Pharmacotherapy plus endoscopic intervention is more effective than pharmacotherapy or endoscopy alone in the secondary prevention of esophageal variceal bleeding: a meta-analysis of randomized, controlled trials CME

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Background: Previous clinical trials on the treatment of esophageal variceal bleeding yielded mixed results regarding the efficacy of endoscopic procedures compared with pharmacotherapy only.

Objective: To compare the efficacy of endoscopic procedures with that of pharmacotherapy in the prevention of mortality and rebleeding.

Design and Setting: A systematic literature review was performed to identify randomized, controlled trials of the efficacy of pharmacotherapy and endoscopic therapy. A meta-analysis was performed by using the Comprehensive MetaAnalysis software package. A 2-sided α error $<.05$ was considered statistically significant ($P < .05$).

Patients: Twenty-five clinical trials with a total of 2159 patients were eligible for meta-analysis.

Outcome Measurements: Relative risk (RR) with 95% confidence interval (CI) was computed for all-cause mortality, mortality from rebleeding, all-cause rebleeding, and rebleeding caused by varices.

Results: Pharmacotherapy was as effective as endoscopic procedures in preventing rebleeding (RR 1.067; 95% CI, 0.865-1.316; $P = .546$), variceal rebleeding (RR 1.143; 95% CI, 0.791-1.651; $P = .476$), all-cause mortality (RR 0.997; 95% CI, 0.827-1.202, $P = .978$), and mortality from rebleeding (RR 1.171; 95% CI, 0.816-1.679; $P = .39$). Pharmacotherapy combined with endoscopic procedures did not reduce all-cause mortality (RR 0.787; 95% CI, 0.587-1.054; $P = .108$) or mortality caused by rebleeding (RR 0.786; 95% CI, 0.445-1.387; $P = .405$) compared with endoscopic procedures. However, combination therapy (endoscopic procedure plus pharmacotherapy) significantly reduced the incidence of all rebleeding (RR 0.623; 95% CI, 0.523-0.741; $P < .001$) and variceal rebleeding (RR 0.601; 95% CI, 0.440-0.820; $P < .001$).

Limitations: Heterogeneity of patient population and different treatment protocols may have affected our meta-analysis.

Conclusion: Pharmacotherapy may be as effective as endoscopic therapy in reducing rebleeding rates and all-cause mortality. Pharmacotherapy plus endoscopic intervention is more effective than endoscopic intervention alone. (Gastrointest Endosc 2009;70:658-64.)

Bleeding from esophageal varices is a serious complication of portal hypertension. After an initial episode of acute variceal bleed, patients with cirrhosis have a 70% risk of rebleeding, and of those who do rebleed, there is a 20% to 35% mortality rate.[1,2] Sclerotherapy, ligation, and pharmacological treatment are recommended therapeutic modalities for the prevention of variceal bleeding.[3] Endoscopic sclerotherapy involves intravariceal or paravariceal injections of a sclerosant agent. Sclerotherapy is performed every 10 to 14 days until the varices are resolved, which usually takes 5 to 6 sessions. Polidocanol, ethanolamine, ethanol, tetradecyl sulfate, and sodium morrhuate are the various sclerosing agents used. In endoscopic

Abbreviation: RR, relative risk.

DISCLOSURE: *All authors disclosed no financial relationships relevant to this publication.*

See CME section; p. 748.

0016-5107/$36.00
doi:10.1016/j.gie.2009.02.029

band ligation, varices are ligated and strangled with elastic O-rings on the varix. Five to 8 elastic bands are used per session. Ligation is performed every 2 to 3 weeks until the varices have been obliterated, usually in 3 to 4 sessions.

Pharmacological treatment of varices with drugs such as β-blockers and nitrates has also been studied in various trials. β-Blockers decrease portal pressure by decreasing cardiac output via β_1 receptor blockage.[4] In addition, β_2 receptor blockage leads to unopposed α-adrenergic activity, resulting in splanchnic vasoconstriction and decreased portal pressure. Nonselective β-blockers (nadolol, propranolol, timolol) are more effective than selective β_1-blockers in reducing the hepatic venous pressure gradient.[5] Nitrates (most commonly isosorbide mononitrate) reduce portal pressure by selective vasodilatation in the splanchnic circulation and also by reducing intrahepatic resistance.[6,7] However, patients with advanced cirrhosis have marked vasodilatation, which leads to a decrease in arterial pressure and hepatic blood flow. This, when combined with the reduction of preload and cardiac output caused by nitrates, may have deleterious effects including deterioration of renal function.[8] Thus, nitrates should not be used alone as therapy for portal hypertension. Conversely, drug intolerance and side effects can impede the use of medications.

Capsule Summary

What is already known on this topic

- During the first 6 weeks after a variceal hemorrhage, there is a 30% to 40% chance for recurrent bleeding.
- Those who do rebleed have a 20% to 35% mortality rate.

What this study adds to our knowledge

- In a meta-analysis of 25 clinical trials on treatment of esophageal varices:
  - Pharmacotherapy was as effective as endoscopic therapy in preventing rebleeding and all-cause mortality.
  - Pharmacotherapy combined with endoscopy was more effective at reducing rebleeding than endoscopic intervention alone.

BACKGROUND

Although there are many randomized, controlled trials that used various combinations of treatment for esophageal varices, there was no consensus on the treatment with regard to reduction of recurrent bleeding and death because of different criteria, study power, and endpoint inadequacy of the studies. To date, there were 3 meta-analyses[9-11] comparing sclerotherapy with pharmacotherapy. A meta-analysis by Pagliaro et al[9] showed no significant difference in risk of recurrent bleeding or mortality with both treatment modalities. Meta-analyses by D'Amico et al[10] and Bernard et al[11] found less recurrent variceal bleeding in the sclerotherapy group, but there was no significant difference in survival.

A meta-analysis by D'Amico et al[10] comparing the combination of sclerotherapy and pharmacotherapy with sclerotherapy alone did show significantly lower rebleeding and mortality rates in the combination therapy group; however, the results should be interpreted cautiously because of significant heterogeneity. A meta-analysis by Maria et al[12] comparing pharmacotherapy with ligation for secondary prophylaxis of esophageal varices showed pharmacotherapy to be as effective as ligation.

Although there are many previous studies and meta-analyses, there was no meta-analysis comparing endoscopic procedures alone or in combination with pharmacotherapy with pharmacotherapy alone. This is important because clinical practice often combines several modalities in the treatment of an individual patient. The aims of our study were to (1) compare the efficacy of pharmacotherapy with that of endoscopic therapy in reducing the incidence of rebleeding and death and (2) compare the additive effect of pharmacotherapy with that of endoscopic therapy on reducing the incidence of rebleeding and death.

METHODS

Data sources and study selection

We performed literature searches of the PubMed, EMBASE, and Cochrane Central databases up to November 2006 by using the key terms ''endoscopic variceal ligation,'' ''endoscopic sclerotherapy,'' ''endoscopic variceal bleeding,'' and ''esophageal and gastric varices'' as our search terms. In addition, a manual search was performed of reference lists of published articles and abstracts. The inclusion criteria for selection of clinical trials for the meta-analysis were the following: (1) the trials need to be randomized, controlled trials comparing pharmacotherapy with or without sclerotherapy with sclerotherapy alone or pharmacotherapy with or without ligation with ligation alone; (2) the study participants should be older than 16 years of age with at least 1 previous episode of gastroesophageal bleeding; and (3) the studies need to have measured at least one of the following outcomes as their endpoint: the overall mortality, mortality caused by gastroesophageal bleeding, recurrence of bleeding, or recurrence of bleeding from esophageal varices. Studies comparing these outcomes in the primary prevention of gastroesophageal bleeding and those that included patients with gastric varices alone were excluded from our analysis.

Data extraction

Data extraction was done by 2 authors who independently abstracted study design information, study participant information, and results. We resolved discrepancies by repeated review and discussion. With our search terms,

a total of 172 studies were identified, but after applying our inclusion and exclusion criteria, 26 studies were eligible for meta-analysis. Of these, 7 studies[13-19] compared the clinical benefit of sclerotherapy with that of pharmacotherapy, and 11 studies[20-30] evaluated the combination of pharmacotherapy and sclerotherapy compared with sclerotherapy alone in treating esophageal varices. There were also 4 studies[31-34] comparing pharmacotherapy with ligation and 3 studies[35-37] assessing the combined effect of pharmacotherapy and ligation and that of ligation alone. Romero et al[38] organized the only study that compared the efficacy of pharmacotherapy with that of the combination of sclerotherapy and ligation. In the current meta-analysis, patients receiving either sclerotherapy or band ligation were categorized into an endoscopy group. Then, patients receiving endoscopic therapy were compared with those receiving pharmacotherapy in terms of all 4 outcomes (overall mortality, mortality caused by gastroesophageal bleeding, recurrence of all-cause bleeding, and recurrence of bleeding from esophageal varices). The additive effect of pharmacotherapy and endoscopy versus endoscopy alone was also evaluated in these outcomes.

Statistical analysis

The heterogeneity of the studies was analyzed by Cochran's Q statistics by using the Comprehensive Meta-Analysis software (Biostat, Englewood, NJ). In our analysis of pharmacotherapy versus endoscopy, the studies were found to be homogeneous for all-cause mortality ($P = .41$) and mortality caused by bleeding ($P = .28$) and heterozygous for the risk of rebleeding ($P = .001$) and rebleeding from varices ($P = .001$). In our analysis comparing the dual effect of endoscopy and pharmacotherapy with the effect of endoscopy alone, the studies were found to be homogeneous for all the 4 endpoints (all-cause mortality [$P = .97$], mortality caused by bleeding [$P = .94$], risk of all-cause rebleeding [$P = .09$], and risk of rebleeding from varices [$P = .5$]). Funnel plots were drawn based on standard error by log-risk ratio for all outcome measures. Inspection of these plots did not reveal any publication bias in our analysis. The Mantel-Haenszel fixed-effect model was used to calculate combined relative risks (RRs) for those outcomes when the studies were homogeneous, and the random-effect model was used when the studies were heterogenic. A 2-sided α error $<.05$ was considered to be statistically significant ($P < .05$).

RESULTS

Study design and participants

Clinical characteristics of patients included in the trials are described in Appendixes 1 through 5 available online at www.giejournal.org). The etiology of cirrhosis in all the trials was alcoholism (available online at www.giejournal.org) and virus related, except in 2 studies,[28,30] in which it was related to schistosomiasis. The β-blocker used was either propranolol or nadolol in these studies, with most of the trials opting for propranolol. Nadolol in combination with nitrates was used in 4 trials,[18,31,32,38] and sucralfate was used in 1 study.[33] However, nadolol alone was used in 2 studies.[22,24] The doses of β-blocker were titrated according to the pulse rate. The mean time interval between endoscopic sessions was 7 to 14 days except in 3 studies; it was 30 days in 2 studies[23,29] and 90 days in the third study.[28] Although Dasarathy et al[14] included patients only with Child-Pugh classes B and C, Alexandrino et al[13] enrolled patients with Child-Pugh classes A and B.

The definition of rebleeding and variceal bleeding varied in different studies. Rebleeding was defined as (1) hemetemesis or melena with either a hemoglobin decrease of 2 to 3 mg/dL or requiring blood transfusion[12,15,19,33]; (2) bleeding that required blood transfusion[11,14,15,17,24,26,28,29,31]; (3) hemetemesis or melena[13-18,20,23,25,30,33]; (4) endoscopic findings such as spurting or oozing varix, adherent clot, and esophageal varices with red spots[21]; (5) endoscopic findings such as active bleeding or the presence of blood in the stomach in a patient with an esophageal varix.[34] Variceal bleeding is defined as (1) an actively bleeding varix, (2) adherent clots or fibrin plug on varices,[13,15,17,20,26,28] (3) bleeding along with a decrease in hemoglobin of more than 2 mg/dL or requiring more than 2 units of blood and gastroesophageal varices as the only source of bleeding,[17] and (4) the presence of hemetemesis or melena.[31]

Pharmacological versus endoscopic therapy

A total of 12 studies including 1252 patients evaluated the clinical benefit of pharmacotherapy and that of endoscopic intervention in reducing mortality and other adverse GI events in patients with esophageal varices (Table 1). These trials assessed the RR of these outcomes with medications compared with that of sclerotherapy in 7 studies[13-19] and of band ligation in 4 studies.[31-34] Romero et al[38] assessed the RR by comparing the combination of sclerotherapy ligation to pharmacotherapy.

All-cause mortality was lower with endoscopy in 6 studies[13-18] and with pharmacotherapy in 4 studies,[18,31,32,34] but the risk reduction was not statistically significant with the pooled RR ratio of 0.997 (95% CI, 0.827-1.202; $P = .98$). Although the risk of death caused by bleeding was lower with endoscopy in 5 studies,[11,14,15,19,38] only 1 study[14] found a statistically significant risk reduction ($P = .035$) of death caused by bleeding. Medications were effective in reducing the risk of death caused by bleeding in 5 studies,[16-18,31,34] but the combined RR showed no statistically significant difference between endoscopic and pharmacotherapy (RR 1.171; 95% CI, 0.816-1.67; $P = .391$).

Of 12 studies, the risk of rebleeding from all causes was lower with endoscopic therapy in 7 studies,[13,14,16,19,31,34,38] whereas in the other 5 studies, it was lower with

TABLE 1. Results of the endpoints in the studies included in the meta-analysis

	Rebleeding (%)				Rebleeding from varices (%)				Mortality (%)				Mortality caused by bleeding (%)			
Study	T	C	RR (95% CI)	*P* value	T	C	RR (95% CI)	*P* value	T	C	RR (95% CI)	*P* value	T	C	RR (95% CI)	*P* value
M vs S																
Dasarathy et al[14]	67	42	1.60 (1.07-2.4)	.02	NG				41	22	1.86 (0.97-3.55)	.06	30	11	2.74 (1.08-6.98)	.04
Westaby et al[19]	54	45	1.20 (0.82-1.18)	.5	NG				42	37	1.12 (0.71-1.79)	.61	25	14	1.75 (0.79-3.88)	1.67
Fleig et al[15]	35	47	0.74 (0.42-1.32)	.31	27	28	1.06 (0.55-2.22)	.9	15	8	1.77 (0.46-6.82)	.41	3	0	3.17 (1.3-75.2)	.47
Rossi et al[17]	48	50	0.96 (0.56-1.67)	.89	41	35	1.17 (0.59-2.36)	.64	36	23	1.12 (0.44-2.9)	.81	15	19	0.77 (0.23-2.56)	.67
Teres et al[16]	64	45	1.42 (1.01-2.01)	.05	60	40	1.52 (1.04-2.22)	.03	40	36	1.10 (0.69-1.75)	.70	15	17	0.90 (0.4-2.05)	.80
Villanueva et al[18]	26	53	0.48 (0.27-0.85)	.01	21	51	0.41 (0.21-0.78)	.01	9	21	0.45 (0.15-1.33)	.15	0	46	0.20 (0.01-4.04)	.29
Alexandrino et al[13]	85	64	1.32 (0.98-1.78)	.07	62	39	2.12 (1.15-3.91)	.15	32	29	1.22 (0.6-2.52)	.59	9	3	3.0 (0.33-27.28)	.32
M+S vs S																
Jensen and Krarup[23]	20	75	0.27 (0.09-0.76)	.01	NG				7	6	1.07 (0.73-5.57)	.96	0	6	0.35 (0.02-8.07)	.51
Lundell et al[29]	58	45	1.27 (0.70-2.31)	.42	NG				5	23	0.23 (0.03-1.81)	.16	NG		NG	
Vinel et al[26]	18	40	0.45 (0.20-0.98)	.45	10	29	0.36 (0.12-1.04)	.06	13	14	0.9 (0.28-2.84)	.85	10	8	1.19 (0.3-5.0)	.80
Avegrinos et al[21]	49	87	0.56 (0.40-0.77)	.00	42	62	0.68 (0.44-1.03)	.07	18	23	0.79 (0.33-1.85)	.59	6	5	1.33 (0.23-7.60)	.75
Elsayed et al[28]	14	38	0.37 (0.19-0.70)	.00	NG				13	14	0.9 (2.17-2.82)	.8	NG			
Bertoni et al[22]	7	28	0.25 (0.03-1.97)	.19	NG				7	21	0.33 (0.04-2.82)	.31	NG			
Vickers et al[25]	43	41	1.06 (0.61-1.8)	.83	NG				23	26	0.87 (0.39-1.94)	.74	10	11	0.87 (0.23-3.22)	.83
Dowidar et al[30]	25	30	0.83 (0.30-2.29)	.72	20	20	1.0 (0.29-3.45)	1.0	20	30	0.67 (0.22-2.00)	.47	NG			
Westaby et al[27]	27	30	0.90 (0.38-2.14)	82	NG				35	26	1.34 (0.58-3.05)	.49	8	7	1.04 (9/16-6.84)	.17
Acharya et al[20]	17	21	0.80 (0.37-1.71)	.57	10	11	0.97 (0.33-2.81)	.95	9	12	1.69 (0.23-2.04)	.50	5	5	0.97 (0.20-4.59)	.97
Gerunda et al[24]	20	23	0.86 (0.32-2.25)	.75	NG				3	10	0.33 (0.04-3.02)	.33	NG			
M vs L																
Lo et al[31]	57	38	1.5 (1.01-2.20)	.04	43	20	2.13 (1.19-3.82)	.01	73	25	0.52 (0.24-1.15)	.10	3	6	0.49 (0.09-2.58)	.40
Sarin et al[34]	27	14	1.94 (0.97-3.89)	.06	23	7	3.23 (1.24-8.39)	.01	6	8	0.71 (0.21-2.42)	.59	1	1	1.08 (0.07-16.85)	.96
Villanueva et al[32]	33	49	0.69 (0.46-1.03)	.07	28	44	0.63 (0.40-0.99)	.04	32	42	0.77 (0.50-1.18)	.23	5	14	0.40 (1.31-1.21)	.11
Patch et al[33]	37	53	0.70 (0.45-1.09)	.12	22	35	0.61 (0.32-1.16)	.13	33	33	1.00 (0.58-1.73)	1.00	NG			
M+L vs L																
Lo et al[35]	23	47	0.50 (0.29-0.84)	.01	10	24	0.41 (0.17-0.99)	.05	17	32	0.69 (0.34-1.41)	.31	7	15	0.46 (0.15-1.41)	.17
De la Pena et al[36]	14	11	0.37 (0.16-0.86)	.02	9	27	0.34 (0.11-1.01)	.05	12	11	0.71 (0.23-2.16)	.55	0	3	0.29 (0.01-6.86)	.44
Jain et al[37]	13	22	0.59 (0.27-1.28)	.18	NG	NG			NG	NG			NG	NG		
M vs L+S																
Romero et al[38]			1.17 (0.93-1.48)	.18			1.22 (0.87-1.73)	.24			1.00 (0.47-2.16)	.99			1.37 (0.52-3.58)	.52

T, Treatment group; *C*, control group; *M*, medications; *S*, sclerotherapy; *L*, ligation; *NG*, not given.

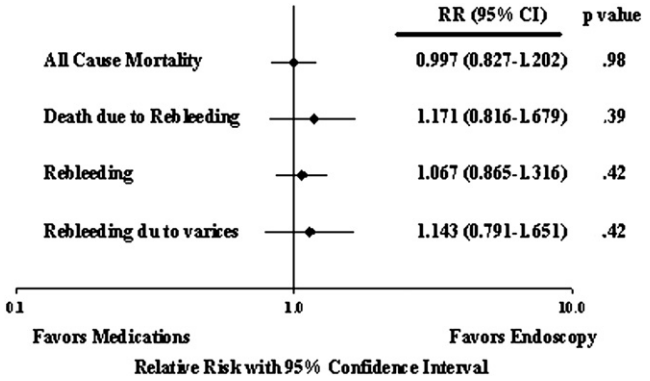

Figure 1. Summary of RRs: pharmacotherapy versus endoscopic therapy.

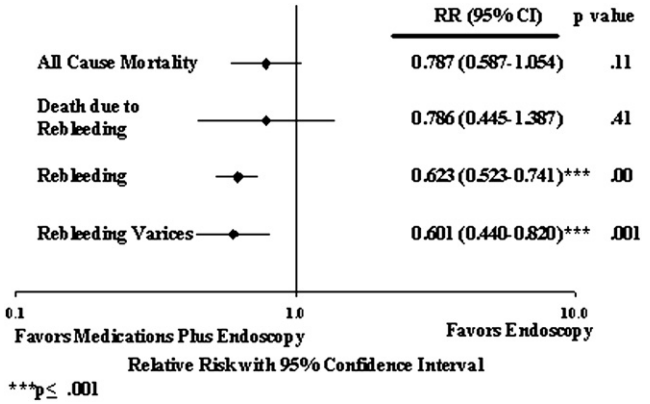

Figure 2. Summary of RRs: pharmacotherapy plus endoscopic therapy versus endoscopic therapy alone.

pharmacological therapy. The overall pooled RR ratio was 1.067 (95% CI, 0.865-1.316; $P = .546$). The risk of rebleeding from varices was found to be lower with endoscopy in 6 studies,[13,15,17,31,33,38] with a statistically significant reduction seen in 4 of them.[13,16,31,34] Three studies[18,32,33] found a decreased risk of rebleeding from varices with medications. The overall combined RR did not reveal any significant difference between the treatment modalities (RR 1.143; 95% CI, 0.791-1.651; $P = .476$) (Fig. 1).

Hence, based on the pooled RR of each endpoint, endoscopic therapy has no significant advantage over pharmacotherapy, and treatment of esophageal varices with medications is as effective as endoscopy in preventing adverse clinical outcomes.

Pharmacotherapy plus endoscopy versus endoscopy alone

Fourteen randomized, controlled trials[20-30,35-37] (2 from abstracts[24,37]) that included 1069 patients compared the effectiveness of combining pharmacotherapy with endoscopy compared with that of endoscopy alone. Eleven of these[20-30] assessed the dual effect of pharmacotherapy and sclerotherapy and the effect of sclerotherapy alone, and 3 trials[35-37] evaluated the combination of pharmacotherapy and ligation with ligation alone (Table 1). Propranolol was the β-blocker used in most of the trials,[20,21,23,24-29,37] with nadolol and sucralfate being used in 4[20,33,34] and 1[35] randomized, controlled trials, respectively.

All-cause mortality was found to be lower with combination therapy in 11 trials[20-22,24-26,28-30,35,36] and with endoscopy in 2 trials,[23,27] but collectively there was no statistically significant difference between the groups (RR 0.787; 95% CI, 0.587-1.054; $P = .108$). Three trials[23,35,36] found a decreased risk of death caused by bleeding with combination therapy, and 2 trials[21,26] found this risk to be lower with endoscopy. The overall RR ratio did not show any difference between the groups (RR 0.786; 95% CI, 0.445-1.387; $P = .405$) (Fig. 2).

In our meta-analysis, the risk of all-cause rebleeding and rebleeding from varices is significantly different in both of the treatment arms. The RR of rebleeding was decreased with combination therapy in 11 studies,[20-24,26,28,30,35-37] significantly in 6 of them,[21,23,26,28,36,37] with an overall RR of 0.62 (95% CI, 0.52-0.74). The cumulative risk of rebleeding from varices was also significantly lower with combination therapy (RR 0.60; 95% CI, 0.44-0.82).

DISCUSSION

After an initial variceal hemorrhage, the frequency of recurrent bleeding ranges from 30% to 40% in the first 6 weeks.[39] The risk is maximal in the first 5 days and decreases slowly over the first 6 weeks. The risk of rebleeding depends on the severity of liver disease, variceal size, concomitant renal failure, continued alcoholism, and the presence of hepatoma.[40] There is a close correlation between increased portal pressure and the risk of recurrent bleeding and survival rate.[41]

β-Blockers, sclerotherapy and band ligation are all effective therapies in secondary prevention of variceal bleeding.[42] However, rebleeding rates are as high as 50% after repeat sclerotherapy,[43] and sclerotherapy has been replaced almost universally by endoscopic variceal ligation. Although endoscopic ligation achieves rapid variceal obliteration, studies have shown that rebleeding rates from esophageal varices range from 13% to 51%.[44,45] Moreover, portal pressure was increased in 68% of patients undergoing repeat endoscopic ligation.[46] Conversely, β-blockers have been shown to decrease portal pressure,[47] prevent portal hypertensive gastropathy,[48] and decrease post-sclerotherapy variceal recurrence.[49,50] β-Blockers attained target reduction of hepatic pressure gradients in approximately one third of patients.[51]

Pharmacotherapy versus endoscopy

In our meta-analysis of 12 studies comparing pharmacotherapy with endoscopic therapy, pharmacotherapy was as effective as endoscopic procedures in decreasing the risk of all-cause mortality, death caused by bleeding, the risk of rebleeding, and rebleeding from varices in the patients included in these studies. This is consistent with the study by Sarin et al,[34] which found that medications were as effective as endoscopic therapy; however, a subset of their patients with noncirrhotic portal fibrosis had increased risk of rebleeding with medications. The study by Dasarathy et al,[14] which included decompensated patients with cirrhosis (Child classes B and C), showed that the sclerotherapy group had significant reduction in all-cause mortality, mortality caused by bleeding, and the risk of rebleeding. An increased risk of rebleeding in a study by Lo et al[31] could be attributed to large varices in the pharmacotherapy group of patients. Alexandrino et al[13] demonstrated an increased risk of rebleeding with propranolol compared with sclerotherapy. However, patients in this study were randomized 15 days after their index bleed, and strict compliance to medications was not observed. Villanueva et al[18] matched both the treatments groups with respect to prognostic variables such as the severity of liver disease, the interval between initial bleed and randomization, and abstinence from alcohol. In their study, pharmacotherapy significantly reduced risk of rebleeding and rebleeding from varices. Thus, with evidence from the above studies, we conclude that when all the prognostic variables are matched, β-blockers are as effective as endoscopic procedures in reducing mortality and rebleeding.

Pharmacotherapy plus endoscopy versus endoscopy

In our meta-analysis of 13 studies evaluating the additive effect of pharmacotherapy compared with that of endoscopy, we found that combination therapy significantly reduced the risk of rebleeding and rebleeding from varices compared with endoscopy alone. However, no significant benefit was observed in terms of all-cause mortality or mortality caused by bleeding. In the study by De la Pena et al,[36] apart from decreasing the risk of bleeding, combining pharmacotherapy and ligation therapy slowed the frequency of variceal reappearance and decreased the number of endoscopic sessions. Lo et al[37] found a significant decrease in rebleeding risk among patients treated with triple therapy (nadolol, sucralfate, and ligation). This beneficial effect could be attributed to the reduction of mucosal ulcers because of sucralfate and reduction of variceal bleeding caused by the lowering of portal pressure by β-blockers.

Study limitations

Our meta-analysis has limitations intrinsic to this type of analysis. The amount of the pooled data is important because the results become more reliable and the margin for error decreases as the amount of data increases. Trials with negative findings are less likely to be published, and some of the data used in our meta-analysis were extracted from published abstracts, which could have affected our results. Moreover, the heterogeneity of patient populations and different treatment protocols may also be a concern in our meta-analysis. In addition, widely different definitions of what constitutes rebleeding used by various studies in the analysis can confound any conclusions from this data set. The statistical ''heterogenicity'' of the results obtained by endoscopic therapy is owing to the lack of rules regarding its application.

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Received August 14, 2008. Accepted February 26, 2009.

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APPENDIX 1. Clinical characteristics of patients receiving β-blocker therapy versus those receiving endoscopic sclerotherapy

Study	β/ES					Child-Pugh score	β-blocker dose	Type of sclerosant	Mean time interval between sessions (days)
	No. pts	Mean age, y	Male	Alcohol	Viral	A B C			
Dasarathy et al[14]	46/45	47/43	40/40	12/13	13/10	0/0 30/30 16/15	160 mg/day	1% P	10
Westaby et al[19]	52/56	54/52	31/34	32/26	2/6	22/22 30/34 0/0	120 mg/day	NG	7-28
Fleig et al[15]	34/36	49/44	26/22	27/31	5/5	5/5 17/21 12/9	161 mg/day	1% P	3-4
Rossi et al[17]	27/26	54/52	21/11	27/26	0/0	NR	54 mg BID	1% P	5-7
Teres et al[16]	58/58	59/57	40/35	33/31	NG	NR	103 mg BID	5% EO	7
Villanueva et al[18]	43/43	58/60	29/29	25/24	NG	9/11 27/22 7/10	80 40 mg BID	5% EO	0, 4, 10, 30
Alexandrino et al[13]	34/31	50/45	28/24	26/26	NG	24/23 10/8 0/0	130 mg/day	5% EO	4

β/ES, β-Blocker therapy/endoscopic sclerotherapy; *pts*, patients; *P*, polidocanol; *NG*, not given; *EO*, ethanolamine oleate; *BID*, twice a day.

APPENDIX 2. Clinical characteristics of patients receiving β-blocker therapy + endoscopic sclerotherapy versus those receiving pharmacotherapy

Study	β/ES No. pts	Mean age, y	Male	Alcohol	Viral	Child-Pugh score A B C	Mean β-blocker dose	Type of sclerosant	Mean time interval between sessions (days)
Jensen and Krarup[23]	15/16	46/47	15/12	12/14	1/4	4/4	160 mg/day	2% E	30
						7/7			
						4/5			
Lundell et al[29]	19/22	58/55	9/13	11/15	0/0	4/5	100 mg BID	1% E	30
						6/5			
						9/12			
Vinel et al[26]	39/35	54.6/57	30/28	32/33	0/0	NG	54.6 mg/day	1% P	0, 1, 3
Avegrinos et al[21]	45/40	57.8/58.6	29/32	9/13	25/18	33/30	96.5 mg/day	5% EA	7
						8/8			
						4/2			
Elsayed et al[28]	70/70	43/43	58/60	—	12/1	38/39	90 mg initial and 30 mg/day maintenance	5% EA	90
						20/20			
						12/11			
Bertoni et al[22]*	14/14	63.4/55	8/10	9/2	2/4	5/5	40-120 mg/day	1% P	NG
						4/5			
						5/5			
Dowidar et al[30]	20/20	49/43	17/19	0/0	0/0	11/7	40 mg/day	2.5% EA	7
						9/11			
						0/2			
Acharya et al[20]	58/56	35.8/33.6	49/48	3/4	4/20	37/31	160 mg/day	1% P	10
						31/25			
						0/0			
Gerunda et al[24]*	30/30						80 mg/day	NG	7
Vickers et al[25]	39/34	57/53	25/18	13/12	2/3	11/8	160 mg/day	2% EA	21
						20/17			
						8/9			
Westaby et al[27]	26/27	46/51	16/17	10/9	3/4	5/2	120 mg/day	NG	7 days for 3 wk, thereafter 21 days
						6/13			
						10/8			

β+*ES/ES*, β-Blocker therapy + endoscopic sclerotherapy/endoscopic sclerotherapy only; *pts*, patients, *E*, ethoxysclerol; *P*, polidocanol; *EA*, ethanolamine; *NG*, not given.
*Trials used nadolol.

APPENDIX 3. Clinical characteristics of patients receiving β-blocker therapy versus those undergoing endoscopic variceal ligation

Study	β/ES					Child-Pugh score A B C	Mean β-blocker dose (mg/day)	No bands	Mean time interval between sessions (days)
	No. pts	Mean age, y	Male	Alcohol	Viral				
Lo et al[31]*	61/60	51/52	47/46	22/16	36/39	13/13	40	NG	21-28
						35/35			
						13/12			
Sarin et al[34]	66/71	36.2/35/8	45/51	15/18	23/25	27/35	240	2-10	14
						28/26			
						11/10			
Villanueva et al[32]*	72/72	52.4+13.4	43/47	33/30	24/26	19/11	80	8	14-21
						39/43			
						14/18			
Patch et al[33]	51/51	50.7/52.4	35/35	32/36	—	8/5	80	NG	14
						19/18			
						24/28			

β/*EVL*, β-Blocker therapy/endoscopic variceal ligation; *pts*, patients; *NG*, not given.

APPENDIX 4. Clinical characteristics of patients receiving β-blocker therapy + endoscopic variceal ligation versus those undergoing endoscopic variceal ligation only

Study	β+EVL/EVL					Child-Pugh score*	Mean β-blocker dose (mg/day)	No. bands	Mean time interval between sessions (days)
	No. pts	Mean age	Male	Alcohol	Viral	A B C			
Lo et al[31,35]†‡	60/62	53/51	45/49	17/20	41/41	11/12 12/18 19/22	60	1-2	21
De la Pena et al[36,†]	43/37	60/60	33/27	27/26	12/8	6/6 25/20 2/11	58	NG	10-12
Jain et al[37]	61/67	NG	NG			26/24 23/37 12/6	114.3		

β+*EVL/EVL EVL*, β-Blocker therapy + endoscopic variceal ligation/endoscopic variceal ligation only; *pts*, patients; *Pugh score*, A, B, C, β, patients treated with β-blockers; NG, not given.

*The Child-Pugh class was determined on the basis of data collected at randomization. Class A denotes good hepatic function (a score of 5 or 6), class B intermediate function (a score of 7 to 9), and class C poor function (a score of 10 to 12).

†Trials used nadolol.

‡Trials used sucralfate.

APPENDIX 5. Clinical characteristics of patients receiving pharmacotherapy versus those undergoing endoscopic variceal ligation + sclerotherapy

	β/EVL+ES								
Study	No. pts	Age, y	Male	Alcohol	Viral	Mean β- blocker dose (mg/day)	Mean no. bands	Type of sclerosant	Mean time interval between sessions (days)
Romero et al[38]	57/52	51/53	37/35	30/24	8/7	40	10	2% P	14

β/*EVL+ES*, β-Blocker therapy/endoscopic variceal ligation + endoscopic sclerotherapy; *pts*, patients; *P*, polidocanol.