Efficacy of endoscopic treatments for acute esophageal variceal bleeding in cirrhotic patients: systematic review and meta-analysis

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🌐 Supplementary Material
Online content viewable at:
https://doi.org/10.1055/a-0901-7146

ABSTRACT

Background and aim Guidelines recommend use of ligation and vasoactive drugs as first-line therapy and as grade A evidence for acute variceal bleeding (AVB), although Western studies about this issue are lacking.

Methods We performed a systematic review and meta-analysis of randomized controlled trials (RCT) to evaluate the efficacy of endoscopic treatments for AVB in patients with cirrhosis. Trials that included patients with hepatocellular carcinoma, use of portocaval shunts or esophageal resection, balloon tamponade as first bleeding control measure, or that received placebo or elective treatment in one study arm were excluded.

Results A total of 8382 publications were searched, of which 36 RCTs with 3593 patients were included. Ligation was associated with a significant improvement in bleeding control (relative risk [RR] 1.08; 95% confidence interval [CI] 1.02 – 1.15) when compared to sclerotherapy. Sclerotherapy combined with vasoactive drugs showed higher efficacy in active bleeding control compared to sclerotherapy alone (RR 1.17; 95% CI 1.10 – 1.25). The combination of ligation and vasoactive drugs was not superior to ligation alone in terms of overall rebleeding (RR 2.21; 95%CI 0.55 – 8.92) and in-hospital mortality (RR 1.97; 95%CI 0.78 – 4.97). Other treatments did not generate meta-analysis.

Conclusions This study showed that ligation is superior to sclerotherapy, although with moderate heterogeneity. The combination of sclerotherapy and vasoactive drugs was more effective than sclerotherapy alone. Although current guidelines recommend combined use of ligation with vasoactive drugs in treatment of esophageal variceal bleeding, this study failed to demonstrate the superiority of this combined treatment.

Introduction

Bleeding from gastroesophageal varices is the most common life-threatening complication in patients with cirrhosis, being associated with mortality rates from 10% to 50% per episode [1, 2]. More than half of patients who survive the first episode suffer from recurrent bleeding within 1 year [3, 4]. Management of acute variceal bleeding (AVB) remains a clinical challenge with high mortality, in spite of standardization in supportive and new therapeutic treatments in the last two decades [5].

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A beneficial effect on survival has been observed in parallel with introduction of drugs that are capable of decreasing portal pressure, optimization of endoscopic therapy, and use of antibiotics and interventional radiologic procedures. During the same period, the 6-week mortality rate has decreased from approximately 40 % to 15 % [5, 6].

Although overall survival has improved in recent years, mortality is still closely related to failure to control the initial bleeding or early rebleeding, which occurs in up to 30 % to 40 % of patients within the first 5 days after the index bleeding episode [5, 6]. As a consequence, many patients with cirrhosis and AVB still suffer from failure to control bleeding and most of them die very early [2]. Therapeutic options include vasoactive drugs such as somatostatin, octreotide, and terlipressin; endoscopic treatments such as sclerotherapy and band ligation; and most recently, radiologic interventions, such as early-TIPS (transjugular intrahepatic portosystemic shunt) placement. Therefore, the goal of this study was to evaluate the efficacy and safety of the most-used endoscopic treatments for controlling AVB.

Methods

A meta-analysis and systematic review of published randomized controlled trials (RCTs) were carried out.

Search strategy

Medline (PubMed), Embase, Cochrane library and manual searches were combined and last performed on 16 March 2018. Key search terms were "esophageal and gastric varices," "esophageal varices," "esophageal varix," "oesophageal varices," "oesophageal varix," "esophagogastric varices," "esophagogastric varix," "gastroesophageal varices," "gastroesophageal varix," "oesophagogastric varices," "oesophagogastric varix," "oesophago-gastric varices," "oesophago-gastric varix," "esophago-gastric varices," "esophago-gastric varix," upper gastrointestinal bleeding," "bleeding, upper gastrointestinal," "upper digestive haemorrhage," "upper digestive hemorrhage," "upperdigestive tract haemorrhage," "upper digestive tract hemorrhage," "uppergastrointestinal haemorrhage," "upper gastrointestinal hemorrhage, "upper gastrointestinal tract bleeding," "variceal bleeding," "esophagus varices bleeding," "esophagus bleeding varix," "esophagus varices haemorrhage," "esophagus varices hemorrhage," and "esophagus varix bleeding". MeSH terms and free-text terms, as well as variation of root words were searched. Terms were combined within each database. The study has been registered in PROSPERO database under code CRD42017058139.

Criteria for inclusion and exclusion of studies

Only RCTs were included. To reduce the risk of bias, strict inclusion and exclusion criteria were defined prior to literature search. To be considered, a study had to include patients exclusively with cirrhosis, patients with acute variceal bleeding, have more than 10 patients in each arm, include only adults, and include treatments performed in the first 24 to 48 hours after bleeding. Studies were excluded if they included patients with hepatocellular carcinoma or other malignancies, use of porto-caval shunts or esophageal resection, recent use of balloon tamponade as first bleeding control measure, placebo or elective treatment in one study arm. When two publications existed covering the same study population, only the most recent was taken into account.

Endpoints

Endpoints were defined prior to the beginning of the meta-analysis. Main endpoints were treatment efficacy for bleeding control and in-hospital mortality. Secondary endpoints were rate of rebleeding from active bleeders at initial endoscopy, rate of overall rebleeding, rate of overall mortality, and rate of adverse events (AEs) related to each treatment.

Data extraction and assessment of quality

Two reviewers independently abstracted data from included articles (F.Q.O. and F.M.V.). Disagreements were resolved by consensus of all authors. Extracted information included patient population characteristics, intervention characteristics, comparator characteristics, outcomes assessed, and study quality. The latter used the framework suggested by the Cochrane Handbook for Systematic Reviews of Interventions (version 5·1·0), with evaluation of the following trial characteristics: random sequence generator method, concealment of treatment allocation, blinding of participants and personnel, blinding of outcome assessment, and for selective reporting [7]. Intention-to-treat analysis and the funding source of the studies were also assessed. The GRADE methodology [7] was used to define risk of bias for each of the outcomes that had available data.

Sources of support

This systematic review and meta-analysis was not supported by any grant.

Statistical analysis

We performed direct random effects model meta-analyses of head-to-head comparisons for pooling effect sizes of reported comparisons and outcomes whenever enough data were provided in published studies. No data imputation was done, and studies not reporting information that allowed treatment-effect calculation were not included in the meta-analyses. Summary effect for binary outcomes was calculated from risk ratios. Heterogeneity was evaluated with the inconsistency test proposed by Higgins (I^2), where values below 25 % were considered as low heterogeneity, and above 75 %, high heterogeneity [8, 9]. Publication bias was assessed with funnel plots of comparisons with seven or more studies. Meta-analyses were carried out in Review Manager 5·3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Prediction intervals were calculated with the Paule-Mandel estimator for tau squared and the Hartung-Knapp adjustment for random effects model. Prediction interval calculations were done with the software "R" (v 3.5.0) and package "Meta" (v 4.9 – 4) [10].

Results

Studies selection

A total of 8382 citations were screened, of them 6691 were evaluated after duplicates were removed (▶ Fig. 1). Of these, 69 were selected for full-text evaluation. Among them, only 36 randomized trials [11–46] were identified that fulfilled the inclusion criteria (▶ Table 1): seven studies compared sclerotherapy with vasoactive drugs (two studies with somatostatin, three studies with octreotide, one with terlipressin and one with vasopressin plus nitroglycerin); two studies compared ligation with vasoactive drugs (one with octreotide and one with somatostatin); one study compared ligation with cyanoacrylate injection; 10 studies compared sclerotherapy with ligation; seven studies compared sclerotherapy with the combination of sclerotherapy and vasoactive drugs (six with octreotide and one with somatostatin); five studies compared ligation with sclerotherapy and ligation; two studies compared ligation with ligation and vasoactive drugs (one with somatostatin and with octreotide); one study compared sclerotherapy and octreotide with octreotide alone; and one study compared ligation and octreotide with octreotide alone.


Search strategy for AVB
(PUBMED, EMBASE, Cochrane CENTRAL).
8382 citations

1691 duplicates excluded.

6691 citations after duplicates removed.

6622 citations excluded.
After evaluation of title and abstract.

69 citations selected for full text evaluation.

33 citations excluded
- article not in English **(2)**
- not enough information **(10)**
- met exclusion criteria **(11)**
- did not meet inclusion criteria **(8)**
- publications related to the same study **(2)**

36 Randomized clinical trials included in the qualitative syntheses.

▶ **Fig. 1** Study selection flowchart.

▶ **Table 1** Demographic data from included studies.

Author (year)	Patients, n [a/b]	Mean age, years	Men, n %	Main cause of cirrhosis, n [a/b]	Child-pugh class c % [a/b]	Active bleeding % [a/b]	Follow-up for initial control of bleeding (hours)
Intervention axb							
Sclerotherapy x VP + NG							
Westaby (1989)	33/31	54.2	56.3	Alcohol 13/alcohol 22	36/32	100/100	12
Sclerotherapy x somatostatin							
Shields (1992)	41/39	58	67.5	Alcohol 26/alcohol 28	41/64	61/69	120
Planas (1994)	35/35	57	71.4	Alcohol 28/alcohol 22	34/34	48.5/51.4	48
Sclerotherapy x octreotide							
Sung (1993)	49/49	55.7	84.7	HBV 32/HBV 36	42/43	37/51	48
Sivri (2000)	36/30	47	24.2	Viral 8/viral 14	53/55	100/100	6
Bildozola (2000)	37/39	52.6	78.9	Alcohol 27/alcohol 28	8/13	48.6/38.5	12
Sclerotherapy x terlipressin							
Escorsell (2000)	114/105	55.5	72.1	Alcohol 47/alcohol 41	31/32	42.9/35.2	48
Sclerotherapy x sclerotherapy + octreotide							
Besson (1995)	101/98	56	76.4	Alcohol 93/alcohol 89	46/26	46.5/428	24
Shiha (1996)	96/93	49.6	81.5	HCV 45/HCV 44	12/15	100/100	168
Faraoqi (2000)	69/72					100/100	Not clearly stated
Zuberi (2000)	35/35	38.5	80.0	HBV 28/HBV 26	0/0	100/100	24

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▶ Table 1 (Continuation)

Author (year)	Patients, n [a/b]	Mean age, years	Men, n %	Main cause of cirrhosis, n [a/b]	Child-pugh class c % [a/b]	Active bleeding % [a/b]	Follow-up for initial control of bleeding (hours)
Shah (2005)	54/51	49.8	64.8	Viral 52/viral 49	26/21	44.4/45	Not clearly stated
Morales (2007)	28/40	51.8	66.2	HCV 14/HCV + alcohol 11	36/60	46/65	Not clearly stated
Sclerotherapy x sclerotherapy + somatostain							
Avgerinos (1997)	101/104	58.6	70.7	Alcohol 59/alcohol 61	28/25	40.3/26.7	Not clearly stated
Octreotide + sclerotherapy x octreotide							
Patsanas (2002)	15/15	51	70.0	Alcohol 8/viral 5	60/53	33/43	120
Sclerotherapy x ligation							
Stiegmann (1992)	65/64	52.0	80.6	Alcohol 52/alcohol 53	20/19	20/22	8
Laine (1993)	38/39	46.0	75.3	Alcohol 30/alcohol 31	12,8/34,2	23/24	Not clearly stated
Gimson (1993)	49/54	51.4	55.3	Alcohol 24/alcohol 25	24/28	23/39	12
Lo (1995)	59/61	55.5	80.8	Viral 43/viral 41	47/49	25/29	72
Hou (1995)	67/67	60.6	79.9	Viral 47/viral 43	34/43	23/29.8	24
Lo (1997)	34/37	54.0	86.1	HCV 11 + alcohol 11/HBV 15	59/59	100/100	72
Shafqat (1998)	30/28	52.0	63.8	HCV 21/HCV 18	13/11	93/86	12
De la Peña (1999)	46/42	59.0	72.7	Alcohol 29/alcohol 29	28/24	47.8/42.8	Not clearly stated
Luz (2011)	50/50	52.3	72.0	Alcohol 19 + virus 19/ alcohol 17	40/30	10/20	120
Sahu (2014)	103/111						Not clearly stated
Ligation x octreotide							
Ximing (2013)							Not clearly stated
Ligation x somatostatin							
Chen (2006)	62/63	53.2	76.0	Alcohol 24/alcohol 29	29/28	27.4/20.6	48
Ligation x cyanoacrylate injection							
Ljubicic (2011)	21/22	58	72.1	Alcohol/ alcohol	19/41	52.4/90.9	24
Ligation x ligation + sclerotherapy							
Laine (1996)	20/21	47	73.2	Alcohol 16/alcohol 15	45/43	20/19	Not clearly stated
Saeed (1997)	25/22	53.1	91.5	Alcohol 22/alcohol 16	16/41	28/18	Not clearly stated
Al traif (1999)	31/29	48.8	61.7	HCV 10/HCV 14	32/17	22.5/31	Not clearly stated
Djurdjevic (1999)	51/52	55.6	61.2	Alcohol 25/alcohol 28	23/19	23.5/19,2	Not clearly stated
Mansour (2017)	60/60	0.0	65.0	HCV 52/HCV 52	53/40		48
Ligation + octreotide x octreotide							
Liu (2009)	51/50	41	81.2		55/48	35.2/34	72
Ligation x ligation + somatostatin							
Sarin (2008)	24/23	43.6	74.0			40.0	Not clearly stated
Ligation x ligation + octreotide							
Sung (1995)	47/47	57.0	71.3	Hepatitis 29/hepatitis 27	40.4/42.6	44.7/34.0	24
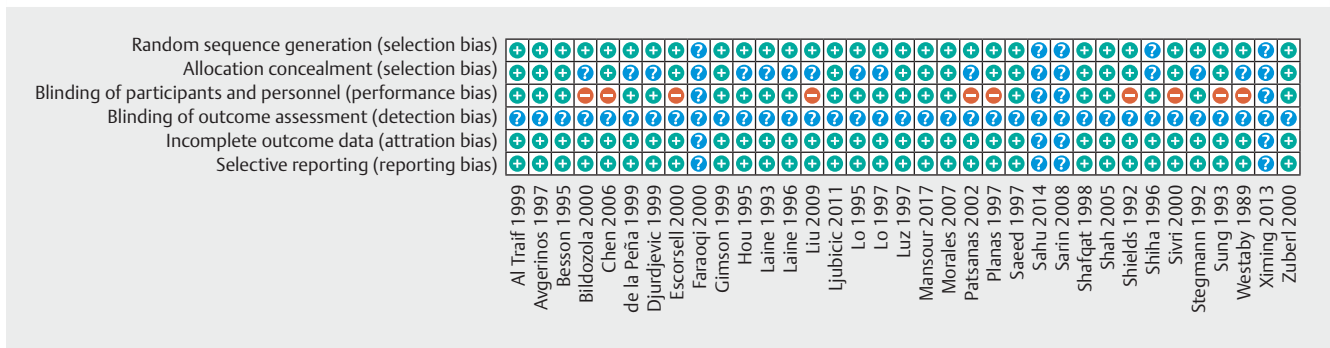
Fig. 2 Risk of bias assessment of included studies. Green circles: low risk of bias for a given quality assessment domain; blue circles: unclear risk of bias for a given quality assessment domain; red circles: high risk of bias for a given quality assessment domain.

Studies characteristics

Only 32 RCTs had been published as full papers. Four trials were published as abstracts [32, 40, 44, 45]. In six studies [11, 23, 24, 31, 32, 35], patients were included only if they had ongoing bleeding at time of initial endoscopy. Alcoholic cirrhosis was the predominant cause of portal hypertension in 18 studies. In contrast, cirrhosis due to viral hepatitis infection was the leading cause in 13 studies (patients from Asia, Brazil, and the Middle East). Otherwise, baseline characteristics of the study populations, such as gender ratio, Child-Pugh class or mean age, were comparable (▶ Table 1). Only 11 of the 36 trials described separately the rebleeding rate of the different treatment modalities in active bleeders at the time of endoscopy, i.e., 25 studies analyzed together active and non-active bleeders (**Supplementary Table 1 – Supporting Information**).

Risk of bias within trials

The included trials had risk of bias evaluated according to the Cochrane recommendations for meta-analyses and systematic reviews (▶ Fig. 2). None of the included trials were placebo-controlled. The randomization-method of the majority of the trials was computer-generated random sequences, with only four trials (abstracts) having no information about randomization. Eighteen trials had low risk for concealment of treatment allocation. Blinding of outcome assessment was not stated in any of the peer-reviewed articles.

Prediction intervals for random effects meta-analyses are presented in ▶ Table 2.

Risk of bias across trials

With respect to risk of publication bias, funnel plots were generally symmetrical, which indicates a low probability of publication bias in the present systematic review.

Comparison of sclerotherapy with vasoactive medications

Sclerotherapy was compared to somatostatin, octreotide, and vasopressin plus nitroglycerin in seven trials. The rate of complications was significantly higher with sclerotherapy (6 trials; relative risk [RR] 2.10; 95 % confidence interval [CI] 1.52 – 2.90; $P < 0.00001$; $I^2 = 0\%$) when compared to vasoactive drug alone. There was no significant difference in the other analyzed outcomes. The studies by Planas and Escorsell had no specific description of in-hospital mortality, so they were not included in this analysis.

In patients with active bleeding at endoscopy, sclerotherapy was needed in 17 patients to achieve active bleeding control in one of them when compared to vasoactive drug alone (number needed to treat [NNT] 17, $I^2 = 0\%$, $P < 0.05$).

Comparison of ligation with vasoactive medications

Only two trials [38, 44] compared ligation with vasoactive medications (somatostatin and octreotide). However, the study by Ximing was published as an abstract and did not have enough information to be included in the analysis.

Comparison of sclerotherapy with ligation

Ligation was associated with significant improvement in bleeding control (10 trials; RR 1.08; CI 1.02 – 1.15; $P = 0.01$; $I^2 = 49\%$) compared to sclerotherapy (▶ Fig. 3). The heterogeneity was potentially explained by the differences in two identified subgroups: one formed by Lo [19], Hou [21], Lo [24], Squafat [27] and de la Peña [29] (mostly Asian studies) in which ligation was clearly superior to sclerotherapy and another group of five trials (mostly Western trials) in which both techniques had similar results.

Risk of overall rebleeding was statistically significantly higher (10 trials; RR 1.41 95 % CI 1.03 – 1.94; $P = 0.03$; $I^2 = 62\%$) with sclerotherapy than with ligation. The high heterogeneity was explained by the same reasons as mentioned above.

Overall mortality was 38 % higher in patients treated with sclerotherapy compared to ligation (9 trials; RR 0.72 95 % CI 0.54 – 0.97; $P = 0.03$; $I^2 = 35\%$) (▶ Fig. 4). Overall mortality was not reported in the study by Laine et al [14].

Rebleeding rate from active bleeders (only 1 trial) could not generate meta-analysis. In-hospital mortality analysis (only 3 trials) had not shown statistical difference.
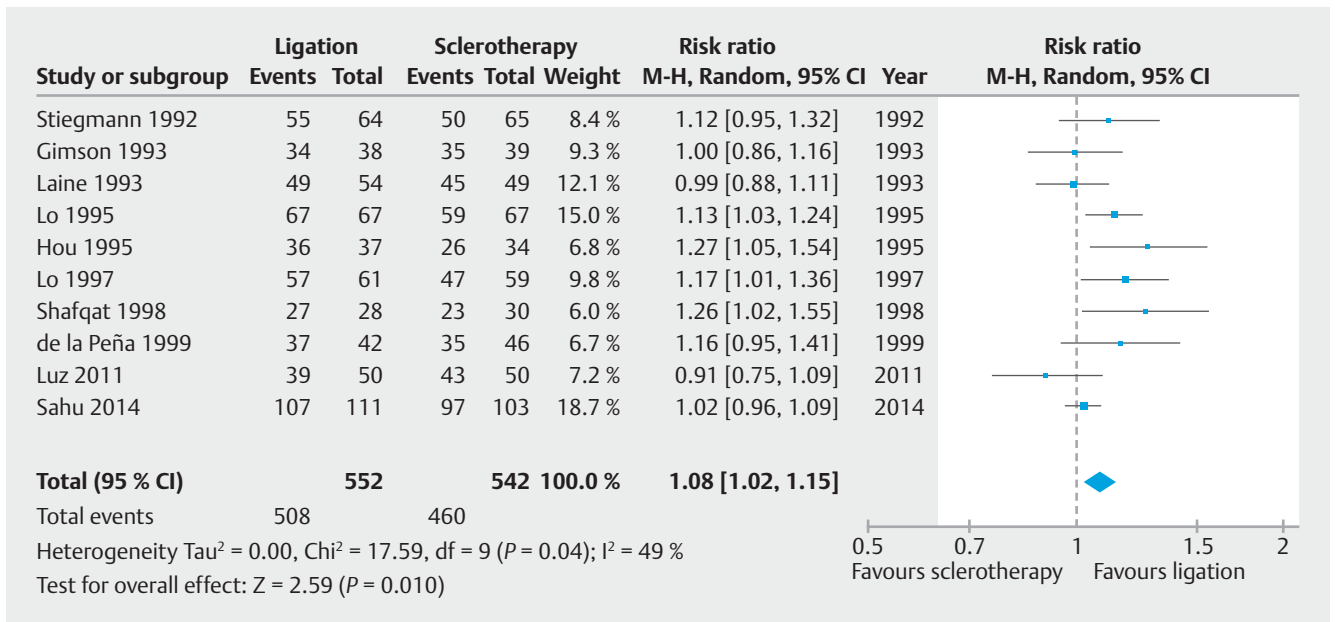
The rate of complications was significantly lower with ligation (8 trials; RR 0.29 95 %CI 0.20 – 0.44; $P < 0.00001$; $I^2 = 0\%$) when compared to sclerotherapy.

▶ **Table 2** Prediction intervals for random-effects models.

Comparison	Outcome	Prediction interval	Meta-analysis and prediction interval interpretation
Ligation x sclerotherapy			
	Efficacy of bleeding control	0.91 to 1.29	Random effects meta-analysis statistically signiffican but prediction interval indicating uncertainty on true effect size and direction
	Overall rebleeding	0.25 to 1.99	Random effects meta-analysis statistically signiffican but prediction interval indicating uncertainty on true effect size and direction
	In-hospital mortality	Zero to infinity	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating complete uncertainty on true effect size and direction
	Overall mortality	0.33 to 1.57	Random effects meta-analysis statistically signiffican but prediction interval indicating uncertainty on true effect size and direction
	Complications	0.18 to 0.47	Random effects meta-analysis statistically signifficant and prediction interval indicating low uncertainty on true effect size and no uncertainty on true effect direction
Sclerotherapy x drug			
	Efficacy of bleeding control	0.99 to 1.17	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction
	Overall rebleeding	0.71 to 1.06	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction
	Rebleeding from active bleeders	0.92 to 1.48	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating some uncertainty on true effect size and direction
	In-hospital mortality	0.43 to 1.42	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction
	Overall mortality	0.41 to 1.49	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating some uncertainty on true effect size and direction
	Complications	1.34 to 3.29	Random effects meta-analysis statistically signifficant and prediction interval indicating some uncertainty on true effect size and no uncertainty on true effect direction
Sclerotherapy + drug x sclerotherapy			
	Efficacy of bleeding Control	1.04 to 1.31	Random effects meta-analysis statistically signifficant and prediction interval indicating low uncertainty on true effect size and no uncertainty on true effect direction
	Overall rebleeding	0.08 to 1.40	Random effects meta-analysis statistically signifficant and prediction interval indicating some uncertainty on true effect size and direction
	Rebleeding from active bleeders	0.02 to 3.45	Random effects meta-analysis statistically signiffican but prediction interval indicating uncertainty on true effect size and direction
	In-hospital mortality	0.52 to 1.32	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction
	Overall mortality	0.64 to 1.28	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction
Ligation x ligation + sclerotherapy			
	Efficacy of bleeding control	0.70 to 1.45	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating high uncertainty on true effect size and direction
	Overall rebleeding	0.60 to 1.48	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating some uncertainty on true effect size and direction
	In-hospital mortality	0.04 to 13.65	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating high uncertainty on true effect size and direction
	Overall mortality	0.06 to 14.32	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating high uncertainty on true effect size and direction
	Complications	0.30 to 0.86	Random effects meta-analysis statistically signifficant and prediction interval indicating low uncertainty on true effect size and no uncertainty on true effect direction

▶ **Table 2** (Continuation)

Com-parison	Outcome	Prediction interval	Meta-analysis and prediction interval interpretation
Ligation x drug			
	Efficacy of bleeding control	0.98 to 1.88	Random effects meta-analysis statistically significant and prediction interval indicating some uncertainty on true effect size and little uncertainty on true effect direction
	Overall rebleeding	Zero to infinity	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating complete uncertainty on true effect size and direction
	Overall mortality	Zero to infinity	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating complete uncertainty on true effect size and direction
Ligation x ligation + drug			
	Overall rebleeding	Zero to infinity	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating complete uncertainty on true effect size and direction
	Overall mortality	0.15 to 26.64	No statistically significant differences in random-effects meta-analysis estimate and prediction interval indicating low uncertainty on true effect size and direction

	Ligation		Sclerotherapy			Risk ratio		Risk ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% CI
Stiegmann 1992	55	64	50	65	8.4 %	1.12 [0.95, 1.32]	1992	
Gimson 1993	34	38	35	39	9.3 %	1.00 [0.86, 1.16]	1993	
Laine 1993	49	54	45	49	12.1 %	0.99 [0.88, 1.11]	1993	
Lo 1995	67	67	59	67	15.0 %	1.13 [1.03, 1.24]	1995	
Hou 1995	36	37	26	34	6.8 %	1.27 [1.05, 1.54]	1995	
Lo 1997	57	61	47	59	9.8 %	1.17 [1.01, 1.36]	1997	
Shafqat 1998	27	28	23	30	6.0 %	1.26 [1.02, 1.55]	1998	
de la Peña 1999	37	42	35	46	6.7 %	1.16 [0.95, 1.41]	1999	
Luz 2011	39	50	43	50	7.2 %	0.91 [0.75, 1.09]	2011	
Sahu 2014	107	111	97	103	18.7 %	1.02 [0.96, 1.09]	2014	
Total (95 % CI)		**552**		**542**	**100.0 %**	**1.08 [1.02, 1.15]**		
Total events	508		460					

Heterogeneity Tau^2 = 0.00, Chi^2 = 17.59, df = 9 (P = 0.04); I^2 = 49 %
Test for overall effect: Z = 2.59 (P = 0.010)

0.5　0.7　1　1.5　2
Favours sclerotherapy　Favours ligation

▶ **Fig. 3** Forest plot of risk ratio for efficacy of bleeding control with ligation versus sclerotherapy.

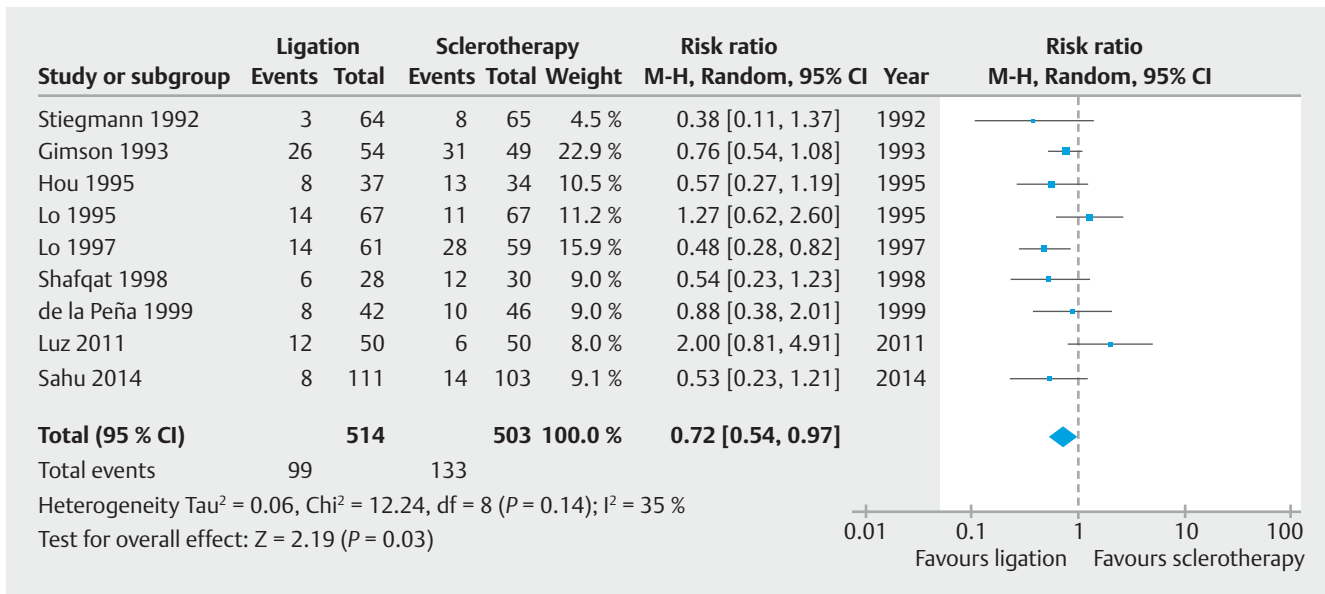## Comparison of sclerotherapy and vasoactive medications with sclerotherapy alone

Efficacy of bleeding control was 17 % higher with the combination of sclerotherapy and vasoactive drugs in comparison to sclerotherapy alone (7 trials; RR of 1.17; 95 % CI 1.10–1.25; P<0.00001; I^2=25 %) (▶ Fig. 5).

Overall rebleeding was 66 % lower (6 trials, RR 0.34; 95 % CI 0.19–0.61; P=0.0003; I^2=42 %) with the association of sclerotherapy plus vasoactive drug compared to sclerotherapy alone (▶ Fig. 6).

Risk of rebleeding from active bleeders at initial endoscopy was 73 % lower (4 trials; RR 0.27; 0.12–0.60; P=0.001; I^2=35 %) with the combination of sclerotherapy and vasoactive drugs compared to sclerotherapy alone (▶ Fig. 7).

In-hospital mortality and overall mortality did not show difference in effect.

Combining sclerotherapy with vasoactive drug in seven patients resulted in control of active bleeding and reduced risk of rebleeding in one patient when compared to sclerotherapy alone (NNT 7, I^2=0 %, P<0.05) . In addition, the combination of sclerotherapy with vasoactive drug was needed in six patients to reduce rebleeding from active bleeders in one of them when compared to sclerotherapy alone (NNT–6, I^2=0 %, P<0.05).

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Study or subgroup	Ligation Events	Total	Sclerotherapy Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
Stiegmann 1992	3	64	8	65	4.5 %	0.38 [0.11, 1.37]	1992	
Gimson 1993	26	54	31	49	22.9 %	0.76 [0.54, 1.08]	1993	
Hou 1995	8	37	13	34	10.5 %	0.57 [0.27, 1.19]	1995	
Lo 1995	14	67	11	67	11.2 %	1.27 [0.62, 2.60]	1995	
Lo 1997	14	61	28	59	15.9 %	0.48 [0.28, 0.82]	1997	
Shafqat 1998	6	28	12	30	9.0 %	0.54 [0.23, 1.23]	1998	
de la Peña 1999	8	42	10	46	9.0 %	0.88 [0.38, 2.01]	1999	
Luz 2011	12	50	6	50	8.0 %	2.00 [0.81, 4.91]	2011	
Sahu 2014	8	111	14	103	9.1 %	0.53 [0.23, 1.21]	2014	
Total (95 % CI)		**514**		**503**	**100.0 %**	**0.72 [0.54, 0.97]**		
Total events	99		133					

Heterogeneity Tau^2 = 0.06, Chi^2 = 12.24, df = 8 (P = 0.14); I^2 = 35 %
Test for overall effect: Z = 2.19 (P = 0.03)

▶ **Fig. 4** Forest plot of risk ratio for overall mortality with ligation versus sclerotherapy.

Study or subgroup	Sclerotherapy+drug Events	Total	Sclerotherapy Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Year	Risk ratio M-H, Random, 95% CI
Besson 1995	95	98	86	101	27.2 %	1.14 [1.04, 1.24]	1995	
Shiha 1996	89	93	72	96	18.1 %	1.28 [1.13, 1.44]	1996	
Avgerinos 1997	66	101	47	104	5.5 %	1.45 [1.12, 1.87]	1997	
Faraoqi 2000	69	72	58	69	20.2 %	1.14 [1.02, 1.28]	2000	
Zuberi 2000	33	35	30	35	12.5 %	1.10 [0.94, 1.29]	2000	
Shah 2005	46	51	41	54	10.6 %	1.19 [1.00, 1.42]	2005	
Morales 2007	32	40	22	28	5.8 %	1.02 [0.79, 1.30]	2007	
Total (95 % CI)		**490**		**487**	**100.0 %**	**1.17 [1.10, 1.25]**		
Total events	430		356					

Heterogeneity Tau^2 = 0.00, Chi^2 = 7.98, df = 6 (P = 0.24); I^2 = 25 %
Test for overall effect: Z = 4.91 (P = 0.00001)

▶ **Fig. 5** Forest plot of risk ratio for efficacy of bleeding control with sclerotherapy and vasoactive drug versus sclerotherapy alone.

Comparison of ligation with the combination of ligation and sclerotherapy

Five trials [22, 26, 28, 30, 46] had evaluated ligation versus the combination of ligation and sclerotherapy. Risk of complications was significantly lower with ligation (5 trials, RR 0.58; 95 %CI 0.39 – 0.88; P = 0.01; I^2 0%) when compared to the combination of ligation and sclerotherapy. However, there were no statistically significant differences among the other analyzed outcomes.
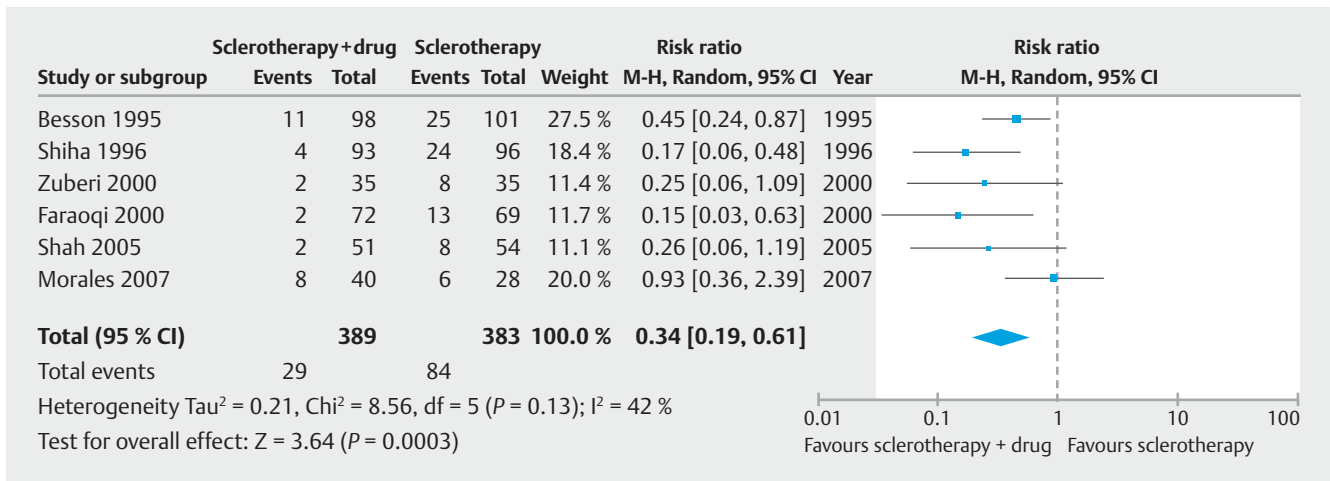
Comparison of ligation with cyanoacrylate injection

Only one trial [42] evaluated ligation with cyanoacrylate injection and, therefore, could not generate meta-analysis. This trial showed no difference in efficacy of bleeding control, rebleed-

ing rate, or mortality rate with cyanoacrylate injection compared with endoscopic ligation.
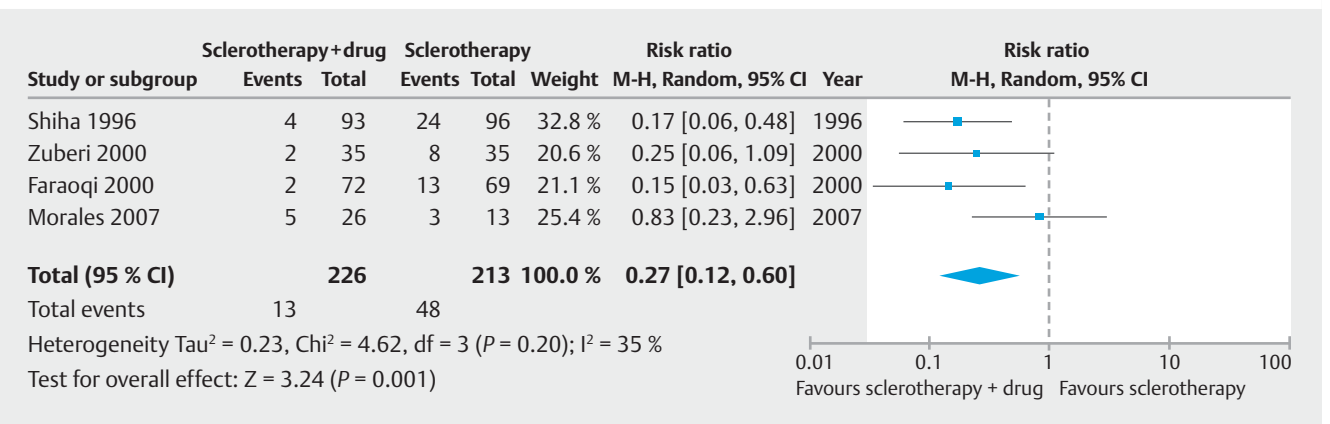
Comparison of ligation with ligation and vasoactive drugs

Only two trials evaluated this treatment combination, one with somatostatin and other with octreotide [20, 39]. Among the outcomes analyzed, only overall rebleeding (▶ Fig. 8) and in-hospital mortality (▶ Fig. 9) generated meta-analysis, but with no significant statistical difference.

| Study or subgroup | Sclerotherapy+drug | | Sclerotherapy | | Weight | Risk ratio M-H, Random, 95% CI | Year |
	Events	Total	Events	Total			
Besson 1995	11	98	25	101	27.5 %	0.45 [0.24, 0.87]	1995
Shiha 1996	4	93	24	96	18.4 %	0.17 [0.06, 0.48]	1996
Zuberi 2000	2	35	8	35	11.4 %	0.25 [0.06, 1.09]	2000
Faraoqi 2000	2	72	13	69	11.7 %	0.15 [0.03, 0.63]	2000
Shah 2005	2	51	8	54	11.1 %	0.26 [0.06, 1.19]	2005
Morales 2007	8	40	6	28	20.0 %	0.93 [0.36, 2.39]	2007
Total (95 % CI)		**389**		**383**	**100.0 %**	**0.34 [0.19, 0.61]**	
Total events	29		84				

Heterogeneity Tau^2 = 0.21, Chi^2 = 8.56, df = 5 (P = 0.13); I^2 = 42 %
Test for overall effect: Z = 3.64 (P = 0.0003)

▶ **Fig. 6** Forest plot of risk ratio for overall rebleeding with sclerotherapy and vasoactive drug versus sclerotherapy alone.

| Study or subgroup | Sclerotherapy+drug | | Sclerotherapy | | Weight | Risk ratio M-H, Random, 95% CI | Year |
	Events	Total	Events	Total			
Shiha 1996	4	93	24	96	32.8 %	0.17 [0.06, 0.48]	1996
Zuberi 2000	2	35	8	35	20.6 %	0.25 [0.06, 1.09]	2000
Faraoqi 2000	2	72	13	69	21.1 %	0.15 [0.03, 0.63]	2000
Morales 2007	5	26	3	13	25.4 %	0.83 [0.23, 2.96]	2007
Total (95 % CI)		**226**		**213**	**100.0 %**	**0.27 [0.12, 0.60]**	
Total events	13		48				

Heterogeneity Tau^2 = 0.23, Chi^2 = 4.62, df = 3 (P = 0.20); I^2 = 35 %
Test for overall effect: Z = 3.24 (P = 0.001)

▶ **Fig. 7** Forest plot of risk ratio for rebleeding from active bleeders comparing sclerotherapy and vasoactive drug versus sclerotherapy alone.

Discussion

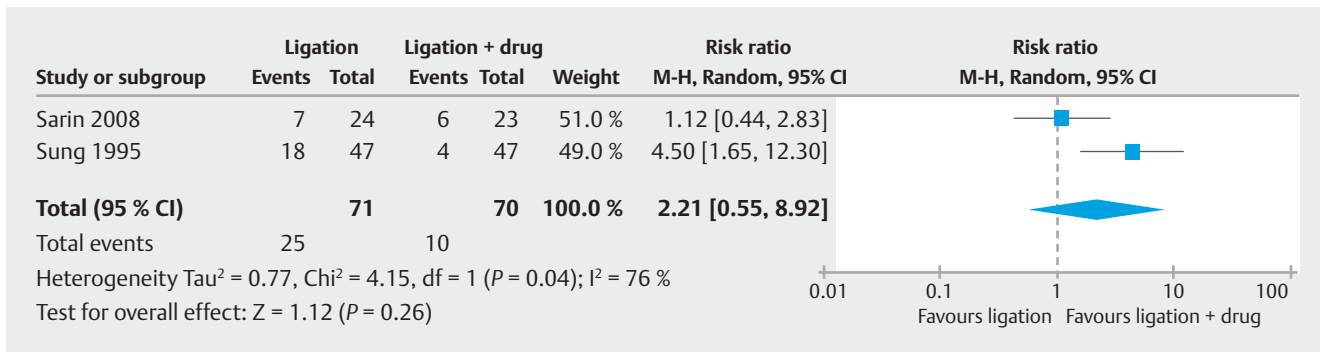Thirty-six trials, including 3593 patients, evaluated treatments for AVB control.

Among them, 10 trials compared sclerotherapy with ligation, favoring ligation in terms of efficacy of bleeding control, rebleeding, overall mortality, and rate of complications in a statistically significant fashion. However, this comparison showed a moderate heterogeneity.

The heterogeneity was potentially explained by the differences in two identified subgroups as stated above (results chapter): one formed mostly by Asian studies [19, 21, 24, 27, 29] in which ligation was clearly superior to sclerotherapy and another formed mostly by Western trials [13 – 15, 43, 45] in which both techniques had similar results. In the first subgroup of studies, the main cause of cirrhosis was viral and in three of five trials, the sclerosant used was tetradecyl sulfate with 50 % dextrose. In the second subgroup, the majority of patients had cirrhosis secondary to excessive alcohol intake and only one study used tetradecyl sulfate with 50 % dextrose as sclerosant. Moreover, the second subgroup had higher percentages of active bleeders at initial endos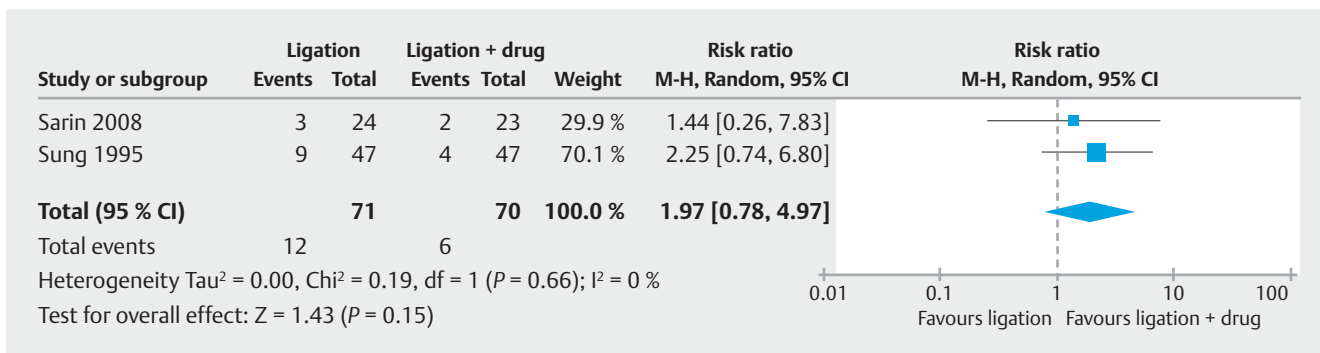copy in all ligation arms compared to the sclerotherapy arms, which was not noticed in the first subgroup of studies. Prevalence of Child-Pugh C patients was similar in both subgroups.

Although ligation currently is considered the gold standard endoscopic method compared to sclerotherapy, this meta-analysis could not demonstrate clearly the superiority of one technique over the other, because there was a moderate heterogeneity (I^2 = 49 %) among the studies included. We have no doubt that ligation is better than sclerotherapy, but the advantage of ligation may not be in the bleeding episode, but in the secondary prophylaxis with a faster and safer variceal eradication.

Sclerotherapy and vasoactive drugs combined were superior to sclerotherapy alone in regard to efficacy of bleeding control, overall rebleeding rate, and rebleeding rate from active bleeders in seven, six and four trials, respectively (▶ Fig. 5, ▶ Fig. 6, ▶ Fig. 7). There is a compelling body of evidence that the combination of sclerotherapy and vasoactive drugs is more effective than sclerotherapy alone in hemorrhage control. This meta-analysis confirmed that with a highly significant statistical difference and a low heterogeneity among the studies (7 trials; RR of 1.17; 95 % CI 1.10 – 1.25; P < 0.00001; I^2 = 25 %). However, there

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Study or subgroup	Ligation Events	Total	Ligation + drug Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
Sarin 2008	7	24	6	23	51.0 %	1.12 [0.44, 2.83]	
Sung 1995	18	47	4	47	49.0 %	4.50 [1.65, 12.30]	
Total (95 % CI)		71		70	100.0 %	2.21 [0.55, 8.92]	
Total events	25		10				

Heterogeneity Tau² = 0.77, Chi² = 4.15, df = 1 (P = 0.04); I² = 76 %
Test for overall effect: Z = 1.12 (P = 0.26)

▶ **Fig. 8** Forest plot of risk ratio for overall rebleeding with ligation alone versus ligation and vasoactive drug.

Study or subgroup	Ligation Events	Total	Ligation + drug Events	Total	Weight	Risk ratio M-H, Random, 95% CI	Risk ratio M-H, Random, 95% CI
Sarin 2008	3	24	2	23	29.9 %	1.44 [0.26, 7.83]	
Sung 1995	9	47	4	47	70.1 %	2.25 [0.74, 6.80]	
Total (95 % CI)		71		70	100.0 %	1.97 [0.78, 4.97]	
Total events	12		6				

Heterogeneity Tau² = 0.00, Chi² = 0.19, df = 1 (P = 0.66); I² = 0 %
Test for overall effect: Z = 1.43 (P = 0.15)

▶ **Fig. 9** Forest plot of risk ratio for in-hospital mortality with ligation alone versus ligation and vasoactive drug.

was no difference in respect to mortality in the meta-analysis and in any individual RCT. It is interesting to note that none of these studies were performed in North America (2 European, 1 Brazilian and 4 Asian trials).

Many previous trials and meta-analyses have shown that vasoactive drugs are better than placebo, vasoactive drugs are similar to sclerotherapy, and the combination of vasoactive drugs and sclerotherapy is superior to sclerotherapy alone [25, 47, 48]. A recent meta-analysis [47] even compared therapeutic interventions for AVB with placebo, which has been unacceptable as a treatment option since the early 1990 s.

Another technique that generated a meta-analysis and is not performed anymore is the combination of ligation and sclerotherapy. This therapy was abandoned due to a high incidence of side effects, which was confirmed by our study; nonetheless in this meta-analysis, it was demonstrated to be as effective as ligation alone in bleeding control, rebleeding, and mortality.

In this study, when we analyzed separately active bleeders at the moment of initial endoscopy, use of sclerotherapy with vasoactive drugs was superior to sclerotherapy alone. In 439 patients from four studies, combined therapy reduced rebleeding by 22 % (95%CI 1.13 – 1.32) with no heterogeneity. We could not evaluate mortality in this subgroup of patients because the studies, when quoting mortality, did not state this outcome separately (they quoted mortality for both active and non-active bleeders).

Although most studies reported in the literature included patients with recent and ongoing hemorrhage, it should be em-phasized that therapies used after bleeding had spontaneously stopped will have their results overestimated. Active bleeding at endoscopy is a well-known risk factor for worse outcomes in patients with variceal as well as non-variceal bleeding [3]. Only six studies of the 36 analyzed included only patients with active variceal bleeding, four of them compared sclerotherapy with the combination of sclerotherapy and octreotide. The other 30 RCTs pooled together the results of the different treatments among active and non-active bleeders at time of endoscopy.

Notwithstanding we have done a meta-analysis with solely two studies comparing ligation plus vasoactive drug versus ligation alone, this is the only available meta-analysis grouping this treatment, which is recommended by AASLD, the American Society of Gastrointestinal Endoscopy (ASGE) and EASL guidelines as the gold standard in management of variceal bleeding (considered as level of evidence 1a, grade A recommendation) [49 – 51]. ESGE has no current guideline about this issue. Although that recommendation is routinely used in clinical practice, just two Asian studies evaluated use of ligation plus vasoactive drugs in comparison to ligation alone [20, 40] and another trial compared ligation plus octreotide versus octreotide alone [42].

In the study by Sung et al., ligation and somatostatin was highly superior to ligation alone in management of variceal bleeding. On the other hand, in the study by Sarin et al., published as an abstract, the combination of ligation and octreotide did not show an advantage over ligation alone. When performing a meta-analysis of both these studies, there was clearly

no benefit of combination therapy in terms of rebleeding and mortality. It is important to note that no Western study evaluated the role of ligation plus vasoactive drug in treatment of AVB.

There was no study evaluating use of early TIPS in AVB included in this meta-analysis. The only study using early TIPS selected was excluded because all patients received ligation or sclerotherapy in the first 24 hours, before randomization [52].

As in every meta-analysis, comparison of studies may have been impaired by differing in-hospital follow-up, which in some studies is evaluated at 5 days and in others at 6 weeks. In this study, those data have been pooled together as overall mortality. Time until rebleeding occurred also varied among studies, ranging from 2 to 5 days and was considered as one sole group. Notably, we excluded patients with hepatocellular carcinoma, who comprise at least one-fifth of bleeders. However, this population of patients has a worse response to any treatment and should be evaluated separately.

Furthermore, we also excluded a few articles that were not published in English due to their unavailability, although their inclusion would not affect the final analysis. Other possible limitations of our study are the unclear risk for concealment of treatment allocation in 18 trials and high risk for blinding of participants/personnel in 10 trials. Meanwhile, the blinding of endoscopists and patients undergoing upper digestive endoscopy is impossible, as in studies involving surgical interventions. Moreover, only nine of 36 studies mentioned conflict of interest. In addition, prediction intervals indicated a significant amount of uncertainty on treatment effect sizes and direction for several of the meta-analytic comparisons performed, which means that many of the research questions addressed are still unanswered. Larger and well-designed trials are needed in this field.

On the other hand, studies using placebo as a treatment were not included because there are well-established treatments available for AVB.

During the last decade, mortality rates with acute variceal bleeds have decreased. Routine medical care varied with respect to use of diagnostic and/or therapeutic endoscopy, balloon tamponade, resuscitation policy, and antibiotic prophylaxis for spontaneous bacterial peritonitis.

Conclusion

In summary, the combination of sclerotherapy and vasoactive drugs is superior to sclerotherapy or vasoactive drugs alone in management of variceal bleeding. Ligation was better than sclerotherapy as a treatment option for variceal bleeding, although heterogeneity of the results may invalidate this assumption. Although society guidelines recommend the combination of endoscopic band ligation and vasoactive medications for treatment of AVB, this statement could not be evidenced in the literature.

Competing interests

Author J.P.L. is a proctor of Boston Scientific. The other authors declare no Conflict of Interests for this article.

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