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REVIEW ARTICLE

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Endoscopic band ligation compared to thermal therapy for gastric antral vascular ectasia: A systematic review and meta-analysis

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Abstract

Background: Gastric antral vascular ectasia is an infrequent cause of gastrointestinal-related blood loss manifesting as iron-deficiency anemia or overt gastrointestinal bleeding, and is associated with increased healthcare burdens. Endoscopic therapy of gastric antral vascular ectasia most commonly involves endoscopic thermal therapy. Endoscopic band ligation has been studied as an alternative therapy with promising results in gastric antral vascular ectasia.

Aims: The primary aim was to compare the efficacy of endoscopic band ligation and endoscopic thermal therapy by argon plasma coagulation for the management of bleeding gastric antral vascular ectasia in terms of the mean post-procedural transfusion requirements and the mean hemoglobin level change. Secondary outcomes included a comparison of the number of sessions needed for cessation of bleeding, the change in transfusion requirements, and the adverse events rate.

Methods: PubMed, Medline, SCOPUS, Google Scholar, and the Cochrane Controlled Trials Register were reviewed. Randomized controlled clinical trials and retrospective studies comparing endoscopic band ligation and endoscopic thermal therapy in bleeding gastric antral vascular ectasia, with a follow-up period of at least 6 months, were included. Statistical analysis was done using Review Manager.

Results: Our search yielded 516 papers. After removing duplicates and studies not fitting the criteria of selection, five studies including 207 patients were selected for analysis. Over a follow-up period of at least 6 months, patients treated with endoscopic band ligation had significantly lower post-procedural transfusion requirements (MD −2.10; 95% confidence interval (−2.42 to −1.77)) and a significantly higher change in the mean hemoglobin with endoscopic band ligation versus endoscopic thermal therapy (MD 0.92; 95% confidence interval [0.39–1.45]). Endoscopic band ligation led to a fewer number of required sessions (MD −1.15; 95% confidence interval [−2.30 to −0.01]) and a more pronounced change in

transfusion requirements (MD −3.26; 95% confidence interval [−4.84 to −1.68]). There was no difference in adverse events.

Conclusion: Results should be interpreted cautiously due to the limited literature concerning the management of gastric antral vascular ectasia. Compared to endoscopic thermal therapy, endoscopic band ligation for the management of bleeding gastric antral vascular ectasia led to significantly lower transfusion requirements, showed a trend toward more remarkable post-procedural hemoglobin elevation, and a fewer number of procedures. Endoscopic band ligation may improve outcomes and lead to decreased healthcare burden and costs.

KEYWORDS
argon plasma coagulation, band ligation, gastric antral vascular ectasia, hemostasis, transfusion

INTRODUCTION

Gastric antral vascular ectasia (GAVE) is a pathological condition of the stomach antrum characterized by chronic blood loss. Histologically it is described by ectatic mucosal capillaries in the antrum, which lends a red, streaky appearance to the antral mucosa, and hence is often called "watermelon stomach."

It is associated with multiple chronic medical conditions, including liver, kidney, cardiac, and connective tissue diseases.[1,2] Whereas it classically manifests as iron-deficiency anemia due to chronic gastrointestinal (GI) blood loss, overt GI bleeding is also sometimes seen, accounting for up to 4% of non-variceal upper GI bleeding.[3]

Management of blood loss secondary to GAVE is primarily endoscopic. Endoscopic thermal therapy (ETT) has been found to be successful, with argon plasma coagulation (APC) and electrocautery with heater probe historically being used for this purpose. APC has been the mainstay treatment of GAVE, but is often limited by recurrence of bleeding.[4] More recently radiofrequency ablation (RFA) and endoscopic band ligation (EBL) have also been performed with promising results.[5,6] A recent meta-analysis on short-term data showed that RFA has comparable efficacy and tolerability compared to APC and is also effective in cases refractory to APC.[7] However, compared to APC and RFA which only provide superficial mucosal therapy, EBL remains the only modality that involves deep submucosal therapy and is thought to achieve better outcomes.[8] In addition to being safe, EBL requires less endoscopic expertise, is more widely available, and is thought to be cheaper than APC and EBL.[8,9] No meta-analyses have compared the use of APC and EBL for GAVE management.

Initial case reports documenting the management of GAVE with EBL were published in 2006.[10,11] In recent years, studies have compared the efficacy of APC versus EBL, including head-to-head, prospective trials. While all studies concluded that EBL is safe and effective in the management of EBL, some studies mention its superiority over ETT in terms of lower transfusion requirements. In fact, in the pediatric population a randomized controlled trial (RCT) showed that, compared to ETT, EBL was associated with fewer sessions, shorter procedure times, less hospitalizations, and a lower rate of GAVE recurrence.[12]

The purpose of this meta-analysis was to identify comparative studies performed in adult patients comparing the efficacy of EBL to that of ETT in the management of GI blood losses related to GAVE.

METHODS

Inclusion and exclusion criteria

RCTs and retrospective studies comparing EBL and ETT in bleeding GAVE were included in this meta-analysis. All selected studies had a follow-up period of at least 6 months, and compared the change in hemoglobin (Hb) levels after therapy, number of transfusions, the change in transfusion requirement after therapy, and the number of sessions needed for eradication of GAVE. Additionally, the adverse event (AE) rate and the change in hospitalization rate were also evaluated in some included articles. Studies published in abstract form, those that did not include the outcomes of interest, pediatric studies, and those published in a language other than English were not included.

Search strategy and data sources

Our search was performed across PubMed, Medline (via OVID), SCOPUS, Google Scholar, and the Cochrane Controlled Trials Register, since initiation until 7 April 2020, without any language restrictions. Search keywords included “gastric antral vascular ectasia,” “GAVE,” “watermelon stomach,” “vascular ectasia of the stomach,” “band,” and “ligation,” as Medical Subject Headings (MeSH) and free text terms. Root variations of these keywords were used in an attempt to improve search outcomes. Since the literature assessing our outcome of interest is limited, we used broad keywords to expand our search outcomes. Additionally, we individually reviewed the references of selected studies to increase our search yield.

Study outcomes

The primary aim was to compare the efficacy of EBL and ETT in terms of the mean post-procedural transfusion requirements and mean Hb level change. Secondary outcomes included a comparison of the number of sessions needed for cessation of bleeding from GAVE, the change in transfusion requirements, as well as the AE rate between both study arms.

Of note, mean Hb change was calculated as the difference between mean Hb levels before and after the procedure in each study arm. The same applied to mean transfusion change.

Study selection

Titles and abstracts of all retrieved articles were reviewed for eligibility for inclusion in our meta-analysis. The investigators collected study characteristics on standardized data sheets after full-text assessment. The senior author addressed discrepancies and made the final decision to whether include or exclude a study. This manuscript follows the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) agreement reporting guidelines and the flow diagram for study selection is summarized in Figure 1.

Data extraction

Our literature search identified 21 studies in English, and so full-text review of these selected studies was performed. Characteristics of the studies—first author, year of publication, study design, number of participants, inclusion criteria, and outcomes of interest—were extracted after identifying all relevant articles.

Statistical analysis

In this meta-analysis, we followed the PRISMA criteria. Analysis was performed using Review Manager 5.3 (RevMan, The Cochrane Collaboration), and odds ratios (ORs) with 95% confidence intervals (CIs) were evaluated for the quantitative analyses of all outcomes. Moreover, means and mean difference (MD) were compared for continuous outcome variables with a 95% CI. The χ^2 test and I^2 statistic were used to assess statistical heterogeneity among trials. The I^2 statistic reflects the percentage of variation between studies due to heterogeneity rather than chance only, with values ranging from 0% (no heterogeneity) to 100% (maximal heterogeneity). An $I^2 > 50\%$ and a p-value of <0.1 for the χ^2 were considered as markers of significant heterogeneity.

We planned subgroup and sensitivity analysis in advance, and used the random-effects method for conducting this meta-analysis. Subgroup analysis was performed for all primary outcomes based on the following criteria: (a) studies with average sample age ≥60 versus <60, (b) those with a sample size ≥40 patients versus <40 patients, (c) studies in which endoscopies were done at intervals ≤2 weeks versus >2 weeks, and (d) prospective studies versus retrospective studies. The risk of bias among studies was evaluated using Review Manager (RevMan, The Cochrane Collaboration) risk assessment tool for RCTs, and the NewcastleOttawa scale (NOS) for

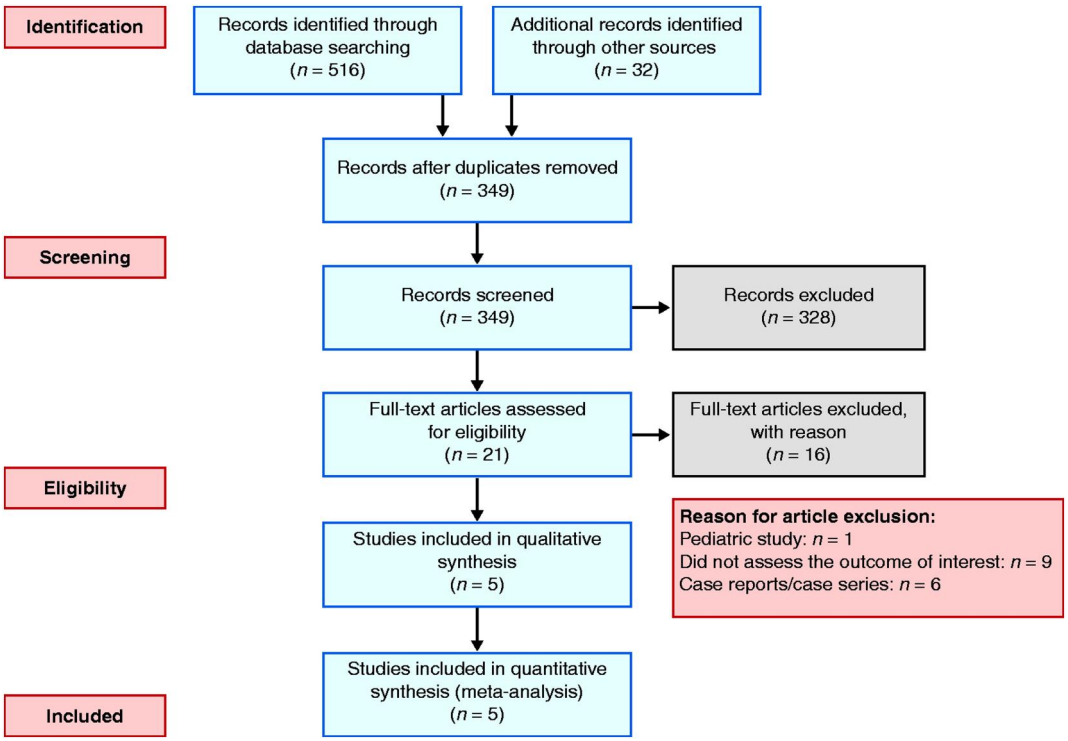

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow chart of the literature search

non-randomized studies.[13] The Review Manager risk assessment tool accounts for selection, performance, detection, attrition, and reporting bias, in addition to any other potential source of bias. The NOS takes into consideration selection, comparability, and outcome bias. Sensitivity analysis was done by stratifying studies with unclear or high risk of any type of bias versus studies with low risk of bias, regardless of study design. Given the small number of studies, a funnel plot could not performed to evaluate publication bias, however, publication bias was likely minimal given our extensive literature review.[14]

RESULTS

Literature search

Our literature search yielded 349 publications. These were screened based on their title and abstract, and 21 articles met our initial inclusion criteria. Of these, 16 articles were excluded, as they were case reports or case series ($n = 6$), did not assess our outcome of interest ($n = 9$), or were performed in the pediatric population ($n = 1$). Therefore, five studies were selected for analysis.[6,13,15–17] A summary of the study selection process is available in Figure 1.

Characteristics of selected trials

Studies included in this meta-analysis had different designs, inclusion criteria, and primary outcomes of interest. Of the selected studies, three were retrospective cohort trials and two were randomized control trials. All studies included patients with GAVE and subsequent evidence of blood loss, excluding those with anemia attributable to other reasons. Cirrhosis was not a prerequisite for inclusion, however, most included patients across the five studies had reported portal hypertension. There was no difference in gender distribution among the study arms in individual studies, however, the average patient age in three studies was ≥60 years.[4,16,17] Pre-procedure Hb levels were not statistically different between patients in both arms in individual studies. Patient stratification based on Child-Turcotte-Pugh (CTP) scores was not performed in all studies, however, from the available data, there was no statistically significant difference in terms of CTP scores between the EBL and ETT arms in individual studies. None of the included studies compared outcomes in cirrhotic and non-cirrhotic patients. Most included patients undergoing EBL in the five studies were previously treated with ETT. Except for one study where the use of proton pump inhibitors (PPI) was not reported,[6] patients were placed on PPI for at least 1 week after the EBL or ETT. All studies used APC with a 60 W power and argon gas flow of 2 L/min, ablating lesions in a distal to proximal fashion. A thermal probe was applied for ETT in one study only, in two patients as a supplement to APC, and in one patient as the only therapy.[4] Intervals of repeat endoscopy ranged between 1 and 6 weeks depending on the studies, with endoscopies performed as needed in the interim for bleeding. The number of bands placed in a single procedure was not reported for all studies, however, when reported, it ranged from 6-18 bands. The pooled average follow-up period was 10.6 months with a range between 6 and 26 months.

Regarding individual study primary outcomes, all of them aimed at comparing the efficacy of EBL and ETT, however, the definition of efficacy varied between studies. The mean post-procedure number of transfusions, and the number of sessions required to obliterate GAVE were reported in all five studies. Mean Hb levels, mean change in Hb, mean change in transfusions, AE rate, and post-procedure hospitalizations were not assessed by all studies. Reported AEs were all mild including nausea, abdominal distention, and discomfort.

The pooled number of included patients was 207, out of which 93 underwent EBL and 114 received ETT.

Our assessment of the included studies for possible bias using the Review Manager risk assessment tool and NOS, yielded a higher risk of comparability and outcome bias in two of the five studies (Table S1). The two RCTs had a higher risk of performance and detection bias (Figure S6). All non-RCTs had a score of six or more on the NOS, which implies that it is less likely that results of the meta-analysis are explained by bias. Despite the high quality of the studies reflected by the high NOS score, two of the six studies had at least one component of bias, so we performed our sensitivity analysis accordingly. Outcome bias based on adequacy of follow-up was detected in one study.[15] Comparability bias, which is minimized by matching study patients or by adjusting for confounders in data analysis, was evident in two studies.[15,16] The characteristics of the selected studies are summarized in Table 1.

Primary outcomes

Post-procedure transfusion requirements

All five studies looked at post-procedure transfusion requirements, however, only four could be analyzed, as one study had missing data (standard deviations). Overall, 173 subjects were included in this analysis. Our meta-analysis showed that over a follow-up period of at least 6 months, patients treated with EBL had significantly lower post-procedural transfusion requirements with a mean of 1.9 transfusions compared to 4.60 in those in ETT group, with a mean difference of around two transfusions (MD −2.10; 95% CI [−2.42 to −1.77]) (Figure 2a). Heterogeneity was not significant with an I^2 of 0% and p-value of 0.73. Among the subgroup analyses performed, a statistically significant difference between EBL and ETT was only noted in studies with patients of average age <60, studies including ≥40 patients, and those with a prospective design (MD −2.09; 95% CI [−2.42 to −1.76]) (Figure S1a). Regardless of the time interval between endoscopies (≤2 weeks vs. >2 weeks), EBL showed statistically significant lower transfusion requirements (Figure S1a). Our sensitivity analysis showed that in studies with a higher risk of bias, patients undergoing EBL required significantly a lower number of post-procedural transfusions compared to those undergoing ETT (Figure S2).

TABLE 1 Characteristics of selected trials

Study	Design	Inclusion criteria	Exclusion criteria	*N*	Cirrhotic patients	Mean patient age		Females		PPI after procedure	Prior ETT in EBL patients (n/N)	Repeat EGD	Mean follow-up
						EBL	ETT	EBL (n/N)	ETT (n/N)				
Abdelhalim 2014	RCT	Adults Bleeding GAVE Cirrhosis/portal hypertension	Age <18 years Bleeding not from GAVE	40	40	55.6	57.1	11/20	10/20	Yes	N/a	Every 3 weeks until improved If bleeding in the interim 6 months after achieving complete ablation	6 months
Elhendawy 2015	RCT	Adults Bleeding GAVE Cirrhosis/portal hypertension	Age <18 years Bleeding not from GAVE	88	88	51.4	53.1	25/44	29/44	N/a	9/44	Every 2 weeks until improved At 6 months	6 months
Keohane 2013	Retrospective cohort	Adults Bleeding GAVE	Age <18 years Bleeding not from GAVE	23	N/a	70.4	75.9	6/8	11/15	Yes	6/8	N/a	26 months
Sato 2011	Retrospective cohort	Adults Bleeding GAVE Portal hypertension	Age <18 years Bleeding not from GAVE	34	32	68.5		6/12	13/22	Yes	6/12	Weekly until improved	15.9 months
Wells 2008	Retrospective cohort	Adults Bleeding GAVE	Age <18 years Bleeding not from GAVE	22	10	70.4	75.9	4/9	8/13	Yes	4/9	Every 4-6 weeks If bleeding in the interim If warranted by treating physician	13 months

Abbreviations: EBL, endoscopic band ligation; EGD, esophagogastroduodenoscopy; ETT, endoscopic thermal therapy; GAVE, gastric antral vascular ectasia; PPI, proton pump inhibitors; RCT, randomized controlled trial.

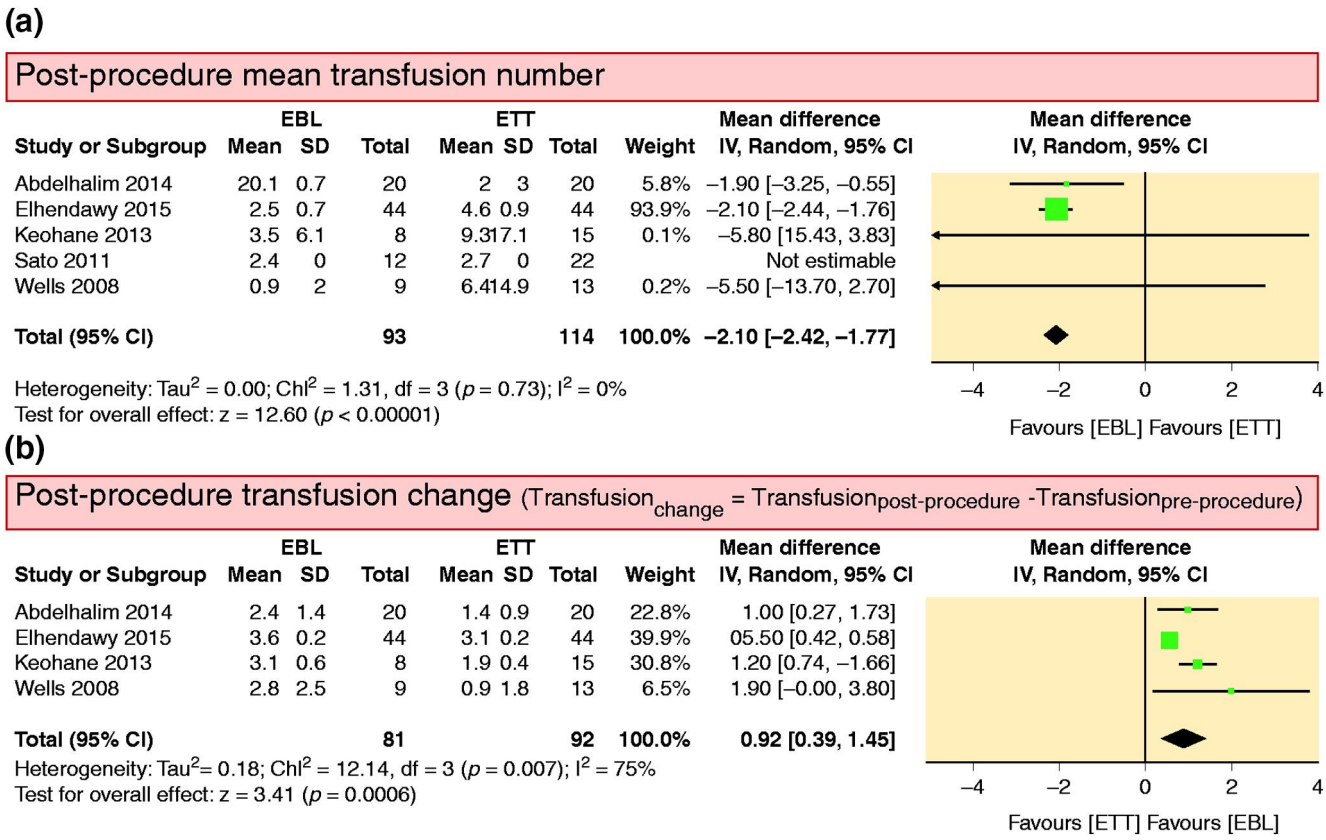

FIGURE 2 Forest plot comparing post-procedural (a) transfusion requirements and (b) hemoglobin (Hb) change between EBL and ETT. CI, confidence interval; EBL, endoscopic band ligation; ETT, endoscopic thermal therapy; SD, standard deviation

Post-procedure Hb change

Hb change was evaluated in four studies, with a total of 173 patients. The analysis showed that patients undergoing EBL had a more pronounced change in Hb after the procedure that was almost 1 gm/dl higher than the change seen with ETT (MD 0.92; 95% CI [0.39–1.45]). The mean postprocedure Hb change in the EBL group was 3.16 compared to 2.22 in the ETT counterpart. Heterogeneity was remarkable with I^2 of 75% and p-value of 0.007 (Figure 2b).

Subgroup analyses showed statically significant results favoring EBL over ETT, regardless of subgroup stratification (Figure S3). Sensitivity analysis only showed statistically significant outcomes favoring EBL over ETT in studies with a component of bias, while studies with a lower risk of bias did not show any statically significant difference between the two study arms (Figure S4).

Secondary outcomes

Sessions required to obliterate GAVE

All studies evaluated the number of sessions required to obliterate GAVE. A total of 207 patients were included in this analysis. Patients undergoing EBL required less sessions (mean 2.63) to achieve obliteration of GAVE compared to those undergoing ETT (mean 3.83) with a mean difference of −1.15 sessions (MD −1.15; 95% CI [−2.30 to −0.01]; I^2 92%, $p < 0.001$) (Figure 3a). Heterogeneity was remarkable and as a result, sensitivity analysis was performed, revealing a statistically significant difference in the number of sessions required only in studies with a higher risk of bias, while those with a lower risk of bias showed no difference (Figure S5).

Post-procedure change in transfusion requirements

The change in transfusion requirements after the procedure was only evaluated in three studies with a total of 80 subjects. The mean change in transfusion requirements for patients in the EBL arm was −6.2 compared to −1.78 for patients in the ETT group. The analysis showed that patients in the EBL arm had a significantly higher change in transfusion requirement, with a mean difference of 3.26 (MD −3.26; 95% CI [−4.84 to −1.68]; I^2 19%, $p = 0.29$), compared to those undergoing ETT (Figure 3b).

AE rate

The AE rate was only assessed in three studies which included a total of 133 included patients. The majority of reported AEs were mild and included abdominal pain, distention, nausea, vomiting, and fever.

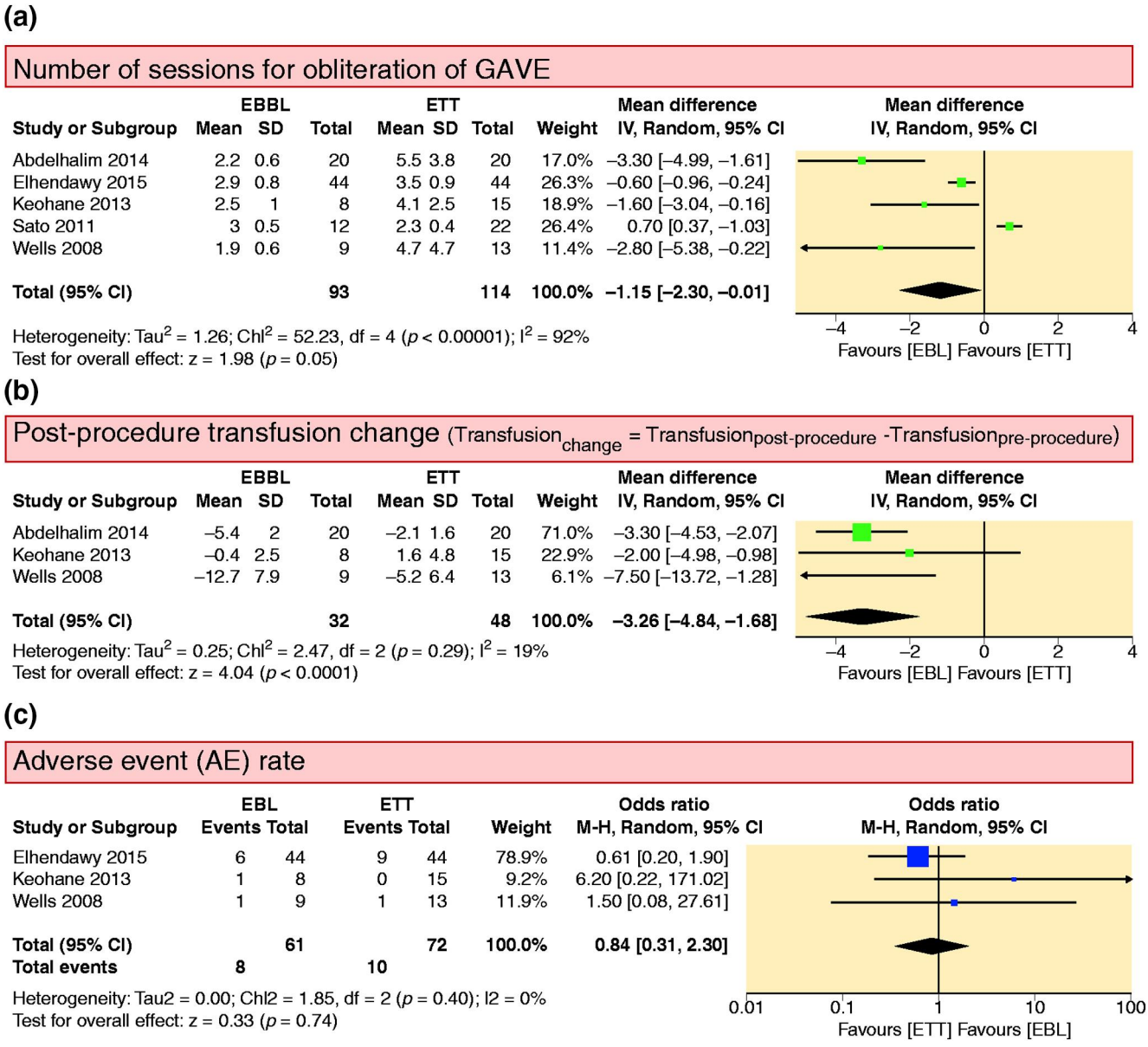

FIGURE 3 Forest plot comparing (a) the number of sessions required to obliterate gastric antral vascular ectasia (GAVE), (b) the change in transfusion requirements after the procedure, and (c) adverse event (AE) rate between EBL and ETT. CI, confidence interval; EBL, endoscopic band ligation; ETT, endoscopic thermal therapy; SD, standard deviation

There was only one reported case of immediate post-procedural bleeding requiring repeat endoscopy.[4] There was a total of eight AEs reported in the EBL group and 10 in the ETT group with no statistical difference between patients in the two arms (OR 0.84; 95% CI [0.31–2.30]; I^2 0%, $p = 0.40$) (Figure 3c).

DISCUSSION

This systematic review and meta-analysis suggests that over a follow-up period of at least 6 months, the use of EBL compared to ETT for the management of GAVE associated with GI blood loss and anemia led to an average of two fewer blood transfusions with a remarkable change in transfusion requirements, a trend towards a greater change in post-procedural Hb and a lower number of required sessions to obliterate GAVE. There was no difference in AEs between the two groups.

Five studies were included and the metrics used to compare efficacy differed between them. The number of post-procedure transfusions required, the change in transfusion requirements, Hb levels after the procedure, change in Hb levels, and number of sessions required were the most commonly evaluated criteria to define efficacy. Only two studies evaluated interval bleeding between procedures and GAVE recurrence. Given (a) the lack of a universally used efficacy metric, (b) the absence of a statistically significant difference in the preprocedural transfusion requirements between EBL

and ETT in each individual study, and (c) since the number of post-procedure transfusions and the change in Hb pre- and post-procedure were mentioned in all studies, we opted to use the latter two metrics (post-procedural transfusions and change in Hb) to reflect the efficacy of the procedure. In addition, we reviewed the literature about GI angiodyspla-sias which are vascular malformations like GAVE, that similarly result in slow occult bleeding. Most studies used transfusion requirements and the change in Hb levels as markers to assess interventional efficacy.[18]

We postulated that the number of sessions required to obliterate GAVE was not an optimal criterion to assess efficacy. The first reason being that included studies had variable time intervals between endoscopies, leading to the possibility of more GAVE recurrence and bleeding in studies with longer intervals. Another reason is the potential for more interventions required to eradicate GAVE in studies with a shorter interval between procedures. In retrospect, and after reviewing our results, we think that the varying intervals between endoscopies in different studies did not impact the primary outcomes and the number of sessions required as the ranges of results were not significantly large.

Moreover, procedural methods between study groups could be expected to vary, making it difficult to provide an objective assessment of efficacy. Although four studies reported post-procedure Hb levels, we postulated that the absolute value of the Hb was less useful as a marker of efficacy. Rather, we thought that the change in Hb from pre-to post-procedure ($Hb_{change} = Hb_{post\text{-}procedure} - Hb_{pre\_procedure}$) was a more realistic measure of efficacy.

With respect to post-procedure transfusions requirements, subgroup analysis only showed a statistically significant difference between EBL and ETT in studies with an average age <60 years, studies with ≥40 patients, and those with a prospective design. Of note, and by coincidence, the same two prospective studies happened to include ≥40 patients with average age <60.[6,15] Among the three remaining retrospective, small-sized studies, any difference between the two study arms was likely limited by the small number of pooled patients. In addition, sensitivity analysis showed a difference between EBL and ETT only in studies with a higher risk of bias. However, we would like to note that this was limited by the available literature and by the fact that the two available RCTs were non-blinded. In addition, in the lower risk of bias group, only two small studies were included, and the analysis was effectively performed on one study as the other one had non-estimable outcomes due to the lack of reported standard deviations.

Regarding post-procedure Hb change and the number of sessions required, the analysis was limited by the remarkable heterogeneity, which is likely secondary to the difference in methods between the studies. This assumption was also supported by the sensitivity analysis showing that only studies with a higher risk of bias favored EBL in terms of a more remarkable Hb change and a lower number of sessions. Unfortunately, due to the scarce literature, both heterogeneity and the potentially higher risk of bias in included studies remained a limiting factor of this analysis.

As for the difference in transfusion requirements before and after the procedure, the data is limited by the small number of included patients, but the results suggest a decrease in the number of transfusions needed after EBL versus ETT.

This is the first systematic review and meta-analysis evaluating five head-to-head trials comparing EBL and ETT in GAVE, comprising 207 patients followed for at least 6 months. In the absence of large, well designed RCTs comparing the efficacy of both techniques, our study provides a pooled analysis of the currently available data. In fact, the study results are in line with the currently available RCTs, suggesting that the fairly under-utilized EBL procedure may be more effective than ETT, at least in terms of the post-procedural transfusion requirements and possibly the number of sessions needed for complete eradication of the GAVE. Unfortunately, the limited literature and the lack of large prospective trials have limited the use of EBL in the management of GAVE for salvage therapy in refractory GAVE. In our experience, it seems that ETT and specifically APC are more commonly used despite being more expensive, not as widely available, and offering limited superficial therapy. Theoretically, EBL is thought to have a deeper effect involving the submucosa, leading to fibrosis and potentially longer effects with less recurrence.[8]

Nonetheless, as previously mentioned, this meta-analysis is limited by the small number of pooled patients. In addition, our analyses were limited by the different methodologies, reflected with high heterogeneity, and also by the difference in the reported outcomes between studies. In fact, the occurrence and timing of bleeding in the interval between procedures would have been more objective outcomes of interest to compare efficacy, but those were not reported in any adult study. Additionally, individual studies lacked a comparison of outcomes between cirrhotic versus non-cirrhotic patients, and did not stratify patients according to prior therapy for GAVE (i.e. treatment naïve, exposed (prior ETT), or refractory to ETT). Also, the included studies are limited by a short follow-up period. The durability of the response over a long period would be another potentially significant marker of efficacy, especially in light of a recent study reporting up to 44% recurrence of GAVE within 2 years of clinical response to therapy with EBL.[19]

In conclusion, EBL appears to be both safe and effective in the management of GAVE-related blood loss. The limited literature suggests that compared to ETT, the use of EBL was associated with significantly lower transfusion requirements, and showed a trend towards more encouraging post-procedural Hb changes and lower number of procedures required to obliterate GAVE. This meta-analysis suggests that the use of EBL in the management of bleeding GAVE has the potential to reduce the healthcare burdens and costs. Those results should be interpreted cautiously until well-designed RCTs emerge to further our understanding of the short- and long-term efficacy of EBL in the management of GAVE.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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