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Pharmacological Treatment in Upper Gastrointestinal Bleeding

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Abstract

Acute upper gastrointestinal bleeding (AUGIB) is a common medical emergency. Bleeding peptic ulcers account for the majority of causes in patients presenting with AUGIB, whereas variceal bleeding in cirrhotic patients represents a more severe form of bleeding. Endoscopic therapy is the mainstay of treatment in patients with active bleeding, as it achieves hemostasis and improves patient outcomes. Pharmacotherapy is an important adjunct to endoscopic hemostasis. In the management of patients with bleeding peptic ulcers, acid suppression after endoscopic hemostasis reduces rates of further bleeding and interventions. In patients with stable hemodynamics awaiting endoscopy, acid suppression starts ulcer healing and downstages stigmata of bleeding, thereby reducing the need for endoscopic therapy. In managing patients with variceal bleeding, early administration of vasoactive drugs lowers splanchnic blood flow, promotes hemostasis, and makes subsequent endoscopic treatment easier. The use of vasoactive agents and antibiotics have both been shown to reduce mortality. In this review article, strategies of acid suppression therapy for peptic ulcer bleeds, vasoactive agents, and antibiotics for variceal bleeding, together with recent evidence on the use of tranexamic acid in gastrointestinal bleeding, are discussed.

Introduction

Acute upper gastrointestinal bleeding (AUGIB) is characterized by fresh hematemesis, coffee-ground vomiting, and/or melena and is defined anatomically as arising proximal to the ligament of Treitz. Causes of UGIB can be divided into those from esophago-gastric varices and non-variceal causes, such as peptic ulcer bleeds (PUB). In the National United Kingdom Audit [1] conducted in 2007, the annual hospitalization rates for variceal and non-variceal bleeding were 2.83 and 84.6 per 100,000 persons, respectively. Peptic ulcer bleeding accounted for 36 % of cases. The crude overall mortality was 10 %.

Pharmacotherapy plays an important role in the management of patients with AUGIB. A combination of endoscopic and pharmacological therapies offers our patients the best possible clinical outcomes. In the management of PUB, endoscopic treatment, in comparison to no endoscopic therapy, has been shown to reduce further bleeding, surgery, and mortality [2]. Contact thermal devices were shown to have the best efficacy in reducing bleeding (RR 0.44; 95 % CI 0.36–0.54, NNT=4), the need for surgery (RR 0.39; 95 % CI 0.27–0.55, NNT=8) and mortality (RR 0.58; 95 % CI 0.34–0.98, NNT=33). Acid suppression using proton pump inhibitors (PPIs) as an adjunct further improves outcomes by reducing further bleeding and the need for surgery. In patients with variceal bleeding, early use of a vasoactive drug is associated with increased survival and its use after endoscopy reduces further bleeding. In addition, the use of antibiotics in cirrhotic patients reduces septic complications and also improves survival. This chapter focuses on the role of pharmacotherapy in the acute management of patients with AUGIB.

Pharmacotherapy for Non-Variceal Bleeding

Rationale for PPI Therapy in PUB

In in vitro studies, disaggregation of platelets occurs when plasma pH is titrated with hydrochloric acid [3–5]. An acidic milieu favors clot lysis; specifically at an intragastric pH <6, pepsinogen is converted to pepsin which can digest clots in the stomach. These observations have led to the notion that gastric pH neutrality would confer clot stability and hemostasis. To achieve complete and sustained acid suppression, a high-dose intravenous infusion with PPI is required. Netzer et al. [6] compared the use of high-dose PPI and ranitidine infusions over 72 h in healthy subjects and found that PPI infusion was superior to histamine H_2-receptor antagonist (H_2RA) infusion in the control of gastric pH over 3 days. Because of tachyphylaxis, gastric pH control was lost with the use of H_2RA by days 2 and 3. The authors also studied the effect of intermittent PPI injections and found comparable gastric pH control to continuous infusion.

Clinical Trials in the Use of PPI in PUB

PPIs alone appear to have a therapeutic effect on PUB. In an early placebo-controlled randomized control trial (RCT) by Khuroo et al. [7], in which endoscopic treatment was not available, oral omeprazole alone (40 mg twice daily) after diagnostic endoscopy reduced further bleeding (36.4 vs 11 %) and the need for surgery (23.6 vs 7.2 %) in 220 patients with bleeding peptic ulcers. Significant reductions in recurrent bleeding were observed only in ulcers with non-bleeding visible vessels or adherent clots.

In a placebo-controlled trial [8], our group applied the concept that complete gastric neutrality would confer clot stability and therefore reduce rate of recurrent bleeding. During endoscopy, patients with PUB were triaged. Only those with high-risk stigmata (active bleeding or with non-visible vessels) were enrolled. After endoscopic hemostasis, patients were then randomized to an infusion of either high-dose omeprazole or placebo. Bleeding recurred in 8 of 120 patients given omeprazole compared to 27 of 120 patients given placebo when followed up for 30 days (hazard ratio 3.9). In an international multicenter study [9] with an almost identical design but with the use of esomeprazole, a similar treatment effect was observed. Of 764 patients analyzed by the intention-to-treat principle, use of esomeprazole as compared to placebo was associated with a reduction in rate of further bleeding (5.9 vs 10.3 % in 72 h, p=0.026). In addition, the use of esomeprazole was associated with fewer surgeries (2.7 vs 5.4 %) and deaths (0.8 vs 2.1 %).

There have been many published RCTs on the use of PPI in PUB. Leontiadis et al. [10] summarized findings from 24 RCTs that compared PPI to either placebo or H_2RA in patients with acute PUB. These trials were heterogeneous in their designs, and PPI therapy was used in a variety of settings and doses. In this pooled analysis, PPI led to reduction in further bleeding (10.6 vs 17.3 %) and surgeries (6.1 vs 9.3 %) but not in deaths (3.9 vs 3.8 %).

The optimal dose of PPI to use and its preferred route of administration remain subjects of intense debate. In a Cochrane Review, Neumann et al. [11] summarized findings from 13 studies that compared high-dose to non-high-dose regimens. Many of the studies had small numbers of patients. Patients with low-risk stigmata were also included. The inclusion of such patients potentially diluted the treatment effect of a high-dose regimen. Pooled risk ratios (RRs) for rebleeding and surgery were 1.27 (95 % CI 0.96–1.67) and 1.33 (95 % CI 0.63–2.77), suggesting no benefit of high-dose over low-dose regimens. There were positive studies in favor of a high-dose regimen not included in the meta-analysis [12]. Recently, our group published a double-dummy placebo-controlled trial [13] using high-dose PPI versus oral low-dose PPI as adjunct to endoscopic therapy. The trial included 118 patients with a low-risk profile and did not demonstrate a difference between the two dose regimens. High-dose PPI infusion as an adjunct to endoscopic treatment carries around 7–10 % rate of recurrent bleeding. It is unlikely that a trial of sufficient size to declare equivalence or non-inferiority will be published. Our group has continued to use high dose infusion after endoscopic hemostatic therapy. We feel that optimal acid suppression is desirable. It is also cost saving because of reduced resource utilization for recurrent bleeding.

Intermittent PPI therapy achieves a similar intragastric pH profile to that after PPI infusion therapy. If intermittent PPI treatment has comparable clinical efficacy, it would be the preferred regimen given the greater ease of administration. A meta-analysis in 2014 compared intermittent PPI therapy with continuous PPI infusion for reduction of ulcer rebleeding within 7 days [14••]. It was a non-inferiority study design with a margin predefined as an absolute risk difference of 3 %. The RR of recurrent bleeding within 7 days for intermittent versus continuous PPI administration was 0.72 (one-sided 95 % CI upper boundary of 0.97). The absolute risk difference was −0.28 %, which was below the predefined margin of 3 %. There was no difference in recurrent bleeding within 30 days, surgery and mortality. The authors concluded that intermittent PPI therapy is comparable to the current guideline-recommended regimen of intravenous bolus of PPI followed by a continuous infusion in patients with endoscopically treated high-risk bleeding ulcers.

Given an identical dose, intragastric pH control after oral PPI can be similar to that after intravenous administration. Laine et al. [15] compared intragastric pH in patients with PUB given either oral or intravenous PPI infusion at identical doses. At 1 h, mean pH for intravenous PPI was significantly higher than with the oral PPI. Thereafter, intragastric pH profiles were comparable in both groups. In terms of pH control, the route of administration did not differ significantly given the same high-dose regimens.

Pre-Endoscopic PPI

In clinical practice, most patients who present with AUGIB undergo endoscopic examinations the following day, and PPI is initiated prior to endoscopy. Early PPI administration is a logical approach particularly in areas with a high prevalence of peptic ulcer disease. It is clear that PPI administration, even in the absence of endoscopic therapy, has a therapeutic effect on PUB as already mentioned. However, the use of PPI alone should not delay endoscopic therapy in those with ongoing bleeding and signs of circulatory instability. In our published study [16] on the use of PPI infusion before endoscopy, we enrolled only patients who were stable or could be stabilized while awaiting endoscopy. Patients who needed endoscopic hemostasis to their bleeding ulcers were then treated openly with IV PPI infusions. It was no surprise that we did not observe any significant difference in clinical outcomes between the two groups. Nonetheless, after a mean infusion time of around 16 h, we observed a significant reduction in the number of ulcers with active bleeding (12 of 187 vs 28 of 190, p=0.01), and numerically fewer patients with high-risk stigmata of bleeding. As a consequence, we showed a significant reduction in the requirement for endoscopic therapy (60 of 314 or 19.1 % vs 90 of 317 or 28.4 %) Again, PPI appears to have a clot-stabilizing effect.

A Cochrane meta-analysis [17] through January 2010 included six RCTs that assessed clinical outcomes in patients with PPI therapy initiated before endoscopy. The updated meta-analysis consisted of 2223 patients and included one study that assessed oral PPI and five that assessed IV PPI, with only our study using a high-dose regimen. The meta-analysis showed no statistically significant differences in clinically important outcomes including mortality, recurrent bleeding, or surgery between the PPI and control groups. Similar to findings from our study, pre-endoscopic PPI treatment significantly reduced the proportion of patients with high-risk stigmata (OR 0.67; 95 % CI 0.54–0.84) and the need for endoscopic therapy (OR 0.68; 95 % CI 0.50–0.93) compared with patients in the control group who

received H_2RA or placebo. Pre-endoscopic use of PPI has also been shown to be cost-effective [18, 19]. Our group calculated the cost-effectiveness ratio per endoscopic therapy averted in both the pre-emptive PPI and placebo groups, and concluded that the PPI strategy was less costly. The strategy remains cost saving when the proportion of patients with bleeding peptic ulcers is higher than 8.7 %. Of note, cost calculation varies enormously in different parts of the world.

Our group has continued to use a high-dose PPI infusion in patients after endoscopic hemostasis. A high dose given either as bolus injections or orally may be acceptable alternatives. The overall rate of recurrent bleeding should be between 5 and 8 %. There remains a subgroup at high risk of recurrent bleeding despite profound acid suppression and optimal endoscopic treatment [20]. These ulcers are usually found in elderly patients who often have significant comorbid illnesses and who present with major bleeding and hypotension. Their ulcers are often large (>2 cm in size) and erode into subserosal arterial complexes such as the gastroduodenal artery or left gastric artery. They are often located along the lesser curvature of the stomach or in the duodenal bulb. Our group has focused our clinical research targeting at this group of patients at high risk of failure after endoscopic treatment and profound acid suppression. One of the strategies that we have evaluated is to pre-emptively embolize the bleeding artery in the larger ulcers using percutaneous angiography [21].

Tranexamic Acid

Tranexamic acid (TXA) is an anti-fibrinolytic drug. It inhibits plasmin, which impairs clot stability and worsens bleeding. TXA is now widely used in surgery and trauma. A meta-analysis of clinical trials on the use of TXA in a variety of surgical conditions showed that TXA reduced the need for transfusion (RR 0.62; 95 % CI 0.58–0.65) in 95 trials and mortality (RR 0.61; 95 % CI 0.38–0.98) in 72 trials [22]. In the CRASH-2 trial [23], 20,127 trauma patients with any significant bleeding in general were enrolled, and the use of TXA was associated with reduced mortality (14.5 vs 16 %, RR 0.91; 95 % CI 0.85–0.97, p= 0.0035). Bennett et al. [24] summarized the published literature on the use of TXA in AUGIB and found eight trials (seven of which were placebo-controlled). There was a mortality difference in favor of TXA (42 of 851 vs 71 of 850, RR 0.60; 95 % CI 0.42–0.87). However, most of these trials were published in the 1980s, predating the era of PPI use, and therefore, this practice is considered non-contemporary. A major concern with the use of TXA is the occurrence of thromboembolic events. Individual trials were too small to detect a significant difference. The pooled rate of thromboembolic events was 11 in 522 and 6 in 526 in the TXA and placebo groups, respectively. Despite these limitations, the use of TXA appeared beneficial in patients with AUGIB.

The Hemorrhage Alleviation with Tranexamic Acid–Intestinal System (HALT-IT) trial [25] addresses the question of whether TXA can reduce deaths in patients with upper gastrointestinal bleeding. The trial aims to enroll 8000 patients, randomizing them to receive TXA 1 g as a bolus followed by 3 g in 24 h, or placebo. The primary endpoint of the HALT-IT trial is 30-day all-cause mortality. Such a large sample size is required to be able to detect a similar difference as that observed in the CRASH-2 trial, where the absolute risk reduction in morality was 1.5 % (NNT=67).

Pharmacotherapy for Variceal Bleeding

Vasoactive Medications for Variceal Hemorrhage

Variceal hemorrhage is one of the most serious complications of decompensated cirrhosis, conferring a 6-week mortality of at least 20 % [26, 27]. Esophageal and gastric varices develop as portosystemic collaterals when portal hypertension, and specifically a hepatic venous pressure gradient of >12 mmHg, are present [28]. Portal hypertension in turn develops because of increased portal venous inflow from splanchnic vasodilation, intrahepatic vasoconstriction from loss of endogenous nitric oxide, and structural resistance to intrahepatic blood flow from fibrous tissue and regenerative nodules [29, 30]. Pharmacotherapy targeting these abnormalities, such as the vasoactive agents vasopressin, terlipressin, somatostatin, octreotide, and vapreotide, have been studied extensively. The introduction of vasoactive therapy, together with antibiotics and endoscopic treatments, has contributed to improved survival after variceal bleeding over the past two decades [27].

Vasopressin was one of the earliest vasoactive agents investigated for control of variceal bleeding. Although some studies have shown it to be more effective compared to then conventional therapy for hemostasis, survival did not improve [31, 32]. Due to its systemic and splanchnic vasoconstriction, its

potential adverse events include cardiac, bowel and peripheral ischemia, cardiac arrhythmias, hypertension, hyponatremia, and fluid retention. These have limited its clinical use in variceal hemorrhage, despite evidence of the attenuation of side effects by the addition of nitroglycerin [33, 34]. In contrast, terlipressin, a triglycyl lysine synthetic derivative of vasopressin, has the advantages of fewer side effects, and intermittent administration due to a longer half-life. Terlipressin has likewise been studied in combination with glyceryl trinitrate, and early administration together led to more successful hemostasis and increased short-term mortality compared to placebo [35]. Terlipressin's overall efficacy was shown in a 2009 meta-analysis of seven studies with over 400 patients, with a 34 % relative risk reduction in all-cause mortality compared to placebo [36].

Perhaps used more widely around the world currently are somatostatin and one of its synthetic analogues, octreotide, which blunt postprandial hyperemia among cirrhotics, and inhibit release of the vasodilator glucagon, thereby resulting in splanchnic vasoconstriction [37]. The efficacy of somatostatin for control of variceal bleeding was initially shown in the 1990s when Burroughs et al. noted that its use was associated with greater hemostasis and reduced need for balloon tamponade, despite no difference in mortality, compared to placebo in a double blind RCT [38]. Since then, other studies have emerged questioning these benefits, with a 2008 Cochrane review of 21 randomized trials comparing somatostatin or its analogue with placebo, and finding these agents did not reduce rebleeding or mortality [39].

Overall, a meta-analysis of 30 studies involving over 3000 patients in 2012 concluded as a group, vasoactive medications and their analogues (vasopressin, terlipressin, somatostatin, octreotide, and vapreotide) improved hemostasis (RR 1.21; 95 % CI 1.13–1.30), resulted in shorter hospitalization (mean difference –0.71 days; 95 % CI –1.23–0.19) and reduced 7-day mortality (RR 0.74; 95 % CI 0.57–0.95) compared to control, although there was some heterogeneity among studies [40••]. As for differences in the effect between the various vasoactive agents, a recent multicenter non-inferiority trial randomizing 780 patients with variceal bleeding to pre-endoscopy terlipressin, somatostatin, or octreotide showed no differences in 5-day treatment success, rebleeding, or mortality [41•].

Regarding the basis of current recommendations for combined medical and endoscopic therapy, multiple trials have evaluated this with positive results. In the ABOVE trial, pre-endoscopy somatostatin led to fewer actively bleeding esophageal varices being found, easier completion of sclerotherapy at endoscopy, and fewer composite treatment failures over the 5-day infusion period, compared to placebo [42]. Sung et al. randomized variceal bleeders to endoscopic variceal ligation with octreotide versus ligation alone and showed that combination treatment was associated with less recurrent bleeding and reduced need for balloon tamponade [43]. Likewise, vapreotide followed by endoscopic treatment resulted in more patients meeting a primary outcome consisting of control of bleeding and mortality during the 5-day infusion than endoscopy alone [44]. A 2002 meta-analysis of eight randomized trials confirmed the above findings with combined treatment achieving greater initial and 5-day hemostasis, with no difference in mortality [45]. Dosages of currently recommended vasoactive medications for acute variceal bleeding are listed in Table 1.

Use of Antibiotics in Variceal Bleeding

In addition to vasoactive agents, antibiotics have an important role in the acute management of variceal hemorrhage. Cirrhosis is considered an immunocompromised state; hospitalized patients, particularly those with gastrointestinal bleeding, are at risk of infections including spontaneous bacterial peritonitis (SBP), urinary tract infections, and pneumonia, which may contribute to septic shock, multiorgan failure, and death [47]. An updated meta-analysis in 2011 including more than 1000 patients found that antibiotic prophylaxis reduced bacterial

Table 1. Currently recommended vasoactive agents and dosages used for active variceal hemorrhage

Vasoactive agent	Recommended dosage
Terlipressin	2 mg IV q4h then 1 mg IV q4h
Somatostatin	250 µg IV bolus then 250 µg/h IV infusion
Octreotide/vapreotide	50 µg IV bolus then 50 µg/h IV infusion

Source: [46]

infections (RR 0.35, 95 % CI 0.26–0.47), mortality from bacterial infections (RR 0.43, 95 % CI 0.19–0.97), overall mortality (RR 0.79, 95 % CI 0.63–0.98), and rebleeding (RR 0.53, 95 % CI 0.38–0.74) [48]. Among patients with advanced cirrhosis (defined as two of hepatic encephalopathy, ascites, malnutrition, or bilirubin >3 mg/dL), Fernandez et al. showed that intravenous ceftriaxone 1 g per day reduced proven infection (26 vs 11 %, $p=0.03$), and spontaneous bacteremia or SBP (12 vs 2 %, $p=0.03$), with no difference in hospital mortality, compared to oral norfloxacin 400 mg twice a day [49].

In conclusion, vasoactive pharmacotherapy, in combination with antibiotic prophylaxis, and endoscopic modalities represent the current standard of care for the acute management of variceal hemorrhage.

Compliance with Ethics Guidelines

Conflict of Interest

Kelvin L.Y. Lam declare that he have no conflict of interest.
John C. T. Wong declare that he have no conflict of interest.
James Y. W. Lau declare that he have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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