Proton pump inhibitors versus histamine-2-receptor antagonists for the management of iatrogenic gastric ulcer after endoscopic mucosal resection or endoscopic submucosal dissection: a meta-analysis of randomized trials

CRD summary
The review concluded that proton pump inhibitors were superior to histamine-2-receptor antagonists for the prevention of delayed bleeding with no evidence of differences in the reduction of epigastric pain or ulcer healing after endoscopic mucosal resection or submucosal dissection. The review was well conducted but, given the limitations in the evidence base, the conclusions should be considered tentative.

Authors' objectives
To compare the effects of proton pump inhibitors (PPIs) with histamine-2-receptor antagonists (H₂RAs) for the management of iatrogenic gastric ulcers after endoscopic mucosal resection or endoscopic submucosal dissection.

Searching
PubMed, The Cochrane Library and Google Scholar were searched from 1950 to October 2010 for relevant studies without language restriction; limited search terms were reported. The reference lists of retrieved articles and abstracts from relevant meetings from 2002 to 2009 were also searched.

Study selection
Eligible randomised controlled trials (RCTs) included more than 10 patients who underwent endoscopic mucosal resection or endoscopic submucosal dissection where PPIs were compared with H₂RAs. Studies were required to measure at least one of the following outcomes: bleeding, epigastric pain or healing rate.

In the included studies, mean age of participants ranged from 61 to 73 years and the proportion of male participants ranged from 59% to 88%. One study had solely endoscopic mucosal resection, two studies had both endoscopic mucosal resection and endoscopic submucosal dissection and three studies had only endoscopic submucosal dissection. The dosage duration of medications ranged from 28 to 56 days. PPIs included omeprazole 20mg/day, rabeprazole 10mg or 20mg/day and pantoprazole 40mg/day. H₂RAs included famotidine 40mg/day, cimetidine 800mg/day or lafutidine 20mg/day. The size of lesions varied from 11mm to 41mm. Studies were undertaken in Japan or Korea.

Two reviewers independently selected studies for the review.

Assessment of study quality
Studies were assessed for quality using the Cochrane risk of bias tool; criteria included sequence generation, allocation concealment, blinding, dealing with incomplete data, absence of selective reporting, absence of baseline imbalance, sample size calculation and absence of funding bias. Each component was rated as yes, no or unclear.

Two reviewers assessed studies for quality, with disagreements resolved by discussion with a third reviewer.

Data extraction
Data were extracted on the outcomes and odds ratios (ORs), with 95% confidence intervals (CIs), were calculated.

Two reviewers extracted data, with disparities reconciled by discussion with a third reviewer.

Methods of synthesis
Where possible, studies were combined in meta-analyses, using a Mantel-Haenszel fixed-effect model if no heterogeneity was identified; otherwise a derSimonian and Laird random-effects model was used. Heterogeneity was assessed by $X^2$ and quantified by $I^2$ (with $I^2$ above 50% being considered substantial heterogeneity). Subgroup analyses were undertaken according to the two different endoscopic treatments or according to duration of medication (four or eight weeks). Sensitivity analysis was also undertaken by excluding the trial which used a new generation H₂RA. A
funnel plot was used to assess publication bias.

The results of one outcome were presented in narrative format.

**Results of the review**

Six studies (522 patients) were included in the review. No studies met all the quality criteria; the number of criteria met ranged from three to seven (out of eight). Two studies had adequate sequence generation or adequate allocation concealment, three had adequate blinding or adequate addressing of incomplete data, four had sample size calculations, five were free from baseline imbalances and all six were free from selective reporting. Follow up ranged from 28 to 90 days.

Compared to the H₂RA group, the PPI group had a significantly lower bleeding rate (OR 0.5, 95% CI 0.3 to 1.0; $I^2=39\%$; five studies). Subgroup analysis according to type of endoscopic treatment indicated that PPI was significantly more effective than H₂RA in preventing bleeding for endoscopic submucosal dissection induced ulcer (OR 0.4, 95% CI 0.2 to 0.9; $I^2=31\%$; five trials) but there was no evidence of a difference between groups with endoscopic mucosal resection induced ulcer. Subgroup analysis according to duration of medication indicated that PPI was significantly more effective than H₂RA in preventing bleeding with eight weeks of medication (OR 0.4, 95% CI 0.2 to 0.8; $I^2=0\%$; three trials), but not with four weeks of medication. Sensitivity analysis did not change the results markedly.

There was no evidence of significant differences in epigastric pain between comparison groups. No studies found evidence of a difference in healing rates between comparison groups (data not reported).

There was no evidence of publication bias.

**Authors' conclusions**

Proton pump inhibitors (PPIs) were superior to H₂RA for the prevention of delayed bleeding with no evidence of differences in the reduction of epigastric pain or ulcer healing after endoscopic mucosal resection or endoscopic submucosal dissection.

**CRD commentary**

The review addressed a clear research question, supported by appropriate inclusion criteria. A range of relevant sources was searched for studies without language or publication restriction, which minimised the chance of publication or language bias. Adequate methods were used to select studies, extract data and assess studies for quality, which minimised the chance of reviewer error or bias.

A valid tool was used for quality assessment of the studies. Not all studies met all criteria; the proportion of criteria met ranged from three to seven out of eight components. Sample sizes were generally small ranging from 16 to 164 participants. Synthesis of studies and assessment of heterogeneity were appropriate. Formal assessment of publication bias by inspection of funnel plots may not have been appropriate given the small number of trials. The authors acknowledged that there was variation in the kinds of PPIs and regimens of PPI administration which may have caused bias and were not investigated in the review. The included studies were undertaken in Asian countries which may have limited generalisability. The review was generally well conducted but, given the limitations in the evidence base, the authors' conclusions should be considered tentative.

**Implications of the review for practice and research**

**Practice:** The authors stated that they recommended using PPIs for artificial ulcer induced by endoscopic submucosal dissection with an eight week duration of treatment.

**Research:** The authors stated that further high quality randomised controlled trials were needed, particularly in Western countries, to confirm the findings.

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