

# **A Comparison of Continuous Infusion or Twice-Daily Dosage of Pantoprazole to Prevent Recurrent Bleeding in Hospitalized Patients Presenting with Upper GI Bleeding Secondary to Peptic Ulcer Disease**

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## **A. Study Purpose and Rationale**

The purpose of the study is to compare the efficacy of continuous IV infusion to BID dosage of a proton-pump inhibitor (PPI) to prevent rebleeding in post-endoscopy patients who present to the hospital with an acute peptic ulcer bleed and receive endoscopy.

There are approximately 150,000 hospitalizations per year in the U.S. for evaluation and treatment of bleeding ulcers, and peptic ulcer is the most common cause of acute gastrointestinal hemorrhage, accounting for about 50 percent of the cases(1). The mortality rate has remained around 6 to 7 percent for the past 30 years despite advances in diagnoses and treatment. A majority of patients undergo esophagogastroduodenoscopy within 24 hours of hospitalization. The endoscopic appearance of an ulcer may provide the most helpful prognostic information regarding rebleeding. Several recent studies have shown that rebleeding occurs in 6 to 22 percent of patients post-endoscopy (4-7). Ulcers which possess a "high stigmata" of re-hemorrhage include those with a visible vessel, an adherent clot, or active bleeding as seen on endoscopy. Patients with ulcers larger than 1 or 2 cm in diameter also have increased rates of rebleeding, even after endoscopic hemostatic therapy.

Most episodes of rebleeding occur within three days after the initial episode. Data from in vitro studies suggest that clotting proceeds more efficiently at higher pH levels, and that platelet aggregation and fibrin formation occurs at a pH of 6 or higher. Two recent studies have shown no significant differences between rebleeding rates in patients taking an H2 blocker (famotidine) or placebo either in the acute setting or as maintenance therapy (3). In 2000, a double-blind trial in Hong Kong showed that patients treated with IV infusion of high dose proton-pump inhibitor (omeprazole) after presenting to the hospital for an acute peptic ulcer bleed rebled at a rate of 6.7 percent as compared to 22.5 percent in the placebo group (2).

There has been evidence that aggressive acid suppression with intravenous omeprazole reduces the rate of recurrent bleeding in patients hospitalized for bleeding ulcers, but there has not yet been a head-to-head trial comparing continuous IV infusion versus IV BID dosing, as is routinely done in our institution.

## **B. Study Design and Statistical Analysis**

The study will be a prospective, double-blinded randomized study. Patients who present to the hospital with symptoms of an upper GI bleed will undergo standard endoscopy per routine. Consent is obtained prior to endoscopy. Pre-endoscopy, patients will be treated with standard medical procedure. Post-endoscopy, patients who qualify for the study will be enrolled and randomized to receive a continuous IV administration of pantoprazole or a BID IV dosage of pantoprazole. All subjects will receive continuous infusion of either normal saline or pantoprazole, and all subjects will receive BID IV injections of pantoprazole or normal saline. Nurses and physicians caring for the subject will be blinded as to which protocol is administered.

Rebleeding will be defined as vomiting fresh blood, hypotension (SBP of 90mm Hg or less or a pulse rate of 110 per minute or more) and melena, BRBPR, or a requirement of more than 2U of PRBC

within 72 hours post-endoscopy (2). Subjects will undergo repeat endoscopy as per routine if rebleeding occurs. If after 72 hours of endoscopy, there is no evidence of rebleeding and the subject tolerates a regular diet, they will be discharged.

Power calculations indicate that 588 subjects will be needed for each arm to indicate a difference of 5% in rebleeding rates (12% in the BID dosage group, and 7% in the continuous IV infusion group). The endpoint of the study is recurrent bleeding after endoscopy, as defined previously, or discharge. Data will be analyzed to the intention-to-treat principle. Pearson's chi-square test will be used to analyze categorical data.

### **C. Study Procedure**

Upon admission to the hospital, patients will be treated with standardized therapy: IVF, PPI bolus, serial CBC, transfusions as needed. They will be admitted to the ICU or regular floor per hospital protocol. After informed consent is obtained, endoscopy will be performed. Post-endoscopy, qualified patients will be enrolled in the study.

Post-endoscopy, subjects will have bloods drawn twice a day (unless bleeding occurs), and will have an IV until discharge (minimum of 72 hours after endoscopy).

### **D. Study Drugs**

Pantoprazole is a proton-inhibitor that is approved by the FDA for treatment of acute peptic ulcer bleeding. Previous clinical studies have shown that both the IV and PO dosing are safe and efficacious for use in acute peptic ulcer bleeding. The dosage for continuous IV infusion is 8mg/hr, and the twice-daily dosage is 40mg IV BID. Pantoprazole may also be administered PO, but in the acute setting, IV administration allows the pH of the GI tract to reach an ideal level more rapidly to allow platelet aggregation and fibrin formation.

Known rare side effects include blood dyscrasias, hepatic dysfunction, anaphylaxis, pancreatitis, and interstitial nephritis. Common reactions include headache, diarrhea, and thrombophlebitis. Pantoprazole is classified as pregnancy class B.

### **E. Medical Device**

Endoscopy will be performed by board-certified and experienced gastroenterologists per routine at the hospital.

### **F. Study Questionnaires**

N/A

### **G. Study Subjects**

Inclusion criteria: age above 18, GI bleed secondary to peptic ulcer disease, "high stigmata" of rebleeding from the ulcer as seen on endoscopy. The definition of high stigmata: active bleeding, a nonbleeding visible vessel, or a vessel hidden beneath a clot.

Exclusion criteria: pregnant women in 1<sup>st</sup> trimester of pregnancy.

### **H. Recruitment of Subjects**

Potential subjects will be identified in the emergency room. Patients presenting with symptoms of an upper GI bleed (abdominal pain, melana, BRPBR, h/o NSAID use, h/o peptic ulcer disease) and

who will be undergoing upper endoscopy will be approached. Informed consent will be obtained with consent for endoscopy.

#### **I. Confidentiality of Study Data**

All study data will be coded. Once enrolled, patients will be identified with a number. Only the investigator will have information regarding which number represents which patient. Data will be stored in a secure location, accessible only to the investigators.

#### **J. Potential Conflict of Interest**

N/A

#### **K. Location of Study**

The emergency room, endoscopy suite, ICU, and regular floors at CPMC and those equivalent locations at other participating institutions.

#### **L. Potential Risks**

Both arms of the study population will be receiving standard treatment for an acute peptic ulcer bleed. The endoscopy, the insertion of a working IV, and the twice daily blood draws could provide discomfort to the patient, but this is all standard hospital protocol.

#### **M. Potential Benefits**

The subjects enrolled might benefit from a decrease in mortality/morbidity.

#### **N. Alternative Therapies**

N/A

#### **O. Compensation to Subjects**

N/A

#### **P. Costs to Subjects**

N/A

#### **Q. Minors as Research Subjects**

N/A

#### **R. Radiation or Radioactive Substances**

N/A

#### **S. References**

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