Addition of a Second Endoscopic Treatment Following Epinephrine Injection Improves Outcome in High-Risk Bleeding Ulcers

XAVIER CALVET,* MERCEDES VERGARA,* ENRIC BRULLET,* JAVIER P. GISBERT,† and RAFEL CAMPO*
*Unitat de Malalties Digestives, Hospital de Sabadell/UDIAT, Institut Universitari Parc Taulí, Universitat Autònoma de Barcelona, Barcelona; and †Servicio de Aparato Digestivo Hospital de la Princesa, Madrid, Spain

Background & Aims: Endoscopic therapy reduces the rebleeding rate, the need for surgery, and the mortality in patients with peptic ulcer and active bleeding or visible vessel. Injection of epinephrine is the most popular therapeutic method. Guidelines disagree on the need for a second hemostatic procedure immediately after epinephrine; although it seems to reduce further bleeding, its effects on morbidity, surgery rates, and mortality remain unclear. The aim of this study was to perform a systematic review and meta-analysis to determine whether the addition of a second procedure improves hemostatic efficacy and/or patient outcomes after epinephrine injection.

Methods: An extensive search for randomized trials comparing epinephrine alone vs. epinephrine plus a second method was performed in MEDLINE and EMBASE and in the abstracts of the AGA Congresses between 1990 and 2002. Selected articles were included in a meta-analysis.

Results: Sixteen studies including 1673 patients met inclusion criteria. Adding a second procedure reduced the further bleeding rate from 18.4% to 10.6% (Peto odds ratio 0.53, 95% CI: 0.40–0.69) and emergency surgery from 11.3% to 7.6% (OR: 0.64, 95% CI: 0.46–0.90). Mortality fell from 5.1% to 2.6% (OR: 0.51, 95% CI: 0.31–0.84). Subanalysis showed that the risk of further bleeding decreased regardless of which second procedure was applied. In addition, the risk was reduced in all subgroups, although reduction was more evident in high-risk patients and when no scheduled follow-up endoscopies were performed.

Conclusions: Additional endoscopic treatment after epinephrine injection reduces further bleeding, need for surgery, and mortality in patients with bleeding peptic ulcer.

Endoscopic therapy reduces the rebleeding rate, the need for surgery, and the morbidity and mortality of patients bleeding from a peptic ulcer.1 Many different endoscopic hemostatic techniques have been developed and studied over the last 25 years. Methods are based on the injection of vasoconstrictor substances (epinephrine), sclerosant substances (polidocanol, absolute alcohol), clotting factors (thrombin, fibrin glue), or adhesives (cyanoacrylate). Thermal therapies include laser, monopolar electrocoagulation, argon plasma coagulation, bipolar probes, and heater probe. More recently, the use of mechanical devices to clip the bleeding vessel (hemoclip) has been incorporated. Epinephrine injection—alone or in combination with another technique—has become the most popular endoscopic method for emergency endoscopic hemostasis because of its safety, low cost, and easy application.2

Although some randomized studies have established that epinephrine in combination with a second hemostatic technique is better than epinephrine alone, the guidelines do not make clear recommendations on this point.3,4 The addition of a second endoscopic technique can increase the cost and the risk of complication of the procedure, and it remains unclear whether the reduction of further bleeding actually offsets these drawbacks.

The aim of the present study was to perform a meta-analysis of the studies comparing the safety and efficacy of endoscopic injection of epinephrine alone vs. epinephrine plus a second hemostatic method in the treatment of patients with a bleeding peptic ulcer.

Materials and Methods

Literature Search and Identification of Primary Studies

A literature search was performed in September 2002 using the MEDLINE and EMBASE databases and the Cochrane Controlled Trials Register. The strategy included the words "(peptic ulcer OR gastric ulcer OR duodenal ulcer) AND (bleeding OR haemorrhage OR hemorrhage) AND (sclerotherapy OR sclerosis OR injection)." We also conducted
Table 1. Criteria for Further Bleeding and Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for clinical further bleeding</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baianzo et al.</td>
<td>Not specified</td>
<td>30-Day mortality</td>
</tr>
<tr>
<td>Choudari and Palmer</td>
<td>Fresh hematemesis or melena + shock or fall in hemoglobin &gt;2 g/dL</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Chung et al.</td>
<td>Fresh hematemesis or melena + shock or fall in hemoglobin &gt;2 g/dL</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Chung et al.</td>
<td>Not specified</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Chung et al.</td>
<td>Fresh hematemesis or melena + shock or transfusion &gt;8 U</td>
<td>Not specified</td>
</tr>
<tr>
<td>Garrido et al.</td>
<td>Hematemesis or fresh melena</td>
<td>30-Day mortality</td>
</tr>
<tr>
<td>Kubba et al.</td>
<td>Fresh hematemesis or melena + shock or fall in hemoglobin &gt;2 g/dL</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lee et al.</td>
<td>Not specified</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Unstable vital signs or continued bloody stools or hematemesis</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>Unstable vital signs or continued bloody stools or hematemesis</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Loizou and Brown</td>
<td>Fresh hematemesis or melena + shock or fall in hemoglobin despite transfusion</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Pescatore et al.</td>
<td>Fresh hematemesis or melena + shock or fall in hemoglobin despite transfusion</td>
<td>30-Day mortality</td>
</tr>
<tr>
<td>Sollano et al.</td>
<td>Recurrence of hematemesis, melena, or anemia</td>
<td>Not specified</td>
</tr>
<tr>
<td>Villanueva et al.</td>
<td>Fresh hematemesis or melena + hypovolemia or fall of hemoglobin requiring transfusion</td>
<td>Hospital mortality</td>
</tr>
<tr>
<td>Villanueva et al.</td>
<td>Not specified</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

A manual search of abstracts submitted to the Digestive Diseases Week between 1990 and 2002. The search was primarily planned to include articles in English, French, or Spanish.

Articles selected in the search were reviewed separately by 2 of the authors, and those fulfilling the inclusion criteria were selected for further analysis. In addition, a fully recursive search of reference lists of the original studies was performed to find studies not identified by the previous searches. Papers recorded in the personal databases of the authors were also reviewed and included when appropriate.

Studies Selection

Studies designed to compare the efficacy of different endoscopic methods to achieve definitive hemostasis in peptic ulcer patients were evaluated separately by 2 of the authors. The inclusion criteria were as follows: (1) Articles or abstracts should report the results of comparative, randomized trials. (2) Studies must include patients with hemorrhage from peptic ulcer disease (gastric or duodenal) with major stigmata of bleeding as defined by groups Ia (spurting hemorrhage), Ib (oozing hemorrhage), Ila (nonbleeding visible vessel), and IIb (adherent clot) of the Forrest classification. (3) Studies had to include at least 2 branches of endoscopic treatment: epinephrine alone vs. epinephrine associated with a second hemostatic method. (4) The data on the baseline characteristics of the patients (number, age, sex, and others), inclusion and exclusion criteria, and results should allow adequate evaluation.

Further clinically significant bleeding was defined according to the criteria established in each study (Table 1). Bleeding had to be confirmed by endoscopy.

Criteria Used for the End Points of the Study

Primary end point: further bleeding. In most of the studies, the primary end point was defined as endoscopic therapy failure, i.e., a combination of persistent hemorrhage and recurrence during follow-up. Here, for the sake of simplicity, this primary end point is referred to throughout the text as further bleeding—a more usual term and one that gives a clearer image. Clinical criteria used for presuming further bleeding differed between the studies and are shown in Table 1. Bleeding was confirmed by endoscopy in all the studies. Clinically silent bleeding observed at scheduled endoscopies was not considered for the analysis. A subanalysis comparing data separately for persistent hemorrhage and recurrence during follow-up was also performed.

Surgery and mortality. Criteria for emergency surgery were not specified in the majority of the studies, and few gave the criteria for mortality; 30-day mortality or inhospital mortality were the most often used (Table 1).

Data Extraction

Data were extracted separately by 2 of the authors and reviewed by a third. If results were discordant, papers were jointly reviewed until the differences were resolved.

Quality Assessment

The quality of the studies included was assessed using the criteria proposed by Chalmers et al. This method evaluates the design, implementation, and analysis of randomized controlled trials. The overall index of trial quality was weighted as follows: trial design and protocol (0.60), statistical analysis (0.30), and presentation of results (0.10). Final quality score ranged from 0 to 1, with maximum quality studies rating 1.

Statistical Analysis

Main comparisons contrasted epinephrine injection vs. epinephrine injection plus another hemostatic method. The primary outcome variable was further bleeding, defined as persistence or recurrence of bleeding during follow-up. Emergency surgery during hospitalization, morbidity, and mortality rate were also analyzed. Subanalysis for further bleeding was performed to examine the efficacy of the different techniques (sclerosant agents, mechanical hemostasis, or thermal devices) associated to epinephrine injection vs. epinephrine alone. Subanalysis was also performed depending on the type of
peptic ulcer hemorrhage: active spurting or oozing (Forrest Ia or Ib), nonbleeding visible vessel (Forrest IIa), or adherent clot (Forrest IIb). Also, further bleeding rates were divided into failure to achieve initial hemostasis and recurrence during follow-up and analyzed separately. Finally, to ascertain the influence of second-look endoscopy on the results, studies that performed this procedure were also analyzed separately.

Peto odds ratios and 95% confidence intervals were used for comparisons. Prior to meta-analysis, the heterogeneity of results was assessed by means of a Q test. Because of the low power of the test, a cutoff \( P \) value of 0.20 was established as a threshold for homogeneity. In case of lower values indicating heterogeneity, a random-effect model was used for the analysis. If no heterogeneity was observed, odds ratios for all studies were pooled in a global odds ratio by means of a fixed-effects model.

All results were obtained using the freeware program Review Manager 4.1.3. The statistical tests and formula implemented in RevMan are described in the RevMan User Guide.

### Results

#### Included and Excluded Studies

The preliminary search identified 27 studies (26 in English, 1 in Spanish, and none in French). A wider search including articles in other languages did not find any additional papers suitable for inclusion. Eleven studies were excluded from further analysis. Reasons for exclusion are outlined in Table 2. Sixteen studies were included in the meta-analysis. Characteristics of the studies are shown in Tables 1, 3, and 4.

#### Quality Assessment

The articles included ranged in quality from 0.38 to 0.88. Individual assessment of quality is shown in Table 3. Most of the studies were published as full papers and were rated high in the quality scores.

#### Epinephrine vs. Epinephrine and a Second Endoscopic Method

Sixteen articles compared epinephrine injection vs. epinephrine plus other endoscopic methods for the endoscopic treatment of peptic ulcers. A total of 1673 patients were included. The further bleeding rate in the epinephrine group was 155 of 840 (18.4%) vs. 88 of 833 (10.6%) patients in the combined therapy group. Peto odds ratio was 0.53 (95% CI: 0.40–0.69) (Figure 1). The need for emergency surgery was evaluated in 15 studies with a total of 1588 patients. In the epinephrine group, 90 of 795 (11.3%) patients needed surgical intervention and 60 of 793 (7.6%) in the combined therapy. Peto odds ratio was 0.64 (95% CI: 0.46–0.90) (Figure 2). The mortality rate was evaluated in 15 studies and 1588

### Table 2. Reasons for Excluding Articles

<table>
<thead>
<tr>
<th>Study</th>
<th>Reasons for exclusion</th>
</tr>
</thead>
</table>
| Pescatore et al.⁸   | Preliminary results of Pescatore et al.⁷
| Male et al.⁹        | Preliminary results of Lin et al.²⁰                                    |
| Gevers et al.¹⁰     | Combines epinephrine plus polidocanol plus hemoclip                      |
| De Goede et al.¹¹   | Preliminary results of Givers et al.¹⁰                                    |
| Chung et al.¹²      | Preliminary results of Chung et al.²²                                    |
| Chung et al.¹³      | Preliminary results of Chung et al.²³                                    |
| Chung et al.¹⁴      | Not randomized                                                           |
| Chua et al.¹⁵       | Not randomized                                                           |
| Buffoli et al.¹⁶    | Does not specify number of patients in each group                         |
| Dedeu et al.¹⁷      | Does not specify number of patients in each group                         |

### Table 3. Characteristics of the Studies Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (N)</th>
<th>Quality</th>
<th>Additional treatment</th>
<th>Second look</th>
<th>Medical treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balanzo et al.²⁹</td>
<td>64</td>
<td>0.73</td>
<td>Thrombin injection</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Choudari and Palmer²⁰</td>
<td>107</td>
<td>0.79</td>
<td>Ethanolamine injection</td>
<td>Yes</td>
<td>H2 antagonists</td>
</tr>
<tr>
<td>Chung et al.²¹</td>
<td>83</td>
<td>0.82</td>
<td>Hemoclip</td>
<td>Yes</td>
<td>Ranitidine 50 mg/6 h IV</td>
</tr>
<tr>
<td>Chung et al.²²</td>
<td>196</td>
<td>0.77</td>
<td>Sodium tetradecyl sulfate</td>
<td>Yes</td>
<td>AntiH2</td>
</tr>
<tr>
<td>Chung et al.²³</td>
<td>160</td>
<td>0.75</td>
<td>Ethanol injection</td>
<td>Yes</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Chung et al.²⁴</td>
<td>270</td>
<td>0.88</td>
<td>Heat probe</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Garrido et al.²⁵</td>
<td>85</td>
<td>0.59</td>
<td>Polidocanol injection</td>
<td>No</td>
<td>Not specified</td>
</tr>
<tr>
<td>Kubbha et al.²⁶</td>
<td>140</td>
<td>0.83</td>
<td>Thrombin injection</td>
<td>No</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lee et al.²⁷</td>
<td>60</td>
<td>Abstract</td>
<td>Ethanol injection</td>
<td>No</td>
<td>Not specified</td>
</tr>
<tr>
<td>Lin et al.²⁸</td>
<td>64</td>
<td>0.74</td>
<td>Ethanol injection</td>
<td>No</td>
<td>Ranitidine or cimetidine</td>
</tr>
<tr>
<td>Lin et al.²⁹</td>
<td>64</td>
<td>0.64</td>
<td>Bipolar electrocoagulation</td>
<td>Yes</td>
<td>Omeprazole 40 mg/6 h IV</td>
</tr>
<tr>
<td>Loizou and Brown³⁰</td>
<td>42</td>
<td>0.70</td>
<td>NYAG laser</td>
<td>No</td>
<td>Ranitidine 300 mg/12 h PO</td>
</tr>
<tr>
<td>Pescatore et al.³¹</td>
<td>135</td>
<td>0.76</td>
<td>Fibrin glue injection</td>
<td>Yes</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sollano et al.³²</td>
<td>61</td>
<td>0.38</td>
<td>Polidocanol injection</td>
<td>No</td>
<td>Not specified</td>
</tr>
<tr>
<td>Villanueva et al.³³</td>
<td>63</td>
<td>0.86</td>
<td>Polidocanol injection</td>
<td>Yes</td>
<td>Ranitidine</td>
</tr>
<tr>
<td>Villanueva et al.³⁴</td>
<td>79</td>
<td>Abstract</td>
<td>Hemoclip</td>
<td>No</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

IV, intravenously; PO, per os.
patients, with a total of 41 of 795 (5.1%) patients in the epinephrine group and 21 of 793 (2.6%) in the combined therapy group. Peto odds ratio was 0.51 (95% CI: 0.31–0.84) (Figure 3). In addition, 10 studies, including 1118 patients, reported data about complications of endoscopic therapy. The number and type of complications in each group are detailed in Table 4. Significant complications were found in 6 of 560 (1.1%) patients in the epinephrine group and in 6 of 558 patients (1.1%) in the combined therapy group. Peto odds ratio was 1.01 (95% CI: 0.91–1.13).
CI: 0.32–3.16). No significant heterogeneity was found in any of the analyses.

Epinephrine vs. Epinephrine and a Second Injected Agent

All articles that compared substances administered by endoscopic injection (sclerosants such as ethanol, polidocanol, ethanolamine, or tetradecyl sulfate; adhesive agents such as cyanoacrylate, and thrombotic substances such as a fibrin glue or thrombin) were analyzed together. Eleven studies with 1135 patients were included. The further bleeding rate was 108 of 575 (18.8%) patients in the epinephrine group and 68 of 560 (12.1%) in the combined therapy group. Peto odds ratio was 0.60 (95% CI: 0.43–0.82).

The need for surgery was evaluated in 10 studies with a total of 1050 patients. Fifty-nine of 530 (11.1%) patients in the epinephrine group and 49 of 520 (9.4%) in the combined therapy group needed surgical intervention; Peto odds ratio was 0.82 (95% CI: 0.55–1.22). Mortality rate was evaluated in 10 studies with a total of 1050 patients. In the epinephrine group, 28 of 530 patients died (5.3%) vs. 11 of 520 (2.1%) in the combined group; Peto odds ratio was 0.41 (95% CI: 0.21–0.77).

Epinephrine vs. Epinephrine and Mechanical Endoscopic Methods

Two studies analyzed the efficacy of adding a mechanical hemoclip to achieve hemostasis in bleeding peptic ulcers. A total of 162 patients were evaluated. The further bleeding rate was 15 of 78 (19.2%) in the epinephrine group and 7 of 84 (8.3%) in the combined therapy group. The Peto odds ratio was 0.40 (95% CI: 0.16–0.98). Both studies evaluated the need for surgery. Nine of 78 (11.5%) patients in the epinephrine group and 2 of 84 (2.4%) in the combined therapy group required surgical intervention. Peto odds ratio was 0.24 (95% CI: 0.07–0.82). Mortality rate was 3 of 78 (3.8%) patients in the epinephrine group compared with 1 of 84 (1.2%) in the combined therapy group. Peto odds ratio was 0.34 (95% CI: 0.05–2.42).

Epinephrine vs. Epinephrine and Thermal Methods

Three studies compared epinephrine alone with epinephrine combined with thermal hemostatic methods (contact heat probe, N-YAG laser or bipolar electrocoagulation). A total of 576 patients were evaluated.
The further bleeding rate was 32 of 187 (17.1%) patients in the epinephrine group vs. 13 of 189 (6.9%) in the combined therapy group. Peto odds ratio was 0.37 (95% CI: 0.19–0.69). The surgery rate was analyzed in 376 patients, being required in 22 of 187 (11.8%) patients in the epinephrine group and in 9 of 189 (4.8%) in the combined therapy group. Peto odds ratio was 0.40 (95% CI: 0.19–0.83). The mortality rate was also analyzed in 376 patients. It was 10 of 187 (5.3%) patients in the epinephrine group and 9 of 189 (4.8%) in the combined therapy group. Peto odds ratio was 0.88 (95% CI: 0.35–2.23).

Further Bleeding Rates in Patients With Active Hemorrhage (Forrest Ia or Ib) or Nonbleeding Visible Vessel (Forrest IIa) or Adherent Clot (Forrest IIb)

Eleven studies with a total of 913 patients analyzed further bleeding rates when peptic ulcers were actively bleeding (spurting or oozing, Forrest Ia or Ib).19–21,25,26,30,33 Eighty-nine of 453 (19.6%) patients further bled in the epinephrine alone group vs. 54 of 460 (11.7%) in the combined therapy group. Peto odds ratio was 0.55 (95% CI: 0.38–0.79).

Seven studies with a total of 353 patients gave data on peptic ulcers with nonbleeding visible vessel (Forrest IIa).19–21,25,26,30,33 Twenty-three of 182 (12.6%) patients in the epinephrine alone group presented further bleeding vs. 14 of 171 (8.2%) in the combined therapy group. Peto odds ratio was 0.62 (95% CI: 0.31–1.22). Only 1 study25 included patients with adherent clot (Forrest IIb), and, therefore, a meta-analysis could not be performed.

Initial Failure of Hemostasis vs. Recurrence During Follow-up

Thirteen studies gave separate data on the patients who did not achieve initial hemostasis.19,21,24,26–33 A total of 1402 patients were evaluated. Of these, 20 of 703 (2.8%) patients in the epinephrine group and 17 of 699 (2.4%) in the combined therapy group presented initial failure of hemostasis. Peto odds ratio 0.84 (95% CI: 0.44–1.62).

In the 1365 patients with initial hemostasis, the rate of recurrence of bleeding during follow-up was 108 of 683 (15.8%) in the epinephrine group and 61 of 682 (8.9%) in the combined therapy group. Peto odds ratio was 0.53 (95% CI: 0.38–0.73).
Role of Second Look Endoscopy

Ten studies performed one or more second look endoscopies 24 to 72 hours after the initial technique.19–24,29,31–33 When active bleeding or persistent high-risk stigmata were observed, a second therapeutic procedure was performed. A total of 1202 patients were included in these studies. The further bleeding rate was 95 of 605 (15.7%) patients in the epinephrine group and 68 of 597 (11.4%) in the combined therapy group. Peto odds ratio was 0.69 (95% CI: 0.49–0.96).

Six studies with a total of 470 patients did not schedule a second-look endoscopy.25–28,30,34 Sixty of 235 (25.5%) patients in the epinephrine group further bled after the first endoscopic procedure compared with 20 of 235 (8.5%) in the combined therapy group. Peto odds ratio was 0.27 (95% CI: 0.15–0.46).

Discussion

Guidelines agree that there is no clear evidence that any technique is superior to injection of epinephrine alone for the endoscopic treatment of high-risk bleeding peptic ulcers.3–4 However, a few individual studies have shown a significant reduction in the further bleeding rates with the addition of a second endoscopic treatment24–26,29 (Figure 1). Advancing further in this direction, the results of the present meta-analysis clearly suggest that combined therapy is the treatment of choice for high-risk bleeding peptic ulcers. Although the absolute improvements in hemostatic efficacy are relatively small (from 5% to 10%), they represent a 30% to 50% reduction in the relative risk of a recurrent hemorrhage. Failure of endoscopic therapy is the main predictor of the need for surgery and morbidity and mortality in bleeding peptic ulcer patients.35 Therefore, it is no surprise that reduction of further bleeding rates decreased the need for surgery and improved survival.

One of the major fears about using combined therapy is the possible risk of gastric wall necrosis and/or perforation. The present meta-analysis shows that the risk of significant complications is very low (1.1% in the epinephrine group and 1.1% in the combined therapy group) and that there were no differences between groups. Looking at the complications in detail, induction of massive bleeding requiring surgery was the most frequent in the group of adrenaline alone; gastric wall necrosis appeared in 3 patients (2 in the combined therapy group and 1 in the adrenaline alone group), and perforation (4 patients) was observed only in the combined therapy group. These complications appeared with both further injection and thermal methods. Thus, it would seem that perforation or necrosis was slightly more frequent in the combined therapy group (6/558 patients) than in the adrenaline alone group (1/560 patients), although this difference did not achieve statistical significance. In any case, this possible small increase in the risk of perforation or necrosis is clearly compensated for by the benefits in reducing further bleeding, which result in a significant decrease in the need for surgery and mortality; it is therefore not a reason for avoiding combined therapy.

The subanalysis shows many interesting data: first, that the improvement in prognosis seems to be more evident in higher risk patients—that is, those with Forrest I bleeding ulcers—or when no second-look endoscopy is performed. However, because the basal risk of further bleeding is much lower in Forrest II patients or when repeated endoscopy is performed, the sample size needed to demonstrate a significant reduction in further bleeding may be larger than those available for the subanalysis. Second, that beneficial effects of combined therapy seem to derive from the reduction of recurrent bleeding during follow-up rates, and the ability to achieve initial hemostasis seems very similar in the 2 groups.

The subanalysis also raises many unanswered questions. First, although it could be taken to suggest that the efficacy of the injection of a second agent is similar to that achieved with thermal and mechanical methods, this interpretation should be treated with extreme care. The only conclusion that can be drawn from the study is that, whichever second treatment is used, combined therapy seems to work better than adrenaline alone. By contrast, it cannot be concluded that a particular form of treatment is equal to another. There are 2 main reasons for this. First, the subgroups (further injection, thermal, or mechanical methods) include different procedures, which may present heterogeneous activity. In fact, each endoscopic treatment had different characteristics: epinephrine produces vasoconstriction, vessel compression, and platelet aggregation but seems not to induce permanent thrombosis in blood vessels.36 Sclerosant agents such as polidocanol or ethanol can produce thrombosis of vessels favoring hemostasis, although they may also induce significant tissue injury.37,38 Whether human thrombin injection could reduce the risk of tissue damage remains unclear, and thrombin is more expensive than other additional treatments.39 Thermal agents also produce thrombosis of vessels and also risk, therefore, of damaging tissue. Among them, laser photocoagulation seems to be associated with higher risks of perforation, optical hazard, high cost, and imperfect hemostatic effect. Mul-
tipolar electrocoagulation and heater probe thermocoagulation have been reported to produce excellent results; they are also less expensive and more easily portable than a laser. Mechanical methods also closed the vessel. They were also associated with few complications, but there was a certain amount of technical difficulty in applying the hemoclip on the posterior wall of the proximal body and cardia of the stomach and on the posterior wall of the duodenum because of the requirement that the hemoclip meet the lesion at a right angle.

Even more important, the statistical treatment of the study is not designed to compare additional treatments head to head. In fact, we lack randomized trials comparing different additional treatments after epinephrine injection and must await future comprehensive studies to establish which is the best therapy to add to adrenaline.

Nor did our study determine whether combined therapy is better than sclerosants or thermal or mechanical methods alone. The evidence in the literature to suggest so is scarce. In a small study Lin et al. found that combined therapy seems better than bipolar electrocoagulation alone. Also, a recent meta-analysis concluded that combined injection is superior to a sclerosant alone. In any event, the clinical relevance of this question may be minor. Adrenaline injection is cheap, easy to perform, and safe. In addition, according to our analysis, epinephrine is as good as combined therapy for achieving initial hemostasis. Therefore, by controlling active bleeding, it could allow a better endoscopic view and a more accurate targeting of the additional therapy. Therefore, there are few medical or economic arguments against adrenaline injection.

An important methodologic point about the study was the definition of the primary end point. The marked heterogeneity in defining further bleeding among the studies precluded the definition of a homogeneous, predetermined criteria for the primary end point. We therefore accepted the definition established for each study. Further bleeding definitions are shown in Table 1. Because the analysis includes only randomized, comparative studies, the criteria were similar for the 2 groups (adrenaline alone and combined therapy) in each study, thus allowing further comparison. Furthermore, endoscopic confirmation of bleeding was required, thus reducing heterogeneity. Finally, results on further bleeding are consistent with those of variables with a lower degree of subjectivity in their evaluation, such as the need for surgery or mortality. This indirectly confirms that the assessment of further bleeding was adequate.

An interesting question is how other therapeutic approaches—such as the use of high-dose PPI or second-look endoscopy—could influence the efficacy of combined therapy. The use of high-dose proton pump inhibitors in bleeding peptic ulcer patients is gaining acceptance. The evidence clearly suggests that these drugs reduce the risk of rebleeding. However, many points remain unclear, such as the cost effectiveness of this approach, the ideal drug dosage, and whether this strategy should be reserved for patients at high risk of rebleeding. Both combined therapy and proton pump inhibitor infusion are safe and comfortable for the patient. Furthermore, there is no reason to suspect that associating high-dose proton pump inhibitors and combined endoscopic therapy will show ill effects or decrease efficacy. Therefore, although the extent of the benefit of combining the 2 approaches remains uncertain, it seems reasonable to do so until more evidence becomes available.

As far as second-look endoscopy is concerned, a recent meta-analysis showed that, although scheduled second-look endoscopies reduced the rebleeding rate, they did not decrease the need for surgery or mortality. Recently, it has been suggested that selective second-look endoscopy for selected high-risk patients could be a cost-effective approach. However, this strategy exposes patients to uncomfortable and somewhat risky procedures and increases the workload of the endoscopy unit. The results of the present study indirectly suggest that the effect of associating a second hemostatic procedure after epinephrine injection is similar to that obtained using second-look endoscopy. For all these reasons, it remains unclear whether second-look endoscopy offers any added benefit to combined therapy associated with proton pump inhibitor infusion.

In conclusion, the present study shows that adding a second endoscopic procedure after adrenaline injection reduces the rates of recurrence in high-risk bleeding peptic ulcer patients, thus reducing the need for surgery and mortality. Currently, there is no justification for preferring a specific second hemostatic method after adrenaline injection. In view of the evidence—and while we await the results of further studies—combined therapy should be considered as the standard procedure.

References


