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CRC Research Protocol
1/26/11

Title of Protocol: Rebalanced hemostasis: Is there a role for prophylactically correcting hemostatic abnormalities in patients with liver disease before liver biopsies?

1. Study Purpose and Rationale

Patients with chronic liver disease frequently acquire a complex disorder of hemostasis secondary to their disease. A major contributor to coagulation disturbances in liver disease is decreased plasma levels of hemostatic proteins due to impaired synthesis[1]. Thrombocytopenia via decreased production, increased turnover, or increased splenic sequestration secondary to portal hypertension[2-4] also contributes to altered hemostasis. Portal hypertension alone leads to hemodynamic changes that impact endothelial function[5].

Routine laboratory measures of hemostasis such as the platelet count, the prothrombin time (PT), and the activated partial thrombin time (APTT) are frequently abnormal in liver disease[6] and the combination of these are suggestive of a bleeding diathesis. Clinicians have traditionally assumed that liver patients with these hemostatic changes are at risk for bleeding and consequently have prophylactically corrected a prolonged PT and PTT or a thrombocytopenia before an invasive procedure per the recommendations of the American Society of Anesthesiology[7] (ASA). A study comparing the use of FFP during minor invasive procedures according to five different international guidelines, including the ASA, revealed that local practices vary tremendously in liver disease from prophylaxis to no recommendation and are seldom evidence-based[8].

Recent data from the liver transplant literature has questioned the role of prophylactic transfusion in preventing bleeding. Multiple transplant centers have reported that they are capable of performing transplantation without any requirement for blood products[9-13], having anywhere from 55%-90% transfusion-free procedures. These observational studies have shown that the extent of coagulopathy or the severity of liver disease as assessed by the MELD score does not predict the proportion of patients who require perioperative transfusion[14]. Two randomized control trials comparing restrictive versus liberal prophylactic transfusion policies during liver transplantation showed a reduced incidence of perioperative bleeding and transfusion requirement in the restrictive group[10, 15] and found that the central venous pressures correlated with the tendency to bleed, independent of the coagulopathy indices. Follow-up studies where CVP was maintained less than nine mm hg via phlebotomy and through strict transfusion avoidance also revealed a reduced incidence of bleeding requiring transfusion, and morbidity and mortality at 1 and 5 yrs[16].

Aside from the well-documented, but rare side effects of receiving a viral infection (Hepatitis B 1/200,000, Hepatitis C 1/1-2 million), and HIV 1/1-2 million), other life-threatening transfusion reactions include transfusion-related acute lung injury (TRALI), with an incidence 1/5000 units of blood products[17]. Aside from the enormous direct and indirect costs associated with the morbidity from unnecessary transfusions, the efficacy of FFP and platelet infusions to avoid bleeding has never been demonstrated[18]. Additionally, complete normalization of hemostatic parameters is rarely ever achieved in cirrhotics receiving FFP or platelets[19-20].

The purpose of this study is to evaluate the safety and efficacy of a restrictive transfusion policy in patients with a baseline coagulopathy from liver disease undergoing liver biopsy. The hypothesis is that prophylactic transfusion based on the current ASA guidelines will lead to a greater rate of transfusion post procedure.

2. Study Design and Statistical Procedures

The potential patients will include anyone being referred by a hepatologist or gastroenterologist for a liver biopsy who meets *any* of the current ASA prophylactic transfusion guidelines based on:

- PT or APTT > 1.5 the midrange of normal, requiring FFP
- platelet count < less than 50 time 10(9)/L
- hemoglobin < less than 6g/dL)

From this group, the patients will be randomized to either the liberal transfusion group whereby the hemostatic pertubance is corrected pre-procedurally as per current local practices or a restrictive transfusion protocol whereby transfusion is held and only utilized during the post-procedure phase if clinically significant bleeding occurs.

The primary outcome will be the categorical variable need for transfusion. Since 90% of post-biopsy bleeding occurs in the first 24 hours, patients will be monitored for 24 hours in the clinical research center. To assess for clinically significant bleeding requiring transfusion, q 8hr complete blood counts will be drawn, q 4hr vital signs, and q4hr physical exams by a blinded CRC physician will be performed.

In order to achieve 80% power with a P value of 0.05, assuming that the rates of needing transfusion under current practices is 4% and the estimated bleeding rate in the restrictive transfusion group would be around 1%, an absolute effect size of 3% or relative reduction in transfusion rate by 75% would need 488 patients in each arm, 976 overall, based on Chi-square test.

The 4% of liver biopsies requiring post-procedural transfusion while following current practices is derived from a composite bleeding rate of multiple case series over time, with a range of bleeding rates quoted from 3.0-6.0%. This composite rate takes into account the following factors:

- difference in transfusion rates depending on if biopsy is percutaneous approach (higher bleeding rate, but greater diagnostic histological sensitivity) compared to transjugular
- variability in operator skill and availability of technology and knowledge to perform the different biopsy techniques

The 1% estimate transfusion rate in the restrictive transfusion group, which is a 75% reduction compared to the composite bleeding rate of 4%, is based upon the 55-85% reduction in transfusion seen in the liver transplant literature when employing the liberal versus restrictive transfusion protocols.

The following data will be analyzed using descriptive statistics (mean and standard deviations) and a t-test to compare group differences.

- Gender, Age, Wt, Ht,
- Pre-biopsy hemoglobin, PT, APTT, platelet count, creatinine, transaminases, total and indirect bilirubin
- Calculated MELD and Pugh's score
- Type of liver disease: cholestatic vs. non-cholestatic

- Known cancer

Post-hoc logistic regression analysis will be performed to see if creatinine, hemostatic variables, type of liver disease or having a prior malignancy may confound the effect of pre-transfusion on the need for post-procedure transfusion secondary to bleeding. Additionally, histologic diagnosis, number of needle passes and length of specimen will also be analyzed to evaluate if factors specific to the biopsy technique have a similar confounding effect.

3. Study Procedures

Patients who meet the inclusion criteria and who are referred for a liver biopsy from any of the 10 international sites will be randomized to either intervention group using a random number generator.

Initial labs will be drawn 7 days before the scheduled biopsy date. On the morning of the biopsy, the patient will come to the CRC and another set of labs will be drawn. Pending that their hemoglobin, creatinine, and hemostatic parameters meet the exclusion criteria, the patients will then either begin receiving blood products per the ASA guidelines or they will proceed directly to the biopsy suite. The patients will not be blinded to whether or not they received blood products, but both the physician performing the biopsy and the CRC physician and nursing team will be blinded to whether or not blood was given pre-biopsy to eliminate any bias.

The patients will be observed for 24 hours post biopsy with clinical monitoring for bleeding as previously described. Patients will follow-up with the referring hepatologist/gastroenterologist in 2 weeks post biopsy to discuss the results of the biopsy and for on-going care.

4. Study Drugs or Devices N/A

5. Study Questionnaires N/A

6. Study Subjects

Patients will include anyone being referred by a hepatologist or gastroenterologist for a liver biopsy who meets *any* of the current ASA prophylactic transfusion guidelines:

- PT or APTT > 1.5 the midrange of normal, requiring FFP
- platelet count < less than 50 time 10(9)/L
- hemoglobin < less than 6g/dL)

Exclusion criteria include:

- Patients who meet the above criteria but who have been admitted to the hospital for any other reason
- Platelet count <20,000
- INR >3.0
- A change in any of the following parameters from 1 week prior to biopsy day:
    - Drop in hemoglobin by >2 g/dl
    - Drop in platelets >25,000
    - Increase in INR >1.5x
    - Increase in creatinine >1.5x
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7. **Recruitment**

Patients will be recruited at hepatology and gastroenterology practices at the 10 participating international academic medical centers.

8. **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.

9. **Potential Conflicts of Interest**

There are no conflicts of interest.

10. **Potential Risks**

All of these patients will have clinical indications for the liver biopsy. The risks incurred would be no different than a normal biopsy under the standard of care. Being randomized to the restrictive transfusion group will reduce the risks normally associated with transfusions (viral transmissions, TRALI, etc.), which is currently the standard of care.

11. **Potential Benefits**

The main benefit of the study will be having a liver biopsy without subjecting yourself to the risks associated with transfusions and also having a reduced probability of post-biopsy bleeding requiring transfusion.

12. **Alternatives**

Patients may opt to not have the biopsy as part of this study and make other arrangements with their referring hepatologist or gastroenterologist.

O. Compensation of Subjects

All medical visits and laboratory tests will also be provided free of charge the all subjects. Pt's will be compensated for their initial laboratory visit and for the biopsy hospitalization at the CRC.

P. Costs to Subjects

There will be no cost to the subjects.

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.

S. References

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