Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials

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CRD summary
This review concluded that epinephrine injections alone should not be used for the treatment of bleeding ulcers, but other endoscopic treatments were effective. It also concluded that proton pump inhibitors should be given following endoscopic therapy. The conclusions reflected the results of the review and, despite a limited search and some concerns about the synthesis, are probably reliable.

Authors' objectives
To determine appropriate endoscopic treatment of patients with bleeding ulcers.

Searching
MEDLINE (1950 to March 2008) and Cochrane Central Register of Controlled Trials were searched without language restriction. Search terms were reported. References of identified systematic reviews and meta-analyses were checked.

Study selection
Randomised controlled trials (RCTs) that compared any endoscopic treatment with either no treatment or another endoscopic therapy for the treatment of bleeding ulcers were eligible for inclusion. Eligible interventions were: thermal contact devices including heater probe and bipolar electrocoagulation; argon plasma coagulation; injection of epinephrine or sclerosants including alcohol, thrombin and fibrin glue; and clips. Studies of laser therapy, monopolar electrocoagulation and microwave, and injection of water, saline or tissue adhesives were excluded. Bleeding ulcers were defined as those where active bleeding, a non-bleeding visible vessel or a clot was found on endoscopy. Studies that included only patients from a selected population were excluded, as were those that included patients with bleeding lesions other than gastric or duodenal ulcers (unless such data was reported separately). Studies that included patients with flat spots and clean-based ulcers were also excluded unless this data was reported separately. The primary outcome was further bleeding, including persistent bleeding and recurrent bleeding. Also assessed were initial haemostasis in active bleeding, need for surgery, need for urgent intervention, mortality and complications that could not be controlled with the therapy being assessed.

Included studies assessed a wide range of comparisons. Some included studies employed second-look endoscopy with re-treatment.

Two reviewers independently assessed the studies for inclusion in the review.

Assessment of study quality
The studies were assessed for validity using a seven-point scale that incorporated the criteria of the Jadad scale (randomisation, blinding of observer and treatment of withdrawals and dropouts) as well as allocation concealment, objective definitions of initial haemostasis or rebleeding and power calculations. An additional blinding criterion was added for studies that compared proton pump inhibitor with no proton pump inhibitor therapy after endoscopic treatment. The authors noted that this assessment scale had not been validated. The authors did not state how many reviewers carried out the validity assessment.

Data extraction
Two reviewers independently abstracted data for the calculation of relative risks with 95% confidence intervals (CI) using a standardised form; disagreements were resolved through consensus.

Methods of synthesis
Studies were combined using a fixed effect model to calculate a pooled relative risk with 95% CI unless significant statistical heterogeneity was detected, in which case a random effects model was employed. Statistical heterogeneity
was assessed using the $\chi^2$ test. Where significant between-group differences were found the number needed to treat was calculated. Sensitivity analyses of studies without second-look endoscopy with re-treatment were conducted. Subgroup analyses were employed to explore individual comparisons.

**Results of the review**

Seventy-eight RCTs were included in the review ($n=7,562$). Sixty-five studies assessed endoscopic therapies ($n=3,954$). Thirteen studies assessed proton pump inhibitor treatment as an adjunct to endoscopic therapy ($n=3,608$). All results reported were for studies without second-look endoscopy, as these were the basis of the conclusions.

**Epinephrine versus no therapy:** One study showed a benefit in patients with active bleeding. A significant number of patients had re-treatment at second-look endoscopy. A second study showed no benefit of epinephrine.

**Epinephrine versus other monotherapy:** Other therapies reduced further bleeding significantly more than epinephrine (relative risk was 0.58, 95% CI: 0.36 to 0.93 and number needed to treat was 9, 95% CI: 5 to 53; three RCTs).

**Epinephrine versus epinephrine plus second modality:** There was a significant benefit of dual therapy for further bleeding (relative risk was 0.34, 95% CI: 0.23 to 0.50 and number needed to treat was 5, 95% CI: 5 to 7; seven RCTs).

**Thermal contact therapy versus no therapy:** Thermal contact significantly reduced further bleeding compared with no treatment (relative risk was 0.44, 95% CI: 0.36 to 0.54 and number needed to treat was 4, 95% CI: 3 to 5; 14 RCTs).

**Injection of sclerosants versus no therapy:** Sclerosant therapy significantly reduced further bleeding compared with no treatment (relative risk was 0.56, 95% CI: 0.38 to 0.83 and number needed to treat was 5, 95% CI: 4 to 13; three RCTs). Results of epinephrine plus sclerosant compared to no therapy showed a trend towards significance (relative risk was 0.60, 95% CI: 0.36 to 1.00; six RCTs).

**Thermal contact versus sclerosant injection:** There were no statistically significant differences between thermal contact and sclerosant alone or sclerosant plus epinephrine.

**Injection plus thermal contact versus thermal contact:** Injection plus thermal contact significantly reduced further bleeding compared with thermal contact alone (relative risk was 0.35, 95% CI: 0.18 to 0.71; two RCTs).

**Clips:** Clips were more effective in reducing further bleeding than epinephrine (relative risk was 0.22, 95% CI: 0.09 to 0.55 and number needed to treat was 5, 95% CI: 4 to 9; two RCTs), but did not significantly differ from other therapies.

**Thrombin/fibrin glue:** Thrombin was significantly better in reducing further bleeding than no treatment in one RCT (relative risk not reported), but fibrin glue did not differ from epinephrine treatment in one evaluable study. Epinephrine plus thrombin was significantly better in reducing further bleeding than epinephrine alone (relative risk was 0.21, 95% CI: 0.06 to 0.71; one RCT). No other comparisons were statistically significant.

**Argon plasma coagulation:** There were no significant differences between argon plasma coagulation and other treatments.

**Proton pump inhibitor as adjunctive therapy:** A bolus followed by continuous intravenous infusion of proton pump inhibitor significantly improved outcome compared with placebo or no therapy (relative risk was 0.40, 95% CI: 0.28 to 0.59 and number needed to treat was 12, 95% CI: 10 to 18), but not compared with histamine receptor antagonists.

Results for other outcomes, including haemostasis, urgent intervention and mortality were reported.

**Authors' conclusions**

Epinephrine injection alone should not be used. Thermal therapy, sclerosant therapy, clips and thrombin/fibrin glue all appeared to be effective haemostatic therapies. Endoscopic therapy should be used for ulcers with active bleeding and non-bleeding visible vessels, but its role for ulcers with adherent clots was unclear. Bolus followed by continuous intravenous infusion of proton pump inhibitors should be given following endoscopic therapy.
CRD commentary
The review question and inclusion criteria were clear. A limited literature search was undertaken without language restrictions, which reduced the likelihood of language bias. The lack of a systematic search for unpublished studies may have increased the risk of publication bias and exclusion of relevant studies. The authors reported using methods designed to reduce reviewer bias and error in the selection of studies and the extraction of data, but not in the assessment of validity. The validity assessment appeared to use appropriate criteria, but the results of the assessment were not reported and were not used to inform the synthesis. Limited details of the included studies were reported. The decision to use meta-analysis appeared reasonable, although the conclusions were based on sensitivity analyses in which studies with second-look endoscopy were excluded. This was clinically reasonable, but it suggested that the main analyses may not have been appropriate. Statistical heterogeneity was not systematically reported, although clinical heterogeneity was present in many of the analyses. The authors’ conclusions appear to be in line with the results of the review and are probably reliable despite the relatively limited search and some concerns about the synthesis.

Implications of the review for practice and research
Practice: The authors made the following recommendations for practice: epinephrine injection alone should not be used; thermal therapy, sclerosant therapy, clips, and thrombin/fibrin glue all appeared to be effective haemostatic therapies; epinephrine injection before these therapies may be beneficial, particularly for an actively spurting ulcer but data were limited; endoscopic therapy should be used for ulcers with active bleeding and non-bleeding visible vessels; the role of endoscopic therapy for ulcers with adherent clots was unclear and intensive proton pump inhibitor therapy may be sufficient; proton pump inhibitors should be given following endoscopic therapy for ulcers, with most consistent evidence for a bolus followed by continuous intravenous infusion for 72 hours.

Research: The authors did not state any recommendations for further research.

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