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BRIEF ARTICLE

Efficacy of β-adrenergic blocker plus 5-isosorbide mononitrate and endoscopic band ligation for prophylaxis of esophageal variceal rebleeding: A meta-analysis

Shi-Hua Ding, Jun Liu, Jian-Ping Wang

Shi-Hua Ding, Jun Liu, Jian-Ping Wang, Department of Gastroenterology, The Affiliated Shenzhen Hospital, Nanfang Medical University, Shenzhen 518035, Guangdong Province, China

Author contributions: Ding SH designed the study and wrote the manuscript; Wang JP collected the data; Liu J analyzed the available data and assessed the methodological quality of each study in accordance with the criteria by Jadad.

Correspondence to: Shi-Hua Ding, Department of Gastroenterology, The Affiliated Shenzhen Hospital, Nanfang Medical University, Shenzhen 518035, Guangdong Province, China. shding123@163.com

Telephone: +86-755-83366388 Fax: +86-755-83356952

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Abstract

AIM: To systematically assess the efficacy and safety of β-adrenergic blocker plus 5-isosorbide mononitrate (BB + ISMN) and endoscopic band ligation (EBL) on prophylaxis of esophageal variceal rebleeding.

METHODS: Randomized controlled trials (RCTs) comparing the efficacy and safety of BB + ISMN and EBL on prophylaxis of esophageal variceal rebleeding were gathered from Medline, Embase, Cochrane Controlled Trial Registry and China Biological Medicine database between January 1980 and August 2007. Data from five trials were extracted and pooled. The analyses of the available data using the Revman 4.2 software were based on the intention-to-treat principle.

RESULTS: Four RCTs met the inclusion criteria. In comparison with BB + ISMN with EBL in prophylaxis of esophageal variceal rebleeding, there was no significant difference in the rate of rebleeding [relative risk (RR), 0.79; 95% CI: 0.62-1.00; $P = 0.05$], bleeding-related mortality (RR, 0.76; 95% CI: 0.31-1.42; $P = 0.40$), overall mortality (RR, 0.81; 95% CI: 0.61-1.08; $P = 0.15$) and complications (RR, 1.26; 95% CI: 0.93-1.70; $P = 0.13$).

CONCLUSION: In the prevention of esophageal variceal rebleeding, BB + ISMN are as effective as EBL. There are few complications with the two treatment modalities. Both BB + ISMN and EBL would be considered as the first-line therapy in the prevention of esophageal variceal rebleeding.

Key words: Meta-analysis; Esophageal variceal rebleeding; Endoscopic band ligation; β-adrenergic blocker; 5-isosorbide mononitrate; Prophylaxis

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INTRODUCTION

Cirrhotic patients with esophageal variceal bleeding have a very high incidence of rebleeding and a significant risk of death. Therefore, it was radical to adopt some interventional measures to prevent esophageal variceal rebleeding. Both endoscopic band ligation (EBL) and β-adrenergic blocker (BB) are the main therapies for secondary prophylaxis of esophageal variceal bleeding. Compared with untreated controls, these treatments can decrease the rate of variceal rebleeding and mortality[1-2]. Despite using adequate BBs, the portal pressure does not decrease in over one-third of patients[3]. Combined β-adrenergic blocker and 5-isosorbide mononitrate (BB + ISMN) was more effective than BBs alone in the prevention of esophageal variceal rebleeding[4-5]. It is still unknown whether drug therapy is superior to EBL for preventing variceal rebleeding. Several randomized controlled trials have shown different results[6-9].

Meta-analyses can statistically combine the results of several studies and resolve discrepancies among single studies. Because of combining the sample of individual studies, a meta-analysis greatly increases the overall sample size, which increases the statistical power of the

analysis, as well as the precision of the estimation of the therapeutic effect. The purpose of this study was to perform a meta-analysis of randomized controlled trials (RCTs) comparing BB + ISMN with EBL for secondary prophylaxis of esophageal variceal bleeding, and draw an overall conclusion about the safety and efficacy of the two treatments.

MATERIALS AND METHODS

Study selection

Any studies that met all of the following inclusion criteria were included: (1) the study was an RCT comparing the efficacy and safety of BB + ISMN and EBL on prophylaxis of esophageal variceal rebleeding; (2) duration of follow-up was at least 6 mo; and (3) outcome evaluation included at least one of the following: rebleeding, all-cause mortality, bleeding-related deaths and complications.

Search strategy

Medline, Embase, Cochrane Controlled Trial Registry and China Biological Medicine database were searched from January 1980 to August 2007 to locate published research in the area of esophageal variceal rebleeding. Key words used for searching included: esophageal variceal bleeding, BB, EBL, 5-ISMN, rebleeding, prevention and RCT. There was no language restriction applied to the search.

Assessment of study quality

Two of us independently assessed the methodological quality of each study in accordance with the criteria of Moher *et al*[10]. The trials were considered of high quality if the methodological quality score was three or more. The Jadad standard included four components: allocation sequence generation (computer-generated random number or similar, 2; not described, 1; and inadequate, 0); allocation concealment (central randomization and sealed envelops, 2; not described, 1; inadequate, 0); double blinding (identical placebo tablets or double dummy, 2; double blind but method not described, 1; no double blinding or inadequate method, 0); and description of protocol deviations, withdrawals and dropouts (numbers and reasons described, 1; not described, 0).

Statistical analysis

The measurement of association used in this meta-analysis was relative risk (RR) with 95% CI. Statistical heterogeneity between trials was evaluated by the Cochran Chi-square test and defined at a P value less than 0.1. In the absence of statistically significant heterogeneity, summary RR with 95% CI was calculated using fixed-effect models whereas potential reasons for heterogeneity was explored by subgroup analysis and sensitivity analysis using random-effect model. P value less than 0.05 was considered significantly different. All analyses and calculations were performed using the Revman 4.2 software.

RESULTS

Description of selected trials

Five RCTs met the inclusion criteria after searching the electronic databases, and one was excluded because it did not provide the same data. Four RCTs included 476 patients. The characteristics and quality of these four RCTs are summarized in Table 1. Two RCTs showed that BB + ISMN were as effective as EBL, one showed that pharmaceutical therapy was better, and the other showed a benefit of EBL. Three studies compared nadolol plus 5-ISMN with EBL, and propranolol plus 5-ISMN were administered in one study. A few patients in the EBL group received one or two sessions of sclerotherapy simultaneously in the Romero 2006 study.

Outcome evaluation

Rebleeding: Data from four randomized trials included 476 patients available for the assessment of rebleeding. Rebleeding was seen in 105 of 240 patients in the BB + ISMN group and in 109 of 236 patients in the EBL group. Summary RR for all four trials showed no significant difference in the rate of rebleeding between the BB + ISMN and EBL groups (RR, 0.94; 95% CI: 0.64-1.38; $P = 0.76$) using a randomized-effect model (Figure 1A). Test of heterogeneity for the rate of rebleeding was significant ($\chi^2 = 10.54$, $P = 0.01$). Clinical parameters were used to explore the cause of statistical heterogeneity. The proportion of patients who had large varices was higher in the BB + ISMN (30/61) than in the EBL group (19/60) in the LO2002 study[7]. Excluding this trial, the heterogeneity of χ^2 value for the remaining three trials was 2.37, $P = 0.31$. Summary RR for all these three trials showed no significant difference in the rate of rebleeding between the BB + ISMN and EBL groups (RR, 0.79; 95% CI: 0.62-1.00; $P = 0.05$) using a fixed-effect model.

All-cause mortality: Fifty-nine patients died in the BB + ISMN group and 72 in the EBL group. There was no significant heterogeneity between the studies ($P = 0.58$). Summary RR for all four trials showed no significant difference in the rate of all-cause mortality between the BB + ISMN and EBL groups (RR, 0.81; 95% CI: 0.61-1.08; $P = 0.15$) using a fixed-effect model (Figure 1B).

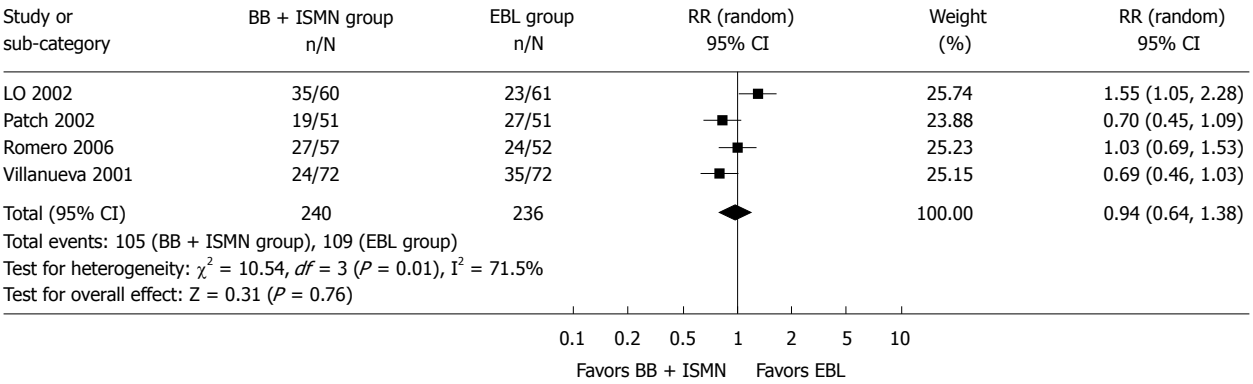
Bleeding-related deaths: Three trials evaluated bleeding-related deaths. There was no significant heterogeneity among studies ($P = 0.58$) and no significant difference in the rate of bleeding-related deaths between the BB + ISMN and EBL groups (RR, 0.76; 95% CI: 0.31-1.42; $P = 0.40$) (Figure 1C).

Complications: Adverse events were found in 76 patients in the BB + ISMN group including bradycardia, hypotension and headache, and 55 patients in the EBL group including bleeding ulcers, perforation, stenosis and chest pain. There was no mortality resulting from complications in either group. Summary RR for all four trials showed no significant difference in the occurrence of

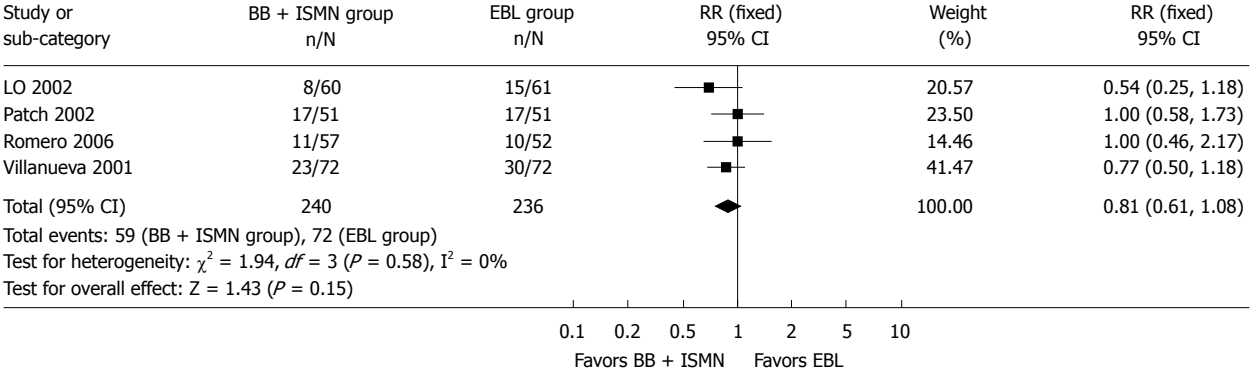
Table 1 Patient characteristics and Jadad score of included trials

Trials	Number of patients (BB + I/EBL)	Mean age (yr) (BB + I/EBL)	Males (BB + I/EBL)	Follow-up duration (BB + I/EBL)	Child-Pugh (A:B:C) (BB + I/EBL)	EBL mean sessions	BB + ISMN (mg/d)	Jadad score
Romero 2006	57/52	51 ± 10/53 ± 10	37:20/35:17	12/11.5 mo	23:25:9/ 17:30:5	3.4 ± 1.2	Nadolol 88 ± 68 5-ISMN 57.7 ± 27	6
PATCH 2002	51/51	50.7 ± 13.2/ 52.4 ± 13.4	35:16/35:16	248/356 d	8:19:24/ 5:18:28	2	Pronolol 80 (40-240) 5-ISMN	5
LO 2002	61/60	51 ± 13/52 ± 12	47:14/46:14	24/25 mo	13:35:13/ 13:35:12	3.3 ± 1.1	Nadolol 48 ± 10 5-ISMN 30 ± 6	5
Villanueva 2001	72/72	60 ± 12/58 ± 14	43:29/47:25	20/22 mo	19:39:14/ 11:43:18	2.1	Nadolol 96 ± 56 5-ISMN 66 ± 22	6

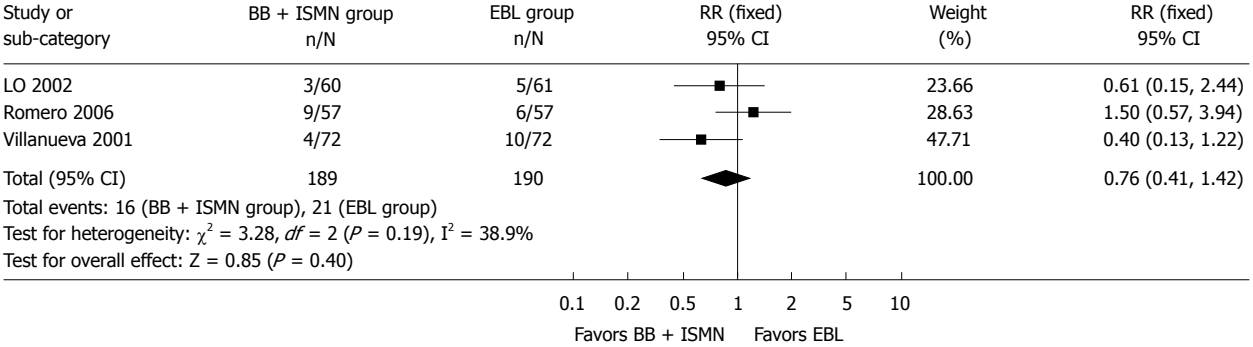
A Review: Prophylaxis of esophageal variceal rebleeding
Comparison: 01 BB + ISMN group *vs* EBL group
Outcome: 01 rebleeding rate



B Review: Prophylaxis of esophageal variceal rebleeding
Comparison: 01 BB + ISMN group *vs* EBL group
Outcome: 02 all-cause deaths



C Review: Prophylaxis of esophageal variceal rebleeding
Comparison: 01 BB + ISMN group *vs* EBL group
Outcome: 03 bleed-related deaths



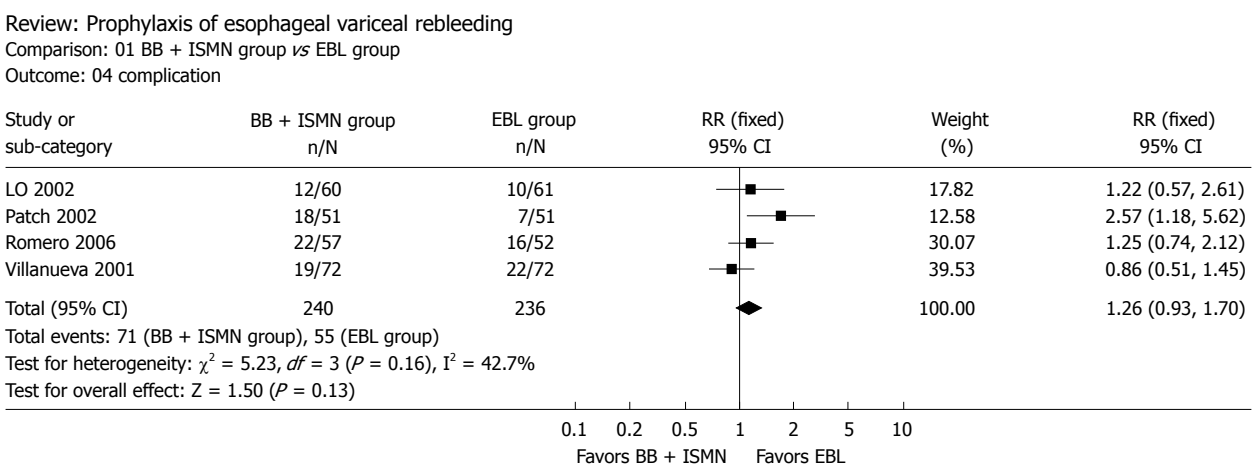


Figure 1 Comparison between BB + ISMN and EBL. A: Rebleeding rate; B: All-cause mortality; C: Bleeding-related mortality; D: Complication rate.

complications between the BB + ISMN and EBL groups (RR, 1.26; 95% CI: 0.93-1.70; $P = 0.13$) using a fixed-effect model (Figure 1D). Test of heterogeneity was not significant in the occurrence of complications ($P = 0.16$).

DISCUSSION

EBL has significantly reduced the frequency of variceal rebleeding, mortality and complications, and has replaced endoscopic injection sclerotherapy as the first-line therapy in the prevention of esophageal variceal rebleeding[11]. However, this treatment has a high recurrence, needs advanced technique and incurs a high cost[12]. The association of BB + ISMN enhances the reduction in portal pressure. Some clinical trials have found that combined BB + ISMN is superior to sclerotherapy and BB alone in the prevention of esophageal variceal rebleeding, with few complications, low cost and convenient administration[13]. It is still unknown whether drug therapy is superior to EBL for preventing variceal rebleeding. Our study included four RCTs and systematically assessed the efficacy and safety of BB + ISMN and EBL on prophylaxis of esophageal variceal rebleeding.

The meta-analysis showed that the overall rebleeding rate with BB + ISMN (43.8%) did not differ significantly from that of EBL (46.2%). There was a significant heterogeneity among the individual trials. The proportion of patients who had large varices was higher in the BB + ISMN (30/61) group than in the EBL group (19/60) in the LO2002 study, which may be the cause of the significant difference. Excluding this trial, there was no significant difference among the individual trials. Summary RR for all these three trials showed no significant difference in the rate of rebleeding between the BB + ISMN and EBL groups (RR, 0.79; 95% CI: 0.62-1.00; $P = 0.05$) using a fixed-effect model. The result showed that BB + ISMN was as effective as EBL in the prevention of esophageal variceal rebleeding. Decreasing the portal pressure by EBL did not result in increasing the bleeding at other local sites.

A total of 59 (24.5%) patients died in the BB + ISMN group and 72 (35.1%) in the EBL group. The mortality rate was similar in both groups (RR, 0.81; 95% CI: 0.61-1.08; $P = 0.15$). Three trials further evaluated the bleeding-related deaths, and there was no significant difference between the BB + ISMN and EBL groups (RR, 0.76; 95% CI: 0.31-1.42; $P = 0.40$). The comparative results between the BB + ISMN and EBL groups did not affect the all-cause and bleeding-related mortality.

Complications occurred in 71 (29.5%) patients in the BB + ISMN group and 55 (23.3%) in the EBL group ($P = 0.13$). None of the complications was fatal in either group. The occurrence rate of complications in our study was higher than that in other similar studies[14-15] because minor complications were included. Although Villanueva *et al*[6] showed that the incidence of severe adverse events was higher in the EBL group (12%) than in the BB + ISMN group (3%), this did not affect the overall result of our meta-analysis. However, the occurrence of complications was higher in the BB + ISMN group (29.5%) than in the EBL group (23.3%), and more patients withdrew from the study in the BB + ISMN group because they could not tolerate the complications of BBs.

In summary, combined therapy with BB + ISMN is as effective as EBL in the prevention of variceal rebleeding. The complications and survival are similar in the two interventional treatments. Both BB + ISMN and EBL are considered as the first-line therapy in the prevention of esophageal variceal rebleeding.

This meta-analysis was only based on published data and publication bias has not been evaluated because of the paucity of RCT data. The conclusion of this meta-analysis should be further demonstrated by large-scale and multicenter RCTs.

COMMENTS

Background

Cirrhotic patients who bleed from esophageal varices have a very high incidence of rebleeding and a significant risk of death. Both endoscopic band ligation (EBL) and β-adrenergic blocker plus 5-isosorbide mononitrate (BB + ISMN) are the main therapies for secondary prophylaxis of esophageal variceal bleeding. It is still unknown whether the drug therapy is superior to EBL for preventing variceal rebleeding. Several randomized controlled trials (RCTs)

have displayed different results. The authors performed a meta-analysis of RCTs comparing BB + ISMN with EBL for secondary prophylaxis of esophageal variceal bleeding, to draw an overall conclusion about the safety and efficacy of the two treatments.

Research frontiers

EBL has significantly reduced the frequency of variceal rebleeding, mortality and complications. However, this treatment has a higher recurrence, needs advanced techniques and is expensive. Some clinical trials have found that the combination of BB + ISMN is superior to sclerotherapy and BB alone in the prevention of esophageal variceal rebleeding, with few complications, and is cheap and convenient in administration.

Innovations and breakthroughs

To the best of our knowledge, this is the first published meta-analysis comparing BB + ISMN with EBL for secondary prophylaxis of esophageal variceal bleeding.

Applications

The research showed that combined therapy with BB + ISMN is as effective as EBL in the prevention of variceal rebleeding. BB + ISMN can be considered as the first-line therapy in the prevention of esophageal variceal rebleeding.

Peer review

Although good work has been done by this meta-analysis study, this paper needs some revisions.

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