What is the Efficacy of Initial Therapies for Bleeding from Esophageal Varices in Adult Patients With Cirrhosis?

TAKE-HOME MESSAGE

Compared to sclerotherapy, somatostatin analogues or vasopressin analogues alone increase mortality. Sclerotherapy plus somatostatin analogues does not reduce mortality but may decrease symptomatic rebleeding when compared to sclerotherapy alone.

METHODS

DATA SOURCES

The authors searched Cochrane CENTRAL, MEDLINE Ovid, Embase Ovid, and Web of Science databases for registered studies from database inception to December 17, 2019, for all possible comparisons formed by the interventions of interest, without language restrictions. Authors also searched for ongoing or completed trials using ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform, the European Medicines Agency, the United States Food and Drug Administration, and references of identified trials.

STUDY SELECTION

The authors included randomized controlled trials of adults with acutely bleeding esophageal varices due to decompensated liver cirrhosis. They included trials in which patients with esophageal varices also had gastric varices, but they excluded trials in which the target of therapy was gastric varices, those including patients with prior liver transplantation, and those in which patients had failed

EBEM Commentators
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Jestin N. Carlson, MD, MS, Alan Jones, MD, and Michael Gottlieb, MD, serve as editors of the SRS series.

Results

Summary of therapy comparison outcomes.

Interventions Compared to Sclerotherapy	Number of Studies (Number of Participants)	OR (95% CrI)
Somatostatin analogues alone outcome:		
Mortality	4 (353)	1.57 (1.04–2.41)*
Serious adverse events	-	-
Symptomatic variceal rebleed	2 (146)	1.48 (0.05–41.68)
Vasopressin analogues alone outcome:		
Mortality	2 (438)	1.70 (1.13–2.62)*
Serious adverse events	1 (219)	1.10 (0.01–227.47)
Symptomatic variceal rebleed	-	-
Somatostatin analogues plus sclerotherapy outcome:		
Mortality	6 (693)	0.84 (0.56–1.26)
Serious adverse events	-	-
Symptomatic variceal rebleed	1 (105)	0.21 (0.03–0.94)*
Balloon tamponade alone outcome:		
Mortality	1 (43)	2.34 (0.96–5.92)

prior therapies or where initial hemostasis was achieved before randomization. Authors included any of the following interventions for comparison with one another alone or in combination: vasopressin or analogues, somatostatin or analogues, endoscopic sclerotherapy, balloon tamponade, tranexamic acid, no active intervention, and several others.

DATA EXTRACTION AND SYNTHESIS

Two authors independently screened articles for inclusion and resolved any discrepancies through discussion. Pairs of review authors independently extracted the data from selected studies, with differences in opinion resolved through discussion. Meta-analysis authors attempted to contact individual trial authors in the case of missing or unclear data. Primary outcomes included the proportion of patients who died from any cause, health-related quality of life based on a validated scale such as the European Quality of Life–5 Dimensions or 36-Item Short Form Health Survey, and serious adverse events (defined as any event that would increase mortality; is life-threatening; requires hospitalization; results in persistent or significant disability; is a congenital anomaly/birth defect; or any important medical event that may jeopardize the person or require intervention for prevention). Secondary outcomes included any adverse event, the proportion of patients with variceal bleeding at 6 weeks, and the proportion of patients with other features of decompensation at 6 weeks. Sclerotherapy was used as the reference standard. Authors conducted a network meta-analysis to compare multiple interventions simultaneously through direct

Continued.

Interventions Compared to Sclerotherapy	Number of Studies (Number of Participants)	OR (95% CrI)
Serious adverse events	No direct randomized controlled trial	0.13 (0–954.32)
Symptomatic variceal rebleed	-	-
Balloon tamponade plus sclerotherapy outcome:		
Mortality	1 (60)	2.37 (0.75–7.77)
Serious adverse events	1 (60)	4.23 (1.22–17.80)*
Symptomatic variceal rebleed	1 (60)	2.53 (0.02–299.17)

OR, Odds ratio; *CrI,* credible interval.
*Statistically significant.

This network meta-analysis included 52 trials comprising 4,580 patients. The mean patient age ranged from 39 to 62 years, and females accounted for 0% to 50% of patients in the included trials. Nineteen interventions were compared in included trials, and 48 trials reported 1 or more outcomes. Fifty trials compared 2 interventions, whereas 2 trials compared 3 interventions. Overall, 15.8% of patients who received sclerotherapy died (follow-up period of 3 days to 6 weeks). Somatostatin analogues or vasopressin analogues alone demonstrated higher mortality when compared to sclerotherapy (Table). Fewer patients developed symptomatic variceal rebleed with sclerotherapy plus somatostatin analogues compared to sclerotherapy alone. Based on moderate-certainty evidence, people receiving vasopressin analogues alone had fewer adverse events than those receiving only sclerotherapy (rate ratio 0.40; 95% credible interval 0.21 to 0.74). Balloon tamponade plus sclerotherapy resulted in higher serious adverse events compared to sclerotherapy alone. However, balloon tamponade alone or in combination with other therapies compared to sclerotherapy did not demonstrate significant effects on other outcomes. Other comparisons suffered from considerable uncertainty and no statistically significant outcomes. Significant heterogeneity was present in outcomes including serious adverse events, any adverse event, and length of hospital stay. Risk of bias was high for all included trials, resulting in inability to rank effectiveness.

Commentary

Portal hypertension leading to variceal bleeding is a major cause of morbidity and mortality in patients with liver cirrhosis.[2,3] The short-term mortality of an acute episode of variceal bleeding approximates 15% to 30%.[4-6] Recommendations for the emergency management of variceal bleeding in patients with cirrhosis includes the use of somatostatin or octreotide or their analogues, with consideration of balloon tamponade as a temporizing measure until endoscopic therapy or a transjugular intrahepatic portosystemic shunt procedure can be performed.[2,3,7]

comparisons if possible and indirectly when not possible. Authors assessed dichotomous outcomes using odds ratios and continuous variables with mean differences and 95% confidence intervals. For count outcomes, authors calculated rate ratios, and they estimated ranking probabilities when network meta-analysis was performed. Authors assessed statistical heterogeneity by comparing results of the fixed-effects model and random-effects model meta-analyses, lack of overlap of 95% credible intervals of between-study variance, and by calculating the network meta-analysis-specific I^2 statistic. Risk of bias was determined by the revised Cochrane risk of bias tool.[1]

There have been prior Cochrane reviews comparing several treatments for acute esophageal variceal bleeding,[4-6] but this is the first network meta-analysis comparing the benefits and harms of different therapies.[8] Network meta-analyses are similar to traditional meta-analyses, but they allow researchers to evaluate several endpoints in a single analysis using direct and indirect evidence.[9,10] The results of this network meta-analysis suggest that in patients with bleeding from esophageal varices, somatostatin or vasopressin analogues alone increase mortality compared to endoscopic sclerotherapy. However, sclerotherapy plus somatostatin analogues likely result in decreased symptomatic rebleed compared to sclerotherapy alone.[8] Although further studies are needed, emergency clinicians should consider administering somatostatin analogues with emergency gastroenterology consultation for further management including sclerotherapy. Balloon tamponade is a potential therapy, but this network meta-analysis did not demonstrate reduced mortality or symptomatic variceal rebleed compared to sclerotherapy when used alone or in combination with other therapies. However, the data evaluating balloon tamponade suffered from significant heterogeneity and poor evidence quality.

This network meta-analysis has several limitations. First, despite the inclusion of 52 randomized controlled trials, few of the studies were of high quality, which limited evidence certainty. The available data for most comparisons were limited, with the highest certainty of evidence for somatostatin or vasopressin analogues alone compared to sclerotherapy. Blinding was also not possible for most of the endoscopic interventions, and none of the direct comparisons had sufficient sample sizes, resulting in imprecision. No trials reported health-related quality of life. Additionally, these results are not applicable to pediatric patients, patients with other causes of upper gastrointestinal bleeding, those with esophageal bleeding due to causes other than cirrhosis, patients who failed initial therapy for esophageal varices, and those who responded successfully to initial therapy. There was also significant heterogeneity in outcomes including serious adverse events, any adverse events, blood transfusion, length of stay, and decompensation events. Moreover, the risk of bias was unclear or high in all trials. Further randomized controlled trials are required to evaluate patient-centered outcomes such as mortality, adverse events, and health-related quality of life in patients with liver cirrhosis and acutely bleeding esophageal varices.

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1. Sterne JAC, Savović J, Page MJ, et al. RoB 2: revised tool for assessing risk of bias in randomized trials. *Cochrane Database Syst Rev*. 2016;10:29-31.
2. de Franchis R, VI Faculty Baveno. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. *J Hepatol*. 2015;63:743-752.
3. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406-460.
4. Ioannou GN, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev*; 2003:CD002147.
5. Gøtzsche PC, Hróbjartsson A. Somatostatin analogues for acute bleeding oesophageal varices. *Cochrane Database Syst Rev*. 2008;2008(3): CD000193.
6. D'Amico G, Pagliaro L, Pietrosi G, et al. Emergency sclerotherapy versus vasoactive drugs for bleeding oesophageal varices in cirrhotic patients. *Cochrane Database Syst Rev*. 2010;2010:CD002233.
7. Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology*. 2017;65:310-335.
8. Roberts D, Best LM, Freeman SC, et al. Treatment for bleeding oesophageal varices

in people with decompensated liver cirrhosis: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;4:CD013155.

9. Rouse B, Chaimani A, Li T. Network meta-analysis: an introduction for clinicians. *Intern Emerg Med*. 2017;12:103-111.
10. Shim S, Yoon BH, Shin IS, et al. Network meta-analysis: application and practice using Stata. *Epidemiol Health*. 2017;39:e2017047. https://doi.org/10.4178/epih.e2017047.

IMAGES IN EMERGENCY MEDICINE

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DIAGNOSIS:

Abdominal cocoon sign. Abdominal cocoon sign is a result of encapsulating peritoneal sclerosis. Given its rarity, the incidence rates of encapsulating peritoneal sclerosis vary widely and have been reported from 0.5% to 17.2%. On CT, it is characterized by a cluster of thickened or dilated loops of small bowel surrounded by a fibrous, encapsulating membrane[1] as though it were within a cocoon.

In addition to idiopathic forms, there are numerous, multifactorial etiologies such as cirrhosis, peritoneal dialysis, and any irritation of the peritoneum[2], resulting in stimulation of collagen formation and fibrosis.[2,3] Patients present with nonspecific symptoms such as abdominal pain, constipation, and vomiting. Physical examination may reveal a palpable mass, representing the encapsulated small bowel.[1,4] Given the nonspecific symptoms, there is an exhaustive list of differential diagnoses. There are no specific laboratory tests for encapsulating peritoneal sclerosis and diagnosis is primarily suggested by imaging. Although ultrasound, magnetic resonance imaging, and fluoroscopy can demonstrate findings of encapsulating peritoneal sclerosis, CT is the mainstay imaging choice.[1,2]

Conservative management includes cessation of any inciting causes. Medications such as immunosuppressants and tamoxifen may be of benefit. Surgical management is indicated with overt signs of obstruction or ischemia.[3,4]

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REFERENCES

1. Singhal M, Krishna S, Lal A, et al. Encapsulating peritoneal sclerosis: the abdominal cocoon. *Radiographics*. 2019;39:62-77.
2. Danford CJ, Lin SC, Smith MP, et al. Encapsulating peritoneal sclerosis. *World J Gastroenterol*. 2018;24:3101-3111.
3. Jagirdar RM, Bozikas A, Zarogiannis SG, et al. Encapsulating peritoneal sclerosis: pathophysiology and current treatment options. *Int J Mol Sci*. 2019;20:5765.
4. Brown EA, Bargman J, van Biesen W, et al. Length of time on peritoneal dialysis and encapsulating peritoneal sclerosis—Position paper for ISPD: 2017 update. *Perit Dial Int*. 2017;37:362-374.