ACUTE UPPER GASTROINTESTINAL HEMORRHAGE: PHARMACOLOGIC MANAGEMENT

SUMMARY

Non-variceal Bleeding: Recurrent gastrointestinal bleeding (GIB) occurs in 15-20% of patients with upper gastrointestinal (GI) hemorrhage. Maintaining a local pH > 5.9 is necessary for coagulation and platelet aggregation. Intravenous proton pump inhibitor (PPI) therapy, administered after successful endoscopic therapy, has been shown to decrease the incidence of rebleeding in high-risk patients and are preferred over H_2-receptor antagonists (H_2RA) (3,4). The eradication of *Helicobacter pylori* has been shown to decrease recurrence of peptic ulcer disease as well as rebleeding (5,6).

Variceal Bleeding: Endoscopic therapy is first-line therapy in the management of bleeding esophageal varices. Although octreotide should not be considered a substitute, it has been successfully used to achieve hemostasis and provides an option in the circumstances where endoscopy is not immediately available or possible. Octreotide is also effective in the prevention of rebleeding following sclerotherapy or ligation and is preferred over vasopressin due to similar efficacy and fewer adverse effects.

RECOMMENDATIONS

- **Level 1**

  Non-variceal Bleeding
  - **Endoscopy should be performed within 24 hours of presentation.**
  - **Proton pump inhibitors (PPI) (pantoprazole 40mg IV Q12H) should be administered to decrease the incidence of rebleeding for up to 72 hours.**
  - **Patients should be continued on oral PPI therapy (pantoprazole 40mg PO Q24H) – duration dependent on indication.**
  - **H_2-receptor antagonists (H_2RA) should not be used in the acute management of non-variceal gastrointestinal hemorrhage.**
  - **Test for and treat *Helicobacter pylori* infection.**

  Variceal Bleeding:
  - **Endoscopy should be performed within 12 hours of presentation.**
  - **Octreotide (25-50 mcg/hr for 2-5 days) is the drug of choice for patients with bleeding esophageal varices.**

- **Level 2**
  - **None**

- **Level 3**
  - **None**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

Approved 12/11/01
Revised 5/16/06, 06/05/12

INTRODUCTION

Non-variceal Bleeding:

The management of acute GI hemorrhage includes volume resuscitation (crystalloid, colloid, and blood), endoscopic therapy, and/or surgery. Unfortunately, recurrent bleeding occurs in 15-20% of cases (1). Patients with endoscopic evidence of active arterial bleeding or non-bleeding visible vessel (NVBB) are at highest risk (90% and 50%, respectively) (2). Those with non-bleeding adherent clot, flat spot, or clean ulcer base have a 25%, <10%, and <5% rebleeding risk, respectively (2). The potential benefit of pharmacologically raising local pH arises from *in vitro* studies demonstrating that coagulation and platelet aggregation are pH dependent (8).Despite medical and surgical advances, the mortality associated with recurrent bleeding remains 10-14% (3). Multiple meta-analysis have demonstrated more consistent pH attainment and probably decreased rate of rebleeding associated with PPIs compared to H_2RAs (4,9,10). Current consensus guidelines recommend high-dose PPI therapy only due to consistently demonstrated reduction in risk of rebleeding and need for surgical intervention (11). More recently, the need for high-dose continuous infusion PPI therapy has been investigated and there was no difference in rebleeding, hospital length of stay, or mortality (12).

Variceal Bleeding:

Primary management of esophageal variceal bleeding is endoscopic therapy (7). However, several medications have been evaluated as adjunctive therapy to endoscopy. These agents include vasopressin, glypressin (or terlipressin), somatostatin, and octreotide. Vasopressin and octreotide are the only agents commercially available in the United States. The use of vasopressin is intended to decrease portal venous pressure and increase clotting and hemostasis. Although vasopressin may provide effective control of bleeding, there is no evidence that overall survival is improved and it has several potential adverse effects including myocardial ischemia. Octreotide, a synthetic somatostatin analogue, is more effective in achieving initial control of bleeding and also as an adjunct to endoscopic sclerotherapy to prevent rebleeding. Octreotide also has fewer complications compared to vasopressin (7, 13-19).

LITERATURE REVIEW

Non-variceal Bleeding:

Green FW, et.al. conducted an *in vitro* study demonstrating that coagulation and platelet aggregation are optimal at a local pH of 7.4. Clotting times doubled at a pH of 6.4 and quadrupled at a pH of 6. Platelet aggregation was 77% (normal 70-84%) at a pH of 7.4 but this decreased to 24% at a pH of 6.8 and no aggregation was observed at a pH of 5.9 (8). Based on this information, the goal of pharmacologic therapy is to maintain an intragastric pH ≥ 6 to facilitate adequate clotting.

The use of H_2RAs versus PPIs has been reviewed in a few clinical trials and a number of meta-analyses (4,9,10). Based on the currently available information, PPIs have been demonstrated to more consistently maintain an intragastric pH ~6, are associated with fewer rebleeding episodes or need for surgery compared to either H_2RAs or placebo (3,4). In patients with actively bleeding ulcers or NBVV, PPIs have been shown to decrease mortality (3).

Current guidelines recommend high-dose continuous infusion PPIs (e.g., pantoprazole 80 mg IV bolus, then pantoprazole 8 mg/hr). However, two recent trials and two meta-analyses have demonstrated no difference in efficacy with low-dose therapy (e.g. pantoprazole 40 mg IV Q12-24H) compared to the high-dose continuous infusion (12, 20-22). Andriulli A, et.al. randomized 474 patients to receive either high-dose (PPI 80 mg bolus, 8mg/hr infusion, n=238) therapy or low-dose (PPI 40 mg IV q24, n=236). The authors demonstrated no difference in rebleeding (11.8% vs. 8.1%, p=0.18), need for surgery (1.3% vs. 0.4%, p=0.62), or mortality (0.8% both) (12). Similarly, Hus Y, et.al. randomized 120 patients to either high dose (PPI 80 mg bolus, 8mg/hr, n=60) or low-dose (PPI 80mg bolus, 40 mg IV Q6H, n=60). The authors demonstrated no difference in rebleeding (6% vs. 8.3%), hospital length of stay, need for surgery or mortality (20).

The treatment of patients who are demonstrated to have *Helicobacter pylori* infection has been demonstrated to decrease rebleeding rates and facilitate ulcer healing. Jaspersen D, et.al. evaluated 51 patients with bleeding duodenal ulcers, who were biopsy-proven *H. pylori* positive. Patients were randomized to receive 40 mg omeprazole each day with ampicillin 1g twice daily in the treatment group

versus omeprazole alone in the control group. Eradication of *H. pylori* was evaluated at repeat endoscopy, both histologically and by urease testing. Ulcer recurrence was reduced in the treatment group to 10% (3/29) versus 41% (9/22) in the control group ($p<0.05$). Rebleeding was also significantly reduced in the treatment group (0%, 0/29) compared to 27% (6/22) in the control group ($p<0.01$) (5).

In summary, proton pump inhibitors are the preferred agents for the treatment of non-variceal gastrointestinal bleeds. As there appears to be no difference in outcome, it is recommended that a once- or twice-daily PPI regimen be used instead of the high-dose continuous infusion. Patients who are confirmed positive for *H. pylori* should be treated with appropriate antimicrobial agents in addition to their PPI therapy.

Variceal Bleeding:
Management of bleeding esophageal varices remains primarily endoscopic with the medications playing an adjunctive role in an effort to decrease rebleeding and improve survival. There are a number of agents which have been studied including vasopressin, glypressin (or terlipressin), somatostatin, and octreotide. Only vasopressin and octreotide are available in the United States (7, 13-19). Two controversies exist within the literature: 1) octreotide versus vasopressin and 2) octreotide alone compared with octreotide plus endoscopic therapy.

Several studies have been conducted comparing vasopressin to octreotide. The first, a randomized, controlled trial, Hwang SJ, et.al. compared the safety and efficacy of vasopressin andoctreotide in the treatment of 48 cirrhotic patients with acute variceal hemorrhage (no mention of endoscopic intervention during treatment). Patients were randomized to receive a continuous infusion of either octreotide (100mcg bolus followed by 25 mcg/hr infusion) or vasopressin (0.4 units/minute infusion) for 24 hours. Initial control of bleeding was achieved in 88% of the octreotide patients versus 54% of the vasopressin patients ($p=0.03$). There was no significant difference in rebleeding at 24 hours. Vasopressin was associated with more adverse effects (including headache, chest pain, and abdominal pain) than octreotide (46% versus 13%, $p=0.02$) (13). Corley DA, et.al. performed a meta-analysis of all trials comparing octreotide versus vasopressin or terlispressin. Octreotide was found to have a significant benefit over vasopressin or terlipressin in preventing rebleeding (RR 0.58; 95% CI 0.42-0.81) (15).

Three studies have been conducted evaluating initial bleeding control with octreotide alone, endoscopic sclerotherapy alone or the combination. Jenkins SA, et.al. conducted a multicenter, open-label, randomized trial comparing octreotide with endoscopic sclerotherapy (ES) in 150 patients with acute variceal hemorrhage. Octreotide was administered as a continuous infusion (50 mcg/hr) for 48 hours. All patients in the octreotide group received ES at the end of the 48-hour infusion. There was no significant difference in bleeding control at 48 hours between the ES only group and the octreotide group (82% versus 85%) (16). Similarly, Besson I, et.al. conducted a multicenter, prospective, double-blind, randomized trial to compare ES alone with ES plus octreotide (25 mcg/hr for 5 days) in 199 patients with cirrhosis and acute variceal bleeding. For the primary endpoint of survival without rebleeding at 5 days, the combination of ES plus octreotide was more effective than ES alone (87% versus 71%, $p=0.009$) (17). Finally, Freitas DS, et.al. conducted a prospective, randomized trial comparing octreotide alone verse ES for the prevention of early rebleeding in patients with recent bleeding from esophageal varices. They also compared ES alone with ES plus octreotide in patients with actively bleeding esophageal varices. Octreotide was administered as a continuous infusion (25 mcg/hr for 48 hours). In patients with recent bleeding, there was no significant difference in hemostasis between ES and octreotide at 48 hours. In patients with active bleeding, ES plus octreotide was superior to ES alone in achieving initial hemostasis (98% vs. 74%, $p<0.001$). The difference remained significant at 48 hours (81% vs. 60%, $p < 0.04$) (18).

In summary, endoscopic therapy remains the most effective modality for managing variceal hemorrhage. However, the addition of octreotide at 25-50 mcg/hr appears to further improve rates of early rebleeding and is well tolerated. Vasopressin should not be used due to its significant side effect profile. There is little evidence that any of the treatment modalities have any significant impact on overall mortality.

REFERENCES

1. Savides TJ, Jenson DM. Severe gastrointestinal hemorrhage. In: Grenvik A, Ayres SM, Holbrook PR, Shoemaker WC (Eds). *Textbook of Critical Care.* Fourth Edition. Philadelphia, WB Suanders Company, 2000; pp 1609-16.
2. Freeman ML. The current endoscopic diagnosis and intensive care unit management of severe ulcer and other nonvariceal upper gastrointestinal hemorrhage. *Gastrointest Endosc Clin N Amer*. 1991;1:209-39.
3. Barkun AN, Bardou M, Kulpers EJ, et.al. International concensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010;152:101-13.
4. Huggins RM, Scates AC, Latour J. Intravenous proton-pump inhibitors versus H_2-antagonists for treatment of GI bleeding. *Ann Pharmacother.* 2003;37:433-7.
5. Jaspersen D, Koerner T, Schorr W, et.al. *Helicobacter pylori* eradication reduces the rate of rebleeding in ulcer hemorrhage. *Gastrointest Endosc.* 1995;41:5-7.
6. Rokkas T, Karameris A, Mavrogeorgis A, et.al. Eradication of *Helicobacter pylori* reduces the possibility of rebleeding in peptic ulcer disease. *Gastrointest Endosc.* 1995;41:1-4.
7. Garcia-Tsao G, Sanyal AJ, Grace ND, et.al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatoogy.* 2007;46(3):922-38.
8. Green FW, Kaplan MM, Curtis LE, et.al. Effect of acid and pepsin on blood coagulation and platelet aggregation. *Gastroenterology.* 1978;74:38-43.
9. Netzer P, Gaia C, Sandoz M, et.al. Efffect of repeated injection and continuous infusion of omeprazole and ranitidine on intragastric pH over 72 hours. *Am J Gastroenterol.* 1999;94:351-7.
10. Labenz J, Peitz U, Leusing C, et.al. Efficacy of primed infusions with high dose ranitidine and omeprazole to maintain high intragastric pH in patients with peptic ulcer bleeding: a randomized controlled study. *Gut.* 1997;40:36-41.
11. Lau JY, Sung JJ, Lee KK, et.al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med.* 2000;343:310-6.
12. Andriulli A, Loperfido S, Focareta R, et.al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. *Am J Gastroenterol.* 2008;103:3011-18.
13. Hwang SJ, Lin HC, Chang CF, et.al. A randomized controlled trial comparing octreotide and vasopressin in the control of acute esophageal variceal bleeding. *J Hepatol.* 1992;16:320-5.
14. Avgerinos A, Armonis A, Raptis S. Somatostatin and octreotide in the management of acute variceal hemorrhage. *Hepato Gastroenterol.* 1995;42:145-50.
15. Corley DA, Cello JP, Adkisson W, et.al. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology.* 2001;120:946-54.
16. Jenkins SA, Shields R, Davies M, et.al. A multicentre randomized trial comparing octreotide and injection therapy in the management and outcome of acute variceal haemorrhage. *Gut.* 1997;41:526-33.
17. Besson I, Ingrand P, Person B, et.al. Schlerotherapy with or without octreotide for acute variceal bleeding. *N Engl J Med.* 1995;333:555-60.
18. Freitas DS, Sofia C, Pontes JM, et.al. Octreotide in acute bleeding esophageal varices: a prospective randomized study. *Hepato Gastroenterol.* 2000;47:1310-14.
19. Sung JJ, Chung SCS, Yung MY, et.al. Prospective, randomized study of the effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. *Lancet.*1995;346:1666-9.
20. Hsu Y, Perng C, Yang T, et.la. A randomized controlled trial comparing two different dosages of infusional pantroparzole in peptic ulcer bleeding. *Br J Clin Pharmacol.*2010;69(3):245-51.
21. Wu L, Cao Y, Huang J, et.al. High-dose *vs* low-dose proton pump inhibitors for upper gastrointestinal bleeding: a meta-analysis. *World J Gastroenterol.* 2010:16(20):2558-65.
22. Wang C, Ma MH, Chou H, et.al. High-dose vs non-high-dose proton pump inhibitors after endscopic treatment in patients with bleeding peptic ulcer. *Arch Intern Med.* 2010:170(9):751-8.