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Venous Thromboembolism Prophylaxis in High-Risk Pediatric Trauma Patients

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IMPORTANCE The indications, safety, and efficacy of chemical venous thromboembolism prophylaxis (cVTE) in pediatric trauma patients remain unclear. A set of high-risk criteria to guide cVTE use was recently recommended; however, these criteria have not been evaluated prospectively.

OBJECTIVE To examine high-risk criteria and cVTE use in a prospective multi-institutional study of pediatric trauma patients.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was completed between October 2019 and October 2022 in 8 free-standing pediatric hospitals designated as American College of Surgeons level I pediatric trauma centers. Participants were pediatric trauma patients younger than 18 years who met defined high-risk criteria on admission. It was hypothesized that cVTE would be safe and reduce the incidence of VTE.

EXPOSURES Receipt and timing of chemical VTE prophylaxis.

MAIN OUTCOMES AND MEASURES The primary outcome was overall VTE rate stratified by receipt and timing of cVTE. The secondary outcome was safety of cVTE as measured by bleeding or other complications from anticoagulation.

RESULTS Among 460 high-risk pediatric trauma patients, the median (IQR) age was 14.5 years (10.4-16.2 years); 313 patients (68%) were male and 147 female (32%). The median (IQR) Injury Severity Score (ISS) was 23 (16-30), and median (IQR) number of high-risk factors was 3 (2-4). A total of 251 (54.5%) patients received cVTE; 62 (13.5%) received cVTE within 24 hours of admission. Patients who received cVTE after 24 hours had more high-risk factors and higher ISS. The most common reason for delayed cVTE was central nervous system bleed (120 patients; 30.2%). There were 28 VTE events among 25 patients (5.4%). VTE occurred in 1 of 62 patients (1.6%) receiving cVTE within 24 hours, 13 of 189 patients (6.9%) receiving cVTE after 24 hours, and 11 of 209 (5.3%) who had no cVTE (P = .31). Increasing time between admission and cVTE initiation was significantly associated with VTE (odds ratio, 1.01; 95% CI, 1.00-1.01; P = .01). No bleeding complications were observed while patients received cVTE.

CONCLUSIONS AND RELEVANCE In this prospective study, use of cVTE based on a set of high-risk criteria was safe and did not lead to bleeding complications. Delay to initiation of cVTE was significantly associated with development of VTE. Quality improvement in pediatric VTE prevention may center on timing of prophylaxis and barriers to implementation.

Invited Commentary

Supplemental content

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Venous thromboembolism (VTE), including deep vein thrombosis (DVT), pulmonary embolism, and embolic stroke, is a rare but significant complication among pediatric trauma patients. The consequences of VTE include increased length of hospitalization, increased cost of health care, and complications such as recurrence, postthrombotic syndrome, and even death.[1-3] The use of chemical prophylaxis to lower the risk of developing VTE is well defined in adult trauma care, but best practices are ill defined for injured children.[4] Additionally, the risk of bleeding complications from chemical VTE prophylaxis (cVTE) in children is unknown. The overall rate of VTE occurrence in pediatric trauma patients is low, ranging from 0.3% to 1.2%.[5,6] However, several retrospective studies have demonstrated a subset of patients at much higher risk, approaching 10%.[1,5] High-risk factors for VTE after pediatric trauma include increased severity of injury, prolonged intensive care unit (ICU) stay, and presence of central venous lines (CVL), among others.[5,7,8]

Previous guidelines and prediction tools have attempted to answer the question of which pediatric trauma patients would benefit most from cVTE. In 2017, the Pediatric Trauma Society and Eastern Association for the Surgery of Trauma (PTS/EAST) published guidelines on VTE prophylaxis in pediatric trauma patients based on available evidence; however, the authors acknowledged the limited and low-quality data available to provide these recommendations.[6] Landisch et al[9] and Hansen et al[10] also previously developed a screening and treatment algorithm for children at high risk of VTE, demonstrating reduced incidence of VTE when implemented prospectively at a single center. However, neither of these guidelines have been prospectively validated in a multi-institutional setting, nor have the safety and effectiveness of an evidence-based approach to VTE prevention been rigorously evaluated in pediatric trauma.

Altogether, a critical research gap exists in identifying which pediatric trauma patients need cVTE. The aims of this study were to (1) develop and institute screening criteria to identify VTE events in high-risk pediatric trauma patients, (2) validate these criteria in a multi-institutional, prospective, observational pediatric trial, and (3) demonstrate the safety of chemical prophylaxis in pediatric trauma patients at high risk of VTE. We hypothesized that use of cVTE was safe and would reduce the incidence of VTE in a high-risk pediatric trauma population.

Methods

Eight centers within the Midwest Pediatric Surgery Consortium were included in this prospective observational cohort study.[11] All participating centers are free-standing pediatric hospitals designated as American College of Surgeons level I pediatric trauma centers. Each institution underwent local institutional review board approval with a waiver of consent and included patients from October 2019 through October 2022. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was used to ensure proper reporting of the methods, results, and discussion.[12]

Key Points

Question Does the application of high-risk guidelines allow for safe and appropriate administration of venous thromboembolism (VTE) prophylaxis following pediatric trauma?

Findings In this cohort study applying high-risk criteria to guide VTE prophylaxis, more than half of patients received prophylaxis without any documented bleeding complications. Increased time to prophylaxis initiation was significantly associated with increased likelihood of developing VTE.

Meaning Use of VTE prophylaxis in high-risk pediatric trauma patients is safe, and further studies may focus on timing of prophylaxis and barriers to implementation of guidelines.

All pediatric trauma patients were screened to determine their risk for developing VTE within 24 hours of admission. Any patient unlikely to ambulate within 48 hours postinjury with 1 high-risk factor (if age >8 years) or 2 high-risk factors (age ≤8 years) was determined to be at high risk for VTE and included in the study (**Box**). Patients not meeting high-risk criteria and those older than 18 years were excluded. High-risk patients were prospectively tracked throughout their hospitalization, up to 30 days. The guardians of patients discharged before 30 days from injury received a follow-up telephone call or letter to determine if there were any delayed findings of VTE within

Box. Criteria Used to Define Patients at High Risk for VTE, Exceptions to Giving Prophylaxis Within 24 Hours of Admission

High-Risk Criteria

Any patient unable to ambulate within 48 hours postinjury and (1) age older than 8 years with 1 of the following or (2) age 8 years and younger with 2 or more of the following:

- Central venous line
- Spinal cord injury
- Moderate to severe TBI
- Non–weight-bearing fracture
- Vascular injury
- ICU stay expected to be longer than 48 hours
- History of shock (need for transfusions, CPR, or inotropes)
- Major thoracoabdominal operation
- History of VTE
- History of chronic inflammatory diseases (inflammatory bowel disease, vasculitis, nephrotic syndrome)
- Current use of estrogen
- Family history of VTE (first-degree relative)
- Obesity (BMI ≥95th percentile for age)

Exceptions to Initial Prophylaxis Guidelines

- Central nervous system bleed (head or spine): do not start for at least 48 hours.
- Solid organ injury: do not start until the patient is stable for at least 24 hours.
- Planned operative intervention: hold for 12 hours before and after surgery.
- Surgeon concern for risk of bleeding with prophylaxis.
- Surgeon discretion.

Abbreviations: BMI, body mass index; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; TBI, traumatic brain injury; VTE, venous thromboembolism.

Table 1. Patient Demographics by Chemical Prophylaxis Status

Variable	No. (%)				*P* value
	All patients (n = 460)	Never received cVTE (n = 209)	Received cVTE >24 h (n = 189)	Received cVTE ≤24 h (n = 62)	
Sex					.93
Male	313 (68)	144 (69)	127 (67)	42 (68)	
Female	147 (32)	65 (31)	62 (33)	20 (32)	
Age, median (IQR), y	14.5 (10.4-16.2)	12.9 (7.1-15.5)	15.2 (13.7-16.6)	15.2 (11.0-15.9)	<.001
>8 y	385 (84)	150 (72)	180 (95)	55 (89)	<.001
≤8 y	75 (16)	59 (28)	9 (5)	7 (11)	
Admitted to ICU	391 (85)	184 (88)	157 (83)	50 (81)	.22
Length of stay, median (IQR), d					
ICU	4 (1-11)	4 (1-8)	6 (2-15)	4 (1-8)	.001
Total hospitalization	14 (7-28)	10 (5-19)	20 (10-40)	15 (8-30)	<.001
Injury Severity Score, median (IQR)	23 (16-30)	21 (14-29)	26 (17-34)	22 (14-30)	<.001
Initial GCS score, median (IQR)	12 (3-15)	11 (3-15)	14 (3-15)	15 (6-15)	.02
Intubation	302 (66)	140 (67)	122 (65)	40 (65)	.86
Ventilator time, median (IQR), d	5 (2-10)	3 (1-8)	8 (4-13)	3 (2-7)	<.001
Central line placement	224 (49)	94 (45)	103 (54)	27 (44)	.11
Blood transfusion	245 (53)	98 (47)	110 (58)	37 (60)	.04
≥1 Operation	352 (77)	138 (66)	163 (86)	51 (82)	<.001
Survival to discharge	430 (93)	188 (90)	182 (96)	60 (97)	.02

Abbreviations: cVTE, chemical venous thromboembolism prophylaxis; GCS, Glasgow Coma Scale; ICU, intensive care unit.

30 days in case follow-up care was pursued in another hospital system.

All patients in the study were recommended to receive cVTE twice daily with 0.5 mg/kg (up to maximum 30 mg) low-molecular-weight heparin; cVTE was recommended to be started within 24 hours postinjury except in cases of high bleeding risk (Box). The ultimate decision on use and type of cVTE was based on the clinical judgment of the treating physician. All patients were recommended to have sequential compression devices placed on admission unless lower extremity fractures or small size prevented placement. All patients were recommended to undergo weekly screening ultrasounds of the extremities by a certified pediatric ultrasonography technician, regardless of whether receiving cVTE or not, although considerable institutional variability was expected and allowed.

Data collected included demographic details, type and severity of injury, and significant events during hospitalization up to 30 days; adherence to cVTE use, bleeding complications related to cVTE, and any VTE events (deep vein thrombosis, pulmonary embolism, and embolic stroke) were also tracked. Diagnostic imaging confirming VTE events were interpreted by pediatric radiologists, and ultrasounds were obtained by certified pediatric ultrasonography technicians. Each participating institution conducted individual medical record reviews. Study data were collected and managed using REDCap electronic data capture tools.[13,14] Statistical analyses were conducted using R statistical software (R Foundation).[15] Descriptive statistics and bivariate analyses were reported, including overall VTE events and comparison of patients who received cVTE vs those who did not. Subgroup analyses were performed based on age, severity of injury, prophylaxis status, and development of VTE. Nonparametric data were reported as median (IQR). Statistical significance was defined at *P* value less than .05 and determined using Pearson χ^2 tests, Fisher exact tests, Wilcoxon rank sum tests, or Kruskal-Wallis rank sum tests, as appropriate.

Results

Across the 8 participating pediatric level I trauma centers, 460 patients met high-risk criteria during the 3 years and were included in the study. The median (IQR) age was 14.5 years (10.4-16.2 years); 313 patients (68%) were male and 147 female (32%) (**Table 1**). The median (IQR) number of high-risk factors was 3 (2-4). Patients in the study represented a severely injured patient population with a median (IQR) Injury Severity Score (ISS) of 23 (16-30) and a median (IQR) initial Glasgow Coma Scale score of 12 (3-15). A total of 391 of 460 patients (85%) were admitted to the ICU with a median (IQR) ICU length of stay of 4 days (1-11 days). Median hospitalization length was 14 days (7-28 days). Thirty of 460 patients (7%) died from their traumatic injuries, and the most common cause of death was secondary to sequelae of traumatic brain injury (27/30; 90%).

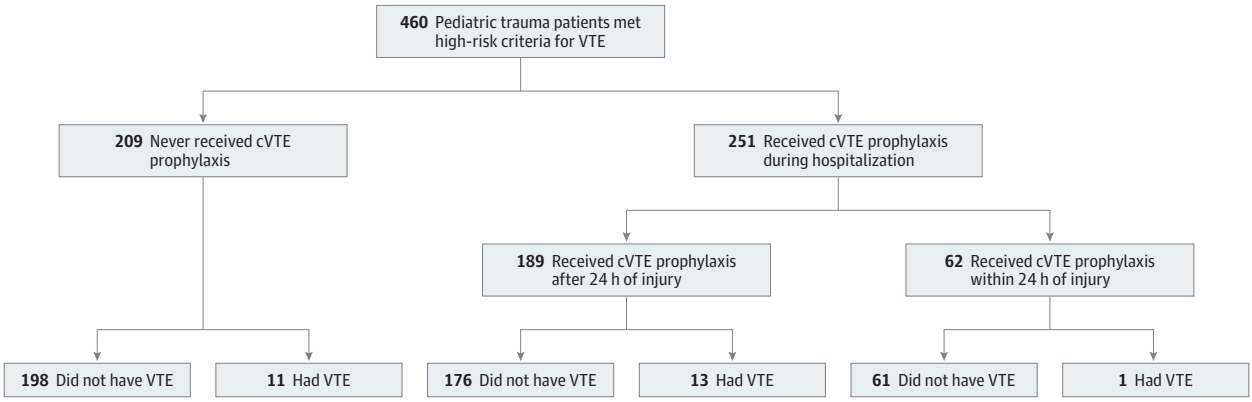
The most common high-risk factor for VTE was a predicted ICU stay of more than 48 hours (370/460 patients; 80.4%), followed by moderate to severe traumatic brain injury (224/460; 48.7%) (**Table 2**). Among 460 patients, 194 (42%)

Table 2. High-Risk Criteria on Admission in Patients With and Without VTE

High-risk factor	No. (%)			*P* value
	All patients (n = 460)	Patients without VTE (n = 435)	Patients with VTE (n = 25)	
Predicted ICU stay >48 h	370 (80.4)	347 (79.8)	23 (92.0)	.19
Moderate-severe traumatic brain injury	224 (48.7)	208 (47.8)	16 (64.0)	.12
Shock within 24 h	194 (42.2)	180 (41.4)	14 (56.0)	.15
Non-weight-bearing fracture	178 (38.7)	167 (38.4)	11 (44.0)	.58
Central venous line placement	176 (38.3)	162 (37.2)	14 (56.0)	.06
Spinal cord injury	73 (15.9)	68 (15.6)	5 (20.0)	.57
Obesity	68 (14.8)	61 (14.0)	7 (28.0)	.08
Vascular injury	66 (14.3)	61 (14.0)	5 (20.0)	.38
Major thoracoabdominal operation	60 (13.0)	56 (12.9)	4 (16.0)	.55
Current use of estrogen	6 (1.3)	6 (1.4)	0	>.99
Family history of VTE	5 (1.1)	4 (0.9)	1 (4.0)	.25
History of VTE	2 (0.4)	2 (0.5)	0	>.99
History of inflammatory disease	1 (0.2)	1 (0.2)	0	>.99
Total high-risk factors, median (IQR)				
All ages	3 (2-4)	3 (2-4)	4 (3-5)	.001
Age >8 y	3 (2-4)	3 (2-4)	4 (3-5)	.001
Age ≤8 y	4 (3-4)	4 (3-4)	4 (4-4)	.32

Abbreviations: ICU, intensive care unit; VTE, venous thromboembolism.

Figure. Timing of Chemical Venous Thromboembolism (cVTE) Prophylaxis and Development of VTE



experienced shock (defined as requiring blood transfusions or vasopressors) within 24 hours of their traumatic injury, and 176 (38.3%) had a CVL placed.

Among all patients, 251 (54.5%) received cVTE during their hospitalization, with 62 (13.5%) receiving cVTE within 24 hours of injury; 209 (45%) never received cVTE (**Figure**). Patients who received cVTE after 24 hours of injury had the highest median ISS, ventilator days, total ICU days and length of stay; the group that never received cVTE had the lowest median age, lowest initial Glasgow Coma Scale score, and highest rate of mortality (Table 1). The most common cause for holding cVTE in the first 24 hours was central nervous system bleed (120 patients; 30.2%), followed by physician discretion (102 patients; 25.6%) (**Table 3**). Among 251 children receiving cVTE, 231 (92%) received low-molecular-weight heparin, 17 (6.8%) received unfractionated heparin, and 3 (1.2%) received rivaroxaban. Three hundred twenty-two patients (70%) had sequential compression devices ordered on admission. There were no bleeding events or other complications attributed to the use of cVTE, such as heparin-induced thrombocytopenia.

Of the 460 patients included, there were 28 VTE events in 25 patients (5.4%). The majority of VTE events were DVT (26/28; 92.8%) with 14 of 26 DVT (53.8%) located in the lower extremity, 9 of 26 (34.6%) in the upper extremity, and 3 of 26 (11.5%) in the neck. There were 2 symptomatic pulmonary embolisms (overall rate, 0.4%) with concurrent DVT; 1 patient had never received cVTE before their diagnosis, and the other patient had delayed cVTE initiated on day 7 after trauma. Both patients with pulmonary embolism were treated with therapeutic anticoagulation and survived without any additional interventions. There were no thrombotic or embolic strokes. Five of the 25 VTE events (20%) occurred in patients aged 0 to 4 years, 1 (4%) in a patient aged 5 to 9 years, 5 (20%) in patients aged 10 to 14 years, and 14 (56%) in patients 15 years and older. One patient was diagnosed with DVT as an outpatient 6 days postinjury; the remainder of VTE events were di-

Table 3. Reasons for Withholding Prophylaxis Within 24 Hours After Injury

Reason	No. (%)		P value
	Never received cVTE (n = 189)	cVTE >24 h (n = 209)	
Central nervous system bleed	79 (38)	41 (22)	<.001
Physician discretion	55 (26)	47 (25)	.74
Planned operative intervention	30 (14)	40 (21)	.08
Solid organ injury	24 (11)	22 (12)	.96
Surgeon concern for bleeding risk	12 (5.7)	26 (14)	.007
Other	9 (4.3)	9 (4.8)	.83

Abbreviation: cVTE, chemical venous thromboembolism prophylaxis.

agnosed while inpatient at a median (IQR) of 6 days (3-8 days) postinjury. Thirteen patients (52%) with VTE presented with symptomatic DVT, and the most common presenting symptoms were swelling (6/13; 46.2%) and fever (5/13; 38.5%). Twelve of 25 patients (48%) with VTE were asymptomatic; in these cases, the VTE was either captured on screening ultrasound (10/12; 83.3%) or found incidentally while performing other imaging (2/12; 16.7%). Fifteen of 25 patients (60%) had a previous or current CVL at the same location of the DVT. Injury Severity Score, total number of high-risk criteria, and total length of ICU and hospital stay were all significantly higher in patients with VTE than those without (eTable in Supplement 1).

In the children who received cVTE (n = 251), the likelihood of VTE was significantly associated with increasing time between admission and cVTE initiation (odds ratio, 1.01; 95% CI, 1.00-1.01; *P* = .01). For children who had received cVTE prior to diagnosis of VTE, the median (IQR) time from admission to initiation of cVTE was 4.2 days (2.5-7.5 days) compared with 2.5 days (1.0-4.0 days) for those who received cVTE without diagnosis of VTE (*P* = .008). There was no statistically significant difference in VTE risk based on receipt of cVTE (*P* = .31) with VTE occurring in 1 of 62 patients (1.6%) receiving cVTE within 24 hours, 13 of 189 patients (6.9%) receiving cVTE after 24 hours, and 11 of 209 (5.3%) who never received VTE (Figure). After diagnosis of VTE, 23 of 25 patients (92%) were treated with therapeutic anticoagulation. Six bleeding events were attributed to the use of therapeutic anticoagulation; 2 of the bleeding events occurred in patients treated for VTE, and the other 4 patients were receiving therapeutic dose anticoagulation in the setting of vascular injury without a diagnosis of VTE. All bleeding complications were intramuscular or subcutaneous hematomas; 1 intramuscular hematoma required operative intervention, 1 subcutaneous hematoma resulted in a return to the emergency department, and the remainder resolved with additional observation. No deaths were attributed to complications of a VTE or therapeutic anticoagulation. Multivariable analysis was limited because of the overall low rate of VTE.

Discussion

In the presence of high-risk factors, VTE remains a potentially preventable morbidity after trauma for pediatric patients of all ages. In this prospective multi-institutional study involving high-risk pediatric trauma patients, we identified an overall VTE rate of 5.4%. Additionally, the true VTE rate in this high-risk patient population may even be higher when considering those with asymptomatic DVT not captured by screening, subclinical pulmonary embolism or embolic stroke, and the possibility of fatal pulmonary embolism or embolic stroke because autopsy data were not obtained. While not all traumatically injured pediatric patients require cVTE, the application of risk-based VTE guidelines focuses on the use of cVTE in pediatric patients at highest risk. Patients who developed VTE in this study had a higher total number of risk factors than those without VTE (4 vs 3, *P* = .001) but overall had a similar distribution of the most common risk factors. This study demonstrated that the use of cVTE based on established high-risk criteria in children is safe, with no documented bleeding attributable to cVTE.

Although this study was not powered to identify VTE risk from each individual risk factor, several risk factors emerge as concerning for increasing risk. We found that 28% of patients with VTE were obese (defined as body mass index ≥95 percentile for age), which was nearly twice the rate of obesity in all study patients (68/460; 14.8%; *P* = .08). Though there are limited data in children, obesity is a known risk factor for VTE in adults, and this may be due to physiologic differences or inadequate dosing of cVTE.[7,16,17] As such, children with higher body mass index may warrant extra attention in posttraumatic cVTE guidelines. Additionally, 15 of 25 VTE events (60%) in this study were CVL-related DVT, representing a 6.7% VTE rate in all patients with CVL in the study. The high risk of VTE in the presence of CVL has been previously described in the pediatric critical care literature; McLaughlin et al[18] and others reported a 6% rate of symptomatic CVL-associated DVT in pediatric trauma patients.[19,20] Use and duration of CVL represents a potentially modifiable risk factor in the development of posttraumatic VTE; therefore, CVL should be used judiciously in the care of pediatric trauma patients. Despite the large cohort of high-risk pediatric trauma patients included in this multi-institutional study, the overall VTE event rate was relatively low, limiting the ability to conduct adequately powered multivariate analyses based on individual high-risk factors and other variables.

Existing guidelines frequently omit younger children from receiving cVTE, although the age of cutoff for recommended prophylaxis varies. In a set of 2017 guidelines, PTS/EAST conditionally recommended against cVTE in prepubertal patients while acknowledging paucity and low quality of

evidence.[6] A 2015 consensus statement from an expert multidisciplinary panel based on available evidence recommended against routine cVTE in patients 12 years old or younger.[21] Many other prediction tools assign greater weight to pediatric patients of older age.[7,9,22,23] A previous single-institution application of a similar high-risk algorithm more strongly weighed those 13 years and older but found a median age of VTE occurrence at 9 years, leading us to adjust the age threshold to 8 years in the current prophylaxis algorithm.[9,10] Our study population included 16.3% patients (75/460) who were 8 years old or younger (eFigure in the Supplement). While this younger group had statistically increased total ICU and hospital days, they had similar ISS and total ventilator days to those for patients older than 8 years. High-risk patients who were 8 years old or younger had a VTE rate of 8% (6/75 events), and 24% (6/25) of the VTE events captured in the study occurred within this younger population. Our study found that total number of risk factors alone did not discriminate those who developed VTE in this younger population. Still, these findings demonstrate that younger traumatically injured children develop VTE at a rate comparable with that of older children and thus should not be omitted from prophylaxis guidelines, although further study may focus on the specific risk factors of this younger-aged population.

A concern that potential bleeding from prophylaxis outweighs VTE risk reduction is often given as reason for withholding anticoagulation in pediatric patients.[24-26] For those patients at an initial high risk of bleeding, safety with appropriate delays of cVTE has been repeatedly demonstrated in the adult literature; however, hesitancy still remains.[4,27] Our study found no bleeding complications secondary to the use of prophylactic anticoagulation. However, with the use of therapeutic anticoagulation, a total of 6 bleeding complications were observed, though this finding is not unexpected and previously reported.[28] Our findings emphasize the importance of early prophylaxis in high-risk patients to prevent VTE that necessitates therapeutic anticoagulation, which carries a more significant bleeding risk. Of interest, since the design of this study in 2018, emerging adult data have shown utility in tracking anti-factor Xa to determine appropriate prophylactic anticoagulation dosing with low-molecular-weight heparin.[4,29] Use of anti-factor Xa may also hold potential in dose adjustment of prophylactic dosing of anticoagulation in children, but it is not yet widely used and requires additional study.[30] Ensuring cVTE is within target range with assessment of anti-factor Xa levels has the potential to minimize both breakthrough VTE and bleeding events over fixed or purely weight-based dosing. While using a simple weight-based regimen may lessen barriers to implementation of cVTE, inclusion of anti-factor Xa measurements to confirm adequate dosing may be a consideration in future work.

Adult trauma literature has shown that early initiation of cVTE after trauma reduces the incidence of VTE, even in the presence of solid organ injuries and traumatic brain injury.[31-34] This study also suggests that the greatest reduction in VTE risk may be seen when cVTE is used early following traumatic injury. We found that median (IQR) time from admission to initiation of cVTE was significantly different between patients who developed VTE (4.2 days [2.5-7.5 days]) and those without VTE (2.5 days [1.0-4.0 days]; $P = .008$). Among the children who received cVTE, increased time to initiation of cVTE was associated with an increased likelihood of developing VTE, though the effect size was small. Thus, the absence of a statistically significant difference in VTE rate between children who received prophylaxis and those who did not may be due to decreased benefit of cVTE when significantly delayed, in addition to an overall low VTE event rate in the study. Given the highly variable rates of VTE reported in the pediatric population, as well as the uniqueness of studying a high-risk patient population of all ages, an evidence-derived baseline VTE rate was not available to conduct a prestudy power analysis. It is important to consider that we cannot exclude that significance would have been achieved with additional patients, and thus a type II error may be present in determining the significance of VTE rate based on receipt of prophylaxis. Additionally, clinical heterogeneity between each prophylaxis group (received ≤24 hours, >24 hours, or never) was present. Children who received cVTE after 24 hours had the highest median ISS, number of operations, ventilator days, and ICU and total length of stays when compared to those who received early or no prophylaxis. The cohort that never received cVTE may include both patients at a perceived lower VTE risk and also those at highest VTE risk with concurrent high bleeding risk, as evidenced by lowest Glasgow Coma Scale and highest mortality rates (Table 1). This nonuniformity in degree of injury, and subsequent variations in care, limits conclusive findings regarding cVTE efficacy in this high-risk population. Regardless, our findings emphasize the importance of early cVTE for VTE prevention in high-risk children, and future studies may center on the optimal timing of early cVTE.

Another limitation of this study was the relatively low use of cVTE despite recommended study guidelines. Nearly half of the study population did not receive cVTE despite their high risk. Many other large pediatric VTE studies show prophylaxis adherence rates of less than 20%.[9,10,35] Allowing physician discretion to deviate from the anticoagulation protocol may introduce selection bias because of their assumptions about an individual patient's risk of VTE or the perceived risks of cVTE. When compared with children who received cVTE, those who did not receive cVTE tended to be younger (median [IQR] age, 12.9 years [7.1-15.5 years]) (eFigure in the Supplement). This group of patients saw a rate of VTE similar to those who had delayed receipt of anticoagulation (5.3% vs 6.9%) (Figure) and an increased VTE rate compared with those who received early anticoagulation (1.6%). While many patients had documented clinical reasons for delaying cVTE, the most common of which was central nervous system bleed (30.1%), the second most common reason for initial withholding of cVTE was physician discretion (25.6%). This may reflect the hesitancy of pediatric physicians to administer cVTE, especially to patients at younger ages who are commonly perceived to be at lower risk of VTE and excluded from existing guidelines.[6,7,21] A survey based study of 129 trauma physicians caring for children revealed significant practice variation in the administration of cVTE with 51% of physicians having no standard practice for screening; many physicians were unaware that

guidelines existed, and even if aware, they had low rates of guideline implementation.[36] The increased rate of VTE when prophylaxis was delayed or withheld represents potentially preventable morbidity that can be improved on with evidence-based guidelines and increased physician adherence. Further investigation is needed to determine underlying reasons surrounding delay or withheld prophylaxis in the pediatric trauma population.

Limitations

The limitations of this study are described above. Briefly, despite the large cohort, the overall VTE event rate was relatively low, limiting the ability to conduct adequately powered multivariate analyses based on individual high-risk factors and other variables. Second, an evidence-derived baseline VTE rate was not available to conduct a prestudy power analysis. Third, there was a relatively low use of cVTE despite recommended study guidelines. Fourth, there was clinical heterogeneity between each prophylaxis group; the nonuniformity in degree of injury, and subsequent variations in care, limits conclusive findings regarding cVTE efficacy. Regardless, our findings emphasize the importance of early cVTE for VTE prevention in high-risk children, and future studies may center on the optimal timing of early cVTE.

Conclusions

In this large prospective study including high-risk pediatric trauma patients, use of cVTE based on a set of high-risk criteria was safe and did not lead to bleeding complications. Delay to initiation of cVTE was significantly associated with development of VTE. Quality improvement in pediatric VTE prevention may center on timing of prophylaxis and barriers to implementation. Further investigation is needed to determine underlying reasons surrounding delay or withheld prophylaxis in the pediatric trauma population.

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