Endoscopic hemostasis in peptic ulcer bleeding for patients with high-risk lesions: a series of meta-analyses

Barkun AN, Martel M, Toubouti Y, Rahme E, Bardou M

CRD summary
The authors concluded that all endoscopic treatments were superior to pharmacotherapy alone with optimal therapies including thermal therapy or clips either alone or in combination with other methods. This was a well-conducted review. The authors acknowledged shortcomings in the analysis, which involved small sample sizes. The limitations highlighted by the authors should be borne in mind.

Authors’ objectives
To assess contemporary methods of endoscopic haemostasis for patients with bleeding ulcers that exhibited high-risk stigmata.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for published studies in from 1990 to 2006. Search terms were not reported.

Study selection
Randomised controlled trials (RCTs) that assessed contemporary haemostatic techniques in patients with peptic ulcer bleeding who exhibited high-risk stigmata/lesions were eligible for inclusion. Sole placebo-controlled studies were excluded as were those that compared different accessories of the same haemostatic method and those that varied the volumes of similar injectates. Studies that assessed postoperative or stress ulcer bleeding prophylaxis or lesions other than ulcers were excluded. Studies had to report sufficient levels of information on the number of patients randomised to each group, treatment procedures and rates of re-bleeding, surgery and mortality. Eligible techniques comprised endoscopic injection, thermal treatment (heat probe, monopolar and bipolar electrocoagulation, microwave and argon plasma coagulation), clips (alone or in combination) and combination treatment (injection followed by thermal therapy). The primary outcome was peptic ulcer re-bleeding; secondary outcomes included the proportion of patients who underwent surgery for ulcer re-bleeding and overall mortality.

In the included studies endoscopic therapy was compared with pharmacotherapy (either proton pump inhibition therapy or H2 receptor antagonists). Injection therapy was compared with pharmacotherapy, thermal therapy, combination therapy and endoscopic clips. Thermal therapy was compared with pharmacotherapy, injection therapy, combinations and endoscopic clips. Combinations of some form of injection with some method of thermal therapy were compared with pharmacotherapy, injection therapy and thermal therapy. The role of endoscopic clips was assessed through comparing them with injection therapy, thermal therapy, combination therapy, endoscopic clips plus injection versus injection alone and endoscopic clips plus injection versus clips alone. Specific details of the comparisons were presented in the paper.

Two reviewers independently assessed studies for inclusion; disagreements were resolved through consultation with a third reviewer.

Assessment of study quality
Studies were graded using a previously published 10-quality criteria scoring system modified from Cook et al (1992) and Bardou et al (2005) that assessed criteria of study population, intervention (including randomisation and blinding), endoscopic treatment, pharmacologic treatment and outcomes. The maximum score was 10.

Study quality was independently assessed by two reviewers; disagreements were resolved through discussion with a third reviewer.
Data extraction
Odds ratios (OR), risk ratios (RR) or absolute risk differences (ARD), together with 95% confidence intervals (CI), were calculated for each outcome; odds ratios and risk ratios were analysed on a logarithmic scale. Where cells contained zero, 0.5 was added to all cells. Authors of included trials were contacted for missing information.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Odds ratios, risk ratios and absolute risk differences, and 95% CI, were pooled using a fixed-effect model for all endoscopic techniques and by type of technique and control group; where statistical heterogeneity was present a random-effects model was used. Statistical heterogeneity was assessed using $I^2$ and $X^2$. Numbers needed to treat (NNT) were calculated. Sensitivity analyses was undertaken by excluding studies one by one; where a comparison comprised more than 10 studies meta-regression was performed using a mixed-effects model including quality scores, year of publication, severity of bleeding and mean age. Publication bias was assessed with funnel plots.

Results of the review
Forty-one RCTs (n=4,261 participants) were included in the review. The mean quality score was 7 (range 3 to 10).

Overall results showed that endoscopic techniques were significantly superior to pharmacotherapy for reducing bleeding (OR 0.35, 95% CI 0.27 to 0.46; 18 studies), surgery (OR 0.57, 95% CI 0.41 to 0.81) and mortality (OR 0.57, 95% CI 0.37 to 0.89).

Compared with sole pharmacotherapy (principally non-high-dose proton pump inhibition), injection therapy (OR 0.43, 95% CI 0.24 to 0.78; n=614, NNT=6), thermal therapy (OR 0.41, 95% CI 0.26 to 0.65; n=493, NNT=6) and combination (injection followed by thermal therapy) (OR 0.18, 95% CI 0.08 to 0.41; n=399, NNT=7) all significantly decreased re-bleeding.

Compared with injection therapy, combination therapy significantly decreased re-bleeding (OR 0.27, 95% CI 0.11 to 0.66; n=340, NNT=14). Endoscopic clips were superior to both thermal (OR 0.24, 95% CI 0.06 to 0.95; n=193, NNT=10) and injection therapy (OR 0.36, 95% CI 0.17 to 0.76; n=306, NNT=10) for reducing re-bleeding. Re-bleeding was significantly reduced by clips and injection compared with injection alone (OR 0.38, 95% CI 0.16 to 0.86; n=272, NNT=10).

There were no statistically significant differences between any treatments for mortality and only significant differences between thermal versus pharmacotherapy and between clips plus injection versus injection for the proportion of patients who underwent surgery. There were no significant differences for any outcomes between thermal versus injection therapy, combination versus thermal therapy, clips versus combination and clips plus injections versus clips alone.

Low heterogeneity was observed for endoscopy versus proton pump inhibitors for re-bleeding ($I^2=49\%$). High heterogeneity was observed for two comparisons assessing re-bleeding: injection versus pharmacotherapy ($I^2=51\%$) and injection followed by thermal therapy versus thermal therapy alone ($I^2=63\%$).

Results for subgroups were reported.

There was some evidence of publication bias for re-bleeding and mortality using injection versus injection and clips as well as for mortality using injection followed by thermal endotherapy versus pharmacotherapy.

Authors’ conclusions
All endoscopic treatments were superior to pharmacotherapy alone; only one study assessed high dose IV proton pump inhibition. Optimal endoscopic therapies include thermal therapy or clips, either alone or in combination with other methods.
The review question and supporting inclusion criteria were clear. Three databases were searched. Language restrictions were applied, so language bias may have been introduced. Unpublished studies were excluded from the review, which raised the possibility of publication bias. Publication bias was assessed and was considered likely to be present for some comparisons. Study selection and quality assessment were conducted in duplicate, which reduced the potential for reviewer error and bias; it was unclear whether this extended to data extraction. Study quality was assessed using a modified version of previously published criteria, but only composite scores were reported. There was a lack of reporting of patient and study characteristics, which made it difficult to assess whether pooling of the results was appropriate. The chosen method of synthesis appeared to be suitable and explorations of statistical heterogeneity and potential influences on results were carried out. There was some potential for bias in the review process and shortcomings in the analysis involving small sample sizes were acknowledged by the authors.

The authors’ conclusions reflect the data presented and are likely to be reliable, but the limitations highlighted by the authors should be borne in mind.

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

**Practice:** The authors stated that endoscopic therapy in non-bleeding lesions appeared to be more effective than sole pharmacotherapy; injection should not be practiced alone and endoscopists should familiarise themselves with other methods of haemostasis.

**Research:** The authors stated that further studies were required to assess the comparative efficacy of sole thermal therapy versus combination therapy and dual modality approaches that used clips compared with clips alone or other dual-modality therapies. Further research should assess the possible tailored choice of haemostatic method based on lesion appearance and location, comparative efficacies of different injectates, of their varying volumes, different thermal probes, different clip technologies and the safety of endoscopic methods and the efficacy of a second-look strategy in the era of profound acid suppression.

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