Beta-blockers alone or with endoscopic therapy for prevention of variceal rebleeding in portal hypertension (Protocol)

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[Intervention Protocol]

Beta-blockers alone or with endoscopic therapy for prevention of variceal rebleeding in portal hypertension

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

The objectives will be to assess the benefits and harms of beta-blockers alone or with endoscopic therapy for prevention of rebleeding in patients with oesophageal varices.

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BACKGROUND

Varices are present in 30% of patients with cirrhosis and in 60% of patients with cirrhosis and ascites (D'Amico 1997; Tripathi 2001). Variceal bleeding occurs in one-third of these patients with mortality of 50% (Tripathi 2001). Patients with portal hypertension who have bled from oesophageal varices have a high risk of rebleeding. The risk is 60% to 70% at one year if no preventive therapy is instituted (Bernard 1997; Bernard-Chabert 2004). Predictors of recurrent bleeding include bleeding on endoscopy, large oesophageal varices, severity of index bleed, severity of portal hypertension as determined by hepatic venous pressure gradient (HVPG) measurement and presence of encephalopathy, ascites, or renal impairment (Gluud 1988; de Franchis 1992; Zaman 2005). Since there is a high risk of recurrence of variceal haemorrhage, patients should be offered secondary prophylaxis to prevent rebleeding.

Drugs, endoscopic modes of treatment, surgery, or transjugular intrahepatic portosystemic shunt are used for prevention of recurrent variceal haemorrhage (Zaman 2005). Drug therapy in portal hypertension is administered to normalize the increased portal blood inflow by using beta-blockers or isosorbide mononitrate. Beta-blockers (propranolol or nadolol) are the most effective agents for prevention of variceal rebleeding (Tripathi 2001). Addition of isosorbide mononitrate increases the efficacy of beta-blockers (Tripathi 2001). The therapeutic goals of drug therapy are to attain reduction in HVPG to 20% of baseline value or to 12 mm Hg to prevent or reduce the risk of rebleeding from varices (Groszmann 1990; Feu 1995; D'Amico 2006). Achieving a reduction in HVPG to 12 mm Hg or to 20% of baseline value is used for labelling responders. Patients not showing reduction in HVPG of this degree are called nonresponders. With drug therapy, about 45% to 63% of patients are non-responders. Non-responders with recurrence of variceal haemorrhage on drug therapy are 46% to 65%compared to 7% to 13% of responders (Zaman 2005). It has been found that the haemodynamic response to drug therapy in terms of the reduction in HVPG is stable during long-term follow-up (Villanueva 2004).

Randomised trials, meta-analyses, and narrative reviews have found that beta-blockers are effective in prevention of variceal rebleeding (Hayes 1990; D'Amico 1995; Bernard 1997; Tripathi 2001; Zaman 2005). However, the estimated effects in different trials vary, possibly depending on the treatment strategy or control of bias in the individual trials. Furthermore, a number of endoscopic treatments including sclerotherapy and banding ligation are increasingly used to prevent rebleeding. Hence, it is important to assess whether the use of concomitant endoscopic therapy affects the effect of beta-blockers on the risk of rebleeding and mortality. The question has been assessed in a number of trials, but the results are equivocal. We, therefore, will perform a Cochrane systematic review on the beneficial and harmful effects of beta-blockers without or with concomitant endoscopic therapy for prevention of rebleeding from oesophageal varices.

OBJECTIVES

The objectives will be to assess the benefits and harms of beta-blockers alone or with endoscopic therapy for prevention of re-bleeding in patients with oesophageal varices.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials irrespective of blinding, publication status, or language.

Types of participants

Patients with oesophageal varices and a history of upper gastrointestinal bleeding, likely to be variceal in origin will be included irrespective of the aetiology of portal hypertension, ie, cirrhosis or other liver disease.

Types of interventions

We will perform the following comparisons:
- Beta-blockers versus no intervention or placebo.
- Beta-blockers plus sclerotherapy versus sclerotherapy.
- Beta-blockers plus band ligation versus band ligation.

Types of outcome measures

Primary outcome measure
(1) Rebleeding diagnosed by endoscopy or identification of haematemesis, melena, or gastric aspirate containing blood.
(2) All-cause mortality.
Secondary outcome measures
(3) Rebleeding-related mortality.
(4) Adverse events defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment, but resulting in a dose reduction or discontinuation of the intervention (ICH-GCP 1997).
(5) Quality-of-life measures (as reported by authors).
(6) Obliteration and recurrence of oesophageal varices after endoscopic therapy.
All outcome measures will be assessed at the maximum follow-up in the individual trials.

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Search methods for identification of studies

We will search for eligible trials in *The Cochrane Hepato-Biliary Group Controlled Trials Register*, the *Cochrane Central Register of Controlled Trials* in *The Cochrane Library*, *MEDLINE*, *EMBASE*, and *Science Citation Index Expanded* (Royle 2003). All searches will be performed using the electronic search strategies described in Appendix 1. Additional trials will be identified through scanning of reference lists in relevant papers and conference proceedings and through correspondence with experts and pharmaceutical companies.

Data collection and analysis

We will follow the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2005) and *The Cochrane Hepato-Biliary Group Module* (Gluud 2006).

One author (BCS) will perform the searches. Two authors (BCS and SKS) will decide on inclusion of trials and extract data independently. One author (LLG) will validate the extracted data. Disagreements will be resolved through discussion. Excluded trials will be listed with the reason for exclusion. Primary authors of the included trials will be contacted for additional information if outcome measures are not included in the published trial reports. The methodological quality will be defined as the control of bias in the individual trials. Allocation sequence generation, allocation concealment, blinding, and follow-up will be extracted as measures of bias control (Gluud 2001; Kjaergard 2001) using the following definitions:

Generation of the allocation sequence

- adequate (computer generated random numbers, table of random numbers, or similar);
- unclear (the trial was described as randomised, but the generation of the allocation sequence was not described); or
- inadequate (quasi-randomised trials).

Allocation concealment

- adequate (concealed up to the point of treatment by central randomisation, sealed envelopes, or similar);
- unclear (the allocation concealment was not described); or
- inadequate (open table of random numbers or similar).

Trials in which the allocation sequence generation or allocation concealment was inadequate (ie, using allocation systems based on dates, names, admittance numbers, or similar) will be excluded from the present review.

Blinding

- Adequate an identical placebo was used to achieve blinding.

Trials will be classified as single or double blind using the descriptions provided in the individual trial reports. Data on whether patients or investigators (eg, health-care providers, outcome assessors, or data analysis) were blinded will also be extracted.

Follow-up

The number and reasons for losses to follow-up will be extracted to assess the risk of attrition bias. We will also extract whether a pre-planned sample size calculation was performed and whether the planned sample size was reached.

From the individual trials, we will also extract data on the baseline characteristics of patients (inclusions criteria, mean age, sex, and number of patients with cirrhosis), treatments (type and dose of therapy), and trials (country of origin, publication status, funding, duration of follow-up, and all outcomes).

Statistical analyses

The analyses will be performed in RevMan (RevMan 2003) and STATA version 8.0 for Windows. Results of the meta-analyses will be presented as relative risks (RR) with 95% confidence intervals (95% CI). Random-effects models will be used in the primary analyses because of the expected clinical heterogeneity. Chi-squared analyses will be performed to estimate inter-trial heterogeneity. All analyses will be performed using the intention-to-treat principle including all randomised patients irrespective of compliance or follow-up. For patients with missing data, carry forward of the last observed response will be used. Sensitivity analyses assessing potential sources of heterogeneity and bias included random-effect meta-regression, worst-case scenario analyses, and regression analyses of funnel plots. To achieve the maximum statistical power in the sensitivity analyses, all trials will be combined. The outcome measures assessed in the meta-regression will include rebleeding and mortality. Fixed-effect subgroup meta-analyses will be performed for significant predictors identified in the meta-regression. In the worst-case scenario analyses, patients with missing data will be counted as treatment failures to assess the risk of attrition bias.

ACKNOWLEDGEMENTS

Wendong Chen et al wrote a Cochrane Hepato-Biliary Group protocol, but was unable to continue his work due to other commitments. The protocol formed the basis for the present protocol. Thank you to Christian Gluud and Dimitrinka Nikolova for their expert guidance and assistance in the review process.

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* *Indicates the major publication for the study*

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APPENDICES

Appendix 1. Search Strategies

Database	Date of search	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(beta-blocker* OR 'adrenergic beta antagonist*') AND ('variceal rebleeding' OR (recurren* AND variceal AND (bleeding OR hemorrhage)) OR 'secondary prophylaxis of variceal bleeding')
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Latest issue.	#1 MeSH descriptor Adrenergic beta-Antagonists explode all trees #2 beta-blocker* or adrenergic beta antagonist* #3 (#1 OR #2) #4 MeSH descriptor Esophageal and Gastric Varices explode all trees #5 variceal rebleeding or (recurren* and variceal and (bleeding or hemorrhage)) or secondary prophylaxis of variceal bleeding #6 (#4 OR #5) #7 (#3 AND #6)
MEDLINE (WinSPIRS 5.0)	1950 to date search is performed.	#1 explode "Adrenergic-beta-Antagonists"/all subheadings #2 beta-blocker* or adrenergic beta antagonist* #3 #1 or #2 #4 explode "Esophageal-and-Gastric-Varices"/all subheadings #5 variceal rebleeding or (recurren* and variceal and (bleeding or hemorrhage)) or secondary prophylaxis of variceal bleeding #6 #4 or #5 #7 #3 and #6 #8 random* or blind* or placebo* or meta-analysis #9 #7 and #8
EMBASE (WinSPIRS 5.0)	1980 to date search is performed	#1 explode "beta-adrenergic-receptor-blocking-agent"/all subheadings #2 beta-blocker* or adrenergic beta antagonist* #3 #1 or #2 #4 explode "esophagus-varices"/all subheadings #5 variceal rebleeding or (recurren* and variceal and (bleeding or hemorrhage)) or secondary prophylaxis of variceal bleeding #6 #4 or #5 #7 #3 and #6 #8 random* or blind* or placebo* or meta-analysis

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(*Continued*)

		#9 #7 and #8
Science Citation Index Expanded (http://portal.isiknowledge.com/portal.cgi?DestApp=WOS&Func=Frame)	1945 to date search is performed.	#5 #4 AND #3 #4 TS=(random* or blind* or placebo* or meta-analysis) #3 #2 AND #1 #2 TS=(variceal rebleeding or (recurren* and variceal and (bleeding or hemorrhage)) or secondary prophylaxis of variceal bleeding) #1 TS=(beta-blocker* OR adrenergic beta antagonist*)

WHAT'S NEW

22 October 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2007

CONTRIBUTIONS OF AUTHORS

BCS drafted the protocol and will draft the review. LLG and SKS revised the protocol and will revise the review. All authors approved of the final version of the protocol.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

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Internal sources

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External sources

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