Central venous catheterization and thrombosis in newborns: update on diagnosis and management

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Very low birth weight and other critically ill neonates require prolonged vascular access, which is achieved in current practice with central venous catheters. The initiation of adequate parenteral nutrition and prolonged intravenous medications represent the most important applications. Central vascular access in neonates is associated with a high risk for mechanical, infectious and thrombotic complications. The use of central lines is the most common cause for thrombosis in neonates and infants. The management of line-related thrombosis is based on expert opinion guidelines and is largely dependent on patient symptoms and the further requirement of the catheter. This review article focuses on pathophysiology, diagnosis, and acute and long-term management of catheter thrombosis in neonates.

Keywords: Newborn, central venous catheter, thrombosis, heparin.

Introduction

Vascular access is a major challenge in the management of preterm and critically-ill term infants in neonatal intensive care units (NICUs). In sick neonates, these catheters have been shown to provide long-term vascular access necessary for the prolonged administration of parenteral nutrition and intravenous medications. Despite their many valuable applications in neonates and infants, the use of intravascular central lines carries many risks, such as mechanical, infectious and thrombotic complications [1].

The use of central lines is the most common cause of thrombosis in neonates and infants. Factors associated with initiation and propagation of thrombosis include: endothelial damage during catheter placement, blood vessel occlusion, low flow states, turbulent flow, patient and infusion characteristics and thrombogenic catheter materials.

Incidence

A commonly-cited paper published in 1995 reported that approximately 2.4/1000 of newborns admitted to NICUs experience a symptomatic thromboembolic event (TE), 89% of which were related to the use of a central venous line [2]. However, these numbers are expected to have been on the rise since that time as a result of ever-more-invasive therapeutic interventions, including an increasing use of central venous catheters (CVC), and of venous and arterial umbilical catheters (UVC and UAC).

It is very difficult to estimate the true incidence of CVC-associated TE. While clinical studies report incidences from 13 up to 30%, autopsy findings report UVC-related TE in 20 to 65% of neonates who have an UVC in place at the time of demise [3,4]. Peripherally-inserted central catheters (PICCs) in neonates and infants are also associated with thrombosis. In one study, ultrasound screening 72h after removal of PICCs showed an incidence of 18% [5]. A retrospective large cohort of 882 infants with 1540 PICCs reported occurrence of clinical thrombosis (cord, phlebitis, extremity oedema, extremity perfusion and inability to draw or flush the catheter) in 14% of infants [6]. There are only a few studies published on the distribution of neonatal thrombosis or TEs. The synopsis of these few reports is that venous thromboses are predominantly located in the renal vein, portal vein and the inferior and superior vena cava. Other frequently affected locations include the femoral and axillary veins and the right atrium.

Risk factors

Newborns are at a higher risk for TEs because of their underdeveloped clotting mechanisms, small vessel diameters, and haemostatic imbalance caused by complications such as congenital heart disease (CHD), asphyxia or dehydration [7]. In neonates of <1250g birth weight and with a haematocrit of >55%, those that were small for gestational age and maternal pre-eclampsia were found to be risk factors for thrombosis. Sepsis and infection were also associated with a high risk of thrombosis. Infection promotes clotting activation and catheters provide a centre for thrombus formation. The duration of the period when the central lines were in situ was also associated with thrombosis, and the use of central lines is thus recommended for as short a period as possible.

Several other catheter-related risk factors were identified. The use of heparin-bonded polyurethane catheters was not associated with a lower risk of thrombosis. The long-term administration of total parenteral nutrition (TPN) can result in increased endothelial damage, occlusion by foreign materials and thrombosis. Other therapies such as hyperosmolar solutions and blood product transfusions were also associated with a higher risk of thrombosis.

The contribution of inherited and acquired thrombophilia to CVC-related thrombosis is controversial and data are insufficiently consistent to make a firm recommendation for thrombophilia screening for neonates and infants with CVC-related thrombosis. Most experts recommend assessing a thrombophilia work-up in the context of a significant thrombosis event.

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avoiding any thrombophilia work-up in cases of subclinical and asymptomatic CVC-related thrombosis [7]. There are still question about the potential value of a thrombophilia work-up on parents.

Diagnosis

Clinical
The clinical picture of vascular incidents in neonates is extremely variable and largely dependent on the location and the size of the thrombus or embolus. Presentation may vary from discrete symptoms or asymptomatic events to life-threatening acute events. Although TEs are usually categorised as arterial, venous and CNS events, several right-to-left shunts remain patent for a considerable time even in the term neonate. Thus, a paradoxical embolus cannot be ruled out even in the absence of CHD [8].

Limb swelling, pain and cyanotic or hyperaemic colour should raise a suspicion of venous thrombosis. Renal vein thrombosis may present with an abdominal mass and haematuria or proteinuria. Signs of impaired liver function, hepatomegaly and splenomegaly should raise a suspicion of portal venous thrombosis (PVT); however, only about 10% of children with PVT develop acute clinical symptoms. Thrombosis of the inferior vena cava can present with signs resembling obstruction of the renal vein, but these will occur bilaterally when the inferior vena cava is affected. In addition, the lower limbs may be oedematous and, if blood flow is substantially impaired, the child may be in respiratory distress and may have high blood pressure.

Most paediatric CVC-related venous thrombi are still located in the upper venous system. Many are asymptomatic. When symptoms occur, they may include swelling, pain and discoloration of the upper extremity, superior vena cava syndrome, chylothorax and chylopericardium.

Imaging
Imaging using either echocardiography or abdominal ultrasound is the most commonly applied diagnostic method to confirm a clinical suspicion of TE or to screen babies for clinically silent disease. However, despite its advantages, the overall performance of ultrasound to detect thrombi is poor. One study comparing echocardiographic investigations to venograms reported a sensitivity of 21–43% and specificity ranging from 76 to 94% [4]. This study concluded that venography is required to accurately diagnose UVC-related TE in neonates. Even though contrast venography is considered as the gold standard in the diagnosis of neonatal catheter-induced TE, it exposes the infant to radiation and contrast agents.

Laboratory
An initial laboratory work-up in a neonate in whom thrombosis is suspected should include a full blood count as well as a coagulation screening with determination of D-dimers, platelets, prothrombin time, thrombin time and activated partial thromboplastin time [8].

Prophylaxis
A 2008 Cochrane review, updated in 2011, supports the prophylactic use of heparin infusion for percutaneous CVC in neonates [9]. The combined estimate of effect, derived from three studies, revealed that addition of heparin for PICCs allows completion of intended therapeutic use of catheters in neonates with reduced risk of catheter occlusion. The duration of catheter use was not significantly different between heparin and placebo: this could be explained by the fact that these catheters were removed at the end of their intended use. Although heparin seems to be effective in reducing the risk of catheter occlusion, none of the studies included was correctly designed to evaluate a lower incidence rate of adverse events.

The 9th American College of Chest Physicians consensus conference on antithrombotic therapy for neonates with central venous access devices (CVADs) recommends maintenance of catheter patency through the use of unfractionated heparin (UFH) as a continuous infusion at a rate of 0.5 U/kg/h [10].

Management
The management of line-related thrombosis is still based on expert opinion guidelines and is largely dependent on the clinical scenario, type of catheter and the further requirements of the catheter. Thus, consultation with a paediatric haematologist is recommended for patient-specific management guidelines. In general, the recommended management of acute and symptomatic CVC-related thrombosis largely depends on the requirement for the central line [7].

The 9th American College of Chest Physicians consensus conference on antithrombotic therapy suggests that CVADs or UVCs associated with confirmed thrombosis be removed after 3–5 days of therapeutic anticoagulation rather than left in situ. It is suggested that either initial anticoagulation or supportive care with radiological monitoring for extension of thrombosis be provided. Anticoagulation therapy should be performed with either low-molecular-weight heparin (LMWH) or UFH followed by LMWH. The suggested total duration of anticoagulation therapy is between 6 weeks and 3 months. If either a CVAD or a UVC is still in place on completion of therapeutic anticoagulation, a prophylactic dose of anticoagulation is recommended until such time as the CVAD or UVC is removed.

Thrombolytic therapy for neonatal venous thromboembolism is not suggested unless major vessel occlusion is causing critical compromise of organs or limbs. If thrombolysis is required, tissue plasminogen activator (tPA) should be used rather than other lysis agents and plasminogen (fresh frozen plasma) should be administered prior to commencing therapy.

The recommended management of radiographically detected asymptomatic central-line-related thrombosis is less clear. If the central line is no longer required, the line should be removed. In venous lines, short term anticoagulation prior to line removal is suggested. If central line access is still required, the recommended management is based mainly on expert opinion and less on evidence-based data.

The management of asymptomatic central-line-related thrombosis that is radiographically detected after the catheter has been removed is even more problematic. As spontaneous resolution is reported in most cases, a good option seems to be close clinical follow-up and therapy only for symptomatic cases [10].

Conclusion
Although the benefits from using central lines in neonates and infants balance the potential risks from those lines, better understanding of the risk factors for development of thrombosis and improved prophylaxis and treatment of CVC-related thrombosis
may further decrease the rate of complications and increase the benefit of these lines.

Diagnosis and management of CVC-related thrombosis is still based on expert opinion guidelines. Use and implementation of a thrombosis registry represents a key point in improving our management of these patients.

Where possible, paediatric haematologists should handle neonates with thromboembolism, in collaboration with radiologists and cardiologists experienced in neonatology.

Declaration of Interest: The authors report no conflict of interest in this work.

References