PROTOCOL TITLE:

Comparison of 24-hours versus 72-hours of octreotide infusion along with endoscopic therapy in preventing early rebleed from esophageal varices: a multi-center, randomized clinical study

PRINCIPAL INVESTIGATOR:

Don Rockey, MD

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1.0 Objectives / Specific Aims

The objective of this study is to determine the safety and efficacy of 24-hours vs. 72-hours continuous infusion of octreotide after successful endoscopic treatment of esophageal varices and overt gastrointestinal bleeding.

2.0 Background

Esophageal variceal hemorrhage due to portal hypertension is a dreaded clinical complication in patients with cirrhosis and is associated with significant morbidity and mortality.[1] It is usually managed with pharmacologic, endoscopic, and radiological techniques, and sometimes surgery.[1] The current standard of care includes intravenous infusion of the somatostatin analogue, octreotide, which is usually started as soon as variceal hemorrhage is suspected, followed by urgent or emergent endoscopy, and treatment typically with band ligation (EBL) within 8 to 24 hours.[1,2] Intravenous octreotide is then continued for three, and up to five days, although currently available guidelines are not clear on the appropriate duration of therapy.

The rational for using octreotide is that it reduces portal blood flow, which reduces portal pressure, and hence reduces the propensity for variceal bleeding. The pharmacology of octreotide suggests that the benefits are transient due to desensitization and/or tachyphylaxis.[3] The appropriate duration of continuous octreotide infusion is uncertain and largely based on expert opinion. Prolonged infusion of octreotide is thus likely to be unnecessary, and may inappropriately increase hospital and medical costs.

In randomized-controlled trials, the duration of vasoactive drugs has varied between 8-hours and 6-days.[4,5] Most studies that show benefits of octreotide in decreasing recurrent variceal bleeding compared octreotide with other vasoactive agents, such as vasopressin and terlipressin.[6-8] A few also compared octreotide with endoscopic sclerotherapy. The standard of care for bleeding esophageal varices is octreotide and EBL. However, the role of continuing octreotide after successful EBL is unclear. One pharmaceutical-sponsored randomized trial in 1995 showed that the relative risk (RR) of rebleeding was lower in patients when octreotide infusion was continued for 5-days after EBL compared to patients with EBL alone (RR=0.22).[9] In this study, however, octreotide was not given prior to endoscopy, which is now part of the standard-of-care. A second pharmaceutical-sponsored multicenter, randomized, double-blind study compared vapreotide (another synthetic somatostatin analogue) to placebo in patients with suspected esophageal or gastric variceal bleeding.[10,11] Patients were randomized to receive vapreotide or placebo at the time of presentation and the treatment was continued for 5-days after endoscopic treatment (sclerotherapy or band ligation). Control of bleeding and survival was significantly better on vapreotide (compared to placebo) at the time of endoscopy (69% vs. 54%), at 48-hours (73% vs. 54%), and at Day 5 (66% vs 50%). There was no difference in recurrent bleeding after 3 days, duration of hospitalization, or mortality. Notably, the difference in bleeding and survival occurred within the first 6-hours of vapreotide infusion vs. placebo, and then became non-significant suggesting that the effect occurs early on.

In a recent randomized-controlled trial, patients were started on octreotide infusion before endoscopic therapy (band ligation or sclerotherapy) and then octreotide was continued for 2-days vs. 5-days.[5] Two days of octreotide infusion were found to be as efficacious as the 5-days of infusion in preventing early rebleed, suggesting that prolonged infusion of octreotide may be unnecessary.

The above studies suggest that octreotide infusion for longer than 24 hours may be clinically unnecessary, which also raises the issue of the expense of continuing the medication. Hence we propose a randomized study to determine whether shortening the length of time of octreotide after endoscopic band ligation affects the rate of variceal rebleeding.

3.0 Intervention to be studied (if applicable)

The study will be a prospective, randomized-controlled multi-center study.

- Patients with overt, or active, variceal bleeding will be randomized to octreotide infusion for either 24-hours or 72-hours following successful endoscopic band ligation (EBL).

4.0 Study Endpoints (if applicable)

Primary Endpoint:

- Rebleeding within 72-hours after control of hemostasis with EBL

Secondary Endpoints:

- Rebleeding within 7 and 30-days
- Survival within 7 and 30-days
- Complications from octreotide, including, but not limited to: pneumonia, cardiac complications (arrhythmias, heart failure, cardiac ischemia), paralytic ileus, hyperglycemia, diarrhea, abdominal pain, nausea

Rebleeding within 72-hours will be defined as any of the following:

- A drop in hemoglobin by more than 20 percentage points from baseline
- Sustained tachycardia above 100 beats per minute, with or without hematochezia or melena
- Transfusion of >2 unites packed red blood cells after EBP
- Recurrence of hematemesis or ongoing melena
- Urgent or emergent need for Transjugular Intrahepatic Portosystemic Shunt (TIPS)." to control suspected rebleeding

Rebleeding after 72-hours will be defined as:

- Any new episode of hematemesis, melena, or hematochezia (with hemodynamic instability)
- Drop in hemoglobin by more than 20 percentage points OR the need for >2 units packed red blood cells
- Need for TIPS or surgery to control suspected bleeding

Patients who rebleed will be treated per hospital standard of care and physician preference. Treatment of rebleeding will be recorded.

Follow-up Endpoints:

Thirty, 60, 90,180-day, and 1-year follow-up.
Rebleeding after 72-hours will be defined as:

- Any new episode of hematemesis, melena, or hematochezia (with hemodynamic instability)
- Drop in hemoglobin by 20 percentage points OR need for >2 units packed red blood cells
- Need for TIPS or surgery to control suspected bleeding

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria
All patients over the age of 18-years with suspected upper gastrointestinal bleed (GIB) due to esophageal varices and in whom octreotide is initiated will be eligible.

Inclusion Criteria:

1. Adult males and females who are 18 years of age or older.
2. Evidence or suspicion of upper GIB at presentation defined as either:
    a. Patient presenting with melena or hematemesis
    b. Patient presenting with bright red blood per rectum, along with hypotension (systolic blood pressure <90mmHg and diastolic blood pressure <60mmHg) and tachycardia (heart rate >155 beats per minute)
3. Patient with known or suspected cirrhosis:
    a. Historical biopsy indicating cirrhosis
    b. Suspected cirrhosis defined as both:
        i. Clinical data (ex: platelets less than 120,000/L)
        ii. Nodular liver on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI)

4. Upper GIB secondary to bleeding esophageal varices as show by esophageal endoscopy, requiring endoscopic band ligation (EBL) at presentation
5. Willing and able to provide informed consent for study.

Exclusion Criteria

1. Known upper gastrointestinal malignancy
2. Bleeding from gastric varices, with or without esophageal varices
3. Use of any other endoscopic method to stop GI bleeding beyond endoscopic band ligation, including injectables such as sclerosants, epinephrine, saline, endoscopic clips, endoscopic suturing, etc.
4. Variceal bleeding in the last 90 days
5. History of TIPS or vascular decompression surgery
6. Pregnant females
7. Incarcerated individuals
8. Myocardial infarct, cerebrovascular accident, sepsis, respiratory failure, or severe intercurrent illness within the previous 6 weeks
9. Non-cirrhotic portal hypertension causing esophageal varices
10. Known or suspected allergy to octreotide

Linkages to subjects: Sequential numbers will be assigned to patient information collected and entered into a database. Patient identifiers will be stored separately (with the informed consent forms) from extracted data – with data code-linked to identifiers. Only study staff personal at the institution where the patient has been enrolled will have access to PHI. Therefore, while patient data will be stored on the secure server where MUSC study staff will have access the patient identities from other sites will not be stored here. This is to keep the patients identities confidential. All records will be kept on a secure server that will be erased six years after the completion of the study.

6.0 Number of Subjects

We anticipate enrolling approximately 40 subjects at the local MUSC site, with a goal of 160 patients for the entire study)

7.0 Setting

This study will be conducted at the inpatient wards at MUSC.

Study Sites

Study Sites

Lead Site: Medical University of South Carolina
Lead Investigator: Don C. Rockey

Ohio State University

University of Florida-Jacksonville

University of Texas, at Austin

Texas Tech University Health Sciences Center, El Paso

University of Illinois in Chicago

Oregon Health & Science University

The other investigators will be obtaining their own IRB approvals at their respective sites listed above. Dr Rockey (MUSC) will serves as the lead investigator for this study, he will oversee the validity of the data and eligibility of all enrolled subjects. All study data will be kept on REDCap. Only the Primary site (MUSC) will have access to other site's data. Collected data will include patient demographics, clinical data, labs, images, hospital stay course during enrollment period and follow up visits.

8.0 Recruitment Methods

Cirrhosis patients presenting with suspected upper GI bleeds presenting to the involved hospital sites are always seen by consultant– either the attending or fellow – from the Gastroenterology and Hepatology Services. Therefore, identification of potential subject for the study will be through chart reviews of current inpatients by the consult and study team and by consult requests to the GI/Hepatology team. All members of the study team can access the consult lists as well as inpatient lists for individuals presenting with upper GIB and all consult team members and study team members will be added as additional study members to this protocol in order to have IRB-approval to recruit subjects.

9.0 Consent Process

This research study will involve obtaining informed consent from potential subjects.

The need for endoscopic therapy cannot be anticipated, so informed consent will be obtained prior to endoscopy from the patient when appropriate, upon presentation to MUSC with a suspected variceal bleed. Potential patients will be approached for participation in this study by a member of the IRB-approved study team and the informed consent form and HIPAA form will be reviewed – verbal review and a written/printed consent available for review with the subject.

Ample time will be allocated between informing the prospective participant and obtaining written consent will vary but will ultimately depend on how long the potential participant requires for all his/her questions to be answered to the best of the study team's ability.

Additionally, the patient will have time to read the consent and HIPAA forms on their own prior to discussing with research staff.

10.0 Study Design / Methods

This prospective and randomized controlled trial will involve administration of either octreotide infusion for 24-hours (Group A) or for 72-hours (Group B). This study involve the following:

Screening

Esophageal varices as the sole cause of upper gastrointestinal (GI) bleeding will need to be confirmed. Endoscopic band ligation will be performed per standard of care when deemed appropriate by the treating physician.

During this time, and regardless of participation in the research study, octreotide will be administered per standard-of-care before endoscopy. Endoscopy with band ligation will be performed per standard-of-care, if needed. Not all patients may have variceal bleeding and even if varices are present, not all may need EBL. Only patients who receive EBL for varices with stigmata of bleeding will be randomized for the study, to receive octreotide infusion for 24- or 72-hours after successful EBL. Subsequent care will be per the primary team and not affected by participation in the study.

Treatment:

Randomization will be conducted for all enrolled subjects at all site by the study coordinator and coinvestigators at MUSC. Only after undergoing EBL will patients be randomized by computer-generated blocked randomization for treatment allocation. The randomization schedule will be blinded in sequentially numbered opaque envelopes.

Patients will be randomized to receive octreotide as a continuous intravenous infusion for 24-hours or 72-hours after the infusion is started. Following standard-of-care for variceal bleeding, all patients will be monitored in the hospital for at least 72-hours after undergoing esophagogastroduodenoscopy (EGD) and EBL. Any recurrent bleeding will be managed per standard-of-care, which may include a combination of octreotide infusion, placement of an esophageal balloon tamponade tube (i.e. Minnesota tube, or similar), repeat endoscopic intervention, referral to Interventional Radiology for transjugular intrahepatic portocaval shunt (TIPS), or surgery.

Follow-Up:

The follow-up of this study will take place until 1-year after the initial bleeding episode and information will be collected via chart reviews of the medical records and follow-up phone calls at: 30-days, 60-days, 90-days, 180-days, and 1-year after the initial visit. Phone calls will take

approximately 15 minutes and will consist of questions regarding the patients general health status, cirrhosis related health complications and possible side effects of octreotide.

Collected Data:

Additional data collected from medical records during this study will include:

1. Patient demographics including race and ethnicity
2. Presenting symptoms and physical exam findings
3. Past medical history
4. Laboratory results – complete blood count (CBC), liver function tests, ammonia (if checked per hospital standard of care), hepatitis serologies
5. Imaging findings – liver morphology, patency of portal vein
6. Medications – outpatient and during admission
7. Paracentesis
8. Use of antibiotics
9. Time to endoscopy
10. Endoscopic findings
11. Endoscopic treatment
12. Thirty, 60, 90, 180-day and 1 year follow-up will gather the following information as available:
    a. Patient alive or not
    b. Laboratory results – complete blood count (CBC), liver function tests, ammonia (if checked per hospital standard of care), hepatitis serologies
    c. Medication
        i. Betablockers
        ii. Antibiotics
    d. Rebleeding
    e. Endoscopic findings and treatment

11.0 Data Management

Statistical Analysis:

The study design is a non-inferiority study. Primary hemostasis of esophageal variceal bleeding is highly successful (90%), despite rebleeding rates of 10-30%. A superiority trial of primary hemostasis would require a very large number of patients, would require significant resources and would take a long time to recruit.
A non-inferiority trial is appropriate to demonstrate that receiving octreotide for 24 hours is not inferior to the standard of care of 72 hours.

Assuming a primary hemostasis rate of 90% and a non-inferiority margin of 15%, 69 patients will be needed in each group to achieve 90% power. This calculation assumes a type I error rate of 0.05 and equal sample sizes. Anticipating patient drop-out of approximately 15%, a sample size of 80 patients will be required.

Qualitative variables in the two groups will be compared using chi-squire test with Yates' correction of Fisher's exact test, when applicable, and represented as percentages. The Mann-Whitney test will be used to compare quantitative variables, which will be expressed as means ± standard deviations (SD).

Factors associated with re-bleeding and complications will be identified. Logistic regression modeling will be used to assess differences in re-bleeding between the two groups adjusting for significant confounding variables.

All data collected from patients at all sites will be entered in a Redcap project that will be created at MUSC. All sites will have access to this project, however each site will only have viewing and editing rights to the subjects that have been entered by that specific site.

Costs and Payments:

All costs associated with the protocol are part of the routine and standard-of-care for patients with variceal hemorrhage. The researchers, the study patients, or the participating sites will not be remunerated for their participation.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects (if applicable)

Data Safety Monitoring Board (DSMB):

After 25, 50, and 75% of the research subjects are enrolled in the study an independent, internal data safety and monitoring board (DSMB) meeting in which we will present accrual and safety data to group members. If the accrual rate is not reached, we will conduct a DSMB meeting at least semi-annually. The DSMB will review any SAEs as they occur. The DSMB will be composed to non-study associated members, specifically: 2 gastroenterologists and 1 statistician at the Lead Investigating Site (MUSC) and it will be responsible for reviewing the data at all sites individually and the data for the study as a whole.

All adverse events including incidences of bleeding in both the control and experimental group will be recorded and submitted to the Institutional Review Board (IRB) within 10 business days. If a serious adverse event occurs, this will be reported to the IRB within 2 business days. The descriptions and definitions of adverse or serious adverse events will be followed and if any adverse events occur, we will report these to the IRB.

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14.0 Risks to Subjects

Octreotide:
Octreotide infusion has been documented to cause tachyphylaxis and hence not effective when given longer than 24 hours. However, it is possible that a shorter duration of 24-hour compared to 72-hour of octreotide may lead to a higher re-bleeding rate, even after endoscopic evaluation and treatment.

Confidentiality:
A confidentiality breach is a risk associated with any study. However, the information attained from this study will be minimized by (1) removing direct participant identifiers, such as medical record numbers and names; (2) securing, in a separate location, and limiting access to information linking codes (i.e. linkage codes) with direct participant identifiers; and (3) limiting access to information to the study team

15.0 Potential Benefits to Subjects or Others

Individual subjects are not likely to derive direct benefit from participating in the study. Potential benefits associate with participation in this study include that length of stay or intensive care unit stay may be shorter for patients receiving octreotide treatment for 24 hours. Thus, it is possible that the hospital stay associated costs or complications related to hospitalization would be avoided. It is anticipated that important data will be obtained in this study, which will help other patients with esophageal variceal hemorrhage and enrich the medical literature.

The reduction in duration of octreotide therapy poses a potential benefit (reduction in exposure to medication and hospital resources, potential reduction in hospital length of stay, etc), but data supporting a longer octreotide infusion requires confirmation. All procedures and medical therapy are standard of care and therefore additional risks due to these interventions are not anticipated. The data generated from this study are likely to alter management paradigms in patients with esophageal variceal hemorrhage.

16.0 Sharing of Results with Subjects

All results during study treatment and during the inpatient admission for the initial bleed will be shared with subjects and will be part of the subject's MUSC medical record. If the subject has never been an MUSC patient, then a MUSC medical record will be created upon their presentation with an upper GIB. All information within the medical record can be viewed by individuals authorized to access the record and every effort will be made to keep confidential all research information in the medical record that can identify a subject to the extent allowed by law.

Information collected during follow-up endpoints will be stored on a password-secure database created by the Clinical Data Warehouse at MUSC – the WebDCU – which is accessible only to members of the IRB-approved study team. All information in the WebDCU is code-linked to each subject and code-linked data is stored separately and will be accessible only if absolutely necessary by members of the IRB-approved study team.

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