The Clinical Efficacy and Safety of Simvastatin in the Management of Portal Hypertension in Cirrhotic Patients: A Systematic Review

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ABSTRACT

Background: *Variceal bleeding is a serious complication of portal hypertension in liver cirrhosis. Current guidelines recommend non-selective beta blockers (NSBBs) and endoscopic variceal ligation for primary prophylaxis of variceal bleeding. However, NSBBs are associated with low response rates and systemic adverse effects. Simvastatin has been shown to reduce portal hypertension in previous studies. Our aim was to assess its clinical efficacy and safety in reducing portal hypertension in cirrhotic patients.*

Method: *We searched PubMed, The Cochrane Library, ScienceDirect, ProQuest, CINAHL, Scopus, and Clinicaltrials.gov, and manually browsed abstracts of major hepatology conferences for selection of studies. We selected randomized controlled trials with a population of cirrhotic patients, simvastatin as an intervention, HVPG change as an outcome, and English as the primary language. The quality of selected studies was assessed using the Cochrane Risk of Bias tool. We extracted change in HVPG from baseline to post-treatment as the principal summary measure, with safety as the secondary outcome.*

Results: *Two full articles were included for qualitative analysis. Both studies reported reductions in HVPG from baseline to post-treatment in the simvastatin group, with this reduction being significantly higher as compared to the control group. Adverse effects were homogenously distributed in both groups, and good safety was reported by both studies. Simvastatin's HVPG lowering effects are possibly additive to those of NSBBs.*

Conclusion: *Simvastatin effectively reduces HVPG in cirrhotic patients with portal hypertension, although more clinical trials are needed to validate these results. Simvastatin could potentially be combined with NSBBs to achieve greater results.*

Keywords: *Liver Cirrhosis; Clinical Efficacy; Portal Hypertension; Safety; Simvastatin*

ABSTRAK

Latar belakang: *Perdarahan varises merupakan salah satu komplikasi fatal dari hipertensi porta pada sirosis hati. Pedoman terbaru menyarankan untuk menggunakan Beta Bloker non-selektif (NSBB) dan ligasi varises melalui endoskopi sebagai profilaksis primer perdarahan variseal. Akan tetapi, NSBB berhubngan dengan respon yang rendah dan efek samping sistemik. Simvastatin dapat meningkatkan produksi oksida nitrat intrahepatik*

dan menurunkan hipertensi porta dalam studi-studi sebelumnya. Tujuan dari studi ini adalah untuk mengetahui efikasi dan keamanan dalam menurunkan hipertensi porta pada pasien sirosis.

Metode: *Kami melakukan pencarian pada PubMed, The Cochrane Library, ScienceDirect, ProQuest, CINAHL, Scopus, dan Clinicaltrials.gov, dan juga mencari abstrak dari konferensi-konferensi hepatologi untuk memperoleh studi. Kami memilih uji klinis acak terkontrol yang mengevaluasi perubahan gradien tekanan vena hepatik (HVPG) pada pasien sirosis yang mengalami hipertensi porta dan ditatalaksana dengan simvastatin. Kualitas studi dinilai dengan menggunakan pedoman Cochrane Risk of Bias. Data perubahan HVPG dari nilai dasar ke pasca-terapi merupakan luaran utama studi dan keamanan dari simvastatin merupakan luaran sekunder.*

Hasil: *Dua artikel dimasukkan dalam analisis kualitatif. Kedua studi menunjukkan adanya perubahan/ reduksi yang besar dan signifikan terhadap HVPG dari nilai dasar ke pasca-terapi pada kelompok simvastatin dibandingkan kontrol. Efek samping terdistribusi secara homogen pada kedua kelompok dengan tingkat keamanan yang baik. Simvastatin dapat menjadi terapi tambahan pada penggunaan NSBB untuk menurunkan HVPG.*

Simpulan: *Simvastatin merupakan pengobatan yang efektif dalam menurunkan HVPG pada pasien sirosis dengan hipertensi porta. Uji klinis lebih lanjut diperlukan untuk memvalidasi hasil ini. Simvastatin berpotensi sebagai obat kombinasi bersama dengan NSBB untuk memperoleh hasil yang lebih baik.*

Kata kunci: *Sirosis hati, efikasi klinis, hipertensi porta, keamanan, simvastatin*

INTRODUCTION

Portal hypertension is a common hemodynamic outcome of liver cirrhosis and is responsible for many of its complications. The Baveno VI consensus defines portal hypertension by a hepatic venous pressure gradient (HVPG) of more than 5 mmHg, with a value above 10 mmHg being clinically significant. One of the most important outcomes of portal hypertension is the formation of gastroesophageal varices, which are portosystemic collaterals prone to bleeding. Variceal bleeding is associated with a 6-week mortality of approximately 10-20%, making it one of the deadliest complications of liver cirrhosis.[1] Strong evidence suggests that reducing HVPG significantly reduces the risk of bleeding and mortality in cirrhotic patients.[2] Hence, reducing HVPG is an important therapeutic target to prevent variceal bleeding and improve the prognosis of patients with portal hypertension.

Current guidelines recommend Non-selective beta-blockers (NSBBs) for primary prophylaxis against variceal bleeding, with endoscopic variceal ligation (EVL) as an option for medium or large sized varices.[1] However, several reports suggest that about half of the population does not respond well to beta-blocker therapy.[3-7] Additionally, beta-blockers are frequently associated with contraindications and systemic adverse effects.[4] This calls for the availability of a wider range of pharmacological agents for managing portal hypertension.

Over the years, increasing evidence supporting the use of Simvastatin for the management of portal hypertension has emerged. One of the factors contributing to portal hypertension in cirrhosis is the reduced formation of intrahepatic nitric oxide by the dysfunctional sinusoidal endothelium.[8] Several animal[9,10] and human-experimental studies[11] have shown that simvastatin increases intrahepatic nitric oxide production by improving sinusoidal endothelial function in cirrhosis, thus decreasing hepatic vascular tone. Abraldes, et al.[9] reported improved endothelial nitric oxide synthase (eNOS) expression and nitric oxide activity in liver samples of simvastatin-treated cirrhotic rats as compared to the vehicle control group. A clinical study by Zafra, et al.[11] supports this, reporting a significant increase in hepatic nitric oxide products 30 minutes after simvastatin administration in cirrhotic patients. Studies have suggested that this enhancement in eNOS expression occurs due to induction of Kruppel-Like Factor 2 (KLF-2), which is a transcription factor that promotes endothelial protection.[12,13] Simvastatin was reported to be the most potent statin in upregulating KLF-2.[12]

The above evidence is suggestive of simvastatin as a potential therapy for managing portal hypertension in cirrhotic patients. The aim of this current study is to systematically review the current evidence on the clinical efficacy and safety of simvastatin in reducing HVPG in cirrhotic patients with portal hypertension.

METHOD

We conducted a systematic review of literature according to the PRISMA[14] guidelines to fulfill our objectives. A comprehensive search was initially done on June 12th-14th 2017, and was repeated on 8th

May 2018 to ensure that results were up to date. The databases *PubMed, The Cochrane Library, Scopus, CINAHL, ScienceDirect,* and *ProQuest* were searched by two independent reviewers, and any differences in search results were discussed before a decision was made. The following keywords were applied to all databases: "Portal Hypertension AND Simvastatin AND (Hepatic Venous Pressure Gradient OR HVPG)". We also searched *Clinicaltrials.gov* and manually browsed abstracts from major hepatology conferences between 2010-2018 to ensure that no trial was left unincluded. Abstracts booklets were browsed from annual meetings of the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), The Asian Pacific Association for the Study of the Liver (APASL), and Indian National Association for the Study of the Liver (INASL).

Inclusion and exclusion criteria were set prior to the search. We selected therapeutic studies with: (1) design of randomized controlled trial; (2) a population of cirrhotic patients of any age; (3) simvastatin as the intervention; (4) use of a control group, either placebo or other pharmacological agents such as NSBBs; (5) change in hepatic venous pressure gradient as an outcome; (6) English as primary language. No publication year restrictions were applied. We excluded studies that were not suitable to our study design.

For all selected studies, a risk of bias assessment was conducted using The Cochrane Risk of Bias Tool which allows assessors to judge studies based on seven domains of bias.[15] The bias assessment was conducted at study level by two separate authors (VFJ and MB). Any discrepancies in judgement was discussed between all authors of this review before a final consensus was reached.

We collected information about the study designs from each study, including patient characteristics, intervention regimen, control regimen, and method of assessing outcomes. As a primary outcome, we extracted values of HVPG at baseline and after treatment for the patients. We also extracted data of safety and adverse effects from treatment as a secondary outcome. The principal summary measure used in this review was the difference in mean HVPG value from baseline to post-treatment.

RESULTS

The results of our latest search conducted in May 2018 can be seen in Figure 1. After removal of duplicates, we ended up with six relevant records. Of these, two were conference abstracts. The authors of one of these conference abstracts was contacted for request of full paper but there was no response. The other conference abstract is already published as a full paper and included in our study. Of the remaining four records, two were observational cohort studies and were hence excluded. The remaining two studies were selected for qualitative analysis in this review. These are studies conducted by Pollo-Flores et al and Abraldes et al.[16,17]

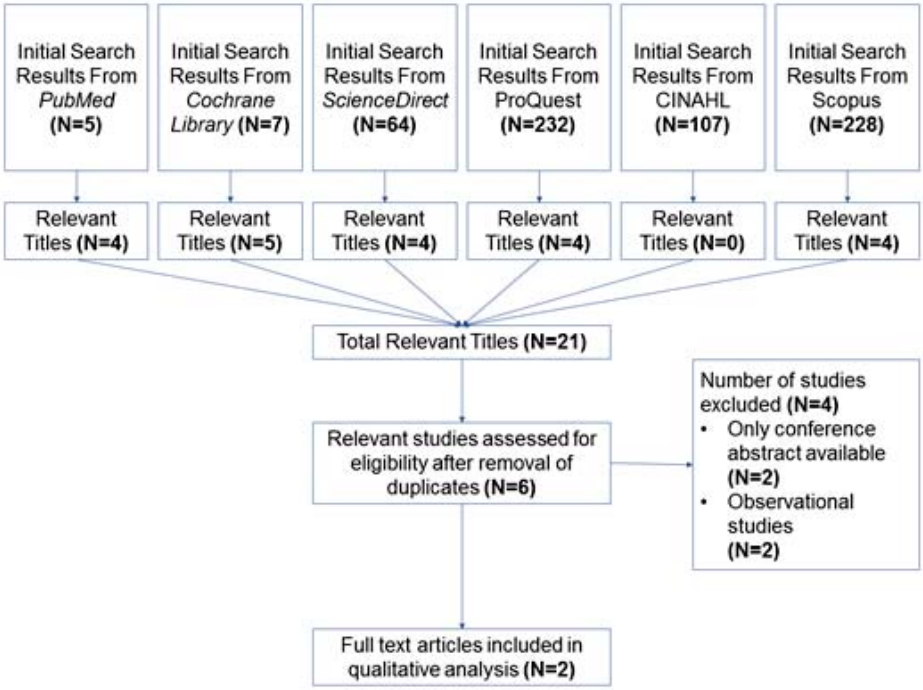

Figure 1. Search flowchart

We also searched Clinicaltrials.gov to look for any registered trials on the topic that we may have missed in our search. A total of six clinical trials using simvastatin for the treatment of portal hypertension were registered. Of these, two are included in this study as stated above.[16,17] The other four trials were excluded – one of them did not assess change in HVPG as an outcome measure, and the other three did not have a published full paper. No additional relevant studies were found from abstracts of the annual meetings of AASLD, EASL, APASL, and INASL.

The risk of bias assessment was independently conducted by two authors (VFJ and MB). Information about the authors' collective judgements and comments supporting the authors' judgements based on the articles of the included studies can be seen in Table 1.

We extracted information on the patient characteristics, inclusion and exclusion criteria, intervention regimens, control, and outcome measures from the two included studies. These results are presented in Table 2.

Table 1. Risk of bias assessment

Study	Domain of bias	Authors' judgement	Support for judgement
Pollo-Flores et al[16]	Random Sequence Generation (Selection Bias)	Low Risk	Computer generated randomization was used
	Allocation Concealment (Selection Bias)	Low Risk	"Both capsules were similar in appearance"[14]
	Blinding of Participants and Personnel (Performance Bias)	Low Risk	Triple blinded study
	Blinding of Outcome Assessments (Detection Bias)	Unclear	Not mentioned whether outcome was measured blindly or not
	Incomplete Outcome Data (Attrition Bias)	High Risk	High dropout in placebo group as compared to treatment group
	Selective Reporting (Reporting Bias)	Low Risk	No strict reporting protocol available but all expected outcomes of interest are reported
	Other Bias	Low Risk	No evidence of bias from other sources
Abraldes et al[17]	Random Sequence Generation (Selection Bias)	Low Risk	Computer generated randomization was used
	Allocation Concealment (Selection Bias)	Low Risk	Both treatments had similar appearance, prepared "in sealed opaque boxes with consecutive Numbers"[15]
	Blinding of Participants and Personnel (Performance Bias)	Low Risk	Double blinded study
	Blinding of Outcome Assessments (Detection Bias)	Low Risk	Outcomes were measured and read blindly
	Incomplete Outcome Data (Attrition Bias)	Low Risk	2 dropouts from each group for similar reasons
	Selective Reporting (Reporting Bias)	Low Risk	No strict reporting protocol available but all expected outcomes of interest are reported
	Other Bias	Low Risk	No evidence of bias from other sources

Table 2. Summary of experimental designs of selected studies

Study	Patient criteria and study design	Intervention and control	Outcome
Pollo-Flores et al[16]	Age Range: 18-75 years (Median of 56.5 years and 58.5 in simvastatin and intervention groups respectively) Inclusion Criteria: Cirrhotic patients with portal hypertension (minimum HVPG of 5mmHg) Exclusion criteria: Aminotransferase level >3x Upper limit of normal, Recent (within 6 months) or current simvastatin use, Portal vein thrombosis, Contrast medium allergy, Any malignancy, Renal failure, Bleeding disorder, Decompensated cirrhosis Number of Patients: 34 (24 completed the full follow-up) Study Design: RCT	Simvastatin or Placebo for 3 months. Simvastatin was started at 20 mg/day for 2 weeks and doubled to 40mg/day if there was no sign of drug intolerance. Propanolol was maintained on all patients who were already using it	HVPG measurement (At the end of treatment): Insertion of a 6F occlusion balloon catheter to the right or middle hepatic vein, right atrium, and inferior vena cava. The difference between the 3 pairs of measurements gives HVPG Any adverse effects were also recorded, and in case of a rise in AST level > 3 times baseline, simvastatin/placebo was stopped.
Abraldeset al[17]	Age Range: 18-75 years (mean age 58 and 56 years in simvastatin and control groups respectively) Inclusion Criteria: Cirrhotic patients with severe portal hypertension (minimum HVPG of 12 mmHg) Exclusion Criteria: Pregnancy, Cholestatic liver disease, Severe liver failure, Prothrombin rate <40%, Hepatic encephalopathy grade 2-4, Child-Pugh score >12, Serum creatinine >1.5mg/dL, Hepatocellular carcinoma, Portal vein thrombosis, Previous surgical shunt, Calcium channel antagonist, Statin treatment in previous 3 months. Number of Patients: 59 (55 completed full follow-up) Study Design: RCT	Simvastatin or placebo for 30 days. Simvastatin Dose: 20 mg/day up to day 15, 40mg/day thereafter if no safety end point was met Safety endpoints: CK levels >5 times of normal, ALT increase > 3 fold, and any other adverse events judged by investigators.	HVPG Measurement: Insertion of a 7F balloon tipped catheter into right hepatic vein to measure wedged and free hepatic venous pressures. The difference between these two pressures gives HVPG. Primary outcome: Change in HVPG of cirrhotic patients with severe portal hypertension after 1 month of simvastatin. Secondary outcomes: safety of regimen, effects on liver functions, and effects on liver hemodynamics

As a primary outcome, we extracted data for HVPG at baseline and post-treatment from both selected studies. Synthesized data from both studies is portrayed in Figure 2. In the study by Pollo-Flores et al HVPG decreased from a median value of 13 mmHg to 11 mmHg in the intervention group (p = 0.07), while it remained at a constant of 13 mmHg in the control group (p = 0.480).[16] In the study by Abraldes et al, the HVPG value decreased from 18.5 mmHg at baseline to 17.1 mmHg after treatment in the intervention group (p = 0.003).[17] Similiar to Pollo-Flores, *et al.*,[16] HVPG in the control group also remained roughly constant, from a baseline of 19.8 mmHg to 19.5 mmHg post-treatment (p = 0.473).

Additionally, we extracted data comparing the change in HVPG from baseline to post treatment in intervention and control groups as reported in both studies. It must be noted that Pollo-Flores et al expressed this as an absolute change in HVPG (mmHg), whereas Abraldes et al reported this as a percentage change.[16,17] These values can be seen in Table 3.

We extracted author reports of patient safety in both selected trials. Pollo-Flores et al reported no severe side effects in both intervention and control groups, with equal distribution of adverse events in the two groups.[16] The side effects experienced by patients were myalgia, diarrhea, chest pain, and epistaxis (one patient each in the intervention group), with no significant difference in treatment and control groups. Abraldes et al reported seven patients in the control group and three patients in the intervention group who experienced adverse effects, with one patient in each group experiencing severe adverse effects.[17] The severe adverse effect in the control group was worsening appendicitis, whereas in the intervention group it was hydrothorax requiring thoracocentesis. There was no significant difference in the change of AST and ALT levels from baseline to post-treatment in control and intervention groups in both studies. In both studies, adverse effects were similarly distributed in intervention and control groups.[16,17]

DISCUSSION

Currently, only two trials have been reported that fit our selection criteria. The principal summary measure of this review is the change in HVPG from baseline to post-treatment. In both studies, we see a fall in HVPG from baseline to post-treatment in the simvastatin group, as seen in figure 2. In the study by Abraldes, et al HVPG levels fall from 18.6 mmHg at baseline to 17.1 mmHg after one month (p = 0.003).[17] Similarly, we see a fall in median HVPG values from 13 mmHg to 11 mmHg in the study by Pollo-Flores et al although this fall is not statistically significant (p = 0.07).[16]

Table 3. Change in hepatic venous pressure gradient (HVPG) from baseline to post-treatment in both groups

	Simvastatin group	Control group	Difference between groups (p-value) *
Pollo-Flores, et al.[16]	-2 mmHg	0 mmHg	0.020 (< 0.05)
Abraldes, et al.[17]	-8.30%	-1.60%	0.041 (<0.05)

*Reported by the authors of the studies

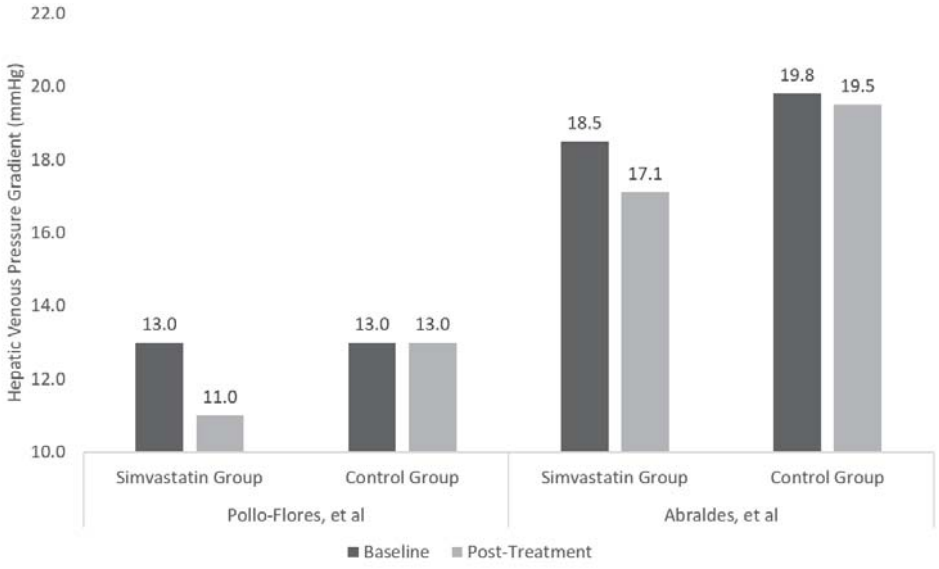

Figure 2. Hepatic venous pressure gradient (HVPG) at baseline and post-treatment in intervention and control groups

Nevertheless, both studies reported a significantly higher drop in HVPG in the simvastatin group as compared to control group (Table 3). Despite the limited number of trials, this review provides evidence for the clinical efficacy of simvastatin in reducing HVPG in cirrhotic patients with portal hypertension.

We noticed a discrepancy in the reporting of difference in HVPG change between two groups, in both trials. Pollo-Flores et al reported this as an absolute change in median HVPG values (mmHg), whereas Abraldes et al expressed this difference as a percentage change (Table 3).[16,17] The Baveno VI consensus defines a clinically meaningful response to treatment as a 10% reduction in HVPG from baseline, or to an absolute value of <12mmHg.[1] Hence, it would be more appropriate for future studies to report average percentage change in HVPG from baseline to post treatment when evaluating treatment efficacy.

Both studies defined hemodynamic response as an HVPG reduction by >20% or to an absolute value of < 12 mmHg.[16,17] Abraldes et al reported a response rate of 32%, whereas Pollo-Flores et al reported a higher response rate of 55% in the simvastatin group.[16,17] Pollo-Flores et al proposed that this could be due to the longer time of treatment in their study (3 months) as compared to Abraldes et al (1 month), suggesting that response to simvastatin may be enhanced by increasing the duration of treatment.[16,17] Under the same definitions for hemodynamic response, the response rate achieved by simvastatin is comparable to those achieved by NSBBs in other studies.[3-7]

There is some evidence that disease severity may increase response to simvastatin. Pollo-Flores et al reported that in the simvastatin group, 83% of patients with medium/large varices or a history of variceal bleeding responded to treatment.[16] Moreover, 83% of all responders had a baseline HVPG value >12 mmHg. However, a correlation between baseline HVPG and drug response was not found using bivariate analysis, possibly due to the study's small sample size.[16] A 2016 trial reported that in a group of patients who survived variceal bleeding once, addition of simvastatin to current standard primary prophylaxis of re-bleeding (beta-blockers and band ligation) significantly reduced mortality in patients as compared to the group that only received standard primary prophylaxis ($p = 0.03$).[18] However, the study by Abraldes et al, only included patients with severe portal hypertension (baseline HVPG > 12 mmHg), but had a low response rate of 32%.[17] This is possibly due to the short duration of treatment in the study, with only 1 month of simvastatin.

There is evidence that the HVPG lowering effects of simvastatin are additive to those of non-selective beta-blockers. A recent clinical trial by Wani et al studied the effect of adding simvastatin to patients who were carvedilol non-responders.[19] They reported that 42% of carvedilol non-responders became responders after simvastatin was added, with a total response rate of nearly 80% in all patients. In addition to this, Abraldes et al reported that HVPG reduction in the simvastatin group was higher in patients who had previously received beta-blockers than those who had not, although this was not statistically significant (-11.0% vs -5.9%, $p = 0.695$).[17] Overall, this provides evidence for the additive effect of the two drugs.

The key to this additive effect lies in the differential mechanism of action of simvastatin and beta-blockers in reducing HVPG. Simvastatin achieves its HVPG-lowering effects by inducing the expression of transcription factor KLF-2 and its target gene eNOS, which improves endothelial function and nitric oxide synthesis in liver sinusoids.[12,13] Non-selective beta blockers like propanolol achieve HVPG reductions by reducing portal blood flow.[20,21]

Another important aspect of the mechanism of action of simvastatin is its selectivity, which contributes to the drug's safety. Abraldes et al reported that simvastatin did not have any effects on the systemic hemodynamics in patients.[17] Because KLF-2 is expressed under stressful conditions, it is possible that simvastatin enhances its expression (and downstream expression of eNOS) in hepatic tissue only, without causing systemic vasodilation.

One of the issues with NSBB therapy for portal hypertension in cirrhotic patients is their array of adverse effects owing to their systemic pharmacodynamics. The studies included in this systematic review show homogeneity in adverse effects across simvastatin and control groups, with none of the two studies reporting severe toxicity associated with simvastatin use.[16,17] This is supported by a 2016 trial by Abraldes et al which also reported homogeneity in adverse effects across simvastatin and control groups in cirrhotic patients.[18] The authors of these studies all reported that simvastatin was a safe drug in cirrhotic patients.[16-18]

Our systematic review does have some limitations that warrant a discussion. Dropouts of different numbers were reported in the trial conducted by Pollo-Flores et al with 3 in the Simvastatin group and 7 in the control group.[16] This significantly reduced the study's sample size from n = 34 to n = 24, reducing the power of the study while also introducing a risk of attrition bias.

Moreover, the volume of evidence available was quite limited, with only two published trials conforming to our selection criteria. Polymorphisms in several genes such as SLCO1B1 cause inter-ethnic variability in the pharmacokinetics of statins,[22] hence further trials evaluating the efficacy and safety of simvastatin in cirrhotic patients of different populations are needed. In addition, we did not include studies from grey literature and our manual searching was limited. We have contacted the author of a relevant conference abstract to request for the full paper, but did not receive a response.

Despite these limitations, results show promising evidence for the use of simvastatin in managing portal hypertension. In patients who are not contraindicated to receive NSBB therapy, simvastatin can potentially be combined with propanolol or carvedilol to achieve greater results.

CONCLUSION

This systematic review provides evidence for the efficacy and safety of simvastatin use for the management of portal hypertension. A combination of beta-blocker therapy with simvastatin has good potential for clinical use to improve overall response rates. More evidence is needed to validate these results before addition of simvastatin becomes a standard practice in cirrhotic patients.

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