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The Short-Term Medical Management of Non-Variceal Upper Gastrointestinal Bleeding

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Contents

Abstract

Upper gastrointestinal (UGI) bleeding occurs frequently and results in substantial patient morbidity, mortality and medical expense. After initial resuscitation to stabilize the patient, carefully performed endoscopy provides an accurate diagnosis and can identify high-risk subgroups in ulcer patients who are likely to rebleed with medical therapy alone and would benefit most from endoscopic haemostasis. Several different pharmacological therapies have been used for patients with bleeding ulcers, including intravenous histamine H_2-receptor antagonists, proton pump inhibitors, somatostatin and octreotide, and tranexamic acid. The results of several studies and meta-analyses favour high-dose, intravenous proton pump inhibitors, such as omeprazole or pantoprazole, after successful endoscopic haemostasis.

For patients with ulcer bleeding and low-risk endoscopic stigmata, high-dose oral proton pump inhibitor therapy is suggested. Medical management with proton pump inhibitors is not a substitute for appropriate endoscopic therapy for patients with UGI bleeding and high-risk ulcer stigmata.

Upper gastrointestinal (UGI) bleeding occurs frequently and is a common cause of hospitalization or inpatient bleeding. Such bleeding results in substantial patient morbidity, mortality and healthcare expense. Ulcer disease is the most common cause of severe UGI haemorrhage, causing about 40–50% of cases, and UGI bleeding is the most common complication of peptic ulcer disease.[1] Although other non-variceal conditions, such as Mallory-Weiss tear, angiodysplasia, watermelon stomach or Dieulafoy's lesion, may also cause UGI haemorrhage, these occur much less frequently.[2] This article re-

views the important aspects of the short-term medical management of UGI bleeding, secondary to ulcers and other peptic or non-variceal lesions.

1. Initial Management of the Patient with Upper Gastrointestinal Bleeding

The initial management of the patient with UGI bleeding should include evaluation of severity of the haemorrhage, patient resuscitation, a brief medical history and physical examination, and consideration of possible interventions.[1] The initial clinical assessment should focus on the patient's haemodynamic state, with a view to early resuscitation. Initial medical therapy should be aimed at restoring blood volume by fluid replacement to ensure that tissue perfusion and oxygen delivery are not compromised. Airway protection with endotracheal intubation should be strongly considered in patients with ongoing haematemesis, altered mental or respiratory status, or severe neuromuscular disorders that prevent aspiration.[1,2]

After patient resuscitation and stabilization, endoscopy is the preferred procedure for diagnosis and treatment because of its high accuracy (diagnostic in about 95% of severe UGI haemorrhage patients) and low complication rate. Endoscopy may also show stigmata of haemorrhage on ulcers that have important prognostic value for the risk of rebleeding.[1,3,4] Patients with high-risk endoscopic findings, such as active bleeding, non-bleeding visible vessel or adherent clot, are likely to rebleed with medical therapy alone and would benefit from endoscopic haemostasis in combination with medical therapies.[1,3,4] Improved outcomes have included control of active bleeding, and decreased rebleeding, transfusion requirements, duration of hospitalization and mortality.[1,3-5] Rebleeding after endoscopic therapy of UGI ulcers occurs in 10–25% of patients and represents a challenging problem.[5] Patients with a clean-based ulcer or a flat dark spot rarely rebleed and do not require endoscopic haemostasis. These patients are best managed medically.

As with endoscopic haemostasis, the main goals of medical management include reduced morbidity, mortality, risk of rebleeding, transfusion needs, duration of hospitalization and need for interventions (endoscopy, angiography or surgery). Histamine H_2-receptor antagonists (H_2RAs), proton pump inhibitors (PPIs), somatostatin and octreotide, and tranexamic acid have been the most extensively studied in the medical management of non-variceal UGI bleeding.

The reason for the use of acid-reducing medications is based on studies showing that acid and pepsin interfere with the haemostatic process of ulcers and non-variceal UGI lesions. *In vitro* studies demonstrated that (i) both the intrinsic and extrinsic pathways were adversely influenced by an acid environment; (ii) platelet aggregation was inhibited by acid; and (iii) pepsin activity was also highly acid sensitive, with maximal clot lysis at a pH of 2, but limited effect at pH above 5.[6] These results suggested that increasing intragastric pH to greater than 6 could improve the coagulation process. Furthermore, since clinical trials have shown that ulcer rebleeding occurs mainly during the first 72 hours, acid suppression should be maintained for at least 72 hours after haemostasis of non-variceal UGI haemorrhage because any formed blood clots could be lysed with a return of an acidic intragastric environment.

After the initial bleed has been treated endoscopically and haemostasis has been achieved, medical management is recommended with PPIs for 6–8 weeks, unless the patient is also *Helicobacter pylori*-positive, requires low-dose aspirin maintenance or uses a non-selective NSAID. *H. pylori*-positive patients should receive eradication therapy and should be retested to document *H. pylori* eradication 6–10 weeks after completion of antibacterial therapy. Patients needing long-term aspirin or NSAIDs should receive PPI maintenance treatment to indefinitely reduce ulcer recurrence.[1,3]

2. Histamine H_2-Receptor Antagonists

There have been many randomized trials using H_2RAs as medical treatment for acute UGI bleeding because they were the first medications available to inhibit acid secretion. In 1985, Collins and Langman[7] reported the results of a meta-analysis of

27 randomized controlled trials on the use of H_2RAs versus placebo in patients with ulcer bleeding. They showed that there was no effect on rebleeding and only a minor decrease in the need for surgery or mortality.[7] Subgroup analysis demonstrated that there was a significant reduction in rebleeding, mortality and surgery for gastric ulcer patients, but not for duodenal ulcer patients.[7] A more recent meta-analysis of H_2RAs compared with placebo for peptic ulcer haemorrhage showed no benefit on rebleeding, mortality or the need for surgery.[8] It should be noted that these meta-analyses are limited because most patients in the older studies did not receive endoscopic haemostasis for high-risk ulcer stigmata.

The reason for these poor results is that intravenous H_2RAs are ineffective in maintaining a sustained high gastric pH. Bolus injections, as frequently as every 4 hours (ranitidine 50 mg), produced an intragastric pH >6 only 35% of the time.[9] Although continuous intravenous infusion of H_2RAs could increase intragastric pH above 6, tolerance developed within the first 12 hours of the infusion.[10] This pharmacological tolerance could not be overcome, even with large doses (ranitidine >500 mg/24 h) and occurred with each of the other H_2RAs (cimetidine and famotidine).[11]

In summary, the results of both pharmacokinetic studies and clinical trials do not support the use of intravenous H_2RAs for the medical management of non-variceal UGI bleeding.

3. Proton Pump Inhibitors

PPIs reduce both basal and stimulated acid secretion by inhibiting the H^+K^+-adenosine triphosphatase, the proton pump of the parietal cell.[12] Several studies have shown that the infusion of PPIs provides sustained, high intragastric pH,[11,13] and that an omeprazole infusion (80 mg bolus followed by 8 mg/h) can maintain intragastric pH steadily above 6 during a 72-hour period[11] without the development of tolerance. In the US, the only PPIs available as intravenous formulation are pantoprazole and esomeprazole. These PPIs have been shown to provide potent and sustained acid suppression.[14]

Several randomized controlled trials have demonstrated the efficacy of high-dose PPI infusion (omeprazole 80 mg bolus followed by 8 mg/h) for 3 days after successful endoscopic treatment of patients with bleeding ulcers and high-risk stigmata of haemorrhage.[15-17] Lau and co-workers[17] showed that after primary haemostasis had been achieved by endoscopic coagulation, high-dose omeprazole infusion reduced the rate of rebleeding, transfusion requirements and duration of hospitalization. Sung and colleagues[18] reported similar prevention of recurrent bleeding in ulcer patients with non-bleeding visible vessels and adherent clots with combination endoscopic therapy and omeprazole infusion, compared with omeprazole infusion alone. These studies illustrated the benefits of combination intravenous PPI infusion after endoscopic haemostasis, but not as a stand-alone therapy.

More recently, several reviews and meta-analyses of PPI use in peptic ulcer bleeding confirm that PPIs reduce rebleeding, surgery, transfusion requirements and duration of hospitalization without decreasing mortality.[19-24]

Further review of the available studies suggested important differences in outcomes of Asian versus non-Asian patients in randomized controlled trials.[23] There was a significant reduction in 30-day mortality with PPI therapy for bleeding ulcers in the Asian trials, but not in the non-Asian studies. The effects of PPI therapy on rebleeding and the reduced need for surgery were also markedly greater in the Asian than non-Asian trials.[23] Possible reasons to account for these different outcomes include: (i) younger age of Asian patients (57 years vs 66 years in non-Asian trials) with fewer co-morbidities; (ii) a lower parietal cell mass in Asian patients leading to a more profound decrease in acid secretion; (iii) a higher rate of *H. pylori* infection in Asian patients, which is associated with a greater PPI effect on acid suppression;[25] and (iv) Asian patients are more likely to be slow metabolizers of PPIs.[26] Each of these factors would produce an increased antisecretory effect of PPI treatment in Asian compared with non-Asian or heterogeneous study groups.

Three recent studies compared intravenous PPIs (pantoprazole 80 mg bolus follow by 8 mg/h continuous infusion for up to 72 hours) with intravenous H_2RAs (ranitidine) in the management of ulcer patients with high-risk stigmata who had been successfully treated with endoscopic haemostasis. In one study,[27] there was no benefit in rebleeding or mortality with PPIs over H_2RAs. In another US study, there was a trend to lower rebleeding with pantoprazole than with ranitidine.[28] However, the small number of patients may have limited the ability of the trial to detect a true treatment difference. A Chinese study compared pantoprazole (40 mg bolus followed by 40 mg every 12 hours for 3 days) with ranitidine (50 mg bolus followed by 50 mg every 18 hours for 3 days) and reported significantly lower rebleeding rates after endoscopic haemostasis with pantoprazole compared with ranitidine, but similar rates of transfusion requirements, hospital stay, need for surgery and mortality.[29]

Two of these studies[27,28] included only *H. pylori*-negative patients, and PPIs are reported to be less effective in reducing acid secretion in *H. pylori*-negative than in *H. pylori*-positive individuals.[25] Also, most subjects were rapid metabolizers of PPIs according to cytochrome P450 2C19 status. These two studies may be more generalizable to the US and other heterogeneous populations, where most patients with ulcer bleeding are likely to be *H. pylori*-negative[30] and the majority of people extensively metabolize PPIs.

Based on published randomized clinical trials, the recommended dose of PPIs for patients with high-risk endoscopic findings is the equivalent of bolus intravenous omeprazole 80 mg followed by an 8 mg/h intravenous infusion for 72 hours.[21] However, PPIs are not approved by the US FDA for such medical therapy of either UGI or peptic ulcer bleeding. After the patient's condition stabilizes, intravenous PPI therapy may be switched to oral PPI therapy. Patients with low-risk endoscopic findings (clean ulcer base or flat spot) should be treated with high-dose (double the standard dose) oral PPIs.

However, recent studies suggest that North American subjects may require an even higher equivalent dose of intravenous PPI. Howden et al.[31] showed that bolus intravenous lansoprazole 90 mg followed by an intravenous infusion of 9 mg/h in *H. pylori*-negative subjects maintained intragastric pH >6 for only 36% of patients during the first 24-hour period and only 61% during the second 24-hour period. Another PPI, pantoprazole (intravenous 80 mg bolus followed by an intravenous infusion of 8 mg/h for 24 hours) produced intragastric pH >6 for only 28% of the 24-hour observation period.[32] Since this was the pantoprazole dose that was used in the two negative trials (pantoprazole vs ranitidine),[27,28] the lack of effect in rebleeding may have been secondary to ineffective acid suppression in the heterogeneous, non-Asian populations. This may explain why these two trials did not provide the beneficial clinical outcomes in UGI bleeding noted in other Asian studies.

Two other aspects of PPI use in the medical management of non-variceal UGI bleeding have recently been considered. The first includes the potential role of PPI use before endoscopy and the second is that of oral administration.

In a retrospective report, Canadian authors found that an intravenous PPI infusion prior to endoscopy in patients with UGI bleeding and high-risk ulcer stigmata lowered the proportion of actively bleeding ulcers noted at endoscopy, without altering rebleeding, surgery or mortality rates compared with those patients receiving PPIs after endoscopy.[33] Another retrospective report suggested that pre-endoscopic use of PPIs (both intravenous and oral) in patients with ulcer haemorrhage significantly reduced adverse outcomes such as rebleeding, surgery, duration of hospitalization and mortality.[34] A recent prospective, randomized, placebo-controlled study in Hong Kong showed that an intravenous omeprazole bolus and infusion before endoscopy in patients with UGI haemorrhage decreased the need for endoscopic therapy, decreased the number of actively bleeding peptic ulcers and decreased the duration of hospitalization.[35] These results raise the possibility that pre-endoscopic high-dose PPI infusion may improve outcomes. A meta-analysis including a total of 1512 patients confirmed that PPI therapy prior to

endoscopy in patients with UGI bleeding significantly decreased the proportion of patients with stigmata of haemorrhage, but did not demonstrate any significant benefit in important clinical outcomes such as mortality, rebleeding or surgery.[36] In patients with UGI haemorrhage, intravenous PPI therapy before endoscopy appears reasonable in view of the previously documented benefits and negligible risks associated with PPI infusion.

Use of oral PPIs in non-variceal UGI bleeding is a controversial aspect. In an Asian population, a high dose of oral omeprazole (40 mg twice daily compared with placebo) significantly reduced rebleeding in ulcer patients with a visible vessel or adherent clots.[37] More recent trials have suggested that (i) high-dose oral PPI (pantoprazole 40 mg twice daily[38] or omeprazole 40 mg/day)[39] was just as effective as an intravenous infusion[38,39] after endoscopy therapy; (ii) oral PPI (omeprazole 40 mg twice daily) was as effective as intravenous omeprazole in ulcer patients with low-risk stigmata of haemorrhage;[40] and (iii) oral PPI (rabeprazole 20 mg twice daily) was as effective as endoscopic treatment with haemoclips.[41] High-dose intravenous PPI treatment is expensive, while oral PPIs are much less costly. Cost-effectiveness analyses in patients with high-risk endoscopic stigmata who had successful endoscopic therapy have shown that both intravenous and oral PPI treatment are very effective and less expensive than intravenous H_2RAs[42] or placebo.[43] When intravenous PPI was compared with oral PPI, divergent results were obtained, with one analysis favouring intravenous administration[43] and the other supporting oral administration.[42]

4. Somatostatin and Octreotide

Somatostatin is a 14 amino-acid peptide hormone, which is widely distributed in the stomach, gastrointestinal tract and pancreas, as well as the CNS. Octreotide, a synthetic analogue of somatostatin has similar biological effects and a longer half-life. Octreotide is available in the US, but somatostatin is not. Somatostatin and octreotide have been successfully used either alone or combined with endoscopic therapy in the treatment of oesophageal and gastric variceal bleeding. They act by decreasing splanchnic blood flow. In addition to reducing gastroduodenal mucosal blood flow, somatostatin and octreotide also decrease gastric acid secretion by inhibiting gastrin release from antral G cells and histamine from enterochromaffine-like cells, decrease pepsin secretion, and stimulate mucus production.[44] The effect on inhibition of pepsin secretion is a potential advantage of somatostatin and analogues over H_2RAs and PPIs, which do not affect pepsin secretion.

Somatostatin and its analogues have been used in the treatment of patients with ulcer bleeding to take advantage of these effects on blood flow and gastric secretion. A small study found that in patients with bleeding peptic ulcers, somatostatin 250 μg bolus injection followed by 500 μg/h infusion was more effective than pantoprazole 80 mg bolus followed by 8 mg/h infusion in maintaining high intragastric pH, especially in the first 12 hours.[45] In another trial comparing intravenous somatostatin with intravenous pantoprazole after endoscopic treatment, somatostatin was not as effective in preventing rebleeding.[46] Mortality and surgery rates were similar in the two treatment groups. However, this study[46] used a lower dose of somatostatin (250 μg bolus followed by 250 μg/h infusion) than the prior one that showed superior control of acid secretion.[45]

Octreotide has usually been administered as a 50–100 μg bolus followed by a continuous infusion of 25 μg/h for up to 3 days. A meta-analysis of available trials comparing somatostatin and octreotide with placebo or H_2RAs in ulcer bleeding reported that somatostatin and octreotide reduced the risk of continued bleeding or rebleeding from ulcers.[47] Surgery was not significantly reduced by somatostatin or octreotide, and mortality was not assessed.[47] None of the trials in this meta-analysis had endoscopic therapy as part of the management, which limited the interpretation and relevance to current management.

At present, although there may be theoretical advantages to their use, there is no firm evidence to

recommend somatostatin or octreotide infusion over PPI therapy for non-variceal UGI haemorrhage. Furthermore, somatostatin and octreotide infusions are more expensive than PPI infusions.[44]

5. Tranexamic Acid

Tranexamic acid is an antifibrinolytic agent that inhibits plasminogen activators. It is not approved by the FDA for the therapy of non-variceal UGI or peptic ulcer haemorrhage. A meta-analysis of six randomized trials of patients with UGI bleeding reported that tranexamic acid significantly reduced mortality compared with placebo, without reducing rebleeding or the need for surgery.[48] However, when the results were reviewed and re-analysed, the mortality effect was no longer significant. Also, these trials did not include endoscopic haemostasis for high-risk ulcer lesions. Tranexamic acid should not be used in the management of ulcer haemorrhage.

6. Conclusions and Recommendations

UGI bleeding, secondary to peptic ulcer bleeding, is a common cause of hospitalization and inpatient bleeding, and results in substantial patient morbidity and mortality. The results of randomized controlled trials and meta-analyses have shown that PPIs improve clinical outcomes in patients with ulcer haemorrhage. Patients with ulcers with high-risk endoscopic stigmata should receive high-dose intravenous PPI therapy after successful endoscopic treatment. Patients with low-risk endoscopic stigmata should receive an oral PPI at twice the usual clinical dose. High-dose intravenous PPI therapy prior to endoscopy appears reasonable but is expensive. The use of oral PPI administration soon after successful endoscopic treatment is still controversial.

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