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IRB Proposal - CRC Rotation

Ecological Study on Rates of Transfusion-Associated Necrotizing Enterocolitis in NICU Infants After Change in Feeding Practices Around Time of Blood Transfusions

A. Study Purpose and Rationale

Necrotizing enterocolitis (NEC) is a disease of the immature intestines of infants that remains one of the most common and serious complications of prematurity. While infants of any gestational age are at risk for NEC, about 90% of cases occur in premature infants.[8] Infants who develop necrotizing enterocolitis have a risk of death as high as 50%, and surgical intervention is required in about 20-40% of case.[8] Infants who survive have an increased risk of neurodevelopmental disability later in life.[18] Unfortunately, the precise pathophysiology of necrotizing enterocolitis remains unknown, although it is suspected that the entity is the clinical end-result of a multitude of risk factors that can vary per infant.

Recently, however, a temporal association between the transfusion of packed red blood cells (PRBCs) and the development of necrotizing enterocolitis (NEC) in infants has been increasingly recognized. Observational studies have suggested that up to 35% of NEC cases may be temporally associated with antecedent PRBC transfusions.[2,12] This particular occurrence has been named “transfusion-associated necrotizing enterocolitis” or TANEC, and it is thought to comprise a unique subset of NEC cases. Proven strategies to prevent TANEC are unknown.

Many theories exist regarding the pathophysiology of TANEC. One theory suggests that the association is primarily epidemiologic, as premature infants are both more likely to develop NEC and more likely to required blood transfusions. However there is likely to be a genuine mechanistic connection between the transfusions and NEC. For example, it is postulated that during hypoxic events, which are further exacerbated by anemia of prematurity and thus require transfusions, an infant's immature intestines are unable to maintain adequate circulatory autoregulation. This in turn leads to gut ischemia.[14-15] Factors specific to transfusions are also suspected to contribute to the association. One theory, referred to as the "storage lesion" phenomenon, suggests that NEC develops as a result of the microcirculatory and inflammatory effects of the biochemical and degradation processes of stored blood.[17]

Observational studies have suggested that withholding feeds around the time of transfusion may confer some protection against the development of TANEC.[3,5] The practice is thought to allow rest to a growing gastrointestinal system that may be further taxed by circulatory and immunologic changes related to PRBC transfusions. Studies utilizing near-infrared spestroscopy to examine perfusion and oxygenation as markers of metabolic demand have shown that oxygenation in the mesentery increases post-prandially compared to oxygenation in other areas of the body that exhibit no change. This increased metabolic demand requires adequate perfusion to the gut of fed infants. A recent small study suggested that post-prandial oxygenation of the mesentery of infants who are fed while transfused is decreased compared to that of infants who are transfused and not fed.[11] It is hypothesized that the increased metabolic demand coupled with the aforementioned microcirculatory and inflammatory changes in the immature gut predispose a feeding-and-transfused infant to NEC.[10] However, the evidence to support this practice remains limited. The results of the aforementioned studies are mixed, with some showing benefit to withholding feeds and others showing no discernible advantage to the practice.[5] Nevertheless, when speculation about the relationship between feeding and TANEC arose, withholding feeds for some hours before, during, and after an infant receives a blood transfusion became a common clinical practice.

Withholding feeds interrupts the nutritional and immunologic benefits of enteral feeding; in addition, it requires the use of parenteral nutrition, placing the infant at risk for the complications of venous catheters, including infection. The rationale for this current study is the

need to evaluate whether, in our institutional experience, the practice of withholding feeds during blood transfusions may be warranted as a preventative measure for the development of TANEC. To do this, we will perform a retrospective review of the incidence of TANEC and concurrent feeding practices during PRBC transfusion in the NICU at Columbia University Medical Center (CUMC) during the past 11 years (2003-2013).

B. Study Design and Statistical Analysis

This is a retrospective ecological study of all infants admitted to the NICU at CUMC during the years 2003-2013, divided into 2 epochs: (2003-2008) and (2009-2013). We will examine unit-wide PRBC transfusion rates and rates of NEC. We will determine the rates of NEC over each study year in transfused and non-transfused infants, as well as within the 2 epochs for each group. Rates of NEC will be defined as number of infants diagnosed with NEC during their NICU admission in a given year or epoch, divided over the total number of NICU admissions that year or epoch. We will do this calculation for transfused infants and for non-transfused infants. We will also look at overall rates of PRBC transfusions. Rates of PRBC transfusions will be defined as number of infants receiving PRBC transfusions according to the CUMC blood bank database on a given year or epoch, divided by total NICU admissions that year or epoch.

We expect to have a sample size of about 11,000 infants. We have an estimated transfusion rate in the CUMC NICU of 50-75%, and an established prevalence of NEC of about 5% of NICU admissions. Our sample size of 4000 transfused infants and 2000 non-transfused infants per epoch will allow us to detect a pre- and post- decrease in rates of NEC of 1.5% or more, with $p<0.05$. We will compare the transfusion group pre- and post- with a Chi square test. Our sample size provides >80% power with the prior prevalence assumptions. The non-transfused groups will serve as controls for time. We expect to see no change in the NEC rates of the non-transfused group. We will do a multiple logistic regression of all 11,000 infants to study the effect of feeding during transfusion, controlling for epoch, transfusion, and other known risk factors for NEC.

To look at feeding data, we will randomly select a subset of 20 infants from NICU census logs per year, for which detailed feeding practices related to PRBC transfusions will be examined. This data will help identify the change in feeding practices as related to PRBC transfusions.

C. Study Procedures

Eligible subjects will include all infants admitted to the NICU during the study period. To identify eligible infants, we will utilize the NICU census list, which includes the name, medical record number, referring institution (if applicable), demographic data, date of admission and date of discharge for each patient. All patients will be assigned a unique study number.

Following IRB approval, we will also request from the Data Discovery committee a list of infants who carried a diagnosis of NEC during their admission, and of all infants who received blood transfusions during their admission. In addition, we will request relevant demographic and clinical data, including covariates like sex, birth weight, and admitting diagnosis (e.g., congenital anomalies, respiratory failure, and retinopathy of prematurity). Transfusion data will be corroborated against a blood bank database, for accuracy.

D. Study Drugs or Devices

N/A

E. Medical Devices

N/A

F. Study Instruments (e.g., Questionnaires, Interview Outlines, Focus Group Guides)

N/A

H. Recruitment of Study Subjects

Eligible subjects will include all infants admitted to the NICU during the study period from January 2003 – December 2013. No recruitment will be performed.

I. Confidentiality of Study Data

The Data Discovery committee data will be linked to a unique study identification number. The link between the infants' medical record numbers and the study identification number will only be known to the study staff and will be maintained on a password protected, certified server. The link between the study number and the patients will be destroyed at the conclusion of the study after data analysis has been completed.

J. Potential Conflict of Interest

No conflicts of interest have been identified.

K. Location of Study

The study will be performed at CUMC.

L. Potential Risks

The only risk for collection of existing demographic and clinical data is the loss of confidentiality.

M. Potential Benefits

Potential benefits to the study population are none. Potential benefits to society include additional data to inform feeding practices during blood transfusions as they related to rates of NEC.

N. Alternative Therapies

N/A

O. Compensation of Subjects. Research at External Sites

None

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