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META-ANALYSIS

Nonselective beta-blockers in cirrhotic patients with no or small varices: A meta-analysis

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Abstract

AIM: To explore effects of nonselective beta-blockers (NSBBs) in cirrhotic patients with no or small varices.

METHODS: The PubMed, EMBASE, Science Direct, and Cochrane library databases were searched for relevant papers. A meta-analysis was performed using ORs with 95%CI as the effect sizes. Subgroup analysis was conducted according to the studies including patients without varices and those with small varices.

RESULTS: Overall, 784 papers were initially retrieved from the database searches, of which six randomized controlled trials were included in the meta-analysis. The incidences of large varices development (OR = 1.05, 95%CI: 0.25-4.36; P = 0.95), first upper gastrointestinal bleeding (OR = 0.59, 95%CI: 0.24-1.47; P = 0.26), and death (OR = 0.70, 95%CI: 0.45-1.10; P = 0.12) were similar between NSBB and placebo groups. However, the incidence of adverse events was significantly higher in the NSBB group compared with the placebo group (OR = 3.47, 95%CI: 1.45-8.33; P = 0.005). The results of subgroup analyses were similar to those of overall analyses.

CONCLUSION: The results of this meta-analysis indicate that NSBBs should not be recommended for cirrhotic patients with no or small varices.

Key words: Beta-blocker; Liver cirrhosis; Portal hypertension; Variceal bleeding; Varices

Core tip: Nonselective beta-blockers have been recommended for the primary and secondary prophylaxis of variceal bleeding in cirrhotic patients with high-risk varices and those with previous bleeding. However, their role remains uncertain in cirrhotic patients with no or small varices. Our meta-analysis demonstrates that the use of nonselective beta-blockers should not be recommended

for cirrhotic patients with no or small varices.

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INTRODUCTION

Variceal bleeding is the most common lethal complication of liver cirrhosis[1]. The first variceal bleeding can lead to a six-week mortality of 15%-20%. Based on the results of meta-analyses and numerous randomized controlled trials (RCTs)[2-7], the current practice guidelines and consensus have clearly recommended the use of nonselective beta-blockers (NSBBs) for the primary prophylaxis of variceal bleeding in cirrhotic patients with medium or large varices without any previous bleeding and for the secondary prophylaxis in those with a history of variceal bleeding[8-10]. However, the recommendations of NSBBs in cirrhotic patients with no or small varices remain obscure. Herein, we collected all available data from RCTs to explore whether the use of NSBBs could prevent the development of large varices and first variceal bleeding, improve the survival, and increase the incidence of adverse events in such patients.

MATERIALS AND METHODS

Study selection

The PubMed, EMBASE, ScienceDirect, and Cochrane library databases were searched for relevant papers. The last search was performed on May 3, 2014. Eligibility criteria were as follows: (1) the study design should be RCT; (2) the outcomes should include the change in the diameter of varices and/or development of variceal bleeding; (3) the participants should include the cirrhotic patients with no varices and those with small or low-risk varices, but without any previous bleeding; (4) the intervention should be NSBBs; and (5) the comparator should be placebo or no active treatment. Because the detailed information regarding small varices was different among studies, we did not arbitrarily employ any sole definition. However, small varices should be identified according to the pre-existing criteria. Notably, the data concerning medium to large varices were excluded from our studies.

Data extraction

The primary items extracted were as follows: the study design, enrollment period, target population, definition of small varices, number of patients, age, sex, underlying etiology of liver diseases, follow-up information, number of patients with no and small varices, incidence of development of large varices, incidence of first upper-gastrointestinal bleeding, mortality, and incidence of adverse events.

Risk of bias assessment

The Cochrane Collaboration's tool for assessing the risk of bias was employed. It included six entries: the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data addressed, and selective reporting. If one study had more than two "high-risk" entries, it was considered to be of low quality; otherwise, it was considered to be of high quality.

Statistical analysis

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the effect of dichotomous data. I^2 and P values were calculated to assess the heterogeneity among studies (I^2 > 50% and/or P < 0.1 were considered statistically significant). The ORs were pooled using only a random effects model to calculate a more conservative result. Publication bias was evaluated by Egger's test. Subgroup analyses were performed according to the patients with small and no varices. The difference of subgroup results was also tested. Sensitivity analyses were performed in the high-quality studies. P < 0.05 was considered to have a statistically significant difference in the outcomes between NSBBs and placebo groups. Review Manager version 5.1.6 software (The Nordic Cochrane Centre, Copenhagen, Denmark) and StatsDirect version 3.0.113 software (StatsDirect Ltd., Cheshire, United Kingdom) were employed for the statistical analyses.

RESULTS

Study selection

A total of 784 papers were retrieved from the four databases, among which seven papers were considered potentially relevant[11-17]. Notably, one of them was excluded because it included only a smaller proportion of patients than another paper by the same team[16,17]. Finally, six papers were included in the meta-analysis[11-16] (Figure 1). Study and patient characteristics are summarized in Tables 1 and 2, respectively.

Study characteristics

In two studies, the target populations were cirrhotic patients with endoscopically documented varices, irrespective of sizes[11,16]. Only the data regarding small varices were employed for meta-analyses. In one study, the target populations included cirrhotic patients with no varices and those with small varices[12]. In one study, the target populations were cirrhotic patients without any varices[13]. In two studies, the target populations were cirrhotic patients with small varices[14,15].

NSBBs included propranolol in four studies[11,12,15,16], timolol in one study[13], and nadolol in one study[14].

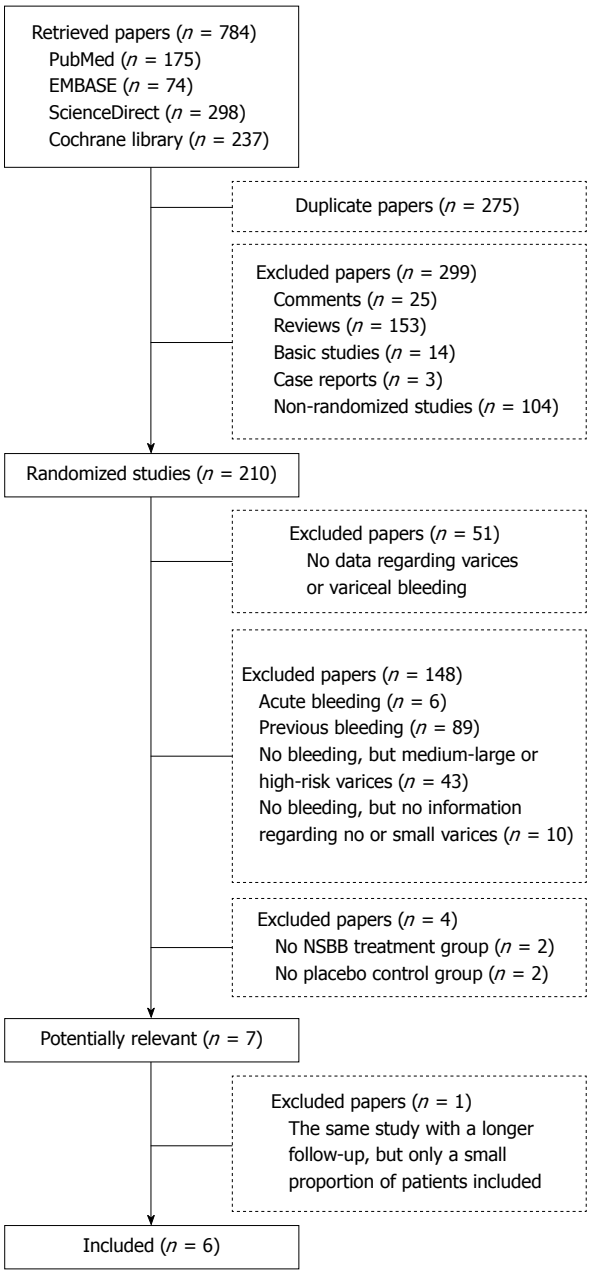

Figure 1 Flowchart of study selection.

Placebo included vitamin K in one study[11] and a tablet that was identical to NSBBs in appearance in two studies[13,16]. The detailed information regarding placebo was not available in three studies[12,14,15].

Patient characteristics

The baseline characteristics regarding age, sex, etiology of liver cirrhosis, and Child-Pugh score of patients were comparable between NSBBs and placebo groups. Notably, only the characteristics of all included patients, but not those of patients with small varices, could be extracted in two studies[11,16].

Risk of bias

Risk of bias assessment for each study is summarized in Table 3. Two studies were of low quality[11,14], and four were of high quality[12,13,15,16].

Outcomes

Development of large varices: Four studies reported the data regarding the development of large varices in cirrhotic patients with no or small varices[12-15]. The incidence of development of large varices was similar between NSBBs and placebo groups (OR = 1.05, 95%CI: 0.25-4.36; P = 0.95) (Figure 2). Heterogeneity among studies was significant (I^2 = 91%; P < 0.01). Publication bias was not significant (Egger's bias = -5.64, 95%CI: -32.848-21.565; P = 0.47).

First upper-gastrointestinal bleeding: Six studies reported the occurrence of first upper-gastrointestinal bleeding in cirrhotic patients with no or small varices[11-16]. The incidence of first upper-gastrointestinal bleeding was not significantly different between NSBBs and placebo group (OR = 0.59, 95%CI: 0.24-1.47; P = 0.26) (Figure 3). Heterogeneity among studies was not significant (I^2 = 20%; P = 0.28). Publication bias was not significant (Egger's bias = 1.55, 95%CI: -4.995-8.086; P = 0.55).

Death: Four studies reported the data regarding the death in cirrhotic patients with no or small varices[12-15]. The incidence of death was lower in the NSBBs group than the placebo group, but the difference was not statistically significant (OR = 0.70, 95%CI: 0.45-1.10; P = 0.12) (Figure 4). Heterogeneity among studies was not significant (I^2 = 0%; P = 0.77). Publication bias was not significant (Egger's bias = 1.53, 95%CI: -0.939-3.993; P = 0.12).

Adverse events: Four studies reported adverse events in cirrhotic patients with no or small varices[12-15]. The incidence of adverse events was significantly higher in the NSBBs group than the placebo group (OR = 3.47, 95%CI: 1.45-8.33; P < 0.01) (Figure 5). Heterogeneity among studies was not significant (I^2 = 39%; P = 0.18). Publication bias was significant (Egger's bias = 1.89, 95%CI: 0.075-3.701; P < 0.05).

Subgroup analyses

The results of the subgroup analyses were similar to those of the overall analysis, with no significant differences between patients with no varices or small varices (Table 4).

Sensitivity analyses

The results of the sensitivity analysis were similar to those of the overall analysis (Table 5).

DISCUSSION

At the first diagnosis of liver cirrhosis, the prevalence of gastroesophageal varices is diagnosed in about 50% of patients[9]. In cirrhotic patients without any pre-existing

Table 1 Information of included studies

Ref.	Year	Study design and regions	Period of enrollment	Target population	Groups	Definitions of small varices	*n*
Andreani *et al*[11]	1990	Multi-center RCT from two centers in Paris	Nov. 1985 to Feb. 1988	LC without previous bleeding, but with esophageal varices (small or large)	Propranolol *vs* placebo	Non-confluent esophageal varices flattened by insufflation	84
Conn *et al*[16]	1991	Multi-center double-blinded RCT from three centers in the United States and Spain	Oct. 1982 to Aug. 1986	LC without previous bleeding, but with esophageal varices (small or large)	Propranolol *vs* placebo	Diameter: 1-3 mm with Valsalva	102
Calés *et al*[12]	1999	Multi-center double-blinded RCT from 14 centers in France	April 1991 to June 1993	LC without varices or small esophageal varices	Propranolol *vs* placebo	Diameter: < 5 mm	206
Merkel *et al*[14]	2004	Multi-center single-blinded RCT from seven hospitals in Italy	Dec. 1996 to April 2000	LC with small varices	Nadolol *vs* placebo	F1 without red signs according to Beppu *et al*[27] (small straight varices, minimally elevated on the esophageal mucosal surface)	161
Groszmann *et al*[13]	2005	Multi-center double-blinded RCT from four hospitals in the United States, Spain, and United Kingdom	Aug. 1993 to March 1999	LC with an HVPG of ³ 6 mmHg, and without gastroesophageal varices	Timolol *vs* placebo	NA	213
Sarin *et al*[15]	2013	Single-center single-blinded RCT in India	Oct. 2004 to June 2007	LC with small varices, without any history of variceal bleed	Propranolol *vs* placebo	Grade 1 or 2 according to the classification of Conn[28] or small according to de Franchis *et al*[29]	150

HVPG: Hepatic venous pressure gradient; LC: Liver cirrhosis; RCT: Randomized controlled trial.

Table 2 Patient characteristics of included studies

Ref.	Groups	*n*	Age (yr)	Sex (M/F)	Etiology (alcohol/viral/other)	Child-Pugh score or class A/B/C	Follow-up (mo)	Lost to follow-up	Small varices, *n*	No varices, *n*
Andreani *et al*[11]	Propranolol	43	55.0 ± 1.3	27/16	33/-/10	10/19/13	NA	6	15	0
	Placebo	41	55.6 ± 1.7	23/18	33/-/8	10/21/10	NA	2	17	0
Conn *et al*[16]	Propranolol	51	54 ± 9	38/13	39/-/12	Mean: 8.0	17.1 ± 10.9	NA	26	0
	Placebo	51	54 ± 11	35/16	41/-/10	Mean: 8.3	16.3 ± 12	NA	29	0
Calés *et al*[12]	Propranolol	102	52.7 ± 10.4	69/33	88/-/24	6.8 ± 2.1	NA	41	60	42
	Placebo	104	52.7 ± 11.4	68/36	81/-/23	6.8 ± 2.0	NA	32	67	37
Merkel *et al*[14]	Nadolol	83	56 ± 9	45/38	47/34/2	6.8 ± 1.6	36 ± 18	11	83	0
	Placebo	78	57 ± 9	38/40	45/28/5	7.1 ± 1.9	35 ± 15	10	78	0
Groszmann *et al*[13]	Timolol	108	46 ± 11	70/38	26/73/9	5.4 ± 0.7	Median: 52.7	0	0	108
	Placebo	105	44 ± 11	56/49	25/69/11	5.4 ± 0.8	Median: 57.9	0	0	105
Sarin *et al*[15]	Propranolol	77	42 ± 13	63/14	27/42/8	7.4 ± 1.9	25 ± 12.6	0	77	0
	Placebo	73	44 ± 13	57/16	26/38/9	7.7 ± 2.3		0	73	0

F: Female; M: Male; NA: Not available. Note: data are expressed as mean ± SD unless otherwise indicated.

Table 3 Risk of bias for the study

Entry	Judgment	Support for judgment
Andreani (1990)		
Random sequence generation (selection bias)	Low risk	Quote: "the patients in each center were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias)	High risk	Quote: "these treatments were not administered blindly"
Blinding of outcome assessment (detection bias)	Unclear risk	Not described
Incomplete outcome data addressed (attrition bias)	High risk	Quote: "Fourteen patients were lost to follow-up after a period of 4.9 ± 1.9 mo (propranolol=six, sclerosis=six, placebo=two)"
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced.
Conn (1991)		
Random sequence generation (selection bias)	Low risk	Quote: "the patients were randomly selected"
Allocation concealment (selection bias)	Low risk	Quote: "using a sealed envelope technique and computer-generated randomization"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blinded", "The placebo and the propranolol tablets were identical in appearance"

Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blinded", "the patients were examined on each visit by a nurse and the postdoctoral fellow assigned to the study"
Incomplete outcome data addressed (attrition bias)	Unclear risk	Not described
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced
Cales (1999)		
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized"
Allocation concealment (selection bias)	Low risk	Quote: "by the opaque sealed envelope method"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "double-blinded", "Patients and physicians were unaware of the treatment"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blinded", "Patients and physicians were unaware of the treatment"
Incomplete outcome data addressed (attrition bias)	High risk	Quote: "In the propranolol group, 41 patients were lost to follow-up, compared with 32 in the placebo group"
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced
Merkel (2004)		
Random sequence generation (selection bias)	Low risk	Quote: "A total of 83 patients were randomized to"
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was generated by tables of random numbers, stratified by participating centers, prepared at the University of Padua, and administered by opaque sealed and consecutively numbered envelopes containing randomization"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The single-blind study design was chosen"
Blinding of outcome assessment (detection bias)	High risk	Quote: "The single-blind study design was chosen"
Incomplete outcome data addressed (attrition bias)	High risk	Quote: "11 patients randomized to nadolol and 10 patients randomized to placebo were lost to follow-up"
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced
Groszmann (2005)		
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned"
Allocation concealment (selection bias)	Low risk	Quote: "The randomization code was generated by computer for each participating center"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "The study was an investigator-initiated, randomized, double-blind, placebo-controlled, clinical trial conducted at four sites"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "double-blinded", "To maintain study blinding, the patient's heart rate was measured by the study nurse and not by the investigators"
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: "The remaining 277 were excluded for the following reasons: …6 were lost to follow-up…" Patients who were lost to follow-up were excluded from the final analysis
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced
Sarin (2012)		
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned"
Allocation concealment (selection bias)	Low risk	Quote: "All randomizations were done by computer-generated random numbers"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "single-blind"
Blinding of outcome assessment (detection bias)	High risk	Quote: "single-blind"
Incomplete outcome data addressed (attrition bias)	Low risk	Quote: "Another 14 patients were excluded because they dropped out before the completion of 6 months of study" Patients who were lost to follow-up were excluded from the final analysis
Selective reporting (reporting bias)	Low risk	Both potential efficacy and complications were reported. Review authors do not believe that bias will be introduced

varices, the incidence of esophageal varices is 5 and 28% at one and three years, respectively. In cirrhotic patients with small varices, the incidence of variceal progression is 12% and 31% at one and three years, respectively[18]. Once large varices develop, the risk of bleeding is significantly increased[19]. Accordingly, pre- and early-primary prophylaxis of variceal bleeding has been proposed in patients with no and small varices, respectively. The former therapeutic objective is to prevent the formation of varices in patients without any pre-existing varices, and the latter aims to inhibit the progression from small to large varices in cirrhotic patients[8-10].

The major mechanisms of NSBBs for the management of portal hypertension in liver cirrhosis include the reduction of cardiac output and splanchnic vasoconstriction, which potentially decrease the portal pressure and blood flow. Currently, the role of NSBBs for delaying and avoiding the occurrence and enlargement of varices has been debated. However, the results of RCTs were not consistent. The present meta-analysis evaluated the efficacy and safety of NSBBs in cirrhotic patients with no and small varices by collecting all available high-level evidence. Unfortunately, we did not

1 Development of large varices

1.1 Total analysis	NSBB		Placebo			Odds ratio		Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%CI	Year	M-H, Random, 95%CI
Cales (1999)	69	102	34	104	26.7%	4.30 [2.40, 7.71]	1999	
Merkel (2004)	9	83	29	78	25.5%	0.21 [0.09, 0.47]	2004	
Groszmann (2005)	4	108	4	105	22.0%	0.97 [0.24, 3.99]	2005	
Sarin (2012)	18	77	14	73	25.8%	1.29 [0.59, 2.82]	2012	
Total (95%CI)		370		360	100.0%	1.05 [0.25, 4.36]		
Total events	100		81					

Heterogeneity: Tau^2 = 1.90; χ^2 = 35.18, df = 3 (P < 0.00001); I^2 = 91%

Test for overall effect: Z = 0.06 (P = 0.95)

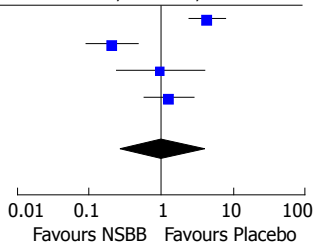

Figure 2 Forest plots comparing the development of large varices between nonselective beta-blockers and placebo groups.

2 First bleeding

2.1 Total analysis	NSBB		Placebo			Odds ratio		Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%CI	Year	M-H, Random, 95%CI
Andreani (1990)	0	15	2	17	7.7%	0.20 [0.01, 4.52]	1990	
Conn (1991)	2	26	2	29	16.0%	1.13 [0.15, 8.61]	1991	
Cales (1999)	2	102	2	104	16.7%	1.02 [0.14, 7.38]	1999	
Merkel (2004)	2	83	9	78	23.8%	0.19 [0.04, 0.91]	2004	
Groszmann (2005)	2	108	5	105	21.9%	0.38 [0.07, 1.99]	2005	
Sarin (2012)	4	77	1	73	13.9%	3.95 [0.43, 36.16]	2012	
Total (95%CI)		411		406	100.0%	0.59 [0.24, 1.47]		
Total events	12		21					

Heterogeneity: Tau^2 = 0.26; χ^2 = 6.27, df = 5 (P = 0.28); I^2 = 20%

Test for overall effect: Z = 1.12 (P = 0.26)

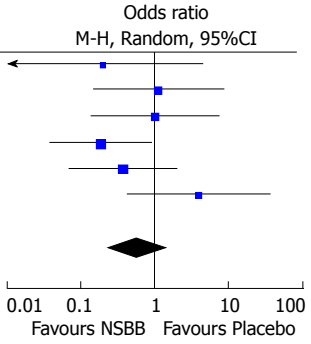

Figure 3 Forest plots comparing first upper-gastrointestinal bleeding between nonselective beta-blockers and placebo groups.

3 Death

3.1 Total analysis	NSBB		Placebo			Odds ratio		Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%CI	Year	M-H, Random, 95%CI
Cales (1999)	9	102	10	104	21.8%	0.91 [0.35, 2.34]	1999	
Merkel (2004)	24	83	31	78	45.3%	0.62 [0.32, 1.19]	2004	
Groszmann (2005)	10	108	15	105	27.0%	0.61 [0.26, 1.43]	2005	
Sarin (2012)	3	77	2	73	5.9%	1.44 [0.23, 8.87]	2012	
Total (95%CI)		370		360	100.0%	0.70 [0.45, 1.10]		
Total events	46		58					

Heterogeneity: Tau^2 = 0.00; χ^2 = 1.14, df = 3 (P = 0.77); I^2 = 0%

Test for overall effect: Z = 1.56 (P = 0.12)

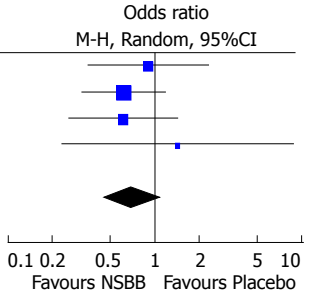

Figure 4 Forest plots comparing the rate of death between nonselective beta-blockers and placebo groups.

4 Adverse events

4.1 Total analysis	NSBB		Placebo			Odds ratio		Odds ratio
Study or subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95%CI	Year	M-H, Random, 95%CI
Cales (1999)	12	102	2	104	21.6%	6.80 [1.48, 31.20]	1999	
Merkel (2004)	9	83	0	78	8.1%	20.02 [1.14, 350.08]	2004	
Groszmann (2005)	52	108	34	105	50.1%	1.94 [1.11, 3.38]	2005	
Sarin (2012)	7	77	2	73	20.2%	3.55 [0.71, 17.68]	2012	
Total (95%CI)		370		360	100.0%	3.47 [1.45, 8.33]		
Total events	80		38					

Heterogeneity: Tau^2 = 0.32; χ^2 = 4.93, df = 3 (P = 0.18); I^2 = 39%

Test for overall effect: Z = 2.79 (P = 0.005)

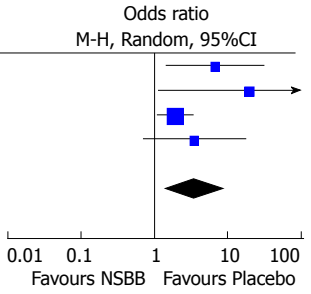

Figure 5 Forest plots comparing the rate of adverse events between nonselective beta-blockers and placebo groups.

Table 4 Results of subgroup analyses

Category	Studies, *n*	Patients, *n*	OR (95%CI)	Heterogeneity	Subgroup difference
Development of large varices					
No varices	2	292	2.43 (0.44-13.55) *P* = 0.31	I^2 = 71% *P* = 0.06	I^2 = 0% *P* = 0.51
Small varices	3	444	1.07 (0.19-6.18) *P* = 0.94	I^2 = 93% *P* < 0.01	
First bleeding					
No varices	1	213	0.38 (0.07-1.99) *P* = 0.25	NA	I^2 = 0% *P* = 0.64
Small varices	4	398	0.64 (0.15-2.79) *P* = 0.55	I^2 = 47% *P* = 0.13	
Death					
No varices	1	213	0.61 (0.26-1.43) *P* = 0.26	NA	I^2 = 0 *P* = 0.84
Small varices	2	311	0.68 (0.37-1.26) *P* = 0.22	I^2 = 0% *P* = 0.39	
Adverse events					
No varices	1	213	1.94 (1.11-3.38) P = 0.02	NA	I^2 = 37.1% *P* = 0.21
Small varices	2	311	5.75 (1.17-28.29) P = 0.03	I^2 = 15% *P* = 0.28	

NA: Not assessed; OR: Odds ratio.

Table 5 Results of sensitivity analyses

Outcomes	Studies, *n*	Patients, *n*	OR (95%CI)	Heterogeneity
Development of large varices	3	569	1.95 (0.73-5.24) *P* = 0.18	I^2 = 74% *P* = 0.02
First bleeding	4	624	0.96 (0.37-2.54) *P* = 0.94	I^2 = 0% *P* = 0.42
Death	3	569	0.79 (0.43-1.43) *P* = 0.43	I^2 = 0% *P* = 0.65
Adverse events	3	569	2.68 (1.33-5.43) *P* = 0.01	I^2 = 24% *P* = 0.27

OR: Odds ratio.

find any significant benefits of NSBBs in preventing the development of large varices, decreasing the incidence of first bleeding, or improving the survival. In contrast, we found a significantly higher incidence of adverse events in the NSBBs group compared to the placebo group. These findings do not support the use of NSBBs in cirrhotic patients with no and small varices.

Considering that the risk of first bleeding was significantly higher in patients with small varices compared to those without[18], subgroup analyses were conducted to explore the treatment effect of NSBBs in both patient groups. Sensitivity analyses were also performed to avoid the potential influence of study quality on the results of our meta-analysis. However, the results of both subgroup and sensitivity analyses were similar to those of the overall analysis.

In spite of a negative result in the overall analysis, we did not readily exclude any slight benefits of NSBBs in pre- and early-primary prophylaxis of variceal bleeding. Undoubtedly, a proportion of cirrhotic patients responded to NSBBs, thereby reducing the hepatic venous pressure gradient that was associated with the reduction of hepatocellular carcinoma and hepatic decompensation[20,21]. On the other hand, we observed a trend towards a lower mortality in the NSBBs group. It is possible that a statistical significance might be achieved if the sample size was increased. Notably, NSBBs might improve the non-hemodynamic outcomes of cirrhotic patients, independently of its hemodynamic benefits (*i.e.*, the prevention of variceal bleeding). A meta-analysis by Senzolo *et al*[22] indicated that NSBBs may protect against the development of bacterial translocation in cirrhotic patients, thereby decreasing the incidence of spontaneous bacterial infection. A recent review by Thiele *et al*[23] also suggested that NSBBs decrease the development of hepatocellular carcinoma. Certainly, the potential deleterious effects of NSBBs on liver cirrhosis should never be neglected, such as a decreased survival in patients with refractory ascites *via* development of paracentesis-induced circulatory dysfunction[24,25] and an increased risk of portal vein thrombosis in cirrhotic patients *via* reduced portal flow[26].

This study had several limitations. First, a small number of included studies limited us to perform more comprehensive subgroup analyses. Second, the small sample sizes of the included studies may produce bias. Third, only three of six included studies were published after 2000, and only one of them was published within the last three years. Thus, the definition of small varices varied greatly among studies. Fourth, a significant heterogeneity among studies was observed in the meta-analysis regarding NSBBs for the development of large varices. But it should be noted that only a random effects model was employed. Fifth, two of six RCTs were considered to be of low quality. However, a sensitivity analysis of high-quality studies was employed to avoid

the potential risk of bias. Sixth, a proportion of patients were lost to follow-up in three studies[11,12,14], which might influence the actual results.

In conclusion, based on the current evidence from a meta-analysis of RCTs, the use of NSBBs might not be recommended for cirrhotic patients with no or small varices. Certainly, further studies with larger sample sizes are warranted to confirm the association of NSBBs with survival in such patients.

COMMENTS

Background

Nonselective beta-blockers (NSBBs) should be recommended for the primary prophylaxis of variceal bleeding in cirrhotic patients with medium or large varices without any previous bleeding and for the secondary prophylaxis in those with a history of variceal bleeding.

Research frontiers

Although NSBBs decreases the hepatic venous pressure gradient, their efficacy and safety remain controversial in cirrhotic patients with no or small varices.

Innovations and breakthroughs

The present meta-analysis evaluated the efficacy and safety of NSBBs in cirrhotic patients with no and small varices by collecting all available high-level evidence. Unfortunately, the authors did not find any significant benefits of NSBBs in preventing the development of large varices, decreasing the incidence of first bleeding, or improving the survival of patients.

Applications

The use of NSBBs might not be recommended for cirrhotic patients with no or small varices.

Terminology

Nonselective beta-blockers are oral drugs that can reduce the cardiac output *via* inhibiting β1 receptor and contract the splanchnic vessels *via* inhibiting β2 receptor, such as propranolol, timolol, and nadolol, *etc*. Portal hypertension is defined as portal venous pressure gradient exceeds 5 mmHg. Varices will develop as portal venous pressure gradient exceeds 10 mmHg, and will bleed as the pressure exceeds 12 mmHg.

Peer-review

Prevention of the development of complications of portal hypertension is an important area of research, and the role of NSBBs remains uncertain in cirrhotic patients with no or small varices. Although this meta-analysis has several limitations, it provides evidence supporting the recommendation of the guidelines and the manuscript is well written.

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