

# Catheter-related thrombosis in a neonatal intensive care unit: a case-control study

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## ABSTRACT

**Introduction:** Catheter-related thrombosis (CRT) accounts for most thrombotic events in the neonate. **Objective:** Investigate CRT frequency, association with days of catheter use until diagnosis, and number of catheters used, in a single-center Neonatal Intensive Care Unit. **Methods:** A case-control study that included 14 cases and 42 controls. Data collection occurred between January 2017 and December 2020 in a public NICU. Crude odds ratios (COR) were calculated. The study complied with ethical standards from national guidelines. **Results:** Two hundred and ninety-four neonates used central venous catheters, of which 14 (4.7%) were diagnosed with CRT. Catheter in use when diagnosis was made was centrally inserted central catheters in 8 (57.1%). Before diagnosis, the cumulative duration of catheter use was 34.5 days and the median number of catheters used was three. A higher SNAPPE-II (COR 1.03; 95% CI 1.01-1.06;  $p=0.03$ ), cumulative days of catheter use  $>30$  (COR 19.11; 95% CI 2.28-160.10;  $p=0.007$ ) and number of catheters used  $\geq 3$  (COR 7.66; 95% CI 1.51-38.70;  $p=0.01$ ) were associated with CRT. **Conclusion:** CRT cases were associated with clinical severity; number of catheters and cumulative days of catheter use. We suggest that screening for thrombosis should be performed in neonates who need a long time of catheter use and more than three catheters. Reducing the duration and number of venous catheters used will help to reduce CRT.

**Keywords:** central venous catheters; venous thrombosis; infant, newborn; Intensive Care, Neonatal; case-control studies.

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## INTRODUCTION

Venous thrombosis is one of the most common complications related to central venous catheter use in the neonatal intensive care unit (NICU) and catheter-related thrombosis (CRT) accounts for most thrombotic events in the neonate<sup>1,2</sup>. Thrombosis in the neonatal period is reported to occur more than in any other pediatric age<sup>3</sup>. According to El-Naggar et al.<sup>4</sup>, venous thrombotic events in the neonatal period were more frequent than the arterial, occurring most commonly in the portal vein. The improvement in neonatal care led to a rise in the survival of the youngest preterm infants and it has been suggested that the increase in the use of venous catheters for the administration of drugs and parenteral nutrition has been responsible for the increase in CRT cases among neonates<sup>5</sup>.

Chojnacka et al.<sup>6</sup> observed 16 cases of CRT in neonates and concluded that thrombosis occurred in 2.6% of all central lines and days of catheter use were a risk factor. El-Naggar et al.<sup>4</sup> also encountered a longer hospital length of stay and days of catheter use in infants with thrombosis. Prematurity, heart conditions, maternal pathologies, perinatal asphyxia, elevated hematocrit, and thrombophilia can be associated with thrombosis<sup>6,7</sup>. Lambert et al.<sup>8</sup> found

that these thrombosis cases in neonates occurred at an incidence of 1.17 per 100 infants and clinically identifiable cases were rare.

In a NICU located in Argentina, 22 CRT cases were registered between 2015 and 2016, reflecting an 8.3% frequency among 264 catheters. Also, it was observed a CRT incidence density of 5.3% /1,000 days, considering the overall time of catheter use, from introduction until withdraw<sup>1</sup>. This frequency was above the one observed by Chojnacka et al.<sup>6</sup>, suggesting that there is no consensus and differences between clinical practices, population, and study design may interfere with results. Brazilian literature regarding venous thrombosis in neonates is scarce. A recent study evaluated severe venous thrombosis in preterm infants admitted to a NICU located in São Paulo, who were treated with anticoagulants. During 15 years, they observed 21 cases, revealing a 0.3% frequency<sup>9</sup>.

Thus, we conducted a case-control study to investigate CRT frequency, its association with days of catheter use until diagnosis, and the number of catheters used, in a single-center Neonatal Intensive Care Unit.

## METHODS

This is a case-control study carried out in a tertiary NICU of a public and university hospital located in São Paulo, Brazil, between January 2017 to December 2020. Medical charts of all infants with venous thrombosis were reviewed.

Inclusion criteria were all inborn neonates who used at least one central venous catheter, did not require chest compressions or epinephrine at birth, and were admitted to the NICU. Exclusion criteria were neonates who were transferred.

Fourteen cases of CRT were enrolled consecutively. Case definition was the detection of a persistent echodense structure within the vein observed in two dimensions, in a radiological exam performed on an infant in the use of a central venous catheter, in the NICU. All cases were diagnosed by a radiologist. To minimize selection bias, for each case, three controls were randomly selected from the database of the NICU, during the same period. To minimize confounding, for each case, we randomly selected controls with the same gestational age ( $\pm$  one week), sex, and birthweight ( $\pm$  100g). Forty-two controls from the same NICU who used central venous catheters were included. The position of the catheter tip was controlled by a radiologic exam.

Individual data included: gestational age, maternal morbidities, sex, birthweight, Score for Neonatal Acute Physiology with Perinatal Extension II (SNAPPE II)<sup>10</sup>, cesarean section, small for gestational age, 5<sup>th</sup> minute Apgar, use of vasoactive drug, diagnosis of disseminated intravascular coagulation (DIC), hematocrit >65% and congenital heart disease. Length of stay (total number of days that an infant stayed at the hospital), and outcome (death or discharge) were registered. We investigated the types of catheters used, umbilical vein catheter (UVC), epicutaneo-caval catheter (ECC), and centrally inserted central catheters (CICC). All ECCs were inserted by the nurse team. UVC

and CICC were inserted by the medical team. The total number of catheters used for each patient, cumulative days of catheter use, type of catheter in use when diagnosis was made, location of thrombosis, and instituted treatment were registered. We did not control the use of ultrasound for catheter insertion. The NICU has bundles for catheter placement and management.

The STROBE statement for case-control studies was applied<sup>11</sup>. The Ethics Committee approved this study. (Registration Number: 43199721.6.0000.0082).

Sample power was calculated considering differences observed in mean cumulative days of catheter use, a sample of 56 participants, an alpha of 0.05, and a standard deviation of 10, resulting in 0.999.

The data were systematized in electronic Excel spreadsheets in double typing, later checked and the possible typing mistakes were corrected. All data were imported to Stata version 13.0 (Stata Corp, L. C.) for statistical analysis. Mann-Whitney U, Chi-square, and Spearman coefficient tests were used for bivariate analysis. Results are expressed in the median and interquartile range (IQR). Crude odds ratios (COR) and 95% confidence intervals (95% CI) were calculated using univariate logistic regression for variables with a  $p < 0.20$  in the previous bivariate analysis. The median number of catheters used before diagnosis and cumulative days of catheter use before diagnosis (in cases) were identified. Significance was defined as  $p < 0.05$ .

## RESULTS

During the study period, 988 infants were admitted to the NICU, 294 (29.8%) used central venous catheters, of which 14 (4.7%) were diagnosed with CRT. Overall median cumulative days of catheter use was 34 (IQR 12, 60), number of catheters used was 3 (IQR 1, 4) and length of stay was 53 days (IQR 22, 115). None of the infants had a hematocrit value >65% and none of the mothers had a diagnosis of thrombophilia. Mortality occurred in 7 (50%) of cases and 12 (28.5%) of controls ( $p = 0.14$ ).

The median cumulative days of catheter use until diagnosis was 34.5 and the number of catheters used was 3. The most common locations of thrombosis were the superior vena cava and the right atrium. In two cases, the type of catheter in use at diagnosis was UVC (Table 1). All cases of CRT were treated with enoxaparin. Each infant used from 1 to 8 catheters. A comparison of the type of catheter from the first until the eighth revealed that the second (35.7% *versus* 9.5%) and third catheters (42.8% *versus* 14.2%) used in CRT cases were more frequently CICC (Figure 1).

Infants who had a CRT diagnosis had higher SNAPPE II, length of stay, cumulative days of catheter use, and they used more catheters (Table 2).

To explore confounding, we investigated the correlation between SNAPPE II, cumulative days of catheter use (Spearman=0.23;  $p = 0.10$ ), and overall number of catheters used (Spearman=0.24;

**Table 1:** Location of catheter-related thrombosis, type of catheter in use at diagnosis, number of catheters used until diagnosis, duration of catheter uses until diagnosis and exam realized to diagnosis.

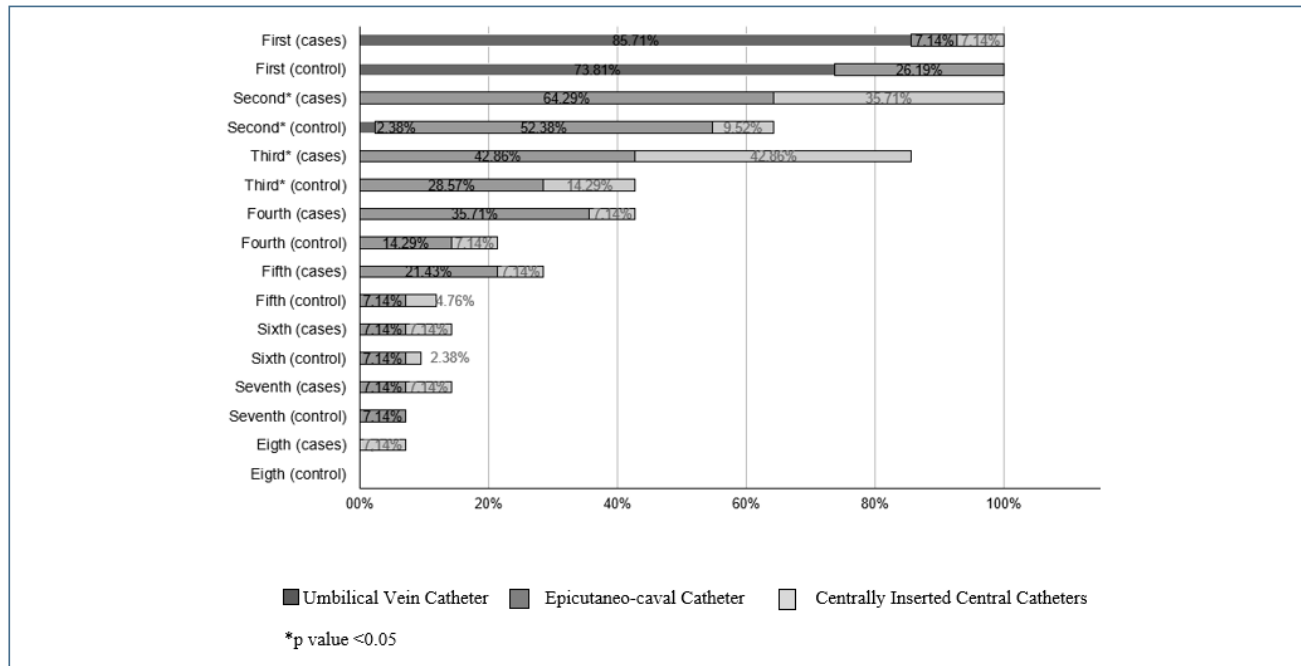
Characteristic	Cases (n=14)
Location of thrombosis, n (%)	
Superior vena cava	4 (28.5)
Right atrium	4 (28.5)
Superior vena cava to right atrium junction	2 (14.3)
Right arm	2 (14.3)
Left arm.	1 (7.2)
Umbilical vein (intraluminal)	1 (7.2)
Type of catheter in use at diagnosis, n (%)	
CICC	8 (57.1)
ECC	4 (28.6)
UVC	2 (14.3)
Number of catheters used until the diagnosis of thrombosis, median (IQR)	3 (2, 4)
Days of catheter use until diagnosis of thrombosis in days, median (IQR)	34.5 (17, 68)
Exam realized to diagnosis, n (%)	
Echocardiogram	9 (64.2)
Doppler	5 (35.8)

CICC: centrally inserted central catheter; ECC: epicutaneo-caval catheter; UVC: umbilical venous catheter; IQR: interquartile range.

**Table 2:** Maternal and neonate characteristics according to the presence of catheter-related thrombosis

Characteristics	Cases (n=14)	Controls (n=42)	P value*
Gestational age (weeks), median (IQR)	27 1/7 (25, 31 5/7)	27 1/7 (25 5/7, 31 5/7)	0.80
Birth weight (g), median (IQR)	885 (700, 1,285)	882 (710, 1,335)	0.98
Male sex, n (%)	4 (21.4)	12 (28.5)	>0.99
Maternal hypertension, n (%)	3 (21.4)	9 (21.4)	>0.99
Maternal diabetes, n (%)	1 (7.1)	1 (2.3)	0.40
Chorioamnionitis, n (%)	1	6 (14.2)	0.13
Cesarean section, n (%)	8 (57.1)	20 (47.6)	0.53
Small for gestational age, n (%)	3 (21.4)	9 (21.4)	>0.99
5 <sup>th</sup> minute Apgar, median (IQR)	8 (6, 8)	8 (7, 9)	0.14
SNAPPE II, median (IQR)	42 (31, 60)	24.5 (12, 45)	0.03
Sepsis, n (%)	3 (21.4)	3 (7.3)	0.14
DIC, n (%)	5 (35.7)	13 (30.9)	0.74
Congenital heart disease, n (%)	3 (21.4)	19 (45.2)	0.11
Use of vasoactive drugs, n (%)	10 (71.4)	25 (59.5)	0.42
Length of stay in days, median (IQR)	110 (46, 192)	41 (10, 88)	0.005
Cumulative days of catheter use, median (IQR)	56 (44, 72)	27 (7, 56)	0.002
Number of catheters used, median (IQR)	3 (3, 5)	2 (1, 3)	0.006

IQR: interquartile range; DIC: disseminated intravascular coagulation; SNAPPE II: Score for Neonatal Acute Physiology with Perinatal Extension II; \*P value associated with Mann-Whitney U test or Chi-square test.



**Figure 1:** Comparison of type of catheter used from the first until the eighth, between cases and controls.

p=0.08). Univariate logistic regression revealed that higher SNAPPE II (COR 1.03; 95% CI 1.01-1.06; p=0.03), cumulative days of catheter use > 30 (COR 19.11; 95% CI 2.28-160.10; p=0.007) and number of catheters used ≥3 (COR 7.66; 95% CI 1.51-38.70; p=0.01) were associated with CRT.

## DISCUSSION

Venous catheters are frequently used in NICU, due to the severity of patients and the need to infuse solutions and medications. However, their use may be associated with some complications such as venous thrombosis.

Considering all NICU admissions, we observed a 1.4% frequency of CRT. These results agree with other studies, although the profile of patients was different from the present study, which included infants with lower gestational age and birth weight. The epidemiology of neonatal thrombosis has been variable in studies, ranging from 6.9 to 15 per 1,000 NICU admissions<sup>7</sup>. El-Naggar et al.<sup>4</sup> observed an incidence of neonatal thrombosis of 1.4% to 1.7%. Chojnacka et al.<sup>6</sup> observed a frequency of 2.6%. Longo et al. observed a higher frequency of CRT (8.3%), related to characteristics of patients, who were surgical cases in 63% and congenital heart disease<sup>1</sup> cases in 13%.

We observed in cases that cumulative days of catheter use until the diagnosis was 34.5 days and the number of catheters used was three. Chojnacka et al.<sup>6</sup> observed that overall days of CICC use were longer in cases, but they did not report the time before the diagnosis. El-Naggar et al.<sup>4</sup> observed that hospital length of stay was longer for cases. Again, the authors did not report the time before diagnosis.

The most frequent location of CRT was the superior vena cava, followed by the right atrium. In other studies, the portal vein was observed as the most frequent location<sup>4,6,12</sup>. Incidence and location of thrombosis in children are influenced by the study design, the population, and the location of the central line<sup>13</sup>.

Although we observed that infants with CRT had a longer length of stay, the logistic regression did not associate a significant odds ratio. Robinson et al. observed that thrombosis was associated with a longer hospital stay (57 days vs 10 days)<sup>14</sup>. It has been emphasized by literature that hospital-acquired venous thromboembolism in children is associated with an increased length of stay and higher costs and this aspect must not be neglected<sup>15</sup>.

SNAPPE II was an independent factor associated with CRT. As we matched infants by birth weight and gestational age, the other factors that comprise this score explain this association. The literature has emphasized that neonates are at risk of thrombosis due to a combination of factors, such as systemic inflammation and fluid fluctuations<sup>16</sup>. Amankawah et al.<sup>17</sup> analyzed the risk factors for neonatal thromboembolism, in a case-control study but they also included infants that did not use venous catheters. Central line use, mechanical ventilation, and length of stay >15 days were risks for thromboembolism. El-Naggar et al.<sup>4</sup> and Chojnacka et al.<sup>6</sup> did not report severity scores.

Overall cumulative days of catheter use was 34 days. Cases used catheters for 56 days and controls for 27 days. We consider this time as a long duration and its reduction, as an opportunity to improve the quality of care in the NICU studied. CRT is considered an adverse event associated with venous catheter use, such as bloodstream infection, tip migration, malposition, and extravasation, and should be monitored for quality improvement<sup>18,19</sup>. The duration of catheter use was related to immaturity and birth weight. El-Naggar et al.<sup>4</sup> observed that catheters were used during 17 days in more mature infants. Chojnacka et al.<sup>6</sup> observed that catheters were used during 23.1 days in cases, in a study that also included infants more mature than those included in the present study.

A comparison of the type of catheter from the first until the eighth revealed that the second and third catheters used in CRT cases were more frequently CICC. Longo et al.<sup>1</sup> observed that cardiovascular surgery and the use of catheters different from ECC increased the risk of CRT. On the other hand, Chojnacka et al.<sup>6</sup> observed CRT associated with ECC in 10 neonates, CICC in 4, and UVC in 2. Grizante-Lopes et al.<sup>9</sup> reported that among 21 preterm neonates with severe venous thrombosis, 18 (85.7%) were associated with CICC and 2 (9.5%) with ECC.

When the diagnosis was made, the type of catheter in use was CICC in 57.1%. This was related to the site most frequently reported, the right internal jugular vein, assessed by cannulation. Chojnacka et al.<sup>6</sup> observed in 16 cases of CRT that 4 (25%) were associated with CICC. Konstantinidi et al.<sup>20</sup> compared UVC and ECC in neonates <32 weeks and they did not observe differences in complications. They reported one case of portal vein thrombosis on the 12<sup>th</sup> day of hospitalization. Goh et al.<sup>21</sup> observed 1.8% of thrombosis associated with UVC.

All cases were treated with enoxaparin. Chojnacka et al.<sup>6</sup> reported a similar treatment. A large cohort study in the neonatal population observed that low molecular weight heparin (LMWH) was the anticoagulation most frequently used<sup>19</sup>. Although low molecular weight heparin is well tolerated and effective<sup>22</sup>, the management of thrombosis in neonates is a challenging task. All recommendations are based on scarce and low-level pediatric evidence<sup>23</sup>. Low molecular weight heparin is safer, as it carries a lower risk of bleeding and heparin-induced thrombocytopenia<sup>24,25</sup>. Some authors suggest that the decision to use antithrombotic agents should be made on an individual basis<sup>26</sup>.

Mortality was not statistically different between cases and controls, but cases revealed a trend of increased mortality (50% vs 28.5%). This result is by El-Naggar et al.<sup>4</sup> and Chojnacka et al.<sup>6</sup> who did not report mortality differences. On the other hand, Robinson et al. observed that overall mortality was increased in infants with thrombosis (11% vs 2%)<sup>14</sup>. Methodological differences imply different interpretations of results.

Our study has limitations; as a retrospective study, it is subject to reporting bias. We did not control the use of ultrasound for catheter insertion and catheter size. As a case-control study, the risk ratio could not be directly estimated, and few cases were observed during the study period. Our findings should be interpreted with caution, as they were collected on a single-center basis. The strengths of our study include controls selected from the same populational basis, the observation of how many catheters were, and the duration of catheter use until CRT was diagnosed.

In conclusion, CRT cases were associated with clinical severity, number of catheters, and cumulative days of catheter use. We suggest that screening for thrombosis should be performed in neonates who need a long time of catheter use and more than three catheters. Reducing the duration and number of venous catheters used will help to reduce CRT.

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