Can Non-Selective Beta-Blockers (NSBBs) Prevent Enlargement of Small Esophageal Varices in Patients with Cirrhosis? A Meta-analysis

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Background: Non-selective beta-blockers (NSBBs) are recommended for prophylaxis of first variceal bleeding in patients of cirrhosis with large esophageal varices. However, the data is conflicting whether NSBBs can also prevent growth of small esophageal varices to large size. **Aim:** To perform a meta-analysis of the randomized clinical trials comparing NSBBs with placebo for prevention of development of large esophageal varices in patients of cirrhosis with small esophageal varices. **Methods:** The PubMed, EMBASE, Science Direct, and Cochrane library databases were searched for relevant papers. A meta-analysis was performed using risk ratios (RRs) with 95% confidence interval (CI) as the effect sizes. **Results:** Overall, 314 trials were initially retrieved from the database searches, of which five randomized controlled trials were included in the meta-analysis. The incidence of development of large varices (RR = 0.91, 95%CI: 0.29–2.86; $P = 0.87$) was similar between NSBB and placebo groups. However, the heterogeneity among studies was significant ($P < 0.01$) with an I^2 of 93%. The incidences of first variceal bleeding (RR = 0.72, 95%CI: 0.25–2.12; $P = 0.55$) and death (RR = 0.76, 95%CI: 0.50–1.15; $P = 0.19$) were also similar between NSBB and placebo groups; with no heterogeneity. The incidence of adverse events was significantly higher in the NSBB group compared with the placebo group (RR = 4.66, 95%CI: 1.36–15.91; $P = 0.01$). **Conclusion:** The results of this meta-analysis indicate that NSBBs are not effective in preventing growth of small varices and may lead to significant adverse effects. Hence, NSBBs should not be recommended for cirrhotic patients with small varices. (J CLIN EXP HEPATOL 2017;7:275–283)

Non-selective beta-blockers (NSBBs) are recommended for prophylaxis of first variceal bleeding in patients of cirrhosis with large esophageal varices. However, the data is conflicting whether NSBBs can also prevent growth of small esophageal varices to large size. We performed a meta-analysis of the randomized clinical trials comparing NSBBs with placebo for prevention of development of large esophageal varices in patients of cirrhosis with small esophageal varices.

MATERIALS AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement and guidelines were consulted during the stages of design, analysis, and reporting of this meta-analysis.^{1,2} Since, this is a meta-analysis, therefore an ethics committee and/or institutional board approval was not required. The meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) vide number CRD42016038230 and is available in full on the NIHR (National Institute for Health Research) website.

Study Selection

Relevant papers were searched from following databases: MEDLINE, PubMed, EMBASE, Science Direct, and the Cochrane Central Register of Controlled Trials. The last search was performed on April 25, 2016. Following keywords were used for the search “esophageal varices”; “cirrhosis”; “chronic liver disease”; “beta-blockers”; “propranolol”; “nadolol”; “bleeding”; and “hemorrhage”. The eligibility criteria for included studies were as follows: (1) The studies should be in English language; (2) The studies should be

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Abbreviations: CI: confidence interval; NIHR: National Institute for Health Research; NSBB: non-selective beta-blockers; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO:

published in full; (3) the study design should be randomized controlled trial; (4) the participants should include the adult cirrhotic patients with small varices, but without any previous history of variceal bleeding; (5) the intervention applied should be oral NSBBs; (6) the comparator should be placebo or no active treatment; and (7) the outcomes should include development of large esophageal varices. Studies published only in abstract form were excluded. Small esophageal varices should be identified according to the pre-existing criteria. The data of patients having no varices, or already having medium to large varices, or history of variceal bleeding, were excluded from our studies.

Data Extraction

The following data were extracted from each study: the study design, enrollment period, target population, definition of small varices, number of patients, age, gender, underlying etiology of cirrhosis, follow-up information, incidence of development of large varices, incidence of first variceal bleeding, mortality, and incidence of adverse events.

Risk of Bias Assessment

The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).³ It included seven entries: the random sequence generation (for selection bias), allocation concealment (for selection bias), blinding of participants and personnel (for performance bias), blinding of outcome assessment (for detection bias), incomplete outcome data (for attrition bias), selective reporting (for reporting bias), and sample size calculation (for type II statistical error). For each domain the risk of bias was evaluated as high, low or unclear. If any 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

The meta-analysis was performed using risk ratios (RRs) with 95% confidence intervals (CIs) as the effect sizes of dichotomous data. The RRs were pooled using only a random effects model to calculate a more conservative result. $P < 0.05$ was considered to have a statistically significant difference in the outcomes between NSBBs and placebo groups. To assess the heterogeneity among studies I^2 and P values were calculated ($I^2 > 50\%$ and/or $P < 0.1$ were considered statistically significant). Sensitivity analyses were performed in the high-quality studies. Publication bias was not investigated graphically (funnel plots) nor by testing (the rank correlation test) because there were fewer than 10 studies in the meta-analysis, which limits the usefulness of these methods.⁴ Review Manager version 5.3.5 software (The Nordic Cochrane

Centre, Copenhagen, Denmark) was employed for the statistical analyses.

RESULTS

Study Selection and Data Collection

Overall, 314 trials were initially retrieved from the database searches and other sources, which were screened for relevance. After carefully cross-referencing the titles, abstracts and keywords, 303 studies were excluded and only 11 potentially relevant studies were evaluated in detail for potential inclusion. Of these 11 studies, another 6 studies were excluded, because five of these studies included patients who only had large varices,^{5–9} while one study included only those patients who had no varices.¹⁰ Hence only 5 studies^{11–15} met the inclusion criteria and were included in the meta-analysis. Figure 1 summarizes the meta-analysis flow.

Characteristics of the Included Studies

The study characteristics of the included five studies are given in Table 1. There were notable differences in the inclusion criteria of these studies: two studies (Andreani et al.¹⁴ and Conn et al.¹⁵) had included patients with both small and large varices; two studies (Merkel et al.¹² and Sarin et al.¹¹) had included patients with only small varices; while one study (Calés et al.¹³) had included patients with both small and no varices. Hence, of the 703 total patients, 525 had small varices, 99 had large varice, and 79 had no varices. Since the primary aim of this meta-analysis was to study the effect of NSBBs on small varices, we used the data of 525 patients with small varices from all the included studies. The NSBB used in each of the studies was propranolol except in the study by Merkel et al.,¹² which used nadolol. There were also notable differences in blinding: two were double-blind^{13,15}; two single blind^{11,12}; and one unblinded.¹⁴ Except for the study by Conn et al.,¹⁵ the follow-up in all the other studies was more than two years.

Baseline Clinical Characteristics of the Included Patients

Since the baseline clinical characteristics of patients with only small varices ($n = 525$) could not be extracted from all the studies, hence characteristics of all the patients regardless of variceal size ($n = 703$) were compared. The combined mean age of patients was 52 ± 11.2 years. There were 467 (66%) males and 236 (34%) females. The etiology of cirrhosis was alcohol in 459 (65%) patients and non-alcoholic in 244 (35%) patients. Majority of patients belonged to Child class A and B. The characteristics of patients in individual studies are given in Table 2 and they were comparable between NSBBs and placebo groups.

Figure 1 Study flow diagram.

Risk of Bias

Risk of bias assessment for each study is summarized in the Figures 2 and 3. Of the five included studies, four^{11,15} were of high quality, having two or less “high risk” entries; while one¹⁴ was of low quality. Since all the studies were randomized and at least four of the studies used allocation concealment, hence studies were mostly free of selection bias. Also since all the studies reported both efficacy as well as adverse effects, hence none of them had reporting bias. In four of the studies,^{11,15} the participants were blinded to treatment offered; hence these four studies were free of performance bias. There was significant detection bias in three of the studies,^{11,12,14} since investigators were not blinded for the outcome assessment. Similarly, there was significant attrition bias in three of the studies¹²⁻¹⁴ due to patients being lost to follow-up. Also there could be significant type II statistical error in three studies¹³⁻¹⁵ because sample size calculation specifically

for patients with small varices was not done in these studies.

Development of Large Varices

The primary aim of this meta-analysis was to investigate the effect of NSBBs for prevention of enlargement of varices from small to large. Only three studies¹¹⁻¹³ addressed this issue involving a total of 438 patients. A total of 220 patients received NSBBs and 218 received placebo. The probability of development of large varices was similar between the NSBB and placebo groups (RR = 0.91, 95%CI: 0.29–2.86; $P = 0.87$) (Figure 4). The heterogeneity among studies was significant ($P < 0.01$) with an I^2 of 93%.

Development of First Variceal Bleeding

All the five studies¹¹⁻¹⁵ had data regarding development of first variceal bleeding in patients who had small varices at

Table 1 Characteristics Of The Included Studies.

Author	Year	Place of study	Patients studied	Study design	Total number of patients in study	Patients with small varices receiving NSBB or placebo	Follow-up
Andreani et al. ¹⁴	1990	Paris (two centers)	Cirrhosis, with small or large varices, without previous bleeding	Unblinded RCT comparing propranolol, sclerotherapy and placebo	84 ^a	32	2 years
Conn et al. ¹⁵	1991	USA (two centers) Spain (one center)	Cirrhosis, with small or large varices, HVP >12 mmHg, without previous bleeding	Double blind RCT comparing propranolol and placebo	102	55	Placebo group 16.3 ± 12 mo Propranolol group 17.1 ± 10.9 mo
Calés et al. ¹³	1999	France (fourteen centers)	Cirrhosis, with no or small varices	Double blind RCT comparing propranolol and placebo	206	127	3 years
Merkel et al. ¹²	2004	Italy (eight centers)	Cirrhosis, with small varices, without previous bleeding	Single blind RCT comparing nadolol and placebo	161	161	3 years
Sarin et al. ¹¹	2013	India (single center)	Cirrhosis, with small varices, without previous bleeding	Single blind RCT comparing propranolol and placebo	150	150	25.0 (±12.6) mo

^aThis study had an additional group of 42 patients that underwent sclerotherapy.

baseline. There were a total of 525 patients, 261 randomized to NSBB group and 264 randomized to placebo group. The risk of first variceal bleeding was similar between the two groups (RR = 0.72, 95%CI: 0.25–2.12; $P = 0.55$). The heterogeneity among studies was low to moderate ($P = 0.21$) with an I^2 of 32% (Figure 5).

Mortality

Only two studies^{11,12} had data regarding mortality in patients who had small esophageal varices at baseline. Of 311 total patients, 160 were randomized to NSBB group and 151 were randomized to placebo group. The probability of death was similar between the two groups (RR = 0.76, 95%CI: 0.50–1.15; $P = 0.19$) were similar between NSBB and placebo groups. There was no heterogeneity between the two studies with an I^2 of 0% ($P = 0.47$) (Figure 6).

Adverse Events

Only two studies^{11,12} had data regarding adverse effects of treatment in patients who had small esophageal varices at baseline. Of 311 total patients, 160 were randomized to NSBB group and 151 were randomized to placebo group. The probability of adverse effects was higher with NSBB compared to placebo (RR = 4.66, 95%CI: 1.36–15.91; $P = 0.01$). There was no heterogeneity between the two studies with an I^2 of 0% ($P = 0.47$) (Figure 7).

Sensitivity Analysis

Of the five included studies, four^{11,15} were of high quality, having two or less “high risk” entries; while one¹⁴ was of low quality. Sensitivity analysis was performed after excluding the low quality study. Only the analysis about development of first variceal bleeding required sensitivity analysis as it had used the low quality study while all other analyses (development of large varices, mortality and adverse events) had not used the low quality study. Figure 8 shows the sensitivity analysis for first variceal bleeding. There were a total of 493 patients, 246 randomized to NSBB group and 247 randomized to placebo group. The risk of first variceal bleeding was similar between the two groups (RR = 0.85, 95%CI: 0.25–2.91; $P = 0.80$). The heterogeneity among studies was low to moderate ($P = 0.15$) with an I^2 of 43%.

DISCUSSION

The present meta-analysis evaluated the efficacy and safety of NSBBs in patients of cirrhosis with small varices. The results of this meta-analysis indicate that NSBBs are not effective in preventing the enlargement of small varices and may lead to significant adverse effects. NSBBs are also not effective in prevention of first variceal bleeding in patients who had small varices and also does not have

Table 2 Characteristics Of The Included Patients.

Author	Groups	Number of patients with small varices of total (n/n)	Age (years)	Sex (M:F, n/n)	Etiology of cirrhosis (%)	Severity of cirrhosis (%)
Andreani et al. ¹⁴	Propranolol	15/43	55.0 ± 1.3	27:16	ALD 77% Non-ALD 23%	Child class A 24% Child class B 45% Child class C 31%
	Placebo	17/41	55.6 ± 1.7	23:18	ALD 81% Non-ALD 19%	Child class A 24% Child class B 52% Child class C 24%
Conn et al. ¹⁵	Propranolol	26/51	54 ± 9	38:13	ALD 76% Non-ALD 24%	Child class A 68% Child class B 22% Child class C 10%
	Placebo	29/51	54 ± 11	35:16	ALD 80% Non-ALD 20%	Child class A 47% Child class B 47% Child class C 6%
Calés et al. ¹³	Propranolol	60/102	52.7 ± 10.4	70:32	ALD 86% Non-ALD 14%	Child class A 55% Child class B 31% Child class C 14%
	Placebo	67/104	52.7 ± 11.4	71:33	ALD 78% Non-ALD 22%	Child class A 56% Child class B 32% Child class C 12%
Merkel et al. ¹²	Nadolol	83/83	56 ± 9	45:38	ALD 57% Non-ALD 43%	Child–Pugh score 6.8 ± 1.6
	Placebo	78/78	57 ± 9	38:40	ALD 58% Non-ALD 42%	Child–Pugh score 7.1 ± 1.9
Sarin et al. ¹¹	Propranolol	77/77	42 ± 13	63:14	ALD 35% Non-ALD 65%	Child–Pugh score 7.4 ± 1.9
	Placebo	73/73	44 ± 13	57:16	ALD 36% Non-ALD 64%	Child–Pugh score 7.7 ± 2.3

any effect on mortality of these patients. Hence, NSBBs should not be recommended for cirrhotic patients with small varices.

The natural course of portal hypertension in patients with cirrhosis is characterized by a progressive increase in the extent and degree of collateral circulation including formation and growth of esophageal varices. Initially, these varices appear as small linear veins, faintly visible on the esophageal surface that may later grow to become tortuous and thin-walled veins, protruding into the lumen and carrying a high risk of rupture. Small varices have a median rate of progression to large varices at 5–23% per year.^{11,16–20} Bleeding usually occurs from the rupture of these large varices, and size of the varices are one of the most important risk factors for bleeding.

Lebrech et al. published the first report of beta-blocker as a medical treatment for portal hypertension in 1980 because of their ability to decrease portal-collateral blood flow and portal pressure.²¹ Since then numerous trials and meta-analyses have been published supporting the use of NSBB, such as propranolol and nadolol, for prevention of variceal bleeding both in the setting of primary prophylaxis and secondary prophylaxis.^{22–29} These agents reduce by half the risk of first bleeding from gastroesophageal varices (for which no effective therapy was previously

available) and are the standard therapy worldwide.³⁰ The Baveno consensus workshop recommends the use of either NSBB or endoscopic variceal ligation (EVL) for the prevention of the first variceal bleeding from medium or large varices and combination of NSBB plus EVL for prevention of variceal rebleeding.³¹ The beneficial effect of NSBB in portal hypertension is probably related to the decrease in blood inflow into the splanchnic system, leading to decrease in portal pressure.

Despite these clear benefits of use of NSBB in the setting of primary and secondary prophylaxis, when NSBB was tried in patients with no varices, it was not able to prevent the development of varices.¹⁰ Whether NSBB could be used for prevention of enlargement of varices, was still not clear since the three studies addressing this issue had given conflicting results.^{11–13} Hence the Baveno consensus conference recommends that the patients with small varices without signs of increased risk may be treated with NSBB to prevent bleeding. However, further studies are required to confirm their benefit.³¹ The Baveno does not say whether NSBB would prevent enlargement of varices.

Since size of the varices is one of the most important factors for variceal bleeding and the risk of bleeding is much higher in patients with moderate/large varices than

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Sample size calculation
Andreani 1990	+	?	-	-	-	+	-
Cales 1999	+	+	+	+	-	+	-
Conn 1991	+	+	+	+	+	+	-
Merkel 2004	+	+	+	-	-	+	+
Sarin 2013	+	+	+	-	+	+	+

Figure 2 Risk of bias summary: review authors' judgments about each risk of bias item for each included study (green dot, low risk; red dot, high risk; yellow dot, unclear risk).

in those with small varices (30% vs ~10% at 2 years, respectively).^{16,30} Any therapy that can prevent variceal enlargement will be very helpful in prevention of variceal bleeding. Size correlates with portal pressure, hence, if pressure can be reduced by NSBB, it is logically expected that varices would not enlarge. However, our meta-analysis disproves this hypothesis and NSBB have not been found to prevent enlargement of varices.

When looking at enlargement of varices as the endpoint, it is not clear why the results of the three published studies are at variance with each other—one in favor of NSBB,¹² one showing no benefit of NSBB,¹¹ and one showing paradoxical enlargement of varices with NSBB.¹³ It is likely that difference in the patient population, the time of intervention, the method of grading of esophageal varices, and the method of hemodynamic monitoring could influence the results. In fact, our meta-analysis suggests that the statistical heterogeneity among studies was significant ($P < 0.01$) with an I^2 of 93%. Because of this heterogeneity, clearly there is a need for further studies that can add to the evidence in either direction.

The data is much more robust when analyzing the development of first variceal bleeding from small varices. Our meta-analysis showed no benefit of NSBB. The heterogeneity among the five included studies was low to moderate ($P = 0.21$) with an I^2 of 32%. Similarly the data on mortality and adverse effects was also robust with no heterogeneity between the studies.

About two years ago Qi et al. published a similar meta-analysis and concluded that NSBBs should not be recommended for cirrhotic patients with no or small varices.³² However, one of the important differences between that meta-analysis and ours is that they also included the studies that enrolled patients with no varices; while in our meta-analysis we have excluded those studies that had patients with no varices.

Figure 3 Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.

Figure 4 Forest plot comparing the development of large varices between NSBBs and placebo groups.

Figure 5 Forest plot comparing the development of first variceal bleeding between NSBBs and placebo groups.

Figure 6 Forest plot comparing mortality between NSBBs and placebo groups.

Figure 7 Forest plot comparing adverse effects of treatment between NSBBs and placebo groups.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Sample size calculation

Figure 8 Sensitivity analysis for first variceal bleeding.

CONCLUSIONS

In conclusion, the results of this meta-analysis indicate that NSBBs are not effective in preventing the enlargement of small varices. However, there was significant heterogeneity among the studies reporting enlargement of varices, hence, further studies with large sample size are warranted to confirm this finding. Besides this, NSBB leads to significant adverse effects; are also not effective in prevention of first variceal bleeding in patients who had small varices; and also does not have any effect on mortality of these patients, hence, NSBBs should not be recommended for cirrhotic patients with small varices.

CONFLICTS OF INTEREST

The authors have none to declare.

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