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Timing of venous thromboembolism chemoprophylaxis with major surgery of lower-extremity long bone fractures

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BACKGROUND: There is debate on the need to withhold chemical venous thromboembolism (VTE) prophylaxis in patients requiring major orthopedic surgery. We hypothesized that the incidence of clinically significant hemorrhage (CSH) does not differ by the timing of prophylaxis in such patients.

METHODS: This was a multicenter, retrospective cohort study conducted at five US trauma centers that included trauma patients admitted between January 1, 2018, to March 1, 2020, requiring surgical fixation of the femoral shaft, hip, or tibia and received VTE chemoprophylaxis during the hospitalization. Exclusions were major and moderate head or spinal injuries, chronic anticoagulant use, or multiple long bone surgeries. Timing of VTE chemoprophylaxis was examined as four groups: (1) initiated preoperatively without interruption for surgery; (2) initiated preoperatively but held perioperatively; (3) initiated within 12 hours postoperatively; and (4) initiated >12 hours postoperatively. The primary outcome was incidence of CSH (%), defined as overt hemorrhage within 24 hours postoperative that was actionable. Multivariate logistic regression evaluated differences in CSH based on timing of VTE chemoprophylaxis.

RESULTS: There were 786 patients, and 65 (8.3%) developed a CSH within 24 hours postoperatively. Nineteen percent of patients received chemoprophylaxis preoperatively without interruption for surgery, 13% had preoperative initiation but dose(s) were held for surgery, 21% initiated within 12 hours postoperatively, and 47% initiated more than 12 hours postoperatively. The incidence and adjusted odds of CSH were similar across groups (11.3%, 9.1%, 7.1%, and 7.3% respectively; overall $p = 0.60$). The incidence of VTE was 0.9% and similar across groups ($p = 0.47$); however, six of seven VTEs occurred when chemoprophylaxis was delayed or interrupted.

CONCLUSION: This study suggests that early and uninterrupted VTE chemoprophylaxis is safe and effective in patients undergoing major orthopedic surgery for long bone fractures. (*J Trauma Acute Care Surg.* 2023;94: 169–176. Copyright © 2022 The Author(s). Published by Wolters Kluwer Health, Inc.)

LEVEL OF EVIDENCE: Therapeutic/Care Management; Level IV.

KEY WORDS: VTE chemoprophylaxis; orthopedic surgery; postoperative hemorrhage.

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Approximately 40% of all trauma patients present with lower-extremity injuries.[1] A lower-extremity long-bone fracture categorizes a patient into the highest-possible venous thromboembolism (VTE) risk category.[2] Current clinical practice is to prevent the formation of VTE in high-risk patients by administration of either mechanical or pharmacological prophylaxis to reduce the chance of blood clot formation.[3–5] However, VTE chemoprophylaxis is associated with a small but significant increased risk of bleeding.[6–8] For this reason, VTE chemoprophylaxis is often halted in advance of a planned surgical procedure, or initiation is delayed until after a surgical procedure is performed.

The 2021 consensus document of the American Association for the Surgery of Trauma (AAST) critical care committee provides a series of recommendations on VTE thromboprophylaxis in trauma patients; chief among them are that early initiation is standard of care and continuous therapy is essential.[9] Absolute indications for holding VTE chemoprophylaxis for surgery are active hemorrhage and recent spinal or intracranial surgery; outside these events, there are little to no data supporting the notion that perioperative chemoprophylaxis leads to greater bleeding events. As such, the guideline considers impending surgery as a relative indication for holding VTE chemoprophylaxis.

Because the timing of VTE chemoprophylaxis for major orthopedic surgery is not supported by appropriately powered studies and remains contentious, this study sought to investigate the safety of VTE chemoprophylaxis in relation to long bone fracture surgery, as measured by the incidence of postoperative bleeding events. We hypothesized that the incidence of clinically significant hemorrhages (CSHs) is not significantly different by VTE chemoprophylaxis timing in patients undergoing major orthopedic surgery.

PATIENTS AND METHODS

Design, Setting, Population

This retrospective multicenter cohort study included five level I trauma centers in the United States. Institutional review board approval was obtained with a waiver of informed consent. The Strengthening the Reporting of Observational Studies in Epidemiology recommendations were followed for reporting (Supplemental Digital Content, Supplementary Data 1, http://links.lww.com/TA/C666). Variables were collected from the individual trauma registries by dedicated trauma registrars and from the electronic health record (EHR) by clinical study coordinators at each participating site.

The primary aim was to investigate the timing of VTE chemoprophylaxis on clinically significant postoperative bleeding events (CSH). Secondary aims were to investigate the timing of VTE chemoprophylaxis on incidence of VTEs and other clinical outcomes.

Inclusion criteria were as follows: admission to a participating trauma center between January 1, 2018, and March 1, 2020; index admission for femur (hip or shaft) or tibia fracture;

Submitted: May 4, 2022, Revised: July 28, 2022, Accepted: August 11, 2022, Published online: August 24, 2022.

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This study was presented at the SCCM 2022 meeting, April 2022 (virtual).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

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DOI: 10.1097/TA.0000000000003773

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surgical fixation of the femur or tibia; 18 years or older; receipt of Unfractionated heparin (UFH) or Low molecular weight heparin (LMWH) for VTE chemoprophylaxis during the index hospitalization (>1 dose). Exclusion criteria were moderate or severe head or spinal injury, as identified by Abbreviated Injury Scale (AIS) score of ≥2 to the head or spine regions, and patients on chronic anticoagulation before admission. In addition, 30 patients undergoing multiple long bone surgeries were excluded.

Outcomes

The primary outcome of interest was the incidence (%) of a CSH, which was defined as overt hemorrhage within 24 hours postoperative that was actionable (i.e., blood transfusion associated with a decrease in hemoglobin level of at least 2 g/dL or for intraoperative bleeding, wound dehiscence, compartment syndrome, return to the operating room). Bleeding events were abstracted from the EHR and related to surgeries to repair long bone fracture.

Secondary outcomes were the incidence of symptomatic VTE during the acute hospitalization period, total observed intraoperative blood loss (mL), hospital length of stay (LOS), intensive care unit (ICU) admission, and mortality. One of the sites routinely performs duplex screening on admission and at Day 7. Asymptomatic DVTs were identified on admission duplex screening (n = 6) or Day 7 duplex screen (n = 1). These asymptomatic VTEs identified on routine VTE surveillance were not included in the secondary outcome of symptomatic VTE.

Study Covariates

The primary independent variable was timing of VTE chemoprophylaxis, which was abstracted from the EHR. Patients were categorized into four groups: (1) initiated preoperatively without interruption for surgery; (2) initiated preoperatively, but preoperative dose(s) were held for orthopedic surgery; (3) initiated within 12 hours postoperatively; and (4) initiated >12 hours postoperatively. Timing of VTE chemoprophylaxis was defined in relation to the long bone surgery.

Additional covariates from the registry included patient demographics (age, sex, race, preinjury antiplatelet therapy) and clinical descriptors (cause of injury, emergency department [ED] vital signs, ED Glasgow Coma Scale [GCS] score). Additional covariates abstracted from the EHR included surgical and prophylactic descriptors (time to surgery, time in surgery, time of ambulation determined by physical therapy/occupational therapy notes, inferior vena cava filter use, sequential compression device use, surgical procedures) and hemoglobin levels (initial reading, preoperative level, first postoperative level, and lowest documented level). We also evaluated the change in hemoglobin, defined as postoperative − preoperative values.

Statistical Analysis

This study was performed using a power analysis of the primary endpoint of CSHs. The sample size of at least 612 patients was calculated using a Fisher's exact conditional test for two proportions with the following assumptions: α of 0.05, power of 80%, and clinically significant bleeding based on previously reported rates of patients undergoing elective hip surgery: major bleeding occurred in 1.4% of the preoperative VTE chemoprophylaxis group, 6.3% of the perioperative VTE chemoprophylaxis group, and 2.5% of the postoperative VTE chemoprophylaxis group.[10] This study was not powered to examine secondary outcomes.

Analyses were performed with SAS (SAS Institute, Cary NC). A significance level of $p = 0.05$ was used. There was no imputation of missing covariates, and no observations were missing exposure status or outcomes. χ^2 Tests were used to determine whether significant differences existed between the four VTE chemoprophylaxis exposure groups with the study outcomes of CSH, VTE, ICU admission, and in-hospital mortality, as well as categorical covariates. Wilcoxon rank-sum tests were used to determine differences between the four VTE chemoprophylaxis exposure groups in total operative blood loss (mL) and hospital LOS (days), as well as continuous covariates. Interactions were examined with Cochran-Mantel-Haenszel tests.

Multivariate logistic regression was used to determine variables that were independently associated with the primary outcome of postoperative CSH within 24 hours. Covariates that had an association with the exposure or outcome with $p < 0.05$ were adjusted for in the model. The exposure referent group was VTE chemoprophylaxis initiation >12 hours postoperative.

A second multivariate logistic regression model was performed as a sensitivity analysis examining the outcome of postoperative CSH within 48 hours.

We also used multivariate logistic regression to examine subgroups, presented as a Forest plot. Subgroups included fracture location (tibia, femoral shaft, femoral hip), and number of surgical procedures (long bone only, long bone plus additional surgical procedures). For the Forest plot, VTE chemoprophylaxis initiation >12 hours postoperative was the referent group and all other exposure groups were combined.

RESULTS

The total population included 786 patients, evenly distributed across facilities (% admissions by facility ranged from 15%

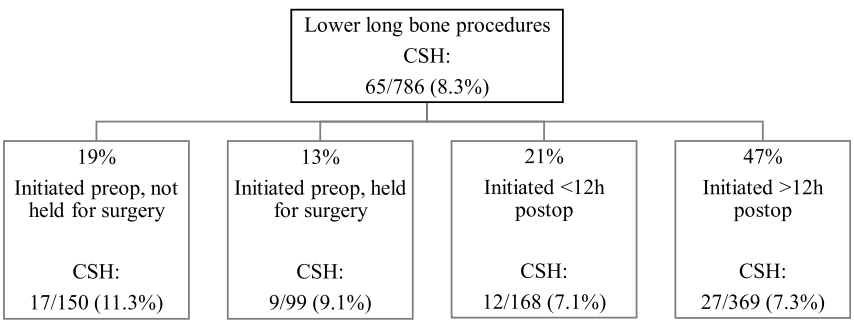

Figure 1. Association between timing of VTE chemoprophylaxis and CSH. Preop, preoperative; Postop, postoperative.

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TABLE 1. Demographics and Injury Characteristics by Timing of VTE Chemoprophylaxis

Covariate, n (%) or Median (IQR)	Initiated Preop, Not Held for Surgery, n = 150	Initiated Preop, Held for Surgery, n = 99	Initiated <12 h Postop, n = 168	Initiated >12 h Postop, n = 369	*p*
Age ≥65 y	105 (70.0)	63 (63.6)	109 (64.9)	229 (62.1)	0.40
Male sex	68 (45.3)	40 (40.4)	62 (36.9)	148 (40.1)	0.50
White race	129 (86.0)	81 (81.8)	144 (85.7)	326 (88.4)	0.38
Fall injury	124 (82.7)	79 (79.8)	129 (76.8)	271 (73.4)	0.13
ED GCS score <15	18 (12.4)	13 (13.8)	18 (11.3)	50 (13.6)	0.86
Abnormal ED SBP <90 mm Hg	1 (0.7)	1 (1.1)	2 (1.2)	5 (1.4)	0.93
Preinjury antiplatelet therapy	43 (28.9)	23 (23.5)	38 (22.6)	100 (27.3)	0.52
>1 Surgical procedure*	10 (6.7)	11 (11.1)	21 (12.5)	47 (12.7)	0.24
Other orthopedic procedure	9 (6.0)	10 (10.1)	19 (11.3)	38 (10.3)	0.39
Nonorthopedic procedure	1 (0.7)	2 (2.0)	2 (1.2)	10 (2.7)	0.40
Tibial fracture	33 (22.0)	35 (35.4)	39 (23.2)	80 (21.7)	**0.04**
Femoral shaft fracture	50 (33.3)	30 (30.3)	51 (20.4)	106 (28.7)	0.78
Femoral hip fracture	67 (44.7)	34 (34.3)	78 (46.4)	184 (49.9)	0.05
Open fracture	3 (2.0)	3 (3.0)	15 (8.9)	28 (7.6)	**0.02**
Open, Gustilo grade III	0 (0)	0 (0)	1 (0.6)	8 (2.2)	0.08
Hours to start VTE prophylaxis	6.1 (4–9)	7.5 (5–13)	24.0 (15–29)	38.3 (29–44)	**<0.001**
Hours from arrival to surgery	19.9 (16–24)	27.9 (22–55)	14.5 (7–20)	16.9 (9–23)	**<0.001**
Total hours in surgery	0.6 (0.4–1.1)	1.1 (0.6–1.7)	0.8 (0.6–1.6)	1.1 (0.7–1.8)	**<0.001**
Preoperative SCDs	40 (26.7)	54 (54.6)	98 (58.3)	263 (71.3)	**<0.001**
Postoperative SCDs	79 (52.7)	74 (74.5)	104 (61.9)	304 (82.4)	**<0.001**
Hemoglobin values					
Initial value	13.6 (12–15)	13.2 (12–15)	13.6 (12–14)	13.4 (12–15)	0.67
Preoperative value	12.5 (11–14)	12.4 (11–13)	12.8 (11–14)	12.6 (11–14)	0.08
Postoperative value	10.5 (9–12)	10.7 (9–12)	10.1 (9–12)	10.7 (9–12)	0.33
Lowest value	9.8 (8–12)	9.4 (8–12)	8.8 (8–11)	9.3 (7–11)	0.26
Change in hemoglobin**	−1.8 (−2.8 to −0.7)	−1.4 (−2.3 to −0.5)	−2.3 (−3.1 to −1.3)	−1.9 (−2.8 to −1.2)	**<0.001**

*Surgical procedures in addition to the long bone surgery.
**Change: postoperative − preoperative.
Boldface denotes statistical significance.
Preop, preoperatively; Postop, postoperatively; SBP, systolic blood pressure; SCD, sequential compression device.

to 23%). Demographically, the median (interquartile range [IQR]) age was 70 (52–81) years, 60% were female, 87% were White, and 26% were on preinjury antiplatelet therapy. Injury characteristics included a median (IQR) Injury Severity Score of 9,[9,10] 6% of fractures were open (40 grade I/II, 9 grade III), and 77% of patients had a fall as the cause of injury.

Long bone fractures included tibia (24%), femoral shaft (30%) and femoral hip (46%). The median (IQR) time to long bone surgery was 18 (11–24) hours from admission. In addition, 10% of patients had another orthopedic surgery (e.g., patella, fibula), and 2% of patients had a nonorthopedic surgery.

VTE Chemoprophylaxis

Overall, the median (IQR) time to initiate VTE chemoprophylaxis was 25 (10–38) hours, and the median number of doses received was 5.[4–8] Most patients (93%) received LMWH for chemoprophylaxis, 3% received UFH, and 5% received both LMWH and UFH.

Timing of VTE chemoprophylaxis is shown in Figure 1. Nearly half (47%) of all patients had VTE chemoprophylaxis initiated more than 12 hours postoperatively. One fifth of patients had VTE chemoprophylaxis initiated preoperatively and not held for surgery (19%) or initiated within 12 hours postoperatively (21%). The remaining 13% of patients had VTE chemoprophylaxis initiated preoperatively but held perioperatively.

A comparison of demographics and injury characteristics by timing of VTE chemoprophylaxis is shown in Table 1. There were no differences by timing in age, sex, race, injury cause, fracture location, ED vital signs, types of procedures, or number of procedures. The few significant differences included patients who had preoperative initiation that was held for surgery had a longer time from arrival to surgery (28 hours vs. 14–20 hours in the other exposure groups, $p < 0.001$), while patients who had preoperative initiation that was not held for surgery had a shorter total time in the odds ratio (OR) ($p < 0.001$) than the other exposure groups. Patients who had preoperative initiation (either held or not held for surgery) were also less likely to have open fractures (2–3%) than patients with postoperative initiation (8–9%) ($p = 0.02$). There were no differences in hemoglobin values at any of the evaluated time points, but the change in hemoglobin (postoperative − preoperative) was significantly greater for patients who had initiation within 12 hours postoperatively.

Primary Outcome: CSH Within 24 Hours Postoperative

There were 65 CSHs (8.3%). The median (IQR) time to develop a CSH was 13 (6–20) hours. Most CSHs resulted from

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TABLE 2. Demographics and Injury Characteristics by Development of CSH Within 24 Hours Postoperative

Covariate, n (%) or Median (IQR)	CSH, n = 65	No CSH, n = 721	*p*
Age ≥65 y	55 (84.6)	451 (62.6)	**0.01**
Male sex	22 (33.9)	296 (41.1)	0.26
White race	57 (87.7)	623 (86.4)	0.77
Fall injury	56 (86.2)	547 (75.9)	0.06
ED Glasgow coma score <15	20 (31.8)	79 (11.3)	**<0.001**
ED SBP <90 mm Hg	1 (1.6)	8 (1.1)	0.53
Preinjury antiplatelet therapy	24 (37.5)	180 (25.1)	**0.03**
>1 surgical procedure*	8 (12.3)	81 (11.2)	0.79
Other orthopedic procedure	6 (9.2)	70 (9.7)	0.90
Nonorthopedic procedure	2 (3.1)	13 (1.8)	0.36
Tibial fracture	5 (7.7)	182 (25.2)	**0.002**
Femoral shaft fracture	33 (50.8)	204 (28.3)	**<0.001**
Femoral hip fracture	27 (41.5)	336 (46.6)	0.43
Open fracture	4 (6.2)	45 (6.2)	>0.99
Open, Gustilo grade III	0 (0)	9 (1.3)	>0.99
Hours to VTE chemoprophylaxis	26 (8–39)	25 (10–38)	0.97
Hours to first surgery	18 (13–25)	18 (11–24)	0.43
Total hours in surgery	1.3 (0.7–2.1)	0.9 (0.6–1.6)	**0.04**
Preoperative SCDs	45 (69.2)	410 (56.9)	0.07
Postoperative SCDs	46 (70.8)	515 (71.4)	0.91
Hemoglobin value			
Initial value	11.7 (10–14)	13.5 (12–15)	**<0.001**
Preoperative value	10.6 (9–12)	12.7 (11–14)	**<0.001**
Postoperative value	7.6 (7–9)	10.7 (9–12)	**<0.001**
Lowest value	6.8 (7–8)	9.5 (8–11)	**<0.001**
Change in hemoglobin**	−2.6 (−3.6 to −0.9)	−1.8 (−2.7 to −1.0)	**0.01**

*Surgical procedures in addition to the long bone surgery.
**Change: postoperative − preoperative.
Boldface denotes statistical significance.
SBP, systolic blood pressure; SCD, sequential compression device.

a drop in hemoglobin requiring blood transfusion because of surgical site bleeding (n = 55) or an oozing hemorrhage (n = 7), followed by intraoperative blood transfusion (n = 4), and compartment syndrome (n = 1).

Significant univariate associations with developing a CSH are shown in Table 2 and include older age, ED GCS score of <15, preinjury antiplatelet therapy, tibial fracture, femoral shaft fracture, and a longer time in surgery. There were also significant differences in hemoglobin values at all the evaluated time points, as well as the change in hemoglobin (postoperative − preoperative), with values that were lower for patients with CSH than those who did not have a CSH.

Before adjustment, the incidence of CSH was similar based on timing of VTE chemoprophylaxis ($p = 0.45$; Table 3 and Figure 1).

After adjustment, there were similar odds of CSH by timing of VTE chemoprophylaxis (overall $p = 0.60$; Table 4). Specifically, compared with initiation more than 12 hours postoperatively, the adjusted odds (95% confidence interval) of CSH were similar with initiation within 12 hours postoperative (OR, 1.49 [0.72–3.06]), preoperative initiation that was held for surgery (OR, 0.83 [0.31–2.24]), and when VTE chemoprophylaxis was initiated preoperatively but held perioperatively (OR, 1.24 [0.59–2.62]).

Covariates significantly associated with development of CSH were as follows: femoral shaft fracture (OR, 6.03 [2.04–17.82]); ED GCS score of <15 (OR, 3.82 [2.04–7.15]); 65 years or older (OR, 3.35 [1.40–8.05]); longer total time in surgery (OR, 1.13 [1.04–1.22]), which equates to 13% increased odds with each 30-minute increase; and longer time from arrival to surgery (OR, 1.08 [1.00–1.18]), which equates to 8% increased odds for every 6-hour delay.

Subgroup analyses of the primary endpoint are shown in Figure 2. While the incidence of CSH differed by fracture type (2.7% tibial fracture, 7.4% femoral hip fracture, 13.9% femoral shaft fracture), there was no association between timing of VTE chemoprophylaxis and CSH, by fracture type (Supplemental Digital Content, Supplementary Fig. 1, http://links.lww.com/TA/C667). There was also no interaction between fracture type, timing of VTE chemoprophylaxis, and CSH ($p = 0.47$). After adjustment, there were no subgroups that demonstrated a significant association between timing of VTE chemoprophylaxis and developing a CSH within 24 hours postoperative, including location of fracture and whether there was a surgical procedure in addition to the long bone procedure surgery.

The sensitivity analysis examining CSH within 48 hours postoperative identified no relationship with timing of VTE chemoprophylaxis ($p = 0.95$; Table 3). After adjustment, there was no association between CSH within 48 hours postoperative and timing of VTE chemoprophylaxis (overall $p = 0.58$; Supplemental Digital Content, Supplementary Table 1, http://links.lww.

TABLE 3. Unadjusted Outcomes by Timing of VTE Chemoprophylaxis

Outcome, n (%) or Median (IQR)	Initiated Preop, Not Held for Surgery, n = 150	Initiated Preop, Held for Surgery, n = 99	Initiated <12 h Postop, n = 168	Initiated >12 h Postop, n = 369	*p*
CSH — 24 h postoperative	17 (11.3)	9 (9.1)	12 (7.1)	27 (7.3)	0.45
CSH — 48 h postoperative	21 (14.0)	15 (15.2)	27 (16.1)	53 (14.4)	0.95
Total intraoperative blood loss, mL	50 (20–53)	65 (20–100)	58 (28–100)	50 (25–150)	**<0.001**
VTE	1 (0.7)	1 (1.0)	0 (0)	5 (1.4)	0.47
ICU admission	11 (7.3)	9 (9.1)	19 (11.3)	40 (10.8)	0.60
Hospital LOS, d	4 (4–6)	6 (4–7)	4 (4–5)	5 (4–6)	**<0.001**
In-hospital mortality	2 (1.3)	1 (1.0)	1 (0.6)	2 (0.5)	0.80

Boldface denotes statistical significance.
Preop, preoperative; Postop, postoperative.

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TABLE 4. Multivariate Logistic Regression Model of CSH Within 24 Hours Postoperative

Covariate	OR (95% CI)	*p*
*Group 4	Ref	Ref
Group 1 (vs. group 4)	1.49 (0.72–3.06)	0.26
Group 2 (vs. group 4)	0.83 (0.31–2.24)	0.42
Group 3 (vs. group 4)	1.24 (0.59–2.62)	0.70
Age ≥65 y	3.35 (1.40–8.05)	**0.007**
ED Glasgow Coma Scale score <15	3.82 (2.04–7.15)	**<0.001**
Preinjury antiplatelet therapy	1.69 (0.93–3.08)	0.08
Hours to surgery (6-h increment)	1.08 (1.00–1.18)	**0.05**
Time in surgery (30-min increment)	1.13 (1.04–1.22)	**0.003**
Open fracture	2.02 (0.57–7.18)	0.28
Femoral shaft fracture (vs. tibial fracture)	6.03 (2.04–17.82)	**<0.001**
Hip fracture (vs. tibial fracture)	2.36 (0.76–7.35)	0.92

Adjusted for covariates that differed in univariate analysis at $p < 0.05$. Boldface denotes statistical significance.

*Group 1: VTE chemoprophylaxis initiated preoperatively, not held for surgery (continued); Group 2: VTE chemoprophylaxis initiated preop, held for surgery (interrupted); Group 3, VTE chemoprophylaxis initiated <12 hours postoperatively; Group 4: VTE chemoprophylaxis initiated >12 hours postoperatively.

CI, confidence interval; Ref, reference.

com/TA/C668). Covariates independently associated with CSH within 48 hours postoperative were femoral shaft fracture, ED GCS score of <15, preinjury antiplatelet therapy, 65 years or older, and longer time in surgery.

Secondary Outcomes

There were seven symptomatic VTEs; all seven were DVTs, and all patients survived. The incidence of VTE was similar by timing of VTE chemoprophylaxis ($p = 0.47$), Table 3. However, five VTEs occurred in patients who had VTE prophylaxis initiated >12 hours postoperatively and one VTE occurred in a patient who had preoperative initiation that was held (interrupted) for surgery, with one VTE occurring in a patient whose VTE prophylaxis was initiated preoperatively and not held for surgery. Secondary outcomes of ICU admission and in-hospital mortality were similar based on timing of VTE chemoprophylaxis, Table 3. Hospital LOS was longer for patients who had preoperative initiation that was held for surgery ($p < 0.001$). Observed intraoperative blood loss was lowest for patients who had preoperative initiation that was not held for surgery ($p < 0.001$).

DISCUSSION

Lower-extremity fractures often present a treatment challenge because of the severity and complexity of the injury and risk for adverse outcomes. One noteworthy area in which there is currently no consensus is safe timing of VTE chemoprophylaxis in relation to fracture surgery. It is unresolved whether preoperative or perioperative initiation of VTE prophylaxis affects the clinical outcomes of bleeding complications and symptomatic VTE. This study of 786 patients with lower extremity long bone fractures demonstrates no statistically significant association between timing of VTE chemoprophylaxis with either incidence of postoperative hemorrhage or with VTE development.

In elective orthopedic surgery, VTE chemoprophylaxis is generally not initiated until after surgery in the United States, whereas, in Europe, it is traditional to begin prophylaxis before surgery.[10] Recently, Gunning et al.[11] compared VTE prophylaxis practices among severely injured patients at two major trauma centers, in the Netherlands and in Seattle, Washington. The VTE rate was 1.4% in Europe and 3.8% in the United States, with a hemorrhagic complication rate of 1.4% and 1% in Europe and the United States, respectively. Adjusted outcomes were similar, and the authors concluded that chemical thromboprophylaxis is safe to initiate early. An older systematic review examining total hip replacement found that, compared with hospitals that initiated prophylaxis preoperative or postoperatively, hospitals continuing prophylaxis perioperatively had significantly higher bleeding complications (6.3% vs. 1.4%) without a resultant lower VTE rate (12.4% vs. 14.4%); however, these comparisons were indirect, and DVT measures were based primarily on asymptomatic DVT detected through active screening of all patients.[10]

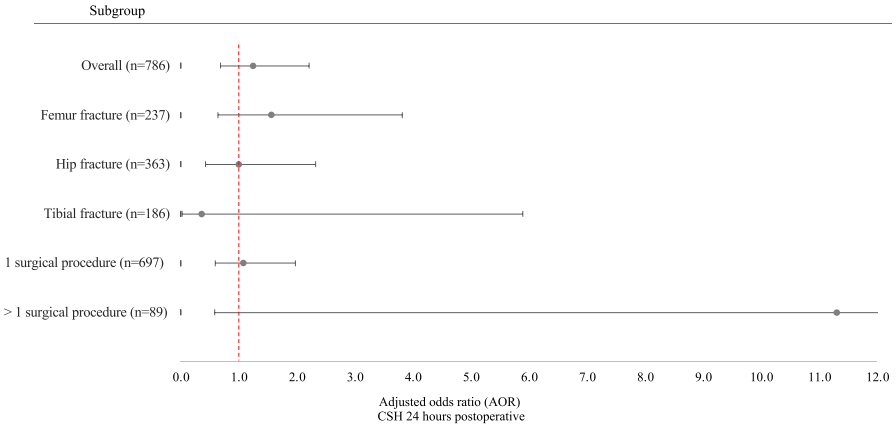

Figure 2. Forest plot of subgroup analyses demonstrating the association between timing of VTE chemoprophylaxis and CSH. Reference group is VTE chemoprophylaxis initiation >12 hours postoperative, versus all other groups.

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Our 8% rate of CSH was slightly lower than reports in the literature, potentially because there is no standard definition. The definition used in this study is similar to a previously proposed definition of major bleeding.[12] When examined as a CSH within 48 hours, our rate of 15% was similar to other reports. Linkins and colleagues[7] performed a meta-analysis of 33 studies to determine the clinical impact of anticoagulant-related bleeding for VTE and reported an overall rate of 13.4% (95% confidence interval, 9–17%). Ullmann et al.[13] examined postoperative bleeding rates in patients with craniotomy; approximately 13% of patients developed a bleed, but the majority (85%) were asymptomatic. Dodd et al.[14] examined complication rates specifically in patients with femur and tibial shaft fractures, reporting complications in 15% with femur shaft fractures and 6% with tibial shaft fractures; however, their definition of complications were death, infection, sepsis, VTE, cardiovascular events, pneumonia, and urinary tract infection. When examined in the sensitivity analysis as a CSH within 48 hours postoperative, there was no association between odds of bleeding and timing of VTE chemoprophylaxis.

Our 0.9% VTE rate was low irrespective of timing of chemoprophylaxis but is similar to what has recently been reported in the literature. Dodd et al.[14] reported a VTE rate of 1.7% with femur fractures and 0.3% with tibial shaft fractures. An National Trauma Data Bank analysis of more than 86,000 patients with tibia or fibula fracture reported an incidence of DVT and pulmonary embolism to be 0.53% and 0.35%, respectively.[15] Historically, much higher rates of VTE are reported, potentially because symptomatic and asymptomatic VTEs were both considered, but trauma centers are moving away from routine screening for VTEs and there exists a large surveillance bias with routine screening for DVTs.[16]

Regarding the significant association with GCS and CSH, the majority (n = 687) of patients had a normal ED GCS score of 15. In the remaining 99 patients with a GCS score of <15, most (72%) had a GCS score of 14. Patients with orthopedic injuries may present to the ED with an abnormal neurologic assessment in the absence of a head or spinal injury; only one patient with a GCS score of <15 had a minor head injury with AIS score of 1 (all others had AIS score of 0). Other possible explanations for an abnormal GCS are substance use or alcoholism (three patients with a GCS score of <15 had these comorbidities) and advanced age. Indeed, we observed that patients with a GCS score of <15 were more likely to be 65 years or older than patients with a GCS score of 15 (81% vs. 57%, $p < 0.001$). Even after adjustment for age, GCS remained a strong independent predictor of CSH. Additional study is needed to evaluate the association between major orthopedic surgery, neurologic impairment, and development of postoperative bleeding events.

This study was not powered to examine VTE rates, which was a secondary endpoint. Prior studies examining missed VTE prophylaxis and VTE events have shown a significant association: interruption of VTE chemoprophylaxis was associated with increased risk of VTE in patients with traumatic brain injury,[17] patients who underwent colectomy for cancer or inflammatory bowel disease,[18] and in a mixed population of trauma and general surgery patients.[19] Patients in this study who had delayed initiation more than 12 hours postoperative also had a numerically higher incidence of VTEs. The 2021 AAST consensus statement on VTE prophylaxis states that VTEs are prevented with earlier and uninterrupted VTE chemoprophylaxis, which our findings support but are not confirmatory. At least 2,058 patients would be needed to detect a significant difference in VTEs at 80% power between those who had interrupted or delayed VTE chemoprophylaxis compared with those with early and uninterrupted VTE chemoprophylaxis.

There are several limitations to this study. First, patients were treated at high-volume, level I trauma centers, limiting the generalizability of our findings to lower-level and nontrauma centers. Second, we excluded patients who did not receive VTE chemoprophylaxis with LMWH or UFH. Approximately 60% of patients received VTE chemoprophylaxis, which was lower than that reported (79%) in the study by Gunning et al.[11] examining chemoprophylaxis use at Harborview Medical Center. However, the mean Injury Severity Score was lower in our population that that of Gunning et al.[11] (9 vs. 27), which might explain the lower rate of VTE chemoprophylaxis use in our study. Our incidence of VTE would have been slightly higher had we included patients who did not receive chemoprophylaxis (1.5% vs. 0.9%). Third, this was a retrospective study that used existing registry data and information in the electronic medical records. Our low rate of clinically insignificant postoperative hemorrhage (0.5%) suggests that there may be a lack of charting if bleeding is not actionable or was asymptomatic. Fourth, patients who initiated VTE chemoprophylaxis preoperatively had fewer open fractures, which could introduce selection bias because minor injuries are less prone to hemorrhage. Still, there was no association between open fractures or grade III fractures and CSH. Fifth, there were institutional preferences in when to initiate VTE chemoprophylaxis that could also introduce selection bias. Because there was no interaction between timing of VTE chemoprophylaxis, CSH, and hospital (Cochran-Mantel Haenszel test, $p = 0.48$), all institutions were modeled together. Sixth, we excluded 4% of patients who had multiple long bone surgeries because most (20 of 30) patients fell into more than one VTE chemoprophylaxis exposure category, complicating the interpretation of the findings. Thirteen patients required 2 surgeries on the same long bone, and 17 patients had surgical repair of 2 different long bones. A seventh and final limitation is that we did not have information on VTEs that developed postdischarge.

In conclusion, our large, multicenter cohort study is the first, to our knowledge, to provide direct evidence to support the 2021 AAST consensus statement on VTE prophylaxis following traumatic injury[9]: patients with lower extremity long bone fractures (e.g., high risk for VTE) who do not otherwise have a high risk of bleeding (e.g., excluding moderate or severe head or spinal injury and chronic anticoagulant use) were demonstrated to have equal odds of a clinically significant bleeding event, whether VTE chemoprophylaxis was initiated preoperatively (and continued or held for surgery), within 12 hours postoperatively, or delayed more than 12 hours postoperatively. These results were adequately powered, were not sensitive to the time to develop a CSH (24 hours and 48 hours were both examined), and were robust in subgroup analyses (including by fracture type). Prior evidence was insufficient and led to soft recommendations to continue VTE chemoprophylaxis perioperatively in the most recent consensus guidelines. Nearly all the VTEs occurred in patients who had delayed initiation or interruption for surgery. Taken together, these findings suggest early and uninterrupted VTE chemoprophylaxis is safe and effective with major orthopedic surgery for long bone fractures.

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AUTHORSHIP

K.S. and N.N. conceptualized the study. K.S. is responsible for methodology, software, formal analysis, and drafting the manuscript. M.C., N.N., R.M., A.T., K.B., and C.C. are responsible for data verification and critical revisions of the manuscript. D.B.-O. is responsible for project administration, supervision, and writing the manuscript. All authors provided final approval of the submitted manuscript.

DISCLOSURE

The authors declare no conflicts of interest. The study was internally funded.

REFERENCES

1. American College of Surgeons: National Trauma Data Bank Annual Report 2016. American College of Surgeons; Chicago, IL. Available at: https://www.facs.org/media/ez1hpdcu/ntdb-annual-report-2016.pdf. Accessed May 4, 2022.
2. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest*. 2016;149(2):315–352.
3. Flevas DA, Megaloikonomos PD, Dimopoulos L, Mitsiokapa E, Koulouvaris P, Mavrogenis AF. Thromboembolism prophylaxis in orthopaedics: an update. *EFORT Open Rev*. 2018;3(4):136–148.
4. Muscatelli SR, Charters MA, Hallstrom BR. Time for an update? A look at current guidelines for venous thromboembolism prophylaxis after hip and knee arthroplasty and hip fracture. *Arthroplast Today*. 2021;10:105–107.
5. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693–4738.
6. Chindamo MC, Marques MA. Bleeding risk assessment for venous thromboembolism prophylaxis. *J Vasc Bras*. 2021;20:e20200109.
7. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: a meta-analysis. *Ann Intern Med*. 2003;139(11):893–900.
8. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. *J Thromb Thrombolysis*. 2013;35(3):312–319.
9. Rappold JF, Sheppard FR, Carmichael Ii SP, Cuschieri J, Ley E, Rangel E, et al. Venous thromboembolism prophylaxis in the trauma intensive care unit: an American Association for the Surgery of Trauma Critical Care Committee clinical consensus document. *Trauma Surg Acute Care Open*. 2021;6(1):e000643.
10. Strebel N, Prins M, Agnelli G, Buller HR. Preoperative or postoperative start of prophylaxis for venous thromboembolism with low-molecular-weight heparin in elective hip surgery? *Arch Intern Med*. 2002;162(13):1451–1456.
11. Gunning AC, Maier RV, de Rooij D, Leenen LPH, Hietbrink F. Venous thromboembolism (VTE) prophylaxis in severely injured patients: an international comparative assessment. *Eur J Trauma Emerg Surg*. 2021;47(1):137–143.
12. Decousus H, Tapson VF, Bergmann JF, Chong BH, Froehlich JB, Kakkar AK, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest*. 2011;139(1):69–79.
13. Ullmann M, Guzman R, Mariani L, Soleman J. The effect of anti-thrombotics on the postoperative bleeding rate in patients undergoing craniotomy for brain tumor. *Br J Neurosurg*. 2021;1–7.
14. Dodd AC, Salib CG, Lakomkin N, Obremskey WT, Sethi MK. Increased risk of adverse events in management of femur and tibial shaft fractures with plating: an analysis of NSQIP data. *J Clin Orthop Trauma*. 2016;7(2):80–85.
15. Auer R, Riehl J. The incidence of deep vein thrombosis and pulmonary embolism after fracture of the tibia: an analysis of the National Trauma Databank. *J Clin Orthop Trauma*. 2017;8(1):38–44.
16. Shackford SR, Cipolle MD, Badiee J, Mosby DL, Knudson MM, Lewis PR, et al. Determining the magnitude of surveillance bias in the assessment of lower extremity deep venous thrombosis: a prospective observational study of two centers. *J Trauma Acute Care Surg*. 2016;80(5):734–739; discussion 40-1.
17. Salottolo K, Offner P, Levy AS, Mains CW, Slone DS, Bar-Or D. Interrupted pharmocologic thromboprophylaxis increases venous thromboembolism in traumatic brain injury. *J Trauma*. 2011;70(1):19–24; discussion 5-6.
18. Khorfan R, Kreutzer L, Love R, Schlick CJR, Chia M, Bilimoria KY, et al. Association between missed doses of chemoprophylaxis and VTE incidence in a statewide colectomy cohort. *Ann Surg*. 2021;273(4):e151–e152.
19. Louis SG, Sato M, Geraci T, Anderson R, Cho SD, Van PY, et al. Correlation of missed doses of enoxaparin with increased incidence of deep vein thrombosis in trauma and general surgery patients. *JAMA Surg*. 2014;149(4):365–370.

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