Risk Factors for Neonatal Venous and Arterial Thromboembolism in the Neonatal Intensive Care Unit—A Case Control Study

Rukhmi Bhat, MD, MS[1], Riten Kumar, MD, MSc[2], Soyang Kwon, PhD[3], Karna Murthy, MD, MSc[4], and Robert I. Liem, MD, MS[1]

Objective To identify risk factors associated with venous and arterial thrombosis in sick neonates admitted to the neonatal intensive care unit.

Study design A case-control study was conducted at 2 centers between January 2010 and March 2014 using the Children's Hospital Neonatal Database dataset. Cases were neonates diagnosed with either arterial or venous thrombosis during their neonatal intensive care unit stay; controls were matched in a 1:4 ratio by gestational age and presence or absence of central access devices. Bivariable and conditional logistic regression analyses for venous and arterial thrombosis were performed separately.

Results The overall incidence of neonatal thrombosis was 15.0 per 1000 admissions. A higher proportion of neonates with thrombosis had presence of central vascular access devices (75% vs 49%; $P < .01$) were of extremely preterm gestational age (22-27 weeks; 26% vs 15.0%; $P < .05$) and stayed ≥31 days in the neonatal intensive care unit (53% vs 32.9%; $P < .01$), when compared with neonates without thrombosis. A final group of 64 eligible patients with thrombosis and 4623 controls were analyzed. In a conditional multivariable logistic regression model, venous thrombosis was significantly associated with male sex (AOR, 2.12; 95% CI, 1.03-4.35; $P = .04$) and blood stream infection (AOR, 3.47; 95% CI, 1.30-9.24; $P = .01$).

Conclusions The incidence of thrombosis was higher in our neonatal population than in previous reports. After matching for central vascular access device and gestational age, male sex and blood stream infection represent independent risk factors of neonatal venous thrombosis. A larger cohort gleaned from multicenter data should be used to confirm the study results and to develop thrombosis prevention strategies. *(J Pediatr 2017;■■:■■-■■).*

Arterial and venous thromboembolism is an important cause of morbidity and mortality in neonates admitted to the neonatal intensive care unit (NICU).[1-3] Thrombosis can result in a longer duration of hospitalization, need for removal of central vascular access lines, or an increase in bleeding risk because of anticoagulation therapy.[4] In rare circumstances, thrombosis can cause end-organ damage or result in mortality.[5,6] As more neonates are surviving longer from complex medical conditions, the presence of a thrombus can complicate their ongoing management.

Most thrombotic complications in neonates occur because of central vascular access devices (CADs), but little is known about the contribution of other risk factors.[6-8] Existing case series have cited both maternal and neonatal risk factors, but as with thrombosis in other settings, the cause of thrombosis in the NICU population is thought to be multifactorial.[9,10] Few recent studies have addressed neonatal thrombosis since the Canadian, German, and Dutch neonatal thrombosis series in the 1990s.[9-11] Important reasons for this include the heterogeneity of neonates admitted to the NICU, the absence of cooperative multicenter efforts, and the relatively small total neonatal population reported in prior studies.

Data from risk factor analyses of children admitted to the pediatric intensive care unit have been useful for the development of thromboprophylaxis policies and protocols that aim to reduce the incidence of thrombosis in critically ill children.[12,13] Such protocols have not been implemented routinely in the NICU owing to the absence of well-designed studies of risk factors in critically ill neonates and the risk of bleeding, particularly intraventricular bleeding, in preterm infants.[14] The objective of our study was to identify risk factors for venous and arterial thrombosis, other than CADs, in sick neonates admitted to the NICU. We hypothesized that analysis of data from 2 large NICUs would identify additional risk factors associated with thrombosis in neonates that could be useful

BSI	Blood stream infection
CADs	Central vascular access devices
CHND	Children's Hospitals Neonatal Database
NICU	Neonatal intensive care unit

From the [1]Division of Hematology, Oncology and Stem Cell Transplant, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Division of Hematology/Oncology, Department of Pediatrics, The Ohio State University, Nationwide Children's Hospital, Columbus, OH; [3]Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago; and [4]Division of Neonatology, Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, IL

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for developing future prospective studies to aid in developing thromboprophylaxis policies and procedures in the neonatal population.

Methods

We conducted a matched, case-control study using data collected from 2 institutions participating in the Children's Hospitals Neonatal Database (CHND).[15] Electronic health record data of patients admitted to Ann & Robert H. Lurie Children's Hospital (Chicago, Illinois) and Nationwide Children's Hospital (Columbus, Ohio) NICUs between January 1, 2010, and March 31, 2014, were obtained (2151 admission records from Lurie Children's Hospital and 4073 admission records from the Nationwide Children's Hospital). Local institutional review board approval was obtained at both sites and, because this was a retrospective analysis, no informed consent was required. Admission records were excluded from analysis if the admission represented a readmission to the NICU, resulted in a hospital stay for ≤3 days, or occurred in neonates with major complex congenital heart disorders needing surgical repair because their care was transferred to the cardiac intensive care unit.

Thrombosis cases were identified using *International Classification of Diseases,* 9th edition, codes 444.10 (aortic), 453.20 (vena cava), 453.30 (renal vein thrombosis), 671.50 (other venous), and 674.00 (other arterial). Four controls per case were randomly selected from eligible controls based on gestational age (22-27 weeks, 28-31 weeks, 32-36 weeks, and ≥37 weeks) and presence of CAD (yes or no). In total, 64 cases were identified involving venous thrombosis (n = 47), arterial thrombosis (n = 19), or both venous and arterial thrombosis (n = 2; **Figure**). Because CAD duration was skewed, the median duration of 13 days was used to examine the association between duration of CAD and thrombosis.

Patient characteristics including sex, mother's race/ethnicity, maternal antenatal medical conditions, gestational age at birth, birth weight, and neonatal medical conditions were extracted from the dataset. Potential risk factors examined in our analysis included maternal history of diabetes or hypertension; duration of CAD; mechanical ventilation for >2 days (prolonged mechanical ventilation); as well as a neonatal history of small for gestational age, respiratory distress syndrome, necrotizing enterocolitis, hypoxic ischemic encephalopathy, meconium aspiration syndrome, blood stream infection (BSI), and abdominal or gastrointestinal surgery. CAD duration was dichotomized into 1-13 days (shorter) or ≥14 days (longer) based on the median duration. Mechanical ventilation for >2 days was chosen as a cutoff to exclude those infants who needed ventilation for transient respiratory conditions (eg, transient tachypnea of the newborn).

Results

A total of 6224 admissions were reviewed at the 2 NICUs between January 1, 2010, and March 31, 2014. Of these total admissions, 93 were identified to be associated with thrombosis for an overall incidence of 15.0 per 1000 admissions. Separately, the incidence for venous and arterial thrombosis was 10.1 and 4.9 per 1000 admissions, respectively. A higher proportion of neonates with thrombosis were in the lowest gestational age category (22-27 weeks; 26.6% vs 15.0%; $P < .05$), had CADs (75% vs 49.3%, $P < .01$), and stayed ≥31 days in the NICU (53% vs 32.9%, $P < .01$), when compared with neonates without thrombosis in the entire dataset. After applying exclusion criteria, a final group of 64 patients with thrombosis and 4623 controls were eligible for analysis (**Figure**).

Table I shows the bivariate comparison between 47 venous thrombosis cases and 188 controls matched by CAD and gestational age. The distribution of birth weight and mother's race/

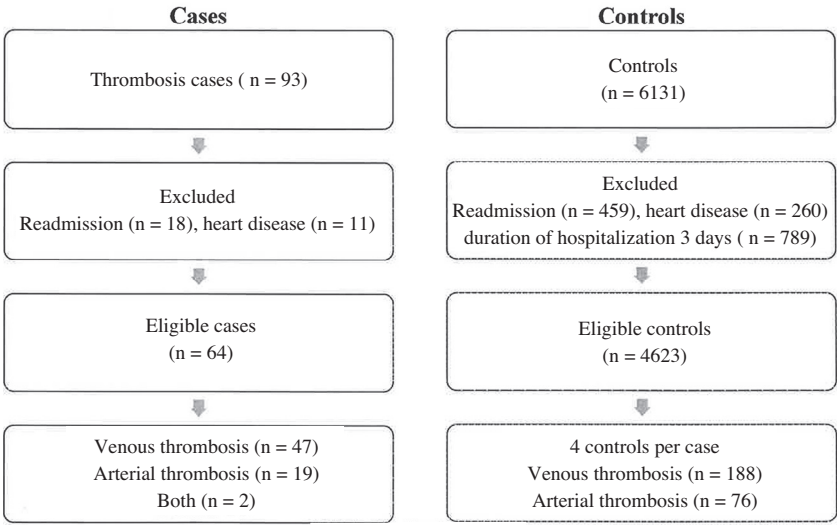

Figure. Flow diagram of cases identified by using *International Classification of Diseases,* 9th edition, codes (444.10, 453.20, 453.30, 671.50, and 674.00) and controls included in the final analysis. There were 6224 total admissions reviewed.

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