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Endoscopic treatment for high-risk bleeding peptic ulcers: a comparison of epinephrine alone with epinephrine plus ethanolamine

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Abstract

Background Among the various methods of combined endoscopic therapy for high-risk bleeding peptic ulcers the use of adrenaline followed by injection of ethanolamine is minimally demanding in terms of the endoscopic skills and instrumentation but has not been adequately studied. The aim of the present study is to determine whether the injection of ethanolamine in combination with epinephrine compared to injection of epinephrine alone reduces rebleeding rates, need for surgery and overall mortality of patients with bleeding ulcers.

Methods Patients with ulcers and endoscopic features indicative of a high risk for spontaneous recurrent bleeding were included. High risk was defined by the Forrest classification. Patients were assigned to injection of epinephrine alone (n = 284) or epinephrine plus ethanolamine (n = 131).

Results Initial hemostasis was achieved in 96% of patients in both groups. We detected significant difference in rates of recurrent bleeding, 16.4% vs. 8.7%, for epinephrine and epinephrine plus ethanolamine respectively ($P<0.05$). When patients were stratified according to Forrest criteria, no significant difference could be found, although there was a trend towards less recurrent bleeding in the case of dual injection therapy in all patient subgroups. There was no significant difference in the proportions of patients who required surgery, 7.7% vs. 7.6% respectively. Mortality was equal (3.2 vs. 3.1%) in the two groups. No major complications from endoscopic treatment were observed in either group.

Conclusion Adding ethanolamine to epinephrine for injection treatment of bleeding peptic ulcers decreases bleeding recurrence rates and represents a safe endoscopic treatment for high-risk bleeding ulcers.

Keywords bleeding peptic ulcer, endoscopic injection, epinephrine, ethanolamine

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Introduction

Ulcers are the major source of upper gastrointestinal (UGI) bleeding and represent the single cause of bleeding in more than half of the cases. Endoscopic or surgical intervention is needed in a subgroup of patients (20-30%) in whom bleeding continues or relapses resulting in an overall mortality of 8-10% [1-4]. Endoscopic hemostasis has been found to decrease the frequency of recurrent bleeding, transfusion needs and length of hospitalization [1,5,6]. Most importantly, meta-analysis studies have proven that endoscopic hemostasis reduces the need for surgery and decreases mortality [5-7].

Endoscopic therapy can be broadly categorized into injection therapy, thermal coagulation, and mechanical hemostasis. When analyzed separately, mostly in early studies, no single hemostatic technique was found to be superior [5,6]. That resulted in the consensus statement that all endoscopic

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Conflict of Interest: None

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techniques are equally efficient, and the decision of which one to use should be based on its availability and the personal experience/preference of the endoscopist [7,8].

Despite the use of endoscopic therapy, bleeding recurs in 4-30% of patients [9]. This population of increased recurrence risk is characterized by the presence of major stigmata of recent hemorrhage on initial endoscopy as defined by the Forrest classification [10]. Therefore, newer recommendations favor combined therapy, in which the injection of diluted epinephrine precedes a second hemostatic technique such as thermal coagulation [11]. In a systematic review aimed to compare the combined endoscopic therapy with epinephrine injection alone, a total of 16 randomized trials involving 1,763 patients were analyzed [12]. The addition of a second procedure such as injection therapy, thermal coagulation, or mechanical hemostasis reduced the rate of recurrent bleeding from 18.8% to 10.4% and that of emergency surgery from 10.8% to 7.1%. Furthermore, mortality rate decreased from 5% to 2.5%. However, the choice of the second hemostatic technique -has yet to be established since subgroup analysis showed that the risk of further bleeding decreased regardless of which second procedure was applied [12].

Among the various methods of combined endoscopic therapy the use of adrenaline followed by injection of ethanolamine is minimally demanding in terms of the endoscopic skills and instrumentation. However, it has not been adequately studied, especially following the widespread use of systemic treatment with proton pump inhibitors (PPIs) that may have influenced the outcome of acute UGI bleeding [13,14]. We studied the effectiveness of dual injection therapy with adrenaline plus ethanolamine as compared with the injection of adrenaline alone for the treatment of acute UGI ulcer bleeding.

Materials and Methods

From January 1996 to December 2002, we prospectively collected data from 2,968 patients presenting to "G. Gennimatas" General Hospital of Athens with acute UGI bleeding. Patients were included in the study if they were over 18 years of age and had overt UGI bleeding (melena or hematemesis), and a bleeding peptic ulcer identified as the source of bleeding during initial endoscopy. Only those patients with ulcers that had endoscopic features indicative of a high risk for spontaneous recurrent bleeding were selected. High risk was defined by the Forrest classification: stage Ia (spurting bleeding). Ib (oozing), IIa (non bleeding visible vessel), and IIb (adherent clot). Patients with other sources of bleeding were excluded. Other exclusion criteria were: pregnancy, inability or unwillingness to consent to endoscopic therapy, severe bleeding that precluded endoscopic treatment, malignancy, or >2 comorbidities including coronary artery disease (CAD), chronic obstructive airway disease (COAPD)/ asthma, chronic renal insufficiency requiring dialysis (CRF), and previous stroke with residual disability. Informed consent was obtained from all patients for recruitment into the study.

Peptic ulcer was the source of bleeding in 2053 (69%) of the 2.968 patients. Of these patients, 415 with high-risk ulcers at first endoscopy that required endoscopic treatment were included in the study. Among those patients, 131 patients were assigned to receive combined endoscopic therapy with epinephrine injection plus ethanolamine oleate 5% (Group B). Treatment efficacy was compared to "standard" endoscopic treatment, i.e., epinephrine injection alone, offered to the remaining 284 patients (Group A). For the patients assigned to the epinephrine group (A), epinephrine (1:10,000 dilution) was injected in 1-2 mL aliquots by multiple punctures into and around the bleeding point until all bleeding stopped. At least 6 mL of epinephrine were injected. For the patients assigned to the ethanolamine group (B), epinephrine was injected as outlined above. Then the remaining epinephrine was washed out from the injection needle and a 5% solution of ethanolamine oleate was injected directly into or closely adjacent to the bleeding point. The volume of ethanolamine injected was 2-3 mL for the duodenal and 3-6 mL for the gastric ulcers. Following endoscopic therapy the lesion was observed for 1-2 min and was repeatedly washed with a total of 120-200 mL of water to confirm successful initial hemostasis. All patients underwent endoscopy within 24 hours of admission. Patients who presented with circulatory instability underwent emergency endoscopy after initial resuscitation. Five experienced endoscopists (AXK, BEM, BXN, IK, AH) proficient at endoscopic treatment of bleeding peptic ulcers formed our gastrointestinal bleeding team. Treatment procedures were performed by these endoscopists or trained registrars under their supervision.

After endoscopy, all patients were closely monitored and blood transfusion was given to maintain the hemoglobin level above 9-10 g/dL. lnitial hemostasis was defined as endoscopically verified cessation of bleeding for at least 2 min after the endoscopic treatment and no evidence of recurrence for the first 24 hours of observation. Recurrent bleeding was defined as signs of bleeding within 10 days of presentation: vomiting of fresh blood, passage of melena or both after the early stabilization of pulse, blood pressure, and hemoglobin concentration; hypotension (systolic pressure <90 mmHg); or a decrease in the hemoglobin concentration by at least 2 g/dL over a 24-hour period. If recurrent bleeding was suspected, a second therapeutic endoscopy was performed. If active bleeding or a fresh blood clot in the ulcer base was found, recurrent bleeding was considered confirmed and re-treatment was performed with the same modality as before. Permanent hemostasis was defined as the absence of recurrent bleeding during the 10-day period after initial or secondary endoscopic hemostasis. Failed endoscopic treatment at first or second therapeutic endoscopy, or a total blood transfusion requirement of greater than 8 units to maintain a hemoglobin level of 10 g/dL, combined with clinical evidence of continuing bleeding, were considered as indications for surgery. Omeprazole (AstraZeneca, Södertälje, Sweden) was administered intravenously (40 mg per 24 hours) during the period in which the patient remained fasting or by mouth as soon as oral intake was possible. Mortality was defined as death

within 30 days of admission that could be related or not to the bleeding episode. The primary outcome of the study was the recurrence of bleeding. Secondary outcome measures were successful initial endoscopic hemostasis, blood transfusion requirements, number of patients requiring surgery and mortality within 30 days.

Continuous variables were summarized by the mean value and standard deviation (SD) and compared using Student's t-test. The chi-square test and the Fisher exact test were used to compare categorical variables. Significance was established at a *P* value of <0.05 for a two-tailed test.

Results

Of the 415 participating patients 313 (75.4%) were males and 102 (24.6%) females with a mean age of 62.8 (range: 18-99) years. A total of 150 (36.1%) had a previous history of peptic ulcer disease, and 129 (31.1%) had at least one prior bleeding episode. Among these patients 217 (52.3%) had received non-steroidal anti-inflammatory drugs or aspirin within the last 10 days prior to admission. Only a small proportion of patients 20 (4.8%) had minor coagulation defects mostly due to coumarin therapy. There were no significant differences between the treatment groups with regard to age, gender, history of peptic ulcer disease and ulcer bleeding, gastric surgery, coagulopathy or the use of non-steroidal anti-inflammatory drugs at presentation. There was a significant difference in the presenting symptom between the two groups with more patients presenting with hematemesis instead of melena in group B. However this difference was not accompanied by significant differences in either the hematocrit level (HCT) or the presence of shock [Table 1].

A duodenal ulcer was the source of bleeding in the majority of cases 232 (N=232, 55.9%), and the ulcer was mostly located on the anterior wall of the duodenum 141 (N=141, 60.8%). A gastric ulcer was the source of bleeding in 135 (32.5%) of cases, with the antrum being the commonest location (N=57, 42.2%). The endoscopic findings indicating a high risk of recurrent bleeding were: spurting in 19 (4.6%), oozing in 161 (38.8%), non-bleeding visible vessel in 172 (41.4%), and an adherent clot in 63 (15.2%) of cases. Fresh blood or blood clots in the stomach were found more frequently in the group of patients that received combined endoscopic treatment (B) [Table 2]. There were no other significant differences in endoscopic findings between the treatment groups including ulcer type, ulcer size or endoscopic findings of active bleeding (Forrest grades Ia, Ib) [Table 2].

Initial hemostasis in response to endoscopic treatment was comparable in the 2 groups [Table 3]. There was an overall failure of 3.4% (14/415 patients). Twelve of these 14 patients underwent emergency surgery, one patient was successfully treated with a second endoscopic therapy and one patient died. The initial hemostasis rates stratified by Forrest classification were also comparable. Group A: Ia, 9/10 (90.0%); Ib, 113/115 (98.3%); IIa, 102/105 (97.1%); IIb, 51/54 (94.4%). Group B: Ia, 8/9 (88.9%); Ib, 46/46 (100%); IIa, 63/67 (94.0%); IIb, 9/9 (100%). There were no differences between groups in terms of volume of epinephrine used during endoscopic hemostasis [Table 3]. However the additional volume of sclerosant injected in the group B was 2.8±1.4 mL, which significantly increased the total injection volume to 11.0±2.4 mL (*P*<0.001), [Table 3].

Following successful initial hemostasis, recurrent bleeding was observed in 56 (14%) patients and it occurred significantly more in the group of patients treated with epinephrine alone (45/275, 16.4%), than in the group of patients treated with combination therapy (11/126, 8.7%, *P*=0.044). Recurrent

Table 1 Patient demographics

	Group A	Group B
No.	284	131
Male gender	218 (76.8%)	95 (72.5%)
Mean age (range) (years)	63.3 (22-99)	61.8 (18-94)
Ulcer history	101 (35.6%)	49 (37.4%)
Previous ulcer bleeding	86 (30.3%)	43 (32.8%)
NSAID/aspirin	145 (51.1%)	72 (55.0%)
Coagulopathy	12 (4.2%)	8 (6.1%)
Gastric surgery	30 (10.6%)	11 (8.4%)
Shock[$]	22 (7.7%)	17 (13.0%)
Presentation		
Melena	212 (74.6%)	81 (61.8%)
Hematemesis	72 (25.4%)	50 (38.2%)[a]
HCT (mean±SD)	29.4±7.5	28.3±6.8

[a]P<0.05, [$]BP<90mmHg and /or HR>110bmp
HCT, Hematocrit; BP, Blood Pressure; HR, Heart Rate

Table 2 Endoscopic findings

	Group A	Group B
Ulcer size ≥2cm	42 (19.4%)	26 (24.1%)
Active bleeding ulcer	125 (44.0%)	55 (42.0%)
(Forrest grade I – spurting/oozing)		
Fresh blood/clots in stomach	88 (60.3%)	47 (81%)[b]
Ulcer Types		
Esophagogastric junction	8 (2.8%)	9 (6.1%)
Gastric ulcer	87 (30.6%)	48 (36.6%)
Duodenal ulcer	164 (57.7%)	68 (51.9%)
Stomal ulcer	25 (8.8%)	7 (5.3%)

[b]*P<0.01*

Table 3 Results in the two treatment groups

	Group A	Group B
Initial hemostasis	275 (96.8%)	126 (96.2%)
Epinephrine (mL)	8.0 (2.8)*	8.2 (3.4)*
Recurrent bleeding	45 (16.4%)	11 (8.7%)[a]
Second hemostasis	11/16 (68.8%)	5/7 (71.4%)
Surgery	22 (7.7%)	10 (7.6%)
Blood Transfusion (units)	2.7 ± 2.5*	2.6 ± 3*
Mortality	9 (3.2%)	4 (3.1%)

[a]*P<0.044, *Mean ± SD*

bleeding was more frequent when the initial endoscopic stigmata were spurting (17.6%) or a non-bleeding visible vessel (18.2%) and it occurred less frequently when an adherent clot (13.3%) or oozing (9.4%) was found. Combined endoscopic therapy decreased re-bleeding rates by almost 50% irrespective of the stigmata found [Table 4].

Major complications from endoscopic treatment, perforation and/or endoscopic therapy induced bleeding were minimal in both treatment groups. No patient suffered perforation and/or gastric wall necrosis. Induction of massive bleeding requiring surgery during endoscopy occurred in 4/415 (1%) of our patients but no difference was observed between the two treatment groups. Severe abdominal pain following hemostasis was observed slightly more frequently in the dual injection therapy group (9/131, 6.9%) than in the epinephrine group (14/248, 5.6%) and the difference was not significant. All patients who developed significant pain were successfully treated with analgesics.

Twenty three of the 56 patients (41.1%) with recurrent bleeding underwent a repeat therapeutic endoscopic procedure using the same technique as in the initial endoscopy. Sixteen of 23 patients belonged to group A and were re-treated with epinephrine, whereas 7 of 23 patients belonged to group B and were re-treated with combination therapy. The repeat endoscopic hemostasis was equally successful in both groups (68.8% vs. 71.4%, respectively, Table 3). Twenty nine patients from group A and 4 patients from group B with recurrent

Table 4 Bleeding recurrence according to Forrest classification

	Group A N (%)	Group B N (%)
Ia (Spurting)	2 (22.2%)	1 (12.5%)
Ib (Oozing)	12 (10.6%)	3 (6.5%)
IIa (Non bleeding visible vessel)	23 (22.5%)	7 (11.1%)
IIb (Adherent clot)	8 (15.7%)	0 (0%)

bleeding were re-treated with combination therapy using epinephrine injection followed by either heater probe or hemoclip application and therefore were excluded from the analysis. Overall, there were no significant differences between the groups in terms of the need for surgery (32/415, 7.7%) and the overall mortality (13/415, 3.1%) [Table 3].

Discussion

Bleeding peptic ulcer is a potentially life-threatening condition. Endoscopic treatment is well accepted as the first-line treatment especially in that subgroup of patients with major stigmata as defined by the Forrest classification. In an effort for more effective hemostasis and to reduce recurrent bleeding, a number of new treatment methods especially thermal devices (heater probe [HP], argon plasma coagulator [APC]) or mechanical methods (hemoclips) are now being combined with epinephrine injection therapy. Although the combination of epinephrine injection followed by thermocoagulation with a HP is considered the current standard therapy, treatment with injection of epinephrine alone is still widely used [15]. One of the reasons might be that combined therapy has not adequately proven its superiority over the injection of epinephrine alone in individual studies [15,16]. Furthermore, the use of contact or mechanical devices is not available in all hospitals and it is more technically demanding. Difficult ulcer location and residual bleeding after adrenaline injection may result in unsatisfactory visualization of the bleeding site and unsuccessful application.

Epinephrine alone induces vessel compression, vasoconstriction, and platelet aggregation, but does not induce vessel thrombosis. Therefore the addition of sclerosing agents such as ethanol, ethanolamine or polidocanol would be advantageous in theory. Despite the theoretical advantage of sclerosant agents, previous clinical trials demonstrated no significant benefit of combination therapy compared to epinephrine alone [17-23]. It is likely that this is the result of the small number of patients in some of the above studies, combined with the fact that epinephrine monotherapy is in most cases adequate to control acute ulcer bleeding. This possibility is highlighted in two recent meta-analyses that examined combination therapy versus monotherapy in the endoscopic treatment of high-risk bleeding ulcers [9,12]. Both studies examined separately the trials that compared epinephrine versus epinephrine and a second injected agent. They considered a total of 11 and 10 trials involving 1,135 and 1,075 patients respectively, and they consistently report a significant reduction in the recurrence risk when dual injection therapy was used [9,12].

The results of the present study are comparable to the reported results from these two meta-analyses on major outcomes like initial hemostasis rates, rebleeding rates, the need for surgery and overall mortality. Specifically, we report initial hemostasis rates of 96.8 and 96.2%, equivalent to the two treatment groups, and suggest that epinephrine and dual injection therapy are equally effective for initial hemostasis. Equal rates of initial hemostasis are also observed in the Vergara M. et al [12] meta-analysis; i.e., initial hemostasis rate of 97.3% in the epinephrine group versus 96.4% in the dual injection therapy group.

Furthermore, we demonstrate a nearly twofold reduction in re-bleeding rates from 16.4% in the monotherapy to 8.7% in the dual injection therapy group. Both meta-analyses of Vergara M. et al [12] and Marmo R. et al [9] also report a significant reduction in further bleeding by dual injection therapy. Rebleeding rates in our study are slightly lower than the average reported in previous studies for epinephrine monotherapy (18.8%) and dual injection therapies (12.1%) [12]. One possible explanation for the latter could be the use of PPIs, resulting in more efficient acid-suppression in the present study [24].

We attribute this favorable effect of dual injection therapy to the hemostatic properties of ethanolamine rather than to an increase in the total injection volume. In our study the volume of sclerosant added in the combination therapy group significantly increased the injection volume. A recent study that addressed the optimal volume of epinephrine for endoscopic injection in patients with Forrest Ia and Ib stigmata reports a 20.3% bleeding recurrence rate using 20 mL of adrenaline, which is comparable to the 19.6 % re-bleeding rate we observed in our patients with Ia or Ib stigmata in the epinephrine group [25]. In the specific subgroup of patients the addition of ethanolamine in our study resulted in a minimal increase in the injection volume from 8.4±3.3 to 9.3±3.5 mL, far below the optimal injection volume reported by Liou et al [25], but reduced re-bleeding rates to 9.1%.

Although the absolute improvement in hemostasis by the addition of ethanolamine is relatively small, it represents an almost 50% reduction in the relative risk for recurrent bleeding, one of the major factors contributing to increased morbidity and mortality in patients with bleeding ulcers [26]. Therefore, it seems likely that the reduction in further bleeding would decrease the need for surgery and improve survival. In the present study, we failed to detect a reduction in the need for surgery and overall mortality in the combination treatment group. However, the size of the study is inadequate to properly address this question and exclude an effect on the above outcomes. No significant effect of the combination therapy on the need for surgery is also reported in the meta-analysis of Vergara M. et al [12] but the mortality was significantly reduced from 5.3 to 2.1% by the use of dual injection therapy.

The effectiveness of endoscopic clipping has been recently analyzed by two meta-analyses [27,28]. The existing published data suggest that the dual-injection therapy used in the present work has comparable results to the results reported from the use of hemoclips alone for the treatment of bleeding ulcers. Specifically, pooled data from 9 randomized clinical trials with a total number of 334 patients demonstrate that endoscopic clipping alone results in initial hemostasis of 92.5%, rebleeding rates of 9.7%, need for surgery in 3.3% of cases and an overall mortality of 3.3% [27,28]. The combination of endoscopic clipping with epinephrine injection therapy might be superior, resulting in initial hemostasis of 94.9%, rebleeding rates of 6.0%, need for surgery in 1.9% and an overall mortality of 1.3% for a total number of 159 patients participating in

four trials [27]. However, more data are needed to establish significant differences of the clips combined with injections versus endoscopic clipping alone or dual-injection therapy. In clinical practice, hemoclip attachment to the bleeding lesion at the correct angle might be technically difficult [29,30]. This is especially true for lesions located over the posterior wall of the body or duodenal bulb or with the lesser curvature of the upper body. That could be the reason for the slightly lower rates of initial hemostasis reported for the use of hemoclips [27]. Our data suggest that for those difficult to approach lesions dual-injection therapy might be a reasonable alternative.

A recent randomized controlled trial with a total of 185 patients has compared the efficacy of epinephrine injection therapy combined with APC or HP for the treatment of bleeding peptic ulcers [31]. The results of the trial for both modalities are comparable to our results. Specifically the combination of HP or APC with epinephrine injection resulted in an initial hemostasis in 95.9 vs. 97.7%, bleeding recurrence in 21.6 vs. 17.0%, requirement for emergency surgery in 9.3% vs. 4,5% and a mortality of 6.2 vs. 5.7% for the two treatments respectively [31]. The addition of thrombin injection to the HP treatment evaluated by Church NI et al, does not confer any additional benefit over HP [32]. Furthermore, the use of HP has been associated with the occurrence of free perforation in 1-1.5% of cases [31-33]. The possible risk of gastric wall necrosis, perforation or induction of intractable bleeding is one of the major fears about using injection therapy with sclerosing agents [34]. In the present study no free perforation was observed and the cases of endoscopically induced bleeding that required surgery occurred with similar frequencies in both groups. Reported complication rates are similar or even lower that rates observed in previous studies and meta-analyses [12].

In conclusion, we herein demonstrated that combination of epinephrine plus ethanolamine injection therapy offers an advantage compared to epinephrine alone in the endoscopic treatment of high-risk bleeding ulcers. According to the recently published international consensus recommendations, epinephrine injection alone is considered suboptimal therapy and a second method such as hemoclips, thermocoagulation or sclerosant injection should be used for treating high-risk stigmata [35]. Due to the favorable safety profile and the minimal technical requirements of ethanolamine injection, we believe that it might represent a reasonable alternative especially when newer methods such as hemoclips or thermal methods are either unavailable or technically difficult to apply.

Summary Box

What is already known:

- The combined endoscopic therapy for high-risk bleeding peptic ulcers decreases: rate of recurrent bleeding, emergency surgery and mortality.
- The choice of the additional to adrenaline hemostatic technique has yet to be established.

What the new findings are:

- The addition of ethanolamine to epinephrine for combined injection treatment of bleeding peptic ulcers:
  - Decreases bleeding recurrence rates
  - Represents a safe endoscopic treatment for high-risk bleeding ulcers.

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