SYSTEMATIC REVIEW

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Venous Thromboembolism Chemoprophylaxis in Trauma and Emergency General Surgery Patients: A Systematic Review

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ABSTRACT

Background: Appropriate venous thromboembolism (VTE) chemoprophylaxis in trauma and emergency general surgery (EGS) patients is crucial.

Objective: The purpose of this study is to review the recent literature and offer recommendations for VTE chemoprophylaxis in trauma and EGS patients.

Methods: We conducted a literature search from 2000 to 2021 for articles investigating VTE chemoprophylaxis in adult trauma and EGS patients. This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Results: Our search resulted in 34 articles. Most studies showed low-molecular-weight heparin (LMWH) is similar to unfractionated heparin (UFH) for VTE prevention; however, LMWH was more commonly used. Adjusted chemoprophylaxis dosing did not change the VTE rate but the timing did. Direct oral anticoagulants (DOACs) have been shown to be safe and effective in trauma and traumatic brain injury (TBI)/spinal cord injury (SCI). Studies showed VTE prophylaxis in EGS can be inconsistent and improves with guidelines that lower VTE events.

Conclusions: There may be no benefit to receiving LMWH over UFH in trauma patients. In addition, different drugs under the class of LMWH do not change the incidence of VTE. Adjusted dosing of enoxaparin does not seem to affect VTE incidence. The use of DOACs in the trauma TBI and SCI setting has been shown to be safe and effective in reducing VTE. One important consideration with VTE prophylaxis may be the timing of prophylaxis initiation, specifically as it relates to TBI, with a higher likelihood of developing VTE as time progresses. EGS patients are at a high risk of VTE. Improved compliance with clinical guidelines in this population is correlated with decreased thrombotic events.

Key Words

Chemoprophylaxis, Emergency general surgery, Outcomes, Traumatic injuries, Venous thromboembolism

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE risk is particularly increased after surgery and trauma (Beckman, Hooper, Critchley, & Ortel, 2010; Karcutskie et al., 2017). Current VTE prevention guidelines from trauma societies recommend the use of low-molecular-weight heparin (LMWH) (Ley et al., 2020; The American Association for the Surgery of Trauma, 2011), but there are no generally accepted guidelines for emergency general surgery (EGS) patients.

EGS patients on average have higher crude morbidity, although lower crude mortality than trauma patients (Ingraham, Haas, Cohen, Ko, & Nathens, 2012; Parent, McArthur, & Sava, 2013). EGS patients are at a high risk of developing VTE with increased associated mortality (Ross et al., 2020).

VTE has been placed in a category of "reasonably preventable" events by national agencies despite an increased risk in high acuity patients (Karcutskie et al., 2017; McCoy et al., 2015; Shaikh, Boneva, Hai, McKenney, & Elkbuli, 2020; The American Association for the Surgery of Trauma, 2012; Yun et al., 2020). Therefore, the purpose of this review is to summarize the recent literature on VTE chemoprophylaxis for the trauma and EGS populations and provide evidence-based recommendations.

OBJECTIVES

The objectives of this review are to assess the efficacy of pharmacological therapies in the prevention of VTE

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and its associated morbidity/mortality in trauma and EGS patients.

PICO 1

In patients with traumatic injuries, how do VTE chemoprophylaxis agents compare in lowering VTE incidence and associated morbidities and/or mortalities?

PICO 2

In patients with traumatic injuries, how does VTE chemoprophylaxis agent dosing affect VTE incidence and associated morbidities and/or mortalities?

PICO 3

In patients with traumatic injuries, how does VTE chemoprophylaxis agent timing affect VTE incidence and associated morbidities and/or mortalities?

PICO 4

In patients undergoing EGS, how is VTE chemoprophylaxis associated with lower VTE rates, morbidities, and/or mortalities?

METHODS

Data Sources and Search Strategy

This study was conducted in accordance with the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Figure 1). We searched PubMed, Cochrane Library, EMBASE, and clinicaltrials.gov using different queries (Figure 1). For the remaining databases, we searched using Boolean syntax with the following key words in various combinations and their truncations when applicable: "venous thromboembolism," "VTE," "trauma or surgery," "trauma surgery," "prevention," "prophylaxis," "chemoprophylaxis," "emergency general surgery," "emergency surgery," "acute surgery," "EGS," and "thrombosis." A literature search was conducted for studies published between January 2000 and February 2021. All articles were first screened for eligibility by title and/or abstract. Duplicates across databases were removed. Articles considered eligible underwent a full-text analysis in which article type, population, intervention, and outcome were assessed.

Study Selection and Eligibility Criteria

A preliminary query identified articles assessing VTE chemoprophylaxis use in trauma or EGS patients (i.e., appendectomies, bowel sections, etc.) generally. To narrow the search, the following study designs were deemed eligible: controlled trials (randomized [RCT] and nonrandomized), retrospective and prospective cohort studies, and case–control studies. In addition, the population was constricted to adult patients who underwent EGS or were involved in trauma. Traumatic injuries included general, orthopedic, and brain (TBI) and/or spinal cord injury (SCI). Studies were excluded if the population studied was limited to patients younger than 18 years or included both pediatric and adult populations without stratification of the results. In addition, studies that investigated both

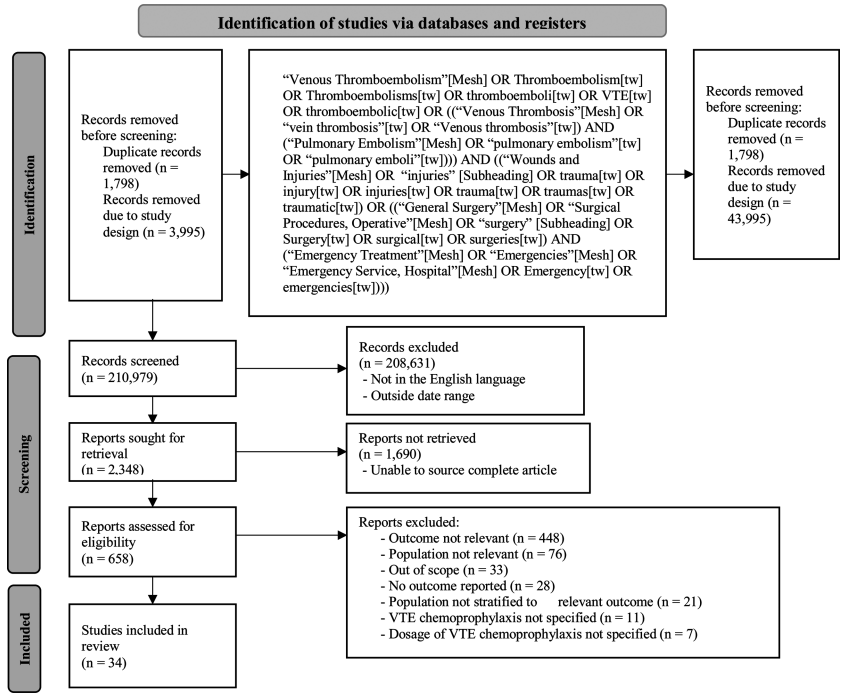

Figure 1. PRISMA flow diagram of studies included in this systematic review.

trauma and nontrauma patients, both EGS and elective surgeries, or nonpharmacological thromboprophylaxis or in combination with pharmacological agents without clear stratification of patient population type were excluded. Articles were limited to those published in English or translated to English.

Data Collection Process

Four authors (C.S., A.B., S.G., J.N., and A.E.) conducted the primary initial literature search and data extraction. A second and final literature search and data extraction was performed by all authors, which was supervised and verified by senior authors (A.E. and M.M.).

Outcomes Measures

Selected studies were limited to those that reported VTE outcomes based on the efficacy of different therapeutics and timing of chemoprophylaxis in trauma and/or EGS patients. After finalizing our article search, primary outcome measures were incidence of VTE. Secondary outcome measures were mortality from VTE, length of stay (LOS), and readmission rates.

Risk of Bias Assessment

Studies that were included in this systematic review were independently assessed for risk of bias utilizing the GRADE Working Group Criteria by multiple reviewers (C.S., A.B., A.E.). Risk of bias, inconsistency, indirectness, imprecision, and publication bias were used to assess the quality of evidence for the articles as related to PICO questions. Quality of evidence was rated very low, low, moderate, or high for each of the five GRADE considerations.

RESULTS

The initial search yielded 256,913 studies (Figure 1). After removal of duplicates and screening for study design, 210,979 studies remained. Of these, 658 studies were eligible for the full-text review, and following inclusion/exclusion criteria, only 34 studies were included in the final review (see Table 1, Supplemental Digital Content, available at: http://links.lww.com/JTN/A40). The overall quality of evidence of the studies was low using GRADE criteria (Table 1).

Chemoprophylaxis Agents in All Trauma Patients

Enoxaparin Versus Unfractionated Heparin

A noninferiority trial assessed the efficacy of enoxaparin 30 mg every (q) 12 hr (h) versus unfractionated heparin (UFH) (5,000U q8h) in 208 trauma patients. Trauma patients with an Injury Severity Score (ISS) of more than 9 and at risk for VTE were randomized to receive enoxaparin or UFH. Results showed UFH was noninferior to enoxaparin (p = .196) (Olson et al., 2015). Another

TABLE 1 Quality Assessment Using GRADE Criteria

	Number of Studies	Study Design	Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Quality of Evidence
Trauma	28	Open-label RCT; observational	Serious[a,b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Low ◯◯⊕⊕
Emergency general surgery	6	Observational; prospective cohort	Serious[b-d]	No serious inconsistency	No serious indirectness	No serious imprecision	None	Low ◯◯⊕⊕

Note. *RCT = randomized controlled trial.*

[a] *Lack of allocation concealment.*

[b] *Small sample size.*

[c] *Measurement bias.*

[d] *Unmeasured confounders.*

retrospective study compared enoxaparin (30 mg bid or 40 mg daily) versus UFH (5,000U q8h) in trauma patients (Arnold et al., 2010). The incidence of DVT and PE was statistically similar between groups.

Jacobs et al. (2017) compared enoxaparin with UFH use among 18,100 trauma database patients and found that patients given enoxaparin (30 mg bid or 40 mg daily) had a decreased risk of mortality (OR = 0.64, 95% CI [0.49, 0.83]), VTE (OR = 0.67, 95% CI [0.53, 0.84]), PE (OR = 0.53, 95% CI [0.35, 0.79]), and DVT (OR = 0.73, 95% CI [0.57, 0.95]); however, differences in baseline between the groups were present.

A retrospective cohort study comparing UFH with enoxaparin in 1,090 geriatric trauma patients found no significant difference in DVT risk ($p = .95$) or PE risk ($p = .96$) (Krantz et al., 2020).

VTE prophylaxis outcomes in 1,253 trauma patients between the University Medical Center Utrecht (UMCU) in the Netherlands and Harborview Medical Center (HMC) in the United States were compared (Gunning, Maier, de Rooij, Leenen, & Hietbrink, 2021). UMCU patients received 5,000 IU dalteparin daily, and HMC patients received enoxaparin 40 mg q12h or UFH 5,000U q8h, and concluded that there were no significant differences in VTE incidence ($p = .102$) or hemorrhagic complications ($p = .393$).

Cothren et al. (2007) investigated 743 multisystem trauma patients with no comparison group and concluded that the use of dalteparin resulted in DVT (3.9%) and PE (0.8%) rates comparable with or lower than similar patients in other studies treated with enoxaparin.

A retrospectively study compared 792 patients receiving UFH (5,000U tid) or enoxaparin (30 mg bid) with medication adjustment based on anti-Xa levels (Karcutskie et al., 2018). VTE rates remained similar between the control and adjustment groups ($p = .57$). However, Ko et al. (2016) studied 205 trauma patients who received adjusted enoxaparin from 30 to 40 mg bid if anti-Xa levels were subtherapeutic (>0.2 IU/ml). The incidence of VTE was significantly lower in this group than in the historical control group ($p = .046$).

Norwood et al. (2001) conducted a prospective study using enoxaparin in 118 high-risk blunt trauma patients with no control group and found that 2% of these patients developed DVT and two patients developed bleeding complications.

Enoxaparin Versus Rivaroxaban

A review of 2,106 trauma patients who either received enoxaparin 30 mg q12h or rivaroxaban 10 mg daily found no significant difference in rates of VTE ($p = .99$) or bleeding ($p > .05$). However, treatment with enoxaparin resulted in a significantly higher mortality rate (1.04%) versus 0% for rivaroxaban ($p < .001$), and the group receiving enoxaparin had a higher physiological injury burden and worse TBI (Kingdon, Miller, & Savage, 2019).

Enoxaparin Versus Aspirin

An open-label RCT compared 329 orthopedic trauma patients with fracture who received either enoxaparin 30 mg bid or aspirin 81 mg bid (Haac et al., 2020). Patients randomized to aspirin maintained daily prophylaxis significantly longer than those randomized to enoxaparin ($p < .01$). The authors concluded no significant evidence of the superiority of enoxaparin over aspirin for VTE prevention in patients with fracture.

Enoxaparin Versus Placebo

Phelan et al. (2012) evaluated the efficacy of enoxaparin in 62 patients with low-risk TBI presenting within 6 hr of their injuries, where patients received either enoxaparin 30 mg bid or a placebo starting 24–96 hr after their initial injury as well as obtaining repeat brain imaging 24 hr after initiating treatment. Radiographic worsening of TBI was the primary endpoint. Patients treated with enoxaparin had a radiographic TBI progression rate of 5.6% versus 3.6% for patients treated with placebo (within the noninferiority margin of 5%).

Direct Oral Anticoagulants Versus Standard of Care

Hoffmeyer et al. (2017) studied 413 orthopedic trauma patients to compare the effect of rivaroxaban and standard of care where standard of care included subcutaneous injection of LMWH or other antithrombotic agents at the discretion of the physician. Symptomatic thromboembolic events only occurred in one (0.5%) patient who was treated with rivaroxaban and two (1.0%) patients who were treated with the standard of care. However, information on the regimen that comprised the standard of care was not provided.

The efficacy and safety of direct oral anticoagulants (DOACs) were compared with LMWH for thromboprophylaxis in trauma patients who sustained lower extremity fractures using matched cohorts of 2,280 patients who received DOACs and 2,280 patients who received LMWH. Both groups had a VTE incidence rate of 1.4% ($p = .992$). However, the DOAC group differed significantly from the LMWH group in comorbidities, vital signs, ISS, surgeries, and processes of care. In addition, LMWH patients were started on thromboprophylaxis significantly earlier than patients receiving DOACs (Nederpelt et al., 2021).

Direct Oral Anticoagulants Versus LMWH

Khan et al. (2018) evaluated 1,056 matched patients with SCI for differences in VTE between DOACs (rivaroxaban, apixaban, and edoxaban) and LMWH and found that patients who received DOACs were less likely to develop a DVT (2.3% vs. 5.7%, $p < .01$), with no differences in the rate of PE ($p = .73$), postprophylaxis surgical decompression of spinal column ($p = .75$), and mortality rate ($p = .77$).

Hamidi et al. (2019) studied 810 SCI patients and compared the use of DOACs with LMWH and found that patients receiving DOACs were less likely to develop DVT (1.8% vs. 7.4%, $p < .01$) and PE (0.3% vs. 2.1%, $p = .04$). However, doses of medications used and type of DOACs were not reported.

Slavik et al. (2007) evaluated 135 patients with an acute traumatic SCI and found there was no difference between dalteparin and enoxaparin in mortality from VTE ($p = .103$). In a separate retrospective study of 90 trauma patients, dalteparin was shown to be as effective as UFH in preventing VTE-related fatality (Worley et al., 2008).

Chemoprophylaxis Versus Nonchemoprophylaxis

Scudday et al. (2011) evaluated the effects of chemoprophylaxis (LMWH or UFH) versus nonchemoprophylaxis on VTE in 812 TBI patients. Chemoprophylaxis patients were older, had a higher ISS, and lower Glasgow Coma Scale score but still had a significantly lower incidence of VTE (1% vs. 3%, $p = .019$) and a similar progression of bleed ($p = .055$) versus the nonchemoprophylaxis group.

Lu et al. (2009) studied 92 trauma patients and showed that DVT developed in 2.5% of patients who received fondaparinux versus 33% of patients who received intermittent pneumatic compression (IPC) only and concluded that fondaparinux was effective in VTE reduction.

A small RCT comparing the use of IPC versus LMWH in 120 patients showed no statistically significant difference regarding a reduction in DVT, PE, or mortality ($p > .05$, for all) (Kurtoglu et al., 2004).

Chemoprophylaxis Dosing in All Trauma Patients

Enoxaparin Dosages

A double-blinded RCT pilot study of 234 patients evaluated VTE between those treated with standard enoxaparin (30 mg bid) versus weight-based enoxaparin (0.5 mg/kg bid) and showed no difference in VTE incidence between groups (Kay et al., 2018).

Kopelman et al. (2013) evaluated 124 patients who received either 30 mg (low dose) or 40 mg bid of enoxaparin and concluded that the low-dose group was more likely to have inadequate peak factor Xa levels ($p = .01$), but no significant difference in VTE incidence was found ($p > .05$).

Assay-Guided Versus Fixed Dosing

Rodier et al. (2020) evaluated blunt TBI progression rates among 70,122 patients using chemoprophylaxis with LMWH or UFH guided by anti-Xa levels versus historical controls (fixed dosing) and demonstrated that the assay-guided and fixed-dose treatments showed similar bleed progression rates, VTE, and mortality rate ($p > .05$ for all). However, the fixed-dose group had a lower intensive care unit admission rate than the other two groups ($p < .0001$) and the highest LOS ($p < .001$).

Chemoprophylaxis Timing in All Trauma Patients

Timing of Prophylaxis

Hachem et al. (2018) evaluated the timing of prophylaxis on VTE in 64 adults with severe TBI and concluded that no significant difference was observed between patients who received early (<3 days) prophylaxis, late (≥3 days), and no prophylaxis (10%, 16%, and 18%, respectively, $p = .86$). Rates of TBI progression between the early and late prophylaxis groups were also not significantly different (0% vs. 7%, $p = .99$). However, there were significantly more deaths in the group not receiving prophylaxis ($p < .001$).

Byrne et al. (2016) assessed the effects of early prophylaxis (<72 hr) compared with late prophylaxis (≥72 hr) with either LMWH or UFH in 3,634 patients with severe TBI and concluded that early prophylaxis was associated with lower rates of both PE (OR = 0.48, 95% CI [0.25, 0.91]) and DVT (OR = 0.51; 95% CI [0.36, 0.72]).

Tracy, Dunne, O'Neal, and Clayton (2016) assessed the effect of chemoprophylaxis timing on VTE among 1,425 neurosurgical trauma patients (TBI and SCI) and found that patients who developed a VTE had a significantly longer time to initiation of chemoprophylaxis (6.7 ± 4.9 days vs. 4.7 ± 4.9 days, $p < .001$). For each 1-day increase in time to prophylaxis initiation, the odds of developing a VTE increased significantly ($p < .001$).

Zeeshan et al. (2018) studied optimal timing of UFH or LMWH thromboprophylaxis in 3,554 patients with isolated spinal trauma managed operatively where early thromboprophylaxis was defined as early (<48 hr postoperatively) or late (>48 hr postoperatively) and demonstrated that individuals receiving UFH or LMWH early were at a decreased risk of developing DVT compared with those who received the chemoprophylaxis late (2.1% vs. 10.8%, $p < .01$). However, there was no statistically significant difference for DVT or PE rates between the two agents.

Chemoprophylaxis in EGS Patients

Early VTE Prophylaxis in EGS Patients

Yang et al. (2020) evaluated VTE incidence in 767 EGS patients where only 66% of patients received appropriate chemoprophylaxis in less than 24 hr of admission and concluded that higher-risk patients (Caprini score of ≥5 points) demonstrated a significantly higher VTE rate (7.4% vs. 2.3%, $p < .001$) and significantly higher mortality (17.6% vs. 4.0%, $p < .001$) compared with low/moderate-risk patients.

Dalteparin Dosages

Balachandran et al. (2020) evaluated the efficacy of VTE chemoprophylaxis in 1,179 EGS patients where VTE incidence was compared between patients receiving 2,500 or 5,000 IU of dalteparin daily and found that higher doses

were associated with an increased risk of complications ($p < .001$) and VTE incidence ($p = .027$).

Guideline Compliance and Quality Improvement

Four studies evaluated guideline compliance for VTE prophylaxis in 1,209 EGS patients. McCulloch et al. (2010) found a significant increase in the proportion of patients receiving adequate VTE prophylaxis administration after guideline intervention (35% vs. 87%, $p < .001$). Kreckler et al. (2013) also found a significant reduction in VTE episodes after guideline intervention in 318 EGS patients (0.75% vs. 0.29%, $p = .01292$).

Another study investigated the use of audits on compliance with VTE prophylaxis for 111 EGS patients (McKenna, Karthikesalingam, Walsh, Tang, & Quick, 2009). Appropriate VTE prophylaxis increased from 37% to 88% after auditing ($p < .001$).

Stevenson et al. (2007) assessed a multistep quality improvement intervention, which included increasing awareness training, in 566 EGS patients. VTE prophylaxis use increased from 72.9% to 86.1% following the interventions, although no statistical analysis was provided.

DISCUSSION

LMWH, particularly enoxaparin, has been the most studied agent in trauma patients. Although LMWH incidence is recommended in clinical guidelines, four studies showed no significant difference in VTE incidence between enoxaparin and UFH (Arnold et al., 2010; Krantz et al., 2020; Olson et al., 2015; Worley et al., 2008). Importantly and common to many of these studies, the incidence rate of DVT after discharge was not assessed. It is a possibility that the efficacy of either drug extends beyond the discharge period and was therefore missed. Jacobs et al. (2017) found contrasting evidence that enoxaparin is superior to UFH in reducing incidence of PE, DVT, and mortality. However, patients included in this study encompassed different baseline demographics and were not matched. Enoxaparin did not demonstrate significant difference in VTE prevention compared with dalteparin or rivaroxaban (Gunning et al., 2021; Slavik et al., 2007). Regarding enoxaparin dosing, there was no difference in developing VTE based on fixed dosing regimens (Kopelman et al., 2013) or weight-based dosing (Kay et al., 2018). Scudday et al. (2011) showed that chemoprophylaxis with either LMWH or UFH significantly reduced VTE compared with patients given placebo and did not demonstrate worsening TBI on imaging. The use of DOACs in trauma patients with fractures was found to be as safe and as effective to LMWH for reducing VTE development (Khan et al., 2018). Two studies showed DOACs to be superior to LMWH in a reduction of DVT among SCI patients (Hamidi et al., 2019; Khan et al., 2018), and one of these also found a reduction in PE incidence (Hamidi et al., 2019).

In addition, early prophylaxis in neurosurgical trauma patients showed lower rates of VTE incidence (Byrne et al., 2016; Tracy et al., 2016; Zeeshan et al., 2018). Optimal chemoprophylaxis timing for TBI patients has been an area of discussion due to concerns of increased intracranial hemorrhage risk. Levy et al. (2010) demonstrated 13-fold increased odds for progression to intracranial hemorrhage in TBI patients receiving VTE chemoprophylaxis if initiated prior to stabilization of the intracranial bleed stabilized. Störmann et al. (2019) found no increased risk of intracranial bleed when progress with chemoprophylaxis was started within 24 hr. As such, the American Association for the Surgery of Trauma recommends initiating VTE prophylaxis as soon as reasonably possible, ideally within 24–72 hr of admission; however, this can be individualized on the basis of multiple factors such as the severity of injury (Rappold et al., 2021).

In EGS patients, high-risk patients with a Caprini score of 5 or more points were associated with a significantly higher VTE incidence and associated mortality (Yang et al., 2020). Creating and following guidelines have been correlated with improved VTE chemoprophylaxis (Kreckler et al., 2013; McCulloch et al., 2010; McKenna et al., 2009; Stevenson et al., 2007). Caution, though, as higher doses of dalteparin (≥5,000 IU daily) have been associated with a higher incidence of complications and VTE and in EGS patients (Balachandran et al., 2020).

Our findings parallel findings from similar trauma reviews but conflict with others. Walker et al. (2017) concluded that weight-based dosing of enoxaparin was beneficial in the reduction of VTE incidence. Chelladurai et al. (2013) concluded that chemoprophylaxis may be useful in reducing DVT rates in TBI.

Barrera et al. (2013) showed that chemoprophylaxis was more effective than mechanical methods at reducing DVT and patients who received both mechanical and pharmacological prophylaxis had a lower risk of DVT and that LMWH appeared to reduce the risk of DVT compared with UFH. As the data presented in the review by Barrera et al. were more than 10 years old and did not include EGS patients, this systematic review was performed to provide more up-to-date information on a wider patient population.

Kakkos et al. (2016) analyzed 22 studies to assess the effectiveness of combined IPC and pharmacological prophylaxis versus single modalities in preventing VTE and concluded that a combination of IPC and pharmacotherapy was superior to IPC alone in reducing DVT and superior to anticoagulation alone in reducing PE. The authors additionally found an increased risk of bleeding with combination therapy compared with IPC alone. In contrast, Mesa Galan et al. (2016) concluded that the potential differences between pharmacological versus nonpharmacological

measures could not be assessed because of the high degree of heterogeneity in available TBI studies. However, they did find that VTE prophylaxis administered within 72 hr after the initial traumatic incident was more effective.

Geerts (2006) recommended that in patients with major trauma, LMWH should be started as soon as hemostasis has been established; for patients who are at high risk of bleeding, initial IPC is recommended. However, considering the more recent published data regarding the safety and efficacy of DOACs, their use should be further investigated in patients with major trauma.

We recommend that chemoprophylaxis should be initiated within 24–72 hr after injury in most traumatically injured patients. The recommended agent of choice is an LMWH, such as enoxaparin, due to its pharmacological and pharmacokinetic properties; however, UFH is a reasonable alternative. Dosage of LMWH can be fixed or weight-based, with careful considerations in the setting of impaired renal function. In addition, the use of DOACs in trauma and EGS has shown to be safe and effective in reducing VTE; therefore, we recommend additional consideration of its use.

There are several limitations of this systematic review that should be mentioned. Many retrospective studies had a small sample size, and only few studies utilized randomization. Moreover, although some cohort studies controlled for confounders, there is the possibility of unmeasured confounders affecting the results. Considerations of asymptomatic VTE were additional limitations in most trials as three studies lacked a comparison group. Most importantly, this systematic review included all types of traumatic injuries ranging from head and spinal cord to trunk and extremities as well as isolated and polytrauma. The inclusion of such a broad population allowed for a more expansive review that focused on overall VTE incidence and morbidity/mortality after chemoprophylaxis. However, it is imperative to note location, severity, and extent of injury among other variables are confounders that could not be controlled for due to lack of data. Future studies should evaluate the role of these factors in chemoprophylaxis efficacy in VTE prevention. Finally, only six studies evaluated EGS patients, illustrating the lack of research in this area. Most EGS studies focused on improved compliance with VTE prophylaxis guidelines. Only one study assessed specific chemotherapeutics, indicating the critical need for more trials for EGS patients by assessing VTE prophylaxis and its efficacy. Despite these limitations, we recommend that VTE chemoprophylaxis in trauma patients is beneficial (Gantz et al., 2020). There seems to be no difference between LMWH (especially enoxaparin), UFH, and DOACs. However, LMWH has been the most used and studied prophylactic agent in trauma patients and has proven to be effective. Thus, we recommend the continued use of LMWH for thromboprophylaxis and further investigation of DOACs. VTE prophylaxis guidelines for EGS patients should be developed at the societal and hospital levels and compliance tracked. To assess and revise the guidelines, a quality measure program should be created to ensure adequate implementation. Murphy et al. (2018) also noted the dearth of studies evaluating VTE therapeutic prophylaxis in this specific population, which hampers further recommendations. Finally, the paucity and heterogeneity (patient population, chemoprophylaxis being used, etc.) of the existing data should be noted, especially for EGS patients. Considering that there is insufficient evidence, we suggest the use of LMWH as it is the current mainstay of VTE prophylaxis. Despite these limitations, this review is one of the few in which the findings are stratified according to the specific population of EGS and trauma patients. In addition, this review provides the most current evidence (last 20 years) on trauma patients and highlights the lack of EGS studies.

CONCLUSION

LMWH should continue to be utilized as the mainstay in VTE chemoprophylaxis in trauma and EGS patients. The various drugs under LMWH class do not change the incidence of VTE, although enoxaparin has been the most studied. Dosing of enoxaparin does not seem to affect VTE incidence in trauma patients. Currently, there may be no benefit to receiving LMWH over UFH or DOACs in trauma and EGS patients, but future studies are needed to further elucidate the value of these therapeutics. One important consideration with VTE prophylaxis may be the timing of initiation, specifically as it relates to TBI, with a higher likelihood of developing VTE and increased mortality as time progresses. Improved compliance with clinical guidelines in this population is correlated to increased appropriate VTE prophylaxis administration and decreased thrombotic events.

KEY POINTS

- VTE incidence is higher in patients of higher acuity such as those undergoing trauma or EGS.
- Although LMWH is the standard for VTE chemoprophylaxis, more novel agents have been approved and studied in the last 20 years.
- This review demonstrates that VTE chemoprophylaxis should be initiated early (within 72 hr) of initial injury and that there is no clear benefit to utilizing LMWH over UFH or DOACs for trauma patients. Future studies are needed to further elucidate the value of these more novel therapeutics.
- We found the literature regarding VTE chemoprophylaxis for EGS-specific patients remains lacking and to address this knowledge gap, future large, well-designed studies are needed to provide concrete guidelines for these patients' population.

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