Endoscopic band ligation in the treatment of gastric antral vascular ectasia: a systematic review and meta-analysis

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ABSTRACT

Background and study aims While argon plasma coagulation (APC) is the first-line treatment for gastric antral vascular ectasia (GAVE), endoscopic band ligation (EBL) has shown promising results. The aim of this study was to perform a systematic review and meta-analysis to evaluate the effectiveness of EBL for the treatment of GAVE.

Methods Individualized search strategies were developed in accordance with PRISMA and MOOSE guidelines through September 1, 2020. Measured outcomes included endoscopic success (defined as GAVE eradication/improvement), change in hemoglobin, transfusion dependency, number of treatment sessions, adverse events, rebleeding, and bleeding-associated mortality. Outcomes were compared among studies evaluating EBL versus APC.

Results Eleven studies (n = 393; 59.39 % female; mean age 58.65 ± 8.85 years) were included. Endoscopic success was achieved in 87.84 % [(95 % CI, 80.25 to 92.78); $I^2 = 11.96\%$] with a mean number of 2.50 ± 0.49 treatment sessions and average of 12.40 ± 3.82 bands applied. For 8 studies comparing EBL (n = 143) versus APC (n = 174), there was no difference in baseline patient characteristics. However, endoscopic success was significantly higher for EBL [OR 6.04 (95 % CI 1.97 to 18.56; $P = 0.002$], requiring fewer treatment sessions (2.56 ± 0.81 versus 3.78 ± 1.17; $P < 0.001$). EBL was also associated with a greater increase in post-procedure hemoglobin [mean difference 0.35 (95 % CI 0.07 to 0.62; $P = 0.0140$], greater reduction in transfusions required [mean difference –1.46 (95 % CI –2.80 to –0.12; $P = 0.033$], and fewer rebleeding events [OR 0.11 (95 % CI, 0.04 to 0.36); $P < 0.001$]. There was no difference in adverse events or bleeding-associated mortality ($P > 0.050$).

Conclusions EBL appears to be safe and effective for treatment of GAVE, with improved outcomes when compared to APC.

Introduction

Gastric antral vascular ectasia (GAVE) is characterized by a collection of dilated submucosal vessels as well as tortuous capillaries within the mucosal layer of the stomach, typically found within the gastric antrum [1, 2]. While the exact pathophysiology of GAVE remains less clear, several potential theories have

been proposed: mechanical stress, abnormal antral motility, hypergastrinemia-associated hormonal imbalances, or vasoactive mediators [1, 3–6]. Endoscopically, common findings of GAVE include erythematous or hemorrhagic lesions, described as having a linear streaking or punctate appearance, leading to the classic description as watermelon stomach or a honeycomb appearance, respectively [7–10]. Although GAVE remains a re-

latively infrequent cause of overt gastrointestinal bleeding, persistent iron deficiency with transfusion-dependent anemia are not uncommon among patients with this condition [11–13].

Currently, thermal therapy with argon plasma coagulation (APC) remains a first-line endoscopic treatment strategy, though emerging data has suggested patients receiving treatment with radiofrequency ablation (RFA) may have improved outcomes including improved endoscopic success rates, fewer treatment sessions required, and lower rates of adverse events [14–18]. Most studies have demonstrated APC and RFA to have an endoscopic success rate from 70 % to 90 % overall [18]. However, while these success rates up to 90 % are impressive with thermal therapy, it is important to highlight that these treatment strategies act mostly upon the mucosal layer, with limited ability to penetrate to the deeper submucosal layer [19].

Given our current understanding of GAVE, with involvement of both the mucosal and submucosal layer, it stands to reason that treatment techniques designed to act upon both gastrointestinal layers may be a more effective strategy [19]. One such treatment strategy, which is already the mainstay treatment for esophageal varices, is endoscopic band ligation (EBL). This non-thermal endoscopic treatment options affords the ability to treat dilated submucosal veins in addition to the tortuous capillaries of the mucosal layer associated with GAVE. Yet, despite this strategy already being familiar to endoscopists and perhaps mechanistically more plausible as a treatment modality, there remains limited data and poor adoption of this technique as both a first-line strategy or salvage therapy.

As such, the primary aim of this study was to perform a structured systematic review and meta-analysis of all eligible studies to evaluate the effectiveness and safety of EBL in the treatment of GAVE. Additional aims were to compare clinical outcomes of EBL versus thermal endoscopic therapies.

Materials and methods

Study design

This study was prospectively submitted in PROSPERO, an international database of prospectively registered systematic reviews in health and social care. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement outline and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) reporting guidelines for reporting systematic reviews and meta-analyses was used to report findings (**Appendix 1** and **Appendix 2**) [20, 21].

Literature search

Two authors (TRM and KEH) independently conducted a comprehensive literature review using a standardized protocol to identify articles that evaluated EBL for the treatment of GAVE. Systematic searches of PubMed, EMBASE, Web of Science, and the Cochrane Library databases were performed from inception through September 1, 2020. Literature search terms included: "gastric antral vascular ectasia (GAVE)" and "endoscopic band ligation (EBL)". After preliminary search results were obtained and duplicate articles excluded, the titles and abstracts of all

potentially relevant studies were screened for eligibility. The reference lists of studies of interest were then manually reviewed to identify additional references through cross-checking bibliographies of retrieved full-text papers.

Study selection criteria

Included studies were required to investigate the use of EBL for the treatment of GAVE. Any retrospective, prospective, or randomized study involving EBL for treatment of GAVE that reported at least one of the pre-defined outcomes was included. Studies involving alternative endoscopic, medical, or surgical modalities were not included in cases where EBL was specifically excluded. A particular 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 <8 patients were excluded. Only adult patients (age ≥ 18 years) were included with studies including pediatric populations excluded from this analysis.
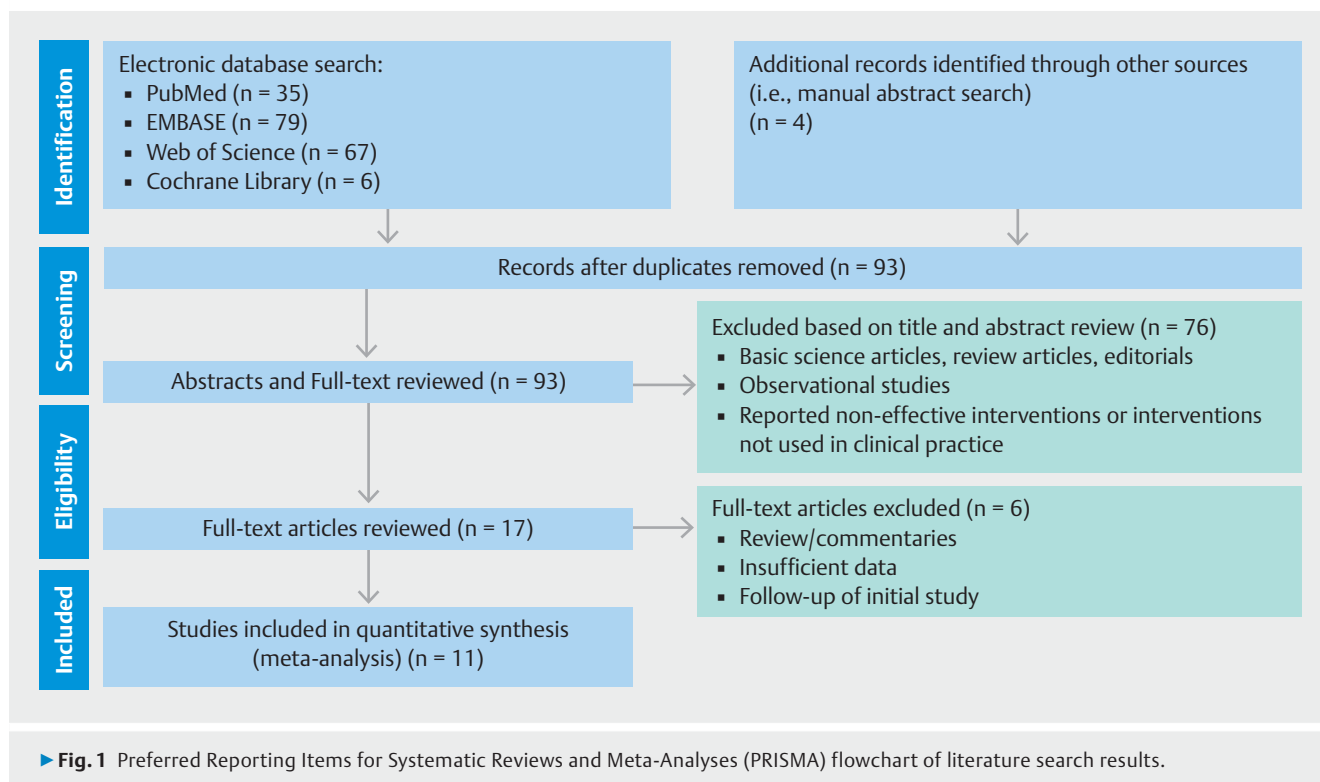
All relevant English language articles (both full-text and published abstracts) were included regardless of year of publication were included. The titles and abstracts of all potentially relevant studies were screened for eligibility. Two reviewers (TRM and KEH) independently screened the titles and 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 (WWC). In the case of studies with incomplete information, contact was attempted with the principal authors to obtain additional data.

Measured outcomes

Multiple outcome measurements were reported in this systematic review and meta-analysis, including endoscopic success of EBL for the treatment of GAVE, defined as complete eradication or evidence of endoscopic improvement of GAVE on follow-up endoscopy. Additional outcomes included clinical success, as measured by average pre- and post-procedure hemoglobin levels, transfusion and hospitalization requirements before and after procedure, as well rates of rebleeding. Further measured outcomes of interest included adverse events and rebleeding-associated mortality rates. Other measured variables abstracted from the literature included baseline patient characteristics, year of publication, type of publication (i.e., full manuscript, abstract, comparative, or non-comparative study), and duration of follow-up.

Statistical analyses

This systematic review and 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, DerSimonian–Laird weights for the random effects model [22, 23]. The pooled rates were estimated using random effects models and presented as point estimates (rates) with 95 % confidence intervals (CIs) [24–26]. For pre- and post-procedure

▶ Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of literature search results.

measurements, pooled or weighted mean difference as calculated with corresponding 95% CIs with corresponding *P* values.

Additional sensitivity analyses were performed for only randomized controlled trial data (excluding prospective and retrospective studies). Further subgroup analyses were performed for direct comparator studies to compare outcomes between EBL therapy versus APC thermal-based treatment. Again, treatment with alternative thermal therapy, including RFA, was excluded from this study. Mean differences between pre- and post-hemoglobin, transfusion, and hospitalizations were compared along with odds ratios (ORs) calculated to compare additional outcomes between treatment modalities. Univariate meta-regression was also performed to assess measured outcomes for patients with treatment naïve versus APC-refractory GAVE. All calculated *P* values were 2-sided, and *P* < 0.05 was considered statistically significant. Tabular and graphical analyses were performing using Comprehensive Meta-Analysis software, version 3 (BioStat, Englewood, New Jersey, United States). Combined weighted proportions were determined by use of the Stata 15.0 software package (Stata Corp LP, College Station, Texas, United States).

Risk of bias and quality assessment

Risk of bias and quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale and JADAD score for quality of randomized trials [27, 28]. In this study, high quality was defined as a Newcastle-Ottawa Quality Assessment Scale score ≥ 4 or a JADAD score ≥ 3. Two authors (TRM and KEH) independently extracted data and assessed the risk of bias and study quality for each of the articles. Any disagree-

ments were resolved by discussion and consensus between the two authors or in consultation with a third author (WCC).

Investigations of heterogeneity and prediction interval

Heterogeneity was assessed for the individual meta-analyses using the chi squared test and the I^2 statistic [29]. Significant heterogeneity was defined as $P < 0.05$, with $I^2 > 50\%$ indicating substantial heterogeneity. Further quantification of heterogeneity was categorized based upon I^2 with values of 25%, 50%, and 75% indicating low, moderate, and high amounts of heterogeneity, respectively. Given the use of random effects model to estimate average effect, a 95% prediction interval was calculated to determine the dispersion of effects and clearly illustrate heterogeneity in the calculated effect size [30–32].

Publication bias

To assess for publication bias, a funnel plot was created and visually inspected for asymmetry and quantitatively using Egger regression testing [33, 34]. The trim and fill method was used to correct for funnel plot asymmetry and provide an adjusted effect [35]. The classic fail-safe test was also applied to assess risk of bias across studies.

Results

Characteristics of included studies

This systematic review and meta-analysis included a total of 11 studies (n = 393) [36–46]. A PRISMA flow chart of search results is shown in ▶ **Fig. 1**. Of the 393 patients with GAVE, 219 patients underwent treatment with EBL, with the remaining pa-

tients receiving thermal therapy with APC. Eight of the 11 included studies were comparative in nature (EBL: n = 143 versus APC: n = 174). ▶ Table 1 demonstrates the baseline patient characteristics of included studies. All but two studies were full-text published manuscripts with the remaining being published abstracts from annual gastroenterology scientific meetings. Four prospective, randomized controlled trials, one prospective observational study, and 6 retrospective cohort studies were included with publication years ranging from 2008 to 2020.

Included patient characteristics

Mean age of included patients who underwent EBL was 58.65 ± 8.85 years. Fifty-nine percent of patients were female. In terms of baseline patient characteristics and presenting symptoms, 71.97 % of patients carried a diagnosis of cirrhosis. More than half (57.14 %) of patients presented with evidence of overt bleeding at time of EBL. Of studies reporting prior therapies, 37.80 % of patients included in this meta-analysis had refractory GAVE despite prior treatment with APC. The mean follow-up period was 14.32 ± 11.10 months.

Endoscopic success

The outcome of endoscopic success, defined as complete eradication or improvement in GAVE on follow-up endoscopy, was noted to occur in 87.84 % [(95 % CI, 80.25 to 92.78); $I^2 = 11.96$ %; prediction interval 72.60 to 95.17] (▶ Fig. 2a). This was accomplished with a mean number of 2.50 ± 0.49 treatment sessions with an average of 12.40 ± 3.82 bands applied per treatment session. On sensitivity analysis limited to randomized trials, endoscopic success was achieved in 88.73 % [(95 % CI, 63.83 to 97.23); $I^2 = 59.39$ %] of patients. Excluding published abstracts, 86.95 % [(95 % CI, 78.58 to 92.37); $I^2 = 11.99$ %] demonstrated treatment success endoscopically. Summary data for endoscopic and clinical success of EBL for the treatment of GAVE is highlighted in ▶ Table 2.

Clinical success

On average, patients required 2.76 ± 2.74 units of red-cell transfusions and were hospitalized 2.06 ± 0.31 times prior to EBL. Mean pre-procedure hemoglobin values were 7.66 ± 0.96 gm/dL with an increase in hemoglobin post-EBL of 2.23 gm/dL [(95 % CI, 1.39 to 3.07); $I^2 = 91.00$ %; $P < 0.001$] (▶ Fig. 2b). The number of transfusions decreased significantly post-EBL [weighted mean difference –1.63 gm/dL (95 % CI, –2.39 to –0.86); $I^2 = 89.39$ %; $P < 0.001$] as did bleeding-associated hospitalizations [weighted mean difference –1.01 times (95 % CI, –1.35 to –0.67); $I^2 = 0.00$ %; $P < 0.001$] (▶ Fig. 2c and ▶ Fig. 2d). Among randomized controlled trial studies, pooled mean hemoglobin increased 1.48 gm/dL [(95 % CI, 0.40 to 2.56); $I^2 = 93.00$ %; $P = 0.007$] after treatment with EBL. Further analyses limited to randomized trials, amplified this decrease in transfusions post-EBL [weighted mean difference –4.28 gm/dL (95 % CI, –7.22 to –1.34); $I^2 = 94.57$ %; $P = 0.004$]. Only 2 studies reported hospitalization data pre- and post-EBL, therefore pooled proportions could not be calculated.

Adverse events and bleeding-associated mortality

Adverse events occurred in 10.90 % [(95 % CI, 5.14 to 21.65); $I^2 = 38.23$ %; prediction interval 1.71 to 46.18] of patients who underwent EBL. All studies reporting adverse events were full-text manuscripts. Rebleeding post-EBL occurred in 9.00 % [(95 % CI, 5.02 to 15.62); $I^2 = 0.00$ %; prediction interval 4.33 to 17.78] of patients. Among only randomized controlled trials, adverse events were reported among 12.59 % [(95 % CI, 4.08 to 32.82); $I^2 = 62.29$ %] of cases. Excluding abstracts, the rebleeding rate was 7.47 % % [(95 % CI, 3.75 to 14.32); $I^2 = 0.00$ %]. Data limited to randomized studies demonstrated a rebleeding rate of 7.06 % % [(95 % CI, 2.73 to 17.05); $I^2 = 23.24$ %]. No patients died as a result of rebleeding after treatment with EBL.

EBL versus APC therapy

Comparison between patients who received non-thermal or thermal therapies revealed no difference in mean age (EBL: 56.27 ± 8.86 versus 55.88 ± 9.54; $P = 0.735$). There was also no difference in gender between EBL and APC groups (54.03 % versus 55.46 % female; $P = 0.824$). Additionally, there was no difference in percentage of patients with underlying cirrhosis (EBL: 86.21 % versus APC: 90.38 %; $P = 0.340$) or patients presenting with overt hemorrhage (EBL: 75.00 % versus APC: 63.75 %; $P = 0.110$) between the two groups. Mean follow-up was not different for patients who underwent EBL versus thermal therapy (8.92 ± 5.38 versus 9.84 ± 6.82 months; $P = 0.212$).

When comparing endoscopic success between EBL versus APC, patients who underwent EBL had a significantly higher endoscopic success rate [OR 6.04 (95 % CI 1.97 to 18.56; $P = 0.002$] (▶ Fig. 3a). This was also accomplished with fewer number of endoscopic treatment sessions (EBL 2.56 ± 0.81 versus APC 3.78 ± 1.17 sessions; $P < 0.001$). Endoscopic success in randomized studies alone was also higher for EBL compared to APC [OR 5.35 (95 % CI 1.46 to 19.58; $P = 0.011$]. Comparison data between EBL versus APC is shown in ▶ Table 2.

Pretreatment hemoglobin was not different between groups (EBL: 7.65 ± 0.88 versus APC: 7.55 ± 0.77 gm/dL; $P = 0.3501$); however, EBL was associated with a greater increase in post-procedure hemoglobin [difference in means 0.59 (95 % CI 0.17 to 1.00; $P = 0.006$] (▶ Fig. 3b). Examination of data from randomized trials, revealed EBL again was associated with a greater increase in hemoglobin when compared to APC [difference in means 0.35 (95 % CI 0.07 to 0.62; $P = 0.0140$]. Endoscopic band ligation was also associated with a greater reduction in transfusions required [difference in means –1.46 (95 % CI –2.80 to –0.12; $P = 0.0330$] (▶ Fig. 3c). The number of transfusions required post-EBL was also greater based upon randomized trial data along [difference in means –2.30 (95 % CI –4.11 to –2.48; $P = 0.0130$].

There was no significant difference in adverse events between EBL versus APC [OR 2.07 (95 % CI, 0.45 to 9.48); $P = 0.347$]. Randomized controlled trial adverse events were also not different [OR 2.59 (95 % CI, 0.09 to 72.27); $P = 0.576$]. With regard to rebleeding, EBL was associated with decreased recurrent bleeding [OR 0.11 (95 % CI, 0.04 to 0.36); $P < 0.001$ (▶ Fig. 3d). Again, this finding was similar for randomized studies [OR

▶ **Table 1** Baseline characteristics of included studies to assess endoscopic band ligation and argon plasma coagulation for the treatment of gastric antral vascular ectasia.

Author	Year	Country of Study	Type of Study	Study design	No. patients	No. males	Mean age (years)	Follow-up (months)	No. treatment sessions	Endoscopic success	Adverse events	Re-bleeding	Bleeding-associated mortality	Risk of bias[1]
EBL therapy														
Wells et al	2008	United States	Full-Text	Retrospective, single-center comparative study vs APC thermal therapy	9	5	68±3	10.1±7.5	1.89±0.6	9/9	0/9	0/9	0/9	4.5
Sato et al	2012	Japan	Full-Text	Retrospective, single-center comparative study vs APC Thermal Therapy	12	6		14.6	3 (2–4)	12/12	1/12	1/12	0/12	4
Koehane et al	2013	Ireland	Full-Text	Retrospective, single-center comparative study vs APC thermal therapy	8	2	70.4	26	2.5 (1–5)	8/8	1/8	0/8	0/8	4
Abdelhalim et al	2014	Egypt	Full-Text	Single-center, randomized controlled trial	20	9	55.65	6	2.25	19/20	0/20	1/20		3
Zepeda-Gomez et al	2014	Canada	Full-Text	Prospective, single-center non-comparative study	21	6	65±13	10 (2–17)	2.28 (1–6)	19/21	0/21			5
Elhendawy et al	2016	Egypt	Full-Text	Single-center, randomized controlled trial	44	19	51.41±7.54	6	2.93±0.85		6/44	1/44		3
Fabian et al	2016	Hungary	Abstract	Retrospective, multi-center comparative study vs APC thermal therapy	12				1.5					4
Abd Al-Waab et al	2019	Egypt	Full-Text	Single-center, randomized controlled trial	18	11	65±9	6	2 (2–3)	13/18	6/18	3/18		3
Abdel Ghaffar et al	2019	Egypt	Full-Text	Single-center, randomized controlled trial	20		42.5±17.6	6	1.85±0.81	19/20	0/20	1/20	0/20	3
Eccles et al	2019	Canada	Full-Text	Retrospective, non-comparative study	33	9	67 (55–77)	35.9 (4.0–76.5)	3 (2–4)	27/33			0/33	4.5

▶ **Table 1** (Continuation)

Author	Year	Country of Study	Type of Study	Study design	No. patients	No. males	Mean age (years)	Follow-up (months)	No. treatment sessions	Endoscopic success	Adverse events	Re-bleeding	Bleeding-associated mortality	Risk of bias[1]
Hasan et al	2020	Bangladesh	Abstract	Retrospective, non-comparative study	22			22	2.8	19/20		3/20	0/20	4.5
Thermal therapy														
Wells et al	2008	United States	Full-Text	Full – retrospective, comparative study vs thermal therapy	13	5	66±11	15.3±13.5	4.69±4.69		1/13	7/13	0/13	4.5
Sato et al	2012	Japan	Full-Text	Full – retrospective, comparative study vs APC thermal therapy	22	9		16.6	2.3 (1–3)	22/22	0/22	15/22	2/22	4
Koehane et al	2013	Ireland	Full-Text	Full – retrospective, comparative study vs APC thermal therapy	15	4	75.9	26	4.1 (1–11)	7/15	0/15	0/15	0/15	4
Abdelhalim et al	2014	Egypt	Full-Text	Single-center, randomized controlled trial	20	10	57.17	6	5.5	12/20	0/20	13/20		3
Elhendawy et al	2016	Egypt	Full-Text	Full – randomized controlled trial	44	15	53.09±7.16	6	3.48±0.90		9/44	0/44		3
Fabian et al	2016	Hungary	Abstract	Retrospective, multi-center comparative study vs APC thermal therapy	22				5.23					4
Abd Al-Waab et al	2019	Egypt	Full-Text	Single-center, randomized controlled trial	18	15	60±11	6	2 (2–4)	10/18	0/18	8/18		3
Abdel Ghaffar et al	2019	Egypt	Full-Text	Single-center, randomized controlled trial	20		42±25.4	6	4.15±1.22	12/20	0/20	7/20	0/20	3

APC, argon plasma coagulation.
[1] Risk of bias and quality of observational studies was evaluated using the Newcastle-Ottawa Quality Assessment Scale and JADAD score for randomized controlled trials.

Endoscopic success with EBL for treatment of GAVE

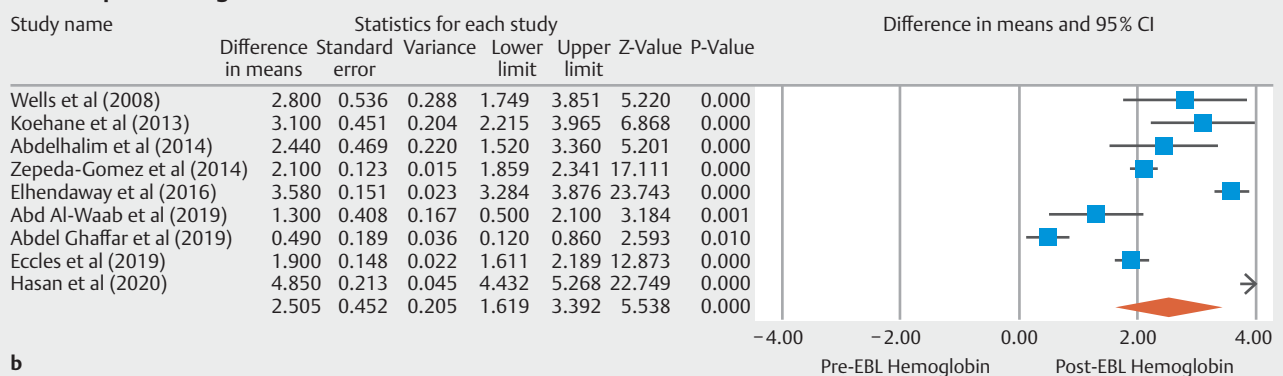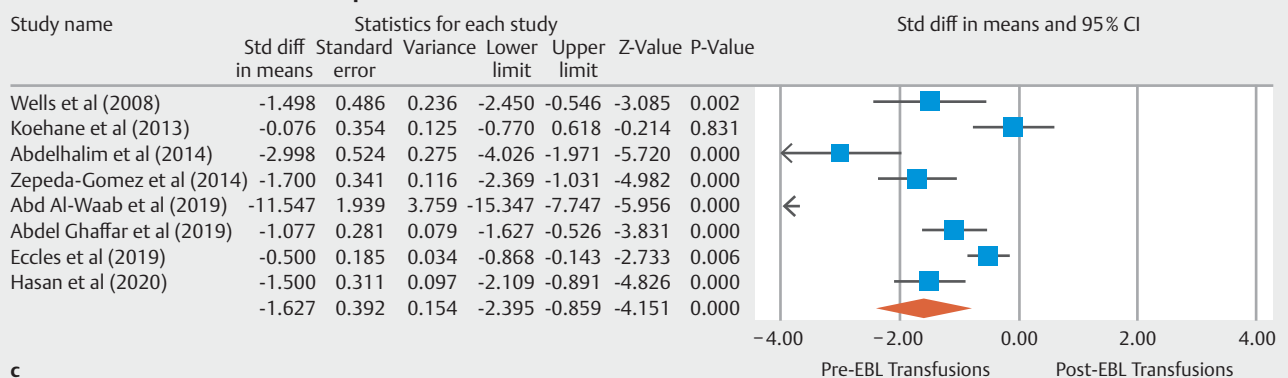| Study name	Event rate	Lower limit	Upper limit	Z-Value	P-Value	Event rate and 95% CI
Wells et al (2008)	0.9500	0.5251	0.9969	2.0293	0.0424	
Sato et al (2013)	0.9615	0.5968	0.9976	2.2319	0.0256	
Koehane et al (2013)	0.9444	0.4953	0.9966	1.9469	0.0515	
Abdelhalim et al (2014)	0.9500	0.7178	0.9930	2.8699	0.0041	
Zepeda-Gomez et al (2014)	0.9048	0.6887	0.9761	3.0284	0.0025	
Abd Al-Waab et al (2019)	0.7222	0.4810	0.8794	1.8158	0.9694	
Abdel Ghaffar et al (2019)	0.9500	0.7178	0.9930	2.9699	0.0041	
Eccles et al (2019)	0.8182	0.6501	0.9160	3.3325	0.0009	
Hasan et al (2020)	0.9500	0.7178	0.9930	2.8699	0.0041	
	0.8784	0.8025	0.9278	6.7339	0.0000	

a

Pre- and post-hemoglobin with EBL for treatment of GAVE

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Difference in means and 95% CI
Wells et al (2008)	2.800	0.536	0.288	1.749	3.851	5.220	0.000	
Koehane et al (2013)	3.100	0.451	0.204	2.215	3.965	6.868	0.000	
Abdelhalim et al (2014)	2.440	0.469	0.220	1.520	3.360	5.201	0.000	
Zepeda-Gomez et al (2014)	2.100	0.123	0.015	1.859	2.341	17.111	0.000	
Elhendaway et al (2016)	3.580	0.151	0.023	3.284	3.876	23.743	0.000	
Abd Al-Waab et al (2019)	1.300	0.408	0.167	0.500	2.100	3.184	0.001	
Abdel Ghaffar et al (2019)	0.490	0.189	0.036	0.120	0.860	2.593	0.010	
Eccles et al (2019)	1.900	0.148	0.022	1.611	2.189	12.873	0.000	
Hasan et al (2020)	4.850	0.213	0.045	4.432	5.268	22.749	0.000	
	2.505	0.452	0.205	1.619	3.392	5.538	0.000	

Pre-EBL Hemoglobin   Post-EBL Hemoglobin

b

Number of transfusions Pre- and post-EBL for treatment of GAVE

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95% CI
Wells et al (2008)	-1.498	0.486	0.236	-2.450	-0.546	-3.085	0.002	
Koehane et al (2013)	-0.076	0.354	0.125	-0.770	0.618	-0.214	0.831	
Abdelhalim et al (2014)	-2.998	0.524	0.275	-4.026	-1.971	-5.720	0.000	
Zepeda-Gomez et al (2014)	-1.700	0.341	0.116	-2.369	-1.031	-4.982	0.000	
Abd Al-Waab et al (2019)	-11.547	1.939	3.759	-15.347	-7.747	-5.956	0.000	
Abdel Ghaffar et al (2019)	-1.077	0.281	0.079	-1.627	-0.526	-3.831	0.000	
Eccles et al (2019)	-0.500	0.185	0.034	-0.868	-0.143	-2.733	0.006	
Hasan et al (2020)	-1.500	0.311	0.097	-2.109	-0.891	-4.826	0.000	
	-1.627	0.392	0.154	-2.395	-0.859	-4.151	0.000	

Pre-EBL Transfusions   Post-EBL Transfusions

c

Bleeding-associated hospitalizations Pre- and post-EBL for treatment of GAVE

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	Std diff in means and 95% CI
Wells et al (2008)	-1.127	0.426	0.182	-1.963	-0.292	-2.644	0.008	
Abdelhalim et al (2014)	-1.069	0.280	0.079	-1.618	-0.520	-3.814	0.000	
Abdel Ghaffar et al (2019)	-0.912	0.266	0.071	-1.434	-0.391	-3.428	0.001	
	-1.011	0.176	0.031	-1.355	-0.666	-5.748	0.000	

Pre-EBL Transfusions   Post-EBL Transfusions

d

▶ **Fig. 2 a** Endoscopic success rate of endoscopic band ligation for the treatment of gastric antral vascular ectasia. **b** Change in hemoglobin with of endoscopic band ligation for the treatment of gastric antral vascular ectasia. **c** Change in red cell transfusions with endoscopic band ligation for the treatment of gastric antral vascular ectasia. **d** Rebleeding-associated hospitalization with endoscopic band ligation for the treatment of gastric antral vascular ectasia.

▶ **Table 2** Cumulative data for endoscopic band ligation and comparison to argon plasma coagulation for the treatment of gastric antral vascular ectasia.

	Cumulative data: EBL	Comparative data: EBL versus APC	P value
Mean age in years	58.65 ± 8.85 (8 studies, n = 173)	56.27 ± 8.86 versus 55.88 ± 9.54 (6 studies, n = 132 vs n = 117)	0.735
No. females	89 (59.39 %) (8 studies, n = 165)	54.03 % versus 55.46 % (6 studies, n = 131 vs n = 132)	0.824
No. with cirrhosis	113 (71.97 %) (7 studies, n = 133)	86.21 % versus 90.38 % (5 studies, n = 103 vs n = 117)	0.340
Overt gastrointestinal bleeding	76 (59.39 %) (7 studies, n = 157)	75.00 % versus 63.75 % (5 studies, n = 79 vs n = 03)	0.110
Follow-up in months	14.32 ± 11.10 (10 studies, n = 207)	8.92 ± 5.38 versus 9.84 ± 6.82 (6 studies, n = 132 vs n = 117)	0.212
No. treatment sessions	2.50 ± 0.49 (11 studies, n = 219)	2.56 ± 0.81 versus 3.78 ± 1.17 (8 studies, n = 143 vs n = 174)	< 0.001
No. bands applied	12.40 ± 3.82 (6 studies, n = 141)	–	–
Endoscopic success	87.84 % (95 % CI, 80.25 to 92.78) I^2 = 11.96 % (9 studies, n = 163)	OR 6.04 (95 % CI 1.97 to 18.56) (5 studies, n = 78 vs n = 95)	0.002
Change in hemoglobin	2.23 gm/dL (95 % CI, 1.39 to 3.07) I^2 = 91.00 % (8 studies, n = 173)	Mean diff 0.59 (95 % CI 0.17 to 1.00) (6 studies, n = 119 vs n = 130)	0.006
Change in transfusion requirements	−1.63 units (95 % CI, −2.39 to −0.86) I^2 = 89.39 % (6 studies, n = 108)	Mean diff −1.46 (95 % CI −2.80 to −0.12) (5 studies, n = 75 vs n = 86)	0.033
Change in number of hospitalizations	−1.01 (95 % CI, −1.35 to −0.67) I^2 = 0.00 % (3 studies, n = 49)	–	–
Adverse events	10.90 % (95 % CI, 5.14 to 21.65) I^2 = 38.23 % (8 studies, n = 152)	OR 2.07 (95 % CI, 0.45 to 9.48) (7 studies, n = 131 vs n = 152)	0.347
Rebleeding events	9.00 % (95 % CI, 5.02 to 15.62) I^2 = 0.00 % (8 studies, n = 153)	OR 0.11 (95 % CI, 0.04 to 0.36) (7 studies, n = 131 vs n = 152)	< 0.001
Bleeding-associated mortality	3.09 % (95 % CI, 1.00 to 9.16) I^2 = 0.00 % (6 studies, n = 104)	OR 0.33 (95 % CI, 0.02 to 7.40) (4 studies, n = 49 vs n = 70)	0.483

EBL, endoscopic band ligation; APC, argon plasma coagulation.

0.17 (95 % CI, 0.04 to 0.82); *P* = 0.027]. There was no statistically significant difference found for bleeding-associated mortality between groups [OR 0.33 (95 % CI, 0.02 to 7.4); *P* = 0.483].
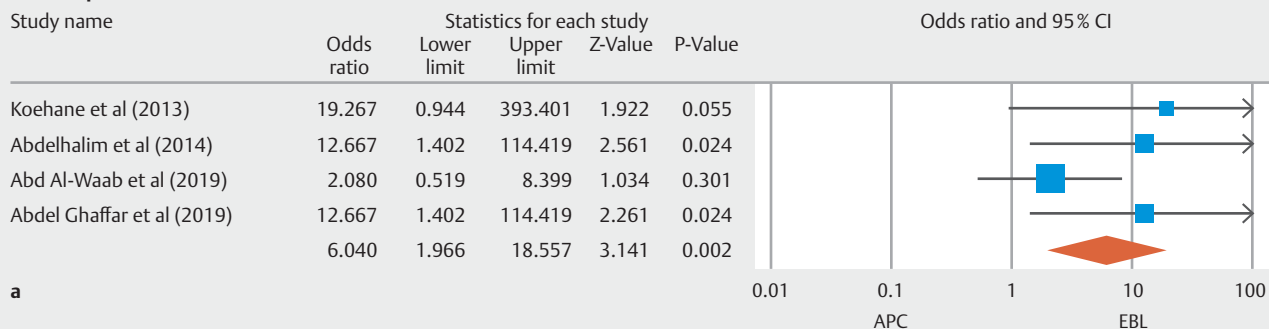
Treatment-naïve versus APC-refractory GAVE

A total of six studies (n = 127 patients) included patients with prior APC therapy, of which 48 patients (37.80 %) reported APC-refractory GAVE. Individual reporting of data from these patients was not possible; however, data from these six studies were compared to the remaining 5 studies that included only treatment naïve patients. Based upon univariate meta-regres-
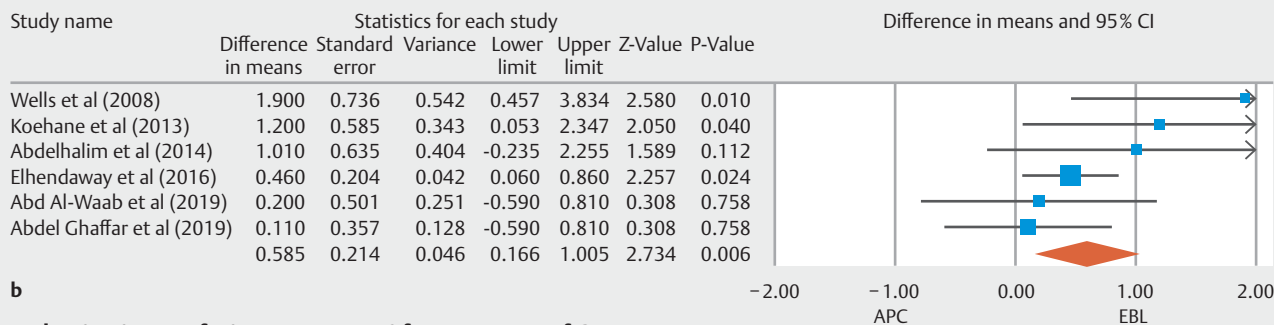
sion, there was no difference in endoscopic success [OR 0.94 (95 % CI 0.26 to 3.46; *P* = 0.927] between groups (**Supplemental Fig. 1**). Mean improvement in hemoglobin was not different between treatment naïve and APC-refractory patients though there was a trend towards more improvement among patients with no prior treatment [OR 0.29 (95 % CI 0.08 to 1.05; *P* = 0.060] (**Supplemental Fig. 2**). Treatment naïve patients did, however, experience a greater reduction in transfusions compared to patients with APC-refractory GAVE [OR 0.20 (95 % CI 0.04 to 0.96; *P* = 0.045] (**Supplemental Fig. 3**). Adverse events were not statistically different between studies that included
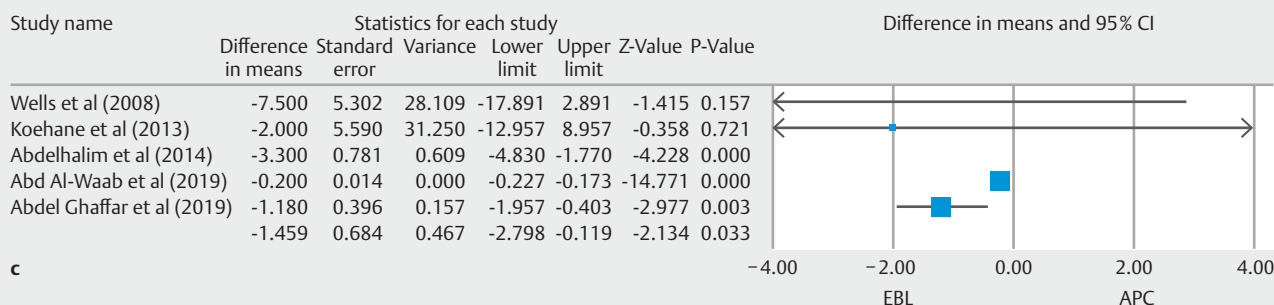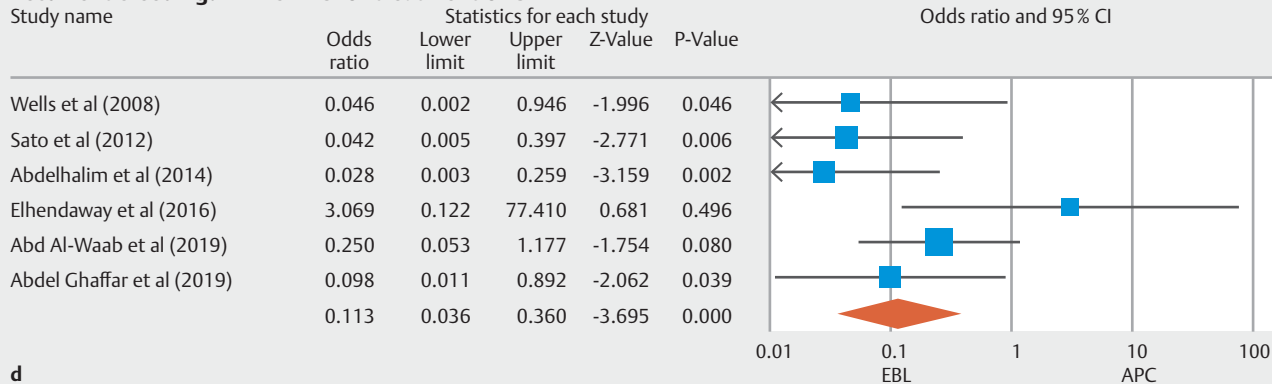
Endoscopic success with EBL vs APC for treatment of GAVE

Study name		Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value	
Koehane et al (2013)	19.267	0.944	393.401	1.922	0.055	
Abdelhalim et al (2014)	12.667	1.402	114.419	2.561	0.024	
Abd Al-Waab et al (2019)	2.080	0.519	8.399	1.034	0.301	
Abdel Ghaffar et al (2019)	12.667	1.402	114.419	2.261	0.024	
	6.040	1.966	18.557	3.141	0.002	

a

0.01 0.1 1 10 100
APC   EBL

Improvement in hemoglobin: EBL vs APC for treatment of GAVE

Study name			Statistics for each study					Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	
Wells et al (2008)	1.900	0.736	0.542	0.457	3.834	2.580	0.010	
Koehane et al (2013)	1.200	0.585	0.343	0.053	2.347	2.050	0.040	
Abdelhalim et al (2014)	1.010	0.635	0.404	-0.235	2.255	1.589	0.112	
Elhendaway et al (2016)	0.460	0.204	0.042	0.060	0.860	2.257	0.024	
Abd Al-Waab et al (2019)	0.200	0.501	0.251	-0.590	0.810	0.308	0.758	
Abdel Ghaffar et al (2019)	0.110	0.357	0.128	-0.590	0.810	0.308	0.758	
	0.585	0.214	0.046	0.166	1.005	2.734	0.006	

b

-2.00 -1.00 0.00 1.00 2.00
APC   EBL

Reduction in transfusions: EBL vs APC for treatment of GAVE

Study name			Statistics for each study					Difference in means and 95% CI
	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	P-Value	
Wells et al (2008)	-7.500	5.302	28.109	-17.891	2.891	-1.415	0.157	
Koehane et al (2013)	-2.000	5.590	31.250	-12.957	8.957	-0.358	0.721	
Abdelhalim et al (2014)	-3.300	0.781	0.609	-4.830	-1.770	-4.228	0.000	
Abd Al-Waab et al (2019)	-0.200	0.014	0.000	-0.227	-0.173	-14.771	0.000	
Abdel Ghaffar et al (2019)	-1.180	0.396	0.157	-1.957	-0.403	-2.977	0.003	
	-1.459	0.684	0.467	-2.798	-0.119	-2.134	0.033	

c

-4.00 -2.00 0.00 2.00 4.00
EBL   APC

Recurrent bleeding: EBL vs APC for treatment of GAVE

Study name		Statistics for each study				Odds ratio and 95% CI
	Odds ratio	Lower limit	Upper limit	Z-Value	P-Value	
Wells et al (2008)	0.046	0.002	0.946	-1.996	0.046	
Sato et al (2012)	0.042	0.005	0.397	-2.771	0.006	
Abdelhalim et al (2014)	0.028	0.003	0.259	-3.159	0.002	
Elhendaway et al (2016)	3.069	0.122	77.410	0.681	0.496	
Abd Al-Waab et al (2019)	0.250	0.053	1.177	-1.754	0.080	
Abdel Ghaffar et al (2019)	0.098	0.011	0.892	-2.062	0.039	
	0.113	0.036	0.360	-3.695	0.000	

0.01 0.1 1 10 100
EBL   APC

d

▶ **Fig. 3 a** Endoscopic success: endoscopic band ligation and comparison to argon plasma coagulation for the treatment of gastric antral vascular ectasia. **b** Change in hemoglobin: endoscopic band ligation and comparison to argon plasma coagulation for the treatment of gastric antral vascular ectasia. **c** Change in red cell transfusions: endoscopic band ligation and comparison to argon plasma coagulation for the treatment of gastric antral vascular ectasia. **d** Change in recurrent bleeding: endoscopic band ligation and comparison to argon plasma coagulation for the treatment of gastric antral vascular ectasia.

patients with and without prior APC therapy [OR 1.60 (95 % CI 0.28 to 9.21)] (**Supplemental Fig. 4**).

Risk of bias assessment

Quality assessment for each study shown in ▶ **Table 1**. Visual inspection of the funnel plot demonstrated that smaller and statistically insignificant studies appeared to be missing likely due to publication bias (▶ **Fig. 4a**). With the Duval and Tweedie's trim and fill method, overall endoscopic success of EBL for the treatment of GAVE was slightly decreased from 87.84 % (95 % CI, 80.25 to 92.78) to 84.55 % (95 % CI 75.80 to 90.53) though this was not statistically significant due to the presence of overlapping confidence intervals (▶ **Fig. 4b**).

Discussion

While GAVE encompasses approximately 4 % of all upper gastrointestinal, non-variceal bleeding etiologies, it remains a condition that is difficult to treat and often associated with profound iron deficiency anemia. Despite thermal therapy with APC being a first-line treatment strategy, this systematic review and meta-analysis demonstrated EBL is associated with a higher rate of ectasia eradication, greater increase in post-procedure hemoglobin, and lower rate of rebleeding. This greater endoscopic success rate was accomplished with fewer treatment sessions as well, with no difference in adverse events compared to APC. Based upon these results, EBL appears to be a safe and effective primary and refractory therapy for the treatment of GAVE.

First described by Rider and colleagues in 1953, GAVE remains a challenging condition to successful treat, with many patient remaining transfusion dependent despite iron supplementation [7]. As the precise etiology of GAVE remains uncertain, multiple treatment modalities have been attempted. While pharmacotherapy has been shown to be ineffective for GAVE, endoscopic management, most commonly with thermal-based therapies such as APC and, less commonly, RFA have traditionally been the preferred treatment modality [47–51]. Yet, based upon this recent systematic review and meta-analysis, EBL appears to be an effective therapy for GAVE.

Available evidence has shown endoscopic treatment of GAVE with RFA may have a better efficacy and tolerability as compared to APC, perhaps due to the difference in thermal technique [17, 18]. Application of RFA involves high frequency alternating electrical current delivered locally to tissue which may provide a more controlled depth of thermal coagulative necrosis, as compared to APC which is a non-contact technique with more variable depth of coagulation [50, 52]. However, given the submucosal involvement of GAVE, it would therefore make sense that EBL may provide better or equivalent outcomes and improved endoscopic success, along with fewer treatment sessions required.

These findings, including higher operator-reported endoscopic success, fewer endoscopic treatment sessions required, lower adverse event rates, and familiarity with the band ligation device, suggest EBL may be a more cost-effective therapy for patients with GAVE. However, at this time, there is no cost-ef-
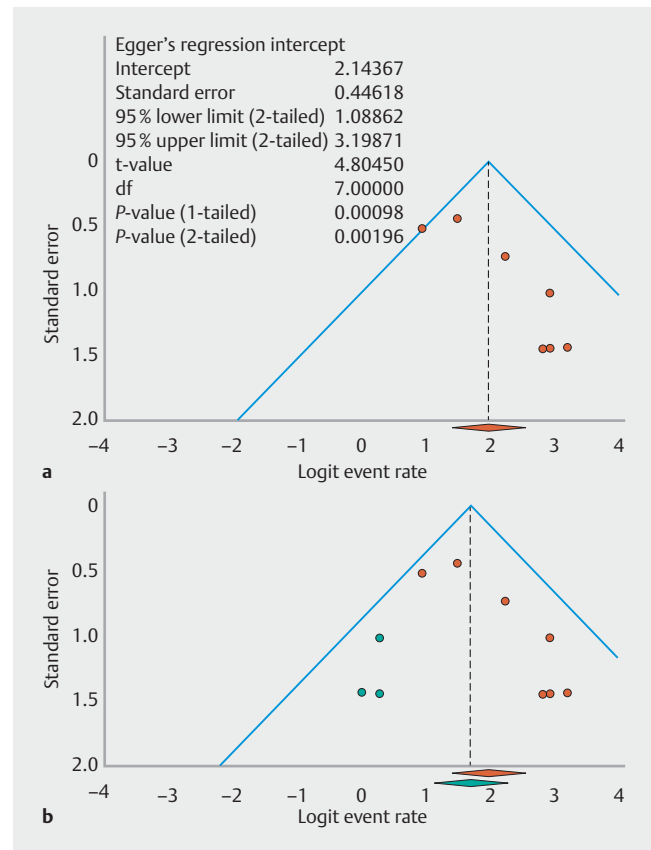
► **Fig. 4** **a** Funnel plot of publication bias and egger's regression test for included studies. **b** Duval and Tweedie's trim and fill method to assess publication bias.

fectiveness data to support this claim. Conventionally, EBL has been considered a salvage therapy, for individuals that may not response to prior treatment with APC. While 37.80 % of patients included in this meta-analysis had GAVE that was refractory to APC, a majority of patients received EBL therapy without prior thermal treatment, perhaps suggesting EBL may be considered an early treatment option for GAVE. One randomized study of 30 participants is underway comparing EBL versus APC for treatment of GAVE (NCT01601639) [53]. However, future, higher-powered randomized studies are needed to directly compare EBL versus APC, as well as RFA among patients with both treatment-naive and refractory GAVE.

A previous meta-analysis, including a total of five studies (n = 207 patients – EBL: 93 patients vs APC: 114 patients) has recently been published on this topic [54]. While this study included fewer studies and shorter duration of follow-up, these authors found similar results regarding the effectiveness of EBL vs APC, including significantly lower transfusion requirements and treatment sessions required to achieve eradication with no differences in adverse events. However, among EBL and APC patients with comparable pre-treatment hemoglobin levels, we found EBL to be associated with a significantly greater increase in post-procedure hemoglobin, different from the previous meta-analysis and likely a result of greater power associated with our study. In this current manuscript, we also com-

pared baseline characteristics of EBL and APC patients and found no differences in age, gender, percentage of patients with cirrhosis, number with overt gastrointestinal hemorrhage, and duration of follow-up, thereby improving the interpretability and generalizability of our findings.

In this systematic review and meta-analysis, we performed additional regression analyses to determine if EBL outcomes differed based upon prior APC therapy. Importantly, based upon our regression analyses, we found no statistically significant differences in endoscopic success, change in hemoglobin, or adverse events among studies that included patients with and without APC-refractory GAVE. It should be noted that there was a trend toward greater improvement in post-EBL hemoglobin among treatment naïve patients ($P = 0.060$) and treatment naïve patients showed a significantly greater reduction in transfusion requirements compared to APC-refractory patients. Despite this, these results should be interpreted with some caution given the lack of individualized data reported and need for dedicated studies to examine this critically important clinical question.

This systematic review and meta-analysis is not without limitations. Firstly, given the cumulative nature of this systematic review and meta-analysis, as well as the variability in type of GAVE and comorbid conditions of patients, it is not surprising heterogeneity was significant for multiple study outcomes. Unfortunately, regression analyses could not be performed to identify if factors such as presence or absence of cirrhosis, acute hemorrhage, type or severity of GAVE (watermelon stomach versus honeycomb appearance), as well as a nodular or flat appearance may impact treatment strategies. Furthermore, observational studies were included alongside randomized trials – introducing the possibility of selection bias and confounding – however, sensitivity analyses were performed for only randomized controlled studies. Additionally, significant variability was noted between study authors' definitions of eradication and subjective visual evidence of endoscopic improvement (i.e., endoscopic success). This variability and lack of standardization in outcome underscores the need for a well-defined clinical or endoscopic grading system; however, objective measures regarding clinical outcomes such as hemoglobin level, transfusion requirements, and adverse events were also reported. While a histologic grading system has been established for GAVE, this is not routinely used in clinical practice and was not reported in the included studies [55, 56]. Lastly, it should be emphasized these results are reported as ORs and not as relative risk, which may overestimate our findings [57].

Despite these limitations, our study has several strengths. Chiefly, this systematic review and meta-analysis is the first to analyze EBL for the treatment of GAVE, and directly compares outcomes to APC among a population of patients that are similar. Additionally, given the familiarity of endoscopists with band ligation for esophageal variceal treatment, there is a minimal learning curve to expand this treatment to GAVE. Furthermore, the inclusion of patients with previous APC may actually under-estimate the true effectiveness of EBL. Lastly, inclusion of endoscopic and clinical outcomes including hemoglobin, transfusion dependency, as well as number of sessions for treatment are highly relevant for clinicians and readily translate to real-world clinical practice.

Conclusions

Based upon the results of this systematic review and meta-analysis, EBL is a safe and effective modality for the treatment of GAVE. Comparing this strategy to traditional thermal therapy, EBL was associated with a higher endoscopic success rate and improved clinical success including a greater increase in hemoglobin, reduction in transfusion dependency, and decreased rate of rebleeding. Ultimately, the endoscopic and clinical success of EBL suggest an emerging role for the use of this modality in patients with GAVE.

Acknowledgements

Competing interests

The authors declare that they have no conflict of interest.

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