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Venous Thromboembolism in Critically Ill Children

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Abstract

Purpose of review—To review the current literature on venous thromboembolism in critically ill children

Recent findings—There is increasing concern for venous thromboembolism and its complications in critically ill children. Critically ill children are at increased risk of thromboembolism because of the treatment that they are receiving and their underlying condition. A complex relationship exists between thrombosis and infection. A thrombus is a nidus for infection while infection increases the risk of thrombosis. Pediatric-specific guidelines for the prevention and treatment of thromboembolism are lacking. Current guidelines are based on data from adults. Novel anticoagulants are now available for use in adults. Studies are ongoing to determine their safety in children. Risk assessment tools have recently been developed to determine the risk of thromboembolism in critically ill children. Certain molecules are associated with thromboembolism in adults.

Summary—Pediatric critical care practitioners should be cognizant of the importance of venous thromboembolism in critically ill children to allow for early identification and treatment. Adequately powered clinical trials are critically needed to generate evidence that will guide the treatment and prevention of thromboembolism in critically ill children. Risk assessment tools that incorporate biomarkers may improve our ability to predict the occurrence of thromboembolism in critically ill children.

Keywords

Deep venous thrombosis; pulmonary embolism; anticoagulant; central venous catheter

Introduction

There is increasing awareness about the incidence and complications of venous thromboembolism (VTE) in critically ill children. Despite paucity of evidence, pediatric intensive care units are developing local guidelines in an attempt to reduce the risk of VTE

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in critically ill children.[1, 2] The purpose of this article is to review the current literature on VTE in children with a focus on VTE in those who are critically ill.

Epidemiology of Venous Thromboembolism in Children

VTE, which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), is a significant public health problem. Among American adults, at least 350,000 are affected each year.[3] For every 3–5 patients with DVT, one develops PE. Approximately 100,000–180,000 deaths in the United States each year are associated with VTE. VTE is an increasing concern among pediatric critical care practitioners. Raffini et al reported a 70% increase over an 8-year period in the incidence of clinically apparent VTE in hospitalized children.[4] Advances in the care of critically ill children are thought to contribute significantly to the increase in the incidence of VTE. Higgerson et al recently reported that 0.8% of critically ill children was diagnosed with clinically apparent VTE during their admission in the pediatric intensive care unit.[5]

VTE is usually diagnosed in critically ill children when they present with signs and symptoms of acute inflammation or venous congestion. Ultrasonography is most commonly used to diagnose DVT.[5] Its sensitivity in detecting DVT ranges from 37% to 88%.[6, 7] These clinically apparent or symptomatic thrombi are associated with prolonged stay in the intensive care unit and prolonged duration of mechanical ventilation.[8] Although there are some concerns about the significance of asymptomatic VTE that are diagnosed by radiologic imaging alone,[9] data suggests that asymptomatic VTE in children also clinically important. Nearly 50% of cases of PE in children result from unrecognized DVT.[10] Only 17% of cases of PE in children that contributed to death are apparent pre-mortem.[11] Asymptomatic DVT is also a nidus of infections, is a cause of paradoxical stroke and may lead to loss of venous access that may be needed for life-saving interventions.[12] In addition, physical examination has poor sensitivity in detecting DVT particularly in critically ill children who may have significant fluid overload.[13] Asymptomatic DVT can also lead to post-thrombotic syndrome. This syndrome, which can occur in nearly half of children with asymptomatic DVT, presents with signs and symptoms of venous hypertension in the affected limb (e.g., edema, pain, dilated superficial collateral veins, stasis dermatitis, and ulceration) months after the thrombotic event.[14, 15] Thus, critical care practitioners should be cognizant of asymptomatic VTE, as they have a high propensity for becoming sources of significant morbidity in critically ill children.

Clinically apparent VTE represents only a small fraction of the total cases of VTE. We recently showed that for every case of clinically apparent catheter-related DVT, there are approximately 8 asymptomatic cases.[16] Studies that include only symptomatic cases of VTE, therefore, underestimate the true frequency of the disease in children.[5] Measures to prevent VTE in critically ill children should consider both clinically apparent and asymptomatic cases.

Risk Factors for Venous Thromboembolism in Critically Ill Children

VTE is significantly less common in children than in adults.[12] In fact, the incidence of VTE does not significantly increase until about the 4th decade of life.[17] It is likely that

developmental changes in the hemostatic system protect children against VTE. Attard et al demonstrated that the coagulation system does not reach adult levels until about 1–5 years of age.[18] Co-morbidities that increase with age, such as cardiovascular diseases and malignancies, may also contribute to the higher incidence of VTE in adults.[4] Unprovoked VTE is less common in children. In 80–90% of cases of VTE in children, an inciting agent can be identified compared with only 50% of cases in adults.[12] Critically ill children with VTE have a median of 2 risk factors that contributed to the disease.[12, 19]

The presence of central venous catheter (CVC) is the single most important risk factor for deep venous thrombosis in children with at least 85% of the cases of thrombosis related to a central venous catheter.[12, 16] We recently demonstrated that nearly half of all children in the intensive care unit have at least one CVC.[19] Clinical trials on the reduction of the risk of DVT in children are, therefore, not surprisingly focused on CVC-related DVT. In a recent review of infants younger than 1 year who with CVC, Gray et al reported that DVT were more commonly associated with CVC in the femoral veins than in the jugular or subclavian veins.[20] Percutaneous and multi-lumen CVC were also associated with higher rates of DVT. Although the risk of DVT with peripherally inserted central catheters is low,[21–23] it is not significantly different from that of tunneled CVC.[24] It is unclear if the risk of DVT with peripherally inserted CVC is different than that of untunneled centrally inserted CVC. Aside from the presence of CVC, other common risk factors for VTE in critically ill children include congenital heart disease,[25] vasopressor administration,[19] mechanical ventilation,[19] immobilization,[19] recent surgery,[19] older age[26] and multiple medical conditions.[26] Potent congenital thrombophilia, such as antiphospholipid antibody syndrome, homozygous anticoagulant deficiency, homozygous factor V Leiden or prothrombin G2010A mutation, may also increase the risk of VTE.[27] Obesity has not been reported to be associated with VTE in critically ill children.

The relationship between infections and DVT is complex. DVT is a nidus for infection. Rowan et al reported nearly 3-fold odds of developing catheter-associated blood stream infection in critically ill children treated with alteplase for malfunctioning CVC.[28] Catheter-associated blood stream infection was the most common presenting symptom of CVC-related DVT in our recent study.[16] However, infection is also a risk factor for DVT. Children with musculoskeletal infection, particularly osteomyelitis, are at increased risk of DVT.[29] Staphylococcus aureus is the predominant pathogen in infection-related DVT.[30]

Treatment of Venous Thromboembolism

In the acute setting, the goals of therapy for VTE include re-establishing flow through the occluded vessel, preventing thrombus extension, and preventing embolism. For chronic VTE, the goals of therapy are to prevent recurrence and prevent embolization of residual thrombus.

Heparin continues to be the most commonly used anticoagulant in children, particularly in the acute setting. In a study by Hanson et al, 78% of critically ill children were treated with systemic anticoagulation.[31] Nearly two-thirds of them were treated with low molecular weight heparin and the rest with intravenous unfractionated heparin. Pediatricians have the

most experience with the use of unfractionated heparin.[32, 33] However, unfractionated heparin has unpredictable pharmacokinetics and requires normal antithrombin III levels. Low molecular weight heparin has the advantage of having lower risks of bleeding and heparin-induced thrombocytopenia compared with unfractionated heparin.[12, 32] Similar to unfractionated heparin, low molecular weight heparin has considerable dose variability and is also affected by fluctuations in antithrombin levels. In their cohort of infants being treated with enoxaparin (a low molecular weight heparin) for thrombosis, Lulic-Botica et al noted that only 40% of the drug levels remained therapeutic during maintenance therapy.[34] Maintaining therapeutic levels seems less difficult in older patients.[35]

For long term therapy, vitamin K antagonists, i.e. warfarin, remains to be the drug of choice because of its oral route of administration.[12] However, its use is complicated by its susceptibility to changes in nutrition, co-medication and inter-current illness, lack of pediatric preparation, and need for frequent monitoring.

The suggested duration of anticoagulation is approximately 3 months.[12] This duration of treatment is derived from adult data. The duration of treatment may be extended depending on whether the VTE event is the first or a recurrence, and based on the presence of identifiable risk factors. Indefinite treatment is recommended for children with potent congenital thrombophilia. There is an ongoing study that aims to determine the duration of anticoagulation in children with VTE (NCT#00687882).

Recent studies suggest that thrombolysis, for example with tissue plasminogen activator, may be more effective than standard anticoagulation in resolving DVT and in preventing post-thrombotic syndrome. Goldenberg et al reported that 89% of children with DVT had complete resolution of the thrombus with thrombolysis compared with 42% with standard anticoagulation.[36] There is no prevailing consensus regarding thrombolysis for DVT in children.[37] Current indications for thrombolysis include limb-threatening circulatory compromise, rapid thrombus extension despite anticoagulation, symptomatic deterioration despite anticoagulation, and as first-line treatment to prevent post-thrombotic syndrome in patients at low risk of bleeding.[38] Thrombolysis should not be given systemically, not be given to most patients with symptoms of DVT for more than 21 days, and not be given to patients at high risk of bleeding.

Prevention of Venous Thromboembolism

In critically ill adults, pharmacologic thromboprophylaxis is highly recommended because of its proven efficacy and safety in preventing DVT and its complications.[39] It is unclear whether a similar practice should be implemented for critically ill children. It is not ideal to extrapolate adult recommendations to children because of the differences in the epidemiology and the coagulation system between adults and children. We recently reported a significant variability in thromboprophylaxis practice in critically ill children.[19] Depending on the intensive care unit that the patient was admitted, anywhere from 0% to 50% of children receive pharmacologic thromboprophylaxis. The variability in practice reflects the paucity of evidence to guide practice.

Most of the efforts in preventing VTE in children have focused around CVC-related DVT and VTE in the adolescent age group. The American College of Chest Physicians currently does not recommend the use of systemic anticoagulation to prevent catheter-related deep venous thrombosis.[12] This recommendation is based on small and underpowered trials. Heparin-bonded catheters may be beneficial in reducing the risk of catheter-related thrombosis. Pierce et al conducted a randomized clinical trial in critically ill children that demonstrated 0% risk of thrombosis with heparin-bonded catheter compared with 8% in non-heparin-bonded catheter.[40] The incidence of blood stream infection was also lower with heparin-bonded catheter. However, in infants with congenital heart disease, a subsequent randomized clinical trial by Anton et al did not demonstrate any reduction in the risk of thrombosis with heparin-bonded catheter.[41] The difference in result may be related to patient characteristics. The use of ultrasound during insertion of the CVC may decrease the risk of DVT.[42] Alten et al reported a trend towards less DVT with ultrasound-guided femoral vein catheterization.[43]

There are no recommendations on the use of thromboprophylaxis in critically ill adolescents. Raffini et al reported their experience using their thromboprophylaxis protocol in critically ill adolescents.[1] They developed a risk assessment tool that identified adolescents at high risk of VTE. These adolescents were then prescribed anticoagulation in the absence of any contraindication, such as bleeding. For other patients at low risk of VTE, early ambulation and/or mechanical thromboprophylaxis was recommended. Although the protocol was generally safe,[44] efficacy data has not yet been reported.

Areas for Future Research

Routine pharmacologic thromboprophylaxis is likely not ideal for all critically ill children. Critically ill children at highest risk of developing VTE should be identified and targeted for prophylaxis.[5, 19] A couple of risk assessment tools have been developed recently for critically ill children. Reiter et al, for example, used a nurse-driven 12-point scoring system to identify which patients were at high risk of VTE.[27] Patients are allotted points for the presence of CVC, immobility, infection, orthopedic surgery, major trauma, malignancy, oral contraceptive use, burns, age, obesity, and hypercoagulable state. A higher score was associated with a higher risk of VTE. Branchford et al also developed another risk assessment tool that was validated in critically ill children.[45] Their tool included mechanical ventilation, systemic infection and duration of hospitalization. The sensitivity and specificity of their tool in predicting VTE in critically ill children were 47% and 88%, respectively. In both risk assessment tools, only clinically apparent VTE were identified as outcomes. Validation of these tools is difficult because of the low frequency of clinically apparent VTE. Asymptomatic VTE should be included in future risk assessment tools.

The use of biomarkers may increase the predictive ability of risk assessment tools. Potential biomarkers include markers of coagulation and endothelial activation.[46] A recent study in adult patients showed that circulating DNA, a marker for fibrin scaffolds called neutrophil extracellular traps, which is upregulated during inflammation, was significantly elevated in patients with DVT, compared with patients with no DVT.[47] Soluble P selectin, a cell adhesion receptor, is also associated with the VTE in adults.[48] These molecules may

represent novel biomarkers that can be used in identifying critically ill children at risk for VTE.

There is an urgent need to conduct adequately powered randomized clinical trials that will test the safety and efficacy of anticoagulants in children, in general, and in critically ill children, in particular. Extrapolation of adult data to children is not ideal because of the differences in the hemostatic system between these 2 age groups. A number of novel anticoagulants have recently been approved for use in adults.[49] These include direct thrombin inhibitors, such as bivalirudin and dabigatran. The main indication for these medications is the treatment of VTE in patients with heparin-induced thrombocytopenia.[32] Because dabigatran is administered orally, it may be an alternative to warfarin for prolonged anticoagulation in children. There is currently a phase III trial for dabigatran in children (NCT#1895777). Fondaparinux is a long-acting synthetic antithrombin-dependent inhibitor of factor Xa.[32] The long half-life of fondaparinux allows for once daily subcutaneous administration of the drug compared with the twice daily dosing for low molecular weight heparin. Young and colleagues conducted a phase II study of fondaparinux in children.[50] Although the study did not evaluate efficacy, it demonstrated an excellent safety profile. Direct factor Xa inhibitors, such as apixaban and raviroxaban, may also be useful for long term management of thrombosis in children. These anticoagulants are administered orally, do not require monitoring of therapeutic levels, and are not adversely affected by diet.[49] Safety studies on the use of these anticoagulants in children are ongoing (NCT#01195727 and #01707394).

Conclusions

VTE is an important problem in the care of critically ill children. Current treatment strategies are patterned after adult data, which is not optimal because of differences in the coagulation system between adults and children. Adequately powered randomized clinical trials are needed to generate pediatric-specific guidelines for the prevention and management of VTE in children. Strategies should also be developed to identify critically ill children at increased risk of VTE and prevent its occurrence and complications.

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Key points

- Asymptomatic VTE, which are significantly more common than clinically apparent VTE, is associated with significant morbidity.
- Pediatric-specific data is needed to guide the treatment and prevention of VTE in critically ill children.
- The use of biomarkers may increase the ability of risk assessment tools to predict the occurrence of VTE.