Original Article

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Evaluation of Guidelines and Risk Factors for Venous Thrombosis and Pulmonary Embolism in Hospitalized Children: A Cross-Sectional Study

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Abstract

Background: Thromboembolism (TE) in pediatric population is rare but may be a fatal situation. There is a lack of clinical guidelines to help decision making for the use of prophylactic measures in pediatrics. This study was designed to evaluate current guidelines and risk factors for the prevention of venous thrombosis and pulmonary embolism (DVT/PE) in children.

Materials and Methods: This cross-sectional, prospective, and observational study was done between October 2014 and April 2017 in Mofid Children Hospital, Tehran, Iran. All children between 40 days to 8 years old admitted to the pediatric critical care unit (PICU) were evaluated for DVT/PE risk factors such as Glasgow coma score (GCS)< 9,complete bed rest, and central venous access catheter (CV line).

Results: For 3 years, 1080 children aged from 40 days to 8 years who hospitalized in PICU were studied. The mean duration of ICU stay was 6 ± 1.1 days. Three hundred and forty (31.5 %) patients had at least 4 risk factors for DVT/PE. Thirty nine (11%) patients with 4 or more risk factors had diagnosed DVT/PE. Among 39 patients with thromboembolic events, 11 (1%) children died. Congenital heart disease was the independent risk factor for DVT and PE. DVT was the most common type of thrombosis (69%).

Conclusion: This study suggested that TE is multi-factorial in children and anticoagulation therapy can be considered in hospitalized children with at least 4 risk factors. It seems that it is necessary to develop new strategies for thromboprophylaxis in PICU.

Keywords: Critical care, Pediatrics, Pulmonary embolism, Venous thrombosis

Introduction

Thromboembolism (TE) can be a dangerous situation in children. It has significant morbidity both in adult and children (1). Approximately 95% of children with deep vein thrombosis (DVT) or pulmonary emboli (PE) have one or more risk factors (2). Congenital heart disease, Glasgow coma score (GCS)< 9,complete bed rest, central venous access catheter (CV line), factor V Leiden, protein C and S deficiency, arterial catheter, paresis, and fractures are important risk factors for TE (3-5). A 70% rise has been seen in rate of pediatric TE from 34 to 58 cases per 10,000 hospital admissions (6). Recurrent thrombosis, bleeding, and death are important complications of TE in children (5, 6).

Developmental hemostasis describes the physiologic changes from neonatal age to pediatric and adult age. It is evidenced that levels of several hemostatic proteins are almost always lower in neonates than adults; however; their levels increase during growing (7, 8). This developmental hemostasis is a determining factor for appropriate treatment of TE. Till now, several guidelines have recommendations for the use of anticoagulants in children

(9). Majority of them have been extensively extrapolated from adult literature. Children differ from adults in blood physiology, pharmacologic responses to drugs, and long-term consequences of thrombosis. Therefore, extrapolation of adult strategies in children is a subject of debate (10). The American College of Chest Physicians recommends anticoagulant therapy for at least 3 months in children hospitalized for venous thromboembolism, but does not recommend such therapies for the prevention of TE in hospitalized children (9).Current practice guidelines recommend that patients with trauma admitted to pediatric intensive care unit (PICU) who is younger than 13 years may receive prophylactic drugs for DVT or PE if 4 or more risk factors are present (6, 11). However, this recommendation is not generalizable to all PICU patients .As mentioned, knowledge about pediatric anticoagulant therapy is limited and well-designed prospective studies are scarce. The value of risk factors for DVT/PE is well understood in the adult population and can help physician make decision about using prophylactic measures both mechanically and pharmacologically. On the other hand, studies about the value of the pediatric risk factors are limited. It seems that current practice guideline can be modified based on high quality trials and observational studies. The present study was designed to undertake an evaluation about current guidelines and risk factors for prevention of pediatric DVT/PE.

Materials and Methods

Hospital, Tehran, Iran, between October 2014 and April 2017. All children between 40 days to 8 years old admitted to the pediatric critical care unit were studied. Patients with diagnosed DVT/PE were evaluated for risk factors of DVT/PE. The risk factors were derived from current literature (9), including Glasgow coma score (GCS)< 9,complete bed rest, central venous access catheter (CV line), arterial catheter, paresis, fracture, use of inotropes, surgery, chronic inflammatory state, malignancy, history of thrombosis, congenital heart disease, and cardiopulmonary resuscitation (CPR). Characteristic data, including sex, age, and length of stay (LOS) were recorded. All patients were examined daily for signs of DVT. Occurrence of DVT was confirmed by Doppler sonography. The mortality related to thrombosis also recorded for the study population.

Statistical Analyses

Data are presented as Mean ± SD. Risk factors for DVT/PE were identified by bivariate analysis, if P was≤0.12. All statistical analyses were conducted by SPSS (version 16).

Results

One thousand and eighty children aged from 40 days to 8 years who hospitalized in PICU were studied. Table I shows clinical characteristics of the patients. The mean duration of ICU stay was 6 ± 1.1 days. Three hundred and forty (31.5 %) patients had at least 4 risk factors for DVT. It was observed that 39 (11%) patients with 4 or more risk factors had diagnosed DVT/PE. Five cases of DVT were seen in children with no risk factors. Congenital heart disease was the independent risk factor for DVT and PE. After diagnosis, they were given anticoagulant treatments according to the routine treatment in children. Comorbid conditions are shown in Table II. No case of factor V Leiden was noted and patients had normal levels of protein C and protein S (50 IU/dL). Among 39 patients with thromboembolic events, 11 (1%) children died. DVT was the most common type of thrombosis (69%). Rate of PE was 31%. No case of superficial thrombosis was seen. About 90 % of children received enoxaparin for treating DVT/PE. The rest was treated by unfractionated heparin.

Table I: Characteristics of patients (Data are shown in mean ± SD or percent)

Characteristic	Value
Age (years)	5.3 ± 1.5
Male (%)	63
SBP (mmHg	112 ±7.2
DBP (mmHg)	60 ± 6.8
Respiratory rate (breaths/min)	24 ± 3.5
Heart rate (beats/min)	111 ± 2.3
Protein C (IU/dL)	47 ± 7.1
Protein S (IU/dL)	51 ± 9.4

Table II: Comorbid conditions of patients

Risk factor	Frequency
GCS < 9	15 (38.4)
Complete bed rest	39 (100)
CV line	30 (77)
Arterial catheter	3 (7.7)
Paresis	10 (25.6)
Fracture	2 (5.1)
Use of inotropes	5 (12.8)
Surgery	13 (33.3)
Chronic inflammatory state	8 (20.5)
Malignancy	5 (12.8)
History of thrombosis	1 (2.5)
Heart diseases	13 (33.3)
CPR	7 (7.9)

Discussion

The results of this observational study showed that a considerable amount of patients with known risk factors for thromboembolic events may develop thrombosis and other related complications such as death possibly due to concurrent diseases or embolism. These findings suggested that anticoagulation therapy can be considered in children with at least 4 risk factors. It should be noted that no children had deficiency in protein C and protein S and no case with factor V Leiden was seen. In contrast to adults, there is no recommendation for prevention of TEs in hospitalized children (9). Current study showed that rate of risk factors for TEs are high in hospitalized children in PICU. Findings of this study were in accordance with previous studies on hospitalized children (3). TEs can be considerably prevented in children with 4 or more risk factors (4). The previous investigation either used the adult inclusion criteria like

Wells criteria in children or focused to assess risk factors in a specific pediatric population like trauma or surgery, and general pediatric hospital population (3, 7, 12). Although these risk factors were identified previously, the relationship between the risk factors and incidence of TE needs to be more emphasized. The rate of TEs among hospitalized children younger than 18 years of age in the United States has increased from 34 to 58 hospital admissions per 10,000 patients from 2001 to 2007 (5). More importantly, the first episodes of TE can increase risk of the second TEs episode by 30% (11). At present, despite absences of FDA approval, unfractionated heparin, low-molecular-weight heparins (LMWH), and warfarin are most commonly used anticoagulants in children (9,13). Due to lack of randomized controlled trials new oral anticoagulants (NOAC) like rivaroxaban and apixaban are not used in children (14,15). Low rate of TEs and high risk of bleeding are the most important barriers against the development of prevention guidelines in children (4,16).When such guidelines develop, it can carry a significant improvement in patients care. A study by Hanson et al., showed that implementing guidelines for thromboprophylaxis statistically decrease the rate of TE without increasing the use of anticoagulants and without any bleeding complications (17). This was achieved by recognizing and implementing important risk factors that reduced both anticoagulants use in low-risk patients and improved identification of high-risk patients for diagnostic and prophylactic interventions. It should be noted that incidence, risk factors, and comorbidities of TE are not the same in pediatric populations (18, 19). Ishola's study proved that adolescent TE is often multi-factorial and new strategies should be developed for thromboprophylaxis (7). Sandoval's study showed that TE is more common in children younger than 5 particularly in critically ill children (3). As the anticoagulant treatment used for TEs in children is largely adopted from adult clinical trials, well-designed prospective trials are required to establish the optimal therapy for children with TEs. Treatment of thromboembolic complications in pediatrics has been the subject of considerable research (20). Prospective studies from Canada and Argentina propose guidelines for administering and monitoring warfarin and acenocoumarol in pediatrics (21). These studies highlighted the difficulty of their applications in pediatric patients. Infants younger than 12 months of age require increased doses to achieve and maintain the therapeutic target INR. Furthermore, the compliance of inpatient and outpatient pediatric population always is a challenge for clinicians. A Study by Rakesh et al., showed that 30% of pediatric patients do not have compliance during the use of anticoagulant medications (22). The low adherence of children to anticoagulants should be addressed by identifying the risk factors for screening at risk population by strong clinical evidence. Allen et al., proposed a scoring system for predicting thromboembolic events after trauma in pediatrics (23). It was shown that major vascular injury and orthopedic surgery were strong predictors for pediatric TE in about 2000 pediatric admissions.

Conclusion

It was shown that complete bed rest and CV line were the most frequent comorbid conditions for TE. In addition, congenital heart disease was the independent risk factor for DVT/PE. This study suggested that anticoagulation therapy can be considered in children with at least 4 risk factors for the prevention of DVT/PE. New strategies should be developed for prophylactic use of anticoagulation in children hospitalized in PICU.

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Conflict of interest

The authors report no conflict of interest.

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