Combined epinephrine and bipolar probe coagulation vs. bipolar probe coagulation alone for bleeding peptic ulcer: a randomized, controlled trial

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Background: Endoscopic treatment with combined modalities is considered standard of care for patients with high-risk peptic ulcer bleeding. This study compared epinephrine injection plus bipolar probe coagulation with bipolar probe coagulation alone in patients with high-risk peptic ulcer bleeding.

Methods: Patients with endoscopically confirmed peptic ulcer bleeding (active or visible vessel) seen from January 2000 through December 2002 were prospectively randomized to two groups. The study group (n = 58) had epinephrine injection followed by bipolar coagulation; the control group (n = 56) was treated by bipolar coagulation alone. The primary outcomes assessed were the rate of initial hemostasis and the rate of recurrent bleeding. Secondary outcomes were the following: need for surgical intervention to control bleeding, transfusion requirements, length of hospital stay (in days), and 30-day mortality.

Results: The rate of initial hemostasis was significantly higher in the combination therapy group (p = 0.02; absolute risk reduction 31.6%: 95% CI [5.4, 57.7]). There was no significant difference between the two treatment groups with respect to all other outcomes measures, except that significantly fewer units of blood were transfused in the combination therapy group (p = 0.006).

Conclusions: In patients with active peptic ulcer bleeding, epinephrine injection plus bipolar coagulation achieved significantly higher rate of initial hemostasis. All other outcome measures were similar with either treatment in patients with non-bleeding stigmata. (Gastrointest Endosc 2004;60:910-5.)

Upper-GI bleeding is a common and potentially life-threatening event; about 100 of 100,000 adults are hospitalized annually with such bleeding.1,2 Peptic ulcer hemorrhage is the most common cause of severe upper-GI bleeding.1 Such bleeding ceases spontaneously in 70% to 80% of patients, but further bleeding in the remaining 20% to 30% may be catastrophic.3 Endoscopic treatment reduces the morbidity and the mortality associated with peptic ulcer bleeding and is significantly better than conservative management for the control of active bleeding and prevention of recurrent hemorrhage.4 Injection therapy is undoubtedly the most popular method, because it is effective, easy to administer, widely available, and relatively inexpensive. Clinical trials have found dilute epinephrine to be an effective agent and that the addition of a sclerosant agent or alcohol provides no incremental benefit and is associated with serious side effects.5,6 Moreover, injection therapy also halts or slows active bleeding so that other therapeutic methods also can be applied. Endoscopic thermal coagulation was introduced as the initial endoscopic hemostatic treatment more than 20 years ago. Contact probes offer good coaptive coagulation (sealing of vessel by combined pressure and heat) and target irrigation. Bipolar and heat probe coagulation have been shown to be more effective than injection therapy alone for the control of active bleeding and for the prevention of recurrent bleeding from visible vessels.7,8 Injection combined with thermal probe coagulation appears to be superior to injection therapy alone in high-risk patients,9-13 but the therapeutic clinical gain over thermal monotherapy may not be substantial.

The primary objective of this study was to test the null hypothesis: that there was no difference in hemostatic rates between combination treatment (injection plus bipolar coagulation) vs. bipolar coagulation alone in patients with clinically severe ulcer hemorrhage. The secondary objective was to...
compare clinical outcomes, such as the requirement for blood transfusion, recurrent bleeding, surgery, mortality, and length of hospital stay, between the two treatment groups.

**PATIENTS AND METHODS**

**Patients**

All patients hospitalized for upper-GI bleeding and those who bleed after admission for unrelated disorders were considered for study entry. Inclusion criteria were the following: (1) hematemesis, melena, hematochezia, or a bloody nasogastric aspirate; (2) hemodynamic instability (systolic blood pressure <100 mm Hg, pulse rate >100 beats per minute, or orthostatic change in systolic blood pressure >20 mm Hg or pulse rate >20 beats per minute); (3) transfusion of two or more units of blood within 12 hours or a decrease in hematocrit of greater than 6% in 12 hours; and (4) endoscopy within 24 hours of admission that revealed a gastric or duodenal ulcer with an actively bleeding vessel (spurring or oozing) or a non-bleeding visible vessel (defined as a raised, rounded, smooth-surfaced plug). Adherent clots were mechanically removed with a snare to expose the underlying ulcer crater. A Rockall score was calculated for each patient after the bleeding event.

Exclusion criteria were the following: (1) age less than 18 years, (2) pregnancy, (3) inability or unwillingness to consent to participation in the study, (4) anticoagulation therapy, (5) severe coagulopathy (prothrombin time >18 seconds), (6) known severe chronic liver disease, (7) advanced malignancy, and (7) identification of two or more potential bleeding lesions.

**Randomization**

Written consent for participation in the study was obtained, either from the patient or, in some cases, from a close relative. The protocol was reviewed and approved by the institutional review board of our hospital.

Endoscopy was undertaken after resuscitation. Patients were randomly assigned at endoscopy to bipolar probe coagulation alone or epinephrine injection followed by bipolar coagulation by using computer-generated randomization sequences in blocks of 25 with concealed allocation. Patients were stratified for active bleeding and visible vessel.

**Endoscopic therapy**

Endoscopy was performed with a forward-viewing therapeutic endoscope (1T130 or 1T140; Olympus Optical Co., Ltd. Tokyo, Japan). All procedures were performed by experienced endoscopists (>15 years’ experience with GI bleeding) with particular skill in the two procedures under evaluation. Bipolar electrocoagulation was performed with a 7F probe (Injector-Gold Probe; Microvasive Endoscopy, Boston Scientific Corp., Natick, Mass.). The probe was applied as forcefully as possible to the bleeding site or the visible vessel and the immediately surrounding area (setting 15-20 W); energy was delivered in 10-second pulses. Injection was performed before thermocoagulation by using either the 25-gauge retraction needle inside the Injector-Gold Probe or a separate 23-gauge disposable injector needle (DVI-23-MH; Cook Ireland Ltd., Cork, Ireland) Boluses of 1 to 2 mL of a 1:10,000 solution of epinephrine were injected to a maximum of 30 mL. Injections were placed in the 4 quadrants surrounding the bleeding site or the vessel, and then into the bleeding site or the vessel directly.

**Follow-up**

After the endoscopic procedure, all patients were treated with omeprazole (40 mg intravenously every 12 hours). Subsequent clinical management decisions were left to the attending physician or surgeon. The patients, those caring for them, and personnel collecting data were blinded to the type of treatment each patient received. The endoscopist who performed the endoscopic treatment did not participate in the further care of the patient.

In all patients, two biopsy specimens were taken from the gastric antrum and body to assess for *Helicobacter pylori* infection. If appropriate, patients were treated with a 7-day course of amoxicillin (1000 mg twice a day) and clarithromycin (500 mg twice a day) plus a proton pump inhibitor.

The primary goals of the trial were the following: (1) to compare the ability of the two endoscopic treatments to achieve initial hemostasis (defined as cessation of active bleeding or coagulative necrosis with flattening of the visible vessel or cavitation effect) and (2) to compare the rate of recurrent bleeding between the two treatment groups. Secondary objectives were to compare the length of hospital stay, the number of units of blood transfused, the need for surgical intervention, and the 30-day mortality between the two groups.

Definitive hemostasis was defined as no endoscopic evidence of bleeding during 5 minutes of observation after therapy and maximal water irrigation for 10 seconds. If any further hemorrhage occurred, the initial procedure was repeated until no further bleeding was evident. If hemorrhage persisted during the initial endoscopy despite therapy, patients in both groups were treated by epinephrine injection followed by further electrocoagulation with the 10F probe; they were referred for surgery if bleeding was not controlled after 15 minutes of endoscopic treatment.

Vital signs and the nasogastric tube aspirate were monitored hourly. Hb concentration was monitored every 6 hours for the first 48 hours and then at 12 and 24 hours thereafter.

Recurrent bleeding was defined as fresh hematemesis or melena or both, together with shock, or a decrease in Hb concentration of at least 2 g/dL in 24 hours. Recurrent bleeding was diagnosed by the attending clinicians, who made all management decisions but who had no knowledge of whether the patient had received combination therapy or thermal therapy alone.

If there was any clinical suspicion of recurrent bleeding, endoscopy was performed immediately. Patients with any
recurrent bleeding were re-treated by using the same method as at randomization. Two treatment sessions were permitted before endoscopic therapy was considered to have failed. Endoscopic treatment was considered successful if there was no further bleeding, or if recurrent hemorrhage was controlled endoscopically, up to the time of discharge.

Surgery was considered for patients with persistent bleeding (treatment failure) and for those with recurrent bleeding that could not be stopped endoscopically (re-treatment failure). After discharge, patients were followed by the trial monitor, either by outpatient interview or by telephone contact 30 days after the initial episode of bleeding.

Statistical methods

The trial was designed to have an 80% power to detect a difference in hemostasis rates of 5% and 15% at the 5% level of significance. A hemostatic rate for combination therapy of 95% was assumed; the hemostatic rate was assumed to be 15% lower for bipolar electrocoagulation alone. It was calculated that 60 patients would be required in each study arm. Data were analyzed by using a statistical software package (SPSS/PC version 7.1; M. J. Norusis, Chicago, Ill.). The efficacy of treatments was analyzed on an intention-to-treat basis. Summary statistics for quantitative data are given as mean (standard deviation [SD]). Differences in proportions were analyzed by using the chi-square test with the Yates’ correction or the Fisher exact test. Baseline characteristics of the treatment groups, which were quantitative, were compared with a t test. Length of hospital stay was compared by using the t test after logarithmic transformation. Blood transfusion requirements were compared by using the Wilcoxon rank sum test. A p value <0.05 was regarded as significant.

It is recognized that there was multiple testing of outcome data arising from individual patients. However, there was no instance where statistical significance was removed if the results for hemostatic rates are taken as the main findings (not subject to correction); the method of Bonferroni was used for all secondary results.

RESULTS

A total of 345 patients met the clinical entry criteria and had an ulcer as the source of bleeding. Of these, 231 patients were excluded because of the presence of minor stigmata of hemorrhage in the ulcer base (134 clean base, 97 flat pigmented spot). A flat spot was exposed after removal of an adherent clot in 9 cases. The remaining 114 patients had either active bleeding (n = 38) or a visible vessel (n = 76). Of these, a major stigmata of hemorrhage was exposed after mechanical removal of an adherent clot in 24 patients (9 oozing, 15 visible vessel) (Fig. 1).

The 114 high-risk patients were randomized to receive bipolar electrocoagulation alone (n = 56) or combination therapy with epinephrine injection plus bipolar electrocoagulation (n = 58). There was no significant difference in the baseline characteristics for the two groups (Table 1).

The results after treatment are shown in Table 2 for all patients. A mean of 12 (3) mL of epinephrine solution was injected per patient. Hemostasis was achieved at initial endoscopy in 19 (68.4%) patients with active bleeding treated by bipolar coagulation alone and in 19 of 19 (100%) actively bleeding patients treated with combination therapy (absolute risk reduction [ARR] 31.6%: 95% CI [5.4, 57.7]; p = 0.02).

Overall, bleeding recurred in 13 patients (8 who had bipolar coagulation alone and 5 treated by combination therapy); the difference between the two groups was not significant (ARR 5.7%: 95% CI [−6, 17], p > 0.50).

Among patients with active bleeding, recurrent bleeding was numerically more common in the group

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**Table 1. Clinical variables at study entry**

<table>
<thead>
<tr>
<th></th>
<th>Gold Probe n = 56</th>
<th>Combined n = 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>59 (6)</td>
<td>58 (5)</td>
</tr>
<tr>
<td>Male gender</td>
<td>42 (75%)</td>
<td>46 (79%)</td>
</tr>
<tr>
<td>Hematocrit at admission</td>
<td>27%</td>
<td>24%</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>109 (5)</td>
<td>111 (3)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>112 (3)</td>
<td>116 (3)</td>
</tr>
<tr>
<td>Rockall score</td>
<td>7 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.8 (2.1)</td>
<td>8.0 (1.8)</td>
</tr>
<tr>
<td>No. units transfused</td>
<td>1.6 (0.3)</td>
<td>2.2 (0.5)</td>
</tr>
<tr>
<td>Previous NSAID intake</td>
<td>31 (55%)</td>
<td>35 (60%)</td>
</tr>
<tr>
<td>Helicobacter pylori positive</td>
<td>34 (79%)</td>
<td>33 (73%)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>19 (34%)</td>
<td>19 (33%)</td>
</tr>
<tr>
<td>Non-bleeding visible vessel</td>
<td>37 (66%)</td>
<td>39 (67%)</td>
</tr>
<tr>
<td>Size of ulcer (range in mm)</td>
<td>11 (8-14)</td>
<td>12 (8-18)</td>
</tr>
<tr>
<td>Gastric/duodenal ulcer</td>
<td>15/41</td>
<td>14/44</td>
</tr>
</tbody>
</table>

p is not significant for all comparisons. Values are numbers (percentage) expressed as mean (standard deviation). NSAID, Non-steroidal anti-inflammatory drug.
Table 2. Outcomes of endoscopic treatments

<table>
<thead>
<tr>
<th></th>
<th>Gold Probe n = 56</th>
<th>COMBINED n = 58</th>
<th>ARR 95% CI</th>
<th>RRR 95% CI</th>
<th>NNT 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemostasis in AB</td>
<td>13/19 (68.4)</td>
<td>19/19 (100)</td>
<td>31.6 (5.4, 57.7)</td>
<td>46 (16, 77)</td>
<td>3 (2, 18)</td>
</tr>
<tr>
<td>Recurrent bleeding</td>
<td>8/56 (14.3)</td>
<td>5/58 (8.2)</td>
<td>5.7 (–6, 17)</td>
<td>40 (–42, 100)</td>
<td>—</td>
</tr>
<tr>
<td>AB</td>
<td>3/13 (23)</td>
<td>1/19 (5.2)</td>
<td>17.8 (–13.7, 49.3)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NBVV</td>
<td>5/37 (13.5)</td>
<td>4/39 (10.2)</td>
<td>1.9 (–6, 17.2)</td>
<td>5 (–7, 2)</td>
<td>—</td>
</tr>
<tr>
<td>Surgery</td>
<td>4/56 (7.1)</td>
<td>1/58 (1.8)</td>
<td>5.4 (–2.1, 12.9)</td>
<td>76 (–30, 100)</td>
<td>—</td>
</tr>
<tr>
<td>AB</td>
<td>2/19 (10.5)</td>
<td>0/19 (0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NBVV</td>
<td>2/37 (5.4)</td>
<td>1/39 (2.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Death</td>
<td>3/56 (5.3)</td>
<td>1/58 (1.7)</td>
<td>3.7 (–3, 10.5)</td>
<td>69 (–57, 100)</td>
<td>—</td>
</tr>
<tr>
<td>AB</td>
<td>1/19 (5.2)</td>
<td>1/19 (5.2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NBVV</td>
<td>2/37 (5.4)</td>
<td>0/39 (0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median units of blood transfused (range)</td>
<td>3 (0-8)†</td>
<td>1 (0-16)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median hospital stay in d (range)</td>
<td>8 (7-34)</td>
<td>7 (4-20)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Values are number (percentage). Combined, Injection epinephrine + Gold Probe; ARR, absolute risk reduction, i.e., the absolute difference between the event rate in controls and experimental; RRR, relative risk reduction, i.e., the proportional reduction of the event vs. the control rate (control event rate experimental event rate/control event rate); NNT, number needed to treat, i.e., the number of patients to treat with the experimental procedure so that at least one avoids the event investigated (e.g., recurrent bleeding) (NNT is a measure of therapeutic gain and is the reciprocal of ARR [1/ARR]; AB, patients with actively bleeding ulcers; NBVV, patients with non-bleeding visible vessels at the ulcer base.

*p = 0.02 Gold Probe vs. combined injection + Gold Probe.
†p = 0.006 Gold Probe vs. combined injection + Gold Probe.

treated by bipolar coagulation alone, but the difference was not statistically significant (ARR 17.8%: 95% CI [–13.7, 49.3], p > 0.50). For the patients with a non-bleeding visible vessel, the rate of recurrent bleeding was similar to the two groups (ARR 3.3%: 95% CI [–8, 32]; p > 0.50). Twelve of the 13 patients with recurrent bleeding had some form of subsequent intervention, either endoscopic alone (multipolar group, 6; combined group, 4) or surgical (multipolar group, 1; combined group, 1). The remaining patient with recurrent bleeding was in the group treated by bipolar therapy alone and died before additional procedures could be performed.

The number of units of blood transfused after treatment was significantly greater in the group treated by bipolar coagulation alone (p = 0.006), but the differences in length of hospital stay and mortality were not significant. Three of the 4 patients who died had recurrent bleeding. One patient (combined group) had recurrent bleeding that was treated endoscopically but died because of a combination of recurrent GI bleeding, end-stage chronic obstructive pulmonary disease, and sepsis. A second patient, who had been randomized to bipolar coagulation alone, with underlying coronary artery disease had recurrent bleeding and a subsequent cardiac arrest ascribed to myocardial infarction. The third patient, also randomized to bipolar coagulation alone, had no further bleeding after a second endoscopic treatment but later died as a result of multi-organ failure.

No patient was lost to follow-up. There was no procedure-related perforation or procedure-related death. Both treatments were similar with respect to induction of bleeding from an initially non-bleeding lesion (37.8% vs. 41%; absolute risk increase 3.2%: 95% CI [–27.8, 21.2], p > 0.50).

**DISCUSSION**

Despite the effectiveness of endoscopic monotherapies for peptic ulcer bleeding, further or recurrent bleeding occurs in about 15% to 25% of cases.¹⁵ Thus, attempts have been made to improve the results of monotherapy by combining it with another modality. There are no hard data to demonstrate that a combination of injection therapies or injection plus hemoclip application is superior to either treatment alone.¹¹,¹²,¹⁶,¹⁷ By contrast, available data for the combination of epinephrine injection and a thermal method show a consistent trend in favor of combined treatment.¹⁰,¹¹ The rationale for the combined approach is the different modes of arterial hemostasis of the two methods: epinephrine activates the intrinsic arterial coagulation cascade, causes vasoconstriction, and facilitates clotting; a thermal probe tamponades the artery, coaptively coagulates the tissue, activates arterial coagulation, and causes edema that helps to compress the artery. In a large series, Chung et al.,⁹ showed that heat probe coagulation after epinephrine injection decreased the need for emergency surgery and blood transfusion, and reduced the length of hospital stay for patients with spurring hemorrhage. In the study by Lin et al.,¹⁰ bipolar coagulation after epinephrine injection was better
than epinephrine injection alone in reducing the rate of recurrent bleeding. Wong et al.\textsuperscript{13} confirmed the excellent performance of epinephrine injection plus heat probe coagulation in series of 1144 patients who required endoscopic treatment; the rate of hemostasis was a remarkable 98.6\%, with a rate of recurrent bleeding of only 8.2\%. A meta-analysis of 16 studies that included 1673 patients provided evidence that the addition of a second endoscopic treatment modality after epinephrine injection improved outcomes for patients with high-risk bleeding ulcers, with further reductions in the rate of recurrent bleeding (odds ratio [OR] 0.53: 95\% CI [0.40, 0.69]), need for emergency surgery (OR 0.64: 95\% CI [0.46, 0.90]), and mortality (OR 0.51: 95\% CI [0.31, 0.84]).\textsuperscript{18} For combined endoscopic therapy, the results obtained with contact vs. non-contact probes\textsuperscript{19} and smaller (7F) vs. larger (10F) probes\textsuperscript{20} appear to be essentially equivalent.

Comparative data for combination therapy vs. thermal methods alone are scarce. Given that thermal methods are highly effective, the therapeutic gain of combined therapy compared with thermal monotherapy may be of lesser clinical relevance. In patients with actively bleeding ulcers, Jensen et al.\textsuperscript{21,22} found a significantly higher rate of initial hemostasis with combination therapy compared with bipolar coagulation alone. For high-risk patients and non-bleeding vessels, those with non-bleeding vessels, rates of recurrent bleeding and surgery were similarly low with either bipolar coagulation or combination therapy. In a multicenter randomized trial, Church et al.\textsuperscript{23} compared heat probe coagulation plus thrombin injection with heat probe coagulation plus placebo in patients with severe peptic ulcer bleeding. In this study, coaptive coagulation plus injection of thrombin did not confer any additional benefit, regardless of whether bleeding was active or if non-bleeding stigmata were present.

The present prospective randomized trial was specifically designed to test the hypothesis that there is a difference in outcomes for patients treated by thermal contact monotherapy or epinephrine injection combined with thermal coagulation. The results demonstrate a beneficial effect of combined therapy in achieving primary hemostasis in the subgroup of patients with active ulcer bleeding (ARR 31.6\%, number needed to treat of 3). With respect to recurrent bleeding, both treatments were equally effective. There was a trend toward a lower rate of recurrent bleeding in the combination therapy arm in the subgroup of patients who initially had an actively bleeding ulcer. The actual values were small (3/13 and 1/19), and the 18\% difference did not reach statistical significance, likely because of a beta error. In the post-hoc analysis, 59 patients with active peptic ulcer bleeding would have to be randomized to each group to demonstrate a statistically significant difference between the two treatment methods. No significant difference was found between the two treatment groups in terms of need for surgery or mortality.

Consistent with the results of previous laboratory\textsuperscript{24} and human studies,\textsuperscript{10} the present study confirms the effectiveness, the ease of use, and the safety of the Injector-Gold Probe. All necessary functions are combined in this device: irrigation, injection, and coagulation. There was no difference in treatment-related complications between combined therapy and bipolar coagulation alone. The most frequent negative outcome encountered was precipitation of bleeding from a non-bleeding lesion. The calculated number needed to harm for this negative outcome was 31: 95\% CI ([3.6, 5]); i.e., for every 31 patients treated with combination therapy, one patient will suffer an exacerbation or a precipitation of hemorrhage that would not have occurred with bipolar coagulation alone.

In conclusion, the combination of injection and bipolar coagulation achieved a significantly higher rate of initial hemostasis and tended to decrease the rate of recurrent bleeding in patients with active arterial bleeding compared with bipolar coagulation alone. Patients with spurting bleeding, therefore, may be the subgroup most likely to benefit from combined endoscopic therapy.

\textbf{REFERENCES}


