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Original Article

# Cerebral Sinovenous Thrombosis in the Asphyxiated Cooled Infants: A Prospective Observational Study

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ABSTRACT

**BACKGROUND:** Cerebral sinovenous thrombosis is unusual in the asphyxiated cooled infants, but reliable data regarding the incidence of this comorbidity are lacking. We assessed the incidence of sinovenous thrombosis in a population of asphyxiated cooled infants by performing routine brain magnetic resonance venography. **METHODS:** All asphyxiated infants who underwent therapeutic cooling at our institution completed brain magnetic resonance venography after rewarming. Assessing the incidence of cerebral sinovenous thrombosis was the primary goal. Secondary analyses included group comparisons for laboratory tests and monitored parameters, relationship between variables, logistic regression models, and receiver operating characteristic curve for cerebral sinovenous thrombosis prediction. **RESULTS:** Cerebral sinovenous thrombosis was detected in 10 of 37 infants (27%), most commonly affecting the superior sagittal sinus (eight of ten). These infants manifested higher blanket ($P < 0.001$) and lower esophageal temperatures ($P = 0.006$), lower platelet counts ($P = 0.045$), and received more red blood cell transfusions ($P = 0.038$) than the cooled infants without thrombosis. Blanket temperature was independently associated with cerebral sinovenous thrombosis ($P = 0.049$), and 32°C/hour was the optimal cutoff value to predict the event (sensitivity, 90%; specificity, 88.5%). **CONCLUSIONS:** High incidence or cerebral sinovenous thrombosis in neonates treated with therapeutic hypothermia suggests that magnetic resonance venography may be reasonable in many of these children. High blanket temperature may be one variable that helps identify patients at higher risk.

***Keywords:*** cerebral sinovenous thrombosis, magnetic resonance venography, neonatal hypoxic–ischemic encephalopathy, stroke, therapeutic hypothermia

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## Introduction

Cerebral sinovenous thrombosis (CSVT) is a rare finding with potential high neurological morbidity, characterized by partial or complete occlusion of one or more cranial venous sinuses and hindering of blood flow in the tributary venous system. CSVT affects at least 0.67 individuals per 100,000 children per year, with higher rates among newborns.[1-3] As in adults and children, the etiology of CSVT in neonates is often multifactorial, but male sex, perinatal complications associated with complicated or assisted deliveries, and systemic illness are more frequently observed.[2,4,5] Early presentation of symptoms, even at birth, may suggest the possibility for a fetal origin and a relationship with birth asphyxia.[6,7] However, this condition is considered an unusual finding in the asphyxiated cooled infants, although accurate data are still lacking.[8-11] The extent of the problem is likely to be underestimated because the clinical signs and symptoms are similar to those

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of asphyxia, and the diagnosis can be missed if proper imaging of cerebral venous circulation is not performed. Our goal was to evaluate CSVT incidence in a population of asphyxiated cooled infants through brain magnetic resonance venography (MRV) routinely performed after rewarming.

## Methods

As of July 2010, we began to treat the asphyxiated infants admitted at our third level neonatal intensive care unit with whole-body cooling to an esophageal temperature of 33.5°C maintained for 72 hours by using the servocontrolled Blanketrol III hyper-hypothermia system (Cincinnati Sub-Zero, OH, USA) in the gradient mode (10C Smart Mode). Eligibility and treatment of the asphyxiated infants were conducted according to the established criteria and methods.[12] Video-electroencephalography recordings were performed at admission, as an entry criterion, during the rewarming phase, and in response to clinical seizures. Correct placement of the esophageal probe (third lower esophageal) was checked with chest X-ray and subsequently verified if abnormal swings of the esophageal or blanket temperatures were noted. All infants received phenobarbital and fentanyl infusion for sedation and pain control as specified by institutional protocol. Esophageal, skin, rectal, and blanket temperatures, vital signs, intravenous fluids, urine output, and inotropic support were hourly recorded on a predesigned data form. Vasoactive-inotropic score was calculated according to the study of Gaies et al.[13] Type and number of transfused blood components were also documented. Laboratory assessment, including platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimer was performed on admission and every 24 hours during the same period; D-dimer values were dropped from the analysis because the method of measurement changed during the study period. Brain magnetic resonance imaging (MRI) was planned within the first week of life for each patient or when clinically feasible. All brain MRIs were executed using institutional protocols for neonatal brain imaging on 1.5-T scanner (Optima MR360 Advance; General Electric Medical Systems, IL, USA) with a contiguous two-dimensional time-of-flight MRV. No contrast agent was administered. All imaging results were independently reviewed by two authors (P.C. and F.L.) experienced in evaluating neonatal brain MRI who were not aware of the clinical conditions. Clearly visible complete or partial absence of flow in one or more cranial venous sinus on brain MRV was recognized as a sign of thrombosis, with or without associated parenchymal lesions. All the CSVT positive infants were subject to follow-up brain MRI/MRV with timing decided at the discretion of the neuroradiologist, and cranial venous sinus patency was assessed as normal, improved, or persistently occluded. Anticoagulation treatment protocol consisted of subcutaneous low-molecular-weight heparin at the starting dose of 1 mg/kg twice daily, titrated to antifactor Xa activity between 0.1 and 0.3 U/mL for at least six weeks. A thorough screening for thrombophilia including antithrombin III deficiency, protein C deficiency, protein S deficiency, activated protein C resistance, factor V Leiden mutation, prothrombin gene mutation G20210A, and thermolabile form of the methylenetetrahydrofolate reductase gene was executed in the CSVT positive infants. We complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving human subjects and had an approval for this study by the local ethics committee.

### *Statistical analysis*

The Shapiro–Wilk test was applied to assess the normal distribution of variables. Because of their asymmetric distribution, the nonparametric Mann–Whitney's *U* test was used for comparisons between CSVT positive and CSVT negative patients, and chi-square test was used for comparisons of categorical variables. Multivariate logistic regression models were fitted for the prediction of the CSVT as binary variable (1 = CSVT; 0 = no CSVT), incorporating as explanatory variables all the variables that showed a *P* value $\leq$0.25 in the bivariate analysis.[14] To avoid multicollinearity problems, predictors that were in strong correlation with other explanatory variables were dropped from the models. Multicollinearity in logistic regression models is a result of strong correlations between independent variables. The existence of multicollinearity inflates the variances of the parameter estimates. That may result, particularly for small and moderate sample sizes, in lack of statistical significance of individual independent variables, although the overall model may be strongly significant. Multicollinearity may also result in wrong signs and magnitudes of regression coefficient estimates, and consequently in incorrect conclusions about relationships between independent and dependent variables. Goodness-of-fit of logistic regression models was checked using the Hosmer and Lemeshow test, and odds ratios (ORs) with 95% confidence intervals (CIs) were also calculated. The predictive accuracy of variables strongly related to the CSVT development was also quantified as the area under the receiver operating characteristic curve. Finally, the relationships between variables were tested using the Spearman rho correlation coefficient analysis. All statistical analysis was performed using IBM-Statistical Package for Social Science version 22.0 (IBM Corp, Armonk, NY, USA, 2013), and a two-sided *P* value $<$0.05 was considered significant.

## Results

Thirty-seven asphyxiated infants underwent whole-body cooling at our institution from July 2010 through November 2015. Two brain MRIs and MRVs were performed in each infant at a median of 7 (interquartile range = 4.5 days) and 29.5 (interquartile range = 15.5 days) days of life, respectively. In the first brain scan, hypoxic–ischemic injuries were detected in 17 of 37 infants

**TABLE 1.**
Overview of the Affected Sinuses, Associated Brain Lesions, and Thrombosis Evolution

| Sex | MRV* | Cerebral Venous Sinus | Brain Hemorrhages | Sinus Patency† |
|---|---|---|---|---|
| M | 7 | Superior sagittal (posterior) | Right temporal | Normal |
| F | 6 | Superior sagittal (anterior) | No | Normal |
| M | 10 | Superior sagittal (posterior) | Left parasagittal and peritrigonal | Normal |
| M | 5 | Superior sagittal (middle) + left straight | No | Normal |
| F | 12 | Superior sagittal (posterior) | No | Normal |
| M | 6 | Superior sagittal (posterior) | No | Improved |
| M | 7 | Left transverse + left sigmoid | No | Improved |
| M | 5 | Superior sagittal (anterior) | No | Improved |
| M | 7 | Superior sagittal (posterior) + right straight | Right frontal and peritrigonal | Improved |
| M | 10 | Right straight + right jugular vein | Right intraventricular and peritrigonal | Obstructed |

Abbreviation:
MRV = Magnetic resonance venography
* Days of life at first brain MRV.
† Follow-up MRV.