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Clinical equipoise on prophylaxis against catheter-associated thrombosis in critically ill children

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ABSTRACT

Purpose: In preparation for a randomized controlled trial of prophylaxis against catheter-associated deep venous thrombosis in critically ill children, we aimed to determine clinical equipoise, defined as willingness to randomize children, among pediatric critical care physicians.
Materials and methods: We conducted a cross-sectional, self-administered electronic survey of pediatric critical care physicians in the United States. The survey focused on the effect of child's age, presence of a central venous catheter, and risk (ie, presence of coagulopathy or recent surgery) and presence of bleeding on their willingness to randomize children to an anticoagulant or placebo.
Results: Responses from 239 (33.0%) of 725 physicians were analyzed. Respondents were willing to randomize children 1 month or older in the presence of a catheter but only those older than 13 years in the absence of a catheter. For children with coagulopathy, they would randomize those with international normalized ratio less than or equal to 2.0, partial thromboplastin time less than or equal to 50 seconds, and platelet count greater than or equal to 50000/mm^3. Respondents were willing to randomize children 2 days after most types of surgery and after 1 to 5 days of a bleeding event.
Conclusions: Clinical equipoise on prophylaxis against catheter-associated thrombosis exists among pediatric critical care physicians, which ethically justifies conducting a randomized controlled trial.

1. Introduction

Deep venous thrombosis (DVT) is a major source of morbidity and mortality in critically ill children [1]. In this population, the presence of a central venous catheter (CVC) is the most important risk factor for DVT [2]. Central venous catheter–associated DVT (CADVT), which occurs in nearly 1 of 5 critically ill children with CVC, is associated with prolonged stay in the pediatric intensive care unit (PICU); prolonged mechanical ventilation; and increased risks of pulmonary embolism, paradoxical stroke, catheter-associated bloodstream infection, and death [1,3,4]. Despite these complications, prophylaxis against DVT is not recommended in children, which is in contrast to critically ill adults in whom prophylaxis is strongly recommended [1,5]. Recommendations for adults should not be routinely applied to children because the hemostatic system that affects the risks of DVT and bleeding dynamically evolves with age [1].

Randomized controlled trials (RCTs) are urgently needed to determine the effectiveness and safety of prophylaxis against CADVT in critically ill children. Prior pediatric RCTs are mostly underpowered and unable to determine the effectiveness of prophylaxis [3]. For example, the largest pediatric RCT of prophylaxis against CADVT was stopped early due to poor enrollment [6]. Only 31% of the estimated sample size was enrolled, and only 36% of the parents of eligible children consented. An important strategy to improve enrollment for similar RCTs is to have members of the clinical care team, particularly the pediatric critical care physicians, be supportive of the RCT [7]. Lack of clinical equipoise or uncertainty regarding the benefit of prophylaxis can be a barrier toward successful enrollment [8]. In preparation for a RCT of prophylaxis against CADVT in critically ill children, we aimed to determine clinical equipoise, which we operationally defined as willingness to randomize children in a RCT, among pediatric critical care physicians.

2. Materials and methods

2.1. Study design

We conducted a cross-sectional, self-administered electronic survey of pediatric critical care physicians in the United States. The study was reviewed and approved by the Human Investigations Committee at

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Yale School of Medicine. The survey was voluntary and anonymous, and participation implied consent.

2.2. Respondents

Target respondents of the survey were board-certified or board-eligible pediatric critical care physicians who were working in the United States in 2015. This group of practitioners will most likely make the decision to approach parents to consent for participation in a RCT. To generate the mailing list, hospitals with PICUs were identified from the directories of the American Hospital Association, Children's Hospital Association, American Medical Association, and Virtual PICU. Electronic addresses of all pediatric critical care physicians working in these PICUs were then obtained from the hospitals' Web sites. Additional electronic addresses were obtained from the membership directory of the Society of Critical Care Medicine. Respondents who identified themselves as neither board certified nor board eligible in pediatric critical care during the survey were excluded. Respondents were requested to answer each survey item based on their personal opinions.

2.3. Survey development and administration

Items in the survey instrument were patterned after the eligibility criteria used in prior RCTs of prophylaxis against DVT in children and in adults and based on discussions between investigators (Supplemental Material) [6,9]. We focused on the effect of the child's age, presence of a CVC, and risk (ie, presence of coagulopathy or recent surgery) and presence of bleeding on the respondent's willingness to randomize children to prophylaxis vs placebo in an RCT. Based on the most commonly used anticoagulants in critically ill children, we defined prophylaxis as low-molecular-weight heparin, unfractionated heparin, or warfarin at doses the respondent would consider prophylactic [10,11]. Age was categorized according to the risks of DVT in children younger than 1 month, 1 month to younger than 1 year, and 1 year to younger than 18 years [1]. An additional category of less than 36 weeks age of gestation was added for children with a CVC based on the criteria used in a prior RCT of CADVT in children [6]. The category of 1 year to younger than 18 years was further divided into 1 year to 13 years and older than 13 years to younger than 18 years in children without a CVC based on the results of our prior survey [12]. Categories of bleeding events were modified from published definitions recommended for safety monitoring in RCTs of prophylaxis against DVT in children [13]. A clinically relevant bleeding event included one that is intracranial, intraspinal, retroperitoneal, or pulmonary; requires surgery; is overt from the gastrointestinal tract; requires a blood transfusion; or is associated with a drop in hemoglobin of at least 2 g/dL in 24 hours. Nonclinically relevant bleeding included epistaxis, one in which no transfusion or surgery is needed, microscopic hematuria, menstruation, or hemoccult from the gastrointestinal tract. Unless otherwise specified, all items pertained to children with a CVC, and the prophylaxis was against CADVT.

Likert scales (1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; and 5, strongly agree) were used to determine agreement with specific statements regarding randomization and prophylaxis against DVT. Sliding scales were used to identify threshold values. For timing of randomization, the sliding scales were divided in 1-day increments (range, 0-14 days), whereas those for coagulation parameters were in 0.5 increments for international normalized ratio (INR) (range, 0.5-5.0), 10-second increments for partial thromboplastin time (PTT) (range, 10-120 seconds), and 10 000/mm^3 increments for platelet count (range, 10 000-150 000/mm^3). Typical normal values were provided for the coagulation parameters. Scales for holding and restarting prophylaxis were in 12-hour increments (range, 0-120 hours). For most scenarios, respondents were given the option to indicate if they were not willing to randomize the child. We also collected the respondents' demographics and the characteristics of their PICU. The survey instrument was pilot tested and revised before distribution.

The survey, which was conducted from March to August 2015, was administered electronically using Qualtrics (Qualtrics Company, Provo, UT). Each potential respondent was sent an introduction electronically, which included a link to the survey instrument. The link was tied to the electronic address and could not be forwarded to others. Reminders were sent every 1 to 2 weeks for those who had not yet completed the survey.

2.4. Statistical analysis

Descriptive data were presented as medians (interquartile ranges [IQRs]) to account for the ordinal variables or the nonnormal distribution of the continuous variables or counts (percentages) for categorical variables. To test the association between the respondent's willingness to randomize and the child's age, we used ordered logistic regression with the Likert score as dependent variable and age category as independent variable controlling for intrarespondent correlation. The magnitude of association was expressed as odds ratio (OR) (95% confidence interval [CI]). Depending on the number of groups being compared, Wilcoxon signed rank or Friedman test with post hoc pairwise comparisons was used to compare threshold values. These tests accounted for intrarespondent correlation. Responses from physicians who were not willing to randomize children were excluded in these analyses.

Statistical significance was evaluated at a 2-sided *P* value of .05, except for post hoc tests in which the *P* value was adjusted for multiple comparisons using Bonferroni correction. All tests were performed using Stata 14.0 (StataCorp, College Station, TX).

3. Results

3.1. Characteristics of the respondents

We initially sent the introduction to the survey using the electronic addresses of 797 pediatric critical care physicians. Of these, 64 introductory messages could not be delivered. A maximum of 12 reminders were sent to nonresponders. A total of 247 physicians, including 8 who were not board certified or board eligible, participated in the survey with 185 of them responding to all items. The responses from 239 physicians were analyzed.

Respondents were mostly male (56.7%), were 40 to younger than 50 years (36.8%), and had been practicing pediatric critical care less than 10 years after fellowship (45.4%) (Table 1). Respondents tended to spend greater than 50% to 75% of their professional time in clinical practice (32.4%), in a mixed medical-surgical and cardiac PICU (47.6%), in a PICU with 11 to 20 beds (42.7%), and in an academic hospital setting (94.1%).

3.2. Child's age and willingness to randomize

In the presence of a CVC, respondents were willing to randomize children at least 1 month old, unsure for children younger than 1 month, and not willing for children less than 36 weeks age of gestation (Fig. 1). The median scores for children 1 year to younger than 18 years, 1 month to younger than 1 year, younger than 1 month, and less than 36 weeks age of gestation were 4 (IQR, 4-5), 4 (IQR, 4-5), 3 (IQR, 2-4), and 2 (IQR, 1-2), respectively. Willingness to randomize increased with the child's age. Compared with children younger than 1 month, the OR of having a 1-point increase in the Likert score for children 1 year to younger than 18 years, 1 month to younger than 1 year, and less than 36 weeks age of gestation were 11.11 (95% CI, 7.75-15.91), 4.08 (95% CI, 3.13- 5.32), and 0.18 (95% CI, 0.13-0.24), respectively.

In the absence of a CVC, respondents were not willing to randomize children at younger ages (Fig. 1). The median scores for children older