Continuation of Low-Dose Aspirin Therapy with Either PR or PO Administration in Patients with Peptic Ulcer Bleeding

IRB Protocol
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A. Study Design and Purpose

Aspirin has been well established to reduce the risk of subsequent vascular events in patients with previous ischemic events by 22%[1]. However aspirin also increases the risk of Peptic ulcer bleeding by 2 to 3 fold [2]. Enteric coded aspirin has not been shown to decrease this risk of bleeding[3]. Switching to other antiplatelet agents, such as clopidogrel, has not decreased rates of peptic ulcer bleeding[4].

Based on the risk of aspirin associated with peptic ulcer bleeding, the standard protocol, when a patient presents with a bleed, is to stop aspirin until the ulcer has fully healed [5]. A recent study suggests that there may be a mortality benefit of continuing aspirin during a peptic ulcer bleed, if the bleeding was controlled, and that might outweigh the increased risk of recurrent bleeding. The study suggested that although the risk of rebleeding roughly doubled, there was 11.6 absolute difference in mortality reduction. Based on this study, if the risk of rebleeding could be reduced, there may be further mortality and morbidly benefit.[5]

It has been postulated that aspirin induces the effect of increased peptic ulcer bleeding in 2 ways: it causes irritation and injury to the gastric mucosa and a systemic effect [3]. This effect is mediated through the inhibition of cyclooxygenase enzymes which decrease production of prostaglandin PG E2 which protects the upper gastrointestinal tract by increasing mucous and bicarbonate secretion, surface epithelial cell hydrophobicity and mucosal blood flow[10]. It is believed that there is a local effect on the mucosa by aspirin. Although the mechanism has not been fully elucidated, it is hypothesized to be secondary to increased local prostaglandin suppression [11]. If a patient were to take rectal aspirin, this may decrease the local effect, thereby decreasing the rebleeding rate. There have been studies that showed that rectal administration of aspirin can achieve the same blood levels as po administration [6]. In this study, we hypothesize that if patients with peptic ulcer bleeding suspected to be caused by aspirin, are switched to rectal aspirin instead of continuing with oral aspirin, their rate of rebleeding will decrease.

B. Study Design and Statistical Analysis

Patients will be randomly assigned to either rectal or po administration of aspirin in a 1:1 fashion in this multi-center, double blind, randomized control trial. The patients will receive both a po and rectal pill daily, one will be a placebo and the other pill will be active depending on the group to which they are assigned. This allows for both the patient and the physician to be blinded. The random allocation sequence will be generated by the Department of Medical statistics with the blocked randomization method.

The primary outcome will be recurrent bleeding within the 30 days after endoscopic treatment. This will be defined as having clinical evidence of rebleeding, which includes: hematemesis, melena after normal stool, hemoglobin drop of 2 or more g/dl in a 24 hour period, requiring 2 or more units of blood in, or unstable vital signs (hypotension systolic bp less than 90 or tachycardia greater that 110) and another endoscopy confirming bleeding (arterial spurter, nonbleeding visible vessel, adherent clot, or fresh blood in the stomach).

Secondary outcomes will include all cause mortality, death attributed to cardiovascular, cerebrovascular or gastrointestinal complication, ischemic events (defined by the American College of cardiology guidelines for cardiac events and the WHO cerebrovascular criteria) [7,8], lower gastrointestinal bleeding, and aspirin blood levels in the two groups.

In order to achieve 80% power with a P value of 0.05, a sample size of 1422 people in each group was calculated using the Chi-square test assuming minimal clinically significant effect size of a 7% versus 10% risk of rebleeding in the rectal versus po aspirin groups.
Data will be analyzed using the Chi-squared test when calculating the primary outcome and a t-test to compare group differences.

C. Study Procedure

Consecutive patients who present with signs suggestive of upper gi bleeding (melena, hematemesis), will be screened and if eligible (as described in the study subject section -- having signs of peptic ulcer bleeding that are successfully treated with endoscopic procedure and are on aspirin for secondary prevention), will be randomized to either 300mg aspirin administered rectally or 81 mg po aspirin [9]. Then they will have an endoscopic exam that will identify that the patient has an upper gastrointestinal bleed, treat the bleed and prove that it is controlled. This must be done within 24 hours of onset of upper gastrointestinal bleeding. They will also be treated with standard therapy for ulcer bleeding, meaning intravenous esomeprazole of 80 mg followed by an infusion of esomeprazole 8mg/h for 72 hours and then transition to 40 mg/d orally. They then will be followed for signs of rebleeding, as described above. If clinical signs were met, the patient would undergo endoscopy to evaluate if the criteria for a rebleed are met. They will also be followed for signs of lower gastrointestinal bleeding, which include the same clinical criteria as for upper bleeding described above, plus bright red blood per rectum. Blood levels of aspirin will be measured at day 1, 15, 30. The care of the patient will be led by the medical teams at the hospital where the patient was admitted while the patient is in the hospital, and that team will determine when the patient is ready for discharge.

The patient will be required to make a clinic visit with a study physician at 15 and 30 days if not still in the hospital, when blood will be drawn. Patients will be advised on what may be signs of rebleeding and educated that they should emergently to go to the hospital if they have those signs.

D. Study Drugs

Aspirin is a white tablet that has many different strengths. In this study, an 81 mg tablet will be taken by mouth and a 300mg tablet that will be administered rectally. There have been many studies on the efficacy and toxicity of aspirin, as discussed in the review section. The toxicity being tested in this study will be gastric mucosa damage leading to impaired healing and increased rebleeding rates.

Inactive ingredients in the tablets will include carnauba wax, corn starch, hypromellose, powdered cellulose, and triacetin. The appropriate number of tablets will be dispensed at time of discharge from their hospital visit. A pill count will also be performed at the 30 day visit to ensure compliance with study medications.

E. Medical Device

Not applicable.

F. Study Questionnaires

Not applicable

G. Study Subjects

Inclusion criteria: Patients must be 18 or older and must have peptic ulcer on endoscopy showing active bleeding, visible blood vessels, or adherent clots that were successfully treated by endoscopic therapy and continue to require low dose aspirin for prophylaxis or treatment of cardiovascular disease. The indications for low dose aspirin include prophylaxis of established cardiovascular or cerebrovascular disease that requires regular anti-platelet therapy.

Exclusion criteria: Asprin use for primary prevention. Any patient whose bleeding was not controlled with hemostasis during endoscopy, with ulcer perforation, known sensitivity to ppi, previous gastrectomy, or vagotomy, patients on concomitant anticoagulant, corticosteroids, NSAIDS, patients who are pregnant, or have a GFR less than 30 at the time of admission.

H. Recruitment of Subjects

Patients will be recruited at the time of admission for suspected upper gastrointestinal bleeding in the emergency department at CPMC, Weill Cornell, Mount Sinai, and NYU medical center.

I. Confidentiality of Study Data

All study data will be stored in a confidential manner. All study materials will be coded with a unique subject identifier, as assigned in the study. This will not include any personal identifiers.

J. Potential Conflict of Interest

There are no conflicts of interest.

K. Location of Study

The study will be conducted in the hospital setting of the following hospitals: CPMC, Weill Cornell, Mount Sinai, and NYU medical center and in the clinic of the study physicians office at CPMC.

L. Potential Risks

Potential risks include: the increased risk of bleeding when taking aspirin while having a bleeding ulcer. This may lead to death or increased hospital stay. There is also the mental discomfort, physical discomfort from blood drawing or taking a medication rectally.

M. Potential benefits

The main effect would be that rectal aspirin would decrease the risk of rebleeding, while preserving the mortality benefit of aspirin in this high risk patient population.

N. Alternative Therapies

There have been no studies showing that there is a reduced risk of bleeding by switching to other antiplatelet medication. However evidence suggests that there may be an increased mortality from stopping aspirin.

O. Compensation of Subjects

Subjects will receive all study medications free of cost. All medical visits outside the hospital admission and laboratory tests will also be provided free of charge. Patients will also be reimbursed for the cost of travel to and from clinic visits. No other compensation will be provided.

P. Costs to Subjects

There will be no cost to subjects outside of the normal charges for hospitalization.

Q. Minors as Research Subjects

Patients under the age of 18 will not be included in this study.

R. Radiation or Radioactive Substances
Not applicable

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