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META-ANALYSIS

Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: A meta-analysis

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Abstract

AIM: To compare the effect of endoscopic variceal ligation (EVL) with that of endoscopic injection sclerotherapy (EIS) in the treatment of patients with esophageal variceal bleeding.

METHODS: We performed a systematic literature search of multiple online electronic databases. Meta-analysis was conducted to evaluate risk ratio (RR) and 95% confidence interval (CI) of combined studies for the treatment of patients with esophageal variceal bleeding between EVL and EIS.

RESULTS: Fourteen studies comprising 1236 patients were included in the meta-analysis. The rebleeding rate in actively bleeding varices patients in the EVL group was significantly lower than that in the EIS group (RR = 0.68, 95%CI: 0.57-0.81). The variceal eradication rate in actively bleeding varices patients in the EVL group was significantly higher than that in the EIS group (RR = 1.06, 95%CI: 1.01-1.12). There was no significant difference about mortality rate between the EVL group and EIS group (RR = 0.95, 95%CI: 0.77-1.17). The rate of complications in actively bleeding varices patients in the EVL group was significantly lower than that in the EIS group (RR = 0.28, 95%CI: 0.13-0.58).

CONCLUSION: Our meta-analysis has found that EVL is better than EIS in terms of the lower rates of rebleeding, complications, and the higher rate of variceal eradication. Therefore, EVL is the first choice for esophageal variceal bleeding.

Key words: Esophageal variceal bleeding; Endoscopic variceal ligation; Endoscopic injection sclerotherapy; Rebleeding; Variceal eradication; Meta-analysis

Core tip: We performed a meta-analysis to evaluate risk ratio and 95% confidence interval (CI) of combined studies for the treatment of patients with esophageal variceal bleeding between endoscopic variceal ligation

(EVL) and endoscopic injection sclerotherapy (EIS). Our meta-analysis has found that EVL is better than EIS in terms of the lower rates of rebleeding, complications, and the higher rate of variceal eradication. Therefore, EVL is the first choice for esophageal variceal bleeding.

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INTRODUCTION

Esophageal variceal bleeding is the most common (as many as 30%) in all patients presenting with upper gastrointestinal tract hemorrhage[1]. Acute esophageal variceal bleeding is an intractable complication of portal hypertension. Patients with esophageal variceal bleeding have higher rates of rebleeding, complications, and death than patients with nonvariceal bleeding such as ulcer bleeding[2-5]. Traditional measures have included balloon tamponade, vasoconstrictors, and surgical intervention, but these measures did not significantly reduce the rate of rebleeding, complications and improve survival.

Endoscopic injection sclerotherapy (EIS) has been gradually applied to the management of esophageal variceal bleeding since the mid-1970s[6]. And EIS performed as the first effective measure proved to be superior to vasoconstrictors or balloon tamponade in the control of acute esophageal variceal bleeding[7-9]. However, EIS is associated with some complications such as adverse pulmonary and renal effects, esophageal ulceration, stricture, perforation, and death[10]. Complications occur in up to 40% of patients, and treatment-related death in 1% to 2%.

Endoscopic variceal ligation (EVL) was introduced in 1986[11], and it is now considered by many clinicians to be the treatment of choice for patients with esophageal variceal bleeding. In theory, this purely mechanical method of obliterating varices should produce no systemic sequelae, and since the quantity of tissue ligated is limited by the design of the device, it should also result in few complications involving the esophageal wall[12]. The incidence of complications, such as pneumonia and esophageal stricture, which were associated with EVL was very low[13,14]. Some randomized controlled trials indicated that EVL is at least as effective and safe as EIS. Now EVL has been gradually adopted to substitute for EIS in the treatment of esophageal variceal bleeding.

Some randomized controlled trials have compared EVL with EIS in terms of sessions required to achieve variceal obliteration, rebleeding rate, mortality rate and complication rate[12,15-26]. However, all of those studies comprised only a small number of patients with active variceal bleeding, and have come to conflicting conclusions.

To critically appraise and synthesize the current evidence on endoscopic therapy for esophageal variceal bleeding, we conducted a meta-analysis combining the results of randomized controlled trials that compared EVL with EIS, and thus provided a quantitative estimate of the risk of rebleeding, mortality, complications and variceal eradication.

MATERIALS AND METHODS

Literature search

We developed and adhered to a standard protocol for study identification, inclusion, and data abstraction in the conduct of this meta-analysis. We performed a systematic literature search of the following electronic databases: MEDLINE (1950-2014), EMBASE (1947-2014), Cochrane library (1993-2014), Web of Science (1900-2014), and PubMed (1950-2014). Bibliographies from relevant gastrointestinal meetings including Digestive Disease Week, The Annual Meeting of the American College of Gastroenterology, and United European Gastroenterology Week during years 2000-2014 were manually searched for relevant studies. Medical subject headings for our literature review included "esophageal varices", "esophageal variceal bleeding ", "variceal bleeding ", "endoscopic injection sclerotherapy", "EIS", "endoscopic variceal ligation", and "EVL". Citations from identified articles were then cross-referenced for completeness.

Study selection and data abstraction

Inclusion criteria included: (1) studies used a case-control, nested case-control, cross-sectional, and cohort study design; (2) the study was a randomized controlled comparison of EIS and EVL; (3) the study population was composed of patients with esophageal variceal bleeding; and (4) outcome measures were the rate of rebleeding, mortality, complications or variceal eradication.

We performed the data extraction *via* a standardized data extraction form, collecting information on the author, publication year, country, number of cases, mean age of patients in the EVL group and EIS group, Child-Pugh grade, and etiology. The outcome of the analysis was the risk ratio (RR) of rebleeding, mortality, complications or variceal eradication in the EIS group *vs* the EVL group. Study references and citations were collected in EndNote X4 software application. All studies were reviewed by two investigators (Dai C and Liu WX) to assess eligibility. The data of studies which meet our eligibility criteria were independently analyzed by two investigators. The collected information included author, publication year, country, number of cases, mean age of patients in the

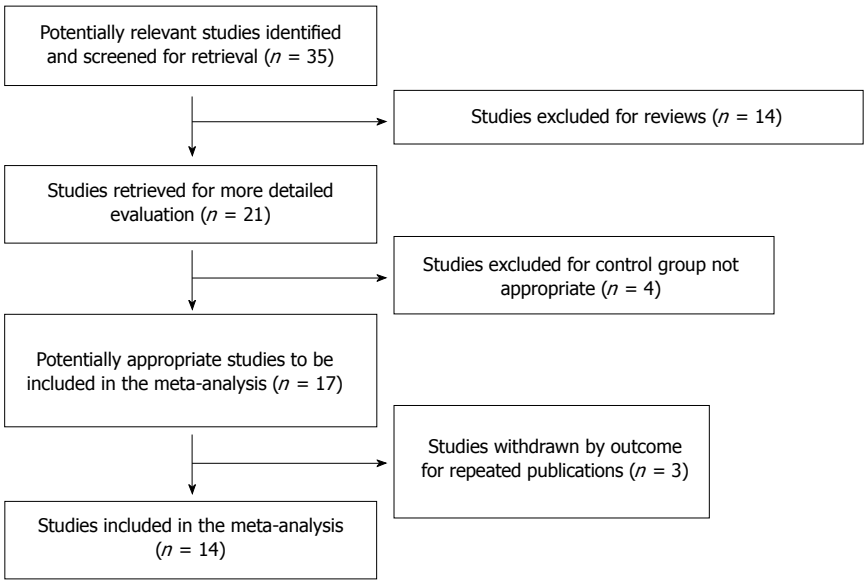

Figure 1 A flow diagram of articles retrieved and inclusion progress through the stage of meta-analysis.

Table 1 Characteristics of the included studies

Ref.	Year	Country	No. of cases	EVL mean age (yr)	EIS mean age (yr)	Child-Pugh grade (A/B/C)	Etiology (alcoholic/viral/others)	Complications	Follow-up
Stiegmann *et al*[12]	1992	United States	129	51 ± 13	53 ± 13	42/62/25	105/-	Esophageal strictures, and other infections	10 mo
Laine *et al*[15]	1993	United States	77	44 ± 1	48 ± 2	13/46/18	61/0/16	Esophageal strictures and esophageal ulcers	3 mo
Hou *et al*[16]	1995	China	134	60.1 ± 12.1	61.0 ± 11.7	32/50/52	22/90/22	Esophageal strictures and esophageal ulcers	3 mo
Lo *et al*[17]	1995	China	120	57 ± 13	54 ± 12	16/46/58	27/-	Esophageal strictures and esophageal ulcers	295 ± 120 d (EIS); 310 ± 105 d (EVL)
Baroncini *et al*[19]	1997	Italy	111	63.0 ± 9.1	61.4 ± 9.8	35/46/30	15/93/3	Esophageal strictures and esophageal ulcers	3 mo
Lo *et al*[20]	1997	China	71	53 ± 15	55 ± 13	5/24/42	20/46/5	Esophageal strictures and esophageal ulcers	1 mo
Al Traif *et al*[27]	1999	Saudi Arabia	60	48.2 ± 3.5	49.4 ± 3.2	22/23/15	1/35/24	Esophageal strictures and esophageal ulcers	3 mo
Masci *et al*[22]	1999	Italy	100	59.5	63.8	33/43/24	-	Esophageal strictures and esophageal ulcers	3 mo
Liu *et al*[28]	1999	China	81	48.2 ± 8.5	50.1 ± 9.1	73/3/5	14/48/19	Esophageal strictures and esophageal ulcers	3 mo
de la Peña *et al*[29]	1999	Spain	88	59	59	21/44/23	58/21/9	Esophageal strictures and esophageal ulcers	3 wk
Zargar *et al*[24]	2002	India	49	9.1 ± 2.7	9.5 ± 2.8	-	-	Esophageal strictures and esophageal ulcers	3 mo
Ferrari *et al*[25]	2005	Brazil	46	49.1 ± 13.2	49.3 ± 10.7	17/22/7	22/18/6	Esophageal strictures and esophageal ulcers	1 yr
Monici *et al*[26]	2010	Brazil	70	48.5	47.8	57/13/0	20/24/26	Esophageal strictures and esophageal ulcers	1 mo
Luz *et al*[30]	2011	Brazil	100	54.48	50.24	5/43/35	36/34/30	Esophageal strictures and esophageal ulcers	6 wk

EVL: Endoscopic variceal ligation; EIS: Endoscopic injection sclerotherapy.

EVL group and EIS group, Child-Pugh grade (A/B/C), etiology (alcoholic/viral/others), complications, and follow-up. Discordant results were adjudicated by the senior author (Sun MJ). The paired agreement among the authors was 0.998. The methodological quality of each trial was assessed using the following criteria: study design, method of esophageal variceal bleeding diagnosis and method of patient enrollment.

Data synthesis and analysis

The presence of inter-study heterogeneity was calculated by the χ^2-based *Q*-test, and significance was set at

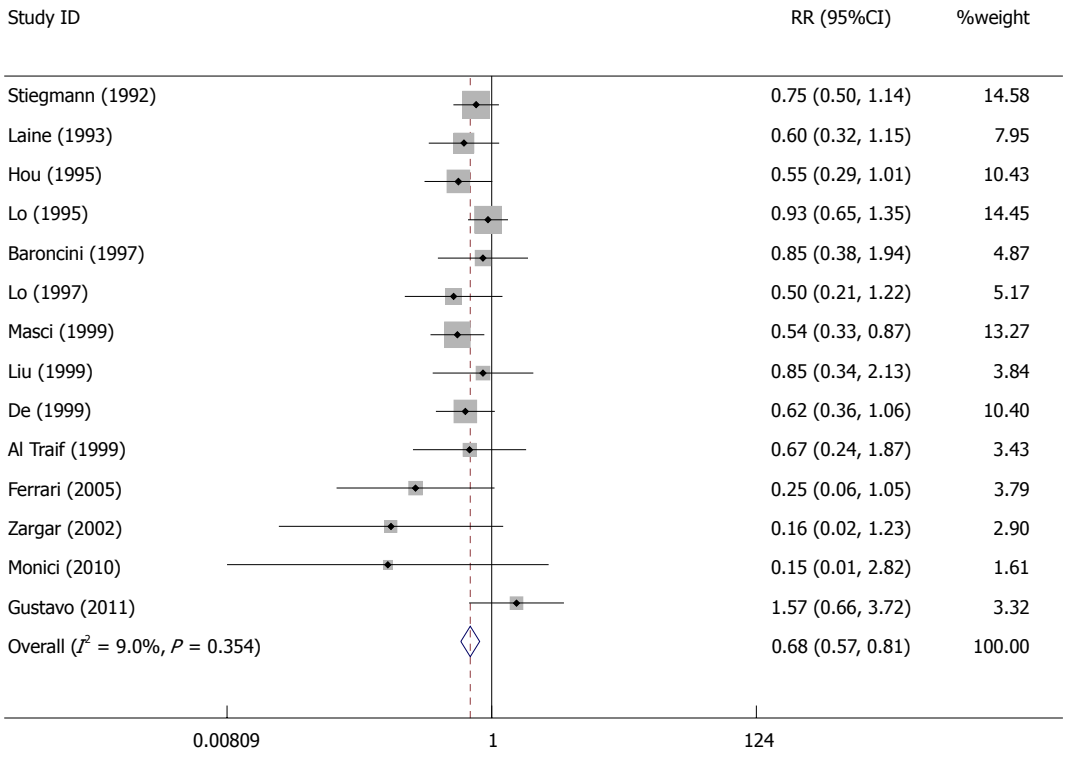

Figure 2 Forest plot of the rebleeding rate in the treatment of esophageal variceal bleeding by endoscopic variceal ligation *vs* endoscopic injection sclerotherapy. EVL: Endoscopic variceal ligation; EIS: Endoscopic injection sclerotherapy.

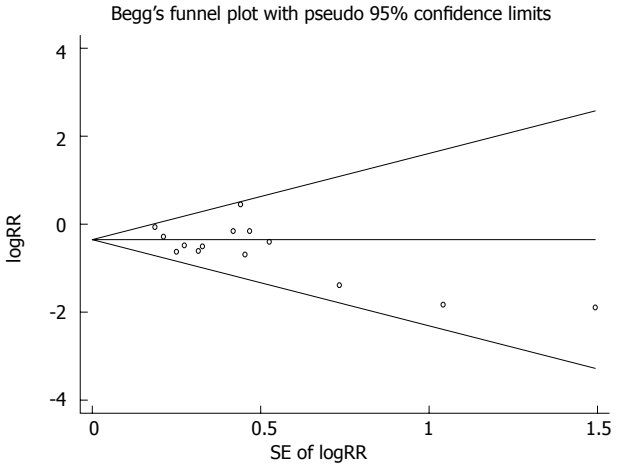

Figure 3 Begg's Funnel plot analysis of each study.

the $P < 0.10$ level. The inconsistency index (I^2) was calculated to assess the variation caused by the heterogeneity. If heterogeneity was observed among the studies, the random-effects model was used to estimate the pooled RR (the DerSimonian and Laird method). Otherwise, the fixed-effects model was adopted (the Mantel-Haenszel method). Summary RR and 95% confidence interval (CI) were used to describe the risk of rebleeding, mortality, complications and variceal eradication in the EIS group *vs* the EVL group. Publication bias was assessed by funnel plot analysis. Meta-analysis was done using STATA 12.0.

RESULTS

Study selection and data collection

Our meta-analysis identified a total of 35 studies. After carefully cross-referencing the titles, abstracts and keywords, potentially relevant studies were evaluated for potential inclusion (Figure 1). Ultimately, 17 studies were reviewed in detail, of which 14 met inclusion criteria and were included in the meta-analysis. Details regarding the included studies, including author, publication year, country, number of cases, mean age of patients in the EVL group and EIS group, Child-Pugh grade (A/B/C), etiology (alcoholic/viral/others), complications, and follow-up, can be found in Table 1. The study sizes ranged from 46 to 134 and the mean age ranged from 6 to 73 years. The mean follow-up period ranged from 6 to 34 mo. More than 80% of patients had cirrhosis. The proportion of patients with alcoholic cirrhosis ranged from 1.7% to 81%, and viral cirrhosis ranged from 0% to 84%. The proportion of patients with Child A liver disease ranged from 7% to 81%, Child B liver disease from 3.7% to 60%, and Child C liver disease from 0% to 59%.

Rebleeding and variceal eradication

Fourteen studies in the meta-analysis included 1236 patients with esophageal variceal bleeding. The rebleeding rate in actively bleeding varices patients in the EVL group was significantly lower than that in the EIS group (RR = 0.68, 95%CI: 0.57-0.81) (Figure

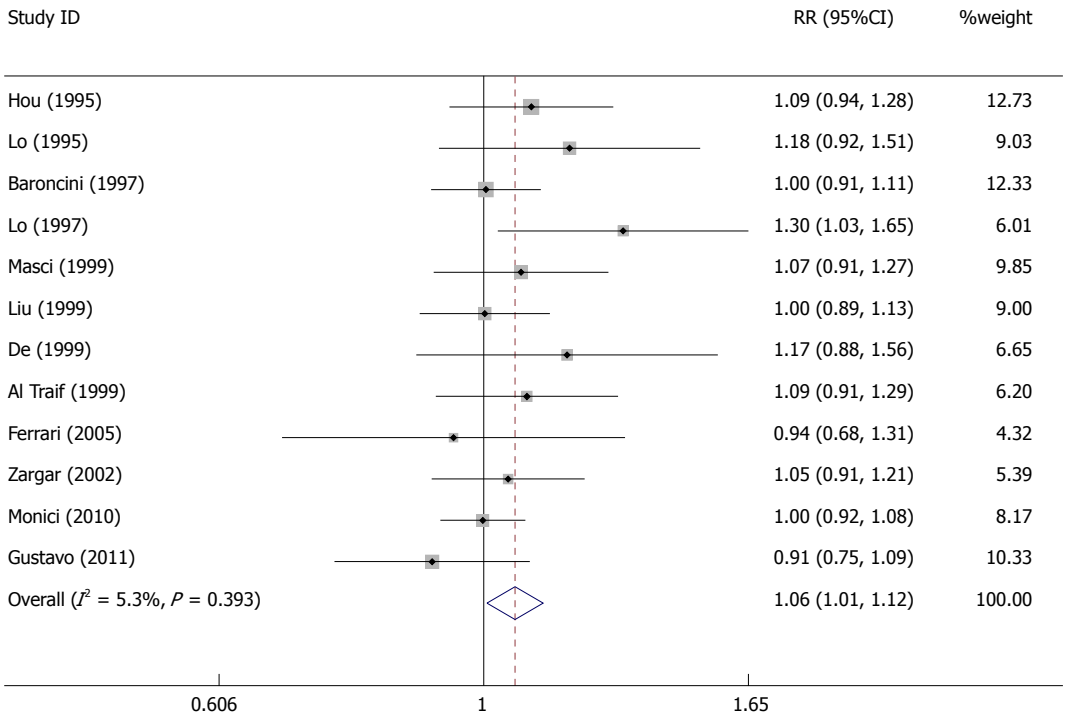

Figure 4 Forest plot of the variceal eradication rate in the treatment of esophageal variceal bleeding by endoscopic variceal ligation *vs* endoscopic injection sclerotherapy. EVL: Endoscopic variceal ligation; EIS: Endoscopic injection sclerotherapy.

2), suggesting that the rebleeding in esophageal variceal bleeding patients was more likely to occur in the EIS group compared with the EVL group. There was statistically significant homogeneity (P = 0.354). The funnel plot (Figure 3) was generally symmetrical, showing no evidence of publication bias (Begg's test, Z = 1.31, P = 0.189).

The variceal eradication rate in actively bleeding varices patients in the EVL group was significantly higher than that in the EIS group (RR = 1.06, 95%CI: 1.01-1.12) (Figure 4), suggesting that EVL was more effective in the variceal eradication in esophageal variceal bleeding patients than EIS.

Mortality and complications

There was no significant difference about mortality rate between the EVL group and EIS group (RR = 0.95, 95%CI: 0.77-1.17) (Figure 5). At the same time, the rate of complications in actively bleeding varices patients in the EVL group was significantly lower than that in the EIS group (RR = 0.28; 95%CI: 0.13-0.58) (Figure 6). Bleeding from treatment-induced ulcers, esophageal perforation and strictures were less frequently in patients treated by EVL, but the difference was not statistically significant. There were significant differences between the two therapies in the proportion of pulmonary infections or episodes of spontaneous bacterial peritonitis.

DISCUSSION

The purpose of this meta-analysis was to compare the effects of EVL with EIS in the treatment of patients with esophageal variceal bleeding. By synthesizing all available data from previous studies, the meta-analysis provide a more precise estimate than the results which can be obtained from all individual studies. The overall rebleeding rate in the EVL group of these studies was 21.7%, while the rebleeding rate in the EIS group was 33.1%. Although only one of these studies (Masci, 1999) showed a significantly lower rebleeding rate in the EVL group than in the EIS group, other studies showed different results. From the results of our meta-analysis, we have found that the rebleeding rate in EVL group was significantly lower than that in the EIS group (Figure 2). The main reason of rebleeding was varices or treatment-induced ulcers.

EVL requires placement of an opaque cylinder in front of the endoscope. This therapy can affect the endoscopic vision. Visualization is very important for treatment in a patient with esophageal variceal bleeding, and may be more impaired when treating by EVL than by EIS. Although the visualization of EIS is better than that of EVL, our meta-analysis shows that EVL achieved a higher variceal eradication rate than EIS in these studies (Figure 4). In the future, the opaque cylinder will be replaced by a clear plastic cylinder which can provide better visualization in patients with esophageal variceal bleeding.

We have not only assessed the efficacy of EIS and EVL, but also evaluated the complications and side effects. The mortality seen with EVL in these studies was 22.8%, while the mortality with EIS was 24.6%. Our meta-analysis shows that there was no significant

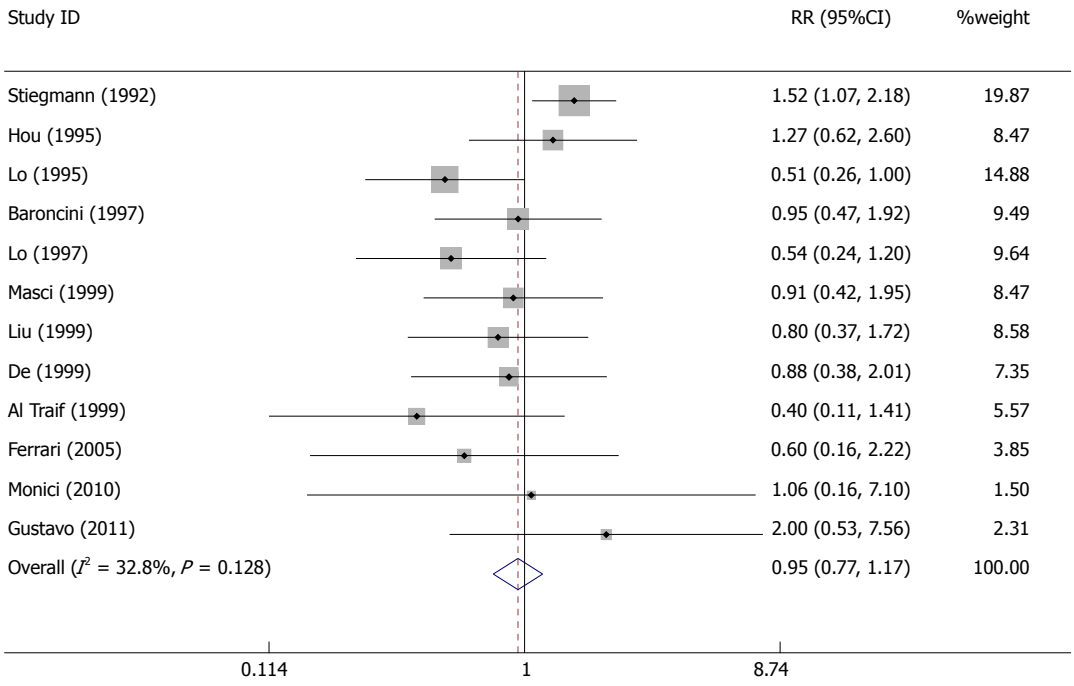

Figure 5 Forest plot of the mortality rate in the treatment of esophageal variceal bleeding by endoscopic variceal ligation *vs* endoscopic injection sclerotherapy. EVL: Endoscopic variceal ligation; EIS: Endoscopic injection sclerotherapy.

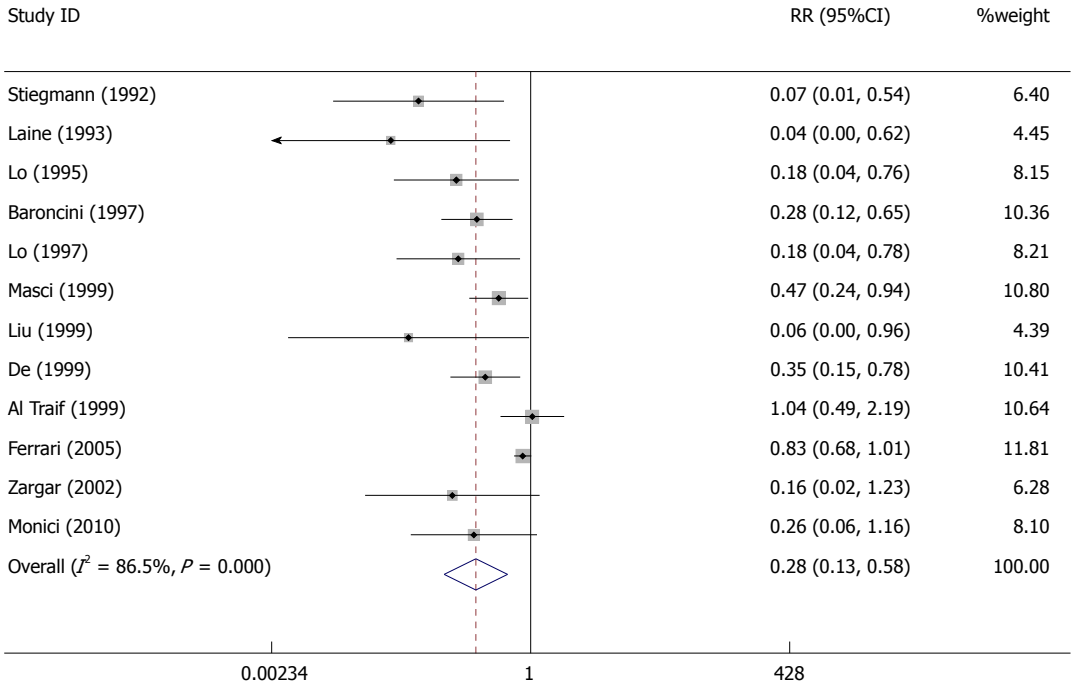

Figure 6 Forest plot of the complication rate in the treatment of esophageal variceal bleeding by endoscopic variceal ligation *vs* endoscopic injection sclerotherapy. EVL: Endoscopic variceal ligation; EIS: Endoscopic injection sclerotherapy.

difference about mortality rate between the EVL group and EIS group (Figure 5). Some studies have demonstrated that prevention of esophageal variceal bleeding by surgical therapy or medical treatment does not necessarily decrease mortality and improve survival. Deaths due to bleeding or other causes occurred less frequently in the EVL group than in the EIS group. Local complications such as esophageal strictures were less common in the EVL group than in the EIS group (Figure 6). There were no significant differences about systemic complications such as pulmonary infections and bacterial peritonitis in the two groups.

The costs of the equipment and material required for EVL or EIS in esophageal variceal bleeding are similar. In addition to cost differentials that may occur

in relation to differences in efficacy (variceal eradication and rebleeding) or complications (local complications and systemic complications), substantial cost savings is likely if the treatment requires fewer endoscopic treatment sessions. However, an in-depth economic evaluation is warranted to carefully evaluate all of the costs and consequences of these two treatments in the management of patients with esophageal variceal bleeding.

Our meta-analysis has several limitations. First, our meta-analysis has included some studies from different countries which have ethnic differences. Second, the etiology and severity of esophageal varices in these studies were different. Third, these medical institutions in the included studies have different medical facilities and medical technology, so the treatment for esophageal variceal bleeding such as EVL and EIS may lead to different results.

In conclusion, on the basis of lower rates of rebleeding, mortality, and complications (local complications and systemic complications) and higher rates of variceal eradication, our meta-analysis has found that EVL should be considered the appropriate endoscopic treatment option for patients with esophageal variceal bleeding. Of course, further large-scale randomized controlled trials will be helpful in more firmly establishing the efficacy of EVL for patients with esophageal variceal bleeding.

COMMENTS

Background

Esophageal variceal bleeding is the most common (as many as 30%) in all patients presenting with upper gastrointestinal tract hemorrhage. Acute esophageal variceal bleeding is an intractable complication of portal hypertension. Traditional measures have included balloon tamponade, vasoconstrictors, and surgical intervention, but these measures did not significantly reduce the rate of rebleeding, complications and improve survival.

Research frontiers

Some randomized controlled trials have compared endoscopic variceal ligation (EVL) with endoscopic injection sclerotherapy (EIS) in terms of sessions required to achieve variceal obliteration, rebleeding rate, mortality rate and complication rate. However, all of those studies comprised only a small number of patients with active variceal bleeding, and have come to conflicting conclusions.

Innovations and breakthroughs

Based on this meta-analysis, the rebleeding rate and the complication rate in actively bleeding varices patients in the EVL group were significantly lower than those in the EIS group. The variceal eradication rate in actively bleeding varices patients in the EVL group was significantly higher than that in the EIS group. There was no significant difference about mortality rate between the EVL group and EIS group.

Applications

EVL is better than EIS in terms of the lower rates of rebleeding, complications, and the higher rate of variceal eradication. Therefore, EVL is the first choice for esophageal variceal bleeding.

Terminology

EIS has been gradually applied to the management of esophageal variceal bleeding since the mid-1970s. EIS performed as the first effective measure proved to be superior to vasoconstrictors or balloon tamponade in the control of acute esophageal variceal bleeding. EVL was introduced in 1986 and was a purely mechanical method of obliterating varices.

Peer-review

This is a good meta-analysis on the endoscopic treatment of bleeding esophageal varices. The authors present a systematic review and meta-analysis to answer the question of preferred treatment modality for patients presenting with variceal bleeding. The primary therapies compared in this study are EVL and EIS. The meta-analysis shows the benefit of EVL compared to EIS in terms of significantly lower rebleeding rates and comparable mortality.

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