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Research Article

Creation of a Neonatal Thrombosis Center and its Use to Successfully Treat Infants with Severe Thromboses

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Abstract

Background: Clinically significant thrombosis, which can be life threatening, is a common problem in the neonatal period, affecting up to 6.8 per 1,000 neonatal intensive care admissions. These infants have increased risk for bleeding complications from anticoagulant therapy due to immature coagulation systems, concomitant infections, inflammation and coagulopathies, and CNS hemorrhage risk due to prematurity. Thus, care for these infants requires a specialized multidisciplinary team, composed of neonatologists and hematologists, along with pharmacy support.

Objectives: We aim to describe the development of a neonatal thrombosis center at our institution, co-run by a neonatologist with expertise in neonatal hematology, and a pediatric hematologist. The utility of the center will be explored through the case review of four neonates with large, life threatening thromboses, successfully treated with systemic tissue plasminogen activator (TPA). We will also describe the development of a neonatal thrombosis database for studying risk factors and treatments for neonatal thrombosis.

Methods: Protocols for evaluation and treatment of neonatal thromboses were prepared, based on literature review and best practices, and presented and approved by the institution's pharmacy and therapeutics committee. Anticoagulation protocols including heparin, low molecular weight heparin, and systemic TPA were created electronically within our computerized order entry system. A protocol for consulting the neonatal thrombosis team was created and presented during grand rounds. All neonates with thromboses are followed by the neonatal thrombosis team as outpatients, with thrombophilia evaluations completed as necessary. Information regarding age, risk factors, diagnoses, treatments and outcomes are then compiled in a neonatal thrombosis database.

Results: Four infants with life-threatening thromboses were successfully treated with systemic TPA using our neonatal thrombosis treatment center. These include a full-term infant with an occlusive thrombus in the main pulmonary artery, a full term infant with a mural thrombus in the heart, a full term infant with an occlusive thrombus in the aortic arch, and a 26-week premature infant with a large right atrial thrombus.

Conclusion: Neonates, especially those in intensive care, are at increased risk for thromboses, which can be life-threatening. Treatment of neonates with significant thromboses requires a multidisciplinary approach. Creation of a neonatal-thrombosis team and treatment center can be used to effectively treat these patients and gather data about their care and outcomes. To our knowledge, this is one of the first dedicated neonatal thrombosis teams.

Keywords: Neonatal thrombosis; Thromboses; Systemic TPA; Neonatal center

Abbreviations: CNS: central nervous system; TPA: tissue plasminogen activator

Introduction

Clinically significant thromboses, which can be life-threatening, are a common problem in the neonatal period, affecting up to 6.8 per 1,000 neonatal intensive care admissions. The presence of venous access devices, sepsis, maternal factors, dehydration, and

prematurity contribute to the development of these thromboses [1]. These infants have increased risk for bleeding, complications from anticoagulant therapy due to immature coagulation systems, concomitant infections, inflammation and coagulopathies, and CNS hemorrhage risk due to prematurity [2]. Thus, care for these infants requires a specialized multidisciplinary team, composed of neonatologists and hematologists, along with pharmacy support. We describe the development of a neonatal thrombosis center, co-run by a neonatologist with expertise in neonatal thrombosis, and a pediatric hematologist. The center focuses on care of neonatal thrombosis through education, treatment, and data collection. Initially, protocols for evaluation and treatment of neonatal thromboses were prepared, based on literature review and best practices, and presented and approved by the institutional pharmacy and therapeutics committee. In order to streamline care across providers, anticoagulation protocols including heparin, low molecular weight heparin, and systemic TPA (tissue plasminogen activator) were created electronically within our computerized order entry system. A protocol for consultation of and between the thrombosis center neonatologist and hematologist was prepared and presented to the department of pediatrics (Figure 1) [3]. This includes follow up of all neonates with clinically significant thromboses post hospital discharge in the outpatient thrombosis clinic, with thrombophilia evaluations completed as necessary. The neonatal thrombosis database collects information such as demographics, diagnostic, treatment and outcome information on neonates treated at our institution with thromboses. Finally, from an education standpoint, our collaborative treatment center physicians conducted a grand rounds presentation on neonatal thromboses and co-published a chapter on neonatal thrombosis diagnosis and management.

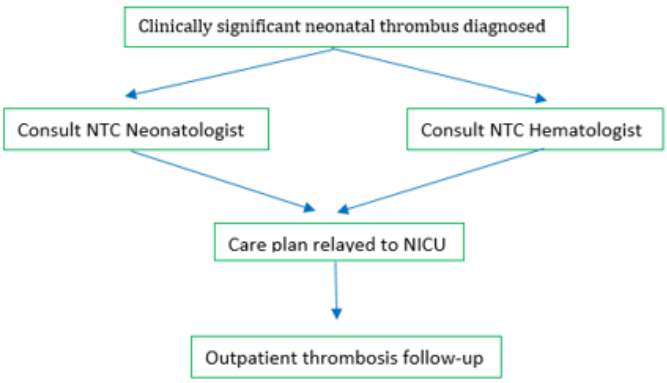

Figure 1: Algorithm for Consultation of Neonatal Thrombosis Center Providers.

Dose titrations should be as follows:
0.03mg/kg/hr→0.06mg/kg/hr→0.1mg/kg/hr→0.3mg/kg/hr
Max dose=0.3mg/kg/hr!

Lab/Imaging	Goal	Factor Replacement	TPA Titration
Fibrinogen q6h	100-200 mg/dL	If <100mg/dL, give cryoprecipitate. If persistently <100mg/dL, decrease TPA by 25%	If >200mg/dL, increase TPA as above
D dimer q6h	Elevated	n/a	If low, increase TPA as above
Platelets	>100,000 x10^3/uL	Give platelets for <100,000 x10^3/uL	
Ultrasound Q8h arterial; Q24h venous	>95% clot lysis	n/a	If <50% lysis, increase TPA as above. 51-94% lysis, continue same TPA dose. If >95% lysis, stop TPA.

Figure 2: Systemic TPA Titration Guidelines.

Case Presentations

Four infants with life-threatening thromboses were successfully treated with systemic TPA using our neonatal thrombosis treatment center. TPA was initiated and titrated based off best practices (figure 2). Infant 1 was a 37/1 gestational age infant who presented at 11 days of life with several days of poor feeding and weight gain, along with fever and watery diarrhea. There was no significant thrombophilia family history. Imaging by echocardiogram revealed

a thrombus in the main pulmonary artery, and therapeutic heparin was initiated. Follow up imaging after one day revealed clot propagation, so he was transitioned to systemic TPA for 72 hours, with improvement in thrombus, followed by a therapeutic course of low molecular weight heparin in outpatient follow up. Infant 2 was a 38/4 gestational age infant with late prenatal care and GBS+ mother. He presented at 10 days of life with hypothermia, hypoglycemia, and respiratory failure. An echocardiogram revealed a mural cardiac thrombus, and he was immediately started on systemic TPA, with clinical and radiographic improvement. He then completed a treatment course of low molecular weight heparin, followed by aspirin prophylaxis. Infant 3 was a 26 week gestational age infant, with a pregnancy complicated by advanced maternal age, gestational hypertension, and maternal history of multiple miscarriages but no known thrombophilias. The infant presented at day of life 17 with acute respiratory failure and coagulase negative staphylococcal sepsis. Ultrasound imaging revealed a significant mobile thrombus in the right atrium. Systemic TPA was given, followed by low molecular weight heparin for 6 weeks, with complete resolution. Finally, infant 4 was 38/6 gestational age infant, whose prenatal course was complicated by teenage pregnancy, limited/late prenatal care, opiate, tobacco and marijuana use, and GBS positivity in the mother. This infant presented on the first day of life with a cardiac murmur and decreased lower extremity pulses. An echocardiogram demonstrated an occlusive thrombus in the aortic arch. Systemic TPA was immediately started, followed by heparin and lower molecular weight heparin, and finally aspirin. All of these infants are doing well and thriving (Table 1).

Table 1: Case Reports: Use of Systemic TPA in High Risk Neonatal Thromboses.

Infant ID	Gestational Age (Weeks)	Maternal Factors	Pregnancy Complications	Age at Thrombus Diagnosis	Location of Thrombus	Presenting Symptoms
Infant 1	37/1	Teenage pregnancy	Pre-eclampsia	11 days	Main pulmonary artery	Poor feeding/weight gain, watery diarrhea
Infant 2	38/4	Late prenatal care	GBS+	10 days	Mural cardiac	Hypothermia, hypoglycemia, respiratory failure
Infant 3	26	Advanced maternal age, history of multiple miscarriages	Pregnancy-induced Hypertension	17 days	Right atrium	Acute respiratory failure
Infant 4	38/6	Teenage pregnancy, late/limited prenatal care	GBS+ untreated, History of opiate, tobacco, marijuana use, small for gestational age	1 day	Aortic Arch	Decreased lower extremity pulses, heart murmur

Infant ID	Family History	Catheter Presence	Relevant Infections	Anticoagulation
Infant 1	Non-contributory	None prior to thrombus formation	No identified infection	Initially heparin. Transitioned to TPA after increased clot burden. Then lovenox.
Infant 2	Non-contributory	None prior to thrombus formation	None	TPA, then 6 months of lovenox, then aspirin prophylaxis
Infant 3	Maternal grandfather with deep venous thrombosis	PICC in Superior Vena Cava	Coagulase-negative Staphylococcus	TPA then lovenox for 3 months
Infant 4	Maternal great grandmother with stroke; paternal grandmother with thrombi, paternal aunt with deep venous thrombosis, maternal family with history of multiple miscarriages	None prior to thrombus formation	None	TPA, then lovenox, then aspirin prophylaxis

Discussion

Through these varied cases, it is apparent that early recognition of thromboses and the need for anti-coagulation is imperative for positive outcomes. Many of these patients presented to area hospitals and clinics prior to being transferred to our center, in order to utilize the Neonatal Thrombosis Center via consultation with both hematology and neonatology. Access to a tertiary care center with expertise in the diagnosis and treatment of complicated neonatal thrombosis, is necessary for prompt and safe anticoagulation. Through use of the center, coordinated follow-up is made easier, continuing to contribute to favorable outcomes, as risk assessments for future thromboses for the infants (or future infants in the case of identified thrombophilias) are completed and outpatient anticoagulation is followed closely through thrombus resolution. As more outlying centers have become aware of the program, phone consultations have also increased, providing resources to areas with poor access to subspecialty care. This unique group of patients often present with non-specific signs and symptoms, as evidenced in our cases. Two of the four had no apparent risk factors or history to suggest a clot as the underlying cause. Thus, high suspicion for a cardiovascular or thromboembolic cause for symptoms in these neonates helps lead to diagnosis and timely treatment.

Another consideration for the treatment of these patients via our dedicated neonatal thrombosis center is the creation of standardized treatment protocols, accessible throughout our health system, which has allowed for rapid and safe initiation of systemic TPA and improved outcomes of these very high-risk neonates. Given the discrepancies in access to care and the limited availability to subspecialists at all locations, these step-by-step algorithms are a valuable resource to all providers faced with emergent presentations, in order to act effectively and quickly to provide the appropriate care [4-7].

Conclusion

In conclusion, neonates, especially those in intensive care, are at increased risk for thromboses, which can be life-threatening. Treatment of neonates with significant thromboses requires a multidisciplinary approach. Creation of a neonatal-thrombosis team and treatment center can be used to effectively treat these patients and gather data about their care and outcomes. To our knowledge, this is one of the first dedicated neonatal thrombosis teams.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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