



Centre for Clinical Effectiveness

Enhancing patient outcomes through clinical application of the best available evidence

EVIDENCE CENTRE
CRITICAL APPRAISAL
Series 2002: Therapy

Proton pump inhibitors versus H₂ antagonists or placebo in treating bleeding peptic ulcer

Omar Abdulwadud PhD

Centre for Clinical Effectiveness
Monash Institute of Health Services Research
Monash Medical Centre
Locked Bag 29
Clayton VIC 3168, Australia

Telephone: +61 3 9594 7505
Fax: +61 3 9594 7505
Email: cce@med.monash.edu.au (quote author of report)
URL: <http://www.med.monash.edu.au/healthservices/cce/>

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SUMMARY STATEMENT:

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Publication of materials – please use the following format when citing this article:

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REQUEST:

Proton pump inhibitors versus H₂ antagonists or placebo in treating bleeding peptic ulcer

REQUESTED BY:

Ian Larmour, Director of Pharmacy, Monash Medical Centre, Clayton.

METHODOLOGY

Search Strategy

The Centre for Clinical Effectiveness defines the 'best available evidence' as that research we can identify that is least susceptible to bias. We determine this according to pre-defined National Health and Medical Research Council (NHMRC, 2000) criteria (see Appendix 1).

First, we search for systematic reviews, evidence based clinical practice guidelines, health technology assessments and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalisable or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting.

Details of Evidence Request

Patient/condition:	Patients with gastrointestinal ulcer bleeding
Intervention:	Proton pump inhibitors (PPIs)
Comparison:	H ₂ antagonists (H ₂ -A), placebo, no treatment
Outcomes:	Bleeding (persistent or recurrent), blood transfusion, endoscopic intervention, need for surgery, length of stay, mortality.

Search terms (see Appendix 2 for exact search strategy)

Table 1. Search terms used in the retrieval of articles from electronic databases and websites

Field of focus	Search term
Patient/condition-related	Exp Gastrointestinal Hemorrhage/ or exp Peptic Ulcer Hemorrhage/, Gastrointestinal-Hemorrhage.tw, Peptic Ulcer hemorrhage.tw.
Intervention-related	Exp Omeprazole/ or proton pump inhibitor\$.mp, (pantoprazole or rabeprazole or lansoprazole or omeprazole).tw, PPI\$.tw.
Comparison-related	Exp Histamine H2 Antagonists/ or histamine h2 antagonist\$.mp, exp CIMETIDINE/ or cimetidine.mp, exp FAMOTIDINE/ or famotidine.mp, exp NIZATIDINE/ or nizatidine.mp, exp RANITIDINE/ or ranitidine.mp.

Resources Searched

We searched the following databases and Internet websites:

Cochrane Library CD-ROM- Issue 4, 2001

Medline (OVID)- 1966 to October week 5 2001

CINAHL (OVID) – 1982 to October week 4 2001

PreMedline (OVID)- November 14, 2001

Current contents (OVID) – 1993 week 26 to 2001 week 47

Australasian Medical Index – December 2001

National Guideline Clearinghouse

NHS Centre for Reviews and Dissemination (Health Technology Assessment database)

Refinements, Searching & Reporting Constraints:

We included items of evidence that were available to us on 15 November 2001. Having identified the 2001 meta-analysis by Gisbert et al, a restriction period of 2001 was applied while searching the above databases. The search was also restricted to humans and articles published in English.

RESULTS:

From our sources we identified 8 articles related to the request. They were all published in 2001 and was categorised as follows:

Table 2. Study designs of articles retrieved by search

Study Design	Number
Systematic reviews or meta-analyses	3
Evidence-based clinical practice guidelines	0
Randomised controlled trials	1
Pseudo-randomised controlled trials	0
Controlled trials, cohort or case-control analytic studies	0
Narrative reviews	4

Articles were excluded from further appraisal as follows:

Table 3: Reason for exclusion of article retrieved by search

Reason for exclusion	Number
Systematic review (Protocol only – review in progress)	1
Level IV studies	4

This left two reviews and one randomized control trial for appraisal. We are reasonably confident these articles represent the most relevant finding published to date based on our refinements, searching and reporting constraints.

EVIDENCE SUMMARIES

Format

Evidence summaries are presented as spreadsheets attached to this report. Each spreadsheet contains the article citation, details of the study design, patient description, scientific validity of the article, results, and pertinent remarks from the authors and Centre for Clinical Effectiveness reviewer.

REFERENCES

ARTICLE CRITICALLY APPRAISED

1. Gisbert, J. P., L. Gonzalez, et al. (2001). "Proton pump inhibitors versus H-2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer." Alimentary Pharmacology & Therapeutics **15**(7): 917-926.
2. Erstad, B. L. (2001). "Proton-pump inhibitors for acute peptic ulcer bleeding." Annals of Pharmacotherapy **35**(6): 730-740.
3. Javid, G., I. Masoodi, et al. (2001). "Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer." American Journal of Medicine **111**(4): 280-284.

ARTICLES NOT CRITICALLY APPRAISED

Systematic review (Protocol only – review in progress)

1. McIntyre L, Schoenfeld P, Peterson W (2001). Proton pump inhibitors for bleeding peptic ulcers (Protocol for a Cochrane Review). In: The Cochrane Library, Issue 4 Oxford: Update Software.

Level IV evidence

1. Kubba, A. K., N. M. Selby, et al. (2001). "Update in the pharmacological management of peptic ulcer haemorrhage." Scandinavian Journal of Gastroenterology **36**(4): 337-342.
2. van Leerdam, M. E. and E. A. Rauws (2001). "The role of acid suppressants in upper gastrointestinal ulcer bleeding." Best Practice & Research in Clinical Gastroenterology **15**(3): 463-75.
3. Collins, D. & Worthley, LI (2001). Acute gastrointestinal bleeding: part I. Critical-Care-and-Resuscitation Jun; 3 (2):105-16
4. Nehme, O. and J. S. Barkin (2001). "Recurrent ulcer bleeding: is intravenous omeprazole the solution?" American Journal of Gastroenterology **96**(2): 594-5.

APPENDIX 1

Copyright

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Levels of Evidence

Based on "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

- | | |
|-------------|--|
| Level I | Evidence obtained from a systematic review of all relevant randomised controlled trials. |
| Level II | Evidence obtained from at least one properly designed randomised controlled trial. |
| Level III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method). |
| Level III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomized, cohort studies, case control studies, or interrupted time series with a control group. |
| Level III-3 | Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group. |
| Level IV | Evidence obtained from case series, either post-test or pre-test/post-test. |

APPENDIX 2

Search strategy (Search terms for Cochrane Library, Medline, CINAHL, PreMedline, Current contents, Australasian Medical Index)

1. exp *Peptic Ulcer/ or peptic ulcer\$.mp.
2. peptic-ulcer\$.tw.
3. gastroduodenal ulcer\$.tw.
4. exp STOMACH ULCER/ or exp DUODENAL ULCER/
5. STOMACH ULCER.tw.
6. DUODENAL ulcer.tw.
7. or/1-6
8. exp Gastrointestinal Hemorrhage/ or exp Peptic Ulcer Hemorrhage/
9. Gastrointestinal-Hemorrhage.tw.
10. Peptic Ulcer hemorrhage.tw.
11. exp HEMORRHAGE/ or hemorrhage.mp.
12. (haemorrhage or bleed\$).tw.
13. or/8-12
14. 7 and 13
15. exp Histamine H2 Antagonists/ or histamine h2 antagonist\$.mp.
16. exp CIMETIDINE/ or cimetidine.mp.
17. exp FAMOTIDINE/ or famotidine.mp.
18. exp NIZATIDINE/ or nizatidine.mp.
19. exp RANITIDINE/ or ranitidine.mp.
20. or/15-19
21. exp Omeprazole/ or proton pump inhibitor\$.mp.
22. (pantoprazole or rabeprazole or lansoprazole or omeprazole).tw.
23. PPI\$.tw.
24. or/21-23
25. 20 and 24
26. 14 and 25
27. limit 26 to (human and english language)

\$ Wildcard indicating truncation

<p style="text-align: center;">Evidence Summary Systematic Review</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> Proton pump inhibitors versus H₂ antagonists or placebo in treating bleeding peptic ulcer </div>	<p style="text-align: center;">Study 1</p> Gisbert, J. P., L. Gonzalez, et al. (2001). "Proton pump inhibitors versus H ₂ -antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer." <i>Alimentary Pharmacology & Therapeutics</i> 15(7): 917-926	<p style="text-align: center;">Study 2</p> Erstad, B. L. (2001). "Proton-pump inhibitors for acute peptic ulcer bleeding." <i>Annals of Pharmacotherapy</i> 35(6): 730-740.
STUDY DESIGN & NHMRC LEVEL OF EVIDENCE	A meta-analysis (Level I)	Systematic Review (Level I)
DESCRIPTION: Patient (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria	Patients: Patients with bleeding gastroduodenal ulcer. Intervention: Proton pump inhibitors (PPIs) Comparisons: H ₂ antagonists (H ₂ -A), no treatment, placebo Outcomes: Bleeding (persistent or recurrent), need for surgery or mortality. Inclusion/exclusion criteria: Comparative randomised trials; at least one branch of treatment consisting of H ₂ -A and another branch with a PPI; studies had to evaluate the therapies in the above patients; the effect of therapy had to be evaluated by at least one of the above outcomes; and only studies that clearly stated information about the number of treated patients in each therapeutic group. Duplicate publications were excluded.	Patient: Patients with acute peptic ulcer bleeding Intervention: Proton pump inhibitors (PPIs) Comparisons: H ₂ antagonists (H ₂ -A), endoscopic, placebo Outcomes: Bleeding (persistent or recurrent), blood transfusion, endoscopic intervention or surgery, length of stay, mortality. Inclusion/exclusion criteria: Randomised studies and pharmacoeconomic evaluations that used PPI therapy for acute peptic ulcer bleeding. Randomised controlled trials and meta-analyses involving other therapies for treating peptic ulcer bleeding were also reviewed. Studies involving fewer than 25 patients were excluded.
VALIDITY: Methodology, rigour, selection, analysis	Focussed question: Yes Search strategy: PubMed (up to January 2000). Search terms included bleeding, cimetidine, ranitidine, famotidine, omeprazole, lansoprazole, pantoprazole, PPI and peptic ulcer. References of reviews were examined. Assessed validity: Yes Consistent results: The homogeneity of effects throughout studies was appraised using a homogeneity test. Appropriate analysis of results: Yes, meta-analysis.	Focussed question: Yes Search strategy: Medline (1966-September 2000), textbooks, and the bibliographies of retrieved publications. Search terms were stated. Assessed validity: No Consistent results: No Appropriate analysis of results: No, did not combine results of the individual studies.
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	Eleven studies were identified (681 patients were treated with PPIs and 671 patients were treated with H ₂ -A). Persistent or recurrent bleeding: PPIs group 6.7% (95% CI 4.9-8.6%) and H ₂ -A group 13.4% (95% CI 10.8-16%) [OR 0.4, 95% CI 0.27-0.59, P=0.09]. Surgery needed: 5.2% (95% CI 3.4-6.9%) in PPIs group, and 6.9% (95% CI 4.9-8.9%) in H ₂ -A group (OR 0.7; 95% CI 0.43-1.13). Mortality: 1.6% (95% CI 0.9-2.9%) in PPIs group and 2.2% (95% CI 1.3-3.7%) in H ₂ -A group (OR 0.69; 95% CI: 0.31-1.57). -Five studies evaluated the effect of both therapies given in bolus injections on persistent or recurrent bleeding rate. Re-bleeding for PPIs was 6% (95% CI 3.6-8.3%) and 8.1% for	Data from double blind, placebo-controlled trials involving more than 1000 patients demonstrate that short-term, high-dose omeprazole therapy is effective for reducing bleeding and transfusion requirements in patients with acute peptic ulcer bleeding. The patients most likely to benefit from this therapy are hospitalised patients at high risk for rebleeding and patients in whom endoscopic evaluation must be delayed or is unavailable.

	<p>H2-A (95% CI 5.3–10.9%), [OR, 0.57; 95% CI 0.31–1.05]. Persistent or recurrent bleeding in high risk patients (Forrest Ia, Ib and IIa) occurred in 13.2% (95% CI 7.9–18%) of the patients treated with PPIs and in 34.5% (95%CI 27–42%) of those treated with H2-A (OR 0.28; 95% CI 0.16–0.48). In patients not having endoscopic therapy, persistent or recurrent bleeding was reported, respectively, in 4.3% (95% CI 2.7–6.7%) and in 12% (95% CI 8.7–15%) (OR 0.24; 95% CI 0.13–0.43). Less marked differences were observed in patients having adjunct endoscopic therapy: 10.3% (95% CI 6.7–13.8%) and 15.2% (95% CI 11.1–19.3%) (OR 0.59; 95% CI 0.36–0.97). Moreover, the significance disappeared in this group when a single outlier study was excluded.</p>	
<p>AUTHORS COMMENTS: Limitations, implications for practice and research</p>	<p>“PPIs are more effective than H2-A in preventing persistent or recurrent bleeding from peptic ulcer, although this advantage seems to be more evident in patients not having adjunct sclerosis therapy. This beneficial effect seems to be similar or even more marked in patients with Forrest Ia, Ib or IIa ulcers. However, PPIs are not more effective than H2-A for reducing surgery or mortality rates. Nevertheless, the data are too scarce and heterogeneous to draw definitive conclusions, and further comparative trials are clearly warranted.”</p>	<p>“Omeprazole (and likely other proton-pump inhibitors) is useful in reducing bleeding and transfusion requirements in patients with acute peptic ulcer bleeding, although better delineation of appropriate candidates is needed. ”</p>
<p>OUR COMMENTS: Opportunity for bias, weakness and strength</p>	<p>Potential for bias: Yes (search was confined to one database). Weakness:</p> <ul style="list-style-type: none"> • Search was limited to PubMed database and review of references in the articles selected for the study. <p>Strength:</p> <ul style="list-style-type: none"> • A meta-analysis • Reported search strategy and search terms • Two reviewers searched articles (independently) • Conducted sub-analysis • Clear inclusion/exclusion criteria • Assessed the qualities of the included studies • Reviewers contacted and obtained data from authors • No language restriction was applied 	<p>Potential for bias: Yes. Weakness:</p> <ul style="list-style-type: none"> • Not a systematic review (level I evidence). • Search was confined to Medline database & bibliography of retrieved publications. • Did not combine the results from individual studies (meta-analysis). • Did not perform appropriate analysis of results. • Not clear how the quality of the included studies was assessed. <p>Strength:</p> <ul style="list-style-type: none"> • Stated inclusion/exclusion criteria. • Stated search strategy

<p style="text-align: center;">Evidence Summary</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> Proton pump inhibitors versus H₂ antagonists or placebo in treating bleeding peptic ulcer </div>	<p style="text-align: center;">Study 3</p> <p style="text-align: center;">Javid, G., I. Masoodi, et al. (2001). "Omeprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer." American Journal of Medicine 111(4): 280-284.</p>
STUDY DESIGN & NHMRC LEVEL OF EVIDENCE	<p style="text-align: center;">Randomised double-blinded trial (level II)</p>
DESCRIPTION: Patient (subjects), Intervention, Comparisons, Outcomes, Inclusion & Exclusion Criteria	<p>Setting: Kashmir, India Patients: Patients (n=166) with gastrointestinal bleeding. Intervention: Omeprazole (40 mg orally) every 12 hours for 5 days (n=82). Comparisons: Identical looking placebo (n=84) for 5 days. Outcomes: recurrent bleeding, surgery, blood transfusion, hospital stay, and mortality. Inclusion/exclusion criteria: Those with duodenal, gastric or stomach ulcers and stigmata of recent hemorrhage. Patients were excluded if they had cancer, were moribund as a result of concomitant illnesses and could not provide a legal consent, or had perforce hemorrhage accompanied by persistent shock. Patients who continued to bleed within the first 4 hours of endoscopic treatment and needed emergency surgery to control bleeding were also excluded.</p>
VALIDITY: Methodology, rigour, selection, analysis	<p>Randomisation: Yes, using sealed opaque envelopes labelled with a code known to only the senior endoscopy technologist. All patients accounted for: Yes Patients treated equally: Yes. All received endoscopic injection sclerotherapy prior to randomisation. Similar groups: Yes</p>
RESULTS: Generally favourable or unfavourable, specific outcomes of interest, estimate of experimental effect and precision if appropriate	<p>Recurrent bleeding: 6 (7%) patients in the Omeprazole group, 18 (21%) in the placebo group (Risk ratio=3.5; 95%CI: 1.3 to 9.2; P=0.02). Surgery: 2 in Omeprazole group and 7 in the placebo group (RR=3.6; 95% CI: 0.7 – 18; p=0.17) needed surgery. Mortality: 1 patient in the omeprazole group and 2 in the placebo group died (risk ratio= 2.0; 95%CI: 0.2 to 22.3; p = 0.98). Blood transfusion: 29 (35%) patients in the omeprazole group and 61 (73%) in the placebo group received transfusion (RR= 4.8; 95%CI: 2.5 to 9.4; P <0.001). Average hospital stay: 4.6 +/- 1.1 days in the omeprazole group and 6.0 +/- 0.7 days in the placebo group (P <0.001).</p>
AUTHORS COMMENTS: Limitations, implications for practice and research	<p>"The addition of oral omeprazole to combination injection sclerotherapy decreases the rate of recurrent bleeding, reduces the need for surgery and transfusion, and shortens the hospital stay for patients with stigmata of recent hemorrhage"</p>
OUR COMMENTS: Opportunity for bias, weakness and strength	<p>Potential for bias: Low potential for bias. Baseline characteristic of the two groups were similar. Randomisation was properly done and most of the research staff and patients were blinded to study group. Weakness:</p> <ul style="list-style-type: none"> • Did not acknowledge the limitation associated with the study. <p>Strength:</p> <ul style="list-style-type: none"> • Clear study objective • Patients gave written informed consent • Study approved by Ethics committee • Double blinded study • Recurrent bleeding was defined clearly • Performed sample size calculation prior to the study

EXPLANATION OF TERMINOLOGY USED IN SPREADSHEET

Level of evidence: A hierarchy of study evidence that indicates the degree to which bias has been eliminated in the study design.

Focussed question: The review should address a clearly focused issue, in terms of the population studies, the intervention given and the outcomes considered.

Search strategy: A description of methods used to identify relevant studies from various computer databases and other sources.

Systematic review: The process of systematically locating, appraising and synthesising evidence from scientific studies in order to obtain a reliable overview.

Validity: The degree to which reviewers assessed the quality of the studies they included

Of measurement: an expression of the degree to which a measurement measures what it purports to measure; it includes construct and content validity.

Of study: the degree to which the inferences drawn from the study are warranted when account is taken of the study methods, the representativeness of the study sample, and the nature of the population from which it is drawn (internal and external validity, applicability, generalisability).

Consistent results: The similarity of results from the included studies. Often called heterogeneity which refers to the differences in treatment effect between studies contributing to a meta analysis (systematic review). If there is significant heterogeneity, this suggests that the trials are not estimating a single common treatment effect.

Appropriate analysis of results: When study results are pooled in a meta-analysis it is important that the results are combined in appropriate manner. The studies should be sufficiently similar in study design, the results of included studies should be clearly displayed and reasons for any variation in results should be discussed.

Potential for bias: Bias is a systematic deviation of a measurement from the 'true' value leading to either an over or underestimation of the treatment effect. Bias can originate from many different sources, such as allocation of patients, measurement, interpretation, publication and review of data.