

## How evidence-based are current guidelines for managing patients with peptic ulcer bleeding?

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### Abstract

Current guidelines for managing ulcer bleeding state that patients with major stigmata should be managed by dual endoscopic therapy (injection with epinephrine plus a thermal or mechanical modality) followed by a high dose intravenous infusion of proton pump inhibitors (PPIs). This paper aims to review and critically evaluate evidence supporting the purported superiority of a continuous infusion over less intensive regimens of PPIs administration and the need for adding a second hemostatic endoscopic procedure to epinephrine injection. Systematic searches of PubMed, EMBASE and the Cochrane library were performed. There is strong evidence for an incremental benefit of PPIs over H<sub>2</sub>-receptor antagonists or placebo for the outcome of patients with peptic ulcer bleeding following endoscopic hemostasis. However, the benefit of PPIs is unrelated to either the dosage (intensive vs standard regimen) or the route of administration (intravenous vs oral). There is significant heterogeneity among the 15 studies that compared epinephrine with epinephrine plus a second modality, which might preclude the validity of reported summary estimates. Studies without second

look endoscopy plus re-treatment of re-bleeding lesions showed a significant benefit of adding a second endoscopic modality for hemostasis, while studies with second-look and re-treatment showed equal efficacy between endoscopic mono and dual therapy. Inconclusive experimental evidence supports the current recommendation of the use of dual endoscopic hemostatic means and infusion of high-dose PPIs as standard therapy for patients with bleeding peptic ulcers. Presently, the combination of epinephrine monotherapy with standard doses of PPIs constitutes an appropriate treatment for the majority of patients.

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**Key words:** Guidelines; Ulcer bleeding; Peptic ulcer; Endoscopic therapy; Pharmacotherapy; Proton pump inhibitors

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### INTRODUCTION

In patients with ulcer bleeding and endoscopic findings that predict an increased risk of further bleeding, current therapeutic guidelines have endorsed the adoption of combining endoscopic hemostatic techniques with post-hemostatic adjuvant pharmacotherapy as primary measures to reduce rate of re-bleeding and need for surgery<sup>[1-3]</sup>. In addition, they authoritatively suggest to deliver endoscopic hemostasis by combining dual procedures

and to administer proton pump inhibitors (PPIs) under an intensive regimen of 80 mg stat followed by an infusion of 8 mg hourly for 72 h. The focus of a guideline is not prescriptive but aspires to recommend ideal therapy recognising that this has to be tempered by practical considerations that vary from patient to patient. However, in an era where medical litigation is increasing, adherence to guideline recommendations is widely adopted to reduce the likelihood of claims for malpractice.

Guideline recommendations are increasingly based on results of meta-analyses that summarize data from available studies in a quantitative fashion. Meta-analyses typically take a number of underpowered studies showing trends with similar point estimates and provide statistical power narrowing the surrounding uncertainty to achieve statistical and hopefully clinical significance. However, integrating the results of these studies is made difficult by variations in experimental design and composition of samples and may end up nullifying the clinical implementation of the summary statistics.

This paper will review available evidence on the appropriate management of patients with peptic ulcer bleeding, concentrating particularly on the purported superiority of a continuous infusion of PPIs administration over less intensive regimens and the need for adding a second hemostatic endoscopic procedure to epinephrine injection.

## OPTIMAL REGIMEN OF PPIs ADMINISTRATION

In the past, pharmacologic agents such as splanchnic blood pressure modifiers (e.g. vasopressin, somatostatin, octreotide) and antifibrinolytic agents (e.g. tranexamic acid) were used to stop initial bleeding and to prevent re-bleeding. Unfortunately, these drugs proved to be of limited value because they do not affect gastric pH<sup>[4,5]</sup>.

The role of gastric acid in bleeding peptic ulcers has been intensively investigated. *In vitro*, platelet aggregation, platelet disaggregation, coagulation, and fibrinolysis are strongly dependent on intragastric pH. Green *et al*<sup>[6]</sup> demonstrated that platelet aggregation and blood coagulation are optimal at pH 7.4. When the pH falls below 6.8, platelet aggregation and blood coagulation become abnormal and below 6.0, platelet aggregation is non-existent and disaggregation occurs. Finally, as pH falls below 4.0, fibrin clots are dissolved by gastric pepsin. *In vivo* studies have shown that a regimen including a high dose of a PPI can maintain intragastric pH at a nearly neutral level and inhibit acid production more effectively than an infusion of H2-receptor antagonists does<sup>[7,8]</sup>. *In vivo*, Laine *et al*<sup>[9]</sup> demonstrated that intragastric pH above 6.0 could be maintained for 67.8% of the 24 h study period in patients receiving intravenous PPI, and in 64.8% in those treated with frequent dosing schedule (3 h) of oral PPI. These *in vitro* and *in vivo* data generated the hypothesis that optimizing intragastric pH during acute bleeding from peptic ulcers by achieving profound

acid suppression is needed to reduce the risk of morbidity and mortality during hospitalization. However, previous experimental evidence represents, at best, surrogate end points, whereas data from appropriate clinical investigations are the essential outcome measures on which clinical decisions should be based.

The British Society of Gastroenterology guidelines issued in 2002 were the first to recommend the use of high dose intravenous omeprazole therapy, consisting of a 80 mg stat dose followed by an infusion of 8 mg hourly for 72 h<sup>[1]</sup>. Four randomized trials were cited to support the recommendation<sup>[10-13]</sup>, but much emphasis was reserved for the Lau *et al*<sup>[13]</sup> trial. In this study, patients randomized to receive the intensive dosage of PPIs had a reduction in the risk of recurrent bleeding from peptic ulcer which amounted to 7% for intravenous PPIs compared to 23% for patients in the placebo group. As the four surveyed trials were all placebo-controlled, a more appropriate conclusion would have indicated that the purported superiority of the intensive regimen of PPIs administration was apparent when compared with the placebo. The value of this schedule of PPIs administration as opposed to less intensive regimens remains unproven.

The benefit associated with the use of the high-dose intravenous PPI regimen was reiterated in recommendation 17 of the consensus conference, endorsed and organized in 2003 by the Canadian Association of Gastroenterology<sup>[2]</sup>. Recommendation 17 was issued after the appreciation of data from an ad-hoc meta-analysis, where the intensive regimen led to a statistically significant reduction in the absolute rate of re-bleeding compared with that registered after the administration of H2-receptor antagonists or placebo<sup>[14]</sup>. A recently updated Cochrane meta-analysis reinforced the recommendation<sup>[15]</sup>. Careful reading of component studies on which this proposition was based, lessens enthusiasm on the generalizability and applicability of the recommendation. Indeed, an inactive placebo or a less than optimal gastric inhibitory drug, the H2-receptor antagonists, were used as comparators in all investigations. Reasons for the lack of benefit of H2-receptor antagonists in bleeding peptic patients may be the failure to maintain optimal intragastric pH during the critical 72 h following the onset of the bleed, and the rapid onset of tolerance to H2-receptor antagonists' antisecretory effect<sup>[16,17]</sup>. In addition, at the time previous guidelines were issued, there were studies proving that either high dose oral<sup>[18,19]</sup> or standard intravenous dose of PPIs<sup>[20,21]</sup> were also very effective in the prevention of re-bleeding in patients with high-risk peptic ulcers. However, the reported results received little consideration. A more judicious appreciation would have focused on those studies that made a direct comparison between the high intensive regimen of PPIs administration and the standard or oral regimens of PPIs use. Indeed, in a meta-analytical evaluation of the only two trials that compared the continuous high-dose infusion versus an intermittent bolus of intravenous PPIs administration, the pooled re-bleeding rates were 11.6% and 9.7% respectively, a non significant difference<sup>[22]</sup>. In

line with these results, four subsequent reports failed to document an incremental benefit of intravenous over oral PPI regimens in the prevention of re-bleeding following endoscopic hemostasis<sup>[23-26]</sup>.

After considering all previous information, the appropriate conclusion would be that there is strong evidence for an incremental benefit of PPIs over H2-receptor antagonists or placebo for the outcome of patients with peptic ulcer bleeding following endoscopic hemostasis. However, the benefit of therapy with PPIs is unrelated to either their dosage (the intensive or the standard regimen of intravenous drug administration) or the route of administration (*iv vs po*). As a practical consequence for the everyday clinical care for patients bleeding from peptic ulcers, we suggest standard doses of PPIs should be used as an adjuvant treatment after a successful endoscopic hemostasis. Preliminary recent investigation has also shown comparable efficacy between oral rabeprazole and intravenous regular doses of omeprazole in preventing re-bleeding in patients with high-risk bleeding peptic ulcer after successful endoscopic injection with epinephrine<sup>[27]</sup>. Future trials should further explore the benefit of the oral route *vs* the intermittent bolus of intravenous PPI administration.

## OPTIMAL ENDOSCOPIC HEMOSTASIS

Controversy has also surrounded the best modality to deliver and achieve endoscopic hemostasis in bleeding peptic ulcers. All endoscopic treatments appear superior to pharmacotherapy alone<sup>[14,22,28]</sup>, while epinephrine monotherapy has been rated less effective in preventing further bleeding than epinephrine injection followed by a second endoscopic modality<sup>[29-32]</sup>. Dual endoscopic therapy is theoretically attractive to increase efficacy, and the combination of epinephrine injection followed by thermal therapy has gained wide acceptance. However, data supporting the superiority of dual endoscopic treatment over epinephrine monotherapy are extremely limited. By referring to the only trial available on the comparison of dual *vs* monotherapy<sup>[28]</sup> at the time guidelines were issued, the British Society of Gastroenterology acknowledged that the combination of adrenaline injection plus heater probe was no better than injection alone for the overall population of peptic ulcer bleeders. They also pointed out the results of a post hoc analysis of the same study showing better outcomes in the subset of patients with active arterial bleeding who received combination therapy<sup>[1]</sup>. This relevant observation would imply that no single endoscopic treatment fits all kinds of bleeding peptic ulcers and that individual patients would benefit from a slightly different approach in endoscopic hemostasis. Unfortunately, this indication has not been pursued further.

Conversely, both the Canadian consensus statements and guidelines issued by the American Society of Gastrointestinal Endoscopy rated epinephrine monotherapy inferior to dual endoscopic therapy in re-bleeding, need for surgery, and mortality<sup>[2,3]</sup>. This statement found support

in several successive meta-analyses<sup>[14,30-33]</sup>. Fifteen clinical trials have compared epinephrine with epinephrine plus a second modality<sup>[28,34-47]</sup>. By inspecting the Forrest plots of these analyses, there was significant heterogeneity among the studies, which might preclude the validity of reported summary estimates. Indeed, an advantage for the combined endoscopic approach was apparent from only 6 of the 15 clinical trials<sup>[34,35,41-44]</sup>, while in the remaining 9 trials, epinephrine monotherapy proved as effective as epinephrine injection plus a second modality. Laine and McQuaid noted that in these trials, assessment of the therapeutic outcome was confounded by second look plus re-treatment. Meta-analyses of studies without second look plus re-treatment showed a significant benefit of adding the second modality for further bleeding and surgery, while studies with second-look and re-treatment showed no suggestion of a difference<sup>[52]</sup>. Consequently, in line with these findings, two strategies seem to be equally effective: the first one would suggest to treat all patients with dual endoscopic modalities and the second one would argue to deliver epinephrine monotherapy to all patients and re-treat only the small proportion of rebleeders with a second endoscopic modality.

In addition, the majority of reviewed studies administered pharmacotherapy as adjuvant treatment to endoscopic therapy. Therefore, it is highly plausible that the outcome of interest, i.e. the rebleeding rate, might be the combined result of either the modality of endotherapy (single or dual) and the type of the pharmacotherapy (placebo, H2-receptor antagonists, or PPIs) being administered. Summary statistics provided by meta-analyses were driven by results of adjuvant medical therapies that are not generally used at present. Marmo *et al*<sup>[31]</sup> handled this heterogeneity among the studies with 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. Since only two studies applied omeprazole as adjuvant treatment<sup>[34,45]</sup>, a strategy presently considered standard practice, the applicability of current guidelines could be limited. In light of this factor, a more appropriate interpretation of the meta-analytical data would have been that dual therapy was superior to epinephrine monotherapy when medical therapy other than PPIs was given.

## CONCLUSION

This paper has highlighted the real difficulties in interpreting the wide array of heterogeneous studies, each examining one aspect of the management of peptic ulcer bleeding. Consequently, insufficient experimental evidence supports current guideline recommendations to treat patients with major stigmata of haemorrhage by dual endoscopic therapy, comprising of injection with epinephrine plus a thermal or mechanical modality, followed by high-dose intravenous infusion of PPI drugs. The significant heterogeneity across the studies invalidates the generalizability of the results of meta-analyses on which these guidelines were based. Whether the indiscriminate use of combined endoscopic

therapy and high-dose infusion of PPIs is uniformly necessary in all patients with peptic ulcer hemorrhage remains questionable. Determination of patient subgroups most likely to benefit from the aggressive therapeutic program, as suggested by available guidelines, is necessary to ensure that the highest risk patients are optimally treated. Algorithms for optimal management of bleeding peptic ulcers will continue to be a subject of research interest. At this time, a two-pronged approach that combines injection monotherapy with adjuvant standard intravenous dose of PPIs can offer protection against early re-bleeding in the great majority of patients with peptic ulcer bleeding.

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