Review Article

Combination therapy *versus* monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis

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ABSTRACT

Cyanoacrylate (CYA), coil embolization, and/or combination thereof are available EUS-guided therapies for the treatment of gastric varices (GV). The primary aim of this study was to perform a structured systematic review and meta-analysis to evaluate the comparative effectiveness of EUS-guided interventions for the treatment of GV. Individualized search strategies were developed for PubMed, EMBASE, and Cochrane Library databases, from inception through November 2018 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. This cumulative meta-analysis was performed using calculating pooled proportions. Measured outcomes included technical success, clinical success, adverse events, and rate of rebleeding or reintervention. Comparative subgroup analyses were performed for three treatment cohorts (EUS-guided CYA injection, EUS-guided coil embolization + CYA injection, and EUS-guided coil injection alone). Heterogeneity was assessed with I^2 statistics. Eleven studies ($n = 536$ patients; 62.20% of males) were included. The mean age was 58.21 ± 4.15 years with an average follow-up of 12.93 ± 7.69 months. Overall technical success, clinical success, and adverse events for EUS treatments was 100% ([95% confidence interval [CI] 98–100]; $I^2 = 30.54\%$), 97% ([95% CI 92–100]; $I^2 = 59.99\%$), and 14% ([95% CI 6–23]; $I^2 = 82.23\%$), respectively. On subgroup analysis, EUS-guided CYA + coil embolization resulted in a better technical and clinical success compared to CYA alone (100% *vs.* 97%; $P < 0.001$ and 98% *vs.* 96%; $P < 0.001$) and coil embolization alone (99% *vs.* 97%; $P < 0.001$ and 96% *vs.* 90%; $P < 0.001$). CYA + coil embolization also resulted in lower adverse event rates compared to CYA alone (10% *vs.* 21%; $P < 0.001$), and comparable rates to coil embolization alone (10% *vs.* 3%; $P = 0.057$). EUS-guided treatment overall appears to be an effective and safe modality for GV. Among a variety of EUS-therapies available, EUS combination therapy with coil embolization + CYA injection appears to be a preferred strategy for the treatment of GV over EUS-based monotherapy.

Key words: Cyanoacrylate, EUS, gastric varices, portal hypertension, vascular coils

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INTRODUCTION

Gastroesophageal varices are a common cause of gastrointestinal bleeding in patients with cirrhosis and portal hypertension. While bleeding from gastric varices (GV) occurs less frequently as compared to esophageal varices (EV), gastric variceal hemorrhage is associated with more severe bleeding, increased transfusion requirements, and higher morbidity and mortality rates.[1,2] In the United States, portal hypertension remains the most common cause of bleeding GV, with splenic vein thrombosis representing another less frequent cause. While multiple societies have established well-defined guidelines for the management of EV, there remains a paucity of data and treatment guidelines for the management of gastric variceal bleeding.[3]

Over the past 20 years, much has changed in the understanding of the pathophysiology and management options among patients with GV.[4] Although decreasing portal pressure through transjugular intrahepatic portosystemic shunt is considered effective in reducing esophageal variceal hemorrhage, it is inconsistently effective for the management of GV, which tend to occur and bleed at lower portal pressures.[5-7] More recently, Balloon-Occluded Retrograde Transvenous Obliteration and Coil-Assisted Retrograde Transvenous Obliteration have emerged as alternative interventional radiology (IR)-guided therapies. However, these therapies remain limited only to centers with advanced IR capabilities. With this notion, conventional endoscopic therapy has been considered the mainstay of treatment for bleeding GV – premised on the injection of acrylate polymers, such as histoacryl and cyanoacrylate (CYA), with or without lipiodol.[8-12] Injection of these glue-like substances aims to induce thrombosis and obliteration of GV. However, despite their effectiveness, CYA injection has been associated with various serious adverse events, including systemic embolization (*e.g.*, pulmonary embolism), posttreatment ulceration and bleeding, and glue adherence to needle causing traumatic needle withdrawal from variceal nest resulting in unroofing of varix.[13-16]

More recently, EUS-guided treatment of GV has emerged as a promising alternative. EUS may assist in varicealography, helping to identify GV venous anatomy and feeder vessels, while also aiding in the injection of coils, CYA, or combination thereof.[17,18] EUS offers direct visualization of CYA injection and coil embolization and thus has emerged as a preferred method of endoscopic intervention for bleeding cessation, especially in centers with expertise. Yet, despite this increased utilization and advantage to conventional non-EUS-guided endoscopic treatment, limited data exist to evaluate the efficacy and safety of the various EUS-guided therapies for the treatment of bleeding GV. The primary aim of this study was to perform a structured systematic review, and meta-analysis to evaluate the comparative effectiveness of EUS-guided interventions for the treatment of GV.

METHODS

Study design and search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline for reporting systematic reviews and meta-analyses and was conducted following *a priori* established protocol.[19] This study was prospectively submitted in PROSPERO, an international database of prospectively registered systematic reviews in health and social care. Individualized searches of PubMed, EMBASE, Web of Science, and Cochrane databases were performed from inception through November 30, 2018. The following medical subject heading terms included: Gastric varices (GV). For articles related to GV, subject heading search terms, and title and abstract were reviewed for: EUS, endosonography, CYA, coil, and injection therapy.

All relevant articles irrespective of year of publication, type of publication, or publication status were included. The titles and abstracts of all potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed for additional articles by cross-checking bibliographies. Two reviewers (TRM and ANB) independently screened the titles and abstracts of all the articles according to predefined inclusion and exclusion criteria. Any differences were resolved by mutual agreement and in consultation with the third reviewer (KEH). In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Study selection criteria

Randomized controlled trials, observational studies, and case series evaluating three treatment cohorts (EUS-guided CYA injection, EUS-guided CYA injection + coil embolization, and EUS-guided coil injection alone) were included in this analysis. Studies

were included if patients were adults ≥18 years of age, had recent or active bleeding GV, and underwent EUS-guided therapy with one of the aforementioned modalities. Included studies were required to report technical success, clinical success, and/or adverse events. Only studies evaluating treatment for GV as defined by the Sarin classification were included (type I gastroesophageal varices [GOV-1], GOV-2, type I isolated gastric varices [IGV-1], and IGV-2).[1] Studies, including the management of isolated EV, were excluded from this analysis. Multiple published works from similar authors were evaluated for overlapping enrollment times to preserve independence of observations. A study was excluded if deemed to have insufficient data, as were review articles, editorials, and correspondence letters that did not report independent data. Case series and reported studies with <5 patients were excluded in an effort to limit selection bias.

Outcome measures

The primary outcome was pooled technical success, clinical success, and adverse event rate for EUS-guided therapy of GV – CYA injection, EUS-guided coil embolization + CYA injection, and EUS-guided coil injection alone. Secondary outcomes were the rate of rebleeding and reintervention for each treatment modality as well as comparative outcomes between the different treatment strategies.

Risk of bias and quality assessment

Risk of bias was assessed using the Cochrane Collaboration's risk of bias in nonrandomized studies of interventions (ROBINS-I) tool for observational studies.[20] In this meta-analysis, publications were deemed low risk of bias if ≥50% of the above domains were judged as low risk. The quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale.[21] Two authors (TRM and ANB) independently extracted data and assessed the risk of bias and study quality for each of the articles. Any disagreements were resolved by discussion and consensus, and in consultation with the (KEH).

Investigations of heterogeneity

Heterogeneity was assessed for the individual meta-analyses using the Chi-squared test and the I^2 statistic.[22] Significant heterogeneity was defined as $P < 0.05$ using the Chi-squared or $I^2 > 50\%$. A random-effect model was used except for when statistical heterogeneity was not significant. Differences in subgroups were assessed using a Chi-squared test for interaction with a $P < 0.05$ defined as statistically significant. Since this was a cumulative meta-analysis, publication bias was not assessed.[23]

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. After appropriate studies were identified through systematic review, the individual study proportion was transformed into a quantity using the Freeman–Tukey variant of the arcsine square root transformed proportion. Then, the pooled proportion was calculated as the back transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian and Laird weights for the random effect model.[4,24] All weighted pool rates involved 95% confidence intervals (CIs) and were analyzed using fixed or random effects models based on the heterogeneity of the sample.

Subgroup analysis was also performed based on comparative effectiveness of varying EUS-guided treatment strategies. One-way analysis of variance was used to determine whether there are any statistically significant differences between the means of two or more independent (unrelated) groups. Pairwise comparisons were computed and then adjusted for multi-comparisons using the Bonferroni correction. Combined weighted proportions, tabular and graphical displays, as well as additional analyses, were performed using the Stata 13.0 software package (Stata Corp LP, College Station, TX, USA).

RESULTS

Included study and patient characteristics

Eleven studies (n = 536 patients) were included in this meta-analysis.[18,25-34] A PRISMA flow chart of search results is shown in Figure 1. Two randomized controlled trials, one prospective study, and eight retrospective articles were included. Two studies evaluated coil embolization + absorbable gelatin foam and coil embolization + thrombin, respectively.[33,34] The mean age of patients was 58.21 ± 4.15 years, with an average follow-up of 12.93 ± 7.69 months. Sixty-two percent of patients were male. Among patients with cirrhosis, the majority (67.83%) had Child-Pugh A classification disease, whereas 19.13% had Child-Pugh B disease, and 13.04% had Child-Pugh C disease. Model for End-Stage Liver Disease score was not uniformly reported. With

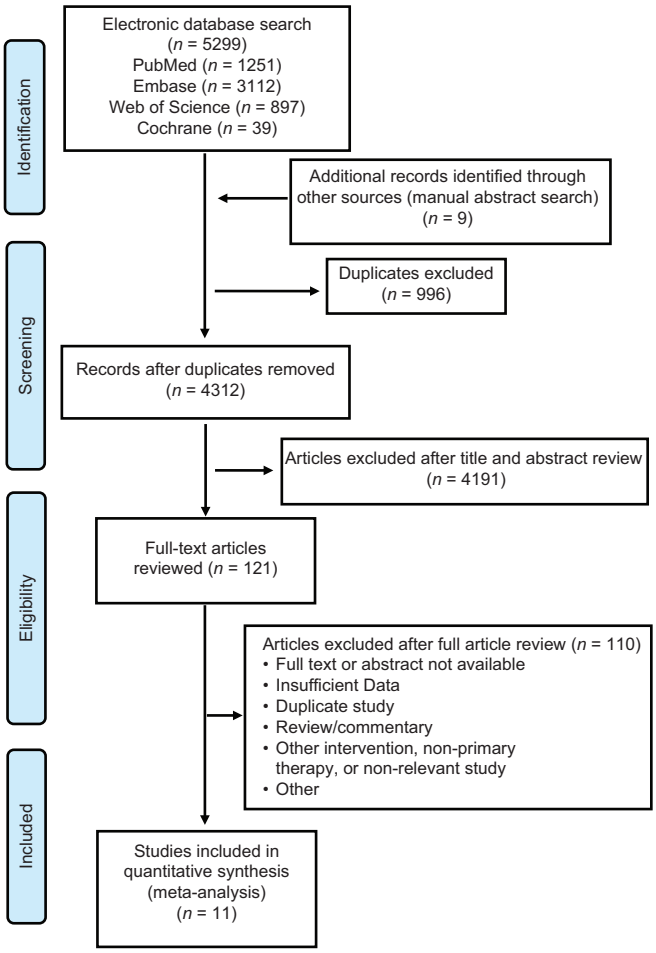

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Chart of search results for EUS-Guided treatment of gastric varices

regard to underlying causes of cirrhosis, 34.26% were due to viral hepatitis, 24.50% secondary to alcohol, and the remaining 41.24% were attributed to combined or other etiologies. IGV-1 was the most common type of varices treated in this cohort (42.24%). Recent or active bleeding occurred in 73.40% of patients who underwent EUS-guided treatment. Baseline cumulative and individualized EUS-guided treatment characteristics are shown in Table 1.

EUS-guided treatment efficacy and safety

Overall technical success and clinical success for all EUS-guided treatments was 100% ([95% CI 98–100]; I^2 = 30.54%) and 97% ([95% CI 92–100]; I^2 = 59.99%), respectively [Figures 2 and 3]. This was achieved in studies with CYA with a mean dose of 1.97 ± 0.44 mL. Among studies utilizing coil embolization, a mean number of 2.16 ± 1.47 coils were placed. Overall, clinical success was achieved over a median of 1.43 ± 0.43 treatment sessions. Rate of adverse events, rate of reintervention, and rate of

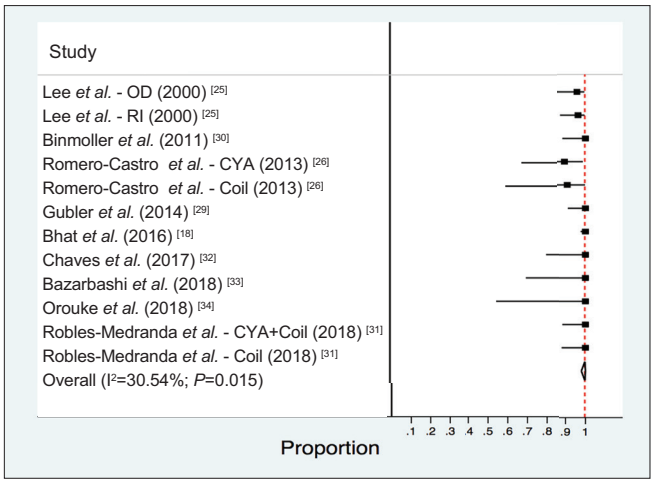

Figure 2. Technical success rate for EUS-Guided treatment of gastric varices

rebleeding was 14% ([95% CI 6–23]; I^2 = 82.23%), 20% ([95% CI 9–33]; I^2 = 65.40%), and 19% ([95% CI 8–32]; I^2 = 87.68%), respectively [Figures 4-6]. All-cause mortality for included patients was 27% (95% CI 5–56); I^2 = 92.80%. Cumulative and subgroup analysis of individual EUS-guided treatments is highlighted in Table 2.

Comparative subgroup analysis

On comparative subgroup analysis, EUS-guided CYA + coil embolization resulted in a significantly higher technical and clinical success as compared to CYA alone (100% [95% CI 100–100]; I^2 = 0.00% *vs.* 97% [95% CI 92–100]; I^2 = 34.57%; $P < 0.001$) and (98% [95% CI 92–100]; I^2 = 22.72% *vs.* 96% [95% CI 85–100]; I^2 = 82.68%; $P < 0.001$) [Table 3]. EUS-guided CYA + coil embolization also demonstrated a better technical and clinical success compared to coil embolization alone (100% [95% CI 100–100]; I^2 = 0.00% *vs.* 99% [95% CI 92–100]; I^2 = 0.00%; $P < 0.001$) and (98% [95% CI 92–100]; I^2 = 22.72% *vs.* 90% [95% CI 73–98]; I^2 = NA%; $P < 0.001$). Adverse events for CYA + coil embolization was also significantly lower as compared to CYA alone (10% [95% CI 1–26]; I^2 = 84.18% *vs.* 21% [95% CI 8–38]; I^2 = 85.36%; $P < 0.001$), and comparable rates to coil embolization alone (10% [95% CI 1–26]; I^2 = 84.18% *vs.* 3% [95% CI 0–12]; I^2 = 0.00%; P = 0.057). Reintervention rate was lower for CYA + coil embolization *versus* CYA alone and coil alone (15% *vs.* 26%; $P < 0.001$) and (15% *vs.* 25%; P = 0.047). Rebleeding was also lower for CYA + coil embolization *versus* CYA alone ($P < 0.001$) and comparable *versus* coil alone (P = 1.000). Detailed subgroup analyses

Table 1. Baseline characteristics of included studies for EUS-guided treatment of gastric varices

	Year	Study type	Number of patients	Age (years)	Number of males	Etiology of liver disease			Child-pugh class			Sarin class of gastric varices		
						Viral	EtOH	Other	A	B	C	GOV1	GOV2	IGV1
EUS CYA alone														
Lee *et al.*[25] (RI)	2000	Prospective	54	61±14	34	28	12	14	-	-	-	20	18	16
Lee *et al.*[25] (OD)	2000	Prospective	47	50±15	35	28	12	7	-	-	-	16	20	11
Romero-Castro *et al.*[26]	2013	Retrospective	19	60.8±8.2	14	7	8	4	6	6	7	1	9	9
Krill *et al.*[27]	2018	Retrospective	10	58.8	-	-	-	-	-	-	-	-	-	-
Bick *et al.*[28]	2018	Retrospective	64	58±2.5	33	10	10	44	-	-	-	2	32	30
Gubler and Bauerfeind[29]	2014	Retrospective	40	65 (14-79)	25	7	12	21	-	-	-	-	-	-
EUS CYA + Coil														
Binmoeller *et al.*[30]	2011	Retrospective	30	54 (19-64)	19	9	13	8	-	-	-	5*	-	25
Robles-Medranda *et al.*[31]	2018	Randomized control trial	30	61.77±7.8	16	0	7	23	28	2	0	-	-	-
Krill *et al.*[27]	2018	Retrospective	12	58.8	-	-	-	-	-	-	-	-	-	-
Chaves *et al.*[32]	2017	Randomized control trial	16	47 (20-75)	8	4	-	12	12	-	-	-	13	3
Bhat *et al.*[18]	2016	Retrospective	152	58 (19-88)	97	73	33	46		-	-	-	-	-
EUS Coil alone or non-CYA														
Romero-Castro *et al.*[26]	2013	Retrospective	11	59±10	8	6	2	3	4	7	0	0	5	6
Robles-Medranda *et al.*[31]	2018	Randomized control trial	29	61.57±12.5	19	0	9	20	25	3	1	-	-	-
Krill *et al.*[27]	2018	Retrospective	6	58.8	-	-	-	-	-	-	-	-	-	-
Bazarbashi *et al.*[33]**	2018	Retrospective	10	63.9	4	0	5	5	3	4	2	1	3	6
Orouke *et al.*[34]***	2018	Retrospective	6	55	4	-	-	-	-	-	5	-	-	-

	Follow-up (months)	Active or recent bleeding (%)	Dose of CYA (mL)	Number of Coils	Number of sessions	Technical success (%)	Clinical success (%)	Rate of adverse events (%)	Rate of reintervention	Rate of rebleeding (%)	All-cause mortality (%)
EUS CYA alone											
Lee *et al.*[25] (RI)	24	54/54 (100)	3 (1-8)	-	2.2 (1.7)	52/54 (96.3)	43/54 (79.6)	22/54 (40.7)	-	19/54 (35.2)	28/54 (51.9)
Lee *et al.*[25] (OD)	24	47/47 (100)	2 (1-6)	-	1.3 (0.5)	45/47 (95.7)	-	9/47 (19.1)	-	33/47 (70.2)	35/47 (74.5)
Romero-Castro *et al.*[26]	20.9±2.4	10/19 (52.6)	1.5 (1-3)	-	1.5	17/19 (89.5)	19/19 (100)	11/19 (57.9)	-	-	-
Krill *et al.*[27]	-	-	-	-	-	-	-	0/10 (0)	8/10 (80.0)	-	-
Bick *et al.*[28]	6.57	57/64 (89.1)	2 (0.8)	-	1.2	-	62/64 (96.9)	13/64 (20.3)	-	5/56 (5.9)	-
Gubler and Bauerfeind[29]	-	36/40 (90)	1.4 (1-7)	-	-	40/40 (100)	36/36 (100)	2/40 (5)	6/40 (15.0)	6/40 (15.0)	6/40 (15.0)
EUS CYA + Coil											
Binmoeller *et al.*[30]	6.43	20/30 (66.7)	1.4 (1-4)	-	1	30/30 (100)	29/30 (96.7)	0/30 (0.0)	-	4/24 (16.6)	1/30 (3.3)
Robles-Medranda *et al.*[31]	1	1/27 (3.7)	1.8 (1.2-2.4)	2 (1-3)	-	30/30 (100)	30/30 (100)	2/30 (6.6)	4/30 (13.3)	2/30 (6.6)	-
Krill *et al.*[27]	-	-	-	-	-	-	-	1/12 (8.0)	1/12 (8.0)	-	-
Chaves *et al.*[32]	9.7	-	1.5	1.5	-	16/16 (100)	-	9/16 (56.3)	4/16 (25.0)	-	-
Bhat *et al.*[18]	14.53	112/152 (73.7)	2 (0.5-6)	1.4 (1-4)	-	151/152 (99.3)	-	9/125 (7.2)	-	20/125 (16.0)	-

Contd...

Table 1. Contd...

	Follow-up (months)	Active or recent bleeding (%)	Dose of CYA (mL)	Number of Coils	Number of sessions	Technical success (%)	Clinical success (%)	Rate of adverse events (%)	Rate of reintervention	Rate of rebleeding (%)	All-cause mortality (%)
EUS Coil alone or non-CYA											
Romero-Castro *et al.*[26]	10.6±1.4	0/11 (0)	-	5.8 (2-13)	1.3	10/11 (90.9)	10/11 (90.9)	1/11 (9.1)	-	-	-
Robles-Medranda *et al.*[31]	1	4/25 (16)	-	3 (1-7)	-	29/29 (100)	26/29 (89.7)	1/29 (3.4)	8/29 (27.6)	5/29 (17.2)	-
Krill *et al.*[27]	-	-	-	-	-	-	-	0/6 (0.0)	1/6 (7.0)	-	-
Bazarbashi *et al.*[33]**	2.57	9/10 (90)	-	7 (3-9)	1	10/10 (100)	10/10 (100)	3/10 (30)	0/10 (0.0)	0/10 (0.00)	1/10 (10.0)
Orouke *et al.*[34]***	9	6/6 (100)	-	5 (2–10)	1	6/6 (100)	4/4 (100)	1/6 (16.7)	1/6 (33.0)	1/6 (16.7)	1/6 (16.7)

*Listed as either GOV1 or GOV2, **Coil + gelfoam study, ***Coil+thrombin study. RI: Repeated injection, OD: On-demand injection, CYA: Cyanoacrylate, Coil: Coil embolization, GOV1: Type I gastroesophageal varies, GOV2: Type II gastroesophageal varies, IGV1: Isolated gastric varices Type 1

Figure 3. Clinical success rate for EUS-guided treatment of gastric varices

Figure 4. Serious adverse events for EUS-guided treatment of gastric varices

Figure 5. Rate of reintervention for EUS-guided treatment of gastric varices

Table 2. Cumulative and subgroup data of EUS-guided treatments for gastric varices

	Cumulative data EUS-guided treatment	Subgroup analyses		
		EUS CYA alone	EUS CYA + Coil	EUS Coil alone
Number of patients (*n*)	536	234	240	46
Mean age (years)	58.21±4.15	58.54±4.88	57.28±3.38	60.59±1.29
Percent male (%)	62.20	62.95	61.40	67.50
Percent with IGV1 (%)	42.24	35.87	60.87	57.12
Follow-up (months)	12.93±7.69	17.62±8.14	11.35±4.93	3.64±4.34
Mean dose of CYA (mL)	1.97±0.44	2.09±0.57	1.86±0.23	-
Mean number of Coils	1.88±1.01	-	1.5±0.21	3.77±1.27
Technical success (%)	100 (95 CI: 98-100) I^2=30.54	97 (95 CI: 92-100) I^2=34.57	100 (95 CI: 100-100) I^2=0.00	99 (95 CI: 92-100) I^2=0.00
Clinical success (%)	97 (95 CI: 92-100) I^2=59.99	96 (95 CI: 85-100) I^2=82.68	98 (95 CI: 92-100) I^2=22.72	90 (95 CI: 73-98) I^2=NA*
Rate of adverse events (%)	14 (95 CI: 6-23) I^2=82.23	21 (95 CI: 8-38) I^2=85.36	10 (95 CI: 1-26) I^2=84.18	3 (95 CI: 0-12) I^2=0.00
Rate of reintervention (%)	20 (95 CI: 9-33) I^2=65.40	26 (95 CI: 14-39) I^2=0.00	15 (95 CI: 6-26) I^2=0.00	25 (95 CI: 11-42) I^2=0.00
Rate of re-bleeding (%)	19 (95 CI: 8-32) I^2=87.68	30 (95 CI: 8-60) I^2=94.34	14 (95 CI: 9-20) I^2=0.00	17 (95 CI: 6-36) I^2=NA*

*Unable to calculate heterogeneity due to limited data/events. IGV1: Isolated gastric varices Type 1, CYA: Cyanoacrylate, Coil: Coil embolization, CI: Confidence interval

Table 3. Subgroup analyses comparing different treatment strategies for gastric varices

Comparison of treatments	Technical success	Clinical success	Rate of adverse events	Rate of reintervention	Rate of re-bleeding
EUS CYA alone *versus* EUS CYA + Coil (*P*)	97% *versus* 100% (<0.001)	96% *versus* 98% (<0.001)	21% *versus* 10% (<0.001)	26% *versus* 15% (<0.001)	30% *versus* 14% (<0.001)
EUS CYA alone *versus* EUS Coil alone (*P*)	97% *versus* 99% (0.005)	96% *versus* 90% (0.146)	21% *versus* 3% (<0.001)	26% *versus* 25% (0.846)	30% *versus* 17% (<0.001)
EUS CYA + coil *versus* EUS Coil alone (*P*)	100% *versus* 99% (<0.001)	98% *versus* 90% (<0.001)	10% *versus* 3% (0.057)	15% *versus* 25% (0.047)	14% *versus* 17% (1.00)

CYA: Cyanoacrylate, Coil: Coil embolization

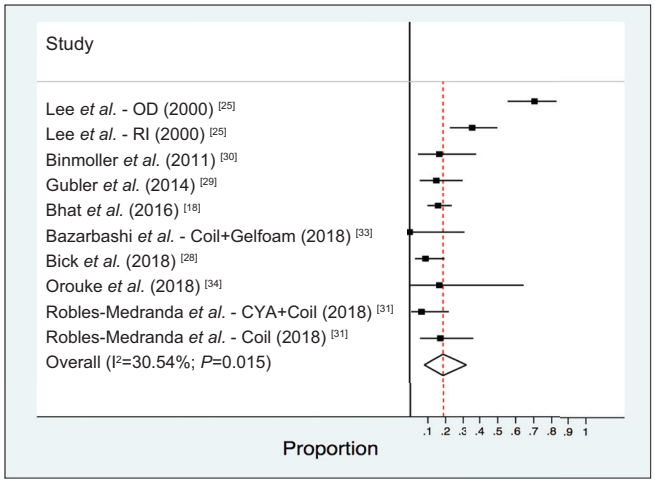

Figure 6. Rate of rebleeding for EUS-guided treatment of gastric varices

comparing different treatment strategies for GV are shown in Table 3.

Risk of bias assessment

All studies were assessed using ROBINS-I and the Newcastle-Ottawa Quality Assessment Scale with the authors' judgments about each risk of bias as highlighted in Figure 7a. Risk of bias summary graph is also available in Figure 7b. Testing for publication bias with funnel plot asymmetry was not performed given this was a cumulative meta-analysis.

DISCUSSION

Previous data have shown that GV are present in 5%–33% of patients with portal hypertension with a bleeding incidence of approximately 25% within 2 years of diagnosis.[35] Within 1 year of diagnosis, the risk of gastric variceal bleeding has been reported to be around 10%–16%, necessitating a streamlined evidence-driven approach. While previous literature has clearly demonstrated risk factors and independent predictors of bleeding (*e.g.*, size of GV, the presence of red signs, and the degree of liver dysfunction), there remains a paucity of the literature regarding treatment efficacy and how endoscopic options fit into the treatment continuum.[36]

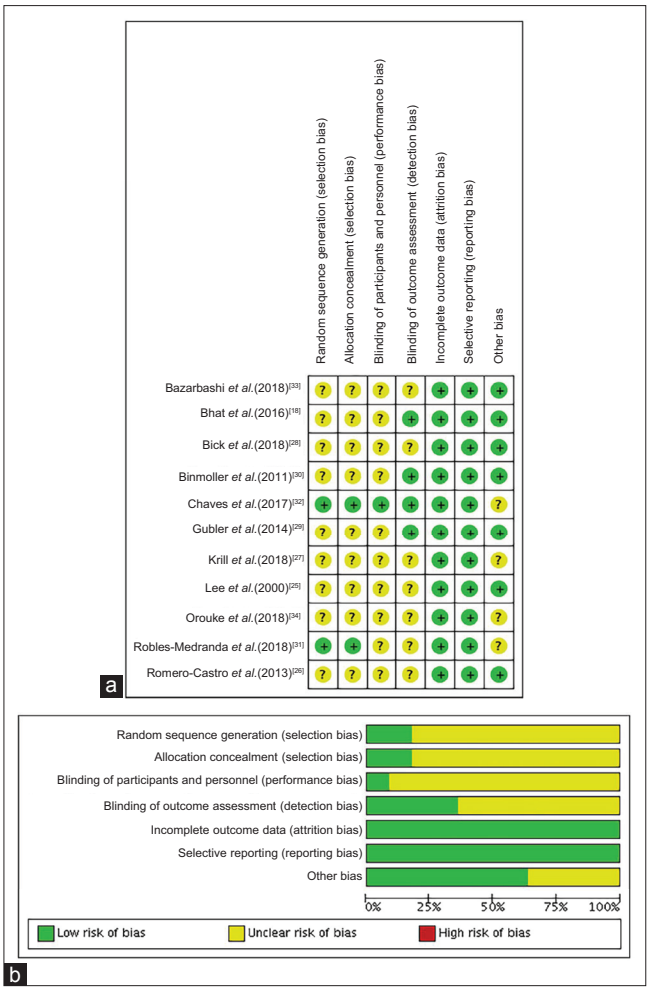

Figure 7. (a) Risk of bias summary: Review Authors' judgments about each risk of bias item for each included study. (b) Risk of bias graph: Review Authors' judgments about each risk of bias item presented as percentages across all included studies

Prior studies have demonstrated that EUS-guided therapy of GV is superior to direct endoscopic injection therapy.[28] However, few studies have evaluated the comparative efficacy and safety of the various EUS techniques. The results of this analysis demonstrate EUS-guided CYA injection + coil embolization to be a preferred strategy with a 100% technical success rate and adverse event rate of 10%. CYA + coil embolization resulted in significantly higher technical and clinical success with lower rate of adverse events as compared to CYA alone. CYA + coil embolization also resulted in significantly higher technical and clinical success when compared to coil therapy alone, with a trend toward fewer adverse events. The findings of this meta-analysis are similar to a recent study by Robles-Medranda *et al.* demonstrating that EUS-guided therapy for GV using CYA or coils is effective; however, coil therapy had higher clinical and technical success and was associated with fewer adverse events compared with EUS-CYA injection.[17] While endoscopes, number of sessions, dose of CYA, and procedure duration were unable to be compared between cohorts, it may be inferred CYA + coil would be a cost-effective strategy. Future cost-utility analysis may help to determine if differences in effectiveness have meaningful impact on future treatment recommendations.

Study limitations include moderate-to-large heterogeneity with regard to overall clinical success rate, rate of adverse events, reintervention rate, as well as rebleeding rate (indicated by $I^2 > 50\%$). In addition, we cannot rule out the risk of inherent study bias, specific differences in the patient population, and inter-operator variability in procedure outcomes. Furthermore, EUS coil embolization alone studies had a significantly shorter duration of follow-up – almost 3–5 times less compared to EUS CYA + coil and EUS CYA alone. While this may explain the lower adverse event rate, it should also be noted that the lack of CYA, which is associated with known complications such as embolization, variceal ulcer formation and others, may more accurately explain the perceived decrease in adverse events. In addition, although statistically significant differences in technical success exist between the types of procedures, it is important to realize these differences are still small with all three strategies achieving a technical success >95%.

The quality of included studies is also limited as only two randomized controlled studies were included in this analysis, with the remaining studies being retrospective in nature. Subgroup analysis based on the use of lipiodol, which has been demonstrated affect the viscosity, density, and interfacial tension of the CYA mixture as well as delay polymerization was not possible.[37] Finally, and perhaps most importantly, one major limitation to the results of this study involves the significant expertise and familiarity with EUS and these procedures to achieve similar results. There remains a significant learning curve required to appropriately perform these procedures, with some institutions more adept at performing one procedure over the other, thereby limiting the generalizability of these results.

Despite these limitations, our study has several strengths. Chiefly, this structured systematic review and meta-analysis methodologically summarize all available data to evaluate the clinical efficacy and safety of EUS-guided treatments available for GV. With no

formal treatment guidelines or algorithms available to guide practitioners, many treatment decisions are based on anecdotal experiences or general familiarity. We sought to evaluate objective data including technical success, clinical success, and adverse events as well as relevant secondary outcomes of rebleeding and reintervention rates. Furthermore, through the inclusion of multiple treatment strategies, we aimed to compare the effectiveness and tolerability of the three most common strategies in clinical practice, which perhaps may guide clinicians with therapeutic EUS expertise in future decision-making. Till date, this remains the only meta-analysis to evaluate cumulative and comparative EUS-specific treatment options for GV. While these procedures are complex and require dedicated devices and EUS expertise, which some centers may not have access to our results may also be underappreciated given the need for more experience.

CONCLUSION

This systematic review and meta-analysis found that EUS-guided therapy is a technically feasible, clinically effective, and safe procedure for the treatment of GV. In particular, for patients undergoing different types of EUS-guided therapy, EUS combination therapy with coil embolization + CYA injection appears to be a preferred strategy for the treatment of GV over EUS-based monotherapy (coil alone or CYA alone). Future randomized control trials are needed to validate these findings as well as to help establish a detailed treatment algorithm for the management of patients with GV.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Sarin SK, Kumar A. Gastric varices: Profile, classification, and management. *Am J Gastroenterol* 1989;84:1244-9.
2. Wani ZA, Bhat RA, Bhadoria AS, *et al*. Gastric varices: Classification, endoscopic and ultrasonographic management. *J Res Med Sci* 2015;20:1200-7.
3. Hwang JH, Shergill AK, Acosta RD, *et al*. The role of endoscopy in the management of variceal hemorrhage. *Gastrointest Endosc* 2014;80:221-7.
4. Al-Osaimi AM, Caldwell SH. Medical and endoscopic management of gastric varices. *Semin Intervent Radiol* 2011;28:273-82.
5. Tripathi D, Therapondos G, Jackson E, *et al*. The role of the transjugular intrahepatic portosystemic stent shunt (TIPSS) in the management of bleeding gastric varices: Clinical and haemodynamic correlations. *Gut* 2002;51:270-4.
6. Sabri SS, Swee W, Turba UC, *et al*. Bleeding gastric varices obliteration with balloon-occluded retrograde transvenous obliteration using sodium tetradecyl sulfate foam. *J Vasc Interv Radiol* 2011;22:309-16.
7. Watanabe K, Kimura K, Matsutani S, *et al*. Portal hemodynamics in patients with gastric varices. A study in 230 patients with esophageal and/or gastric varices using portal vein catheterization. *Gastroenterology* 1988;95:434-40.
8. Soehendra N, Nam VC, Grimm H, *et al*. Endoscopic obliteration of large esophagogastric varices with bucrylate. *Endoscopy* 1986;18:25-6.
9. Ramond MJ, Valla D, Gotlib JP, *et al*. Endoscopic obturation of esophagogastric varices with bucrylate. I. Clinical study of 49 patients. *Gastroenterol Clin Biol* 1986;10:575-9.
10. Iwase H, Maeda O, Shimada M, *et al*. Endoscopic ablation with cyanoacrylate glue for isolated gastric variceal bleeding. *Gastrointest Endosc* 2001;53:585-92.
11. Sarin SK, Jain AK, Jain M, *et al*. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002;97:1010-5.
12. Cheng LF, Wang ZQ, Li CZ, *et al*. Treatment of gastric varices by endoscopic sclerotherapy using butyl cyanoacrylate: 10 years' experience of 635 cases. *Chin Med J (Engl)* 2007;120:2081-5.
13. Fry LC, Neumann H, Olano C, *et al*. Efficacy, complications and clinical outcomes of endoscopic sclerotherapy with N-butyl-2-cyanoacrylate for bleeding gastric varices. *Dig Dis* 2008;26:300-3.
14. Dhiman RK, Chawla Y, Taneja S, *et al*. Endoscopic sclerotherapy of gastric variceal bleeding with N-butyl-2-cyanoacrylate. *J Clin Gastroenterol* 2002;35:222-7.
15. Kok K, Bond RP, Duncan IC, *et al*. Distal embolization and local vessel wall ulceration after gastric variceal obliteration with N-butyl-2-cyanoacrylate: A case report and review of the literature. *Endoscopy* 2004;36:442-6.
16. Rickman OB, Utz JP, Aughenbaugh GL, *et al*. Pulmonary embolization of 2-octyl cyanoacrylate after endoscopic injection therapy for gastric variceal bleeding. *Mayo Clin Proc* 2004;79:1455-8.
17. Robles-Medranda C, Valero M, Nebel JA, *et al*. Endoscopic-ultrasound-guided coil and cyanoacrylate embolization for gastric varices and the roles of endoscopic doppler and endosonographic varicealography in vascular targeting. *Dig Endosc* 2019;31:283-90.
18. Bhat YM, Weilert F, Fredrick RT, *et al*. EUS-guided treatment of gastric fundal varices with combined injection of coils and cyanoacrylate glue: A large U.S. Experience over 6 years (with video). *Gastrointest Endosc* 2016;83:1164-72.
19. Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med* 2009;151:W65-94.
20. Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: A tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
21. Lee EW, Saab S, Gomes AS, *et al*. Coil-assisted retrograde transvenous obliteration (CARTO) for the treatment of portal hypertensive variceal bleeding: Preliminary results. *Clin Transl Gastroenterol* 2014;5:e61.
22. Higgins JP, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
23. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
24. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.
25. Lee YT, Chan FK, Ng EK, *et al*. EUS-guided injection of cyanoacrylate for bleeding gastric varices. *Gastrointest Endosc* 2000;52:168-74.
26. Romero-Castro R, Ellrichmann M, Ortiz-Moyano C, *et al*. EUS-guided coil versus cyanoacrylate therapy for the treatment of gastric varices: A multicenter study (with videos). *Gastrointest Endosc* 2013;78:711-21.
27. Krill JT, Othman MO, Munot K, *et al*. Su1411. EUS-guided coil application with glue injection for gastric variceal obliteration is associated with less endoscopic reintervention compared to glue injection alone. *Gastrointest*

Endosc 2018;87:AB345.
28. Bick BL, Al-Haddad M, Liangpunsakul S, *et al*. EUS-guided fine needle injection is superior to direct endoscopic injection of 2-octyl cyanoacrylate for the treatment of gastric variceal bleeding. *Surg Endosc* 2019;33:1837-45.
29. Gubler C, Bauerfeind P. Safe and successful endoscopic initial treatment and long-term eradication of gastric varices by endoscopic ultrasound-guided histoacryl (N-butyl-2-cyanoacrylate) injection. *Scand J Gastroenterol* 2014;49:1136-42.
30. Binmoeller KF, Weilert F, Shah JN, *et al*. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). *Gastrointest Endosc* 2011;74:1019-25.
31. Robles-Medranda C, Valero M, Soria-Alcivar M, *et al*. 1036. Coils+Cyanoacrylate vs. Coils Alone in the Endoscopy Ultrasound-Guided Management of Gastric Varices (GOV II and IVG I): A Randomized, Controlled Therapeutic Trial. *Gastrointest Endosc*. 2018;87:AB145.
32. Chaves D, Almeida Lobo MR, de Moura DT, *et al*. Mo 1064. EUS-guided coil plus cyanoacrylate versus cyanoacrylate conventional technique to treat gastric varices: A prospective randomized study. *Gastrointest Endosc* 2017;85:AB412.
33. Bazarbashi AN, Wang TJ, Ge PS, *et al*. Endoscopic Ultrasound-Guided Treatment of Gastric Varcies with Coil Embolization and Asborable Gelatin Sponge: A Novel Alternative to Cyanoacrylate. Digestive Disease Week 2019. *Gastroenterology* 2019;156(Suppl 1). p. S116-7.
34. Orouke J, Shekhar C, Tripathi D, *et al*. PWE-093. Treatment of gastric fundal varices with EUS guided embolisation combining coil placement with thrombin injection. *Gut* 2018;67:A118-9.
35. Sarin SK, Lahoti D, Saxena SP, *et al*. Prevalence, classification and natural history of gastric varices: A long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343-9.
36. Garcia-Pagán JC, Barrufet M, Cardenas A, *et al*. Management of gastric varices. *Clin Gastroenterol Hepatol* 2014;12:919-280.
37. Li YJ, Barthès-Biesel D, Salsac AV. Polymerization kinetics of n-butyl cyanoacrylate glues used for vascular embolization. *J Mech Behav Biomed Mater* 2017;69:307-17.