Endoscopic Therapy Versus Medical Therapy for Bleeding Peptic Ulcer With Adherent Clot: A Meta-analysis

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Background & Aims: The optimal management of bleeding peptic ulcer with adherent clot is controversial and may include endoscopic therapy or medical therapy. Methods: We searched MEDLINE, BIOSIS, EMBASE, and the Cochrane Library to identify all randomized controlled trials comparing the 2 interventions. Outcomes evaluated in the meta-analysis were recurrent bleeding, need for surgical intervention, length of hospitalization, transfusion requirement, and mortality. Results: Six studies were identified that included 240 patients from the United States, Hong Kong, South Korea, and Spain. Patients in the endoscopic therapy group underwent endoscopic clot removal and treatment of the underlying lesion with thermal energy, electrocoagulation, and/or injection of sclerosants. Rebleeding occurred in 5 of 61 (8.2%) patients in the endoscopic therapy group, compared with 21 of 85 (24.7%) in the medical therapy group ($P = .01$), for a pooled relative risk of 0.35 (95% confidence interval, 0.14–0.83; number needed to treat, 6.3). There was no difference between endoscopic therapy and medical therapy in length of hospital stay (mean, 6.8 vs 5.6 days; $P = .27$), transfusion requirement (mean, 3.0 vs 2.8 units of packed red blood cells; $P = .75$), or mortality (9.8% vs 7%; $P = .54$). Patients in the endoscopic therapy group were less likely to undergo surgery (pooled relative risk, 0.43; 95% confidence interval, 0.19–0.98; number needed to treat, 13.3); however, this outcome became nonsignificant when only peer-reviewed studies were considered. Conclusions: Endoscopic therapy is superior to medical therapy for preventing recurrent hemorrhage in patients with bleeding peptic ulcers and adherent clots. The interventions are comparable with respect to the need for surgical intervention, length of hospital stay, transfusion requirement, and mortality.

Peptic ulcer hemorrhage is a common cause of morbidity and mortality, accounting for approximately 150,000 annual hospitalizations in the United States and an estimated cost of $750 million. Independent baseline predictors of recurrent bleeding include advanced age, hemodynamic instability, hematemesis or hematochezia, severe comorbidities, and coagulopathy. The endoscopic appearance of gastric and duodenal ulcers also provides important prognostic information and is used to stratify patients according to the risk of rebleeding and the need for endoscopic therapy. Active hemorrhage and nonbleeding visible vessels within an ulcer constitute major stigmata because they portend a high risk of recurrent bleeding and warrant endoscopic therapy and close observation in the hospital. Conversely, ulcers with a clean base or a flat spot rarely rebleed and, thus, define a group of patients who can be treated medically and discharged from the hospital early.

Ulcers with adherent clots have an intermediate risk of recurrent hemorrhage that depends on the underlying lesion. The reported risk of rebleeding has varied widely from 8% to 36%; this underscores the variability among studies of ulcers with clots. Some of the inter-study variability is explained by poor interobserver agreement on what constitutes an adherent clot, the variable intensity of attempts to dislodge clots, and the level of comfort of individual endoscopists in managing such lesions. Older studies have suggested that endoscopic therapy does not reduce the risk of rebleeding for ulcers with clots, and the consensus has been that endoscopic therapy was not indicated in patients with such lesions. However, the data supporting these conclusions came largely from studies conducted in the 1980s in which patients with adherent clots constituted small subgroups combined with patients who had other stigmata and in which the predominant endoscopic treatment modality was laser photoablation.

Abbreviations used in this paper: CI, confidence interval; H2, histamine 2; NNT, number needed to treat; PRBCs, packed red blood cells; RR, relative risk.

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0016-5085/05/$30.00
doi:10.1053/j.gastro.2005.06.070
Until the mid 1990s, no randomized trials specifically addressed the optimal management of peptic ulcers with adherent clots. A randomized trial of heater probe therapy vs epinephrine injection vs medical therapy published in abstract form in 1995 found comparable rebleeding rates between endoscopic and medical modalities (35% vs 30%, respectively). More recently, 2 randomized trials have suggested that combined endoscopic and medical therapy for ulcers with adherent clots significantly decreased the rate of recurrent hemorrhage compared with medical therapy alone. Both have been criticized for not enrolling the prespecified number of patients, because they were stopped early after an interim analysis showed a higher risk of rebleeding in patients who did not undergo endoscopic therapy. Furthermore, in one of the studies, there was an unequal distribution of confounders that favored patients in the endoscopic therapy group. Thus, the optimal management of patients with peptic ulcers with adherent clots remains controversial.

The purpose of this study was to compare, by using meta-analysis, the effectiveness of endoscopic vs medical therapy for patients with bleeding peptic ulcers that contain an adherent clot. The outcomes of interest were the rate of rebleeding, need for surgical intervention, length of hospital stay, transfusion requirement, and mortality.

Patients and Methods

Study Identification and Selection

We searched the medical literature by using MEDLINE (1966 to March week 4, 2005), EMBASE (1974 to week 13 2005), BIOSIS Previews (1969 to week 15 2005), and the Cochrane Central Register of Controlled Trials (first quarter 2005 update). Subject headings and keywords for peptic, gastric, and duodenal ulcers or gastrointestinal endoscopy were combined with textword variants for “clot” or “stigmata of bleeding or recent hemorrhage.” We included human studies published in any language. In addition, a manual search was performed with references from retrieved reports, review articles, editorials, and textbooks of gastroenterology. Studies were selected if they met the following inclusion criteria: (1) study design was a randomized controlled trial; (2) patient population was patients with upper gastrointestinal hemorrhage and endoscopic findings of an ulcer with adherent clot; (3) interventions were endoscopic with medical therapy compared with medical therapy alone; and (4) 1 or more of the following outcomes were present: rate of rebleeding, need for surgical intervention, length of hospital stay, transfusion requirement, and mortality. Studies published in abstract form and studies reporting on adherent clots as a subgroup among patients with other stigmata were included if they satisfied these criteria. We excluded studies in which the endoscopic therapy used was laser photoablation and in which patients with ulcers with clots or flat spots were considered as 1 group and could not be separated for the analysis of outcome. Studies pertaining to a different research question, reviews, editorials, and letters to the editor were also excluded.

Qualitative Analysis

We independently evaluated the quality of each trial with attention to certain methodological standards for measuring study quality: (1) a well-defined study population with clear inclusion and exclusion criteria, (2) concealed allocation to treatment groups at the time of randomization, (3) baseline equivalence of treatment groups, (4) adequate and comparable potency of the interventions, (5) clearly defined outcome variables, and (6) a clinician evaluating the outcome who was blinded to treatment group. A quality score was generated by summing the standards, and this could range from 0 (no standards met) to 6 (all standards met).

Quantitative Analysis

Two investigators (C.J.K. and T.F.I.) independently extracted descriptive data to determine whether the trials could be combined. All discrepancies in data extraction and in rating trial quality were resolved by consensus. The primary authors of articles that were published in peer-reviewed journals were contacted, and each original study database was obtained. For studies in which adherent clots were a subgroup among ulcers with other stigmata, only the data for patients with ulcers containing adherent clots were extracted. A combined database of the original raw data was then constructed and used for a patient-level analysis. All studies, including those published only in abstract form, were used for a separate traditional meta-analysis.

Because of the clinical variability in rebleeding rates, we assumed the presence of statistical heterogeneity and decided to use a random effects model before pooling the data. The random effects model adjusts for variability of results among trials and provides a more conservative estimate of an effect by using wider confidence intervals (CIs). We tested our assumption of heterogeneity with a statistical test for homogeneity by using the method by DerSimonian, based on work by Cochran. For rebleeding, need for surgery, and mortality, the effect of treatment was computed by using pooled relative risks (RRs). Summary point estimates of effect were computed by using weighted averages of stratum-specific RRs. The weights were derived from the reciprocals of the variances with an adjustment factor determined by the amount of statistical heterogeneity. Thus, variation both within and among trials contributed to the variance estimates.

We calculated 95% CIs on the basis of adjusted weights, and for RRs that showed statistical significance (ie, the 95% CI did not include 1), the number needed to treat (NNT) was calculated. For this analysis, the NNT is the number of patients who need to undergo endoscopic therapy for an ulcer with an adherent clot for 1 patient to derive additional benefit for a particular outcome over the benefit provided by medical
therapy alone. These analyses and calculations were performed by using Supercalc spreadsheets (version 5.0; Computer Associates International, Inc, San Jose, CA). Comparisons between endoscopic therapy and medical therapy for differences in the number of units of packed red blood cells (PRBCs) transfused and the number of hospital days were performed with analysis of covariance. Comparisons between endoscopic therapy and medical therapy for differences in baseline characteristics were performed by using Cochran-Mantel-Haenszel tests for stratified categorical data with study as the stratification variable or by using analysis of covariance with study as the covariate, depending on whether the characteristic was categorical or continuous, respectively. We used SAS (version 8.0; SAS Institute, Cary, NC) for these calculations.

Results

Descriptive and Qualitative Assessment

Fifty references were obtained, and 44 were excluded; the remaining 6 reports were included in this meta-analysis.16–18,31–33 Figure 1 summarizes the meta-analysis trial flow. Two of the reports were in abstract form,16,31 and the remaining were full-length articles that included patients with adherent clots exclusively or patients with peptic ulcer bleeding and other high-risk stigmata, including adherent clots.32,33 The original data from these 4 trials were used for the patient-level analysis. All fully published trials were randomized and of comparable quality, with quality scores ranging from 4 to 6 of a possible 6, and all used concealed allocation with sealed opaque envelopes at the time of randomization. Methodological and clinical and characteristics of all 6 trials are shown in Tables 1 and 2.

Patients randomized to the endoscopic therapy group first underwent injection of epinephrine into and/or around the clot in 5 of 6 trials, followed by clot removal with a cold snare in 3 studies.16,18,33 Subsequent therapy included injection of sclerosants,16,31 treatment with a heater probe,16,17 or coaptive coagulation with a bipolar probe.18 One trial used injection of a sclerosing agent as the primary therapy without prior injection of epinephrine.32 All patients who underwent endoscopic therapy also received medical therapy, which included general supportive care, transfusions as needed, monitoring in the intensive care unit if indicated, and acid suppression with intravenous histamine 2 (H2) blockers,16,17 a proton pump inhibitor given orally,17,18,32 or a proton pump inhibitor given intravenously.33

Patients randomized to the medical therapy group received the same treatments as patients in the endoscopic therapy group except for endoscopic therapy for the adherent clot. Three trials used sham endoscopic therapy, in which the visualized clot was washed but not otherwise manipulated endoscopically.17,18,33

Table 3 summarizes the numerical outcomes data of the 6 trials and the authors’ conclusions. The total number of subjects was 240; 112 were randomized to the endoscopic therapy group and 128 to the medical therapy group.32,33 Three trials found that endoscopic therapy combined with medical therapy was superior to medical therapy alone for the prevention of rebleeding,17,18,33 and 1 found no difference.16 In the 2 studies in which adherent clots were combined with nonbleeding visible vessels, subgroup analysis showed that there was no difference in the rate of rebleeding between the 2 treatment groups.32,33

Quantitative Assessment

Patient-level analysis. The total number of subjects in the 4 fully published trials was 146, with 61 patients in the endoscopic therapy group and 85 in the medical therapy group.17,18,32,33 There were no statistically significant differences between the pooled treatment groups at baseline with regard to age, sex, nonsteroidal anti-inflammatory drug use, infection with Helicobacter pylori, ulcer location and size, severity of bleed, or number of comorbid conditions. The groups were also similar with regard to the presence of certain high-risk clinical features that could independently increase the risk of rebleeding: age ≥60 years, hypotension (systolic blood pressure <100 mm Hg), giant ulcer (diameter ≥2 cm), and ulcer located in an area that is difficult to access (fundus, superior body, lesser curvature, or posterior wall of the duodenal bulb).

Rebleeding occurred in 5 of 61 (8.2%) patients in the endoscopic therapy group, compared with 21 of 85 (24.7%) in the medical therapy group (P = .01). The pooled risk of rebleeding was 0.35 (95% CI, 0.22–0.69;
NNT, 6.2) in favor of endoscopic therapy. The pooled RRs for the outcomes of death and surgery did not favor either endoscopic or medical therapy (Table 4). There were no significant differences between endoscopic therapy and medical therapy in duration of hospitalization (mean, 6.8 vs 5.9 days; P = .27) or the number of units of PRBCs transfused (mean, 3.0 vs 2.8; P = .75). The subset of patients that rebled in the endoscopic therapy (n = 5) and medical therapy (n = 21) groups were also no different with regard to the need for surgery (20% vs 29%; P = .21), mortality (40% vs 14%; P = .25), duration of hospitalization (13.5 ± 7.7 days vs 10.1 ± 8.0 days; P = .98), or number of units of PRBCs transfused (6.0 ± 6.7 vs 4.2 ± 2.6; P = .99). This indicates that the severity of rebleeding was similar for both groups; however, this analysis is limited by the low frequency of rebleeding.

### Meta-analysis

In the principal analysis for the outcome of rebleeding, the heterogeneity P value was statistically significant (P = .014). This indicates greater-than-expected variation among trial results and implies that aggregating the quantitative data may be problematic.

Careful inspection of the individual studies showed that most of the heterogeneity was attributable to the 2 fully published randomized trials that exclusively enrolled patients with adherent clots. These 2 studies showed the largest differences in the rate of rebleeding between the endoscopic therapy and medical therapy groups.

The pooled RR of rebleeding was 0.35 (95% CI, 0.14–0.83; NNT, 6.3) and was nearly identical to the result derived from the patient-level analysis. The 2 analyses were also concordant with regard to the outcome of death (Table 4). The pooled RR of surgery in the meta-analysis was 0.43 (95% CI, 0.19–0.98; NNT, 13.3) in favor of endoscopic therapy. Most of this trend

### Table 1. Methodological Characteristics of the Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Setting</th>
<th>Blinding</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen</td>
<td>27</td>
<td>Multicenter, US</td>
<td>Physicians delivering nonendoscopy care</td>
<td>Severe hemorrhage ICU admission Adherent clot</td>
<td>NS</td>
<td>Rebleeding Surgery Mortality Costs</td>
</tr>
<tr>
<td>Gonzalez-Huix</td>
<td>67</td>
<td>Single center, Spain</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Jung</td>
<td>19</td>
<td>Single center, South Korea</td>
<td>No</td>
<td>Patients with duodenal, gastric, or stomal ulcers with nonbleeding visible vessels or fresh adherent clots</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Jensen</td>
<td>32</td>
<td>Multicenter, US</td>
<td>Physicians delivering nonendoscopy care</td>
<td>Severe hemorrhage (ICU) Hct drop ≥8% Transfusion ≥2 units PRBC, Adherent clot</td>
<td>Previous endoscopic therapy for same ulcer Uncorrectable coagulopathy Age &lt;18 y Pregnancy Life expectancy &lt; 30 days</td>
<td>Rebleeding Repeat endoscopy Units PRBC Length of hospital stay Length of ICU stay Surgery (30 days) Mortality (30 days)</td>
</tr>
<tr>
<td>Bleau</td>
<td>56</td>
<td>Multicenter, US</td>
<td>No</td>
<td>Patients with gastric or duodenal ulcers and adherent clot without active bleeding</td>
<td>≥2 ulcers with stigmata Another likely bleeding source Coagulopathy Age &lt;18 y Pregnancy</td>
<td>Rebleeding Repeat endoscopy Units PRBC Length of hospital stay Length of ICU stay Surgery (30 days) Mortality (30 days)</td>
</tr>
<tr>
<td>Sung</td>
<td>39</td>
<td>Single center, Hong Kong</td>
<td>Physicians delivering nonendoscopy care</td>
<td>Age ≥16 y Benign duodenal or gastric ulcers with nonbleeding visible vessels or adherent clots</td>
<td>Epidemiologic studies of UC surgical management and practice patterns in the&lt;br&gt;United States: A focus on the impact of&lt;br&gt;endoscopic therapy on patient outcomes.</td>
<td>Rebleeding Repeat endoscopy Units PRBC Length of hospital stay Length of ICU stay Surgery (30 days) Mortality (30 days)</td>
</tr>
</tbody>
</table>

NS, not stated; PRBC, packed red blood cell; ICU, intensive care unit; Hct, hematocrit, EGD, esophagogastroduodenoscopy. *Study includes patients with nonbleeding visible vessels and adherent clots; n refers to number of patients in the adherent clot subgroup.
Table 2. Clinical Characteristics of the Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Rebleeding definition</th>
<th>Adherent clot definition</th>
<th>Endoscopic therapy</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jensen16</td>
<td>NS</td>
<td>Resistant to catheter washing Obscuring ulcer base Distinguishable from visible vessel</td>
<td>Two arms Epinephrine 1:20,000 into clot pedicle, then clot removal, then ethanol injection up to 1.5 mL Heater probe (120 J) plus medical therapy</td>
<td>IV H2 blocker Transfusions ICU care Correction of coagulopathy</td>
</tr>
<tr>
<td>Gonzalez-Huix31</td>
<td>NS</td>
<td>NS</td>
<td>Epinephrine 1:10,000 then sclerosant (2% etoxiesclerol) injection (2–4 mL) plus medical therapy</td>
<td>NS</td>
</tr>
<tr>
<td>Jung32</td>
<td>Hematemesis or melena with shock or decreased Hgb by ≥2 g/dL over 24 h Red blood on repeat EGD ≥6 h after randomization Hematemesis, melena, or hematochezia Decreased Hgb by ≥2 g/dL Tachycardia, hypotension</td>
<td>Clot over ulcer that cannot be dislodged by washing with water jet via endoscope channel</td>
<td>95% ethanol injection inside and around clot (1–2 mL) IV famotidine</td>
<td>Omeprazole 40 mg orally every 12 h</td>
</tr>
<tr>
<td>Jensen18</td>
<td>Hematemesis, melena, or hematochezia Decreased Hgb by ≥2 g/dL</td>
<td>Resistant to catheter washing Size ≥6 mm, red color, amorphous form, covers stigma</td>
<td>Epinephrine 1:10,000, then clot removal (cold snare guillotine), then coaptive coagulation with bipolar probe plus medical therapy</td>
<td>Sham endoscopic therapy ICU care Correction of coagulopathy PPI orally twice a day Transfusions Helicobacter pylori treatment</td>
</tr>
<tr>
<td>Bleau17</td>
<td>Hemodynamic instability Hematemesis, melena, or hematochezia Decreased Hgb by ≥2 g/dL Confirmation by EGD</td>
<td>Red, maroon, or black protuberance (≥3 mm) over ulcer base Cannot be dislodged by forceful irrigation with 200 mL of water via endoscope channel</td>
<td>Epinephrine 1:10,000, then clot removal (various means), then heater probe (30 J) plus medical therapy</td>
<td>Omeprazole 20 mg orally or famotidine 20 mg IV twice daily</td>
</tr>
<tr>
<td>Sung33</td>
<td>Hematemesis Melena with shock Decreased Hgb by ≥2 g/dL within 24 h of transfusion</td>
<td>Clot that remained attached after 5 min irrigation with a heater probe</td>
<td>Epinephrine 1:10,000, then clot removal (cold snare guillotine), then heater probe (30 J) plus medical therapy</td>
<td>Sham endoscopic therapy Omeprazole 80 mg IV bolus then 8 mg/h for 72 h</td>
</tr>
</tbody>
</table>

NS, not stated; Hgb, hemoglobin; PPI, proton pump inhibitor, EGD, esophagogastroduodenoscopy; IV, intravenous; ICU, intensive care unit.

is due to 1 unpublished trial in which a disproportionately high number of patients in the medical therapy group underwent surgery for control of bleeding (10 of 33 [30.3%]). The criteria for surgical referral followed in that study are not known, and exclusion of this trial yields results identical to those of the patient-level analysis, in which no significant difference was observed between endoscopic therapy and medical therapy with regard to the need for surgery.

**Discussion**

This meta-analysis examined 6 randomized trials comparing endoscopic with medical therapy for the treatment of ulcers with adherent clots. The results suggest that endoscopic therapy is more effective in preventing recurrent hemorrhage and in decreasing the need for surgical intervention and that the 2 approaches are equivalent with regard to mortality, duration of hospitalization, and transfusion requirement. A patient-level analysis was conducted by using the original data from the 4 trials that were fully published; these results confirmed those of the meta-analysis, except for the need for surgery, for which no significant difference was observed between the 2 modalities.
The results must be placed in both a methodological and clinical context. Methodological issues that are of particular importance for meta-analyses are completeness of the literature search and combinability of the studies.35 We used the method of Rosenthal36 to estimate the file drawer effect, which is an estimate of the number of unpublished studies showing “no difference” required to negate the results of this analysis. For the outcome of rebleeding, this number was 14. In addition, we retrieved abstracts that were not published as full articles and included them in the overall meta-analysis. Thus, we believe that our literature search was complete.

As important as the completeness of the literature search is the combinability of the studies. The presence of statistical heterogeneity indicates greater than expected variability in the individual trial results when compared with the “average” results. We assumed that this would occur a priori and, accordingly, used the random effects model, which results in wider confidence limits. We also examined the trials closely and found no obvious differences in study design or in the way outcomes were defined and measured. However, the study populations were different and included Asians, in whom the response to proton pump inhibitors may be different from that of US Caucasians because of genetic polymorphism of cytochrome P-450 2C19.37–39 Misclassification may also be a factor; small adherent clots and nonbleeding visible vessels can be indistinguishable, especially if the clot is in continuity with the vessel. In addition, although the endoscopic therapies described were broadly similar, one cannot exclude variability in technique, including the intensity with which clots were washed to prove adherence, the technique used to expose the underlying stigma (forceful clot removal vs shaving), and the fact that some studies used endoscopic monotherapy16 and others used a multimodality approach.17,18

The type of medical therapy also varied across trials; suppression of gastric acid secretion was achieved with intravenous H2 blockers and/or oral proton pump inhibitors, except for 1 trial, in which intravenous omeprazole was used as the primary therapy in the medical treatment arm.33 In that study, the rate of rebleeding for patients with adherent clots who received medical therapy was remarkably lower than in the other reports (0% vs 30%–39%). This greater difference may reflect a higher efficacy of intravenous proton pump inhibitors in increasing intragastric pH and preventing clot lysis.40,41 A recent meta-analysis of randomized trials that assessed the efficacy of pharmacological therapies for patients with high-risk peptic ulcers showed that high-dose intravenous proton pump inhibitors significantly decreased ulcer rebleeding (15%), surgery (5%), and mortality (3%) compared with placebo and decreased rebleeding (21%) compared with H2 blockers.42 Conversely, oral high-dose proton pump inhibitors significantly reduced only rebleeding (12%). The relatively small number of patients who received intravenous proton pump inhibitors in our study does not allow conclusions about the relative efficacy of this treatment compared with endoscopic therapy; however, this observation is striking and warrants further investigation in an adequately powered trial. Other subtle cointerventions cannot be excluded and may have contributed to the observed heterogeneity. Finally, heterogeneity may be inherent to the fact that we combined data from trials that were designed specifically for patients with adherent clots and trials that also enrolled patients with nonbleeding visible vessels. The patient-level analysis mitigates this limitation, because we were able to analyze data for individual patients, as opposed to aggregate subgroup results. Furthermore, heterogeneity is likely to exist in clinical practice to a greater extent than in hospital-based clinical trials, and this may enhance the generalizability of the results to the practice setting, where variability is the norm.

From the clinical standpoint, the use of meta-analysis allows extrapolation of the results of individual trials and raises new, clinically relevant questions. For example, if we assume that the rate of rebleeding of ulcers with adherent clots was decreased from 35% to 10% with endoscopic therapy, then a hypothetical randomized trial would require 51 patients per group to detect a significant difference with a 2-sided α level of .05 and 80% power. None of the studies we assessed reached that target sample size, either because the study was not

### Table 4. Results of Patient-Level Analysis and Meta-analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Trial subgroup</th>
<th>n</th>
<th>(P_{\text{EndoRx}})</th>
<th>(P_{\text{MedRx}})</th>
<th>RR (95% CI)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebleeding</td>
<td>All trials</td>
<td>240</td>
<td>.13</td>
<td>.29</td>
<td>0.39 (0.22–0.69)</td>
<td>6.2</td>
</tr>
<tr>
<td></td>
<td>Abstracts excluded</td>
<td>146</td>
<td>.095</td>
<td>.25</td>
<td>0.35 (0.14–0.83)</td>
<td>6.3</td>
</tr>
<tr>
<td>Death</td>
<td>All trials</td>
<td>240</td>
<td>.097</td>
<td>.084</td>
<td>1.11 (0.50–2.49)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Abstracts excluded</td>
<td>146</td>
<td>.13</td>
<td>.06</td>
<td>2.27 (0.74–6.95)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>All trials</td>
<td>240</td>
<td>.062</td>
<td>.14</td>
<td>0.43 (0.19–0.98)</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Abstracts excluded</td>
<td>146</td>
<td>.065</td>
<td>.08</td>
<td>0.82 (0.25–2.65)</td>
<td>—</td>
</tr>
</tbody>
</table>

EndoRx, endoscopic therapy; MedRx, medical therapy; RR, relative risk; CI, confidence interval; NNT, number needed to treat.
exclusively targeted at patients with adherent clots or because the study was terminated early. Meta-analysis can overcome this sample size limitation for the primary outcome of recurrent bleeding by combining relatively large numbers of patients in the treatment groups. However, despite the advantage of larger sample sizes, meta-analysis may still not overcome the limitations of individual trials. For example, we were unable to build a predictive model of rebleeding or to define subgroups at a higher risk of rebleeding because of the small number of patients who rebled; studies with larger sample sizes are required to answer this clinically relevant question.

Observational studies conducted in a general clinical practice setting support our findings: Bini and Cohen reported the results of a retrospective study of 244 patients with adherent clots. Of 138 patients who received combination endoscopic and medical therapy, 12 (8.7%) rebled within 7 days, compared with 29 of 106 patients (27.4%) who were treated with medical therapy alone (adjusted odds ratio, 0.07; 95% CI, 0.02–0.22; P < .001).

Given the quantitative results for rebleeding, the results of this meta-analysis suggest that we may expect less rebleeding after endoscopic therapy for an adherent clot, and with a relatively low NNT. However, we also appreciate the clinical heterogeneity of this issue, with variation in ulcer location, the rate and amount of ulcer bleeding, patient comorbidity, and endoscopist experience. There may be subgroups in which clot removal would be ill advised—for example, an ulcer on the posterior wall of the duodenal bulb or one on the high lesser curve. Both locations may involve larger-caliber vessels and are often more technically challenging to treat endoscopically. Before assembling the database for the patient-level analysis, we had hypothesized that ulcers in these 2 locations either would show no difference between the 2 treatment groups or would favor medical therapy. However, because information on ulcer location was not present at the same level of detail in all trials, we were unable to test this hypothesis with sufficient power. Thus, our results must be considered in the context of individual patient circumstances and serve as an aid to, but not a substitute for, clinical judgment.

In conclusion, endoscopic therapy combined with medical therapy is more effective than medical therapy alone to prevent recurrent bleeding from peptic ulcers with adherent clots. The 2 interventions seem equivalent with regard to their effect on mortality, need for surgery, duration of hospitalization, and transfusion requirements. The effect of newer medical interventions on our findings, such as the routine use of high-dose intravenous infusions of proton pump inhibitors, remains unclear and merits further study.

References


Received January 31, 2005. Accepted June 2, 2005.
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The authors thank Thomas Emmett, MD, for help in conducting a thorough literature search, and Beverly Musick for database management.