**SHORT COMMUNICATION**

Successful use of recombinant tissue plasminogen activator (r-TPA) for management of chylothorax associated with central venous thrombosis after neonatal cardiac surgery

Sameh R Ismail *, Mahmoud Elbarbary, Mohamed S Kabbani

King Abdul-Aziz Medical City, King Saud University for Health Sciences, Department of Cardiac Sciences, National Guard hospital Health Affairs, Riyadh, Saudi Arabia

Received 6 January 2015; accepted 14 February 2015
Available online 3 March 2015

**KEYWORDS**
Chylothorax; Venous thrombosis; TPA; Tissue plasminogen activator; Pediatric cardiac surgery

**Abstract** Postoperative chylothorax is a frequently encountered pathology occurring in up to 5% of patients undergoing surgery for repair of congenital heart disease. Neck vein thrombosis can be associated with chylothorax and may contribute to its severity and duration. Furthermore, neck vessel thrombosis resulting in permanent vessel occlusion may hinder future management, diagnostic studies and cardio-surgical interventions. In this report we are describing a neonate who developed chylothorax on the 7th post-operative day following open-heart surgery. The chylothorax was linked to venous thrombosis in the cannulated right internal jugular vein with thrombus extending to the right atrium. After using low dose tissue plasminogen activator (r-TPA) infusion, the thrombi disappeared and the chylothorax resolved with no complications.

© 2015 The Authors. Production and hosting by Elsevier B.V. on behalf of Egyptian Society of Cardiology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. Case report

A newborn boy, weight 3 kg was diagnosed with transposition of great arteries, intact ventricular septum, atrial septal defect and patent ductus arteriosus. The patient was referred to us from a primary care centre at the age of 9 days. On admission the patient had umbilical venous catheter with prostaglandin infusion, the patient was suspected to be septic, and the umbilical catheter was inserted immediately after birth, so antibiotics started and UVC was replaced with a 4 French, double lumen, right internal jugular (RIJ) central venous line (CVL). Catheter insertion was done with ultrasound guidance and was reported to be smooth and uneventful, and kept on fixed low dose heparin of 10 μ/kg/h for line patency.

At 14 days of life, the patient underwent an arterial switch operation and RIJ catheter was still in situ being used for the infusion of the inotropic support and for invasive monitoring, and a left atrial line inserted surgically to help monitoring left atrial pressure. Shortly after surgery there was minimal drainage from the single mediastinal tube. After the 5th post-
operative day, the patient developed thrombocytopenia that was managed with antibiotics presuming septic related causes. Blood cultures remained negative. Echocardiography (ECHO) at that time showed, no residual defects, and no thrombi or vegetations in the heart or major veins. On the 7th post-operative day significant right-sided pleural effusion developed which required chest tube insertion and drainage of a significant amount of milky fluid that was confirmed by laboratory analysis to be chyle. The patient was kept nil per mouth (NPO) along with total parenteral nutrition administration. Doppler ultrasound of neck vessel showed thrombosis of right internal jugular vein with thrombus extending to right atrium (Figs. 1 and 2). Additionally ECHO at that time showed two thrombi, one in the Right Atrium (RA) measuring (0.6 × 1 cm) and the other in the Left atrium (LA) (0.5 × 0.7 cm) (Fig. 3). We investigated the patient for possibility of hyper-coagulable disease, but all investigations were negative. The patient was managed conservatively with anti-coagulation in form of fractionated heparin infusion with no evidence of clinical improvement in venous obstruction despite satisfactory anticoagulation (PTT: double the control value). Furthermore, the chyle drainage remained significant averaging 64 ml/kg/day and total of 1.51 in 8 days. The risk/benefit ratio of using (r-TPA) infusion in recently operated neonate was discussed and judged to be in favor of benefits to start low dose (r-TPA) (0.05 mg/kg/h) for 6 h followed by heparin infusion. We repeated ECHO 24 h after the first dose of (r-TPA) infusion and the RA thrombus was noted to be smaller in size, while the LA thrombus completely disappeared (Fig. 4), so a second low dose (r-TPA) over 6 h was also ensued. ECHO and ultrasonography imaging after the second (r-TPA) dose showed complete resolution of the thrombi in the RIJ vein (Fig. 6), and in both atria, with simultaneous dramatic decrease in the chylothorax drainage followed by complete recovery and there were no complications (Fig. 5). Head ultrasound was done before and after (r-TPA) and ruled out any cerebral hemorrhage.

2. Discussion

Venous thromboembolic disease (VTE) is an increasingly recognized clinical entity in children who are surviving serious underlying disorders such as congenital heart disease (CHD). Children with CHD are the largest identifiable group accounting for 1/3 of children with venous thrombosis. In the general pediatric patient’s population, the most important risk factor for VTE is the use of Central venous lines (CVL), which are present in 30–70% of children with VTE. Central venous lines appear to be major risk factors for VTE, based on the close anatomical relationship found between catheters position and thrombi location. Pathogenic mechanisms of CVL related VTE include vessel wall trauma at insertion site, obstruction of venous flow, endothelial damage by CVL adhering to the venous wall, and the intravascular presence of a foreign surface. About two thirds of VTE in children occur in the upper venous system reflecting the most common location of CVL placement. There is major variability in the reported prevalence of VTE in pediatric population. Petaja et al. described a prevalence of VTE after pediatric surgery, which was higher in neonates 5.8% compared to non-neonates 1.1%. Mortality was (40%) in children with VTE compared to non-VTE (8.3%) (P < 0.001).
Successful use of r-TPA for management of chylothorax

Figure 4 Trans-thoracic ECHO picture, subcostal Biatrial view showing resolution of the left atrial thrombus and a small residual part of the right atrial thrombus after the first r-TPA dose. RA: right atrium, LA: left atrium.

Figure 5 Rate of chylothorax drainage over 25 days (ml/day). This figure is showing the trend of the chylothorax drainage and the dramatic decrease in the rate of drainage after the second dose of TPA (day 10). Ml: milliliter. TPA: Tissue plasminogen activator.

controlled study the authors reported VTE rate much higher with a prevalence of 42.5% in infants under 1 year of age, an age group that likely had an increased prevalence of VTE when compared to older children. However, these data indicate a highly significant prevalence of VTE in infants and neonates. Manlihot noted an 11% incidence of arterial or venous vessel thrombosis in pediatric cardiac surgery patients. Sixteen percent of these intravascular thromboses were associated with CVL. Cardiopulmonary bypass presents a hemostatic challenge associated with an abundance of prothrombotic risk factors. Exposure of blood components to a large synthetic surface causes disturbances in platelet function, coagulation factors, fibrinolytic system, and physiological inhibitors of coagulation. This ultimately leads to platelet activation, which is also exaggerated by the use of deep hypothermic circulatory arrest. Activated platelets provide important procoagulant activity by expressing binding sites for specific coagulation proteins. The activation period tends to be longer and its intensity more pronounced in children with cyanotic congenital heart disease than in healthy infants. Along with direct activation of the coagulation cascade, cardiopulmonary bypass triggers a global inflammatory response in a positive feedback mechanism, leading to further activation of the coagulation system and other systemic manifestations. Neonates already have low levels of antithrombin, protein S and protein C activity (typically between 20% and 60% of adult levels), contact factors (XI, XII, PK, HMWK), and vitamin K-dependent factors (II, VII, IX, X) (all_70% of adult values). Many of these differences are associated with lower capacity to inhibit thrombin generation, increased heparin clearance, and decreased sensitivity to anticoagulants, particularly to standard heparin, the most commonly used agent during and after surgery. The initiation of cardiopulmonary bypass can result in a further 50% decrease in circulating coagulation factors and antithrombin levels, in addition to a 70% drop in platelet counts. In addition to the newly acquired hypercoagulable state and functional resistance to anticoagulation, physical factors increase the risk of thrombosis in this population. The presence of an indwelling access line is generally considered one of the most important risk factors for thrombosis in pediatric patients, and _20% of patients with an indwelling access line will develop a related thrombus. In general we use in our practice low dose heparin infusion 10 IU/kg/hr. in infants and neonates to minimize the risk of CVL thrombosis as supported by some evidence, but thrombosis developed in our patient in spite of that. The benefits of heparin prophylaxis for VTE prevention in children with CVL are unproven. In a recently published evidence-based, clinical practice guideline by Monagle et al., they recommended against routine thrombolysis.

Chylothorax is a potentially life-threatening disorder that can lead to serious metabolic, immunologic and nutritional complications. Initial management is the same regardless of the cause of chylothorax. Low fat diet, total parenteral nutrition (TPN), Octeriotide, and in some cases treatment of the cause is essential for the resolution of chyle drainage. Chylothorax occurs postoperatively in up to 4% of all pediatric patients undergoing surgery for congenital heart disease. Early post-operative chylothorax is usually seen as result of intraoperative thoracic duct injury. However, late presenting chylothorax may have other possible causes that have been described such as venous thrombosis, and high venous pressure. Irrespective of its causes chylothorax has major impact on after cardiac surgery outcome. It has been associated with prolonged ventilator dependence, increased length of hospital stay, malnutrition, nosocomial infection, and death. Though multiple case series and case reports have suggested an association between central venous thrombosis (CVT) and chylothorax development, no large, controlled studies have verified this association. The connection between chylothorax and central venous thrombosis is suggested to be a causative relation supported by several case reports and series. Le Coulter et al. described seven out of twenty-four (29%) pediatric patients with postoperative chylothorax that was associated with superior vena cava (SVC) obstruction; five of them had bilateral chylothorax. Chylothoraces secondary to venous hypertension and thrombosis have a longer interval between operation and diagnosis compared with direct trauma as well as a longer duration and larger volume of chylous drainage. The mechanism for the development of chylotho-
Central venous thrombosis is commonly treated with systemic anticoagulation, catheter removal, Catheter directed thrombolytic therapy or systemic thrombolytic therapy. Manhilt et al. reported Thrombosis in the population of pediatric after open heart surgery, 87% of patients needed treatment, with 108 patients (63%) treated with low-molecular-weight heparin, 76 (44%) treated with unfractionated heparin, and 12 (7.0%) treated with warfarin. Thrombolytic therapy was used for 9 patients (5.3%) with 19 obstructed vessels, and mechanical thrombus catheter removal was performed in 25 patients (15%) with 28 obstructed vessels/intracardiac thrombi. Thrombolytic agents are occasionally indicated in patients with symptomatic thrombi. Mangh et al. published a case report of Down syndrome with chylothorax that was successfully managed by catheter-directed thrombolysis and angioplasty of the venous occlusions. The dose of r-TPA is still a subject of debate; it was addressed in many studies with different regimens. High doses of rTPA can increase rates of serious bleeding complications in children, but this risk should decrease with lower rTPA doses. Weiner et al. used an initial dose of 0.1 mg/kg/h of r-TPA for 6 h that was increased by 0.1 mg/kg/h at 6-h intervals to a maximum of 0.5 mg/kg/h. Two out of seven patients (1 term and 1 small preterm neonate) died at the highest infusion rate of 0.5 mg/kg/h due to severe bleeding complications. Wang et al. reported thrombolysis with a low-dose regimen (0.01–0.06 mg/kg/h). Eight patients in this study were neonates at day 1–2 weeks of age with complete lysis of the thrombus and no bleeding complications. In the present case there was a high risk of bleeding that could be detrimental, so we elected to use low dose regimen of infusion 0.05 mg/kg/h for 6 h. 24 h later and after careful assessment we judged that another dose could be beneficial, which did achieve successful results as the venous and atrial thrombi resolved completely, and the chylothorax also resolved without any bleeding complications.

In conclusion chylothorax associated with venous thrombosis can occur particularly in neonates having CVL. Central venous catheter is known risk for thrombosis and it should be removed as soon as not needed. Low dose r-TPA can be used effectively with satisfactory results in cases of symptomatic thrombosis leading to complications. The benefits of r-TPA should be measured against its risk.

Conflict of Interest

I disclose that there was no conflict of interest and no funding for this study and it was approved by the hospital ethical committee.

References


