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Independent Review Article

Venous thromboembolism prophylaxis in the pediatric trauma population[☆,☆☆]

A. Jill Thompson[a,*], S. David McSwain[b], Sally A. Webb[b], Melanie A. Stroud[c], Christian J. Streck[d]

[a]*Department of Pharmacy Services, Medical University of South Carolina, Charleston, SC, USA*
[b]*Department of Pediatrics, Division of Pediatric Critical Care, Medical University of South Carolina, PO BOX 250566, Charleston, SC 29425, USA*
[c]*Medical University of South Carolina Children's Hospital, Charleston, SC 29425, USA*
[d]*Department of Pediatric Surgery, College of Medicine, Medical University of South Carolina, Charleston, SC 29425, USA*

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Abstract

Background/Purpose: The aim of this study was to review evidence-based literature addressing pertinent questions about venous thromboembolism (VTE) after traumatic injury in children.

Methods: Data were obtained from English-language articles identified through Pubmed published from 1995 until November 2012, and from bibliographies of relevant articles. Studies were included if they contributed evidence to one of the following questions. In the pediatric traumatic injury population: (1) What is the overall incidence of VTE? (2) Is age (adolescence versus pre-adolescence) associated with higher VTE incidence? (3) Which risk factors are associated with higher VTE incidence? (4) Does mechanical and/or pharmacological prophylaxis impact outcomes?

Results: Eighteen articles were included in this systematic review. The evidence regarding each question was evaluated, graded by author consensus, and summarized.

Conclusions: The overall incidence of VTE is low. Older (>13 years) and more severely injured patients are at higher VTE risk. Additional factors including injury type or presence of a central venous catheter also place a patient at higher VTE risk. Implementation of a risk-based clinical practice guideline for VTE prophylaxis has been associated with reduced symptomatic VTE at one institution. Randomized, prospective trials analyzing outcomes of VTE prophylaxis in pediatric trauma victims are needed.

Abbreviations: CVC, central venous catheter; DVT, deep venous thrombosis; ICU, intensive care unit; IPC, intermittent pneumatic compression; ISS, injury severity score; KID, Kids' Inpatient Database; LE, lower extremity; LMWH, low molecular weight heparin; NPTR, National Pediatric Trauma Registry; NTDB, National Trauma Data Bank; PHIS, Pediatric Health Information System; PE, pulmonary embolism; PICU, pediatric intensive care unit; SCI, spinal cord injury; VTE, venous thromboembolism.

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* Corresponding author. Department of Clinical Pharmacy Practice and Outcome Sciences, South Carolina College of Pharmacy, PO BOX 250584, Charleston, SC 29425, USA. Tel.: +1 843 792 5850; fax: +1 843 792 1549.

E-mail addresses: thompsam@musc.edu (A.J. Thompson), mcswains@musc.edu (S.D. McSwain), webbsa@musc.edu (S.A. Webb), stroudmel@musc.edu (M.A. Stroud), streck@musc.edu (C.J. Streck).

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Venous thromboembolism (VTE) is a well-documented complication of traumatic injury in adults. The baseline risk of VTE is estimated to be at least 3% to 5%, and up to 10% in patients with traumatic brain or spinal cord injury [1]. In contrast, VTE is extremely rare in children. The incidence of VTE in hospitalized children was historically described by Andrew et al. using the Canadian Registry of VTE, a prospective database of 15 tertiary care pediatric centers from 1990 to 1992; the incidence of VTE was 5.3 per 10,000 hospital admissions [2]. Although rare, pediatric VTE disease is associated with 2.2% mortality, evenly distributed throughout infancy and childhood. Morbidity due to pediatric VTE includes an 8% incidence of recurrent thrombosis, and 12% to 50% incidence of postphlebitic (postthrombotic) syndrome [3,4]. In pediatric trauma victims, VTE has been associated with increased hospital costs and length of stay [5]. Specific guidance on preventing these unwanted outcomes in adults is available for clinicians [1,6,7]. However, in the pediatric trauma population far less evidence is available, screening for VTE is not standardized, and consensus guidelines for VTE prophylaxis are lacking. Extrapolating adult data to pediatrics is problematic and may subject many patients to the risks of pharmacologic anticoagulation when very little benefit is likely to be achieved.

Currently clinical practice does not implement VTE prophylaxis in most pediatric trauma patients due to the low incidence of VTE in children. The purpose of the present study was to perform an evidenced-based review of the literature to identify which subset of patients, if any, would benefit from prophylaxis. Specifically, we sought to find evidence-based answers to the following questions **in the pediatric traumatic injury population**:

1) What is the overall incidence of VTE?
2) Is age (adolescence versus pre-adolescence) associated with higher VTE incidence?
3) Which risk factors are associated with higher VTE incidence?
4) Does mechanical and/or pharmacological VTE prophylaxis impact outcomes (deep venous thrombosis, pulmonary embolism, bleeding or mortality)?

1. Materials and methods

Our institution is an American College of Surgeons verified Level 1 Trauma Center and a South Carolina state verified Level 1 Pediatric Trauma Center and receives the majority of severely injured patients in the coastal region of South Carolina. Our institution had no guidelines for VTE prophylaxis in pediatric trauma victims. We identified a small workgroup consisting of a pediatric critical care pharmacist, two pediatric intensivists, our pediatric trauma program coordinator, and our pediatric trauma medical director to collaboratively review the literature.

We searched Medline's Pubmed for English-language evidence published from 1995 until November 2012 using keywords "deep venous thrombosis," "pediatric," and "trauma," and the MESH database using index terms "venous thrombosis/prevention and control" or "venous thromboembolism/prevention and control," and "wounds and injuries." Relevant articles were also identified from bibliographies. Only clinical studies in a pediatric trauma population, or those including both adults and pediatrics but with a clear pediatric subset analysis, were included in the evidence review. Evidence quality was decided by consensus and graded as Class 1, 2, or 3 according to the Canadian & US Preventive Task Force criteria (Table 1).

2. Results

Eighteen articles were included in the evidence review; most were Class 2 or 3 evidence. A summary of the evidence addressing each question is included below.

2.1. What is the overall incidence of VTE?

Although trauma is noted as a risk factor in almost every reported series of pediatric patients with VTE, the rate of VTE specific to the pediatric trauma population is not well established. The reported incidence of VTE in the overall pediatric trauma population ranges from 0.02% to 0.33% [5,9–15] and appears to be stable over time [9] (Table 2). These data are derived from retrospective reviews of institutional trauma registries or reviews of large children's hospital databases and the National Trauma Data Bank (NTDB). The reported incidence data reflect the diagnosis of symptomatic VTE when no prospective screening was done, or when screening practices were unknown.

There is only one study reporting the incidence of VTE after pediatric trauma in patients who were prospectively screened with imaging studies [16]. The patient population in this study was in a critical care unit; therefore, findings from this study are not included in the overall population analysis.

Table 1 Canadian & US preventive task force evidence grading criteria.

Class 1	Prospective randomized controlled trials.
Class 2	Clinical studies in which the data were collected prospectively, and retrospective analyses which were based on clearly reliable data. Examples include: observational studies, prospective cohort studies, prevalence studies, and case–control retrospective studies.
Class 3	Clinical studies based on retrospective data collection. Examples include: clinical series, database or registry reviews, large series of case reviews, and expert opinion.

Crit Care Med 2009; 37(12):3127 [8].

Table 2 Incidence of venous thromboembolism in the overall pediatric trauma population.

Reference	Study Design	Number of patients	Age (yr)	Data/Comments	Evidence strength
[9] 2012	Retrospective, PHIS database	260,078	<19	0.26% VTE; stable rate from 2001 to 2008	3
[13] 2011	Retrospective, NTDB	603,889 [a]	<22	0.02% VTE	3
[5] 2009	Retrospective, KID	240,387	<21	0.03% VTE	3
[12] 2006	Retrospective, 2 institutions; patients admitted to PICU or hospitalized > 72 h	3291	<18	0.33% VTE	3
[11] 2005	Retrospective, NTDB	116,357	<18	0.08% VTE	3
[14] 2005	Retrospective, 1 institution	3637	<17	0.03% VTE	2
[15] 2002	Retrospective, state databases	58,716	<16	0.08% VTE	3
[10] 1994	Retrospective, NPTR	28,692	<19	<0.01% pulmonary embolism	3

ICU, intensive care unit; KID, Kids' Inpatient Database; NPTR, National Pediatric Trauma Registry; NTDB, National Trauma Data Bank; PHIS, Pediatric Health Information System; PICU, pediatric intensive care unit; VTE, venous thromboembolism.

[a] Calculated based on data presented in study.

2.2. Is age (adolescence versus pre-adolescence) associated with higher VTE incidence?

Based on the higher rates of VTE documented in adults, concern exists that the onset of puberty places adolescents at higher risk for VTE than younger children. Many small, single-center studies reported that patients who developed VTE were adolescents [14,17–19]. Larger database studies also link adolescence to VTE [5,10,13]. Two multivariate logistic regression analyses of large trauma databases found age to be a significant predictor of VTE. O'Brien et al. found age > 14 years to be predictive (odds ratio 2.34, 95% confidence interval 1.95–2.80) [13], and Vavilala et al. reported that age 10–15 years (the highest age group in that study) had a relative risk for VTE of 5.0 (95% confidence interval 1.5–16.7) [15]. In a third large study of pediatric trauma inpatients involving the KID database (n = 240,387, age < 21 years), the mean age of patients with VTE was 16.6 years vs. 12.1 years without VTE ($p < .001$) [5]. In the spinal cord injury population, patients aged 14–19 years had significantly more VTE (4.4% compared to 1.1% of younger patients; $p = .035$) [20]. In multivariate logistic modeling, the younger age group (< 14 years) had a decreased risk of VTE (odds ratio 0.2, 95% confidence interval 0.1 to 0.9). Table 3 summarizes evidence related to the impact of age on VTE incidence.

2.3. Which risk factors are associated with higher VTE incidence?

Three multivariate logistic regression analyses sought to identify risk factors for VTE in pediatric trauma. Two analyzed large trauma databases [13,15] and one examined hospital-based trauma registries at two institutions [12]. Additionally, retrospective studies [5,17,18,21] and 2 case–control studies [14,22] also addressed risk factors. Injury severity, injury type, and the presence of a central venous catheter were linked to higher VTE incidence. Table 4 summarizes evidence regarding VTE risk factors.

2.3.1. Injury severity score/ICU admission

Focusing on the pediatric intensive care unit (PICU) trauma population in the NTDB, O'Brien et al. found ICU length of stay ≥ 4 days and 4 or more ventilator days to be predictive of VTE. The incidence of VTE was 6.12 per 1000 ICU discharges (0.6%) as compared to 0.02% of all pediatric trauma admissions [13]. Hanson et al. reported a 6.2% incidence of clinically apparent VTE in pediatric trauma victims admitted to a PICU when all admissions were prospectively followed for clinical evidence of VTE [22]. This mirrors the adult trauma incidence of symptomatic VTE (>1% to 7.6%) [1]. However, no surveillance imaging for VTE was performed in this case–control study.

Studies have also analyzed Injury Severity Scores (ISS) to determine if VTE is more common in more severely-injured patients. In the O'Brien study [13], the mean ISS was 28.3 in patients with VTE vs. 17.0 in those without VTE ($p < .0001$). Candrilli et al. found significant differences with stratification of VTE incidence based on ISS. The mean (SD) ISS in patients with and without VTE was 20.65 (21.47) and 10.53 (18.52), respectively ($p < .0001$). The odds ratio (95% confidence interval) for VTE in patients with an ISS > 25 (critical injury) was 3.53 (2.01–6.22), while patients with an ISS 16–25 (severe injury) had an odds ratio of 2.49 (1.56–3.96), and those with an ISS 9–15 (moderate injury) had an odds ratio of 2.13 (1.49–3.05); all compared to the reference group with an ISS < 9 (minor injury) [5]. In another large retrospective study analyzing data from state databases, mean ISS was 17.1 in patients with VTE as compared to 6.2 in patients without VTE ($p < .001$) [15]. Two single-center retrospective studies supported the consideration that injury severity is linked to VTE incidence by reporting that all patients with VTE had ISS scores > 24 (n = 2) [17] or > 25 (n = 3) [14].

2.3.2. Injury type

Several studies have evaluated injury type as a risk factor for VTE in the pediatric trauma population. Patients with a

Table 3 Impact of age on incidence of venous thromboembolism in the pediatric trauma population.

Reference	Study Design	Number of patients	Age (yr)	Data/Comments	Evidence strength
[19] 2012	Retrospective, 1 institution; pelvic or femur fractures	1782	<18	All 3 VTE in age 15 or older	3
[13] 2011	Retrospective, NTDB, ICU ≥ 1 day	135,032	<22	Age <1: 0.38% Age 1–13: 0.20% Age 14–17: 0.62%, Odds ratio 2.34	3
[5] 2009	Retrospective, KID	240,387	<21	Mean age with VTE 16.6 vs. 12.1 without VTE ($p < .001$)	3
[12] 2006	Retrospective, 2 institutions	3291	<18	Odds ratio 19.5 for age 15–18 compared with age 0–5	3
[20] 2005	Retrospective, California Patient Discharge Data Set; spinal cord injuries	1585	<20	Age <14: 1.1%, Odds ratio 0.2 Age 14–19: 4.4%	3
[14] 2005	Case–control, 1 institution	3637	<17	Odds ratio 3.6 for patients age > 8 (3 total cases)	2
[17] 2005	Retrospective, 1 institution	3345	<18	Age <13: 0% Age 13–17: 0.2% (2 total cases)	3
[15] 2002	Retrospective, state databases	58,716	<16	Age <5: 0.02% Age 5–9: 0.04% Age 10–15: 0.13%	3
[18] 2000	Retrospective, 1 institution	2746	<16	All three cases in age 14 or older	3
[10] 1994	Retrospective, NPTR	28,692	<19	Both cases in age 16 or older	3

ICU, intensive care unit; KID, Kids' Inpatient Database; NPTR, National Pediatric Trauma Registry; NTDB, National Trauma Data Bank; SCI, spinal cord injury; VTE, venous thromboembolism.

spinal cord injury (SCI) represent a subset of the trauma population with a higher risk for VTE, although data in children younger than 15 years are sparse. Jones et al. retrospectively reviewed data from over 16,000 acute SCI discharges in California, both pediatric and adult, over an 11-year period [20]. Screening and prophylaxis regimens were unable to be obtained from such a database, but ultrasounds and pharmacologic prophylaxis were noted to be used in general practice during this time. The incidence of VTE after spinal cord injury was 4.4% in pediatric patients (compared to 6% for the combined population), in the first year after injury [20]. Most episodes (90%) of VTE occurred within 91 days of injury.

Spine or spinal cord injury, major vascular injury, pelvic fracture, lower extremity fracture, chest injury and head injury were all found to have an increased risk for VTE in multivariate logistic regression analyses [12,13,15]. After pediatric trauma, major vascular injury (relative risk 17.6, 95% confidence interval 6.0–51.2), severe head injury (relative risk 4.8, 95% confidence interval 2.4–9.7) and severe spine injury (relative risk 5.1, 95% confidence interval 1.2–21.8) were among the risk factors most associated with VTE in a large review of state databases [15]. O'Brien et al. analyzed data from the (784 trauma centers) for VTE incidence in patients aged ≤ 21 years. Head, spinal cord, and major vascular injuries, and pelvic and lower extremity fractures were each associated with odds ratios greater than 1 ($p \le .0001$) [13]. In a retrospective review of the Kids' Inpatient Database (KID), Candrilli et al. found that VTE incidence was higher following vascular, pelvic, spine, lower extremity and head injuries [5]. In a retrospective two-institutional study, Cyr et al. reported spinal cord injury (OR 23.4), thoracic injury (OR 13.8) and abdominal injury (OR 7.7) as important risk factors for VTE [12]. In additional single-institutional studies, head injury [14] and spinal cord, lower extremity and thoracic injury were all reported as risk factors for VTE [17].

2.3.3. Presence of central venous catheters

Central venous catheters (CVCs) are a well-documented risk factor for thrombosis formation in pediatric trauma patients, both for the duration of the catheter placement and afterwards in the same location [13,15,18,22]. Cyr et al. demonstrated that CVC was an independent risk factor for VTE with an odds ratio (95% confidence interval) of 64.0 (16.8–243.9) in a multivariate logistic regression analysis of two hospital-based trauma registries of pediatric patients with severe traumatic injuries [12]. Vavilala et al. showed that the presence of a CVC is the single greatest risk factor for VTE in pediatric trauma, with a relative risk (95% confidence interval) of 39.9 (12.3–128.6), an adjusted relative risk of 5.3 (1.6–18.2), and an absolute rate of 28.6 per 1000 discharges [15]. Hanson et al. evaluated 144 critically ill pediatric trauma patients and found that 67% of the nine patients who developed VTE did so at the site of a previous or existing CVC [22]. Additionally, there was a 7.9-fold increase in the odds of developing a VTE for each CVC in a patient ($p = 0.005$). In their review of the NTDB, O'Brien et al. found that CVC was a strong risk factor for VTE (OR 2.24) regardless of injury pattern [13]. In the KID review by

Candrilli et al., 2.0% of patients with a CVC developed a VTE [5]. Two other single-institutional studies cited CVC as a risk factor for VTE development [14,18]. In summary, the incidence of VTE in pediatric trauma patients with a CVC was reported to be between 1.9% and 2.9% when screening methods were unknown and likely not performed.

Table 4 Risk factors for venous thromboembolism in pediatric trauma population.

Reference	Study Design	Number of patients	Age (yr)	Data/Comments	Evidence strength
Higher Injury Severity Score or Intensive Care Unit Admission					
[13] 2011	Retrospective, NTDB, ICU ≥ 1 day	135,032	<22	Mean ISS: 28.3 with VTE vs. 17.0 without VTE ($p < .0001$) ICU ≥ 1 day: 0.6% VTE	3
[22] 2010	Case–control, 1 institution, PICU	144	<18	6.2% of PICU trauma patients developed VTE	2
[5] 2009	Retrospective, KID	240,387	<21	Mean ISS: 20.7 with VTE vs. 10.5 without VTE ($p < .0001$)	3
[14] 2005	Case–control, 1 institution	3637	<17	ISS ≥ 25 (OR 82)	2
[17] 2005	Retrospective, 1 institution	3345	<18	ISS > 24: 1.02% VTE ISS 15–23: 0.59% VTE ISS < 9: 0% VTE	3
[15] 2002	Retrospective, state databases	58,716	<16	Mean ISS: 17.1 with VTE vs. 6.2 without VTE ($p < .001$)	3
Injury Type					
[13] 2011	Retrospective, NTDB, ICU ≥ 1 day	135,032	<22	Major vascular (OR 2.8), Spine (OR 1.8), LE (OR 1.8), Head (OR 1.3)	3
[5] 2009	Retrospective, KID	240,387	<21	VTE Incidence: Vascular (1.8%), Pelvic (1.2%), Spine (1.0%), LE (0.6%), Head (0.5%)	3
[12] 2006	Retrospective, 2 institutions	3291	<18	Spinal cord (OR 23.4), Thoracic (OR 13.8), Abdomen (OR 7.7)	3
[14] 2005	Case–control, 1 institution	3637	<17	Head (OR 2.9)	2
[20] 2005	Retrospective, California Patient Discharge Data Set; spinal cord injuries	1585	<20	Age <14: 1.1% VTE Age 14–19: 4.4% VTE	3
[17] 2005	Retrospective, 1 institution	3345	<18	$P < .05$ for SCI, LE, or thoracic injury. P = NS for head or pelvic injury	3
[15] 2002	Retrospective, state databases	58,716	<16	Major vascular (RR 17.6), Spine (RR 5.1), Head (RR 4.8), LE (RR 2.5)	3
Presence of Central Venous Catheter					
[13] 2011	Retrospective, NTDB, ICU ≥ 1 day	135,032	<22	CVC (OR 2.24) was strong risk factor regardless of injury pattern. 1.9% of patients with CVC developed a VTE.	3
[22] 2010	Case–control, 1 institution	144	<18	CVC use in 89% of cases vs. 30% controls (OR 19.0)	2
[5] 2009	Retrospective, KID	240,387	<21	2.0% of patients with CVC developed a VTE.	3
[12] 2006	Retrospective, 2 institutions	3291	<18	CVC (Multivariate OR 64.0)	3
[14] 2005	Case–control, 1 institution	3637	<17	All three cases had a CVC	2
[15] 2002	Retrospective, state databases	58,716	<16	CVC (Multivariate OR 6.8). 2.9% of patients with CVC developed a VTE.	3
[18] 2000	Retrospective, 1 institution	2746	<16	2 of 3 cases had a CVC	3

(*continued on next page*)

Table 4 (*continued*)

Reference	Study Design	Number of patients	Age (yr)	Data/Comments	Evidence strength
Other Factors					
[13] 2011	Retrospective, NTDB, ICU ≥ 1 day	135,032	<22	>3 Ventilator days (OR 1.3)	3
[21] 2009	Retrospective, 1 institution	1314	6-20	Obese: 0.7% DVT Non-Obese: 0% (p = 0.008)	3

CVC, central venous catheter; DVT, deep vein thrombosis; ICU, intensive care unit; ISS, injury severity score; KID, Kids' Inpatient Database; LE, lower extremity; NPTR, National Pediatric Trauma Registry; NTDB, National Trauma Data Bank; OR, odds ratio; PICU, pediatric intensive care unit; RR, relative risk; SCI, spinal cord injury; VTE, venous thromboembolism.

2.3.4. Other risk factors

Rana et al. conducted a retrospective review of trauma victims aged 6–20 years to determine if obesity (BMI ≥ 95th %ile for age) was associated with increased risk of complications, two of which were DVT and PE. This study was significantly limited, however, because 73% of patients did not have enough data to calculate a BMI. Of 1314 patients evaluated, 294 were determined to be obese. The incidence of DVT was higher in the obese patients (0.7% vs 0%, p = 0.008) [21].

2.4. What impact does VTE prophylaxis have on outcomes?

Very little published data are available to directly address the impact of VTE prophylaxis on outcomes in pediatric trauma patients (Table 5). A recent survey of adult and pediatric trauma centers performed by O'Brien et al. showed great variability in DVT prophylaxis patterns. The majority of centers provided prophylaxis to patients aged 16–20 but did not for patients aged 11–15 [23]. One large study evaluated the use of enoxaparin for VTE prophylaxis in the Pediatric Health Information System (PHIS) database and found that while enoxaparin prophylaxis had increased from 0.65% to 1.54%, VTE incidence remained stable over the 8-year study period [9]. In a single-institution, prospective observational trial in PICU patients, Hanson et al. demonstrated a significant decrease in symptomatic VTE from 5.2% to 0% (p = .04) following implementation of clinical practice guidelines [16]. In this institution, patients deemed high risk for VTE but low risk for bleeding received enoxaparin 0.5 mg/kg/dose subcutaneously twice a day until hospital discharge. Patients with high VTE risk and high bleeding risk received mechanical prophylaxis (sequential compression devices) as well as a screening ultrasound on day 7 if still in the PICU. There were no bleeding complications reported.

A descriptive study provided a review of trauma registry data of 706 patients up to 21 years old who received LMWH prophylaxis at four Level 1 trauma centers (2 adult centers and 2 pediatric centers) [24]. The mean age was 18.5 years (SD 2.3 years), and the majority (95%) of patients received care at the 2 adult centers. Twelve patients were between the ages of 1 and 13 years. The mean ISS was 15.2 (SD 11.2; range 1–75); 38.5% of patients had severe or critical injuries. Patients received LMWH for a median duration of 4 days (range 1–60 days); 48% continued the LMWH after discharge. The incidence of VTE was 2.1% despite LMWH prophylaxis; all occurred in patients 15 to 21 years old. Neither the diagnostic method for VTE nor whether they were associated with symptoms was described. Three patients (0.4%) had a major bleeding event (classified as "other"; not intracranial, retroperitoneal, gastrointestinal, or an event that required surgery).

A smaller study involving a mixed pediatric population including some with trauma evaluated LMWH for preventing symptomatic VTE [25]. Hofmann et al. performed a single-center retrospective review of LMWH use in a broad pediatric population; 24% (n = 19) of patients received daily subcutaneous nadroparin as VTE prophylaxis after trauma. Details about screening practices were not provided. No trauma patients developed VTE, although this finding is limited by the small number of patients, retrospective nature of the study, and lack of a comparator group [25].

3. Discussion

3.1. VTE incidence

The reported incidence of VTE in all pediatric trauma patients appears to be low (0.02%–0.33%); however, this may be an underestimation of the true incidence because retrospective database reviews have the inherent limitation that data may have been missing (Table 2). The incidence would likely be higher in patients prospectively screened for VTE; however, our review found only one study [16], in a PICU population, that prospectively screened asymptomatic patients with ultrasound or other imaging modalities. Although the overall risk of symptomatic VTE remains lower in children than adults, certain subsets of the pediatric trauma population appear to be at increased risk and may warrant consideration for VTE prophylaxis.

Table 5 Outcomes of venous thromboembolism prophylaxis in the pediatric trauma population.

Reference	Study Design	Number of patients	Age (yr)	Data/Comments	Evidence strength
[24] 2012	Retrospective, 4 institutions; patients who received LMWH prophylaxis	706	<21	VTE: 2.1% incidence (age 15–21) Bleeding: 0.4% (n = 3 patients) had major events	3
[25] 2001	Retrospective, 1 institution; patients who received LMWH prophylaxis	19	<20	No VTE	3
[16] 2012	Prospective, observational; LMWH in high VTE-risk/low bleeding risk patients	546	<19	Clinical practice guidelines for VTE prophylaxis decreased symptomatic VTE (5.2% to 0%)	2
[9] 2012	Retrospective, PHIS database	260,078	<19	Enoxaparin use increased (from 0.65% to 1.54%) while VTE incidence stable (0.23%–0.28%)	3
[23] 2008	Survey of trauma centers	0	NA	VTE prophylaxis variation (Majority prophylaxis in age 16–20 but not age 11–15)	3

LMWH, low molecular weight heparin; NA, not applicable; PHIS, Pediatric Health Information System; VTE, venous thromboembolism.

3.2. Age

Evidence suggests that injured teenagers are at higher risk for VTE than other age groups of pediatric trauma patients (Table 3). When reviewing the trauma literature, it is important to note that some trauma centers may admit adolescents to adult hospitals and so data may be more difficult to track. Infants are known to be at higher risk of VTE compared to children [2], but literature has not identified infants as a high risk age group for trauma-related VTE. The risk of VTE in children is lower than in infants or adolescents; this may be due to a decreased capacity to generate thrombin, increased thrombin inhibition, inherent coagulation inhibition due to increased α-2 macroglobulin, or differences in platelet and vessel wall interactions [2,13]. Although the precise age at which children become more at risk for VTE remains unknown, evidence to date substantiates that children older than age 13 are at greater risk for VTE following trauma than younger patients.

3.3. Additional risk factors

Several retrospective studies involving large databases as well as many single-institutional studies sought to evaluate additional risk factors which could be used to identify high-risk patients for VTE (Table 4). Major VTE risk factors included injury severity, injury type (major vascular injury, severe spine injury, severe head injury, severe thoracic injury, lower extremity fracture), presence of a CVC, number of ventilator days, and major operative procedures. Other risk factors that were not evaluated in most studies but that may be important include smoking history, underlying hematologic abnormalities, and use of hormonal contraceptives.

The evidence suggests that patients with more severe injuries or injuries requiring admission to an ICU are at higher risk of VTE (Table 4). It is not practical to calculate ISS for each patient in real time, thus, ISS remains relegated to research or quality improvement assessments. The considerably higher incidence of VTE in the study of pediatric trauma patients admitted to the PICU by Hanson et al. may be due to the fact that all patients were followed prospectively for evidence of VTE. Although surveillance imaging was not conducted routinely for all patients, it is likely that subtle symptoms of VTE were detected because of the prospective monitoring, resulting in the subsequent VTE diagnoses [22]. Based on injury severity and the likelihood of multiple risk factors being present in patients admitted to a PICU after a traumatic injury, the PICU population represents a targeted subgroup of pediatric trauma patients at higher risk for VTE. The strongest evidence supports an increased risk of VTE in patients with head, major vascular, chest, spine, or lower extremity injuries (findings from case–control or multivariate regression analyses) [12–15]. There is little evidence available to clearly define whether one injury type confers a higher risk than another type, or if specific combinations of injuries would confer substantially more risk.

Central venous catheters are often necessary in the management of pediatric trauma, particularly in critically ill patients, due to frequent requirements for inotropic support, monitoring of central venous pressure, and administration of multiple medications and blood products. Evidence supports that the presence of a CVC considerably increases the risk for VTE in pediatric trauma patients from an incidence of 0.02%–0.33% reported in the overall pediatric trauma population (Table 2) to a 1.9%–2.9% incidence in pediatric trauma patients with a CVC (Table 4).

The site of CVC insertion likely plays a role in the formation of VTE, and several factors may be considered when selecting the optimal site in pediatric patients. Although ultrasound guidance for vascular access in PICUs may change the practice pattern in the future, femoral cannulation may frequently be chosen over other sites for several reasons. Femoral lines are relatively easier to place, particularly in small children, and appropriate positioning for placement of subclavian or internal jugular lines is often made more difficult in trauma patients by the presence of cervical collars and the need to keep the head of the bed elevated in patients with concern for increased intracranial pressure. It remains difficult to give definitive recommendations regarding the choice of insertion site in the pediatric trauma population based on limited prospective data.

3.4. VTE prophylaxis—impact on outcomes

Evidence-based guidelines give clear guidance for VTE prophylaxis in adults who suffer major trauma [1,6,7]. Low-dose unfractionated heparin or an LMWH, with intermittent pneumatic compression, is recommended to be started within 24–48 h of injury, unless contraindicated. If there are contraindications, such as uncontrolled bleeding, presence of an epidural catheter, or severe coagulopathy, then mechanical prophylaxis is suggested, and the pharmacologic anticoagulation should begin once bleeding risk has subsided. The recommended duration of VTE prophylaxis for patients with spinal cord injury is 3 months. Duration of prophylaxis is not clearly stated for other types of trauma; however, patients requiring major orthopedic surgery are recommended to undergo prophylaxis for up to 35 days from the date of surgery, as opposed to only 10 to 14 days. For patients with isolated lower-leg injuries requiring leg immobilization, VTE prophylaxis is not recommended. Screening ultrasounds are not recommended. These guidelines make no recommendations for pediatric trauma patients [1,6,7,26]. There is no evidence regarding outcomes of mechanical prophylaxis devices in pediatric trauma victims.

Few studies examined outcomes of VTE prophylaxis in pediatric trauma patients (Table 5). The strongest evidence to date (a prospective, observational study) favors the implementation of clinical practice guidelines to reduce symptomatic VTE [16]. This practice guideline recommended enoxaparin for high VTE risk patients with low bleeding risk. The use of enoxaparin did not increase due to implementation of the guideline, and bleeding events did not occur. In patients unable to receive enoxaparin due to a high risk of bleeding, screening ultrasounds were recommended on PICU day 7. Compliance with this recommendation was suboptimal, as only 6 of the 23 patients who met criteria for the ultrasound had it performed; of those 6 patients, 3 had VTE (50%). None of these were symptomatic VTE. The authors deemed this a successful approach because subclinical VTE was detected and treated early, thereby decreasing the risk of long-term morbidity. There is generally a lack of evidence for or against screening ultrasounds in pediatric trauma victims. Neither the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines nor the Eastern Association for the Surgery of Trauma (EAST) Guidelines recommend screening ultrasounds in asymptomatic patients [1,6,7].

Adverse outcomes due to prophylaxis in the pediatric trauma population appear to be uncommon. The Hanson et al. study of a practice guideline for pediatric trauma VTE prophylaxis utilized prospective patient monitoring and reported no bleeding complications [16]. Similarly, the incidence of major bleeding events in the retrospective review of 4 institutions' pediatric trauma patients was 0.4% [24]. Two reviews of LMWH in 865 pediatric patients (including trauma patients) reported no serious bleeds or CNS hemorrhages and no required blood transfusions [2] and an overall low incidence of bleeding [27].

4. Conclusions

Randomized, prospective trials of VTE prophylaxis in pediatric trauma victims have not been published. Choosing which pediatric patients should receive pharmacological prophylaxis, with its inherent risks of adverse effects, is a challenge. The overall incidence of VTE is low. Older and more severely injured patients are at higher VTE risk. The patients at highest risk of developing VTE, and, thus, who stand the most to gain by receiving pharmacologic prophylaxis (if not contraindicated), are those with spine or spinal cord injury, or major vascular injury. The presence of one or more of the following risk factors may also place a patient at high enough risk to warrant pharmacologic VTE prophylaxis: admission to an ICU, presence of a CVC, lower extremity or pelvic fracture, or traumatic brain injury. Implementing a risk-based clinical practice guideline for pharmacologic VTE prophylaxis has been shown to reduce symptomatic VTE [16]. Further studies in the pediatric trauma population are needed.

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