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

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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 2018;195:28-32).*

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

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R.B. received internal funding from the Division of Hematology, Oncology and Stem Cell Transplant, Ann & Robert H. Lurie Children's Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois. The other authors declare no conflicts of interest.

Portions of this study were presented at the 57th American Society of Hematology Annual Meeting and Exposition, December 5-8, 2015, Orlando, Florida, and at the 3rd Biennial Summit of the Thrombosis & Hemostasis Societies of North America, April 14-16, 2016, Chicago, Illinois.

https://doi.org10.1016/j.jpeds.2017.12.015

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/

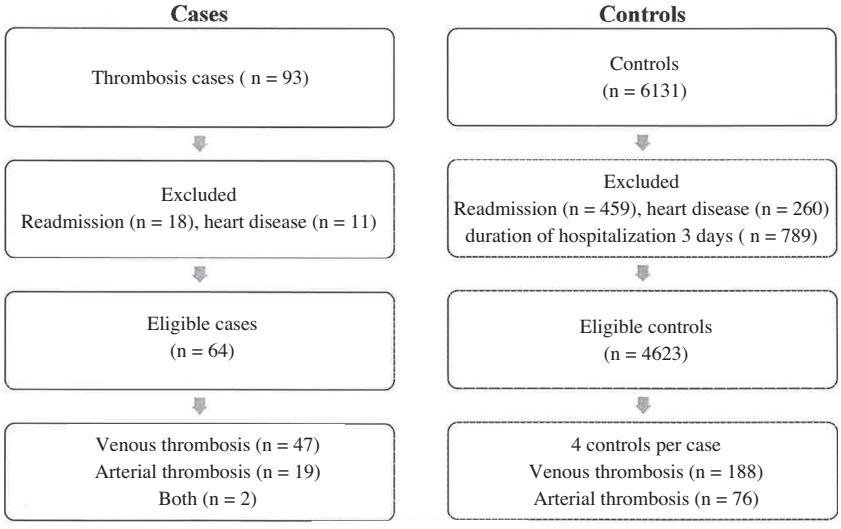

Figure. Flow diagram of cases identified by using *International Classification of Diseases,* 9th edition, codes (444.10, 453.20, 453.30, 671.50, and 674.00) and controls included in the final analysis. There were 6224 total admissions reviewed.

Table I. Comparison of characteristics and potential risk factors between venous thrombosis cases and controls matched for CAD and gestational age

Variables	Patients with thrombosis n (%)	Patients without thrombosis n (%)	*P* value
Total	47	188	
Sex (male)	34 (64.1)	104 (55.3)	.03
Race/ethnicity			
White	31 (65.9)	122 (64.8)	.65
Black	7 (17)	32 (14.8)	
Hispanic	7 (14.8)	19 (10.1)	
Other	2 (4.2)	15 (7.9)	
Birth weight (g)			
<2500	19 (40.5)	83 (44.6)	.60
≥2500	28 (59.5)	103 (55.3)	
Maternal antenatal conditions			
Diabetes	8 (17)	19 (10.1)	.18
Hypertension	11 (23.4)	27 (14.4)	.13
CAD type			
Umbilical arterial or venous	5 (14.3)	33 (23.6)	
Peripherally inserted central	16 (45.7)	55 (39.3)	
CC, cutdown, or tunnel catheter	0 (0)	4 (2.9)	
Multiple types	14 (40)	48 (34.3)	
CAD duration (among those with CAD) (d)			.01
1-13	10 (28.6)	73 (52.1)	
>14	25 (71.4)	67 (47.9)	
Mechanical ventilation >48 h	26 (55.3)	80 (43.8)	.11
Intrauterine growth restriction	2 (4.3)	16 (8.5)	.32
Respiratory distress syndrome	21 (44.7)	80 (42.5)	.79
Necrotizing enterocolitis	7 (14.9)	19 (10.1)	.35
Hypoxic ischemic encephalopathy	3 (6.4)	10 (5.3)	.77
Meconium aspiration syndrome	2 (4.3)	11 (5.85)	.66*
BSIs	10 (21.3)	16 (8.5)	.01
Central line associated BSI	3 (12)	0 (0)	.001*
Abdominal and gastrointestinal surgery	15 (31.9)	55 (29.3)	.72
Duration of hospitalization (d)			.06
4-10	6 (12.8)	56 (29.8)	
11-30	17 (36.2)	54 (28.7)	
≥31	24 (51.1)	78 (41.5)	

CC, central catheter.
*Fisher exact test, when any cell had <5 cases or controls.

ethnicity was similar between venous thrombosis cases and controls. Compared with controls, male sex (64.1% vs 55.3%; $P = .03$) and BSI (21.3% vs 8.5%; $P = .01$) were significantly more common among venous thrombosis cases. The association between duration of hospitalization of ≥31 days and thrombosis did not attain statistical significance ($P = .06$). In a conditional multivariable logistic regression model (**Table II**), male sex (AOR, 2.12; 95% CI, 1.03-4.35; $P = .04$) and BSI (AOR, 3.47; 95% CI, 1.30-9.24; $P = .01$) remained independently associated with venous thrombosis.

Among those venous thrombosis cases with a CAD (n = 35), the presence of a CAD for a longer duration (≥14 days) was more common when compared with that observed among controls (71% vs 48%; $P = .01$). We further investigated the relationship of CAD duration, BSI, and male sex to thrombosis only among patients with a CAD. This subsample analysis showed that BSI (AOR, 3.41; 95% CI, 1.20-9.64; $P = .02$) and CAD duration of ≥14 days (AOR, 2.63; 1.12-6.19; $P = .03$) were associated independently with thrombosis (**Table III**).

We also evaluated for risk factors between 19 arterial thrombosis cases and 76 controls matched for CAD and gestational age. The distribution of birth weight and mother's race/ethnicity was similar between arterial thrombosis cases and controls. Compared with that observed in controls, prolonged

Table II. ORs of venous thrombosis cases from a conditional multivariate logistic regression model (47 cases and 188 controls)

Variables	OR	95% CI	*P* value
Male sex	2.12	1.03-4.35	.04
BSI	3.47	1.30-9.24	.01

Table III. Conditional multivariate logistic regression model among neonates with CAD (35 cases and 140 controls)

Variables	OR	95% CI	*P* value
Male sex	2.16	0.92-5.11	.08
BSI	3.41	1.20-9.64	.02
CAD duration: ≥14 days vs 1-13 days	2.63	1.12-6.191	.03

mechanical ventilation (73.7% vs 47.4%; $P = .04$) was significantly more common among arterial thrombosis cases. The association between arterial thrombosis cases and maternal hypertension did not attain statistical significance ($P = .08$). Multivariable logistic regression analysis was not performed for arterial thrombosis cases given the small number of cases and because only a single risk factor was associated with arterial thrombosis in the bivariable analysis.

Discussion

In our case-control study of admissions to the NICU at 2 large pediatric institutions, we observed a thrombosis incidence of 15.0 per 1000 admissions. We found that gestational age between 22 and 27 weeks, presence of CAD and a duration of stay of ≥31 days in the NICU were more common among neonates with thrombosis versus those without thrombosis. When we matched venous thrombosis cases and controls by CAD and gestational age, we found that male sex and BSI were independently associated with thrombosis. In a subgroup analysis of admissions with a CAD, BSI and CAD duration were associated independently with thrombosis. For arterial thrombosis, we found that only prolonged mechanical ventilation for >2 days was associated significantly with thrombosis.

Our study shows that the combined incidence of neonatal venous and arterial thrombosis is about 6 times higher than previously reported in the Canadian registry (2.4/1000 admissions in the NICU).[6] The German prospective registry showed an even lower incidence of neonatal venous and arterial thrombosis (5.1/100 000 births), and the Dutch prospective registry reported the incidence of only venous neonatal thrombosis at 14.5 in 10 000 children in the 0- to 28-day age range. The lower incidence in the German and Dutch registries was likely because they included healthy newborn babies.[7,8] In support of our data, recent reports from the National Hospital Discharge Survey (18.1-49.6 cases/100 000 admissions) and Pediatric Health Information System database (44-75 cases/10 000 admissions) have shown an increasing incidence of venous thrombosis in hospitalized infants.[16,17] The increase in incidence may in part be attributed to advances in interventions to manage and treat complex neonatal conditions, increased survival of the youngest premature infants, and increased screening and detection.

We identified male sex and BSI as risk factors for venous thrombosis in infants in the NICU matched for CAD and gestational age. Tuckuviene et al reported an increased risk of arterial ischemic stroke in neonates with male sex, but not older children.[10] The same group found a nonsignificant trend toward an increased risk of venous thromboembolism among male infants.[18] The reason for this sex difference in neonates and older infants is unknown. BSI has been implicated as a risk factor for thrombosis in older children admitted to the pediatric intensive care unit,[13,19] but this finding has not been studied in neonates or infants in part because of limitations in sample size. Thornburg et al hypothesized that in neonates with catheter-related thrombosis, thrombosis may be caused by inflammation induced by infection.[20] Finally, mechanical ventilation was associated with arterial thrombosis in our analysis, which likely reflects the complexity of associated medical or surgical conditions requiring its use. The exact pathophysiologic mechanisms for this association, however, is not clear.

One of the well-described risk factors for thrombosis, the presence of a CAD, was confirmed in our analysis. In our study, 75% of cases with neonatal thrombosis had a CAD compared with 49% of controls without thrombosis. This is similar to the Canadian and Dutch registries, which reported that 89% and 94% of thrombotic events identified, respectively, were catheter device related.[6,8] More recently, studies by Demirel et al and Amankwah et al reported that 72% and 96%, respectively, of neonates with thrombosis had an indwelling catheter.[9,11] The relative vessel wall to catheter size, frequent access for drawing blood, and frequent infusion of medications are likely causes for this association.

We also found in our study that longer duration of the CAD increased the risk of thrombosis, which has not been previously reported. Immediately after insertion, the surfaces of the catheter become coated with plasma proteins, particularly fibrin. Electron microscopy studies show that bacteria may migrate from skin along the catheter track and/or from catheter hubs down the lumen and become embedded in this protein sheath within hours of catheter insertion. It is possible that a lag time of 3 to 4 days exists after insertion during which the risk of infection and or thrombosis is low, followed by an increased risk of thrombosis with increasing duration of CAD.[21]

In our study, neonates with thrombosis were more likely to be extremely premature between 22 and 27 weeks gestational age. Tuckuviene et al showed that thrombosis was significantly associated with gestational age less than 37 weeks.[18] However, their study included neonates with arterial ischemic stroke (AIS), who formed a larger portion of infants in their study and have different etiological risk factors. Van Omenn et al and Demirel et al showed that prematurity was a significant risk factor for thrombosis, but both studies had a sample size that was too small to draw any definitive conclusions.[8,9] In our study, a duration of stay of ≥31 days in the NICU was more common among those with thrombosis, but this association was not statistically significant in our univariate analysis. Similarly, Amankwah et al reported that a duration of stay of ≥15 days was significantly associated with hospital-acquired venous thromboembolism in the NICU on univariate analysis, but not on multivariate analysis.[11] The longer duration of stay is likely a marker for the severity of underlying conditions leading to hospitalization.

A major strength of our study was that we matched for CAD among cases and controls, which allowed us to assess the relationship of both venous and arterial thrombosis to other risk factors aside from CAD. We also combined data from 2 large pediatric centers in our analysis, creating a sample size large enough to simultaneously assess multiple risk factors in a multivariable model. Additionally, the CHND database uniformly undergoes several reliability and validity checks, and all definitions were determined a priori so that standardized data entry was ensured across both centers, which reduces the likelihood of errors.

Our study did have some limitations. Because we only included sick infants admitted to level IV, regional NICUs at only 2 institutions,[22] the results of this analysis cannot be extrapolated to the entire neonatal and infant population or to newborn nurseries. However, we repeated our analyses separately for the 2 centers and found no significant differences in risk factors (data not shown). Also, we were not able to exclude infants who had thrombosis present at the time of admission because of the retrospective nature of the database. We also wanted to examine the feasibility of this analysis in the larger CHND dataset where a secondary chart analysis is not practical and, hence, a detailed individual chart analysis was not performed. We could not evaluate for other known risk factors for thrombosis such as dehydration, polycythemia, or inflammation, because information related to these risk factors was not entered in the database. Because this was a retrospective database analysis, we cannot account for coding error or misclassification, which may occur in any secondary data analysis. Although we compared our incidence with that reported in other registries or studies, conclusions about incidence rates may be limited by variability in reporting methodologies across studies that examine hospital admissions versus population-based studies. Finally, thrombosis cases entered by participating centers into the CHND were categorized by a limited set of *International Classification of Diseases,* 9th edition, codes that did not allow us to accurately characterize the location of the different thromboses.

In conclusion, we report an incidence of neonatal thrombosis that suggests, based on previously published studies, an increasing incidence of this complication in the neonatal population. In addition to the presence of a CAD, male sex and BSI may also represent predictors for venous thrombotic events in sick neonates and infants in the NICU. Testing our model using data obtained from additional centers in the CHND may provide validation of these findings and facilitate the design of future prospective studies. Firmly establishing pertinent risk factors for neonatal thrombosis by prospective studies may aid in developing risk stratification models and establishing appropriate thromboprophylaxis protocols in the NICU. ■

We thank Dr Paul Monagle for his scientific suggestions and critically reviewing the manuscript, Dr Leif Nelin for data acquisition and critically reviewing the manuscript, and Dr Alexis Thompson for her scientific suggestions and input in study design and support.

Submitted for publication Jul 17, 2017; last revision received Nov 21, 2017; accepted Dec 6, 2017

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