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Trauma

The survival benefit of low molecular weight heparin over unfractionated heparin in pediatric trauma patients☆

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ABSTRACT

Introduction: Venous thromboembolism (VTE) prophylaxis in pediatric patients is controversial and is mainly dependent on protocols derived from adult practices. Our study aimed to compare outcomes among pediatric trauma patients who received low molecular weight heparin (LMWH) compared to those who received unfractionated heparin (UFH).

Methods: We performed 2 years (2015–2016) retrospective analysis of the Pediatrics ACS-TQIP database. Pediatric trauma patients (age ≤17) who received thromboprophylaxis with either LMWH or UFH were included. Patients were stratified into three age groups. Analysis of each subgroup and the entire cohort was performed. Outcome measures included VTE events (deep vein thrombosis [DVT] and pulmonary embolism [PE]), hospital and ICU length of stay (LOS) among survivors, and mortality. Propensity score matching was used to match the two cohorts LMWH vs UFH.

Results: A matched cohort of 1,678 pediatric trauma patients was analyzed. A significant difference in survival, DVT events, and in-hospital LOS was seen in the age groups above 9 years. Overall, the patients who received LMWH had lower mortality (1.4% vs 3.6%, $p<0.01$), DVT (1.7% vs 3.7%, $p<0.01$), and hospital LOS among survivors (7 days vs 9 days, $p<0.01$) compared to those who received UFH. There was no significant difference in the ICU LOS among survivors and the incidence of PE between the two groups.

Conclusion: LMWH is associated with increased survival, lower rates of DVT, and decreased hospital LOS compared to UFH among pediatric trauma patients age 10–17 years.

Level of Evidence: Level III Prophylactic.

Study Type: Prophylactic.

Traumatic injury is a significant risk factor for developing venous thromboembolism (VTE), irrespective of age [1,2]. While the risk of VTE in adult trauma patients is significantly higher than in children, there is an increasing number of pediatric patients with VTE, which is frequently associated with devastating consequences, including cerebrovascular accident, post-thrombotic syndrome, and mortality [3–9]. Pharmacological and ambulatory prophylactic care is a well-established practice in all adult trauma patients without contraindications [10,11]. However, the standard of care for the pediatric trauma population is less clear, and it is extrapolated from the clinical experience of and management guidelines for adult patients. The Eastern Association for the Surgery of Trauma (EAST) and the Pediatric Trauma Society (PTS) guidelines for the prevention of VTE recommend the use of thromboprophylaxis in pediatric trauma patients older than 15 years and in younger post-pubertal children with an injury severity score (ISS) >25 who are at low risk of bleeding [12]. However, these guidelines have not outlined any specific thromboprophylactic agent associated with improved outcomes.

Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are the most common pharmacological prophylaxis agents used in the adult trauma population to prevent VTE. The minimal monitoring requirement, predictable pharmacokinetics, and cost effectiveness have led to LMWH often being the preferred choice of thromboprophylaxis [13–17]. In addition, LMWH has shown improved outcomes in both in vitro and in vivo animal models due to its neuroprotective and anti-inflammatory properties [18–21]. Multiple studies in adult trauma patients also suggest that LMWH might be more effective than UFH in preventing VTE, and that it might be associated with increased survival [21–25]. However, the effectiveness of LMWH in preventing

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thromboembolic events as well as its effect on survival in pediatric trauma patients is not well elucidated in the literature. In light of this lack of information on the optimal thromboprophylactic agent for pediatric trauma patients, this study aimed to compare venous thromboembolic events and survival in pediatric trauma patients who received LMWH or UFH from a national multi-institutional database. We hypothesized that LMWH is associated with fewer thromboembolic events and increased survival in pediatric trauma patients.

1. Methods

We performed a 2-year (2015–2016) retrospective cohort analysis of the Pediatric American College of Surgeons (ACS) Trauma Quality Improvement Program (TQIP) dataset. The Pediatric ACS-TQIP is one of the largest registries of trauma data ever assembled with over 100 participating hospitals. Trained personnel abstract more than 150 institutional variables, and the data are used for trauma studies, epidemiology, injury care, quality of care, and patient safety. The Pediatric ACS-TQIP includes patients aged 18 and younger. Patients with at least one valid trauma ICD-9 code in the range of 800–959.9 (excluding late effects [905–909.9]), superficial injuries (910–924.9), and foreign bodies (930–939.9) were included in the database. Although the TQIP is administered by the ACS, the authors of this study are solely responsible for the analyses and conclusions presented herein. Our study was exempt from Institutional Review Board approval because the pediatric TQIP database contains already de-identified patient data.

1.1. Inclusion and exclusion criteria

We included all pediatric trauma patients (age ≤17) who received pharmacological VTE prophylaxis with either LMWH or UFH during their hospital stay. The type of pharmacological VTE prophylaxis was defined in the TQIP dictionary as "Type of first dose of VTE prophylaxis administered to the patient at your hospital." We excluded all pediatric trauma patients who died within 48 hours of hospital admission, who were transferred to short-term or long-term care hospitals, or who had a known bleeding disorder. We used the ICD-9 diagnosis code (286.9 = other and unspecified coagulation defects) and the TQIP comorbidities variable to capture bleeding disorder patients. Bleeding disorder was defined in the TQIP dictionary as "A group of conditions that result when the blood cannot clot properly."

1.2. Data points

We abstracted and analyzed numerous variables for each patient, including demographic data (age, gender, and race) and, in the emergency department (ED), the Glasgow coma scale (GCS) as well as admission vitals (systolic blood pressure in mmHg [SBP], heart rate per min [HR], respiratory rate per min [RR], and oxygen saturation). We collected data on injury parameters (mechanism of injury, body regions abbreviated injury scale score [AIS], head-AIS, thorax-AIS, abdomen-AIS, and extremity-AIS, and injury severity score [ISS]). In addition, we gathered data regarding the type and verification level of the trauma center, comorbidities (prematurity, congenital anomalies, chronic obstructive pulmonary disease, and diabetes mellitus), and in-hospital complications (sepsis, cardiac arrest, unplanned intubation, acute kidney injury, pneumonia, and urinary tract infection). We extracted data on major surgical procedures, including craniotomy, craniectomy, laparotomy, and thoracotomy as well as blood product transfusions within the first 24 hours of hospital admission (packed red blood cell [pRBC], plasma, and platelet). Finally, we collected data regarding the type of thromboprophylactic agent used (LMWH or UFH), the timing of the first dose of thromboprophylaxis, thromboembolic events (deep vein thrombosis [DVT] and pulmonary embolism [PE]), inpatient mortality, in-hospital length of stay (LOS), and intensive care unit (ICU) LOS among survivors.

1.3. Patient stratification

Patients were stratified into two groups based on the thromboprophylaxis agents they received (LMWH vs UFH). We sub-stratified our patient population by age. The first group included patients aged 0–9. The second group included patients aged 10–14, and the third group included patients aged 15–17. The sub-stratification of our sample population into these three cohorts was derived from several studies included in the review underlying the joint statement between the EAST and the PTS regarding the use of venous thromboembolism prophylaxis in pediatric trauma patients [5,12,26–28].

1.4. Outcomes

Our primary outcomes of interest were VTE events (PE, DVT) and mortality. Secondary outcomes were hospital and ICU LOS among the survivors. We also looked into an unplanned return to the operating room as well as a craniectomy or craniotomy after 24 hours of hospital admission as surrogate measures of a bleeding complication due to VTE prophylaxis. According to the TQIP dictionary, an unplanned return to the operating room occurs "after initial operative management for a similar or related previous procedure." We used ICD 9 codes to abstract data regarding craniectomy (01.25) and craniotomy (01.24).

1.5. Missing data analysis

Overall, 4% of the data was missing. It was homogeneously distributed across the different age groups, and it did not cluster in specific variables. To account for the missing data in our dataset, we performed a missing value analysis. The original data were analyzed for random missing points using Little's missing completely at random test. Multiple imputations using a missing value analysis technique were performed: the Markov chain Monte Carlo method was used, and five iterations were produced.

1.6. Statistical analysis

We performed propensity score matching, which is a well-established method to control for confounding factors. It allows us to get two comparable groups for which outcomes of interest can be analyzed with minimal confounding bias. Using a logistic regression model, a propensity score was generated for each patient based on confounding factors. The two groups were matched using the nearest neighbor method without replacement. Pediatric trauma patients who received UFH as thromboprophylaxis were matched to the patients who received LMWH in a 1:1 ratio for demographics, admission vitals, injury parameters, type and verification of trauma center, in-hospital complications, comorbidities, time to prophylaxis, major operative interventions, and transfusion of blood products within 24 hours. Patients in each group were matched based on their propensity scores within 0.00001 of the estimated score.

Data were reported as a mean with standard deviation for all normally distributed continuous variables, and all non-normally distributed continuous variables were summarized using a median and an interquartile range. Categorical variables were reported as proportions. To compare the baseline characteristics and the outcomes between the two study groups, we used the independent t-test to compare the means and the Mann-Whitney *U* test to compare the medians. Categorical variables were compared using Pearson's chi-square test. All the statistical analyses were performed using the Statistical Package for Social Services (SPSS, version 23; SPSS, Inc., Armonk, NY).

2. Results

We identified 90,862 pediatric trauma patients, out of which 3,934 received LMWH or UFH as a thromboprophylactic agent. Among those patients, 46 died within 48 hours of hospital admission, 19 had a bleeding disorder, and 63 were transferred to other inpatient facilities. The sample was then stratified into three age groups: 477 patients aged 0–9, 730 patients aged 10–14, and 2,599 patients aged 15–17. The unmatched data of patients before performing propensity-matched analysis are summarized in Table 1. The two groups in the unmatched data were significantly different from each other in terms of admission vitals, injury parameters, trauma center type, trauma center verification level, comorbidities, in-hospital complications, time to prophylaxis, and blood product transfusions. After performing propensity score matching there was no significant difference in the variables of interest between the matched cohorts. The characteristics of the matched cohorts are summarized in Table 2.

In patients 0–9 years old, there was no significant difference in DVT ($p = 0.47$), PE ($p = 0.31$), or mortality ($p = 0.65$) between the two treatment cohorts. Hospital and ICU LOS among the survivors was also the same between the two cohorts in this age group.

In patients 10–14 years old, the incidence of DVT was significantly lower in those who received LMWH compared to those who received UFH (1.6 % vs. 5.2 %; $p = 0.02$). There was no difference in the incidence of PE between the two groups ($p = 0.15$). LMWH was associated with lower mortality compared to UFH (1.6 % vs. 4.8 %; $p = 0.04$). The hospital LOS among survivors was significantly lower in patients who received LMWH compared to those who received UFH ($p < 0.01$). There was no significant difference in ICU LOS among survivors between the two groups ($p = 0.60$).

In patients, 15–17 years old, the incidence of DVT (1.2 % vs. 3.1 %; $p = 0.03$) and PE (0 % vs. 0.6 %; $p = 0.04$) was significantly lower in those who received LMWH compared to those who received UFH. LMWH was associated with lower mortality compared to UFH (1.2 % vs. 2.9 % $p = 0.04$). The hospital LOS was significantly lower in patients who received LMWH compared to those who received UFH ($p < 0.01$). There was no significant difference in ICU LOS among survivors between the two groups ($p = 0.02$).

The overall incidence of VTE in our study population is 2.7%. The incidence of DVT was significantly lower in patients who received LMWH compared to those who received UFH (1.7% vs 3.7 %; $p < 0.01$). There was no difference in the incidence of PE between the two groups (0.1% vs. 0.7 %; $p = 0.05$). LMWH was associated with lower mortality compared to UFH (1.4 % vs 3.6%: $p < 0.01$). Median hospital LOS among survivors was also less in patients who received LMWH

Table 1
Prematch baseline characteristics of the study sample.

Age Group	0–9 years (N = 477)			10–14 years (N = 730)			15–17 years (N = 2599)		
Variable	LMWH (N = 99)	UFH (N = 378)	p-Value	LMWH (N = 478)	UFH (N = 252)	p-Value	LMWH (N = 2111)	UFH (N = 488)	p-Value
Age, y, mean ± SD	3.8 ± 3	3.8 ± 3	0.69	13 ± 1.1	12.1 ± 1.2	0.01	16 ± 0.8	16 ± 0.8	0.35
Male, n (%)	53 (53)	218 (58)	0.45	312 (65)	174 (69)	0.30	1417 (67)	351 (71)	0.04
White, n (%)	61 (61)	246 (65)	0.52	319 (66)	164 (65)	0.65	1291 (61)	219 (59)	0.54
ED vitals									
SBP, mean ± SD	116 ± 19	110 ± 23	0.19	124 ± 20	121 ± 19	0.82	128 ± 22	127 ± 22	0.19
HR, mean ± SD	121 ± 32	124 ± 34	0.59	100 ± 22	102 ± 21	0.68	96 ± 23	95 ± 24	<0.01
O2 Sat, mean ± SD	95 ± 8	93 ± 7	0.40	94 ± 3	94 ± 4	0.52	94 ± 3	96 ± 4	0.02
GCS, median [IQR]	14 [8–15]	9 [4–15]	<0.01	15 [14–15]	15[6–15]	<0.01	15 [8–15]	15 [7–15]	0.75
Injury characteristics									
Blunt, n (%)	74 (74)	290 (77)	0.34	366 (76)	188 (75)	0.87	1571 (74)	369 (75)	0.84
ISS, median [IQR]	16 [9–27]	21 [10–29]	<0.01	10 [6–20]	17 [9–29]	<0.01	10 [8–19]	14 [9–26]	<0.01
Head-AIS, median [IQR]	4 [3–4]	4 [3–5]	0.05	2 [1–4]	3 [3–4]	<0.01	3 [2–3]	3 [2–4]	<0.01
Thorax-AIS, median [IQR]	3 [2–3]	3 [2–3]	0.97	3 [2–3]	3 [2–3]	0.27	3 [2–3]	3 [2–3]	0.87
Abdomen-AIS median [IQR]	2 [1–4]	3 [2–4]	0.66	2 [1–3]	3 [2–4]	0.13	2 [2–3]	2 [2–3]	0.84
Extremity-AIS, median [IQR]	3 [1–3]	2 [1–3]	0.05	2 [2–3]	2 [2–3]	0.07	2 [2–3]	2 [1–3]	<0.01
Pediatric trauma level 1, n (%)	42(42)	46 (38)	0.49	162 (34)	109 (43)	0.13	771 (36)	211 (43)	<0.01
Pediatric trauma level 2, n (%)	19 (19)	63 (16)	0.55	152 (31)	48 (19)	0.01	543 (26)	105 (21)	0.05
Adult trauma level 1, n (%)	36 (36)	163 (43)	0.37	258 (54)	111 (44)	0.11	156 (74)	282 (58)	<0.01
Adult trauma level 2, n (%)	4 (4)	8 (2)	0.22	18 (3.8)	15 (6.0)	0.17	93 (4.4)	40 (8.2)	0.01
In-hospital complications									
Sepsis, n (%)	2(2)	4 (1.1)	0.44	1 (0.2)	3 (1.2)	0.08	7 (0.3)	2 (0.4)	0.79
Cardiac arrest, n (%)	2 (2)	5 (1.3)	0.60	3 (0.6)	4 (1.6)	0.20	6 (0.4)	4 (0.8)	0.19
Unplanned intubation, n (%)	3 (3)	6 (1.6)	0.34	6 (1.3)	7 (2.8)	0.13	12 (0.6)	11 (2.3)	0.01
Acute kidney injury, n (%)	0	3 (0.8)	0.37	0	2 (0.8)	0.41	6 (0.4)	4 (0.8)	0.19
Pneumonia, n (%)	9 (9)	12 (3.2)	0.01	7 (1.5)	10 (4)	0.33	31 (1.5)	19 (3.9)	<0.01
Urinary tract infection, n (%)	5 (5)	7 (7)	0.70	6 (13)	4 (1.6)	0.74	16 (0.8)	7 (1.4)	0.15
Comorbidities									
Prematurity, n (%)	9 (9)	18 (4.8)	0.97	6 (1.3)	2 (0.8)	0.56	5 (0.2)	2 (0.4)	0.50
COPD, n (%)	0	3 (0.8)	0.37	10 (2.1)	6 (2.4)	0.80	14 (2.1)	6 (1.2)	0.21
Congenital, n (%)	5 (5)	12 (3.2)	0.37	14 (2.9)	6 (2.4)	0.66	15 (0.7)	9 (1.8)	0.19
Diabetes mellitus, n (%)	1 (1)	1 (1)	1	4 (0.8)	1 (0.4)	0.49	11 (0.5)	5 (1.0)	0.20
Hours to prophylaxis, median [IQR]	37 [15–74]	20 [14–98]	0.06	39 [18–84]	28 [12–83]	<0.01	25 [12–48]	22 [10–52]	0.26
Laparotomy, n (%)	4 (4)	16 (4.2)	0.93	9 (1.9)	7 (2.8)	0.43	72 (3.2)	24 (4.9)	0.13
Thoracotomy, n (%)	0	1 (0.2)	0.60	1 (0.2)	0	0.47	5 (0.2)	4 (0.8)	0.48
Transfusion in 24 hours									
pRBC, n (%)	21 (21)	93 (24)	0.48	50 (10)	39 (15)	0.04	153 (7.2)	78 (16)	<0.01
Plasma, n (%)	11 (12)	53 (14)	0.45	32 (6.7)	27 (11)	0.04	106 (5.0)	50 (10)	<0.01
Platelet, n (%)	7 (7)	23 (6)	0.71	14 (2.9)	16 (6.3)	0.02	57 (2.7)	31 (6.5)	<0.01

SD, standard deviation; n, number; ED, emergency department; SBP, systolic blood pressure; HR, Heart rate; RR, Respiratory rate; O2, oxygen; GCS, Glasgow Coma Scale; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; LOS, length of stay; d, Days; pRBC, packed RBC, LMWH, low Molecular weight heparin; UFH, unfractionated heparin.

Table 2
Post-match baseline characteristics of the study sample.

Age group	0–9 years (N = 198)			10–14 years (N = 504)			15–17 years (N = 976)		
Variable	LMWH (N = 99)	UFH (N = 99)	p-Value	LMWH (N = 252)	UFH (N = 252)	p-Value	LMWH (N = 488)	UFH (N = 488)	p-Value
Age, y, mean ± SD	3.8 ± 3	3.7 ± 3	0.79	12.6 ± 1.1	12.1 ± 1.2	0.01	16 ± 0.7	16 ± 0.8	0.39
Male, n (%)	53 (53)	57 (57)	0.56	158 (62)	174 (69)	0.13	316 (65)	351 (71)	0.54
White, n (%)	61 (61)	61 (61)	1.00	161 (64)	164 (65)	0.78	300 (61)	219 (59)	0.55
ED Vitals									
SBP, mean ± SD	116 ± 19	117 ± 23	0.77	121 ± 22	121 ± 19	0.51	127 ± 22	127 ± 22	0.14
HR, mean ± SD	121 ± 32	116 ± 34	0.72	102 ± 23	102 ± 21	0.20	96 ± 22	95 ± 24	0.62
O_2 Sat, mean ± SD	95 ± 8	93 ± 7	0.06	91 ± 3	93 ± 4	0.45	96 ± 3	96 ± 4	0.39
GCS, median [IQR]	14 [8–15]	14 [8–15]	0.77	15 [7–15]	15[6–15]	0.15	15 [7–15]	15 [7–15]	0.75
Injury characteristics									
Blunt, n (%)	74 (74)	77 (77)	0.34	182 (72)	188 (75)	0.64	385 (78)	369 (75)	0.45
ISS, median [IQR]	16 [9–27]	15 [9–25]	0.90	16 [9–26]	17 [9–29]	0.32	14 [8–19]	14 [9–26]	0.61
Head-AIS, median [IQR]	4 [3–4]	4 [3–4]	0.76	3 [3–4]	3 [3–4]	0.19	3 [2–4]	3 [2–4]	0.33
Thorax-AIS, median [IQR]	3 [2–3]	3 [2–3]	0.18	3 [2–3]	3 [2–3]	0.23	3 [2–3]	3 [2–3]	0.39
Abdomen-AIS median [IQR]	2 [1–4]	2 [1–3]	0.34	2 [2–4]	3 [2–4]	0.45	2 [2–3]	2 [2–3]	0.92
Extremity-AIS, median [IQR]	3 [1–3]	3 [1–3]	0.37	2 [2–3]	2 [2–3]	0.54	2 [1–3]	2 [1–3]	0.43
Pediatric trauma level 1, n (%)	42(42)	50 (50)	0.24	90 (35)	109 (43)	0.13	217 (44)	211 (43)	0.69
Pediatric trauma level 2, n (%)	19 (19)	14 (14)	0.34	57 (22)	48 (19)	0.01	113 (23)	105 (21)	0.53
Adult trauma level 1, n (%)	36 (36)	45 (45)	0.19	104 (41)	111 (44)	0.11	285 (58)	282 (57)	0.80
Adult trauma level 2, n (%)	4 (4)	1 (1)	0.17	13 (5.2)	15 (6.0)	0.17	38 (7.4)	40 (8.2)	0.81
In-hospital complications									
Sepsis, n (%)	2(2)	1 (1)	0.56	1 (0.4)	3 (1.2)	0.08	1 (0.2)	2 (0.4)	0.56
Cardiac arrest, n (%)	2 (2)	3 (3)	0.65	1 (0.4)	4 (1.6)	0.20	4 (0.8)	4 (0.8)	1
Unplanned intubation, n (%)	3 (3)	2 (2)	0.65	5 (2)	7 (2.8)	0.13	10 (2.0)	11 (2.3)	0.14
Acute kidney injury, n (%)	0	0	0	0S	2 (0.8)	0.82	4 (0.8)	4 (0.8)	1
Pneumonia, n (%)	9 (9)	7 (7)	0.60	5 (2)	10 (4)	0.19	21 (4.3)	19 (3.9)	0.74
Urinary tract infection, n (%)	5 (5)	5 (5)	0.1	3 (1.2)	4 (1.6)	0.74	4 (0.8)	7 (1.4)	0.36
Comorbidities									
Prematurity, n (%)	9 (9)	11 (11)	0.63	2 (0.8)	2 (0.8)	0.56	1 (0.2)	2 (0.4)	0.56
COPD, n (%)	0	0	0	8 (3.2)	6 (2.4)	0.80	6 (1.2)	6 (1.2)	1
Congenital, n (%)	5 (5)	5 (5)	1	6 (2.4)	6 (2.4)	1	3 (0.6)	9 (1.8)	0.80
Diabetes mellitus, n (%)	1 (1)	1 (1)	1	1 (1)	1 (1)	1	1 (0.2)	5 (1.0)	0.10
Hours to prophylaxis, median [IQR]	37 [15–74]	26 [10–93]	0.27	35 [18–80]	28 [12–83]	0.13	28 [13–64]	22 [10–52]	0.22
Laparotomy, n (%)	4 (4)	2 (2)	0.17	6 (2.4)	7 (2.8)	0.79	18 (3.6)	24 (4.9)	0.13
Thoracotomy, n (%)	0	0	0	0	0	0	2 (0.4)	4 (0.8)	0.41
Transfusion in 24 hours									
pRBC, n (%)	21 (21)	15 (15)	0.26	34 (13)	39 (17)	0.45	63 (13)	78 (16)	0.17
Plasma, n (%)	11 (12)	18 (18)	0.46	21 (8.3)	27 (11)	0.36	34 (7)	50 (10)	0.08
Platelet, n (%)	7 (7)	4 (4)	0.35	11 (4.4)	16 (6.3)	0.24	21 (4)	31 (6)	0.15

SD, standard deviation; n, number; ED, emergency department; SBP, systolic blood pressure; HR, heart rate; RR, respiratory rate; O2, oxygen; GCS, Glasgow Coma Scale; IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ISS, Injury Severity Score; AIS, Abbreviated Injury Scale; LOS, length of stay; d, days; pRBC, packed RBC, LMWH, Low molecular weight heparin; UFH, unfractionated heparin.

compared to those received UFH (7 % vs. 9 %: $p < 0.01$). There was no significant difference in ICU LOS among the survivors between the two groups ($p = 0.08$). Table 3 demonstrates the difference in outcomes between the groups.

There was no significant difference in an unplanned return to the operating room or having a craniotomy or craniectomy after 24 hours of hospital admission among patients who received LMWH compared to those who received UFH. Table 4 demonstrates the univariate analysis of operative interventions between the two groups.

3. Discussion

The results of our study demonstrate that LMWH is associated with increased survival, a reduced risk of DVT, and decreased in-hospital LOS among survivors when compared to UFH in pediatric trauma patients aged 10–17. We did not find any difference in the incidence of PE or ICU LOS between the two prophylactic modalities. In our study, we specifically looked into the survival of pediatric trauma patients because of the observed potential benefits of LMWH documented in various

Table 3
Univariate analysis of outcomes.

Age groups	0–9 years (N = 198)			10–14 years (N = 504)			15–17 years (N = 976)			Overall (1,678)		
Outcomes	LMWH (N = 99)	UFH (N = 99)	p-Value	LMWH (N = 252)	UFH (N = 252)	p-Value	LMWH (N = 488)	UFH (N = 488)	p-Value	LMWH (N = 839)	UFH (N = 839)	p-Value
DVT, n (%)	4 (4)	2 (2)	0.47	4 (1.6)	13 (5.2)	**0.02**	6 (1.2)	16 (3.1)	**0.03**	14 (1.7)	32 (3.7)	**<0.01**
PE, n (%)	1 (1)	0	0.31	0	2 (0.8)	0.15	0	4 (0.6)	**0.04**	1 (0.1)	6 (0.7)	0.05
Mortality, n (%)	2 (2)	3 (3)	0.65	4 (1.6)	12 (4.8)	**0.04**	6 (1.2)	15 (2.9)	**0.04**	12 (1.4)	30 (3.6)	**<0.01**
ICU LOS, d, median [IQR]	10 [3–18]	8 [4–13]	0.67	5 [3–10]	6 [4–12]	0.60	5 [3–11]	6 [3–12]	0.22	5 [3–12]	6 [3–12]	0.08
Hospital LOS, d, median [IQR]	14 [5–28]	12 [5–21]	0.49	7 [4–14]	10 [5–20]	**<0.01**	7 [3–13]	9 [4–16]	**<0.01**	7 [3–14]	9 [4–18]	**<0.01**

LMWH, low molecular weight heparin; UFH, unfractionated heparin; n, number; DVT, deep vein thrombosis; PE, pulmonary embolism; d, days; LOS, length of stay.

Table 4
Univariate analysis of operative interventions.

Age groups	0–9 years (N = 198)			10–14 years (N = 504)			15–17 years (N = 976)		
Outcomes	LMWH (N = 99)	UFH (N = 99)	p-Value	LMWH (N = 252)	UFH (N = 252)	p-Value	LMWH (N = 488)	UFH (N = 488)	p-Value
Unplanned return to OR, n (%)	1 (1)	4 (4)	0.17	2 (0.8)	5 (2)	0.25	7 (1.4)	6 (1.2)	0.78
Craniotomy after 24 hours, n (%)	1 (1)	0	0.31	0	2 (0.8)	0.15	4 (0.8)	3 (0.6)	0.70
Craniectomy after 24 hours, n (%)	0	1 (1)	0.31	2 (2)	2 (2)	1	3 (0.6)	1 (0.2)	0.31

LMWH, low molecular weight heparin; UFH, unfractionated heparin; n, number; OR, operating room.

studies conducted in both adult trauma patients and animal models [22,23,29]. LMWH has been shown to have immunomodulatory and neuroprotective properties in animal models, and recent human studies have supported those conclusions [21–23,30–33]. In addition to the proposed immunomodulation and anti-inflammatory effect attributed to LMWH, other favorable pharmacodynamic and pharmacokinetic properties of LMWH, such as a predictable anticoagulation response, a longer plasma half-life, and a reduced risk of complications may significantly contribute to the perceived survival benefit seen in the pediatric trauma patients [13,15,34–37].

Literature investigating thromboprophylaxis in pediatric patients is very limited. Recent work from our group indicated that pediatric trauma patients receiving LMWH demonstrated a survival benefit within our hospital [38]. In that study, we found that LMWH was associated with improved survival compared to UFH (OR = 1.11; 95%CI [1.05–1.20]; p = 0.04). These results are in line with our current study in terms of survival benefit. However, there was no significant difference regarding the incidence of VTE in our earlier institutional study. There is growing evidence that LMWH may be more effective in reducing VTE than UFH after major trauma, and multiple studies support our results in the adult trauma population [24,39]. A study conducted by Luis et al. showed that LMWH appeared to reduce the risk of DVT compared to UFH (RR = 0.68; 95%CI [0.50–0.94]) [39]. Another landmark randomized clinical trial conducted by Greets et al. also showed that LMWH is more effective than UFH in preventing VTE after major trauma in adults, supporting our current results [40].

In our study, we found that LMWH is not associated with the reduced risk of PE when compared to UFH in the pediatric trauma population. One possible explanation of this result is the limited incidence of PE in our study population (N, % = 7, 0.3%). Although the incidence of PE is less in the LMWH group compared to the UFH group (0.1% vs 0.7%), the results do not reach the statistical significance level due to the low incidence of PE (p = 0.05). Nonetheless, multiple studies in the literature show that LMWH is associated with a lower rate of PE compared to UFH, even though all of those studies were conducted in adult trauma patients [23,38].

We divided our study population based on age because the recommendation of VTE prophylaxis in the pediatric population is principally dependent on age. Therefore, we examined age-specific incidence of VTE and the effect of VTE prophylaxis in the specific age groups. For prepubertal children, guidelines conditionally recommend against routine pharmacologic prophylaxis [12]. Additionally, demographics, ED vitals, GCS, injury parameters, operative interventions, time to prophylaxis, and transfusion requirements were significantly different among the two treatment groups. To make the two treatment groups comparable, we opted to divide our study population into three different age groups.

The choice of thromboprophylaxis agent could be a substantial source of bias, as there is a significant difference in the baseline characteristics between the two unmatched cohorts. We performed propensity score matching, which is a robust statistical method to control for all measurable confounders within the scope of the utilized database to control confounding bias. We realize that the use of propensity score matching was at the cost of sample size, but in order to provide the unbiased results after minimizing the difference between the two treatment cohorts, we opted to use this statistical technique.

In our study, LMWH was not associated with an increase in survival or a reduced incidence of VTE when compared to UFH in the prepubertal age group. One possible reason for this finding is the limited sample size in this specific pediatric trauma population. LMWH was associated with increased survival, a reduced incidence of DVT, and a decreased in-hospital LOS for patients aged 10 to 17 years. In all three age subgroups, we did not find any difference in the ICU LOS among the survivors with either thromboprophylactic agents. This can be attributed to the fact that the two groups (LMWH vs UFH) had comparable injury parameters, ED vitals, ED GCS, comorbidities, in-hospital complications, major surgical interventions, and transfusion of blood products.

The limitations of this study are attributed to the retrospective nature of the analysis, the effect of unmeasurable confounding factors (bleeding risk and complications), and erroneous database entries. Due to the retrospective nature of the study, we can only demonstrate an association and not necessarily causality. To look into bleeding complications within the two cohorts due to the specific thromboprophylactic agent used, we included unplanned emergency surgical interventions and major neurosurgical intervention craniotomy or craniectomy after 24 hours of hospital admission as a surrogate measure of a bleeding complication. Although these measures do not precisely depict the bleeding complications, but within the scope of the utilized database these interventions are the closest measure of a bleeding complication. The TQIP database does not provide information regarding the dose, frequency, duration of the treatment, or crossover from one thromboprophylactic agent to another. We are also unable to capture data regarding the use of mechanical prophylaxis in our study cohort. The reported rate of DVT is influenced by screening practices in different institutes, and we did not attempt to collect data on or correct for this surveillance bias [41]. Because our study was restricted to a patient's in-hospital stay, our results only pertain to in-hospital outcomes. The exact cause of death is not recorded in the TQIP database. The finding that LMWH was associated with increased survival cannot be linked to a specific physiological complication or event that resulted in mortality. In addition, we were unable to obtain data on why one form of prophylaxis was used over another.

As a common, costly, and often lethal in-hospital complication that results in approximately 100,000 deaths annually in the United States, prevention of VTE is essential to improve quality of care. Currently, however, there is uncertainty about the optimal thromboprophylactic agent to prevent VTE in pediatric trauma patients. Our study provides an answer regarding this question based on an analysis of a multi-institutional database.

4. Conclusion

The present study has shown that LMWH is associated with increased survival, lower rates of DVT, and decreased hospital LOS compared to UFH among pediatric trauma patients age 10–17 years. Further prospective studies should be done to confirm the observed potential benefit of LMWH in the pediatric trauma population.

Author contributions

All authors participated in data interpretation and manuscript preparation

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Conflict of interest

There are no identifiable conflicts of interests to report

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