Dual therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers: a meta-analysis of controlled trials


CRD summary
This review concluded that dual endoscopic therapy was superior to epinephrine injection alone in improving the outcomes of patients with high-risk peptic ulcer bleeding, but not to either thermal monotherapy or haemoclipping alone. The conclusions of this generally well-conducted review were supported by the evidence, but there may be limitations of the review that must be kept in mind when considering these conclusions.

Authors' objectives
To compare the efficacy of dual endoscopic therapy to endoscopic monotherapy in the treatment of patients with peptic ulcer bleeding or high-risk stigmata.

Searching
MEDLINE, EMBASE Excerpta Medica, Current Contents, and the Cochrane CENTRAL Register were searched to July 2006; the search terms were reported. Abstracts submitted to Digestive Disease Week and United European Gastroenterology Week (to July 2006), bibliographies of retrieved studies, the authors' databases and relevant journal articles were also searched, and companies and researchers in the field were contacted.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Studies comparing dual endoscopic therapy (epinephrine plus another haemostatic method) versus monotherapy (epinephrine or thermal coagulation or mechanical haemostasis) for endoscopic haemostasis were eligible for inclusion. Dual therapies evaluated in the included studies involved at least two of the following: hypertonic saline epinephrine, epinephrine, polidochonol, ethanol, thrombin, haemoclips, bipolar gold probe, heater probe, ethanolamine, tetradecyl sulphate and fibrin glue. Monotherapies included hypertonic saline epinephrine, epinephrine, ethanol, haemoclips, gold probe or heater probe. Several studies reported the use of concomitant therapies.

Participants included in the review
Studies published in any language that included patients with bleeding from peptic ulcer disease (gastric or duodenal), with major stigmata of bleeding at the base of the ulcer (active bleeding, non-bleeding visible vessel, adherent clot), were eligible for inclusion. The studies had to provide data on baseline characteristics and inclusion and exclusion criteria to be included. Few participant details were reported; the included studies recruited patients with stigmata of recent haemorrhage, bleeding stigmata and non-bleeding stigmata.

Outcomes assessed in the review
The studies had to provide information on the safety of the tested procedures and sufficient data to allow evaluation. The outcomes reported in the review were recurrent bleeding, need for surgery, death and safety; the definitions most commonly used in the included studies were reported.

How were decisions on the relevance of primary studies made?
Two authors independently reviewed the articles selected in the search; the authors did not state how any disagreements were resolved.
Assessment of study quality
Study quality was evaluated using the Consolidated Standards of Reporting Trials (CONSORT) statement; the maximum quality score was 21 and the results were presented as a percentage of the criteria met. Attempts were made to reproduce the results from trials. The authors did not state how many investigators evaluated study quality, or how many trials had reproducible results.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The number of patients experiencing each outcome were extracted for each study, and the odds ratio (OR) and 95% confidence intervals (CIs) were calculated.

Methods of synthesis
How were the studies combined?
The pooled OR and 95% CI were calculated using a Peto fixed-effect model in the absence of heterogeneity, and a random-effects model in the presence of heterogeneity; an intention-to-treat analysis was used. The absolute risk difference was calculated by pooling the individual risk difference after weighting individual values by sample size, with the number-needed-to-treat (NNT) as the reciprocal. The NNT was calculated from the pooled results. The studies were divided into five subgroups: injection plus a mechanical therapy compared with injection alone; injection plus thermal therapy compared with injection alone; injection of two agents compared with injection of a single agent; injection plus mechanical therapy compared with mechanical therapy alone; injection plus thermal therapy compared with thermal therapy alone.

Egger’s regression asymmetry test was used to test for publication bias and a funnel plot was presented.

How were differences between studies investigated?
The Cochran Q test was used to test for heterogeneity. Analyses were conducted on each of the subgroups separately. Meta-regression was used to evaluate the effect on the type of dual endoscopic therapy used, publication year, quality score, frequency of active bleeding at endoscopy and concomitant therapies.

Results of the review
Twenty RCTs were included in the review (n=2,472).

The proportion of the 21 quality scores met ranged from 27 to 90%.

There was no evidence of publication bias in relation to recurrent bleeding (p=0.108).

Recurrent bleeding (20 RCTs).
Overall, the risk of recurrent bleeding was significantly lower with dual endoscopic therapy compared with monotherapy (OR 0.59, 95% CI: 0.44, 0.80, p<0.0001); there was significant heterogeneity between studies (p=0.07, I-squared 31.6%). The risk of recurrent bleeding was significantly lower for injection plus mechanical therapy compared with injection alone (OR 0.33, 95% CI: 0.17, 0.63, p=0.006; NNT 9; 4 RCTs), injection plus thermal therapy compared with injection alone (OR 0.36, 95% CI: 0.18, 0.73, p=0.001; NNT 15; 3 RCTs), and injection of two agents versus injection of a single agent (OR 0.65, 95% CI: 0.46, 0.93, p=0.02; NNT 23; 10 RCTs), but not when injection plus mechanical therapy was compared with mechanical therapy alone (3 RCTs) or injection plus thermal therapy was compared with thermal therapy alone (3 RCTs).

Need for surgery (18 RCTs).
Overall, dual endoscopic therapy significantly reduced the risk of emergency surgery compared with monotherapy (OR 0.66, 95% CI: 0.49, 0.89, p=0.03); there was no statistically significant heterogeneity between studies. Only two subgroups showed a reduction in the need for surgery with dual therapy: injection plus mechanical therapy compared with injection alone (OR 0.21, 95% CI: 0.07, 0.60, p=0.003; NNT 15; 4 RCTs), and injection plus thermal therapy...
compared with injection alone (OR 0.40, 95% CI: 0.19, 0.83, p=0.001; NNT 14; 3 RCTs).

Death (19 RCTs).

Overall, there was no statistically significant difference in immortality between dual therapy and monotherapy (OR 0.68, 95% CI: 0.46, 1.02, p=0.06, NNT 93). There was also no significant difference between dual therapy and monotherapy for any of the subgroups.

Safety.

The overall event rate was 3.5% (38 complications; 1,069 patients) with dual endoscopic therapy and 3.3% (35 negative outcomes; 1,098 patients) with monotherapy. The incidences of induced bleeding, perforation gastric wall necrosis and gastric artery thrombosis were reported.

Authors' conclusions
Dual endoscopic therapy was superior to epinephrine injection alone in improving the outcomes of patients with high-risk peptic ulcer bleeding, but was not superior to either thermal monotherapy or haemoclipping alone.

CRD commentary
The review question was clear in terms of the study design, participants, interventions and outcomes of interest. The authors conducted a thorough search for published and unpublished studies, without language restrictions. This would have reduced the potential for publication and language bias. Two authors reviewed publications independently, thereby reducing the risk of selection bias. However, the authors did not provide information about the data extraction or quality assessment processes, therefore reviewer error and bias cannot be ruled out. The quality of the included studies was assessed using appropriate criteria; no cut-offs of the composite score for poor or high quality were defined. The authors stated that they assessed the impact of study quality on the results, but the results were not presented and the quality of the included studies varied considerably. This may affect the reliability of the results of the review.

The authors investigated publication bias and conducted appropriate subgroup analyses. Details of the included studies and results of the meta-analysis were adequately reported. While the authors assessed statistical heterogeneity, the pooling of heterogeneous studies for some outcomes might not have been appropriate. The authors acknowledged that sample sizes were small for some subgroups.

This was generally a well-conducted review, and the authors' conclusions appear to be supported by the evidence (although not necessarily generalisable beyond patients of high risk). However, the small sample sizes, potential impact of poorer quality studies, and the lack of reporting of some review methodology should be kept in mind when considering these conclusions.

Implications of the review for practice and research
Practice: The authors did not recommend the routine use of dual therapy. Research: The authors recommended further research into the efficacy of dual therapy.

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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.