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The Use of Enoxaparin and Insuflon™ Catheter to Direct Treatment of CVL Thrombosis

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ABSTRACT

Neonates are surviving at younger gestational ages and with more significant congenital anomalies. In addition, the clinical interventions required to care for them are also becoming more complex and technical, which, in turn, increases the risk of complications related to these interventions. Included in these risks is the potential for central venous line (CVL)-associated thrombus or, for the purposes of this paper, venous thromboembolism (VTE). Though the true incidence of VTE is not known, CVLs remain the most common cause of VTE in the neonate. Treatment consists of low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) followed by LMWH for a period of 6 weeks to 3 months. The Insuflon™ Subcutaneous Catheter is a safe and effective option for anticoagulation administration for those infants diagnosed with VTEs.

While randomized controlled trials (RCT) studying central venous thrombus in the NICU are rare due to ethical considerations and sample sizes, five studies will be presented here. The topics explored are as follows: the use of enoxaparin sodium (Lovenox®, Sanofi US, Bridgewater, NJ), increase in incidence and general use of anticoagulants, use of heparin to increase line-life, and the association between central-line sepsis and central-line thrombus. One of these studies is an RCT.

Background

Neonates are surviving at younger gestational ages and with more significant congenital anomalies than ever before. Coupled with this, the clinical interventions required to care for these infants are also becoming more complex and technical, which, in turn, increases the risk of complications related to these interventions. Included in these risks is the potential for central venous line (CVL) associated thrombus or, for the purpose of this article, venous thromboembolism (VTE). Venous thromboembolism is a major clinical complication effecting pediatric patients up to 18 years of age.[1] Central venous lines are the most common cause of VTE in neonates and infants.[1–5]

Central venous lines in the neonatal intensive care unit (NICU) are widely utilized and paramount to the maintenance and survival of the sickest neonates. These lines, whether in the form of an umbilical venous catheter (UVC) or a peripherally inserted central catheter (PICC), are used for intravenous fluid (IVF) administration, medication administration, total parenteral nutrition (TPN), and under some circumstances, blood product administration and blood sampling.

The complications of CVL-associated VTEs can be mechanical, infectious and thrombotic. Mechanical complications are due to endothelial damage experienced during catheter placement, blood vessel occlusion due to the small inner diameter of neonatal vessels, and low flow states or turbulent blood flow states as a result of hemodynamic instability. Other complications are related to patient acuity or presence of comorbid conditions, catheter material(s), or infusion characteristics (of particular risk are hyperosmolar solutions).[4,6]

Sick newborns, premature in particular, are at a higher risk for VTE due to their small vasculature, underdeveloped hemostatic systems, congenital heart disease (CHD), potential for dehydration, birth weight less than 1250 g, central hematocrit greater than 55%, small for gestational age (SGA), maternal pre-eclampsia, surgery, genetics and sepsis. Infectious complications can be two-fold. Central venous catheter-associated VTE can act as a nidus for infection *or* sepsis, or more specifically the associated inflammatory cascade, can activate the formation of a thrombus.[4]

In the neonate, VTEs are most frequently noted in the following vessels: renal veins, portal veins, inferior vena cava (IVC), superior vena cava (SVC), femoral veins, and iliac veins.[7] Central venous catheters in the femoral veins are associated with the highest incidence of VTEs.[7] Once an infant has been suspected of or confirmed with a VTE, they are also at risk for common

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Table 1
Review of Literature Highlighting Studies Addressing CVL-Associated VTE.

Author(s), year, level of evidence	Research Design	Key Findings	Main hypothesis(es)/ objectives	Variables	Odds ratio/ relative risk	Potential bias
Authors: Malowany, Knoppert, Chan, Pepelassis and Lee Year: 2007 Level of evidence: III	Retrospective chart review Non-experimental	*Descriptive statistics*: Dosing of enoxaparin was closely related to Anti-Xa levels more so in term infants vs. preterm infants *Inferential statistics*: Preterm infants have higher dosing/kg requirements than term infants. Pharmacokinetics are more unpredictable in preterm infants. AEs and complications are minor in both preterm and term infants	Enoxaparin is safe and efficacious in the NICU	*Independent*: Enoxaparin dosing *Dependent*: Anti-Xa levels	Not discussed	1. Small sample size (16 neonates) 2. Research design-retrospective 3. Convenience sample
Author(s): Raffini, Huang, Witmer and Feudtner Level of evidence: III Year: 2009	Retrospective cohort study of pts <18 years old discharged from Children's Hospital over 7 years	*Descriptive statistics*: ($p < 0.001$) 63% of patients diagnosed with a VTE had a comorbid condition. Cardiac disease was the comorbid condition most associated with VTE. Infants <1 years old and teenagers highest age categories, 55% male, of pts with recurrent VTE, pts <1 year old significantly lower, pts with malignancy have 2× as high recurrence rate *Inferential statistics*: ($p < 0.001$) Rate per year of VTE diagnosis increased by 70%. VTE rate correlated with size of hospital. Enoxaparin use increased by 20% while warfarin use decreased.	There has been an increase in the rate of venous thromboembolism in the pediatric population. Evaluation of the use of anticoagulants	*Independent*: Pediatric patients diagnosed with VTE *Dependent*: Anticoagulant use	Not discussed	1. Retrospective design 2. Limited sample size 3. Sampling: relied on ICD-9 codes. High potential for under sampling
Author(s): Streif, Goebel, Chan and Massicotte Year: 2003 Level of evidence: II	Prospective, consecutive cohort design	*Descriptive statistics*: None *Inferential statistics*: Term infants achieved therapeutic levels more rapidly than preterm infants. Newborns in the NICU achieved therapeutic levels more quickly than those on the floor. Infants in the NICU had more anti-Xa levels in range than those on the floor. Preterm infants had significantly fewer Anti-Xa levels below therapeutic range. Infants with renal/liver function had significantly more dose changes/month. Preterms required a significantly high dose to reach and maintain therapeutic than terms. Those with CHD needed a significantly lower dose to achieve and maintain than all others.	To evaluate the use of low-molecular-weight heparin (enoxaparin) in newborns	*Independent*: Newborn infants diagnosed with VTE *Dependent*: Starting dose of enoxaparin, time to therapeutic, dose to maintain, anti-Xa levels in, above and below therapeutic range, no. of dose changes	Not discussed	1. Non-experimental design (cohort) 2. Relatively small sample size 3. In this sample, CHD may be overrepresented due to hospital site (all CHD surgery done here)
Author(s): Thornburg, Smith, Smithwick, Cotton, Benjamin Year: 2008 Level of evidence: III	Retrospective cohort study design	*Descriptive statistics*: None *Inferential statistics*: Stat significant association between catheter-related thrombus when line was not removed but associated with sepsis	An association exists between catheter-related sepsis and thrombosis	*Independent*: PICC insertions *Dependent*: Central-line associated infection (sepsis) and central-line-associated thrombus	Not discussed in this paper	1. Retrospective design 2. Data not available on central-line insertion attempts 3. Subjective definition of thrombus in this paper 4. No absolute distinction could be made between intraluminal thrombus and fibrin sheath
Author(s): Shah, Kalyn, Satodia, Dunn, Parvez, Daneman, Salem, Glanc, Ohlsson and Shah Year: 2007 Level of evidence: I	Randomized, controlled trial: multicenter and double-blind	*Descriptive statistics*: gender, catheter type, cath tip position not statistically significantly related to duration of use *Inferential statistics*: Use of heparin had a statistically significant effect on the "usability" of the central venous	Use of heparin will increase the "usability" of central venous catheters in neonates	*Independent*: Heparin infusion vs. placebo *Dependent*: Total time of catheter use, catheter occlusion,	OR: 0.53 for heparin vs. placebo. RR: 1.5 for reaching end of therapy w/o complication; 0.2 for catheter	1. Inadequate power to detect relationship between length of time cath used and small increase in infection 2. Only 2 gestation age groups <30 weeks and >30 weeks