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Antacids for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients (Review)

Guo Z, Wu Z, Wang Y

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[Intervention Review]

Antacids for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients

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ABSTRACT

Background

Ruptured gastroesophageal varices are the most severe and frequent cause of gastrointestinal bleeding in cirrhotic patients, leading to death in 5% to 8% of patients during the first 48 hours and oesophagogastric varices account for 60% to 80% of first bleeding in patients with portal hypertension. Antacids are often used for emergency treatment of bleeding oesophageal varices in patients with cirrhosis of the liver.

Objectives

To evaluate the beneficial and harmful effects of antacids for preventing oesophagogastric bleeding and rebleeding.

Search methods

We planned to identify relevant randomised clinical trials by searching *The Cochrane Hepato-Biliary Group Controlled Trials Register* (June 2007), the *Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 2, 2007), *MEDLINE* (1950 to June 2007), *EMBASE* (Excerpta Medica Database) (1980 to June 2007), and the *Science Citation Index Expanded* (SCI-EXPANDED) (1945 to June 2007). Additional randomised trials were sought from the reference lists of the trials found and reviews identified by the electronic searches.

Selection criteria

We planned to include randomised clinical trials.

Data collection and analysis

We planned to summarise data using Cochrane Collaboration methodologies.

Main results

We could not find any randomised clinical trials on antacids for preventing oesophagogastric variceal bleeding and bleeding in cirrhotic patients.

Authors' conclusions

It is not possible to determine whether antacids are beneficial or harmful for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients since randomised clinical trials investigating this question are lacking.

PLAIN LANGUAGE SUMMARY

Evidence to establish the beneficial and harmful effects of antacids for preventing oesophagogastric variceal bleeding and bleeding in cirrhotic patients is lacking

Randomised trials with antacids for preventing oesophagogastric variceal bleeding and bleeding in cirrhotic patients could not be found. Valid evidence for or against the use of antacids for preventing oesophagogastric variceal bleeding and bleeding in cirrhotic patients is lacking.

BACKGROUND

Ruptured gastroesophageal varices are the most severe and frequent cause of gastrointestinal bleeding in cirrhotic patients, leading to death in 5% to 8% of patients during the first 48 hours (Bosch 2004), and oesophagogastric varices account for 60% to 80% of first bleeding in patients with portal hypertension (Triger 1989; Dagher 2001; Zhou 2002). The incidence of rebleeding ranges between 50% and 80%, and mortality ranges from 30% to 70% (Zeng 1998). Early rebleeding is significantly related to death within six weeks.

Because of their effectiveness and safety, antacid drugs are used in the treatment of upper gastrointestinal haemorrhage, caused by peptic ulcer or acid-related diseases (Zhou 2002). Antacids are often used for emergency treatment of bleeding oesophageal varices in patients with cirrhosis of the liver (Zhou 2002). Many controlled trials have been carried out on treatment with antacids, which may stop bleeding and prevent rebleeding (MacDougall 1977; Zuckerman 1984; Snady 1989; Zhou 2002). In cirrhotic patients, the gastric acid secretion may be reduced, but the coexisting reduction of the gastric mucosal defence mechanism and back effusion of H+ may contribute to gastric erosion and bleeding in patients with portal hypertensive gastropathy (Zhou 2002). However, there are different opinions about this question, based on the fact that patients with liver cirrhosis generally have lower gastric acid secretion (Pique 1988; Smart 1991). We could not find any systematic reviews or meta-analyses investigating the beneficial and harmful effects of antacids for preventing oesophagogastric bleeding and rebleeding.

OBJECTIVES

The objective is to evaluate the beneficial and harmful effects of antacids for preventing oesophagogastric bleeding and rebleeding.

We could not identify any randomised clinical trials with antacids for preventing oesophagogastric bleeding and rebleeding, and we could not follow the protocol part below.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials comparing antacids with a placebo or no intervention regardless of whether they are single-blinded, double-blinded, or not blinded and irrespective of language and publication status.

Types of participants

We will include all patients with oesophagogastric varices confirmed by endoscopy and regardless of the causes of portal hypertension, age, sex, or Child-Pugh grade (Pugh 1973), with or without previous oesophagogastric variceal bleeding. Patients with acute bleeding will be excluded.

Types of interventions

- Peroral antacids at any dose versus placebo or no intervention.
- Additional interventions will be allowed in both the antacid and the control arm of the trial as long as these additional interventions do not differ between the two arms of the trial.

Types of outcome measures

Primary outcome measures

- All-cause mortality.
- Mortality due to gastrointestinal bleeding: any death occurring within six weeks of time zero, that is, the time of admission of the patient to hospital with gastrointestinal bleeding, will be considered as related to gastrointestinal bleeding regardless of the mode (de Franchis 2001).
- Mortality due to variceal bleeding/rebleeding: any death occurring within six weeks of time zero, that is, the time of admission of the patient to hospital due to variceal bleeding, will be considered as related to variceal bleeding, regardless of the mode (de Franchis 2001). Variceal bleeding is diagnosed as endoscopy proven active bleeding; or signs of recent bleeding ('white nipple' or 'clot that could not be washed off'); or varices without other potential bleeding source (de Franchis 2001).
- Number of patients experiencing upper gastrointestinal bleeding/rebleeding.
- Number of patients experiencing variceal bleeding/rebleeding, that is, endoscopy proven active bleeding; or signs of recent bleeding ('white nipple' or 'clot that could not be washed off'); or varices without other potential bleeding source (de Franchis 2001).

Secondary outcomes measures

- Number of participants who dropped out from the study after randomisation.
- Quality of life (measured by any scale).
- Adverse events (defined as any untoward medical occurrence not necessarily having a causal relationship with the treatment, but did, however, result in a dose reduction or discontinuation of treatment). The serious adverse events will be any untoward medical occurrence that resulted in death, was life-threatening, required hospitalisation or prolongation of hospitalisation; resulted in persistent or significant disability or in a congenital anomaly/birth defect; any event that jeopardized the patient, or required intervention to prevent one of the above outcomes (ICH-GCP 1997). All other adverse events will be considered non-serious.
- The estimated costs of different types of antacids and used for prophylaxis will be weighed against any possible health gains.

Search methods for identification of studies

To identify relevant randomised clinical trials, we searched *The Cochrane Hepato-Biliary Group Controlled Trials Register* (*CENTRAL*), *The Cochrane Central Register of Controlled Trials* (*CENTRAL*) in *The Cochrane Library* (Issue 2, 2007), *MEDLINE* (1950 to June 2007), *EMBASE* (Excerpta Medica Database) (1980 to June 2007), and *Science Citation Index Expanded* (*SCI-EXPANDED*) (1945 to June 2007) (Royle 2003).

The search strategies used are given in Appendix 1.
Other sources of information on both published and unpublished data included:

- References cited in identical studies and in other published non-systematic reviews.
- Abstracts in Current Contents.

- Conference proceedings of antacids.
- Manufacturers.
- Reference lists.
- Personal communications.
- Hand searching (including Chinese articles).

Data collection and analysis

We followed the instructions given in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2006) and the Cochrane Hepato-Biliary Group Module (Gluud 2007).

Trial selection

All identified studies were reviewed independently by two reviewers (WZ and GZ) in order to determine eligibility. Disagreement were solved by consensus with provision of arbitration of a third reviewer (WY) whenever required. Trials published in abstract form were to be included if full details of the trial and results could be obtained from the authors.

Quality components

We defined the methodological quality as the confidence that the design and report restrict bias in the intervention comparison (Moher 1998; Kjaergard 2001). We planned to assess the methodological quality by four separate components (Kjaergard 2001) because of the risk of overestimation of intervention effects in randomised trials with inadequate methodological quality (Schulz 1995; Moher 1998; Kjaergard 2001). If at a future update randomised trials were to be found, we would analyse the influence of methodological quality by the four separate components:

Generation of the allocation sequence

- Adequate, if the allocation sequence was generated by a computer or random number table. Tossing of a coin, shuffling of cards, or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure.
- Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.
- Inadequate, if a system involving dates, names, or admittance numbers were used for the allocation of patients. These studies are known as quasi-randomised and will be excluded from the present review when assessing beneficial effects.

Allocation concealment

- Adequate, if the allocation of patients involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

- Adequate, if the trial was described as double blind and the method of blinding involved identical placebo or active drugs.
- Unclear, if the trial was described as double blind, but the method of blinding was not described.
- Not performed, if the trial was not double blind.

Follow-up

- Adequate, if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

Furthermore, we will register whether or not the randomised clinical trials have used an 'intention-to-treat' analysis (Gluud 2001) and a sample size calculation.

Study quality will be assessed by one reviewer and checked by a second one. Eventual differences in the quality assessment of trials will be resolved in discussion in order to reach consensus.

Data collection

The authors used a standard form to independently extract data. Two authors were about to extract information on the following: number of randomised participants, types of participants and types of interventions, method of allocation concealment, loss to follow-up, the use of blinding and whether an intention-to-treat analysis was carried out. The outcome data sought are numbers of deaths in each group, numbers of bleeding and rebleeding, and the adverse events. Data were extracted by each author working independently. Recorded data were cross checked by the authors. The following variables were extracted: survival, bleeding, and rebleeding rates.

Statistical analyses

Due to the lack of randomised trials, we could not perform data analyses. If trials are identified and included in the future, we will adhere to the following protocol. We will use the software package RevMan Analyses (RevMan 2003) provided by The Cochrane Collaboration. The analyses will include all patients irrespective of compliance or follow-up, according to the 'intention-to-treat' principle, and using the last reported observed response ('carry forward'). We will perform both a 'worst-best-case scenario' analysis, which considers all dropout patients in the antacids or the acid-suppressive medications group as dead and the dropout patients in the control group as alive, and a 'best-worst-case scenario' analysis, which considers all dropout patients in the antacids or acid-suppressive medications group as alive and the dropout patients in the control group as dead.

The extracted data from the various trials will be combined by calculating a pooled estimate of the relative risk (RR) and 95% confidence interval (CI) for dichotomous data. For continuous data the weighted mean difference (WMD) with 95% CI will be measured. We plan to perform the meta-analysis by both random-effects and fixed-effect model. We will only report the results of fixed effect model if there is no difference between the two methods regarding the significance of intervention effect, otherwise we will report the results produced by both models. We will explore evidence of publication bias and other biases by funnel plot analyses. Funnel plot on the primary outcome will be used to provide a visual assessment of whether treatment estimates are associated with

study size. We will use two tests to assess funnel plot asymmetry, adjusted rank correlation test and regression asymmetry test.

Subgroup/Sensitivity analyses

- Methodological quality of the randomised clinical trials - we will compare the trials with adequate methodological quality to the trials with unclear/inadequate methodological quality.
- We will compare the trials with co-interventions to the trials without co-interventions.
- Etiology of cirrhosis - we will compare the effects of antacids in different etiologies of liver cirrhosis.
- Child-Pugh grade (Pugh 1973) - we will compare the effects of antacids in different Child-Pugh grades (A, B, and C).
- Size of oesophagogastric varices - we will compare the effects of antacids patients with different size of oesophagogastric varices (small, medium, large) at entry into the trials.
- Kinds of antacids - we will compare the effects of different kinds of antacids.

Due to the large number of comparisons planned we will interpret any significant findings conservatively. The main analysis will focus on the primary outcome measures in trials with adequate methodology.

RESULTS

Description of studies

Forty references were identified through the initial bibliographical searches. After manually checking the titles and abstracts, fourteen trials remained to be evaluated further. We evaluated that none of them attempted to answer the research questions of our review (see Characteristics of excluded studies).

Risk of bias in included studies

No trials were included.

Effects of interventions

The searches did not identify any randomised trials eligible for inclusion in this systematic review. We could not identify any ongoing trials either.

There were no quasi-randomised studies, historically controlled studies, or cohort studies, which we could use to assess harmful effects of antacids.

DISCUSSION

In recent times, the 6-week mortality rate of cirrhotic patients with gastrointestinal bleeding has fallen to 20% due to the development of effective treatment strategies (Bosch 2004). Peptic ulceration and reflux oesophagitis are some of the reasons for acute upper gastrointestinal bleeding in patients with cirrhosis (Amitrano 2002; Green 2003). Antacids may be helpful for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients theoretically, but we have been unable to identify evidence supporting the use of antacids for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients. Randomised clinical trials should explore this hypothesis. This would require trials with large sample sizes because the deaths from uncontrolled bleeding or rebleeding are approximately 8% in consecutive patients with cirrhosis and upper digestive bleeding (D'Amico 2003).

It is widely known that clinicians make practical decisions, often on the basis of inadequate information. Decisions about treatment should preferably be taken based on the results of randomised trials (Alderson 2004; Chalmers 2004).

The basis for the rational use of antacids in liver patients with upper gastrointestinal bleeding remains unknown. What could the reason of this uncertainty be? First, randomised clinical trials to answer the research question of our review have not yet been carried out. Second, it is possible that some trials have been carried out, but came with negative results, and thus remained unpublished (Easterbrook 1991; Gluud 1998). This causes publication bias, reducing the possibilities to develop valid systematic reviews in certain areas. The paucity of data on antacids for liver patients with the risk of oesophagogastric variceal bleeding and bleeding should stimulate the development of well-planned randomised trials to inform clinical practice.

AUTHORS' CONCLUSIONS

Implications for practice

No randomised clinical trials of antacids for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients were found for inclusion in this review. Therefore, it is not possible to determine whether antacids are beneficial or harmful for preventing oesophagogastric variceal bleeding and rebleeding in cirrhotic patients. We cannot recommend antacids for use outside randomised clinical trials.

Implications for research

This systematic review has identified the need for well-designed, adequately powered randomised clinical trials to assess the benefits and harms of antacids as a possible way to improve the survival and decrease mortality from oesophagogastric variceal bleeding and rebleeding in cirrhotic patients. The trials regarding this issue should be reported according to the CONSORT Statement for improving the quality of reporting of benefits and harms in clinical research (www.consort-statement.org) (Moher 2004; Ioannidis 2004).

ACKNOWLEDGEMENTS

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We thank the peer-reviewers for their suggestions for improving the quality of the protocol and systematic review.

Peer Reviewers: S Mahadeva, Malaysia.

Contact Editor: C Gluud, Denmark.

REFERENCES

References to studies excluded from this review

Andersen 1983 *{published data only}*

Andersen OK, Farup P, Hasvoll A, Bernklev T. Patient compliance to intensive antacid treatment. *Scandinavian Journal of Gastroenterology* 1983;**86**:3.

Attwell 2005 *{published data only}*

Attwell AR, Chen YK. Endoscopic ligation in the treatment of variceal bleeding. *Techniques in Gastrointestinal Endoscopy* 2005;**7**(1):18-25.

Bachir 1981 *{published data only}*

Bachir GS, Leigh Collis J, Wilson P, Pollak EW. Diagnosis of incipient reflux esophagitis: a new test. *Southern Medical Journal* 1981;**74**(9):1072-4.

Jackson 2003 *{published data only}*

Jackson R, Pencharz PB. Cystic fibrosis. *Bailliere's Best Practice and Research in Clinical Gastroenterology* 2003;**17**(2):213-35.

Kumar 1984 *{published data only}*

Kumar N, Vij JC, Karol A, Anand BS. Controlled therapeutic trial to determine the optimum dose of antacids in duodenal ulcer. *Gut* 1984;**25**(11):1199-202.

Londong 1983 *{published data only}*

Londong W. Drug therapy and prevention of acute upper gastrointestinal hemortroenterologie. *Zeitschrift für Gastroenterologie* 1983;**21**(6):282-9.

Macdougall 1977 *{published data only}*

Macdougall BR, Bailey RJ, Williams R. H2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure Two controlled trials. *Lancet 1977* 1977;**1**(8012):617-9.

Meshkinpour 1977 *{published data only}*

Meshkinpour H, Elashoff J, Stewart H 3rd, Sturdevant RA. Effect of cholestyramine on the symptoms of reflux gastritis A randomized, double blind, crossover study. *Gastroenterology* 1977;**73**(3):441-3.

Narendranathan 1999 *{published data only}*

Narendranathan M, Remla A, Mini PC, Satheesh P. A trial of Phyllanthus Amarus in acute viral hepatitis. *Tropical Gastroenterology* 1999;**20**(4):164-6.

Priebe 1980 *{published data only}*

Priebe HJ, Skillman JJ, Bushnell LS, Long PC, Silen W. Antacid versus cimetidine in preventing acute gastrointestinal bleeding A randomized trial in 75 critically ill patients. *New England Journal of Medicine* 1980;**302**(8):426-30.

Snady 1989 *{published data only}*

Snady H, Rosman AS, Korsten MA. Prevention of stricture formation after endoscopic sclerotherapy of esophageal varices. *Gastrointestinal Endoscopy* 1989;**35**(5):377-80.

Winston 2002 *{published data only}*

Winston DJ, Busuttil RW. Randomized controlled trial of oral itraconazole solution versus intravenous/oral fluconazole for prevention of fungal infections in liver transplant recipients. *Transplantation* 2002;**74**(5):688-95.

Yang 1998 *{published data only}*

Yang WG, Hou MC, Lin HC, Kuo BI, Lee FY, Chang FY, et al. Effect of sucralfate granules in suspension on endoscopic variceal sclerotherapy induced ulcer: analysis of the factors determining ulcer healing. *Journal of Gastroenterology and Hepatology* 1998;**13**(2):225-31.

Zuckerman 1984 *{published data only}*

Zuckerman G, Welch R, Douglas A, Troxell R, Cohen S, Lorber S, et al. Controlled trial of medical therapy for active upper gastrointestinal bleeding and prevention of rebleeding. *American Journal of Medicine* 1984;**76**(3):361-6.

Additional references

Alderson 2004

Alderson P. Absence of evidence is not evidence of absence. *BMJ (Clinical Research Ed.)* 2004;**328**:476-7.

Amitrano 2002

Amitrano L, Guardascione MA, Brancaccio V, Balzano A. Coagulation disorders in liver disease. *Seminars in Liver Disease* 2002;**22**:83-96.

Bosch 2004

Bosch J, Abraldes JG. Management of gastrointestinal bleeding in patients with cirrhosis of the liver. *Seminars in Hematology* 2004;**41**(1 (Suppl)):8-12.

Chalmers 2004

Chalmers I. Well informed uncertainties about the effects of treatments. How clinicians and patients respond?. *BMJ (Clinical Research Ed.)* 2004;**328**:475-6.

D'Amico 2003

D'Amico G, De Franchis R, Cooperative Study Group. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003;**38**(3):599-612.

Dagher 2001

Dagher L, Burroughs A. Variceal bleeding and portal hypertensive gastropathy. *European Journal of Gastroenterology & Hepatology* 2001;**13**:81-8.

de Franchis 2001

de Franchis R. What have we accomplished?. Portal hypertention III: Proceedings of the third Baveno international consensus workshop on definitions, methodology and therapeutic strategies. Oxford: Blackwell Science, 2001:1-12.

Easterbrook 1991

Easterbrook PJ, Berlin J, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;**337**:867-72.

Gluud 1998

Gluud C. "Negative trials" are positive!. *Journal of Hepatology* 1998;**28**(4):731-3.

Gluud 2001

Gluud C. Alcoholic hepatitis: no glucorticocosteroids?. Steatohepatitis (NASH and ASH) - Falk Symposium No 121. Lancaster: Kluwer Academic Publisher, 2001:322-42.

Gluud 2007

Gluud C, Nikolova D, Klingenberg SL, Als-Nielsen B, D'Amico G, Davidson B, et al. Cochrane Hepato-Biliary Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2007, Issue 2. Art. No.: LIVER.

Green 2003

Green BT, Rockey DC. Acute gastrointestinal bleeding. *Seminars in Gastrointestinal Disease* 2003;**14**:44-65.

Higgins 2006

Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. The Cochrane Library, Issue 4, 2006. Chichester, UK: John Wiley & sons, Ltd, 2006.

ICH-GCP 1997

International Conference on Harmonisation Expert Working Group. Code of Federal Regulations & International Conference on Harmonization Guidelines. Media: Parexel Barnett, 1997.

Ioannidis 2004

Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Annals of Internal Medicine* 2004;**141**(10):781-8.

Kjaergard 2001

Kjaergard LL, Villumsen J, Gluud C. Reported methodological quality and discrepancies between large and small randomised trials in meta-analyses. *Annals of Internal Medicine* 2001;**135**:982-9.

MacDougall 1977

MacDougall BRD, Bailey RJ, Williams R. H2-receptor antagonists and antacids in the prevention of acute gastrointestinal haemorrhage in fulminant hepatic failure. Two controlled trials. *Lancet* 1977;**19**(1):617-9.

Moher 1998

Moher D, Jadad AR, Moher M. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet* 1998;**352**:609-13.

Moher 2004

Moher D, Altman DG, Schulz KF, Elbourne DR. Opportunities and challenges for improving the quality of reporting clinical research: CONSORT and beyond. *Canadian Medical Association Journal* 2004;**171**(14):349-50.

Pique 1988

Pique JM, Leung FW, Kitahora T, Sarfeh IJ, Tarnawski A, Guth PH. Gastric mucosal blood flow and acid secretion in portal hypertensive rats. *Gastroenterology* 1988;**95**:727-33.

Pugh 1973

Pugh RNH, Murray-Lyon IM, Dawson JL, Pietoni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. *British Journal of Surgery* 1973;**60**(8):648-52.

RevMan 2003 [Computer program]

Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 4.2 for Windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

Royle 2003

Royle P, Milne R. Literature searching for randomized controlled trials used in Cochrane reviews: rapid versus exhaustive searches. *International Journal of Technology Assessment in Health Care* 2003;**19**(4):591-603.

Schulz 1995

Schulz KF, Chalmers I, Hayers RJ, Altman DG. Emprirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408-12.

Smart 1991

Smart HJ, Trigger DR. Clinical features, pathophysiology and relevence of portal hypertensive gastropathy. *Endoscopy* 1991;**23**:224-8.

Triger 1989

Triger DR. Natural history and treatment of portal hypertensive gastropathy. *Journal of Gastroenterology and Hepatology* 1989;**1(suppl)**:8-14.

Zeng 1998

Zeng MD. Forecast and treatment of esophageal variceal. *Chinese Journal of Liver and Gallbladder* 1998;**6**:65-6.

Zhou 2002

Zhou YN, Liang Q, Jing W, Hu HW, Xu CP. Comparison of the efficacy of octreotide, vasopressin, and omeprazole in the control of acute bleeding in patients with portal hypertensive gastropathy: a controlled study. *Journal of Gastroenterology and Hepatology* 2002;**17**:973-9.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Andersen 1983	It is not a randomised trial.
Attwell 2005	It is not a randomised trial, and the treatment given does not include antacids.
Bachir 1981	It is not a randomised trial.
Jackson 2003	It is not a randomised trial.
Kumar 1984	It is a randomised trial, but the included patients have duodenal ulcers.
Londong 1983	It is not a randomised trial.
Macdougall 1977	It is a randomised trial, but the included patients have fulminant hepatic failure.
Meshkinpour 1977	It is a randomised trial, but the included patients have reflux gastritis.
Narendranathan 1999	It is a randomised trial, but the included patients have acute viral hepatitis.
Priebe 1980	It is a randomised trial, but the included patients are critically ill patients.
Snady 1989	It is a randomised controlled trial, but antacids in this trial were given to prevent stricture formation after endoscopic sclerotherapy of oesophageal varices.
Winston 2002	It is a randomised controlled trial, but the included patients are liver transplant recipients.
Yang 1998	It is a randomised trial, but the included patients have endoscopic variceal sclerotherapy induced ulcer and the trial does not study antacids.
Zuckerman 1984	It is a randomised trial, but it does not include antacids.

APPENDICES

Appendix 1. Search strategies

Database	Time span	Search strategy
The Cochrane Hepato-Biliary Group Controlled Trials Register	June 2007.	antacid*
Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library	Issue 2, 2007.	#1 MeSH descriptor Antacids explode all trees #2 antacid* #3 (#1 OR #2) #4 MeSH descriptor Esophageal and Gastric Varices explode all trees #5 ((oesophag* or esophag*) and varic*) #6 (#4 OR #5) #7 MeSH descriptor Liver Cirrhosis explode all trees

(Continued)

		#8 MeSH descriptor Fibrosis explode all trees #9 cirrho* #10 (#7 OR #8 OR #9) #11 (#3 AND #6 AND #10)
MEDLINE (WinSPIRS 5.0)	1950 to June 2007.	#1 explode "Antacids"/ all subheadings #2 antacid* #3 #1 or #2 #4 explode "Esophageal-and-Gastric-Varices"/ all subheadings #5 (oesophag* or esophag*) and varic* #6 #4 or #5 #7 explode "Liver-Cirrhosis"/ all subheadings #8 explode "Fibrosis"/ all subheadings #9 cirrho* #10 #7 or #8 or #9 #11 #3 and #6 and #10
EMBASE (WinSPIRS 5.0)	1980 to June 2007.	#1 explode "antacid-agent"/ all subheadings #2 antacid* #3 #1 or #2 #4 explode "esophagus-varices"/ all subheadings #5 (oesophag* or esophag*) and varic* #6 #4 or #5 #7 explode "liver-cirrhosis"/ all subheadings #8 cirrho* #9 #7 or #8 #10 #3 and #6 and #9
Science Citation Index Expanded (SCI-EXPANDED)	1945 to June 2007.	#3 #2 AND #1 #2 TS=cirrho* #1 TS=(antacid*)

WHAT'S NEW

Date	Event	Description
28 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Yang J wrote the protocol, which was checked and authorised by Wang Y, Guo Z, and Wu Z reviewed the identified publications for the review eligibility. Wang Y solved disagreements. Guo Z and Wu Z extracted data.
All authors contributed to the preparation of the review and agreed on its final version.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Antacids [*therapeutic use]; Esophageal and Gastric Varices [*complications]; Gastrointestinal Hemorrhage [*prevention & control]; Liver Cirrhosis [*complications]; Secondary Prevention

MeSH check words

Humans