Proton-pump inhibitors and outcome of endoscopic hemostasis in bleeding peptic ulcers: a series of meta-analyses

CRD summary
This review assessed the effects of proton-pump inhibitor (PPI) regimens on bleeding ulcers. The authors concluded that endotherapy plus either PPIs or H2-receptor antagonists are indicated for nonbleeding ulcers, but there are insufficient data to support this combination for Forrest 1A or 1B ulcers. This was generally a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors' objectives
To assess the effects of different proton-pump inhibitor (PPI) regimens on bleeding ulcers, and to determine the effects according to endoscopic stigmata and the use of endotherapy.

Searching
MedlinePlus was searched from January 1990 to August 2003; the search terms were reported. There were no language restrictions, and both abstracts and full publications were eligible. The reference lists of retrieved reports, reviews and meta-analyses were checked. Proceedings of the American Digestive Disease Week (published in Gastroenterology) and proceedings of the United European Gastroenterology Society (published in Gut) were also searched from 1998 to 2003.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. Studies using historical controls were excluded.

Specific interventions included in the review
Studies that compared a PPI with any H2 receptor agonist (H2RA) or placebo were eligible for inclusion. Studies using somatostatin as a control were excluded, as were studies comparing two different regimens of the same PPI. The included studies used various PPI regimens (oral, intravenous infusion or intravenous boluses of omeprazole, pantoprazole and lansoprazole) with and without endotherapy. The control regimens were placebo or an H2RA (cimetidine, ranitidine and famotidine) with and without endoscopy.

Participants included in the review
Studies of patients with bleeding ulcers were included, while those of patients with bleeding from either ulcers or oesophageal varices were excluded. The studies included patients with varying proportions of ulcers classified as Forrest 1A, 1B, 2A, 2B and 2C at baseline endoscopy.

Outcomes assessed in the review
Inclusion criteria were not specified in terms of the outcomes. The outcomes in the review were persistent or recurrent bleeding, the need for surgery, and mortality during the study period.

How were decisions on the relevance of primary studies made?
Three authors screened papers and any disagreements were resolved through discussion.

Assessment of study quality
Validity was assessed and scored using the Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals. The maximum possible score was 5 points. The authors did not state who performed the validity assessment.
Data extraction
Three reviewers reached consensus through discussion on the data extracted. For each study, the incidence of re-bleeding, surgery or death was extracted for each treatment group. Where data were reported for all bleeding ulcers combined, the authors were contacted for separate data for each endoscopic stigmata.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and comparator, and by whether or not endoscopic therapy was used, then combined in a meta-analysis.

Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random-effects model of DerSimonian and Laird. Pooled risk differences (RDs) and 95% CIs were also calculated. The number-needed-to-treat to either benefit (NNTB) or harm (NNTH) was calculated, along with 95% CIs, where a statistically significant difference between treatments was found. Publication bias was assessed using Klein's method, and the fail-safe N was estimated.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the Cochran Q chi-squared test (significance level of P<0.05). Heterogeneity was also examined using Galbraith plots. Where heterogeneity was detected, subgroup analyses were conducted to examine the influence of bleeding stigmata, mode of administration of PPI and study quality. Potential reasons for the heterogeneity were discussed.

Results of the review
Thirty-five RCTs (n=4,843) were included.

Monotherapy with PPIs versus monotherapy with placebo (3 RCTs, 1,045 patients, 29% with active bleeding): the studies were of a high quality (Jadad score 5). There was a reduced risk of re-bleeding with PPIs compared with placebo, but statistical heterogeneity was found; the RD was 13.7% (95% CI: 0.9, 27), the OR was 0.50 (95% CI: 0.26, 0.96), the NNTB was 7 (95% CI: 4, 114) and the fail-safe N was 8. One RCT was an outlier on the Galbraith plot. Only one RCT reported results by bleeding stigmata; it showed RDs varying from 20% in Forrest 1A to 48% in Forrest 2A. There was no statistically significant difference between treatments for surgery and mortality.

Monotherapy with PPIs versus monotherapy with H2RAs (8 RCTs, 816 patients, 23% with active bleeding): the studies were generally of a poor quality (4 scored 2 points on the Jadad scale). There was a reduced risk of re-bleeding with PPIs compared with H2RAs, but statistical heterogeneity was found; the RD was 20% (95% CI: 7, 33), the OR was 0.31 (95% CI: 0.15, 0.66), the NNTB was 5 (95% CI: 3, 15) and the fail-safe N was 20. Two RCTs were outliers on the Galbraith plot. There was a reduced risk of surgery with PPIs, (OR 0.53, 95% CI: 0.29, 0.98) but not mortality. No statistically significant heterogeneity was found.

Monotherapy with PPIs versus endotherapy plus H2RAs (4 RCTs, 357 patients, none had active bleeding): the studies were generally of a poor quality (mean Jadad score 2.75). There was no statistically significant difference between PPI and endotherapy plus H2RA in the risk of re-bleeding (OR 1.30, 95% CI: 0.7, 2.17). No statistically significant heterogeneity was found.

Monotherapy with PPIs versus endotherapy plus PPI (5 RCTs, 816 patients, 91% with nonbleeding): the studies were of a high quality (Jadad score 4 or 5). There was a reduced risk of re-bleeding with PPIs compared with H2RA, (OR 0.19, 95% CI: 0.09, 0.37; NNTB 6, 95% CI: 4, 10). No statistically significant heterogeneity was found. There was a reduced risk of surgery with PPIs compared with H2RAs (OR 0.17, 95% CI: 0.06, 0.45; NNTB 505, 95% CI: 38, -45). There was no significant difference between treatments for mortality.

PPIs plus endotherapy versus endoscopic monotherapy (5 RCTs, 986 patients, 46% with bleeding lesions): the studies were of a high quality (mean Jadad score 4.4). There was a reduced risk of re-bleeding with PPIs plus endotherapy compared with endotherapy alone (OR 0.51, 95% CI: 0.37, 0.71). No statistically significant heterogeneity was found. There was no significant difference between treatments for surgery or mortality.
PPIs plus endotherapy versus H2RAs plus endotherapy (8 RCTs, 947 patients, 42% with active bleeding): the studies were generally of a poor quality (mean Jadad score 2.7). There was no statistically significant difference between treatments for rebleeding, surgery or mortality. No statistically significant heterogeneity was found. The subgroup analysis showed a significantly reduced risk of re-bleeding with PPI plus endotherapy in nonbleeding patients; the OR (2 RCTs) was 0.24 (95% CI: 0.07, 0.76) and the NNTB was 5 (95% CI: 3, 24).

Infusion PPIs versus bolus PPIs used in addition to endotherapy (2 high-quality RCTs, 310 patients): there was no statistically significant difference between treatments for re-bleeding or mortality, and the data were homogeneous (OR 1.21, 95% CI: 0.59, 2.52).

Details of the subgroup analyses were also presented in the paper.

Authors' conclusions
Endotherapy plus either PPIs or H2RAs are indicated for nonbleeding ulcers at endoscopy, but there are insufficient data to support this combination for treating Forrest 1A or 1B ulcers. Oral, bolus and infusions of PPIs appear equally effective.

CRD commentary
The review addressed a clear question defined in terms of the participants, intervention and study design, and the primary review outcomes were clear. Limiting the search to only one database and conference proceedings published in two journals might have resulted in the omission of other relevant or unpublished studies; however, appropriate methods were used to assess the possibility of publication bias. No language restrictions were applied, thus minimising language bias. Methods were used to minimise bias in the study selection and data extraction processes. Only RCTs were included and validity was assessed using established criteria.

Adequate information on the included studies was presented. The studies were pooled, appropriately grouped by comparison. Meta-analyses were performed and meta-analysis graphs were presented, and statistical heterogeneity was assessed. In addition, subgroup analyses were used to explore the influence on the results of factors such as study quality. Significant heterogeneity was found in many of the meta-analyses, but the studies generally showed a similar direction in treatment effect. Overall, this was a well-conducted review and the authors' conclusions are likely to be reliable.

Implications of the review for practice and research
Practice: The authors stated that combining endoscopic treatment with either PPIs or H2RAs is indicated for Forrest 2A and 2B ulcers. There were insufficient data to support this combination for treating Forrest 1A or 1B ulcers.

Research: The authors stated that future studies are required on the pharmacological treatment of patients with a nonvariceal bleeding ulcer.

Bibliographic details

PubMedID
15654802

DOI
10.1111/j.1572-0241.2005.40636.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Anti-Ulcer Agents /therapeutic use; Combined Modality Therapy; Hemostasis, Endoscopic; Histamine H2 Antagonists /therapeutic use; Humans; Peptic Ulcer Hemorrhage /therapy; Proton Pump Inhibitors; Treatment Outcome

AccessionNumber
12005003231

Date bibliographic record published
31/03/2006

Date abstract record published
31/03/2006

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.