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Combination Endoscopic Band Ligation and Sclerotherapy Compared with Endoscopic Band Ligation Alone for the Secondary Prophylaxis of Esophageal Variceal Hemorrhage: A Meta-Analysis

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Endoscopic band ligation (EBL) is the community-accepted standard therapy for the secondary prophylaxis of esophageal variceal hemorrhage. Recent data indicate that combination EBL and sclerotherapy may be a more effective therapy than EBL alone. Yet existing data are conflicting. We therefore performed a meta-analysis to compare the efficacy and safety of EBL and sclerotherapy versus EBL alone for the secondary prophylaxis of esophageal variceal hemorrhage. We performed a systematic review of two computerized databases (MEDLINE and EMBASE) along with manual-searching of published abstracts to identify relevant citations without language restrictions from 1990 to 2002. Eight studies met explicit inclusion criteria. We performed meta-analysis of these studies to pool the relative risk for the following outcomes: esophageal variceal rebleeding, death, number of endoscopic sessions to achieve variceal obliteration, and therapeutic complications. There were no significant differences between EBL and sclerotherapy versus EBL alone in the risk of esophageal variceal rebleeding (RR = 1.05; 95% CI = 0.67–1.64; $P = 0.83$), death (RR = 0.99; 95% CI = 0.68–1.44; $P = 0.96$), or number of endoscopic sessions to variceal obliteration (RR = 0.23; 95% CI = 0.055–0.51; $P = 0.11$). However, the incidence of esophageal stricture formation was significantly higher in the EBL group than in the sclerotherapy group. There is no evidence that the addition of sclerotherapy to endoscopic band ligation changes clinically relevant outcomes (variceal rebleeding, death, time to variceal obliteration) in the secondary prophylaxis of esophageal variceal hemorrhage. Moreover, combination EBL and sclerotherapy had more esophageal stricture formation than EBL alone.

KEY WORDS: meta-analysis; esophageal variceal hemorrhage; Health Services Research.

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Esophageal variceal hemorrhage is a devastating complication of portal hypertension that occurs in approximately one third of cirrhotic patients and is associated with a 30% case-mortality rate (1–4). Moreover, up to 70% of these

patients experience variceal rebleeding, which contributes to poor survival and high health-care resource utilization (1–5).

Early endoscopic therapy effectively localizes and halts the source of variceal bleeding while significantly reducing the rate of rebleeding. A recent meta-analysis reported that endoscopic band ligation (EBL) is associated with improved outcomes (rebleeding, mortality, endoscopic sessions, complications) versus endoscopic sclerotherapy in the secondary prophylaxis of esophageal variceal hemorrhage (6). Thus, EBL has emerged as the standard of care for secondary variceal hemorrhage prophylaxis (3, 4).

In initial pilot studies, investigators proposed that combination EBL and sclerotherapy may significantly decrease variceal rebleeding rates and hasten variceal obliteration versus either therapy alone (7, 8). However, subsequent randomized, controlled trials comparing EBL and sclerotherapy to EBL alone have reported conflicting results (9–16). Due to the harmful consequences of variceal hemorrhage, it is essential to decide on an optimal endoscopic therapeutic modality based on the current available evidence.

To better determine the value of adding sclerotherapy to EBL, we performed a meta-analysis of randomized clinical trials comparing EBL and sclerotherapy versus EBL alone in the *secondary prophylaxis* of esophageal variceal hemorrhage and assessed benefit and risk.

METHODS

Study Identification. We performed a structured search of two computerized bibliographic databases (MEDLINE and EMBASE) to identify publications from January 1990 to January 2002. These years were cited since the first reports of combination EBL and sclerotherapy did not appear in the medical literature until 1991. We designed the search strategy with an expert librarian to maximize search sensitivity for targeted information. The subject headings and key words incorporated into the search strategy were: esophageal and gastric varices OR esophagus varices OR [esophag* AND variceal OR varices] AND sclerotherapy OR sclerosing solutions OR sclerosing agent OR sclero* AND ligat* AND Document type = randomized controlled trials OR randomized controlled trial OR randomization OR random allocation or random* in title or subject heading. Additionally, bibliographies of included studies and key review articles were reviewed for references not captured by the search strategy. We manually searched abstracts from pertinent scientific meetings from 1990 to 2002, including American Association for the Study of Liver Diseases, American College of Gastroenterology, American Society of Gastrointestinal Endoscopy, American Gastroenterological Association, European Society of Gastrointestinal Endoscopy, British Society of Gastroenterology, and International Association for the Study of the Liver. Our search included all languages, and we employed a translator to interpret all non-English citations. Where study methodology was unclear, we contacted the authors for additional information and clarification.

Study Selection. We assessed all titles for relevancy and rejected titles only if they fulfilled prespecified, explicit exclusion criteria including the following: (1) not concerned with human subjects, (2) not related to acute esophageal variceal hemorrhage, (3) not related to endoscopic management of variceal hemorrhage, and (4) not a randomized clinical trial with original data (i.e., review, editorial, letter, practice guideline, consensus statement, case report, etc.).

During review of the complete publication of each study that passed title screening, we included any study that met all of the following inclusion criteria: (1) the study was a randomized trial comparing combination endoscopic therapy (band ligation with sclerotherapy given during the same endoscopic session) versus endoscopic band ligation alone; (2) the patient population was comprised solely of adults; and (3) the outcome measures included at least one of the following—rebleeding, mortality, complications, and endoscopic treatment sessions required for variceal obliteration.

Using a standardized screening form, two investigators (H.A.K. and I.M.G.) independently reviewed all identified studies. After independent evaluation, differences were resolved by consensus discussion, which yielded the final selection of trials for inclusion.

Data Extraction. A priori, we identified four assumptions to identify potential differences among studies. First, we determined that the combination group required both endoscopic band ligation and injection sclerotherapy during the same endoscopic session for inclusion. Second, we allowed any volume and any type of sclerosant to be used in the combination group. Third, if a separate, but similar abstract and a full manuscript by the same author appeared, the manuscript was used for the data analysis. That is, the similar abstract, including perhaps fewer patients and predating the published manuscript, was excluded. Fourth, we questioned whether the results presented in fully published manuscripts would differ systematically from results presented only in abstract form. Thus, we performed a subgroup analysis for published manuscripts versus published abstracts.

Descriptive information of subjects, study design, interventions, outcome measures, features of the analysis, and elements of trial quality (randomization, blinding, and treatment of patients, who withdrew from the trial) were extracted from articles using a standardized data abstraction form and a quality scoring form. We assessed study quality in accordance with the criteria by Jadad *et al*. (17). The Jadad scale is a standardized instrument of study quality that focuses on features related to internal validity. It is most relevant in studies of interventions for which double-blind methods are feasible (such as drug trials). The Jadad scale has been shown across a spectrum of clinical topics to characterize a study's susceptibility to bias, with studies scoring 3 or higher (on a 0–5 scale) being interpreted as higher quality (17).

Statistical Methods. For the efficacy analysis, a random-effects model was used to pool risk ratios for dichotomous outcomes, e.g., esophageal variceal rebleeding and mortality, or effect sizes for the continuous outcome number of endoscopic sessions required for variceal obliteration (18). We examined between-trial heterogeneity using a chi-square test of heterogeneity (19). The possibility of publication bias was assessed using funnel plots, a correlation test (20), and a regression asymmetry test (21). We conducted all analyses in the statistical package Stata (22). For the adverse events analysis, the total number

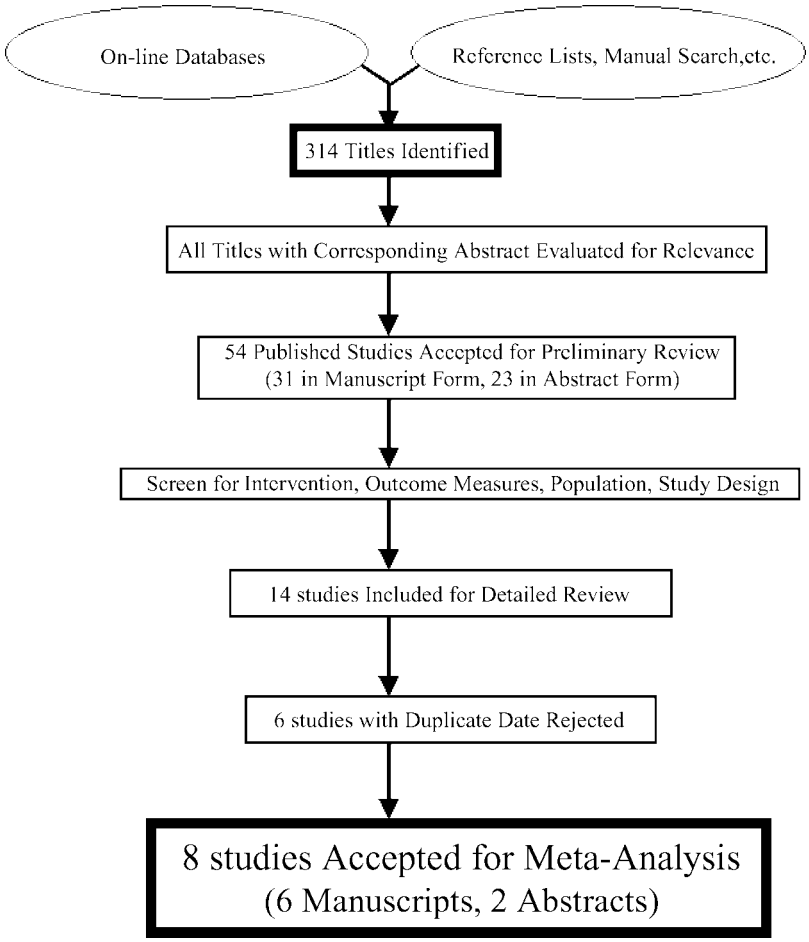

Fig 1. Literature search and review strategy algorithm. After an extensive literature review, screening, and detailed review process, eight trials fulfilled the explicit inclusion and exclusion criteria and were included for meta-analysis.

of events is presented in both groups. For the clinically most important outcome, esophageal stricture formation, we tested for a significant difference between groups by estimating an odds ratio and testing for a difference from one using the "exact" method available in the statistical package StatXact (23). The "exact" method does not require an assumption of continuity and thus a data correction if zero events are observed in a group as asymptotic methods do. Such corrections can have a major impact on the results when the outcome event is rare, as esophageal stricture formation was.

RESULTS

Study Selection and Data Collection. The search strategy identified 314 titles (Figure 1). Of these, we selected 54 for abstract review, of which 14 studies were retained for consideration. Independent review of these remaining studies yielded eight that met our explicit inclusion criteria. Of these studies, six were published manuscripts in peer-reviewed journals, and two were published in abstract form (Table 1). The final analysis described a pooled sample of 520 patients.

In the methodological assessment, five trials scored 2 points and three trials scored 1 point on the Jadad scale (mean = 1.6) (Table 2). Since it is not feasible to double blind these endoscopic interventions, 3 was the maximum attainable Jadad score.

Rebleeding. For the outcome of esophageal variceal rebleeding, three of the eight trials did not specify whether rebleeding was due to esophageal varices, gastric varices, or posthemostasis ulcers (11, 12, 16). Therefore, data from those three trials were not included in the analysis. The pooled relative risk (RR) between the EBL and sclerotherapy *versus* EBL alone was not significant (RR = 1.05; 95% CI = 0.67–1.64; $P = 0.83$) (Figure 2) for the outcome of rebleeding. Importantly, there was no significant heterogeneity across studies ($P = 0.68$) and there was no evidence of publication bias.

TABLE 1. EVIDENCE TABLE

Study 1st author (Ref. No.), year	*Type of publication*	*N*	*Patient characteristics*	*Patients with known cirrhotic portal hypertension*	*Treatment groups*	*Adequately measured outcomes of interest*	*Duration of follow-up*
Laine (9), 1996	Manuscript	41	Chronic liver disease with active esophageal variceal hemorrhage	100%	21 had EBL + 1.5% sodium tetradecyl 20 had EBL	1. Rebleeding 2. Deaths 3. Treatment sessions to eradication 4. Complications	Mean 7 months
Saeed (10), 1997	Manuscript	47	Chronic liver disease with active or recent esophageal variceal hemorrhage	100%	22 had EBL + 5% ethanolamine 25 had EBL	1. Rebleeding 2. Deaths 3. Treatment sessions to eradication 4. Complications	"Up to 30 months"
Balastos (11), 1997	Abstract	31	Cirrhosis with active or recent esophageal variceal hemorrhage	100%	15 had EBL + 5% ethanolamine 16 had EBL	1. Treatment sessions to eradication 2. Complications	Not reported
El Khayat (12), 1997	Abstract	64	Upper GI bleeding due to esophageal varices	Not reported	34 had EBL + 5% ethanolamine 30 had EBL	1. Deaths 2. Treatment sessions to eradication	Mean 7 months
Al Traif (13), 1999	Manuscript	60	Recent or active esophageal variceal hemorrhage	72%	29 had EBL + 1% polidocanol 31 had EBL	1. Rebeleeding 2. Deaths 3. Treatment sessions to eradication 4. Complications	Mean 22 months
Djurdjevic (14), 1999	Manuscript	103	Recent or active esophageal variceal hemorrhage	96%	52 had EBL + 1% aethoxysclerol 51 had EBL	1. Rebleeding 2. Deaths 3. Treatment sessions to eradication 4. Complications	Mean 14 months
Argonz (15), 2000	Manuscript	80	Recent esophageal variceal hemorrhage	100%	39 EBL + 2% polidocanol 41 EBL	1. Rebleeding 2. Deaths 3. Treatment sessions to eradication 4. Complications	Mean 12 months
Hou (16), 2001	Manuscript	94	Recent of active esophageal variceal hemorrhage	100%	47 EBL + 5% ethanolamine 47 EBL	1. Deaths 2. Treatment sessions to eradication 3. Complications	Mean 11 months

Mortality. For the outcome of mortality, one trial did not report mortality and thus was not included in the analysis (11). There was no significant difference in mortality between endoscopic therapies (RR = 0.99; 95% CI = 0.68–1.44; $P = 0.96$) (Figure 3). Again, there was no significant between-trial heterogeneity across studies ($P = 0.59$) and there was no evidence of publication bias for the outcome of mortality in the analysis.

TABLE 2. QUALITY ASSESSMENT OF RANDOMIZED CONTROLLED TRIALS RELATING TO EBL AND SCLEROTHERAPY VERSUS EBL ALONE FOR THE SECONDARY PROPHYLAXIS OF ESOPHAGEAL VARICEAL HEMORRHAGE USING THE JADAD SCALE

Study first author, year	*Randomized trial*	*Described randomization appropriately*	*Double blind*	*Described double blinding*	*Withdrawals and dropouts accounted for*	*Jadad quality score**
Laine, 1996	1	1	0	0	0	2
Saeed, 1997	1	0	0	0	1	2
Balastos, 1997	1	0	0	0	0	1
El Khayat, 1997	1	0	0	0	0	1
Al Traif, 1999	1	0	0	0	1	2
Djurdjevic, 1999	1	0	0	0	0	1
Argonz, 2000	1	1	0	0	0	2
Hou, 2001	1	1	0	0	0	2

*Poor quality score = 0–2; good quality score = 3–5 (5-point scale) (17).

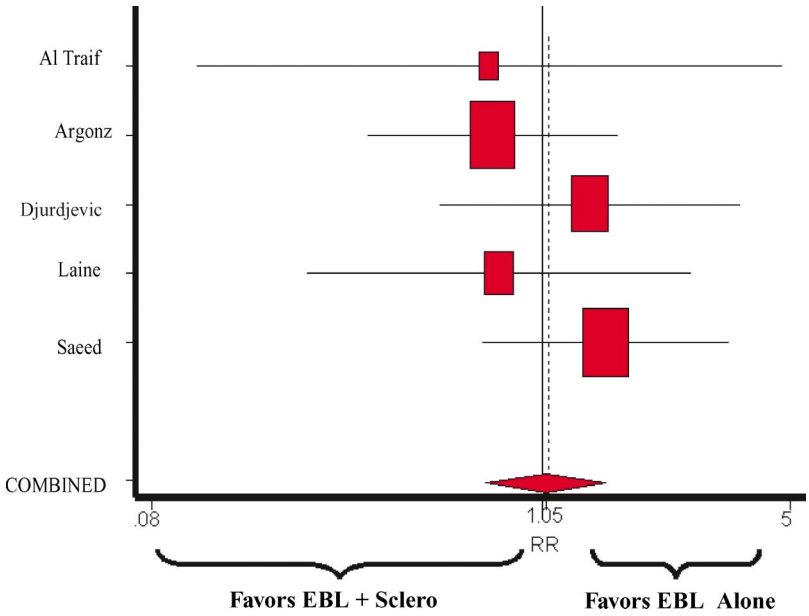

Fig 2. Rebleeding forest plot. Meta-analysis using a random effects model comparing esophageal vericeal rebleeding between EBL plus sclerotherapy and EBL alone. The summary estimate is the relative risk.

Variceal Obliteration. All eight studies reported data regarding endoscopic treatment sessions required to achieve variceal obliteration and, thus, were included in the analysis. There was no significant difference in the mean number of endoscopic sessions required to achieve variceal obliteration between EBL and sclerotherapy and EBL alone (RR = 0.23; 95% CI = 0.055–0.51; P value = 0.11) (Figure 4). However, for this outcome

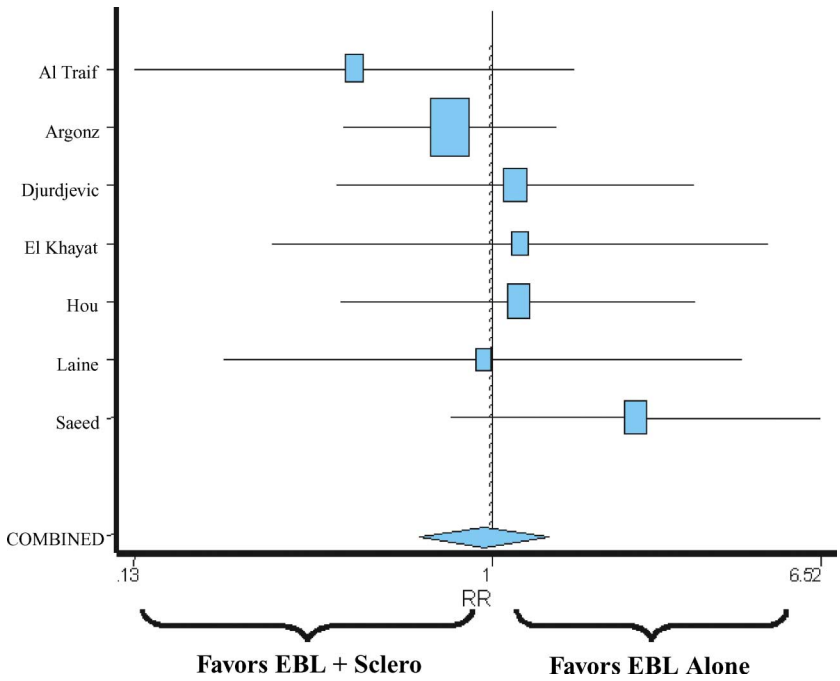

Fig 3. Mortality forest plot. Meta-analysis using a random effects model comparing mortality between EBL plus sclerotherapy and EBL alone. The summary estimate is the relative risk.

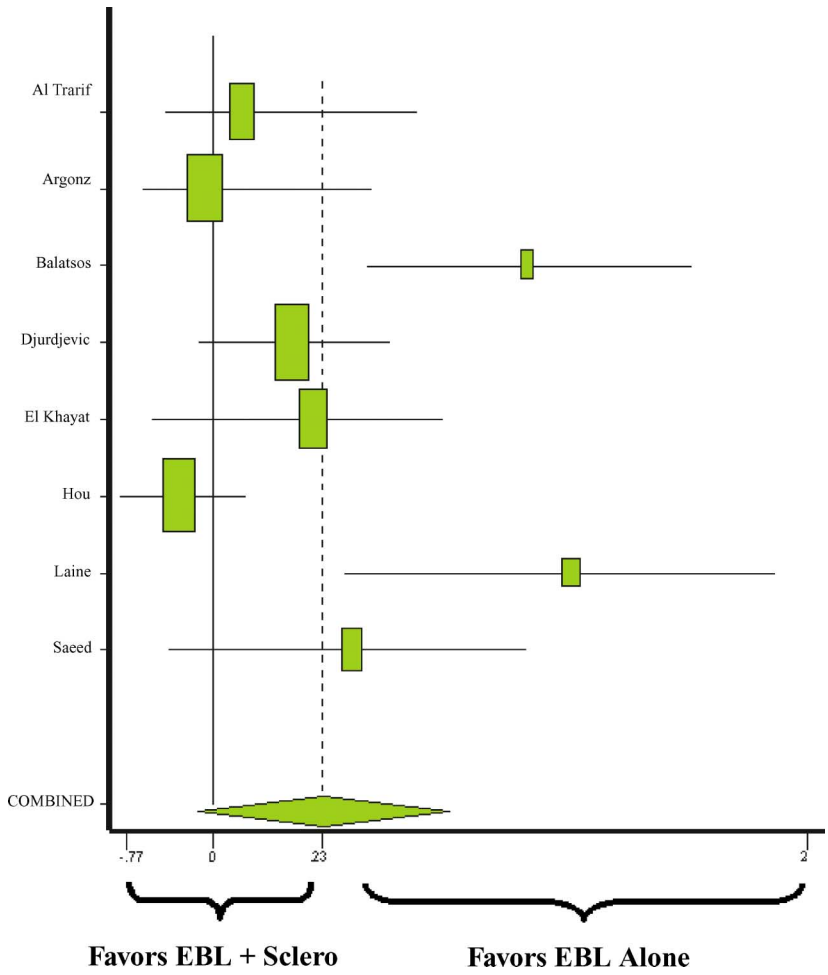

Fig 4. Variceal obliteration forest plot. Meta-analysis using a random effects model comparing the mean number of sessions required for complete esophageal vericeal obliteration between EBL plus sclerotherapy and EBL alone. The summary estimate is the relative risk.

there was significant heterogeneity demonstrated across the eight individual studies ($P = 0.01$). Even when abstracts were excluded in the sensitivity analysis, heterogeneity persisted due to the large variation among the mean number of endoscopic sessions reported in the trials.

Adverse Events. Among complications evaluated, including perforation, infection, posthemostasis ulcer bleeding, and cardiopulmonary arrest, only incidence of esophageal stricture formation differed between endoscopic therapies (Table 3). There was a higher rate of esophageal stricture formation in the combination EBL and sclerotherapy group compared with the EBL alone group. In the combination EBL and sclerotherapy group, 23 of 259 (8.9%) patients developed esophageal strictures. In contrast, only 1 patient of 261 (0.38%) developed a stricture in the EBL alone group. In our pooled analysis, this difference was statistically significant.

DISCUSSION

We found no evidence to suggest that the combination of EBL and sclerotherapy is more effective than EBL alone in the secondary prophylaxis of esophageal variceal hemorrhage. Moreover, our analysis suggests that combination EBL and sclerotherapy had more reported esophageal stricture formation. Therefore, despite the contention that combination EBL and sclerotherapy may be superior to EBL alone on the basis of therapeutic synergy, our meta-analysis does not support this.

A recent meta-analysis by Singh and colleagues also compared EBL and sclerotherapy to EBL alone (24).

TABLE 3. ADVERSE EVENTS

Adverse event	*EBL alone* (n = *261*)	*EBL + sclerotherapy* (n = *259*)
Perforation, *n*	1	1
Infection, *n*	9	9
Posthemostasis ulcer bleed, *n*	6	10
Cardiopulmonary arrest, *n*	0	1
Esophageal stricture, *n*	1	23

That study used a more limited search strategy to identify potential studies, used somewhat different inclusion/exclusion criteria (25, 26), and did not include as many studies as the analysis we report herein (16). However, the Singh meta-analysis results were similar to ours, lending convergent validity to the conclusion that combination EBL and sclerotherapy does not have evidence of superiority to EBL alone in the secondary prophylaxis of esophageal variceal hemorrhage. Although a meta-analysis cannot replace a well-designed, randomized controlled trial, it can provide a more precise estimate of clinically important outcomes than small trials limited by small sample sizes and relatively low incidences of relevant outcomes (27).

Our study has potential limitations. First, there are relatively few studies comparing these therapies, so that the power to detect differences between therapies is small. The 95% confidence intervals on our pooled estimates of effect are wide, meaning that the available data cannot exclude potentially clinically important differences between therapies. Mitigating this concern, however, is that our pooled point estimates do not suggest any difference between treatments, e.g., relative risk of 1.05 and 0.99 for variceal rebleeding and mortality, respectively. Second, there was heterogeneity in some pooled estimates, especially when combining the data for the mean number of endoscopic sessions required for esophageal variceal obliteration. The random effects model we used is designed to help account for this heterogeneity by including a term for between-study variance. Third, an issue that has received attention is that, compared to sclerotherapy, band ligation may be associated with a higher incidence of esophageal variceal recurrence after eradication. Unfortunately, we were unable to estimate rates of esophageal variceal recurrence since this outcome was not evaluated in these published studies.

Furthermore, there was limited information able to be obtained from the two abstracts included in our study. Ideally, a larger number of trials and patients would decrease the uncertainty in our overall conclusions. However, a total of 520 patients were included in this present analysis. Thus, we were able to provide overall assessments based on our pooled data.

In summary, we found no evidence that combination endoscopic therapy improved outcomes compared to sclerotherapy alone for esophageal variceal rebleeding, mortality, or sessions required for variceal obliteration. Moreover, there was a higher rate of esophageal stricture formation with the addition of sclerotherapy to endoscopic band ligation.

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REFERENCES

1. Graham DY, Smith JL: The course of patients after variceal hemorrhage. Gastroenterology 80:800–809, 981
2. The North Italian Endoscopic Club for the Study and Treatment of Esophageal Varices. Prediction of the first variceal hemorrhage in patients with cirrhosis of the liver and esophageal varices: A prospective multicenter study. N Engl J Med 319:983–989, 1988
3. Shahara AI, Rockey DC: Gastroesophageal variceal hemorrhage. N Engl J Med 345:669–681, 2001
4. Dagher L, Burroughs A: Variceal bleeding and portal hypertensive gastropathy. Eur J Gastroenterol Hepatol 13:81–88, 2001
5. Gralnek IM, Jensen DM, Kovacs TOG, *et al*.: The economic impact of esophageal variceal hemorrhage: Cost-effectiveness implications of endoscopic therapy. Hepatology 29:44–50, 1999
6. Laine L, Cook D: Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 123:280–287, 1995
7. Reveille RM, Goff JS, Stiegman GV, Stauffer JT: Combination endoscopic variceal ligation (EVL) and low-volume endoscopic sclerotherapy (ES) for bleeding esophageal varices: A faster route to variceal eradication. Gastrointest Endosc 37:243, 1991 (abstr)
8. Koutsomanias D: Endoscopic variceal ligation combined with low-volume sclerotherapy: A controlled study. Gastroenterology 102:A835, 1992 (abstr)
9. Laine L, Stein C, Sharma V: Randomized comparison of ligation versus ligation plus sclerotherapy in patients with bleeding esophageal varices. Gastroenterology 110:529–533, 1996
10. Saeed ZA, Steigmann GV, Ramirez FC, *et al*.: Endoscopic variceal ligation is superior to combined ligation and sclerotherapy for esophageal varices: A multicenter prospective randomized trial. Hepatology 25:71–74, 1997
11. Balastos V, Delis V, Germanopoulos, *et al*.: Endoscopic ligation plus sclerotherapy versus ligation alone for esophageal variceal bleeding. Endoscopy 29:E44, 1997 (abstr)

12. El Khayat HR, Omar MM, Moustafa I: Comparitive evaluation of combined endoscopic variceal ligation together with low volume sclerotherapy versus ligation alone for bleeding esophageal varices. Hepatology 26:138A, 1997 (abstr)
13. Al Traif I, Fachartz FS, Al Jumah A, *et al*.: Randomized trial of ligation versus combined ligation and sclerotherapy for bleeding esophageal varices. Gastrointest Endosc 50:1–6, 1999
14. Djurdjevic D, Janosevic S, Dapcevic B, *et al*.: Combined ligation plus sclerotherapy versus ligation alone for eradication of bleeding esophageal varices: A randomized and prospective trial. Endoscopy 31:286–290, 1999
15. Argonz J, Kravetz D, Suarez A, *et al*.: Variceal band ligation and variceal band ligation plus sclerotherapy in the prevention of recurrent variceal bleeding in cirrhotic patients: A randomized, prospective and controlled trial. Gastrointest Endosc 51:151–163, 2000
16. Hou M, Chen W, Lin H, *et al*.: A new "sandwich" method of combined endoscopic variceal ligation and sclerotherapy versus ligation alone in the treatment of esophageal variceal bleeding: A randomized trial. Gastrointest Endosc 53:572–578, 2001
17. Jadad AR, Moore RA, Carroll D, *et al*.: Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 17:1–12, 1996
18. DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 7(3):177–188, 1986
19. Hedges LV, Olkin I: Statistical Methods for Meta-Analysis. San Diego, CA, Academic Press, 1985
20. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 50(4):1088–1101, 1994
21. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by simple, graphical test. BMJ 315(7109):629–634, 1997
22. Stata Statistical Software: Release 7.0 [computer program]. College Station, TX: Stata Corporation, 2001
23. StatXact 4 for Windows [computer program]. Version 4.0.1. Cambridge, MA: Cytel Software Corporation, 2000
24. Singh P, Pooran N, Indaram A, *et al*.: Combined ligation and scerotherapy versus ligation alone for secondary prophylaxis of esophageal variceal bleeding: A meta-analysis. Am J Gastroenterol 97:623–629, 2002
25. Bhargava DK, Pokharna R: Endoscopic variceal ligation versus endoscopic variceal ligation and endoscopic variceal sclerotherapy: A prospective randomized study. Am J Gastroenterol 92:950–953, 1997
26. Lo G, Lai K, Cheng J, *et al*.: The additive effect of sclerotherapy to patients receiving repeated endoscopic variceal ligation: A prospective, randomized trial. Hepatology 28:391–395, 1998
27. Dickersin K, Scherer R, Lefebvre C: Identifying relevant studies for systematic reviews. BMJ 309:1286–1291, 1994