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Endoscopic dual versus monotherapy in patients bleeding from high-risk peptic ulcers

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ABSTRACT

Aim: Dual endoscopic and pharmacologic therapy is currently the standard treatment for patients with high-risk peptic ulcer bleeding. The authors assess the efficacy of dual (endoscopic and pharmacologic) therapy versus endoscopic monotherapy in reducing rates of recurrent bleeding and death in patients with high-risk peptic bleeds. **Methods:** The authors carried out a *post-hoc* analysis of data on the use of intravenous proton pump inhibitors for the prevention of rebleeding ulcers and death (from an investigator-supported multicenter randomized trial in Italy). All the patients bleeding from high-risk peptic ulcers with a successful endoscopic hemostasis were treated with epinephrine injections alone (n = 157) or in combination with thermal therapy (n = 219). **Results:** Rebleeding occurred in 20 individuals (12.7%) in the monotherapy group, and in 21 individuals (9.6%) in the dual group (P = 0.33). Seven patients (4.5%) in the former group and 2 (0.9%) in the latter group died, with a 3.6% (95% CI: 0.3 to 8.1) absolute risk reduction. The mean number of units of blood transfused were 2.7 ± 1.7 and 3.2 ± 2.5 (P = 0.14), respectively, and the mean hospital stay was 6.7 ± 3.9 and 7.1 ± 4.3 days (P = 0.40), respectively. Multivariate analysis revealed that the sole independent predictor of death was ulcer size ≥ 20 mm [odds ratio (OR) = 6.56, 95% CI: 1.57 to 27.4]. Dual endoscopic and pharmacologic therapy provided a non-significant reduction in the risk of death (OR = 0.26, 95% CI: 0.05 to 1.34). **Conclusion:** When adjuvant proton pump inhibitors were administered, dual endoscopic and pharmacologic therapy was not superior to injection monotherapy for reducing rates of rebleeding and death.

INTRODUCTION

Combination endoscopic and pharmacologic therapy is currently the standard of care for peptic ulcer patients with major upper gastrointestinal (GI) hemorrhage documented by endoscopy.[1-3] Currently, we can expect to achieve primary hemostasis in over 95% of these patients, but recurrent bleeding still occurs in 10-30% of cases.[4] However, controversies exist regarding both the optimal endoscopic therapy and the optimal dosing regimen for proton pump inhibitors (PPIs).[5] The currently accepted regimen of PPI use is as an initial intravenous bolus equivalent to 80 mg followed by an intravenous infusion equivalent to 8.0 mg/h for 72 h.[2,6,7] Nevertheless, 4 randomized trials[8-11] and 1 meta-analysis[12] failed to show superiority of continuous infusion of high-dose PPIs over regular-dose of PPIs.

Available methods to achieve hemostasis by upper endoscopy include injection therapy with different agents, thermal coagulation, and mechanical therapy with the application of hemoclips and bands. Three meta-analyses have consistently shown that epinephrine injection was less effective than other forms of endotherapy for preventing recurrent bleeding.[13-15] Calvet *et al*.[13] pooled results from 16 studies comparing epinephrine injection alone *vs*. epinephrine plus other endoscopic methods: no single study provided a statistically significant result, but analysis of the pooled data showed that the additional endoscopic treatments after epinephrine injection significantly reduced further bleeding, need for surgery, and mortality, regardless of which second procedure was applied. An updated meta-analysis that pooled 22 randomized trials proved that dual therapy was superior to epinephrine injection alone, but showed no advantage over primary thermal or mechanical monotherapy in improving the outcome of patients.[14] However, careful reading of the component trials revealed that only 5 of the 22 studies registered significantly different results between the 2 endoscopic therapies. This finding points to significant heterogeneity among the studies. In a third meta-analysis of 14 studies by Laine and McQuaid,[15] a significant benefit of adding a second modality to reduce further bleeding, surgery, and urgent intervention was apparent from 7 studies without second-look plus re-treatment, whereas results of a further 7 studies allowing assessment of outcomes beyond initial hemostasis concluded that there was no benefit of adding a second modality to epinephrine.

Clearly, there is still room for improvement in the treatment of bleeding peptic ulcers, and further studies are needed to adequately define the optimal strategy for combinations of endoscopic interventions and PPI therapy in high-risk patients. The aim of the present re-analysis of the data from a previous trial[10] was to clarify the efficacy of dual therapy versus monotherapy in reducing recurrent bleeding and death in high-risk patients with peptic ulcer disease.

METHODS

Data were extracted from a multicenter, randomized Italian trial on the use of PPIs for the prevention of rebleeding in high-risk peptic ulcer patients after endoscopic hemostasis; the main findings of this trial have been published elsewhere.[10] The original investigation was a registered trial (ClinicalTrials.gov number, NCT00374101). Briefly, hemodynamically stable patients with either actively bleeding ulcers (with spurting arterial or persistent oozing) or non-bleeding ulcers (with non-bleeding visible vessels or adherent clot) underwent prompt treatment where an endotherapy was delivered to achieve hemostasis. Exclusion criteria were malignant-appearing ulcers or those with a flat spot or clean base, prior gastric surgery, a need for continuous anticoagulation, or PPI therapy before the index upper GI endoscopy and unsuccessful endoscopic hemostasis.

Patient population

Patients were eligible for enrollment if they had presented to a hospital emergency department with overt gastro-intestinal bleeding or a recent history (< 24 h before presentation) of hematemesis and/or melena, as were patients whose ulcer hemorrhages started after hospitalization for an unrelated medical or surgical condition. Eligible patients were required to have an ulcer with either active bleeding or a non-bleeding lesion at endoscopy.

Endoscopic hemostasis

Attempts to establish hemostasis endoscopically was made by injecting 10 to 15 mL of a 1:10,000 solution of epinephrine around the bleeding site, alone or in conjunction with contact thermal probe coagulation. For thermocoagulation, a heat probe unit (Olympus) with a 10F (3.2 mm) probe was used with power settings of 25 to 30 joules; the probe was positioned directly on the bleeding point, and firm tamponade was applied with the tip before activation. The type of endoscopic treatment delivered was left at the discretion of the participating endoscopist. Hemostasis was considered achieved if bleeding stopped for at least 3 min of observation.

Administration schedule of intravenous proton-pump inhibitors

Immediately after the endoscopic hemostasis, PPIs were infused at a standard regimen (40 mg bolus of PPI once daily for 72 h) or at a high-dose regimen (loading

dose of 80 mg on the first day followed by continuous infusion of 8 mg/h for 72 h), as previously reported.[9] After the initial 72 h, patients were switched to oral PPIs (20 mg twice daily) until discharge. Second look endoscopy was not routinely performed per protocol but was performed in all patients with a clinically suspected or overt rebleeding.

Outcomes

The outcomes assessed were initial recurrence of bleeding, blood transfusion, surgery, length of hospital stay, and mortality. Rebleeding was suspected in case of decrease in blood pressure (≤ 100 mmHg), increase in pulse rate (≥ 100 beats/min), more than 2 gm/dL decline in hemoglobin levels, no change in hemoglobin levels despite red blood cell transfusions, or reappearance of overt bleeding (new episode of hematemesis or melena). Shock was defined as a systolic pressure < 100 mmHg and pulse rate > 100 beats/min. Patients with a clinical suspicion of rebleeding underwent a second upper endoscopy to confirm the recurrent bleeding (actively bleeding lesion or fresh blood in the stomach). When second-look upper endoscopy only showed high-risk stigmata without active bleeding (i.e. adherent clot or visible vessel), the patient was classified as having a rebleed. The patients with rebleeding were again treated with upper endoscopy according to local expertise. Mortality was defined as any death occurring within 30 days from the index endoscopy.

Statistical analysis

The main outcome of the study was the rebleeding rate in patients treated with epinephrine injection alone, or in combination with either heat-coagulation or placement of endoclips by upper endoscopy. A secondary outcome was the mortality rate, compared between the two experimental groups. All results were analyzed on an intent-to-treat basis. Categorical data were expressed as proportions, and continuous data as means ± SD. *P* values for the primary end points were obtained from the two-sided chi-squared test, or Pearson's test and Fisher's exact test when appropriate. To assess the impact of endoscopic and treatment variables on investigated outcomes, one-way analysis of variance was performed first, to take possible confounders into account. Variables with a *P* value < 0.10 by univariate analysis were then entered into a multivariate logistic regression analysis to evaluate independent odds ratios (ORs).

RESULTS

Of the original cohort of 474 patients with upper GI bleeding enrolled in the randomized trial, 98 patients were excluded from the present analysis because they had been managed with non-injective monotherapy consisting of either non-contact thermal monotherapy (*n* = 28) or mechanical monotherapy (*n* = 70). In the remaining 376 patients, hemostasis was successful by epinephrine injection, given alone (*n* = 157) or in combination with contact thermal therapy (*n* = 219) during upper GI endoscopy. The baseline clinical and demographic characteristics of patients in the 2 investigational groups are shown [Table 1]: gender, age, signs of hemodynamic instability, mean Rockall score, location of the peptic ulcer, and active or inactive bleeding had equal frequency in patients treated with epinephrine injection or combined therapy. The only 2 features that differed at baseline were ulcer size > 20 mm, that was more frequent in the monotherapy group (12.7% *vs*. 5.5%, *P* < 0.03), and the intensive regimen of PPI administration, that was more frequent in patients treated with combined endotherapy (40.8% *vs*. 54.3%, *P* < 0.009).

Overall, rebleeding occurred in 41 patients (10.9%). Of these, 20 (12.7%) were in the monotherapy group and 21 (9.6%) were in the dual endotherapy group (*P* = 0.33). The corresponding difference in proportions was 3.1% (95% CI: -3.9 to 10.2), with an OR of 0.73 (95% CI: 0.36 to 1.47). Rebleeding rates between the two endoscopic strategies did not differ after stratifying for each of the demographic, clinical and endoscopic variables considered at baseline. In 217 out the 376 patients (57.7%) the extent of the GI hemorrhage was significant and required transfusion of blood. The need for transfusions was not different between the monotherapy (59%) and the dual endotherapy group (56.6%). The mean ± SD number of units of blood transfused was 2.7 ± 1.7 in the monotherapy group and 3.2 ± 2.5 in the dual therapy group (*P* = 0.14). The mean hospital stay was 6.7 ± 3.9 days in the monotherapy group and 7.1 ± 4.3 days in the dual therapy group (*P* = 0.40).

Nine patients (2.4%) died within the hospital stay, whereas no further death was observed during the 30-day observation period following the index endoscopy. Seven patients (4.5%) died of those who were treated with epinephrine injection alone, and 2 (0.9%) of those in whom dual therapy was applied; the difference was significant (*P* = 0.03). The corresponding absolute risk reduction was 3.6% (95% CI: 0.3 to 8.1), with an OR of 0.20 (95% CI: 0.04 to 0.96). The results of the univariate analysis of potential confounding factors in the assessment of the risk of death in the 2 experimental groups are shown [Table 2]: ulcer size ≥ 20 mm, rebleeding, and endoscopic single therapy carried an increased risk of death. Age, shock at presentation,

Table 1: Clinical and demographic characteristics of the 376 patients included in the analysis by the type of endoscopic treatment delivered at the index endoscopy, *n* (%)

Characteristics	Injection (*n* = 157)	Combined (*n* = 219)	*P* value
Male gender	103 (65.64)	138 (63.0)	< 0.6
Age, years (mean ± SD)	65.4 ± 18	67.1 ± 14	< 0.31
Shock at presentation	20 (12.7)	30 (13.7)	< 0.78
Hemoglobin, g/L (mean ± SD)	9.2 ± 2.5	9.4 ± 2.2	< 0.37
Rockall score (mean ± SD)	4.9 ± 1.5	4.7 ± 1.4	< 0.21
Site of ulcer			
Duodenal	108 (68.8)	137 (62.6)	< 0.20
Gastric	49 (31.2)	82 (37.4)	
Ulcer size ≥ 20 mm	20 (12.7)	12 (5.5)	< 0.03
Type of bleeding at index endoscopy			
Active	73 (46.5)	107 (48.9)	< 0.60
Inactive	84 (53.5)	112 (51.1)	
Regimen of proton pump inhibitor administration			
High dose	64 (40.8)	119 (54.3)	< 0.009
Standard dose	93 (59.2)	100 (45.7)	

Table 2: Crude odds ratios of death based on univariate regression analysis

Variables	No.	Odds ratio (95% CI)	*P* value
Age, ≥ 70 *vs.* < 70 years	237/139	2.05 (0.50-8.4)	< 0.34
Shock at presentation, yes *vs.* no	50/326	1.25 (0.25-6.19)	< 0.78
Hemoglobin, ≤7 *vs.* > 7 g/dL	55/321	4.65 (0.57-37.99)	< 0.114
Location of peptic ulcer, gastric *vs.* duodenal	83/293	0.93 (0.23-3.80)	< 0.923
Ulcer size, ≥ 20 *vs.* < 20 mm	32/344	9.68 (2.38-39.30)	< 0.0001
Type of bleeding at endoscopy, active *vs.* inactive	180/196	3.29 (0.67-16.19)	< 0.119
Dose of proton pump inhibitors administered, standard *vs.* high	193/183	1.33 (0.35-5.03)	< 0.676
Rebleeding, yes *vs.* no	62/314	4.33 (1.03-18.22)	< 0.03
Type of endoscopic treatment, mono *vs.* dual	157/219	4.88 (1.03-23.19)	< 0.03

hemoglobin value < 7 gm/dL, Rockall score > 6, location of peptic ulcer, and the intensive or standard regimen of PPIs administration were not significant confounders. At multivariate analysis of significantly or nearly significant associated predictors of death at the bivariate analysis, the sole independent predictor of death was an ulcer size ≥ 20 mm, with an OR of 6.56 (95% CI: 1.57 to 27.4). Rebleeding carried an increased risk of death (OR 3.02, 95% CI: 0.66 to 13.7) but data were not significant. Combined endoscopic therapy provided a reduction in the risk of death, with an OR of 0.26 (95% CI: 0.26 to 1.34), but data were not significant. The regimen of PPIs administered as well as whether the ulcer was bleeding or not at the index endoscopy were far from having statistical relevance in terms of the risk of death.

DISCUSSION

Our original investigation was designed to compare the efficacy of standard *vs*. high-dose PPI regimens in conjunction with endotherapy, and this demonstrated that standard doses were not inferior to a high dose regimen.[10] In the present *post hoc* analysis of data gathered in the same Italian multicenter study, we assessed whether dual endoscopic modalities confer any added therapeutic benefit over injection monotherapy: in this study we found that rebleeding rates were unaffected by the type of the endotherapy delivered at the time of the index endoscopy.

Our current investigation is somewhat at variance with the routine current practice, which utilizes dual endoscopic therapy on the assumption that it is superior to injection alone for control of rebleeding in peptic ulcers. Previous recommendations stem from the results of recently published meta-analyses.[13-15] In the meta-analysis by Calvet *et al.*,[13] the further bleeding rate was 18.4% (155 of 840 patients) in the epinephrine group and 10.6% (88 of 833 patients) in the comparison group. Moreover, in a meta-analysis by Marmo *et al.*,[14] the pooled data from 22 trials reported parallel rebleeding rates of 15.6% (193 of 1,239 patients) and 9.6% (119 of 1,233 patients), respectively. Corresponding figures in the present investigation were 12.7% (20 of 157 patients) and 9.6% (21 of 219 patients). These divergent results may have resulted from the lower sample size in our study. However, the average sample size of the trials evaluated in the 2 meta-analyses was 104 and 112 patients, respectively, with only 2 trials having enrolled more than 250 patients each.[16,17] Therefore, our study reports outcome data on

the largest population of patients with bleeding peptic ulcers treated with unimodal or dual endotherapy. Moreover, by inspecting the Forrest plots for rebleeding in the meta-analyses, it should be noted that only 5 of 22 studies registered significantly different results between the 2 endoscopic strategies.[18-22] This would indicate that there was significant heterogeneity among the studies concerning recurrent bleeding. Marmo *et al*.[14] handled this heterogeneity by subgroup analysis and meta-regression, and found that the type of dual therapy applied and the post-hemostasis adjuvant therapy with PPIs could explain the heterogeneity. The applicability of the meta-analysis by Calvet *et al*.[13] could be limited by the fact that only a single study used omeprazole as adjuvant treatment,[20] presently considered as "modern" anti-secretory therapy. A much more valuable interpretation of their results would indicate that dual therapy was superior to epinephrine monotherapy when medical therapy other than PPIs was given. Contrariwise, when we administered adjuvant PPIs after endoscopic hemostasis, epinephrine monotherapy proved as effective as in combination with thermal therapy. A single randomized study on patients with peptic ulcer bleeding that used adjuvant PPIs and compared epinephrine monotherapy with epinephrine plus thermal therapy is available:[20] rebleeding episodes were fewer in the combination group (2 of 30, 6.7%) than in the monotherapy group (11 of 31, 35.5%). However, the generalizability of data from this study may be questionable because of its small sample size. Finally, we would also recall that the 12.7% rebleeding rate observed in our patients managed with epinephrine monotherapy and PPIs was substantially lower than the 18.4% figure reported by Calvet *et al*.[13] where injection monotherapy was followed by acid suppression therapy with H2-receptor antagonists, which is no longer a standard therapy. Even in our study, a 3.1% (95% CI: 3.9 to 10.2) difference in the proportion with re-bleeding between the 2 experimental groups was noted, but such a low value is unlikely to attain clinical meaning. It is conceivable that a subset of patients with bleeds exists that might benefit from combined endoscopic therapies, but our data provide evidence against the indiscriminate use of these strategies in all patients with peptic ulcer hemorrhages.

A second finding of interest in the present study is that the only independent predictor of death was a bleeding ulcer greater than 20 mm in size. Overall, the 2.4% death rate observed here is in keeping with the 4.5% value reported in a recent Italian survey on outcome of patients with bleeding ulcers;[23] these figures underline the low risk of dying after a bleeding episode from peptic ulcer in Italy, and indicate that ulcer size and concurrent major diseases affecting the bleeding patient are the main determinants of a fatal outcome in our country. Nevertheless, we documented a reduction in death rate from the 4.5% figure after epinephrine injection alone to a 0.9% value following combined endotherapy, with an absolute risk reduction of 3.6% (95% CI: 0.3 to 8.1) and a risk reduction of 70%. Given the low number of events registered in the present study, there is a possibility of a type I statistical error. This reduction did not attain significance, but nevertheless it might be of clinical relevance.

This study is limited in its pre-post design by the lack of randomization of two groups of patients. A cluster randomized study would be needed to do this, but such a protocol is currently limited by several guidelines that designate dual endoscopic therapy as "usual care". Moreover, as the endoscopic therapy was left to the discretion of the endoscopist and not standardized, we could not control whether some of the treating physicians using their clinical judgement always used the same therapy regardless of patient factors, or whether others administered one type of therapy in some patients and another type in other patients. We have attempted to guard against underestimating the benefit of combined endoscopic modalities by carefully assessing patients' characteristics at baseline and selecting appropriate outcome measures. Our baseline and balance measures were comparable between the two study groups, but we acknowledge that expertise of the treating physicians might differ between participating centers. However, because the outcomes were reasonably consistent (rebleeding, transfusion requirements, hospital stay, and mortality), the methodological bias inherent in a *post-hoc* analysis is likely minimal.

In conclusion, in this *post-hoc* analysis large ulcer size was the sole predictor of bleeding-related fatality, and patients with this endoscopic finding might require more aggressive treatment. Moreover, the lack of randomization in this study does not allow us to control for the behaviors of the endoscopists, and the current guidelines recommend dual endoscopic therapy in all patients with bleeding peptic ulcers. Independent prospective validation of these observational findings will be required.

Authors' contributions

Collecting data: S. Loperfido, G. Napolitano, R. Focareta, F. Fornari, A. Garripoli, A. Merla, A.M. Ippolito, P. Leo, R. Marmo

Analysing data and manuscript writing: A. Andriulli

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Conflicts of interest

There are no conflicts of interest.

Patient consent

All patients have accepted the study by signing written informed consent.

Ethics approval

The study was reviewed and approved by the Casa Sollievo della Sofferenza Hospital Institutional Review Board.

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