Platelet Transfusion During Neonatal Open Heart Surgery

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Title: ***Neurodevelopmental Outcome and Platelet Transfusion During Neonatal Open Heart Surgery***

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Hypothesis:
Dilutional thrombocytopenia after cardiopulmonary bypass (CPB) is universal and there is a recent data supporting administration of donor apheresis platelets just prior to termination of bypass assist in early correction of coagulopathy, early hemostasis and lesser donor exposure of blood products after cardiac surgery. This administration of donor apheresis platelets just prior to termination of bypass also assist in favorable neurodevelopmental outcome.

Background:
Congenital heart disease (CHD) affects about 40,000 births per year in the United States, making it the most common type of birth defect.[1] Advancements in management, either operative or non-operative, for infants with CHD have improved early mortality in this patient population over the past 2-3 decades.[2] However, with improved survival the focus has turned to the neurodevelopmental outcomes of these patients. Studies have begun to elucidate evidence of neurodevelopmental delay in children with CHD, manifest as behavioral difficulties, executive function impairment, attention deficit hyperactivity disorder (ADHD), and other related symptoms.[3, 6] In a prospective cohort study by Medoff-Cooper ***et al***., poor feeding skills and delayed growth rate were suggested as identifying factors for neurodevelopmental disability risk in infants with complex CHD who underwent cardiac intervention within 30 days of birth.[4]
As more infants with complex CHD survive early cardiac intervention, there has also been a growing interest to provide these patients with appropriate resources and/or interventions.[5]

It is known that CPB has been associated with risk for cerebral hypoxic-ischemic/reperfusion injury and embolic complications. However, there are few data to demonstrate details of the CPB and neurodevelopment in the patients with CHD. In a previous study in this institution (IRB#: HSC-MS-16-1034), an administration of donor apheresis platelets just prior to termination of bypass has demonstrated distinct advantages of earlier achievement of hemostasis, reduction in post-CPB transfusion, and improved postoperative outcome (significantly less mediastinal exploration for bleeding, duration of mechanical ventilation, and length of intensive care unit stay). The principal aim of this study is to understand whether the benefit of the timing of the platelet administration extends to the neurodevelopment outcome in the same patient population studied in the previous study.

Objectives:
Primary objectives – To evaluate any significant neurodevelopment differences between two groups: administration of donor apheresis platelets just prior to termination of bypass versus standard transfusion of platelet apheresis after modified ultrafiltration and protamine administration. A standardized assessment tools, Bayley Scales of Infant and Toddler Development 3rd edition (looking into five major

areas of development: cognitive, language (expressive/receptive), motor (gross/fine), will be used to evaluate the study populations' development at around 2 year of age.
Secondary objectives – To seek to provide improved intervention with long term improvement in quality of life for the patients.

Study Method:
Prospective cohort study comparing neurodevelopment between patients who underwent platelet apheresis transfusion prior to termination of CPB versus standard transfusion of platelet apheresis after modified ultrafiltration and protamine administration.

Study Population:
We will be including all the patients reviewed in the previous study in this institution (IRB#: HSC-MS-16-1034)

Treatment group –
Platelet Transfusion Management
1. Pre-Termination of CPB- Platelet Transfusion 10ml/kg to be administered to the patient via central venous access when the patient has been rewarmed to 35*C, (the Sano or BT shunt clip is still on in children with SV physiology)
2. Post CPB- Platelet transfusion 10ml/kg via a central venous line is continued at a rate of 100 ml/hour till completion.

FFP and Cryoprecipitate:
1. 1 unit of cryoprecipitate administered during MUF and or after MUF as needed
2. FFP transfusion 10ml/kg during MUF and or after MUF as needed

PRBC and cell saver Transfusion:
1. Transfuse for target Hematocrit > 40 in neonates with SV physiology; Transfuse for Hematocrit> 33 for 2-Ventricle physiology

3- Factor Concentrate (Bebulin):
1. Based on clinical bleeding and achievement of hemostasis

Control Group –
Platelet Transfusion Management
1. Pre-Termination of CPB- No intervention
2. Post CPB- Platelet transfusion 20ml/kg via a central venous line is continued at a rate of 100 ml/hour till completion.
    a. Initial transfusion to occur proximal to the hemofilter on the MUF circuit for as long as MUF lasts
    b. Subsequent platelet transfusion continued till completion via central venous access to the patient

FFP and Cryoprecipitate:
1. 1 unit of cryoprecipitate administered during MUF and or after MUF as needed
2. FFP transfusion 10ml/kg during MUF and or after MUF as needed

PRBC and cell saver Transfusion:
1. Transfuse for target Hematocrit > 40 in neonates with SV physiology; Transfuse for Hematocrit> 33 for 2-Ventricle physiology

3 Factor Concentrate (Bebulin):
1. Based on clinical bleeding and achievement of hemostasis

Study Procedures:
Either a written informed consent or verbal informed consent over the phone will be obtained.
The patients will be referred to the High Risk Clinic, where a neuropsychiatrist will be performing the Bayley Scales of Infant and Toddler Development at around 2 year old. The High Risk Clinic currently acts as a medical home for patients with chronic illness requiring multiple different specialty needs. We will be utilizing the developmental assessment aspect of the clinic.

Data and Safety Monitoring:
We do not anticipate any direct adverse events.
All data collected will be entered into a secure electronic database that will be encrypted and password protected (https://med.uth.edu/msit/secure-share/). The UT Secure-share sheet will be shared only with the co-investigators. A log-linking file will be maintained to keep patient information separate from the data collection sheet. No paper copies will be maintained.

Statistics**:
We will present data using following statistics, as appropriate and as applicable:
Mean with standard deviation/Median with interquartile range where applicable for continuous variables.
Differences in continuous variables will utilize Wilcoxon sum rank test (e.g. *P*-values for age, weight and head circumference, and results of standardized assessment tool as appropriate)
Differences in categorical variables will utilize either Chi-square test or Fisher's exact test (e.g. *P*-values for gender, types of CHD, other diagnoses (e.g. genetics), types of operation/procedures, and results of standardized assessment tool as appropriate)
P-values <0.05 will be considered as statistically significant
**Statistics methods are subject to change to most appropriately present data

Ethics
IRB review will be requested by UTHealth's IRB
See above Data and Safety monitoring in regard to our plan to protect privacy of subjects
Appropriate consent and documentation of informed consent will be sought

References:

1. Centers of Disease Control and Prevention. Congenital Heart Defects (CHDs): Data & Statistics. *Centers of Disease Control and Prevention* [CDC website]. November 7, 2016. Available at: https://www.cdc.gov/ncbddd/heartdefects/data.html. Accessed March 30, 2019.
2. Brown MD, Wernovsky G, Mussatto KA et al. Long-Term and Developmental Outcomes of Children with Complex Congenital Heart disease. Clin Perinatol 2005;32:1043-1057.
3. Calderon J, Bellinger DC. Executive function deficits in congenital heart disease: why is intervention important? Cardiology in the Young 2015;25:1238-1246.
4. Medoff-Cooper B, Irving SY, Hanlon AL et al. The Association among Feeding Mode, Growth, and Developmental Outcomes in Infants with Complex Congenital Heart Disease at 6 and 12 Months of Age. The Journal of Pediatrics 2016;169:154-159.
5. Gaynor JW, Stopp C, Wypij D, et al. Neurodevelopmental Outcomes After Cardiac Surgery in Infancy. Pediatrics 2015;135:816-825.
6. Schillingford AJ, Glanzman MM, Ittenbach RF, et al. Inattention, Hyperactivity, and School Performance in a Population of School-Age Children With Complex Congenital Heart Disease. Pediatrics 2008;121:759-767.