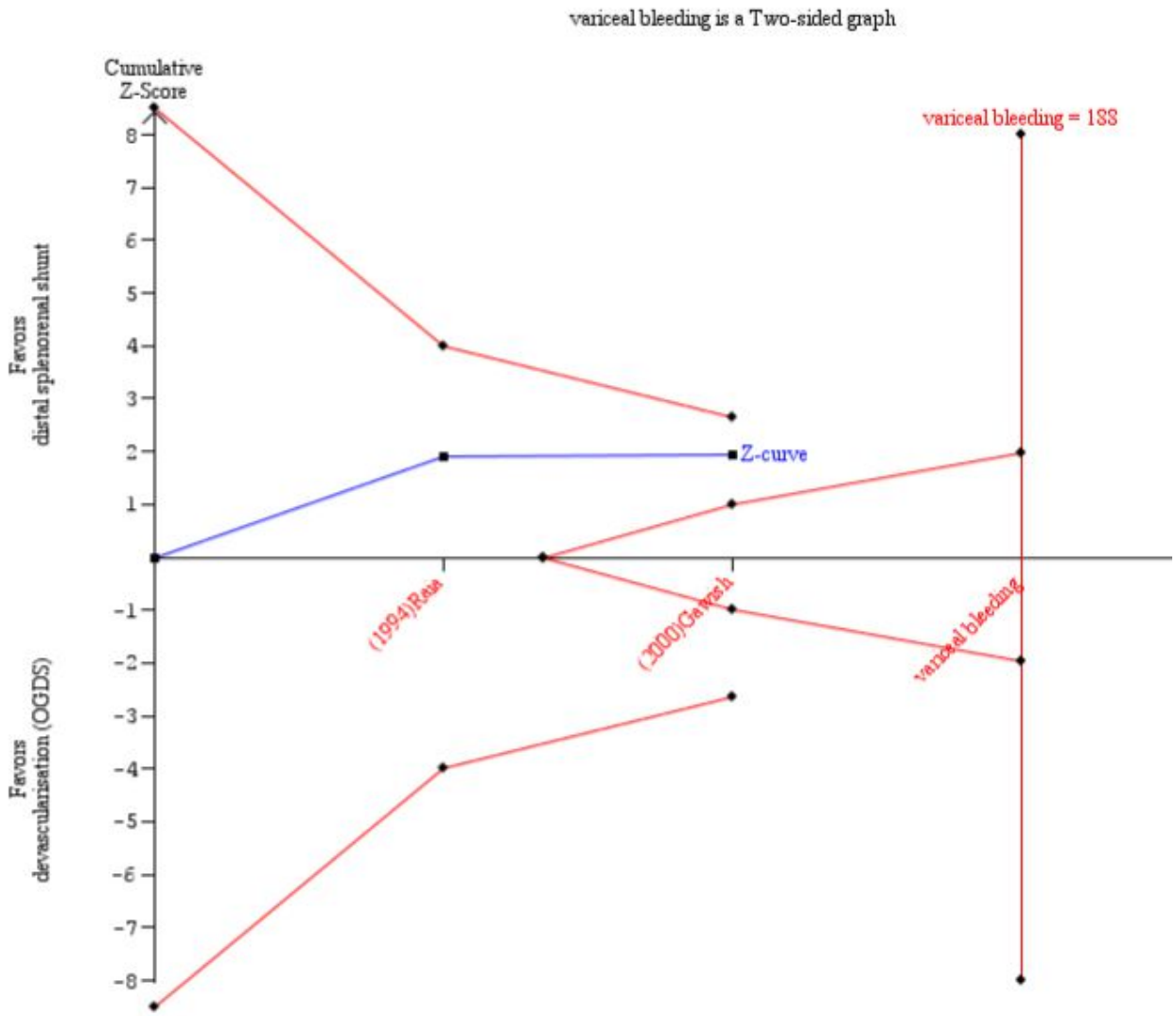
Figure 3



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

Trial sequential graph (variceal rebleeding)

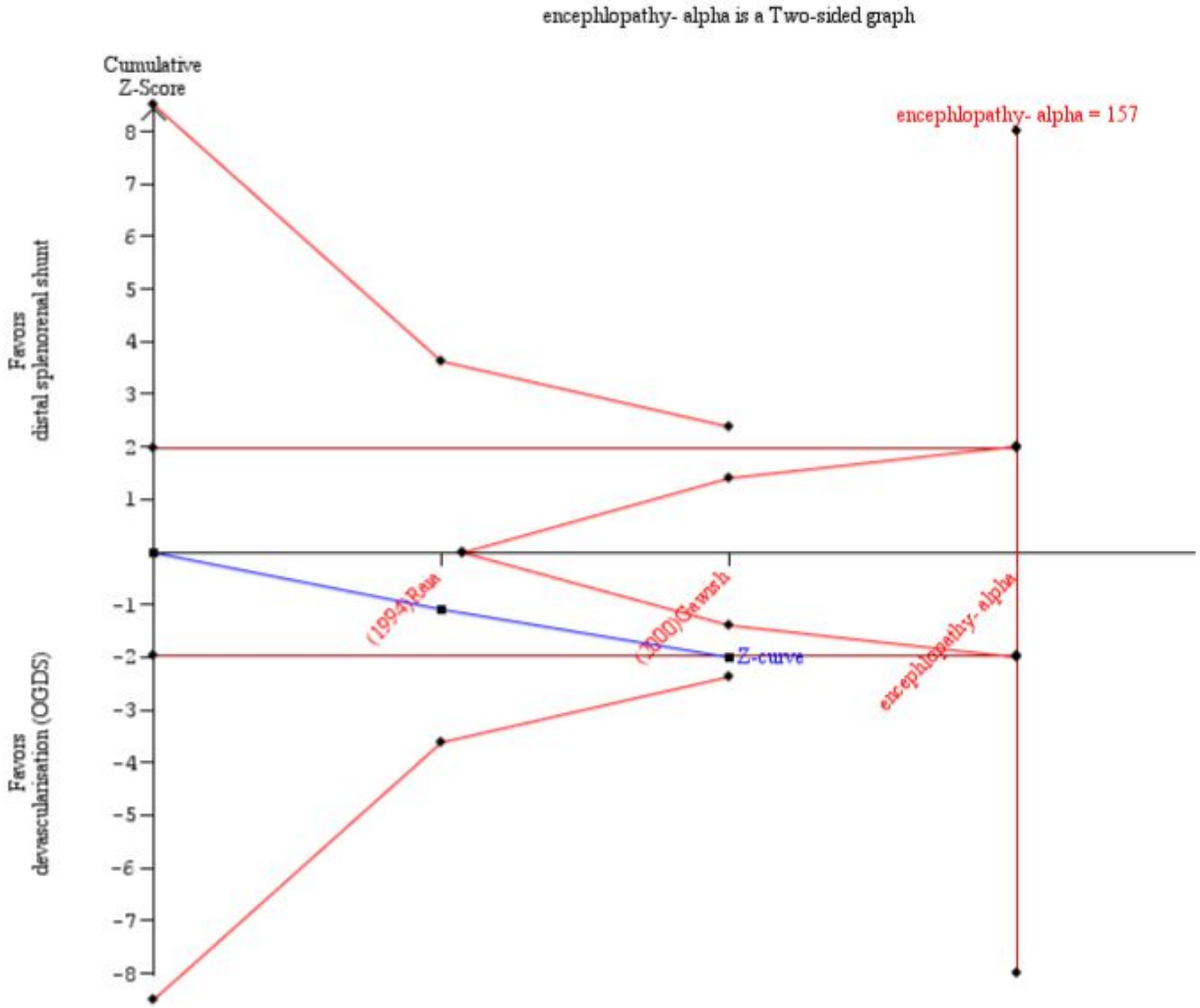
Figure 4



Trial Sequential Analysis of variceal rebleeding for 115 participants of both trials of distal splenorenal shunt versus devascularisation. The diversity-adjusted required information size of 188 was calculated. The blue cumulative Z-curve did not cross the trial sequential boundaries and the required information size was not reached. The protocol predefined type 1 error of 5% and power of 80% was used . Pooled effect of 0.23 and alpha-spending adjusted 95% confidence interval is 0.03 to 1.69

Trial sequential graph (encephalopathy)

Figure 5



Trial Sequential Analysis of encephalopathy for 115 participants from both trials of distal splenorenal shunt versus devascularisation.The diversity-adjusted required information size of 157 was calculated based on a predefined type 1 error of 5% and power of 80%. The blue cumulative Z-curve did not cross the trial sequential monitoring boundary and diversity adjusted required information size was not reached. pooled effect is 8.1, alpha-spending adjusted 95% CI 0.68 to 96.96.

Tables

Characteristics of included studies

Gawish 2000

Methods	Randomized clinical trial
Participants	• Patients with schistosomal hepatic fibrosis with bleeding oesophageal varices • Haemodynamic pattern of hepatopetal flow and Splenic vein flow exceeds the portal vein flow. • Child A and B • Age range 23 to 65 years. Mean 41 years.
Interventions	Distal splenorenal shunt (30) versus oesophagogastric devascularisation with splenectomy (30)
Outcomes	Variceal rebleeding, duplex data, and encephalopathy.
Notes	Duplex data includes: • Portal, and splenic vein diameter, flow, and velocity. • Portal vein and shunt patency. • Presence of ascites.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was not clear from the study how randomisation was achieved. The author was contacted and mentioned that randomisation was done but the method was not clearly stated.
Allocation concealment (selection bias)	Low risk	The authors used sealed envelopes to conceal participants allocations.
Blinding of participants and personnel (performance bias)	Unclear risk	It was not mentioned in the study if any blinding was done. Ethically it is usually impossible to blind people to the surgical procedure.
Blinding of outcome assessment (detection bias)	Low risk	It was not mentioned in the study if any blinding was done. However, absence of blinding could not have affected objective outcomes.
Incomplete outcome data (attrition bias)	High risk	All participants lost to follow-up were replaced, 7 participants in devascularisation, and 6 in shunt group. However, the method of replacement or potential adverse event suffered by these participants were not mentioned. The author was contacted but could not provide clarity.
Selective reporting (reporting bias)	Unclear risk	The study Protocol was not available but outcomes reported were no different from those pre-defined in the method sections.
Other bias	Unclear risk	It was not clear if there were other sources of bias. The source of funding was unclear.

Raia 1994

Methods	Randomised clinical trial
Participants	● Patients with diagnosis of Manson's schistosomiasis, based on epidemiological, clinical and parasitological data, confirmed by histopathological analysis of the wedged liver biopsy specimen taken at the time of operation, ● Age from 18 to 55 yr. ● Minimum interval of 15 days between last haemorrhage and operation ● Chemotherapy for schistosomiasis before operation ● Absent or easily controlled ascites.
Interventions	Proximal splenorenal shunt (32); Distal splenorenal shunt (30); and oesophagogastric devascularisation with splenectomy (32)
Outcomes	Survival, variceal rebleeding, and adverse events: encephalopathy, and haemolysis
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	This study used a table of random numbers to randomise participants
Allocation concealment (selection bias)	Low risk	This study used sealed envelopes to conceal participants allocations
Blinding of participants and personnel (performance bias)	Unclear risk	It was not mentioned in the study if any blinding was done. Ethically it is usually impossible to blind people to the type of surgery performed.
Blinding of outcome assessment (detection bias)	Low risk	It was not mentioned in the study if any blinding was done. However, absence of blinding could not have affected objective outcomes.
Incomplete outcome data (attrition bias)	High risk	All participants lost to follow-up were excluded in the computation of intervention effect
Selective reporting (reporting bias)	Unclear risk	Protocol was not available but all outcomes in the method section were reported on
Other bias	Low risk	The study had grant funding, so was free of industry sponsorship.

Characteristics of excluded studies

Callow 1970

Reason for exclusion	Included cirrhotic participants

de Cleva 2007

Reason for exclusion	Quasi-randomised, Studied haemodynamic changes only. No adverse events reported

Fischer 1981

Reason for exclusion	Included cirrhotic participants

Galambos 1976

Reason for exclusion	Included cirrhotic participants

House 1980

Reason for exclusion	Included cirrhotic participants

Jackson 1971

Reason for exclusion	Included cirrhotic participants

Langer 1985

Reason for exclusion	Included cirrhotic participants

Mercado 1996

Reason for exclusion	Included cirrhotic participants

Nussbaum 1993

Reason for exclusion	Included cirrhotic participants

Nussbaum 1993a

Reason for exclusion	Duplicate study. Included cirrhotic participants

Xiong 2002

Reason for exclusion	Included cirrhotic participants

Xiong 2002a

Reason for exclusion	Duplicate study. Included cirrhotic participants

Summary of findings tables

1 Distal splenorenal shunt (DSRS) compared with devascularisation for prevention of variceal rebleeding due to hepatosplenic schistosomiasis

Distal splenorenal shunt (DSRS) compared to Devascularisation for prevention of variceal rebleeding due to hepatosplenic schistosomiasis						
Patient or population: patients with prevention of variceal rebleeding due to hepatosplenic schistosomiasis **Settings:** Health institution **Intervention:** Distal splenorenal shunt (DSRS) **Comparison:** Devascularisation						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect** (95% CI)	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Devascularisation	**Distal splenorenal shunt (DSRS)**				
All-cause mortality Follow-up: 5 -10 years	**Study population**		**RR 1.4** (0.32 to 6.15)	115 (2 studies)	⊕⊖⊖⊖ **very low**[1]	
	52 per 1000	**72 per 1000** (17 to 318)				
	Moderate					
	52 per 1000	**73 per 1000** (17 to 320)				
Variceal rebleeding Follow-up: 5 to 10 years	**Study population**		**RR 0.23** (0.05 to 1.01)	115 (2 studies)	⊕⊖⊖⊖ very **low**[1]	
	155 per 1000	**36 per 1000** (8 to 157)				
	Moderate					
	155 per 1000	**36 per 1000** (8 to 157)				
Quality of life	**Study population**		Not estimable	0 (0)	See comment	Quality of life was not reported by both trials
	See comment	See comment				
	Moderate					
Encephalo	**Study population**		**RR 8.1**	115	⊕⊖⊖⊖	

pathy Follow-up: 5 to 10 years	**0 per 1000** **Moderate** **0 per 1000**	**0 per 1000** (0 to 0) **0 per 1000** (0 to 0)	(1.04 to 62.83)	(2 studies)	very **low**[1]	
Ascites Follow-up: 5 years	**Study population** **Moderate**		**RR 0.13** (0.05 to 0.3)	30 (1 study)	⊕⊖⊖⊖ **very low**[1]	All ascites reported as mild and resolved on dietary adjustments.
Re-intervention Follow-up: 5 years	**Study population** **Moderate**		**RR 0.03** (0.01 to 0.17)	30 (1 study)	⊕⊖⊖⊖ **very low**[1]	Re-intervention reported for DSRS due to shunt occlusion.
Shunt occlusion Follow-up: 5 to 10 years	**Study population** **Moderate**		**RR 0.07** (0.03 to 0.4)	44 (2 studies)	⊕⊖⊖⊖ **very low**[1]	shunt occlusion reported for DSRS only

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Downgraded three levels for risk of bias based on over-all assessment, imprecision (very large confidence interval,few participants, and heterogeneity) and publication bias (few publications reported the outcome).

2 Proximal splenorenal shunt (PSRS) compared to Distal splenorenal shunt (DSRS) for prevention of variceal rebleeding due to hepatosplenic schistosomiasis

Proximal sprenorenal shunt (PSRS) compared to Distal splenorenal shunt (DSRS) for prevention of variceal rebleeding due to hepatosplenic schistosomiasis						
Patient or population: patients with variceal rebleeding due to hepatosplenic schistosomiasis **Settings:** Health institutions **Intervention:** Proximal splenorenal shunt (PSRS) **Comparison:** Distal splenorenal shunt (DSRS)						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Distal splenorenal shunt (DSRS)	**Proximal splenorenal shunt (PSRS)**				
All-cause mortality Follow-up: 9 to 132 months	**Study population**		**RR 2.89** (1.06 to 7.87)	55 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	148 per 1000	**428 per 1000** (157 to 1000)				
	Moderate					
	148 per 1000	**428 per 1000** (157 to 1000)				
Total rebleeding Follow-up: 9 to 132 months	**Study population**		**RR 1.29** (0.51 to 3.22)	55 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	222 per 1000	**287 per 1000** (113 to 716)				
	Moderate					
	222 per 1000	**286 per 1000** (113 to 715)				

Variceal rebleeding Follow-up: 9 to 132 months	**Study population**		**RR 2.89** (0.32 to 26.12)	55 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	37 per 1000	**107 per 1000** (12 to 967)				
	Moderate					
	37 per 1000	**107 per 1000** (12 to 966)				
Quality of life	**Study population**		Not estimable	0 (0)	See comment	Quality of life not reported
	See comment	See comment				
	Moderate					
Encephalopathy Follow-up: 9 to 132 months	**Study population**		**RR 2.65** (0.96 to 7.32)	55 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	148 per 1000	**393 per 1000** (142 to 1000)				
	Moderate					
	148 per 1000	**392 per 1000** (142 to 1000)				
Haemolysis Follow-up: 9 to 132 months	**Study population**		**RR 0.55** (0.28 to 1.10)	55 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	519 per 1000	**285 per 1000** (145 to 570)				
	Moderate					
Shunt occlusion Follow-up: 9 to 132 months	**Study population**		**RR 1.65** (0.35 to 7.71)	31 (1 study)	⊕⊖⊖⊖ **very low**[1]	
	143 per 1000	**236 per 1000** (50 to 1000)				
	Moderate					

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Footnotes

[1] Downgraded three levels for risk of bias based on over-all assessment, imprecision (very large confidence interval,few participants, and heterogeneity) and publication bias (few publications reported the outcome)

Additional tables

1 Serious adverse events

Type of adverse event	Trials	Procedure	Number of events	Total participants	Percentage 95% CI
Partial portal vein thrombosis Total portal vein thrombosis	Gawish 2000	Devascularisation	17 1	30	60%, (42% to 75%)
Haemolysis	Raia 1994	Distal splenorenal shunt Proximal splenorenal shunt	14 8	55	40%, (28% to 53%)
Ascites	Gawish 2000	Devascularisation	4	30	13%, (5% to 30%)
Shunt occlusion	Raia 1994 Gawish 2000 Raia 1994	Distal splenorenal shunt Proximal splenorenal shunt	3 4	61	11%, (6% to 22%)

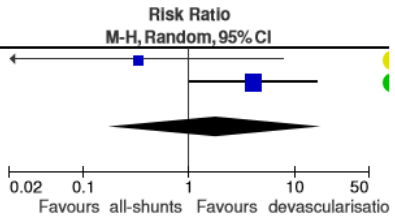
Forest Plot: Analysis

1 All-shunts versus devascularisation

1.1 All-cause mortality

Study or Subgroup	All-shunts Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	0	30	1	30	33.3%	0.33 [0.01, 7.87]
Raia 1994	16	55	2	28	66.7%	4.07 [1.01, 16.48]
Total (95% CI)		**85**		**58**	**100.0%**	**1.77 [0.18, 17.87]**
Total events	16		3			

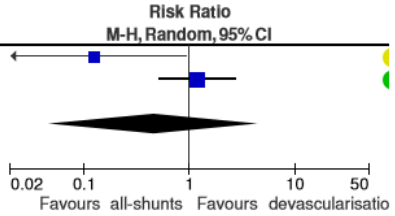
Heterogeneity: Tau² = 1.58; Chi² = 2.01, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.48 (P = 0.63)



1.2 Total rebleeding

Study or Subgroup	All-shunts Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	1	30	8	30	42.2%	0.13 [0.02, 0.94]
Raia 1994	14	55	6	28	57.8%	1.19 [0.51, 2.75]
Total (95% CI)		**85**		**58**	**100.0%**	**0.46 [0.05, 4.55]**
Total events	15		14			

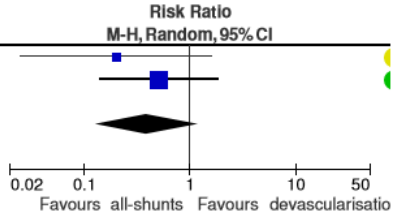
Heterogeneity: Tau² = 2.18; Chi² = 4.52, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 0.67 (P = 0.51)



1.3 Variceal rebleeding

Study or Subgroup	All-shunts Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	1	30	5	30	28.2%	0.20 [0.02, 1.61]
Raia 1994	4	55	4	28	71.8%	0.51 [0.14, 1.89]
Total (95% CI)		**85**		**58**	**100.0%**	**0.39 [0.13, 1.19]**
Total events	5		9			

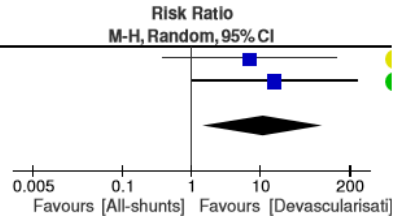
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)



1.4 Encephalopathy

Study or Subgroup	All-shunts Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	3	30	0	30	47.5%	7.00 [0.38, 129.93]
Raia 1994	15	55	0	28	52.5%	16.05 [1.00, 258.83]
Total (95% CI)		**85**		**58**	**100.0%**	**10.82 [1.44, 81.07]**
Total events	18		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

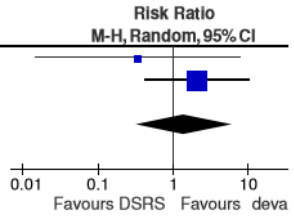


2 Distal splenorenal shunt versus devascularisation

2.1 All-cause mortality

Study or Subgroup	Distal splenorenal shunt Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	0	30	1	30	21.5%	0.33 [0.01, 7.87]
Raia 1994	4	27	2	28	78.5%	2.07 [0.41, 10.41]
Total (95% CI)		**57**		**58**	**100.0%**	**1.40 [0.32, 6.15]**
Total events	4		3			

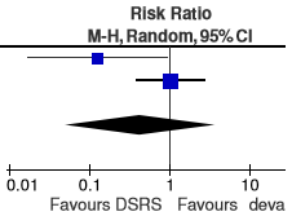
Heterogeneity: Tau² = 0.05; Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 0.45 (P = 0.66)



2.2 Total rebleeding

Study or Subgroup	Distal splenorenal shunt Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	1	30	8	30	42.0%	0.13 [0.02, 0.94]
Raia 1994	6	27	6	28	58.0%	1.04 [0.38, 2.82]
Total (95% CI)		**57**		**58**	**100.0%**	**0.43 [0.05, 3.71]**
Total events	7		14			

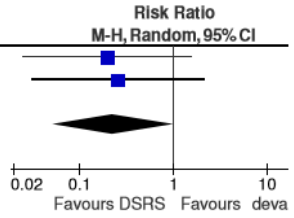
Heterogeneity: Tau² = 1.84; Chi² = 3.79, df = 1 (P = 0.05); I² = 74%
Test for overall effect: Z = 0.77 (P = 0.44)



2.3 Variceal rebleeding

Study or Subgroup	Distal splenorenal shunt Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	1	30	5	30	51.0%	0.20 [0.02, 1.61]
Raia 1994	1	27	4	28	49.0%	0.26 [0.03, 2.17]
Total (95% CI)		**57**		**58**	**100.0%**	**0.23 [0.05, 1.01]**
Total events	2		9			

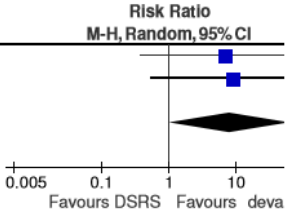
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)



2.4 Encephalopathy

Study or Subgroup	Distal splenorenal shunt Events	Total	Devascularisation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Gawish 2000	3	30	0	30	49.2%	7.00 [0.38, 129.93]
Raia 1994	4	27	0	28	50.8%	9.32 [0.53, 165.26]
Total (95% CI)		**57**		**58**	**100.0%**	**8.10 [1.04, 62.83]**
Total events	7		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.00 (P = 0.05)

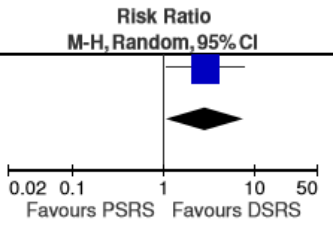


3 Proximal splenorenal shunt versus distal splenorenal shunt

3.1 All-cause mortality

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	12	28	4	27	100.0%	2.89 [1.06, 7.87]
Total (95% CI)		**28**		**27**	**100.0%**	**2.89 [1.06, 7.87]**
Total events	12		4			

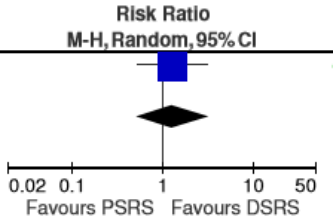
Heterogeneity: Not applicable
Test for overall effect: Z = 2.08 (P = 0.04)



3.2 Total rebleeding

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	8	28	6	27	100.0%	1.29 [0.51, 3.22]
Total (95% CI)		**28**		**27**	**100.0%**	**1.29 [0.51, 3.22]**
Total events	8		6			

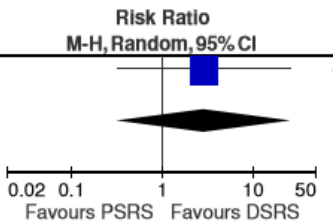
Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)



3.3 Variceal rebleeding

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	3	28	1	27	100.0%	2.89 [0.32, 26.12]
Total (95% CI)		**28**		**27**	**100.0%**	**2.89 [0.32, 26.12]**
Total events	3		1			

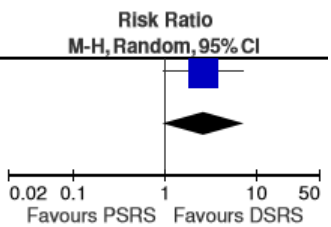
Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



3.4 Encephalopathy

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	11	28	4	27	100.0%	2.65 [0.96, 7.32]
Total (95% CI)		**28**		**27**	**100.0%**	**2.65 [0.96, 7.32]**
Total events	11		4			

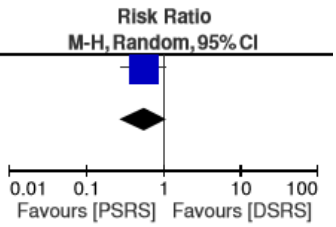
Heterogeneity: Not applicable
Test for overall effect: Z = 1.88 (P = 0.06)



3.5 Haemolysis

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	8	28	14	27	100.0%	0.55 [0.28, 1.10]
Total (95% CI)		**28**		**27**	**100.0%**	**0.55 [0.28, 1.10]**
Total events	8		14			

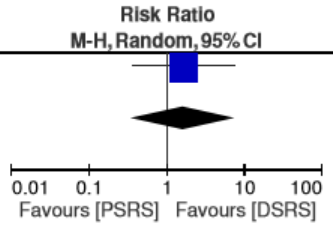
Heterogeneity: Not applicable
Test for overall effect: Z = 1.69 (P = 0.09)



3.6 Shunt occlusion

Study or Subgroup	PSRS Events	PSRS Total	DSRS Events	DSRS Total	Weight	Risk Ratio M-H, Random, 95% CI
Raia 1994	4	17	2	14	100.0%	1.65 [0.35, 7.71]
Total (95% CI)		**17**		**14**	**100.0%**	**1.65 [0.35, 7.71]**
Total events	4		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)



References:

Included studies

Gawish Y, El-Hammadi HAB, Kotb M, Awad AT, Anwar M. Devascularization procedure and DSRS: a controlled randomized trial on selected haemodynamic portal flow pattern in schistosomal portal hypertension with variceal bleeding. International Surgery 2000;85(4):325-30.

Raia S, Da Silva LC, Gayotto LCC, Forster SC, Fukushima J, Strauss E. Portal hypertension in schistosomiasis: A long-term follow-up of a randomized trial comparing three types of surgery. Hepatology (Baltimore, Md.) 1994;20(2):398-403.

Excluded studies

Callow AD, Resnick RH, Chalmers TC, Ishihara AM, Garceau AJ, O'Hara ET. Conclusions from a controlled trial of the prophylactic portacaval shunt. Surgery 1970;67(1):97-103. [PubMed: 5308037]

de Cleva R, Herman P, Carneiro D'Albuquerque LA, Pugliese V, Santarem OL, Saad WA. Pre- and postoperative systemic hemodynamic evaluation in patients subjected to esophagogastric devascularization plus splenectomy and distal splenorenal shunt: A comparative study in schistomomal portal hypertension. World Journal of Gastroenterology 2007;13(41):5471-5.

Fischer JE, Bower RH, Atamian S, Welling R. Comparison of distal and proximal splenorenal shunts: a randomized prospective trial. Annals of Surgery 1981;194(4):531-44. [PubMed: 6974543]

Galambos JT, Warren WD, Rudman D, Smith RB 3rd, Salam AA. Selective and total shunts in the treatment of bleeding varices. A randomized controlled trial. New England Journal of Medicine 1976;295(20):1089-95. [PubMed: 1086428]

House AK, Turner VF. Bleeding oesophageal varices treated by a selective or total protal systemic shunt. Journal of the Royal College of Surgeons of Edinburgh 1980;25(2):117-24. [PubMed: 6965985]

Jackson FC, Perrin EB, Felix WR, Smith AG. A clinical investigation of the portacaval shunt. V. Survival analysis of the therapeutic operation. Annals of Surgery 1971;174(4):672-701. [PubMed: 5098227]

Langer B, Taylor BR, Mackenzie DR, Gilas T, Stone RM, Blendis L. Further report of a prospective randomized trial comparing distal splenorenal shunt with end-to-side portacaval shunt. An analysis of encephalopathy, survival, and quality of life. Gastroenterology 1985;88(2):424-9. [PubMed: 3880715]

Mercado MA, Morales-Linares JC, Granados-Garcia J, Gomez-Mendez TJ, Chan C, Orozco H. Distal splenorenal shunt versus 10-mm low-diameter mesocaval shunt for variceal hemorrhage. American Journal of Surgery 1996;171(6):591-5. [PubMed: 8678206]

Nussbaum MS, Schoettker PJ, Fischer JE. Comparison of distal and proximal splenorenal shunts: a ten-year experience. Surgery 1993;114(4):659-65; discussion 665-6. [PubMed: 8211679]

Nussbaum MS, Schoettker PJ, Fischer JE. Comparison of distal and proximal splenorenal shunts: a ten-year experience. Surgery 1993;114(4):659-65; discussion 665-6. [PubMed: 8211679]

Xiong BX, Xie M, Sun JY, Li HL. Effect of combined operation and portaazygous devascularzation in the treatment of esophageal variceal bleeding. Acta Academiae Medicinae Jiangxi VL 2001;41(5):63-5.

Xiong BX, Xie M, Shun JY, Li HL, Sen W. Comparative study of portaazygous devascularization and combined operation in the treatment of esophageal variceal bleeding. Chinese Journal of General Surgery 2002;11(1):10-2.

Additional references

Andersson KL, Chung RT. Hepatic schistosomiasis. Current Treatment Options in Gastroenterology 2007;10:504-12.

Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.

Bhargava DK, Dasarathy S, Atmakuri SP, Dwivedi M. Comparative efficacy of emergency endoscopic sclerotherapy for active variceal bleeding due to cirrhosis of the liver, non-cirrhotic portal fibrosis and extrahepatic portal venous obstruction. Journal of Gastroenterology and Hepatology 1990;5:432-7.

Bica I, Hamer DH, Stadecker MJ. Hepatic schistosomiasis. Infectious Disease Clinics of North America 2000;14:583-604.

Boyer TD, Haskal ZJ; American Association for the Study of Liver Diseases. The role of transjugular intrahepatic portosystemic shunt (TIPS) in the management of portal hypertension: update 2009. Hepatology 2010;51:306.

Brok J, Thorlund K, Gluud C, Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. Journal of Clinical Epidemiology 2008;61:763-9.

Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive - trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. International Journal of Epidemiology 2009;38(1):287-98.

Burke ML, Jones MK, Gobert GN, Li YS, Ellis MK, McManus DP. Immunopathogenesis of human schistosomiasis. Parasite Immunology 2009;31(4):163-76. [PubMed: 19292768]

Carbonell N, Pauwels A, Serfaty L, Fourdan O, Levy VG, Poupon R. Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology (Baltimore, Md.) 2004;40:652-9.

Cella DF. Measuring quality of life in palliative care. Seminars in Oncology 1995;22:73-81.

Chalasani N, Kahi C, Francois F, Pinto A, Marathe A, Bini EJ, et al. Improved patient survival after acute variceal bleeding: a multicenter, cohort study. American Journal of Gastroenterology 2003;98:653-9.

Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ (Clinical Research Ed.) 2013;346:e7586. [PubMed: 23303884]

Child CG, Turcotte JG. Surgery and portal hypertension. Major Problems in Clinical Surgery 1964;1:1-85.

Chofle AA, Jaka H, Koy M, Smart LR, Kabangila R, Ewings FM, et al. Oesophageal varices, schistosomiasis, and mortality among patients admitted with haematemesis in Mwanza, Tanzania: a prospective cohort study. BMC Infectious Diseases 2014;14:303.

Colley DG, Secor WE. Immunology of human schistosomiasis. Parasite Immunology 2014;36(8):347-57. [PubMed: 25142505]

Colley DG, Bustinduy AL, Secor WE, King CH. Human schistosomiasis. Lancet 2014;383(9936):2253-64. [PubMed: 24698483]

Conn HO. Transjugular intrahepatic portal-systemic shunts: the state of the art. Hepatology 1993;17:148-58.

Conn HO. A randomized comparison of three types of surgery in schistosomal portal hypertension: many fewer answers than questions. Hepatology (Baltimore, Md.) 1994;20(2):526-8. [PubMed: 8045513]

Costa G, Cruz RJ Jr, Abu-Elmagd KM. Surgical shunt versus TIPS for treatment of variceal hemorrhage in the current era of liver and multivisceral transplantation. Surgical Clinics of North America 2010;90:891-905.

D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology (Baltimore, Md.) 1995;22:332-54.

D'Amico G, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology (Baltimore, Md.) 2003;38:599-612.

Da Silva LC, Strauss E, Gayotto LC, Mies S, Macedo AL, da Silva AT, et al. A randomized trial for the study of the elective surgical treatment of portal hypertension in Mansonic schistosomiasis. Annals of Surgery 1986;294(2):148-53.

Da Silva LC, Carrilho FJ. Hepatosplenic schistosomiasis. Pathophysiology and treatment. Gastroenterology Clinics of North America 1992;21:163-77.

De Cock KM, Awadh S, Raja RS, Wankya BM, Lucas SB. Esophageal varices in Nairobi, Kenya: a study of 68 cases. American Journal of Tropical Medicine and Hygiene 1982;31:579-88.

De Cock KM. Hepatosplenic schistosomiasis: a clinical review. Gut 1986;27:734-45.

de Franchis R. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. Journal of Hepatology 2010;53:762-8.

DeMets DL. Methods for combining randomized clinical trials: strengths and limitations. Statistics in Medicine 1987;6:341-50.

Deng D, Liao MS, Qin JP, Li XA. Relationship between pre-TIPS hepatic hemodynamics and postoperative incidence of hepatic encephalopathy. Hepatobiliary & Pancreatic Diseases International 2006;5:232-6.

Denié C, Vachiery F, Elman A, Soupison T, Gadano A, Moreau R, et al. Systemic and splanchnic hemodynamic changes in patients with hepatic schistosomiasis. Liver 1996;16:309-12.

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986;7:177-88.

Eesa M, Clark T. Transjugular intrahepatic portosystemic shunt: state of the art. Seminars in Roentgenology 2011;46:125-32.

Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed.) 1997;315:629-34.

Eguchi A, Hashizume M, Kitano S, Tanoue K, Wada H, Sugimachi K. High rate of portal thrombosis after splenectomy in patients with esophageal varices and idiopathic portal hypertension. Archives of Surgery (Chicago, Ill. : 1960) 1991;126(6):752-5. [PubMed: 2039363]

Evangelista-Neto J, Pereira FF, Franca ST, Amaral FJ, Brandt CT, Fonseca-Neto OC, et al. Splenectomy and gastric vein ligature in hepatosplenic schistosomiasis: effects upon esophageal variceal pressure and endoscopic risk factors of esophageal variceal bleeding. Arquivos Brasileiros de Cirurgia Digestiva 2012;25:41-8.

Ezzat FA, Abu-Elmagd KM, Aly MA, Fathy OM, el-Ghawlby NA, el-Fiky AM, et al. Selective shunt versus nonshunt surgery for management of both schistosomal and nonschistosomal variceal bleeders. Annals of Surgery 1990;212(1):97-108.

Ferreira FG, Forte WCN, Assef JC, Capua Jr A de. Effect of esophagogastric devascularization with splenectomy on schistossomal portal hypertension patients' immunity. Arquivos de Gastroenterologia 2007;44:44-8.

Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. New England Journal of Medicine 2010;362:823-32.

Ginsberg RJ, Waters PF, Zeldin RA, Spratt EH, Shandling B, Stone RM, et al. A modified Sugiura procedure. Annals of Thoracic Surgery 1982;34:258-64.

Gluud C, Nikolova D, Klingenberg SL. Cochrane Hepato-Biliary Group. About Cochrane (Cochrane Review Groups (CRGs)) 2016, Issue 4. Art. No.: LIVER.

Goff JS. Gastroesophageal varices: pathogenesis and therapy of acute bleeding. Gastroenterology Clinics of North America 1993;22:779-800.

Gonzalez R, Zamora J, Gomez-Camarero J, Molinero LM, Banares R, Albillos A. Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. Annals of Internal Medicine 2008;149:109-22.

Gur I, Diggs BS, Orloff SL. Surgical portosystemic shunts in the era of TIPS and liver transplantation are still relevant. HPB : the Official Journal of the International Hepato Pancreato Biliary Association 2014;16:481-93.

Hassab MA. Gastroesophageal decongestion and splenectomy in the treatment of esophageal varices in bilharzial cirrhosis: further studies with a report on 355 operations. Surgery 1967;61:169-76.

Hassab MA. Gastro-esophageal decongestion and splenectomy GEDS (Hassab), in the management of bleeding varices. Review of literature. International Surgery 1998;83(1):38-41. [PubMed: 9706516]

Henderson JM. Surgical methods for the prevention of first and recurrent variceal bleeding. Zeitschrift für Gastroenterologie 1988;26(Suppl 2):49-53.

Henderson JM, Yang Y. Is there still a role for surgery in bleeding portal hypertension? Nature Clinical Practice. Gastroenterology & Hepatology 2005;2(6):246-7. [PubMed: 16265209]

Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002;21:1539-58.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

International Conference on Harmonisation Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH harmonised tripartite guideline. Guideline for good clinical practice CFR & ICH Guidelines. Vol. 1. Pennsylvania: Barnett International/PAREXEL, 1997.

Inokuchi K. Present status of surgical treatment of esophageal varices in Japan: a nationwide survey of 3,588 patients. World Journal of Surgery 1985;9:171-80.

Jakobsen J, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Medical Research Methodology 2014;14:120.

Jin G, Rikkers LF. Transabdominal esophagogastric devascularization as treatment for variceal hemorrhage. Surgery 1996;120:641-7; discussion 647-9.

Johnson M, Rajendran S, Balachandar TG, Kannan D, Jeswanth S, Ravichandran P, et al. Transabdominal modified devascularization procedure with or without esophageal stapler

transection - an operation adequate for effective control of a variceal bleed. Is esophageal stapler transection necessary? World Journal of Surgery 2006;30:1507-18.

Kiire CF. Controlled trial of propranolol to prevent recurrent variceal bleeding in patients with non-cirrhotic portal fibrosis. BMJ (Clinical Research Ed.) 1989;298:1363-5.

Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. Annals of Internal Medicine 2001;135:982-9.

Lacy AM, Navasa M, Gilabert R, Bru C, Garcia-Pagan JC, Garcia-Valdecasas JC, et al. Long-term effects of distal splenorenal shunt on hepatic hemodynamics and liver function in patients with cirrhosis: importance of reversal of portal blood flow. Hepatology (Baltimore, Md.) 1992;15(4):616-22. [PubMed: 1551639]

Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub2.

Ma BY, Gui X, Yang ZC, Xiong Y, Wang HC, Wang ZB. [Effect of splenectomy on disorder of cellular immunoregulation in patients with advanced schistosomiasis]. Chinese Journal of Parasitology & Parasitic Diseases 1993;11(4):288-90. [PubMed: 8082270]

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. Journal of the National Cancer Institute 1959;22:719-48.

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609-13.

Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine 2009;151:264-9, w64.

Mudawi HM, Ibrahim KB. Endoscopic variceal sclerotherapy in patients with Symmers periportal fibroses. Tropical Doctor 2007;37:179-81.

Orloff MJ, Isenberg JI, Wheeler HO, Daily PO, Girard B. Budd-Chiari syndrome revisited: 38 years' experience with surgical portal decompression. Journal of Gastrointestinal Surgery 2012;16:286-300.

Orozco H, Mercado MA, Takahashi T, Hernandez-Ortiz J, Capellan JF, Garcia-Tsao G. Elective treatment of bleeding varices with the Sugiura operation over 10 years. American Journal of Surgery 1992;163:585-9.

Orozco H, Mercado MA, Martinez R, Tielve M, Chan C, Vasquez M, et al. Is splenectomy necessary in devascularization procedures for treatment of bleeding portal hypertension? Archives of Surgery 1998;133:36-8.

Pal S. Current role of surgery in portal hypertension. Indian Journal of Surgery 2012;74(1):55-66. [PubMed: 23372308]

Payne L, Turner-Moss E, Mutengo M, Asombang AW, Kelly P. Prevalence of schistosome antibodies with hepatosplenic signs and symptoms among patients from Kaoma, Western Province, Zambia. BMC Research Notes 2013;6:344. [PubMed: 23987918]

Peracchia A, Ancona E, Battaglia G. A new technique for the treatment of esophageal bleeding in portal hypertension. International Surgery 1980;65:401-4.

Pereira FM, Evangelista-Neto J, Brito N, Amaral F, da Fonseca-Neto OC, Lacerda CM. Angiografic and pressoric changes determined by splenectomy with left gastric vein ligature in mansoni schistosomiasis. Arquivos Brasileiros de Cirurgia Digestiva 2013;26(4):302-8. [PubMed: 24510039]

Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. British Journal of Surgery 1973;60:646-9.

Qazi SA, Khalid K, Hameed AM, Al-Wahabi K, Galul R, Al-Salamah SM. Transabdominal gastro-esophageal devascularization and esophageal transection for bleeding esophageal varices after failed injection sclerotherapy: long-term follow-up report. World Journal of Surgery 2006;30:1329-37.

Raia S, Mies S, Alfieri Junior F. Portal hypertension in mansonic schistosomiasis. World Journal of Surgery 1991;15(2):176-87. [PubMed: 1903230]

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, Cochrane, 2014.

Rikkers LF. The changing spectrum of treatment for variceal bleeding. Annals of Surgery 1998;228:536-46.

Rosemurgy AS, Frohman HA, Teta AF, Luberice K, Ross SB. Prosthetic H-graft portacaval shunts vs transjugular intrahepatic portasystemic stent shunts: 18-year follow-up of a randomized trial. Journal of the American College of Surgeons 2012;214:445-53; discussion 453-5.

Ross AG, Bartley PB, Sleigh AC, Olds GR, Li Y, Williams GM, et al. Schistosomiasis. New England Journal of Medicine 2002;346:1212-20.

Rossle M, Haag K, Ochs A, Sellinger M, Noldge G, Perarnau JM, et al. The transjugular intrahepatic portosystemic stent-shunt procedure for variceal bleeding. New England Journal of Medicine 1994;330:165-71.

Rossle M, Siegerstetter V, Euringer W, Olschewski M, Kromeier J, Kurz K, et al. The use of a polytetrafluoroethylene-covered stent graft for transjugular intrahepatic portosystemic shunt (TIPS): long-term follow-up of 100 patients. Acta Radiologica 2006;47:660-6.

Roszell K, Sandella D, Haig AJ, Yamakawa KS. Spinal Stenosis: Factors That Influence Patients' Decision to Undergo Surgery. Journal of Spinal Disorders & Techniques 2013 May 18 [Epub ahead of print]. [PubMed: 23839025]

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. International Journal of Technology Assessment in Health Care 2003;19:591-603.

Saad A M, Homeida M, Eltom I, Nash T, Bennett JL, Hassan MA. Oesophageal varices in a region of the Sudan endemic for *Schistosoma mansoni*. British Journal of Surgery 1991;78:1252-3.

Sanyal AJ, Bosch J, Blei A, Arroyo V. Portal hypertension and its complications. Gastroenterology 2008;134:1715-28.

Sarfeh IJ, Rypins EB, Mason GR. A systematic appraisal of portacaval H-graft diameters. Clinical and hemodynamic perspectives. Annals of surgery 1986;204(4):356-63. [PubMed: 3490229]

Sarfeh IJ, Rypins EB. Partial versus total portacaval shunt in alcoholic cirrhosis. Results of a prospective, randomized clinical trial. Annals of surgery 1994;219(4):353-61. [PubMed: 8161260]

Sarin SK, Gupta N, Jha SK, Agrawal A, Mishra SR, Sharma BC, et al. Equal efficacy of endoscopic variceal ligation and propranolol in preventing variceal bleeding in patients with noncirrhotic portal hypertension. Gastroenterology 2010;139:1238-45.

Savović J, Jones HE, Altman DG, Harris RJ, Jüni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials. Annals of Internal Medicine 2012;157:429-38.

Savović J, Jones H, Altman D, Harris R, Jűni P, Pildal J, et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technology Assessment 2012;16(35):1-82.

Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. JAMA 1995;273:408-12.

Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine 2010;8:18. [PubMed: 20334633]

Selzner M, Tuttle-Newhall JE, Dahm F, Suhocki P, Clavien PA. Current indication of a modified Sugiura procedure in the management of variceal bleeding. Journal of the American College of Surgeons 2001;193:166-73.

Smith JL, Graham DY. Variceal hemorrhage: a critical evaluation of survival analysis. Gastroenterology 1982;82:968-73.

Stanley AJ, Jalan R, Forrest EH, Redhead DN, Hayes PC. Long term follow up of transjugular intrahepatic portosystemic stent shunt (TIPSS) for the treatment of portal hypertension: results in 130 patients. Gut 1996;39:479-85.

Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. Lancet Infectious Diseases 2006;6:411-25.

Sterne JA, Jüni P, Schulz KF, Altman DG, Bartlett C, Egger M. Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research. Statistics in Medicine 2002;21:1513-24.

Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ (Clinical Research Ed.) 2011;343:d4002.

Strauss E, Sakai P, Gayotto LC, Cardoso RA, Forster S, Raia S. Size of gastroesophageal varices: its behavior after the surgical treatment of portal hypertension. Revista do Hospital das Clinicas; Faculdade de Medicina da Universidade de Sao Paulo 1999;54(6):193-8.

Sugiura M, Futagawa S. A new technique for treating esophageal varices. Journal of Thoracic and Cardiovascular Surgery 1973;66:677-85.

Symmers WSC. Note on a New Form of Liver Cirrhosis Due to the Presence of the Ova of Bilharzia Haematobia. 9th edition. London: Young J. Pentland, 1904.

Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, et al. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses. International Journal of Epidemiology 2009;38(1):276-86.

Thorlund K, Anema A, Mills E. Interpreting meta-analysis according to the adequacy of sample size. An example using isoniazid chemoprophylaxis for tuberculosis in purified protein derivative negative HIV-infected individuals. Clinical Epidemiology 2010;2:57-66.

Thorlund K, Engstrøm J, Wetterslev J, Brok J, Imberger G, Gluud C. User manual for Trial Sequential Analysis (TSA). ctu.dk/tsa/files/tsa_manual.pdf 2011 (accessed 23 May 2016).

Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis - a tutorial and review of methods for enhancing interpretability. Research Synthesis Methods 2011;2:188-203.

Toomey PG, Ross SB, Golkar FC, Hernandez JM, Clark WC, Luberice K, et al. Outcomes after transjugular intrahepatic portosystemic stent shunt: a "bridge" to nowhere. American Journal of Surgery 2013;205:441-6.

Tripathi D, Helmy A, Macbeth K, Balata S, Lui HF, Stanley AJ, et al. Ten years' follow-up of 472 patients following transjugular intrahepatic portosystemic stent-shunt insertion at a single centre. European Journal of Gastroenterology & Hepatology 2004;16:9-18.

TSA - Trial Sequential Analysis [Computer program]. Version 0.9 Beta. Copenhagen: Copenhagen Trial Unit, 2011. www.ctu.dk/tsa/downloads.aspx.

Verhagen AP, de Vet HC, de Bie RA, Boers M, van den Brandt PA. The art of quality assessment of RCTs included in systematic reviews. Journal of Clinical Epidemiology 2001;54:651-4.

Vianello A, Arcaro G, Palmieri A, Ermani M, Braccioni F, Gallan F, et al. Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. Journal of Critical Care 2011;26(3):329.e7-14. [PubMed: 20655697]

Villanueva C, Piqueras M, Aracil C, Gómez C, López-Balaguer JM, Gonzalez B, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. Journal of Hepatology 2006;45:560-7.

Vleggaar FP, van Buuren HR, Schalm SW. Endoscopic sclerotherapy for bleeding oesophagogastric varices secondary to extrahepatic portal vein obstruction in an adult Caucasian population. European Journal of Gastroenterology & Hepatology 1998;10:81-5.

Vons C, Hadengue A, Smadja C, Franco D, Lebrec D. Long-term hemodynamic effects of portocaval shunt and Sugiura procedure in patients with cirrhosis. HPB Surgery 1996;9(4):209-13. [PubMed: 8809580]

Voros D, Polydorou A, Polymeneas G, Vassiliou I, Melemeni A, Chondrogiannis K, et al. Long-term results with the modified Sugiura procedure for the management of variceal bleeding: standing the test of time in the treatment of bleeding esophageal varices. World Journal of Surgery 2012;36:659-66.

Warren WD, Zeppa R, Fomon JJ. Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. Annals of Surgery 1967;166:437-55.

Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. Journal of Clinical Epidemiology 2008;61:64-75.

Wetterslev J, Thorlund K, Brok J, Gluud C. Estimating required information size by quantifying diversity in a random-effects meta-analysis. BMC Medical Research Methodology 2009;9:86.

World Health Organization. Schistosomiasis: number of people receiving preventive chemotherapy in 2012. Weekly Epidemiological Record 2014;89:21-8.

Wilson E. Probable inference, the law of succession, and statistical inference. Journal of the American Statistical Association 1927;22(158):209-12.

Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman GD, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. BMJ (Clinical Research Ed.) 2008;336:601-5.

Yin L, Liu H, Zhang Y, Rong W. The surgical treatment for portal hypertension: a systematic review and meta-analysis. ISRN Gastroenterology 2013;2013:464053.

Zhang Y, Wen T, Yan L, Chen Z, Yang H, Deng X, et al. The changes of hepatic hemodynamics and functional hepatic reserve after splenectomy with periesophagogastric devascularization. Hepato-gastroenterology 2009;56:835-9.

Zong GQ, Fei Y, Liu RM. Comparison of effects of devascularization versus shunt on patients with portal hypertension: a meta-analysis. Hepato-gastroenterology 2015;62(137):144-50. [PubMed: 25911885]

Section 3: Appendix

3.1 Ethics approval

Human Research Ethics Committee (Medical)

Research Office Secretariat: Senate House Room SH10005, 10th floor. Tel +27 (0)11-717-1252
Medical School Secretariat: P V Tobias Building, Room 306, 3rd floor Tel +27 (0)11-717-2700
Private Bag 3, Wits 2050, www.wits.ac.za Fax +27 (0)11-717-1265

Ref: W-CJ-140804-2 04/08/2014

TO WHOM IT MAY CONCERN:

Waiver: This certifies that the following research does not require clearance from the Human Research Ethics Committee (Medical).

Investigator: **Dr Jeffrey Chikwendu.**

Project title: **Surgical portosystemic shunts versus devascularisation procedures for variceal bleeding as a result of hepatosplenic schistosomiasis.**

Reason: This study will be a meta-analysis of literature in the public domain. There are no human participants

Professor Peter Cleaton-Jones

Chair: Human Research Ethics Committee (Medical)

Section 4: Annexure - Proposal

4.1 Background

Oesophagogastric varices occur in patients that suffer from portal hypertension either as sequelae of liver cirrhosis or with presinusoidal causes such as schistosomiasis. In portal hypertension there is a pathological increase in the portocaval pressure gradient (Sanyal *et al.* 2008) resulting in the development of varices, encephalopathy, hypersplenism and ascites (Goff, 1993). Variceal bleeding is a significant cause of death in patients with portal hypertension (approximately 50% from the first bleed in liver cirrhosis) (Graham & Smith, 1981; de Dombal, *et al.* 1986). In survivors of the first episode, recurrent bleeding is not uncommon and the risk of rebleeding is greatest during the first thirty days following the initial bleed (Smith & Graham, 1982).

Schistosomiasis is a parasitic disease that is endemic in poor communities with inadequate sanitation and lack of access to portable water (Steinmann *et al,* 2006). The World Health Organisation estimates the total number of people infected worldwide as over 200 million. More than 90% of these live in Africa (WHO, 2014). The hepatosplenic form of the disease is caused by two species of the blood fluke Schistosoma, namely S. *mansoni* found predominantly in Africa, Arabia and South America, and S. *japonicum* found in South-East Asia, especially mainland China. The adult worms of both species inhabit the mesenteric veins where they mate and deposit eggs. A granulomatous inflammatory reaction to the trapped eggs in portal vein radicles results in portal fibrosis (Symmer's (clay) pipe stem fibrosis) (Symmers, 1904). This fibrosis results in the development of presinusoidal portal hypertension (Ross *et al*. 2002).

Portal Hypertension is defined as a portal venous pressure gradient greater than 8mmHg and clinically obvious variceal bleeding occur when the pressure gradient exceeds 12mmHg (Sanyal *et al.* 2008).

The algorithm for the treatment of acutely bleeding varices in both cirrhotic and non-cirrhotic portal hypertension is the same and includes a combination of pharmacologic and endoscopic therapy, radiological shunt such as transjugular intrahepatic portosystemic shunt (TIPS) and surgery (either a shunt or a devascularization procedure). In acute variceal bleeding early aggressive resuscitation is recommended. A vasoactive agent infusion and endoscopic therapy are the primary treatment measures (de Franchis, 2010; Gonzalez *et al*. 2008). However recurrent bleeding despite these measures occurs in 40-60% of patients (Snady, 1987) and secondary prophylaxis are therefore imperative (de Franchis, 2010; Rikkers *et al*. 1992; Whipple, 1945). The risk of rebleeding without secondary prophylaxis approaches 70% during the first two years (D'Amico *et al*. 1995) with the greatest risk occuring within the first few days following a bleed (Smith & Graham, 1982).

In the era of radiological shunt (TIPS), the use of surgical shunts and devascularization procedures have decreased as TIPS offers a minimally invasive alternative and serve as a bridge to liver transplantation (Boyer & Haskal, 2010; John *et al*. 1996). Nonetheless, only 3% to 14% of eligible cirrhotic patients eventually receive liver transplant (Rosemurgy *et al*. 2012; Toomey *et al*. 2013). The long term patency of TIPS as well as long term survival rates are less than surgical shunts (Orloff, 2014; Rosemurgy *et al.* 1996). The 5-year patency and survival rate for a surgical shunt is 97% and 68% respectively (Gur *et al.* 2014). The median survival after TIPS is 26months compared to 52months after H-graft portocaval shunt (HGPCS) (Rosemurgy *et al*. 2012). The early shunt occlusion occurred within 30days in 17% of patient after TIPS compared to 9% after surgical shunt (Rosemurgy *et al.* 1996). However

this data is only valid in cirrhotic patients. However, there is no literature to my knowledge supporting the use of TIPS in SPH (Eesa & Cark, 2011).

In SPH hepatic venous pressure and hepatic function are largely preserved if there are no other concomitant liver diseases such as viral hepatitis infection (Denie *et al.* 1996; Bica *et al*. 2000). There is firm evidence in support of surgical shunts for portal decompression in SPH as these subgroups of patients are young with preserved liver function (Gur *et al*. 2014; Ferraz *et al.* 2001; Spina et al. 1992; Henderson, 1988).

The aim of surgery is to reduce the high pressure in the portal circulation. This is achieved by diverting portal venous blood into the systemic circulation. Generally, two types of procedures are described, shunt and devascularization (Da Silva & Carrilho, 1992). Surgical shunts are traditionally divided into selective and non-selective types. When compared to selective shunts, the non-selective shunts divert all portal blood away from the liver into the systemic circulation resulting in reduction in effective hepatic blood flow. The risk of encephalopathy after non-selective shunt in SPH approach 39%, hence selective shunts are advocated (Andersson & Chung, 2007; Raia et al. 1994). Perioperative mortality following shunt procedures is 6%, with 5-year survival rate of 68% to 75% (Gur *et al*, 2014;Orloff *et al.* 2009;Rikker *et al.* 1992;Paquet *et al.* 1989).

On the other hand, devascularization procedure have higher rebleeding rate of 7% to 40% (Johnson *et al*. 2006; Henderson, 1988), compared to surgical shunt with rates of 5% to11% depending on the type of shunt (Rikkers, 1998). Also the risk of encephalopathy with devascularization is rare and overall operative mortality higher at 13% (Rikkers, 1998; Qazi et al, 2006; Suigura & Futagawa, 1984). Hence, devascularization procedures have higher mortality and a disappointing long term outcome because of high rate of rebleeding compared to selective surgical shunt.

To date no meta-analysis or systematic review has compared surgical porto-systemic shunts to devascularisation procedures in control of acute or recurrent variceal bleeding due to SPH.

Therefore in this review I will compare surgical porto-systemic shunts to oesophagogastric devascularization procedures in the treatment of variceal bleeding as a result of SPH.

Description of the intervention

Portosystemic shunts are surgically created conduits that divert part or all of portal venous blood flow away from the liver into the systemic circulation. This conduit may be autogenous graft or polytetrafluoroethylene (PTFE) prosthesis.

Commonly created surgical portosystemic shunts include the non-selective 16mm H-graft shunt and the selective DSRS (Warren *et al*. 1967). The H-shunt is created between the portal vein and the inferior vena cava using an 8mm to 16mm ringed PTFE prosthesis. The PTFE graft is nonexpansible and by diminishing its diameter from 16mm to 8mm a partial portal decompression is achieved (Sarfeh et al, 1986; Sarfeh et al, 1994).

The distal splenorenal shunt is created by anastomosing the distal splenic vein to the left renal vein and disconnecting the splenopancreatic and gastric venous connections to the portal system while preserving portal venous blood flow and hepatic function.

Oesophagogastric devascularization includes perihiatal devascularisation of the distal 4cm to 6 cm of abdominal esophagus and ligation of the short and left gastric vessels. This is combined with oesophageal transection and splenectomy (OGDS) (Sugiura & Futagawa, 1972) or without splenectomy

OBJECTIVE

To determine whether or not surgical portosystemic shunts have better outcomes compared to oesophago-gastric devascularisation procedures in the management of variceal bleeding resulting from SPH.

AIMS

To identify all RCTs where surgical portosystemic shunts have been compared to oesophago-gastric devascularisation with or without splenectomy. Controlled clinical trials (CCTs, i.e., trials employing quasi/pseudo-randomisation (e.g. alternate allocation)) (published and unpublished) identified during the search for randomised trials will be considered for evidence of harmful effect of the intervention

M E T H O D S

Inclusion criteria

Patients with hepatobiliary-splenic schistosomiasis complicated by variceal bleeding whether first episode or recurrent that undergo a surgical shunt or devascularisation procedure are eligible for inclusion.

Exclusion criteria

Patients with concomitant cirrhosis from any cause or who have had TIPS will be excluded.

Types of interventions

All types of surgical shunts:

- Portacaval shunt (connecting the portal vein and the vena cava)
- Mesocaval shunt(connecting the mesenteric vein and the vena cava)
- Central splenorenal shunt (CSRS)(connecting splenic vein to proximal left renal vein)

- Distal splenorenal shunt (connecting splenic vein to distal left renal vein with or without spleno-pancreatic venous disconnection)
- The large diameter H-graft shunt (16mm, externally reinforced polytetraflouethylene (PTFE) either as mesocaval or portocaval shunt).Small diameter H-graft shunt (8 mm, externally reinforced polytetrafluoroethylene(PTFE) either as mesocaval or portacaval shunt)

Oesophago-gastric devascularisation with or without splenectomy

Types of outcome measures

Primary:

1. Procedure related mortality
2. Variceal rebleed rate (diagnosed clinically by haematemesis, melena, or blood in gastric aspirate or by endoscopy)
3. Adverse events (AE) (procedure related complication) will be defined as any unfavourable and unintended symptoms, signs, abnormal laboratory results, and disease resulting from the surgical procedure (ICH-GCP, 2001). Adverse event will be considered as
    a. Acute, if developing within 30 days of the procedure.
    b. Chronic, if developing after 30 days following the procedure.
4. Quality of life.

Secondary:

1. All-cause mortality
    a. Immediate (30 days)
    b. Intermediate (one year)
    c. Long-term (five years).

2. Number of patients developing encephalopathy which is defined as:

    a. Classical signs found on physical examination

    b. Signs unequivocally described by patient's relatives

    c. Psychometric testing

    d. Electroencephalogram.

3. Development of new or worsening of pre-existing ascites detected clinically or radiologically

4. Number of patients requiring a re-intervention

Subgroup analysis:

1. Type of surgical shunt compared to devascularisation procedure
2. Trials with low risk of bias compared to trials with high risk of bias

Search methods for identification of studies

I will perform electronic search for relevant trials in the Cochrane Hepato-Biliary Group Controlled Trials Register (Gluud *et al.* 2012); the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; MEDLINE; EMBASE; and Science Citation Index Expanded (Royle & Milne, 2003).

The preliminary strategies for the search and the proposed time span is given in Appendix 2

Additional searches

Journal containing more than one relevant trial will be hand searched provided it has not been hand searched already. Reference list of identified trials will be investigated. Conference/meeting proceedings and abstracts of the following organizations, International Hepato-Pancreato Biliary Association (IHPBA) (1994-2013) and the American Association for the Study of Liver Diseases (AASLD) (1994-2013) will be searched.

Data collection and analysis:

Selection of studies:

Two reviewers (myself (CJ) and my supervisor (MB)) will select studies based on the inclusion criteria. CJ will develop the search strategy. CJ and MB will perform the searches independently. Areas of disagreement will be resolved by discussion. Initially all identified trials will be entered in a trial register. Data will be independently extracted from reports by CJ and MB. CJ will validate the data. Unpublished data will be sought by writing to the authors.

Data extraction and management

I will use the statistical software RevMan 5, 3 provided by the Cochrane collaboration (RevMan, 2012) and also the trial sequential analysis (Thorlund *et al*. 2011) to analyse my data. Recommendations contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins & Green, 2011) and the Cochrane Hepato-Biliary Group Module (Gluud *et al*. 2013) will be used to perform this meta-analysis.

The following data will be collected and recorded in a data extraction form (Appendix 1).

Number of patients evaluated for the study and number excluded.

For each included trial and for each treatment group data collected would be as follows:

Distribution of age of patients.

Number of patients randomised.

Distribution of time from bleeding episode to randomisation.

Distribution of Child's criteria (proportion in each category) (Child & Turcotte, 1964).

Results of biochemical liver function tests.

The following data will be sought post randomisation:

Mortality at 30 days, one year, and five years.

Incidence of rebleeding.

Incidence of encephalopathy.

Result of biochemical liver function tests.

Shunt patency.

Prograde hepatic flow following selective shunt and devascularization

Adverse events (Procedure related complications).

Total length of hospital stay during post-operative period.

Assessment of risk of bias in included studies

In order to eliminate bias due to trials with poor design quality (Schulz *et al.* 1995; Moher *et al.* 1998; Verhagen *et al.* 2001; Kjaergard *et al.* 2001), I will assess the risk of bias in included trial using the guideline provided in the *Cochrane Handbook for Systematic Reviews of* Interventions (Higgins et al. 2011) and the Cochrane Hepato-Biliary Group Module (Gluud et al. 2012) under the following domains:

Allocation sequence generation

Allocation concealment

Blinding of participants, personnel, and outcome assessors

Incomplete outcome data

Selective outcome reporting

For-profit bias

Trials that have been assessed as low risk in all of the above domains will be regarded at low risk of bias. Trials that are deficient in one or more of the specified domains will be considered at high risk of bias (Lundh *et al.* 2012; Higgin & Green, 2011; Kjaergard *et al.* 2001).

Where the required information for bias assessment has not been provided in the trial report, I will write to the authors to provide it.

Measures of treatment effect

I will measure treatment effect using the relative risk with 95% confidence interval (CI) for dichotomous variable, and the standardized mean difference with 95% CI for continuous variables. I will conduct a pooled estimate of effect using the random effect model

(DerSimonian & Laird, 1986), and the fixed-effect model (Demets, 1987). In case of discrepancy between the two models I will report both results; otherwise, I will use only one meta-analysis model with the highest P-value to report on the result of intervention effect. I will measure the degree of heterogeneity between trials using I^2 statistic (Higgin & Thompson, 2002; Sterne *et al.* 2011).

Unit of analysis issues

The unit of analysis will be the patients recruited into the trials.

Dealing with missing data

All analyses will be performed according to the intention-to-treat method, i.e. all randomised patients will be included in the analysis. Where there are missing data I will contact the authors to provide the information. Where I do not receive a reply from the authors I will consider the patients with missing data as treatment failures. I will analyse the impact of the missing data on the review finding in the discussion section.

Assessment of heterogeneity

I will assess heterogeneity by use of Chi-squared test and I^2 statistic. (Sterne *et al*. 2011, Egger 1997)

The calculated I^2 values will be interpreted as follows:

1. 0 to 40%: might not be important
2. 30 to 60%: may represent moderate heterogeneity
3. 50 to 90%: may represent substantial heterogeneity
4. 75 to 100%: represent considerable heterogeneity

An I^2 value above 50% will be considered as significant, and I will investigate the possible cause of heterogeneity by performing sensitivity analysis. I will consider any plausible cause of heterogeneity in the discussion.

Assessment of reporting biases

I will explore for reporting bias in included trial using a funnel plot. I will determine if there is an association between treatment effect and study size by visual inspection of the funnel plot. A test of asymmetry will be conducted if I find at least 10 studies for analysis (Higgins & Green, 2011). Two tests will be used to assess funnel plot asymmetry, the adjusted rank correlation test (Begg & Mazumdar**,** 1994) and regression asymmetry test (Egger *et al*. 1997).

Data synthesis

The recommendations contained in the *Cochrane Handbook for Systematic Reviews of* Interventions (Higgins et al. 2011) and the Cochrane Hepato-Biliary Group Module (Gluud et al. 2012) will be followed in this meta-analysis. The intervention effect will be calculated using relative risk for dichotomous outcome, and standardised mean difference for continuous outcome. The statistical package RevMan 5.2 (RevMan, 2012) will be used for the analysis and the Mantel-Haenzel method will be used for the meta-analysis (Mantel, 1959).

Trial Sequential Analysis

Cumulative meta-analysis can introduce random error because of repetitive analysis of sparse data, so trial sequential analysis will be applied in this meta-analysis. In order to reduce random error, I will calculate the required information size((i.e., the number of participants needed in a meta-analysis to accept or reject a certain intervention effect) (Watterslev *et al.*

2008), by making the following assumption: a relative risk reduction (RRR) of 20%, or RRR observed in the included trials with low risk of bias; a risk of type I error of 5%; a risk of type II error of 20%, and assumed heterogeneity or diversity present in the meta-analysis (Thorlund et al. 2011; Watterslev *et al.* 2008).

Subgroup analysis and investigation of heterogeneity

I will perform sub-group analyses to compare intervention effect in trials of total and selective shunts versus devascularization; trials with high risk of bias compared to those with low risk of bias. The data generated will further be stratified using Child's criteria (Child's classification provides objective assessment of hepatic function and prognosis (Child & Turcotte, 1964)). In case a study has more than two arms, then data will be extracted only from the arms which correspond to the treatment options being considered in this study.

Sensitivity analysis

A sensitivity analysis will be performed at the end of the review to assess whether the review findings are robust to the decisions made during the review process. This will involve assessment of the search method for the included trials, exclusion criteria, the type of data analysed, the process of data analysis, and the measure of intervention outcomes.

Summary of finding table

I will summarise the evidence from all outcomes in a summary of findings table using GRADEpro software (GRADEpro), based on five domains namely: the risk of bias, inconsistency, indirectness, imprecision and publication bias

Summary of statistical Analysis		
1	Measure of intervention effect	Relative risk for dichotomous outcome and standardised mean difference for continous outcome at 95% CI.
2	Assessment of Heterogeneity	Chi-squared test and I^2 statistic. I^2 > 50% Significant
3	Assessment of reporting bias	Funnel plot using the adjusted rank correlation test and regression asymmetry test
4	Trial sequential analysis	Assume RRR 20%, Type I error 5%, and type II error 20%.
5	Statistical significance	P≤ 0.05
6	Meta-analysis models	Random and fixed-effects.

References

Andersson, K.L, Chung, R.T. (2007), Hepatic schistosomiasis. *Curr Treat Options Gastroenterol* **10**:504-512.

Begg, C.B, Mazumdar, M. (1994), Operating characteristics of a rank correlation test for publication bias. *Biometrics* **50**:1088-1101.

Bica, I, Hamer, D.H, Stadecker M.J. (2000), Hepatic Schistosomiasis. *Infectious disease clinics of North America* **14**:583-604.

Boyer, T.D, Haskal, Z.J. (2010), American Association for the Study of Liver Diseases. The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* **51**(1):306

Child, C.G, Turcotte, J.G. (1964), Surgery and portal hypertension. *Major Probl Clin Surg* **1**:1-85.

D'Amico, G, De Franchis, R. (2003), Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* **38**:599-612.

Da Silva, L.C, Carrilho, F.J. (1992), Hepatosplenic schistosomiasis. Pathophysiology and treatment. *Gastroenterology clinics of North America* **21**:163-177.

de Dombal F T, Clarke J R, Clamp Susan E, Malizia G, Kotwal M R, Morgan A G.(1986) Prognostic Factors in Upper G.I. Bleeding. *Endoscopy* **18**:6-10.

de Franchis R. (2010), Revising consensus in portal hypertension: Report of the Baveno V consensus workshop on methodology of diagnosis and therapy in portal hypertension. *Journal of Hepatology* **53**:762-768

Demets, D.L. (1987), Methods for combining randomized clinical trials: strengths and limitations. *Stat Med* **6**:341-350.

Denié, C, Vachiery, F, Elman, A, Soupison, T, Gadano, A, Moreau, R, *et al*. (1996), Systemic and splanchnic hemodynamic changes in patients with hepatic schistosomiasis. *Liver* **16**:309-312.

DerSimonian, R, Laird, N. (1986), Meta-analysis in clinical trials. *Control Clin Trials* **7**:177-188.

Eesa M, Clark T. (2011), Transjugular intrahepatic portosystemic shunt: state of the art. *Semin Roentgenol* **46**:125-132.

Egger, M, Davey, S.G, Schneider, M, Minder, C. (1997), Bias in meta-analysis detected by a simple, graphical test. *Bmj* **315**:629-634.

Ferraz, A.A, Bacelar, T.S, Silveira, M.J, Coelho, A.R, Camara, N.R.D,de Araujo Junior, J.G, et al.(2001), Surgical treatment of schistosomal portal hypertension. *Int Surg* **86**:1-8.

Gluud, C, Nikolova, D, Klingenberg, S.L, Alexakis, N, Als-Nielsen, B, Colli, A, *et al*. (2012), Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)).2012,Issue 4.

Goff, J.S. (1993), Gastroesophageal varices: pathogenesis and therapy of acute bleeding. *Gastroenterol Clin North Am* **22**:779-800.

Gonzalez, R, Zamora, J, Gomez-Camarero, J, Molinero, L M, Banares, R, Albillos, A. (2008), Meta-analysis: Combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis. *Ann Intern Med* **149**:109-22.

Graham, D.Y, Smith J.L. (1981), the course of patients after variceal haemorrhage. *Gastroenterology* **80**:800-809.

Gur, I, Diggs, B.S, Orloff, S.L. (2014), Surgical portosystemic shunts in the era of TIPS and liver transplantation are still relevant. *HPB* **16**:481-493.

Henderson, J.M. (1988), Surgical methods for the prevention of first and recurrent variceal bleeding. *Z Gastroenterol* **26(**Suppl 2):49-53.

Higgins, J.P.T, Thompson, S.G. (2002), Quantifying heterogeneity in a meta-analysis. *Stat Med*; **21:**1539-1558.

Higgins, J.P.T, Green, S. (eds.) (2011*) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0.* [Updated March 2011]. The Cochrane Collaboration.

ICH-GCP (2001). ICH harmonised tripartite guideline: guideline for good clinical practice. 8. Essential documents for the conduct of a clinical trial. *J Postgrad Med* **47**(4):264-267.

John T G, Jalan R, Stanley A J, Redhead D N, Sanfey H A, Hayes P C, et al.(1996), Transjugular intrahepatic portosystemic stent-shunt (TIPSS) insertion as a prelude to orthotopic liver transplantation in patients with severe portal hypertension. *Eur J Gastroenterol Hepatol* **8**:1145-1149.

Johnson, M, Rajendran, S, Balachandar, T.G, Kannan, D, Jeswanth, S, Ravichandran, P, *et al.* (2006), Transabdominal modified devascularization procedure with or without esophageal stapler transection-an operation adequate for effective control of a variceal bleed. Is esophageal stapler transection necessary? *World J Surg* **30**:1507-1519.

Kjaergard, L.L, Villumsen, J, Gluud, C. (2001), Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med* **135**:982-989.

Lundh, A, Sismondo, S, Lexchin, J, Busuioc, O.A, Bero, L. (2012), Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews 2012*, issue 12

Mantel, N, Haenszel, W. (1959), Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* **22**:719-748

Moher, D, Jadad, A.R, Nichol, G, Penman, M, Tugwell, P, Walsh, S. (1995), Assessing the quality of randomized controlled trials: An annotated bibliography of scales and checklists. *Controlled Clinical Trials* **16**:62-73.

Moher, D, Pham, B, Jones, A, Cook, D.J, Jadad, A.R, Moher, M, et al.(1998), Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet* **352**:609-613.

Orloff, M.J, Isenberg, J.I, Wheeler, H.O, Haynes, K.S, Jinich-Brook, H, Rapier, R, et al.(2009), Randomized trial of emergency endoscopic sclerotherapy versus emergency portacaval shunt for acutely bleeding esophageal varices in cirrhosis. *J Am Coll Surg* **209**:25-40.

Orloff, M.J.(2014), Fifty-three years' experience with randomized clinical trials of emergency portacaval shunt for bleeding esophageal varices in Cirrhosis: 1958-2011. *JAMA Surg* **149**:155-169.

Paquet, K.J, Mercado, M.A, Koussouris, P, Kalk, J.F, Siemens, F, Cuan-Orozco, F.(1989), Improved results with selective distal splenorenal shunt in a highly selected patient population. A prospective study. *Ann Surg* **210**:184-189.

Qazi S A, Khalid K, Hameed A M, Al-Wahabi K, Galul R, Al-Salamah S M. (2006),Transabdominal gastro-esophageal devascularization and esophageal transection for bleeding esophageal varices after failed injection sclerotherapy: long-term follow-up report. *World J Surg* **30**:1329-1337

Raia S, da Silva L C, Gayotto L C, Forster S C, Fukushima J, Strauss E. (1994). Portal hypertension in schistosomiasis: a long-term follow-up of a randomized trial comparing three types of surgery. *Hepatology* **20**:398-403.

Review Manager (RevMan)(2012), [Computer program]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration.

Rikkers L F, Sorrell W T, Jin G.(1992), Which portosystemic shunt is best? *Gastroenterology clinics of North America* **21**:179-96.

Rikkers L F. (1998), The changing spectrum of treatment for variceal bleeding. *Ann Surg* **228**:536-546.

Rosemurgy, A.S, Goode, S.E, Zwiebel, B.R, Black, T.J, Brady, P.G.(1996), A prospective trial of transjugular intrahepatic portasystemic stent shunts versus small-diameter prosthetic H-graft portacaval shunts in the treatment of bleeding varices. *Ann Surg* **224**:378-384.

Rosemurgy A S, Frohman H A, Teta A F, Luberice K, Ross S B. (2012), Prosthetic H-graft portacaval shunts vs transjugular intrahepatic portasystemic stent shunts: 18-year follow-up of a randomized trial. *J Am Coll Surg* **214**:445-453

Ross, A.G, Bartley, P.B, Sleigh, A.C, Olds, G.R, Li, Y, Williams, G.M, *et al*.(2002), Schistosomiasis. *N Engl J Med* **346:**1212-1220.

Royle, P, Milne, R.(2003) Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *Int J Technol Assess Health Care* **19**(4):591-603.

Sanyal A J, Bosch J, Blei A, Arroyo V.(2008), Portal hypertension and its complications. *Gastroenterology* **134**:1715-1728.

Sarfeh IJ, Rypins EB, Mason GR.(1986), A systematic appraisal of portacaval H-graft diameters. Clinical and hemodynamic perspectives. *Annals of surgery* **204**(4):356-363.

Sarfeh IJ, Rypins EB.(1994), Partial versus total portacaval shunt in alcoholic cirrhosis. Results of a prospective, randomized clinical trial. *Annals of surgery* **219**(4):353-361.

Schulz K.F, Chalmers, I, Hayes, R.J, Altman, D.G.(1995) Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects in controlled trials.*JAMA* **273**:408-412.

Smith J.L, Graham D.Y.(1982), Variceal hemorrhage: a critical evaluation of survival analysis. *Gastroenterology* **82**:968-973.

Snady H.(1987), The role of sclerotherapy in the treatment of esophageal varices: personal experience and a review of randomized trials. *Am J Gastroenterol* **82**:813-822.

Spina, G.P, Henderson, J.M, Rikkers, L.F, Teres, J, Burroughs, A.K, Conn, H.O, *et al*.(1992), Distal spleno-renal shunt versus endoscopic sclerotherapy in the prevention of variceal rebleeding. A meta-analysis of 4 randomized clinical trials. *J Hepatol* **16**:338-345.

Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J.(2006) Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis* **6**:411-425

Sterne, J.A, Sutton, A.J, Ioannidis, J.P, Terrin, N, Jones, D.R, Lau, J, *et al*.(2011) Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *Bmj* **343**:d4002

Sugiura, M, Futagawa, S.(1973), A new technique for treating esophageal varices. *J Thorac Cardiovasc Surg* **66**:677-685.

Sugiura, M, Futagawa, S.(1984) Esophageal transection with paraesophagogastric devascularizations (the Sugiura procedure) in the treatment of esophageal varices. *World J Surg* **8:**673-679.

Symmers WSC.(1904), Note on a new form of Liver Cirrhosis due to the presence of the Ova of Bilharzia *Haematobia*. *J Pathol Bacteriol* **9**:237-239.

Thorlund, K, Engstrøm, J, Wetterslev, J, Brok, J, Imberger, C, Gluud, C.(2011) *User manual for Trial Sequential Analysis (TSA)*. Copenhagen: Copenhagan Trial Unit.

Toomey, P.G, Ross, S.B, Golkar, F.C, Hernandez, J.M, Clark W.C, Luberice, K, et al. (2013) Outcomes after transjugular intrahepatic portosystemic stent shunt: a "bridge" to nowhere. *Am J Surg* **205**:441-446.

Verhagen, A.P, de Vet, H.C.W, de Bie, R.A, Boers, M.A, van den Brandt, P.A.(2001), The art of quality assessment of RCTs included in systematic reviews. *Journal of clinical epidemiology* **54:**651-654.

Warren, W.D, Zeppa, R, Fomon, J.J.(1967), Selective trans-splenic decompression of gastroesophageal varices by distal splenorenal shunt. *Ann Surg* **166**:437-455

Wetterslev, J, Thorlund, K, Brok, J, Gluud, C.(2008), Trial sequential analysis may establish

when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* **61**:64-75.

Whipple, A.O.(1945), The Problem of Portal Hypertension in Relation to the Hepatosplenopathies. *Ann Surg* **122**:449-475.

World Health Organization (2014),Schistosomiasis: number of people receiving preventive chemotherapy in 2012. *Wkly Epedemiol Rec* **89**(2): 21-28.

Ethics: Ethics waiver obtained. Ref: W-CJ-140804-2

Timing

Process	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan
Project idea	X							
Literature Review	X	X						
Preparing protocol		X	X					
Protocol deadline			20/8/14					
Protocol Assessment				10/9/14				
Ethics application		31/7/14						
Collecting data				X	X	X		
Data analysis						X	X	
Writing up-report						X	X	
Report submission								X
Writing up- paper								X

Section 5

Appendices: 1

Data Extraction Form

Review title: Surgical portosystemic shunts versus devascularisation procedures for prevention of variceal rebleeding due to hepatosplenic schistosomiasis

Review authors: 1. Chikwendu J Ede; 2. Martin Brand

Date:

Study title:

First author	Journal/Conference Proceedings	Date of Publication

Contact address first author:

Email address first author:

Source of sponsorship:

Study eligibility

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

(* Possible selective reporting bias. Awaiting assessment until clarified with trial authors.)

Inclusion criteria:	
Exclusion criteria:	

Participant characteristics

Participant characteristics						
	Whole study (N)	**Shunts**		**Devascularisation**		**Combined/Others**
		PSRS	**DSRS**	**OGD**	**OGDS**	
Age (mean±SD, median, range,)						
Sex of participants (n) (Male/Female)	Male/Female					
Child-Pugh Class(A,B,C)						

PSRS= non-selective proximal portosystemic shunt DSRS= Selective distal splenorenal shunt

OGD = Oesophagogastric devascularization alone. OGDS= Oesophagogastric devascularisation with splenectomy

	Shunts		**Devascularisation**		**Combined/Others**
Parameters of Liver function before intervention. **(Mean±SD)**	**PSRS**	**DSRS**	**OGD**	**OGDS**	
Total Bilirubin					
Conjugated Bilirubin					
AST					
ALT					
Prothrombin time/ INR					
Serum Albumin					
Others					
Parameters of Liver function after intervention. (Mean±SD)					

Total Bilirubin					
Conjugated Bilirubin					
AST					
ALT					
Prothrombin time/ INR					
Serum Albumin					
Others					

Trial characteristics

Study design: O Parallel group O Cross-over O Open label
Comments:

Intervention: O Treatment O Other

Trial characteristics	
	Further details
Single centre / multicentre	
Country / Countries	
Number of participant recruited	
Number excluded before randomization	
Reasons for exclusion	
Number randomized	
Number of participants in each intervention group (Shunt vs devascularisation)	
Number of participants who received	

intended treatment	
Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)	
Number of participants lost to follow up	
Time from bleeding to randomization (mean±SD; Range)	

Risk of bias

Random Sequence generation	
Method:	*Grade (circle)*
Sequence generation was achieved using computer random number generation or a random number table. Drawing lots, coin tossing, shuffling cards or envelopes, and throwing dice by an independent person	Yes/Unclear/No
Allocation Concealment	
Method	Grade (circle)
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., if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes)	Yes/Unclear/No
Blinding of participants and personnel	
Method:	Grade (circle)

Blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding	Yes/Unclear/No
Blinding of outcome assessment	
Method:	Grade (circle)
Blinding was performed adequately, or the assessment of outcomes was not likely to be influenced by lack of blinding	Yes/Unclear/No
Incomplete outcome data (Yes/No)	
Method:	Grade (circle)
Missing data were unlikely to make treatment effects depart from plausible values.	Yes/Unclear/No* (* Trial authors to be contacted for information on missing data)
What method was used to handle missing data?	
Selective outcome reporting	
Method	Grade (circle)
Study protocol available and all pre-specified outcomes of interest in the review have been reported in the pre-specified way	Yes(Low risk) / No(High risk / Unclear
Study protocol is not available but is clear that published reports include all expect outcomes, including those that were pre-specified	Yes / No / Unclear
For-profit bias	
Method:	Grade
The study is free of industry sponsorship or other for profit support that may manipulate design, conductance or result.	Yes/No/Unclear
Other bias	

Study appears to be free of other sources of bias	Yes / No / Unclear
Give example.	

Were withdrawals described? Yes □ No □ not clear □

Discuss if appropriate……

……

Data extraction

Primary outcomes
Secondary outcomes
Other outcomes

Results

Adverse Events: Described □Yes □No

If yes □Procedure related □Overall Statistics

Adverse events:

Number of adverse events:

Type	Shunts		Devascularisation		Combined procedure	Total
	PSRS	DSRS	OGD	OGDS		
Length of Hospital stay post intervention (Mean, median)						
Total						

Comments:

Withdrawals due to adverse events:

	Shunts	Devascularisation	Combined
Number of withdrawals			

Outcomes for Patient Subgroups: specify subgroups

Outcome

For Continuous data						
Outcome	Unit of measurement (n = number of participants, not number of events)	Shunt		Devascularisation		Details if outcome only described in text
		PSRS	DSRS	OGD	OGDS	P-value

For Dichotomous data						
Outcome	Unit of measurement (n = number of participants, not number of events)	Shunt		Devascularisation		Details if outcome only described in text
		PSRS	DSRS	OGD	OGDS	P-value

Other information which are relevant to the results or any other comment that should be followed up

Appendix 2: Search strategy

SPS vs devascularisation procedures for variceal bleeding due to hepatosplenic schistosomiasis

(C Ede)

Updated searches performed 6 May 2016.

Total number of references identified:	**1845 references**
Number of duplicates excluded:	**701 references**
Number of references in final list:	**1144 references**
Number of new references:	**82 references**

BATCH NAME: 160506_C Ede_ SPS vs devascularisation procedure

Cochrane Hepato-Biliary Group Controlled Trials Register (May 2016) (131 hits)

(((port*systemic or portacaval or mesocaval or splenorenal or surgical or selective or non-selective or partial or total) and (shunt* or anastomos*)) or ('dean warren shunt*' or H-shunt* or PSS or devasculari*ation)) AND (varic* and (h*emorrhag* or bleed* or rebleed*))

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4 of 12, 2016) (238 hits in CENTRAL)

#1 MeSH descriptor: [Portasystemic Shunt, Surgical] explode all trees

#2 ((port*systemic or portacaval or mesocaval or splenorenal or surgical or selective or non-selective or partial or total) and (shunt* or anastomos*)) or ('dean warren shunt*' or H-shunt* or PSS or devasculari*ation)

#3 #1 or #2

#4 MeSH descriptor: [Esophageal and Gastric Varices] explode all trees

#5 MeSH descriptor: [Schistosomiasis] explode all trees

#6 varic* and (h*emorrhag* or bleed* or rebleed*)

#7 #4 or #5 or #6

#8 #3 and #7

MEDLINE (Ovid SP) (1946 to May 2016) (302 hits)

1. exp Portasystemic Shunt, Surgical/

2. (((port*systemic or portacaval or mesocaval or splenorenal or surgical or selective or non-selective or partial or total) and (shunt* or anastomos*)) or ('dean warren shunt*' or H-shunt* or PSS or devasculari*ation)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

3. 1 or 2

4. exp "Esophageal and Gastric Varices"/

5. exp Schistosomiasis/

6. (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 word, rare disease supplementary concept word, unique identifier]

7. 4 or 5 or 6

8. 3 and 7

9. (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 word, rare disease supplementary concept word, unique identifier]

10. 8 and 9

EMBASE (Ovid SP) (1974 to May 2016) (514 hits)

1. exp portosystemic anastomosis/

2. (((port*systemic or portacaval or mesocaval or splenorenal or surgical or selective or non-selective or partial or total) and (shunt* or anastomos*)) or ('dean warren shunt*' or H-shunt* or PSS or devasculari*ation)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

3. 1 or 2

4. exp esophagus varices/

5. exp schistosomiasis/

6. (varic* and (h*emorrhag* or bleed* or rebleed*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

7. 4 or 5 or 6

8. 3 and 7

9. (random* or blind* or placebo* or meta-analys*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

10. 8 and 9

Science Citation Index Expanded (1900 to May 2016) (661 hits)
#5 #4 AND #3

#4 TS=(random* or blind* or placebo* or meta-analys*)

#3 #2 AND #1

#2 TS=(varic* and (h*emorrhag* or bleed* or rebleed*))

#1 TS=(((port*systemic or portacaval or mesocaval or splenorenal or surgical or selective or non-selective or partial or total) and (shunt* or anastomos*)) or ('dean warren shunt*' or H-shunt* or PSS or devasculari*ation))