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Banding ligation versus no intervention for primary prevention in adults with oesophageal varices (Protocol)

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[Intervention Protocol]

Banding ligation versus no intervention for primary prevention in adults with oesophageal varices

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the beneficial and harmful effects of banding ligation versus no intervention in adults with cirrhosis and gastro-oesophageal varices that have not bled.

BACKGROUND

Description of the condition

Oesophageal varices develop as a result of portal hypertension (Bosch 2003; Triantos 2007). At the time of diagnosis, approximately 30% of people with cirrhosis have oesophageal varices (D'Amico 1995; D'Amico 1999; D'Amico 2007; De Lisi 2010). In people with cirrhosis who do not have varices at the time of diagnosis, the incidence of oesophageal varices is 5% at one year and 28% at three years (Merli 2003). The factors precipitating variceal haemorrhage are still not clear. The risk of bleeding is increased when the size of the varices is more than five mm. The risk of bleeding also increases with the severity of liver disease. In people with alcohol-related cirrhosis, the risk of bleeding depends on whether or not they continue to drink. Once varices are present, they tend to enlarge. Of people with small varices at the outset, 12% will have large varices at one year and 31% at three years (Merli 2003), resulting in a higher risk of bleeding. The estimated two-year incidence of bleeding is approximately 24% (D'Amico 1995; D'Amico 1999) and most episodes of bleeding from varices (70%) occur within two years of diagnosis. Although the in-hospital mortality associated with variceal bleeding has decreased in recent years due to improvements in endoscopic therapy and the use of antibiotic prophylaxis, the reported mortality rate still lies between 12% to 44%. The risk of death within six weeks of the initial variceal haemorrhage is below 10% in Child-Pugh Class A and greater than 32% in those in Child-Pugh Class C (Carbonell 2004).

Description of the intervention

As approximately 30% of people with cirrhosis with oesophageal varices develop bleeding and 12% to 44% die as a result of the first bleed, prophylactic regimens to prevent bleeding are important (Garcia-Tsao 2007; Garcia-Tsao 2008). Nonselective beta-

blocker therapy reduces azygos blood flow and variceal pressure and is used for the primary prophylaxis of variceal haemorrhage (D'Amico 1999; D'Amico 2007). About one in three patients do not respond to beta-blockers or develop adverse events, leading to a reduction in dose or treatment withdrawal (Gluud 2007; Gonzalez 2008). Randomised clinical trials (RCTs) have been used to assess endoscopic interventions as an alternative option (van Buuren 2003; Gluud 2007; Tripathi 2007). Variceal sclerotherapy, which involves injecting a strong and irritating sclerosant or glue, is associated with serious adverse events including severe bleeding and oesophageal strictures (Schmitz 2001). Banding ligation may provide a safer option (Gluud 2007).

How the intervention might work

Banding devices use a means of capturing the target tissue while a small-diameter circular band is deployed around the base of the tissue (ASGE 2008). The band may be rubber, latex, or a similar material. The ligation procedure results in tight compression with vascular compromise leading to thrombosis, necrosis, and sloughing. Previous banding devices used an overtube for the repeated intubation, allowing the placement of multiple bands (Collins 2001). The insertion of an overtube was associated with adverse events including perforation of the oesophagus (Wong 2000; Gluud 2007; Gluud 2012). At present, multi-band devices (without an overtube) are used, resulting in considerably fewer adverse events (ASGE 2008).

Why it is important to do this review

The effect of banding ligation for preventing variceal bleeding is a clinically-important question. Endoscopic variceal ligation is advocated as an alternative option for primary prophylaxis (Imperiale 1992; Gluud 2007). Although banding ligation is a relatively simple endoscopic procedure, repeated banding is normally required to achieve eradication of varices and for surveillance for variceal recurrence. A systematic review found that banding ligation may be superior to beta-blockers in the prevention of bleeding (Gluud 2007). The review did not include RCTs with a no intervention control. Several RCTs have compared banding ligation versus no intervention (Sarin 1996; Lay 1997; Lo 1999; Svoboda 1999; Triantos 2005). Conducting a systematic review with meta-analyses of these trials may provide important information about the beneficial and harmful effects of banding ligation.

OBJECTIVES

To assess the beneficial and harmful effects of banding ligation versus no intervention in adults with cirrhosis and gastro-oesophageal varices that have not bled.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials (RCTs) irrespective of publication type, publication status, and language. If, during the selection of trials, we identify observational studies (i.e. quasi-randomised studies; cohort studies; or patient reports) reporting adverse events, we will include these studies for a review of the adverse events. We will not specifically search for observational studies for inclusion in this review, which is a known limitation of our systematic review.

Types of participants

We will include people with cirrhosis and endoscopically verified gastro-oesophageal varices that have not bled (primary prevention), irrespective of the size of the varices or the hepatic venous pressure gradient.

Types of interventions

Banding ligation versus no intervention. Considering the nature of the intervention, we do not believe that sham interventions are ethical as they may have associated morbidity and no benefit to the participant. In addition, we do not believe it is possible to adequately double blind banding ligation. If we do identify RCTs using blinding based on sham banding ligation, we will consider including them. We will not compare banding ligation versus non-selective beta-blockers due to overlap with another review (Gluud 2012), but we will include RCTs in which participants received the same supportive treatment in the intervention and control group.

Types of outcome measures

We will assess all outcomes at the maximum duration of follow-up.

Primary outcomes

- All-cause mortality.
- Serious adverse events, defined as any untoward medical occurrence that does not necessarily have a causal relationship with the treatment (ICH-GCP 1997). We will define serious adverse events as those that led to death, were life threatening, or required hospitalisation or prolongation of hospitalisation (ICH-GCP 1997). We will analyse adverse events as a composite outcome (CHBG 2017).

Secondary outcomes

- Upper gastrointestinal bleeding.
- Variceal bleeding.
- Quality-of-life.
- Bleeding-related mortality.
- Non-serious adverse events (all adverse events, which do not fulfil the criteria for serious adverse events as defined above).

Search methods for identification of studies

Electronic searches

We will search The Cochrane Hepato-Biliary Group Controlled Trials Register (CHBG 2017), Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library), MEDLINE (Ovid SP), Embase (Ovid SP), and Science Citation Index Expanded (Web of Science) using the strategies with the expected time spans described in Appendix 1. We also plan to search LILACS, Russian, Chinese and Japanese databases with help from the Cochrane Hepato-Biliary Group.

Searching other resources

We will scan the reference lists of relevant articles and proceedings from meetings of the British Society for Gastroenterology (BSG), the British Association for the Study of the Liver (BASL), the European Association for the Study of the Liver (EASL), the United European Gastroenterology Week (UEGW), the American Gastroenterological Association (AGA), and the American Association for the Study of Liver Diseases (AASLD). We will write to the principal authors of RCTs and the device companies for additional information about completed RCTs and for information about any ongoing RCTs. We will also search online trial registries such as ClinicalTrials.gov (clinicaltrials.gov/), European Medicines Agency (EMA) (www.ema.europa.eu/ema/), WHO International Clinical Trial Registry Platform (www.who.int/ictrp), and the Food and Drug Administration (FDA) (www.fda.gov) for ongoing or unpublished trials. In addition, we plan to search Google Scholar using the terms (band* OR ligat*) AND bleed* AND varic* AND cirrhosis.

Data collection and analysis

Two review authors (CWY and SV) will read the electronic searches, perform additional manual searches, and list potentially eligible RCTs, read the potentially eligible trial reports, and participate in the final selection of those to be included in the analyses. We will reach the final selection through consensus. For RCTs reported in more than one publication, we will select the paper reporting the longest duration of follow-up as the primary reference.

Selection of studies

CWY and SV will participate in the searches for eligible trials and data extraction, and list excluded trials with the reason for exclusion. We will all participate in the final selection of trials and resolve disagreements will through discussion before the analyses.

Data extraction and management

Two review authors (CWY and SV) will independently collect data and resolve contrary opinions through discussion. MYM will act as ombudsman in case disagreements cannot be resolved through discussion. The collected data will include information on: i) RCTs: design (cross-over or parallel), settings (number of clinical sites; inclusion period), country of origin; ii) participants: size of varices; proportion of participants with high risk varices (based on the primary authors' definition), mean age, proportion of men, aetiology of cirrhosis, proportion with Child-Pugh A/B/C, and iii) interventions: number of banding sessions, number of bands used per session.

We will gather the primary and secondary outcome data, including the criteria used in the definition of high and low risk varices, methods and definitions used to assess bleeding, and bias control. If we cannot find the relevant data in the published trial reports, we will write to the primary investigators to ask for additional information.

Assessment of risk of bias in included studies

We will assess bias control using the domains described in the Cochrane Hepato-Biliary (CHB) Module (CHBG 2017), classify the risk of bias for separate domains as high, unclear, or low, and the overall assessment as high or low risk of bias.

Allocation sequence generation

- Low risk of bias: the study authors performed sequence generation using computer random number generation or a random number table. Drawing lots, tossing a coin, shuffling cards, and throwing dice were adequate if an independent person not otherwise involved in the study performed them.
- Unclear risk of bias: the study authors did not specify the method of sequence generation.
- High risk of bias: the sequence generation method was not random.

Allocation concealment

- Low risk of bias: the participant allocations could not have been foreseen in advance of, or during, enrolment. A central and independent randomisation unit controlled allocation. The investigators were unaware of the allocation sequence (e.g. if the allocation sequence was hidden in sequentially numbered, opaque, and sealed envelopes).
- Unclear risk of bias: the study authors did not describe the method used to conceal the allocation so the intervention allocations may have been foreseen before, or during, enrolment.
- High risk of bias: it is likely that the investigators who assigned the participants knew the allocation sequence. We will only include such studies for assessment of harms.

Blinding of participants and personnel

- Low risk of bias: blinding of participants and personnel performed adequately using a placebo. We defined lack of blinding as not likely to affect the evaluation of mortality (Hrobjartsson 2001; Savovic 2012; Savovic 2012a).
- Unclear risk of bias: insufficient information to assess blinding.
- High risk of bias: no blinding or incomplete blinding.

Blinding of outcome assessors

- Low risk of bias: blinding of outcome assessors performed adequately using a placebo. We defined lack of blinding as not likely to affect the evaluation of mortality (Hrobjartsson 2001; Savovic 2012; Savovic 2012a).
- Unclear risk of bias: there was insufficient information to blinding.
- High risk of bias: no blinding or incomplete blinding.

Incomplete outcome data

- Low risk of bias: missing data unlikely to make treatment effects depart from plausible values. The investigators used sufficient methods, such as intention-to-treat analyses with multiple imputations or carry-forward analyses to handle missing data.
- Unclear risk of bias: there was insufficient information to assess whether missing data in combination with the method used to handle missing data were likely to induce bias on the results.
- High risk of bias: the results were likely to be biased due to missing data.

Selective outcome reporting

- Low risk of bias: the trial reported clinically-relevant outcomes (mortality, hepatic encephalopathy, and serious adverse events). If we have access to the original trial protocol, the outcomes selected should be those called for in that protocol. If we obtain information from a trial registry (such as www.clinicaltrials.gov), we will consider that information reliable only if the investigators registered the trial before inclusion of the first participant.
- Unclear risk of bias: not all predefined outcomes were reported fully, or it was unclear whether data on these outcomes were recorded or not.
- High risk of bias: one or more predefined outcomes were not reported.

For-profit bias

- Low risk of bias: the trial appears to be free of industry sponsorship or other type of for-profit support.
- Unclear risk of bias: the trial may or may not be free of for-profit bias as the trial does not provide any information on clinical trial support or sponsorship.
- High risk of bias: the trial is sponsored by industry or received other type of for-profit support.

Other bias

- Low risk of bias: the trial appeared to be free of other factors that could put it at risk of bias (e.g. medicinal dosing problems or follow-up (as defined below).
- Unclear risk of bias: the trial may or may not have been free of other factors that could put it at risk of bias
- High risk of bias: there were other factors in the trial that could put it at risk of bias such as the administration of inappropriate treatments being given to the controls (e.g. an inappropriate dose) or follow-up (e.g. the trial included different follow-up schedules for participants in the allocation groups).

Overall bias assessment

- Low risk of bias: if trials are assessed as 'low risk of bias' in all bias risk domains
- High risk of bias: if trials are assessed as having an 'unclear risk of bias' or a 'high risk of bias' in one or more of the bias risk domains.

Measures of treatment effect

We will use risk ratios (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, both with 95% confidence intervals (CI). For statistically significant outcomes (based on the 95% CI), we will calculate the number needed to treat for an additional beneficial outcome (NNTB) as 1/ risk difference (RD).

Unit of analysis issues

We do not expect to identify cross-over RCTs, but if we do, we will include the first trial period in our analyses.

Dealing with missing data

We will extract data on all randomised participants in order to allow intention-to-treat analyses. To evaluate the importance of missing data, we will conduct a worst-case scenario analysis with inclusion of missing outcomes as treatment failures. In addition, we will conduct 'extreme' best-case and worst-case scenario analyses in which we include missing outcome data as treatment failures in the intervention group and successes in the control group and vice versa.

Assessment of heterogeneity

We will evaluate heterogeneity through visual inspection of forest plots and express heterogeneity as I^2 values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and > 80% (considerable). We will include this information in the 'Summary of findings' tables (GRADEpro).

Assessment of reporting biases

For meta-analyses with at least 10 RCTs, we will assess reporting biases through regression analyses and funnel plots.

Data synthesis

We will perform the analyses in Review Manager 5 (RevMan 2014), STATA (Stata 14), and Trial Sequential Analysis (TSA 2011).

Meta-analysis

We will undertake random-effects and fixed-effect meta-analyses. If the estimates of the random-effects and fixed-effect meta-analyses are similar, then we will assume that any small-study effects have little effect on the intervention effect estimate. If the random-effects estimate is more beneficial, we will re-evaluate whether it is reasonable to conclude that the intervention was more effective in the smaller studies. If the larger studies tend to be those conducted with more methodological rigour, or conducted in circumstances more typical of the use of the intervention in practice, then we will report the results of meta-analyses restricted to the larger, more rigorous studies. Based on the expected clinical heterogeneity, we expect that a number of analyses will display statistical between trial heterogeneity (I^2 > 0%). For random-effect models, precision will decrease with increasing heterogeneity and confidence intervals will widen correspondingly. We therefore expect that the random-effects model will give the most conservative (and a more correct) estimate of the intervention effect. We will base our main conclusions on the model that provides the most conservative estimate.

Trial Sequential Analysis

We will perform Trial Sequential Analysis (TSA 2011) in order to evaluate whether apparently significant beneficial and harmful intervention effects could be caused by random error ('play of chance'). We will define the required information size (also known as the 'diversity-adjusted required information size') as the number of participants needed to detect or reject an intervention effect based on the relative risk reduction (RRR) and control group risk (CGR). The analyses show firm evidence if the Z-curve crosses the monitoring boundary (also known as the 'trial sequential monitoring boundary ') before reaching the required information size. We will set the relative risk reduction (RRR) to the highest upper confidence interval and use the control group proportion observed in the meta-analysis, set alpha to 3.3% (primary outcomes) or 1.66% (secondary outcomes), power to 90%, and use model-based diversity.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses to evaluate the effect of banding:

- trials assessed as having a low risk compared to a high risk of bias;
- people with high risk varices compared to people with low risk varices;
- participants who achieve obliteration of varices compared to those who do not.

Sensitivity analysis

We will conduct a worst-case scenario analysis and extreme-worst-case and best-case scenario analyses as described above.

'Summary of findings' tables

We will use the GRADE system (GradePro 2008) to evaluate the quality of the evidence for the outcomes reported in the review considering the within-study risk of bias (methodological quality), indirectness of evidence, heterogeneity, imprecision of effect estimate, and risk of publication bias.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search terms
The Cochrane Hepato-Biliary Group Controlled Trials Register	Date will be given at review stage.	(beta-blocker* OR 'adrenergic beta antagonist*' OR propranolol OR atenolol OR nadolol OR metoprolol OR bisoprolol OR carvedilol OR tertatolol OR nipradilol OR penbutolol OR timolol OR mepindolol) AND '*esophageal varic*'
Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library)	Latest issue.	#1 MeSH descriptor Adrenergic beta-Antagonists explode all trees 8964 #2 MeSH descriptor Propranolol explode all trees 2458 #3 MeSH descriptor Atenolol explode all trees 1626 #4 MeSH descriptor Nadololexplode all trees 161 #5 MeSH descriptor Metoprololexplode all trees 1308 #6 MeSH descriptor Bisoprololexplode all trees 234 #7 MeSH descriptor Penbutololexplode all trees 51 #8 MeSH descriptor Timololexplode all trees 851 #9 beta-blocker* OR 'adrenergic beta antagonist*' OR propranolol OR atenolol OR nadolol OR metoprolol OR bisoprolol OR carvedilol OR tertatolol OR nipradilol OR penbutolol OR timolol OR mepindolol 12373 #10 (#1 OR #2 OR (#3 AND O#4 AND OR#5) OR #6 OR #7 OR #8 OR #9) 14182 #11 MeSH descriptor Esophageal and Gastric Varices explode all trees 740 #12 *esophageal varic* 1269 #13 (#11 OR #12) 1269 #14 (#10 AND #13) 284
MEDLINE (Ovid SP)	1946 to the date of search.	1. exp Adrenergic beta-Antagonists/ 2. exp Propranolol/ 3. exp Atenolol/ 4. exp Nadolol/

(*Continued*)

		5. exp Metoprolol/ 6. exp Bisoprolol/ 7. exp Penbutolol/ 8. exp Timolol/ 9. (beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 11. exp "Esophageal and Gastric Varices"/ 12. ((oesophageal or esophageal) and varic*).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 13. 11 or 12 14. 10 and 13 15. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] 16. 14 and 15
Embase (Ovid SP)	1974 to the date of search.	1. exp beta adrenergic receptor blocking agent/ 2. exp PROPRANOLOL/ 3. exp ATENOLOL/ 4. exp NADOLOL/ 5. exp METOPROLOL/ 6. exp BISOPROLOL/ 7. exp CARVEDILOL/ 8. exp TERTATOLOL/ 9. exp NIPRADILOL/ 10. exp PENBUTOLOL/ 11. exp TIMOLOL/ 12. exp MEPINDOLOL/ 13. (beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 15. exp esophagus varices/ 16. ((oesophageal or esophageal) and varic*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

(*Continued*)

		17. 15 or 16 18. 14 and 17 19. (random* or blind* or placebo* or meta-analysis).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer] 20. 18 and 19
Science Citation Index Expanded (Web of Science)	1900 to the date of search.	#4 #3 AND #2 AND #1 #3 TS=(random* or blind* or placebo* or meta-analysis) #2 TS=((oesophageal or esophageal) and varic*) #1 TS=(beta-blocker* or adrenergic beta antagonist* or propranolol or atenolol or nadolol or metoprolol or bisoprolol or carvedilol or tertatolol or nipradilol or penbutolol or timolol or mepindolol)

CONTRIBUTIONS OF AUTHORS

LLG drafted the protocol. All authors revised the protocol and approved of the final version.

DECLARATIONS OF INTEREST

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