HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2024 March 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2023 March 01; 94(3): 484–489. doi:10.1097/TA.0000000000003847.

Timing of Venous Thromboembolism (VTE) Prophylaxis Initiation after Injury: Findings from the Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma

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Abstract

Optimizing prophylaxis against venous thromboembolic events (VTE) is a critical issue in the care of injured patients. Although these patients are at significant risk of developing VTE, they also present competing concerns related to exacerbation of bleeding from existing injuries. Especially after high-risk trauma, including injuries to the abdominal solid organs, brain, and spine, trauma providers must delineate the time period in which VTE prophylaxis successfully reduces VTE rates without encouraging bleeding. Although existing data are primarily retrospective in nature and much further study is required, literature supports early VTE chemoprophylaxis initiation even for severely injured patients. Early initiation is most frequently defined as <48 hours from admission but varies from <24-72 hours and occasionally refers to time from initial trauma. Prior

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Author Contribution

TC, MAP, and ERH provided the study concept. MS, BJ, ACB, and ERH contributed to the data collection. MS, TC, BJ, MAP, ACB, and ERH performed the data analysis and interpretation. All authors participated in writing and critically reviewing the final manuscript.

Presentations

This study has not been presented at a meeting.

Social Media Summary

Optimal timing for initiation of pharmacologic VTE after high-risk injury remains controversial. Standardization should be encouraged to encourage optimal care for trauma patients.

#trauma #VTEprophylaxis #evidencebasedmedicine

@elliotthaut @NatTrauma @schellenbergMD

to chemical VTE prophylaxis initiation in patients at risk for bleeding, an observation period is necessary during which injuries must show themselves to be hemostatic, either clinically or radiographically. In the future, prospective examination of optimal timing of VTE prophylaxis is necessary. Further study of specific subsets of trauma patients will allow for development of effective VTE mitigation strategies based upon collective risks of VTE and hemorrhage progression.

Keywords

venous thromboembolism; trauma; optimal timing; chemoprophylaxis

Background

Venous thromboembolic events (VTE) occur frequently after trauma, particularly without prompt initiation of chemoprophylaxis[1–2]. Pharmacologic prophylaxis for VTE prevention is well accepted to prevent events and numerous national guidelines recommend its routine use in trauma patients[3–7]. Delineation of the optimal time to begin prophylaxis is critical to maximize reduction in VTE rates while avoiding bleeding complications. This is particularly true after injuries that present an ongoing hemorrhage risk (e.g. abdominal solid organ trauma) and/or those that occur within a small confined space, in which even small degrees of bleeding or hematoma expansion can have critical or catastrophic consequences, such as traumatic brain injuries (TBI) and spine injuries, including vertebral fractures and spinal cord injuries (SCI).

The competing needs to balance prompt initiatation of VTE chemoprophylaxis (VTEp) early while avoiding promotion of bleeding are incompletely adjudicated by existing literature. The optimal time to initiate VTEp, wherein prevention of VTE will be maximized while minimizing the risk of bleeding, is not yet defined in a nuanced way. Particularly for pateints with selected traumatic injury paterns, the empiric specification of the optimal timeframe within which to begin VTEp is critical to ensure optimal prevention of VTE without provocation of bleeding.

The objective of this manuscript is to summarize the current published literature on the topic of timing of pharmacologic prophylaxis initiation in trauma patients. We will also report on the knowledge gaps as noted at the recent Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma (https://www.nattrauma.org/research/research-policies-templates-guidelines/vte-conference/).

Solid Organ Injuries

Abdominal solid organ injuries (SOI) include the liver, kidneys, and spleen. Because of the frequency with which SOIs are managed nonoperatively, particularly after blunt trauma, the optimal time to initiate these patients on VTEp is a question commonly encountered by trauma providers. Historically, VTE prophylaxis was routinely held for patients with these injuries out of concern for the risk of recurrent bleeding. However, there is now a considerable body of literature, almost entirely retrospective, advocating for the safe and

effective initiation of VTEp <48h of patient arrival to the emergency department (ED) with blunt SOI managed nonoperatively. There are no dedicated studies examining time of VTEp initiation on blunt SOIs managed operatively nor on patients with isolated penetrating SOI, regardless of management strategy. Further study of these specific populations is necessary to more completely understand the optimal time to begin VTEp after solid organ injury. At present, the literature on VTEp initiation after nonoperative blunt SOI is largely extrapolated to these other patient populations in clinical practice.

The existing literature on time to VTEp after blunt solid organ injury managed nonoperatively is comprised of one single-center prospective cohort study[8], a small number of retrospective multicenter or database-driven cohort studies[9–11], and several single-center retrospective studies[12–17]. There are no prospective multicenter examinations of this subject, although an American Association for the Surgery of Trauma (AAST)-sponsored study with this design is currently in the data collection phase and will hopefully provide further evidence to inform patient care.

In addition to the published literature delineated above, this clinical and scientific question has triggered sufficient interest and study as to provoke several meta-analyses and systematic reviews[18–19]. The take-home messages of this body of literature are clear. VTEp initiation <48h of emergency department arrival is associated with a reduction in VTE[8–15] without an increase in failure of nonoperative management[8–17,19] or need for blood transfusion[8,13–17,19]. Key studies on the optimal time to VTEp initiation after solid organ injury are summarized in Table 1.

There are several notable limitations to existing studies. The first is that high grade (AAST grade ≥IV) solid organ injuries and combined solid organ injuries are underrepresented, potentially because these injuries are more likely to necessitate immediate operation. Therefore, the appropriateness of extrapolating existing data to high grade or combined solid organ injuries is unknown. Next, patients with associated TBI are excluded from approximately half of the published studies on the optimal time to initiate VTEp after blunt solid organ injury managed nonoperatively. The rationale for this exclusion is the fact that the presence of a concomitant TBI is likely to delay the initiation of prophylaxis. Moreover, TBIs are associated with coagulopathy and impact a patient's risk of VTE. Therefore, further study is required to further elucidate the impact of an associated TBI on time to initiate prophylaxis and on resultant VTE risk after SOI.

Lastly, the collective interpretation of these studies is hindered by heterogeneity in outcomes definitions. For example, the definition of failure of nonoperative management varies amongst these studies as the need for either laparotomy or angioembolization (AE) at any time or at an interval of time after admission, ranging from >6-24 hours. To better amalgamate the literature and facilitate interstudy comparisons, we propose that failure of nonoperative management of blunt solid organ injury be defined as the need for exploratory laparotomy >6 hours after admission because this was the most common definition employed by related published studies[19]. Next, the inclusion of AE in the definition of failure of nonoperative management is problematic. AE has been touted as an important intervention by which to increase the rates of successful nonoperative management after

blunt solid organ injury[20–22]. It is confusing and counterintuitive, then, to use the need for AE as a barometer of failure of nonoperative management. Furthermore, delayed AE may be undertaken for pseudoaneurysm management after high grade solid organ injury, and not for bleeding control. Such patients have not failed nonoperative management and should not be coded as such. Finally, the definitions of early and late VTEp initiation vary across studies, with early groups defined by prophylaxis initiation anywhere from within 24-72 hours from admission but most commonly <48 hours. Because this is the most frequently utilized time cut-off, we propose that early prophylaxis administration be defined as initiation <48 hours of admission. This time frame also has a pathophysiologic correlate, with basic science studies supporting the transition of patients with SOI from a hypo- to a hypercoagulable state approximately 48 hours out from injury[23]. Since the publication of these studies, however, many trauma surgeons have become more aggressive about early initiation of VTEp and one wonders if <24 hours of admission may be a better target. Fundamentally, once a patient has demonstrated a lack of clinically relevant ongoing bleeding, VTEp should be promptly started as the focus shifts from hemorrhage mitigation to VTE prevention. As thromboelastography (TEG) is being more frequently utilized to trauma centers, perhaps initiation of prophylaxis based on TEG results may be an option to aid decision-making.

Moving forward in the examination of the optimal time to initiate VTEp after solid organ injury, we require further study of patients with high grade injuries; those with combined solid organ injuries and TBIs; patients with penetrating solid organ injuries; and more prospective data on the subject in general. In the interim, standardization of commonly used definitions in the study of these injuries would help literature cohesion.

Traumatic Brain Injuries (TBI)

Patients with TBI present particular concerns surrounding VTEp because provocation of bleeding within the intracranial space can have devastating consequences, even if the expansion in intracranial bleeding is small. Because of the fixed space within the cranial vault and the cerebral compression that can result from hematoma expansion, particularly in young patients, determining a safe window for timing of prophylaxis initiation is critical.

Unlike the literature on solid organ injuries and time to VTEp, the existing data on TBIs and optimal time for VTEp initiation are relatively sparse, particularly in terms of prospective data. This may be the result of persistent clinical equipoise. One prospective study demonstrated that among patients with low-risk TBI, defined by small-volume intracranial hemorrhage with demonstration of radiologic stability on computed tomography (CT) scan of the head at a 24-hour interval, VTEp could be safely initiated at 24 hours without any clinically relevant expansion of the intracranial bleeding[24]. These findings were echoed in a similar retrospective study published shortly thereafter, which showed that VTEp initiation 24 hours after stable CT Head was both effective and safe, i.e. reduced the rate of deep vein thromboses (DVT) without associated progression of intracranial hemorrhage[25].

Based upon these studies and others, the American College of Surgeons (ACS) TQIP Best Practices in the Management of Traumatic Brain Injury guidelines advocate for VTEp initiation 24-72 hours after stable CT Head[26]. These guidelines are predicated on the

intrinsic risk of intracranial hemorrhage expansion, as quantified by the Modified Berne-Norwood criteria. These criteria divide TBI patients into low, moderate, and high risk categories. High risk patients are those who have undergone neurosurgical intervention (craniotomy, craniectomy, and/or intracranial pressure monitor insertion) and/or have intracranial bleed progression on CT scan performed 72 hours after index scan[26]. High risk patients require an individualized approach due to lack of high quality evidence, with consideration of inferior vena caval filter placement. Moderate risk patients are those with epidural or subdural hematoma >8mm, intraventricular hemorrhage or contusion >2cm, multiple contusions/lobe, subarachnoid hemorrhage with abnormal CT angiography of the head, and/or intracranial bleed progression on CT scan at 24 hours[26]. These patients should have VTEp withheld until CT Head at 72h demonstrates radiographic stability. Patients without moderate and high risk features are deemed low risk and can be safely initiated on VTEp at 24 hours from stable CT Head[26].

Safe VTEp initiation after severe TBI is challenging due to a paucity of data. A retrospective cohort study of TBI patients with GCS ≤8 and AIS Head ≥3 demonstrated that VTEp started <72h mitigated VTE risk without increasing mortality or the need for delayed neurosurgical intervention[27]. When TBI patients necessitating neurosurgical intervention (craniotomy/craniectomy or intracranial pressure monitor insertion) within 24 hours were specifically examined, the findings were less clear cut[28]. In this study, earlier VTEp initiation reduced VTE but increased risk of need for repeat neurosurgical intervention and even death in select subgroups. Overall, the authors advocate that VTEp <72h in patients with TBI who have undergone neurosurgical intervention may be ill advised. These disparate findings underline some of the challenges in the examination of this topic among TBI patients, with variables including intracranial intervention significantly impacting the safety of time to VTEp initiation. Key studies on the optimal time to VTEp initiation after TBI are summarized in Table 2.

Evidence is accumulating specifically among TBI patients that low molecular weight heparins (LMWH) may be superior to unfractionated heparin (UH) as a VTEp agent, providing a greater reduction in VTE rates[29–30]. Furthermore, one study demonstrated improvement in in-hospital mortality rates when enoxaparin was used as the chemoprophylactic agent among patients with TBI as opposed to UH[29]. This clinical finding is supported by basic science work using rodent models, wherein LMWH imparted neuroprotective effects via reduction in cerebrovascular permeability and cerebral edema, with associated improved neurologic outcomes[31–32].

It is difficult to provide a simple, uniform recommendation about the optimal time to VTEp in patients with TBI as a result of the heterogeneous nature of this injury itself and the scarcity of existing literature. There is a clear potential for negative outcomes if VTEp is started overzealously early after TBI. Confirmation of radiographic stability via CT scan of the head appears to be an important component of the decision making. In general, VTEp initiation after TBI should occur at an interval of time, such as 48 hours, following stable CT Head and completion of intracranial intervention. Further study on this topic, particularly performed with a prospective multicenter design and with input of a broad multidisciplinary team, is urgently needed.

Spinal Cord Injuries (SCI)

Patients with SCI are well know to be at elevated risk for VTE. However, patients with spinal cord and column injuries are less well studied than patients with TBI in terms of the evidence surrounding optimization of VTEp initiation time. A systematic review published on the topic in 2011 included just five studies[33], only one of which was specifically constructed to examine the optimal time at which to begin VTEp after spine injury[34]. Even major consensus guidelines generated by spine trauma surgeons are unable to suggest a safe window of time within which to initiate VTEp, recommending instead that VTEp simply be initiated “as soon as possible”[35].

Based on the limited available literature, instituting VTEp <72h after SCI appears to be safe[34,36–37]. Recent evidence suggests that even earlier VTEp initiation (<24-48h) may be safe and does not increase bleeding events[38–40]. Even among patients with operatively managed spine trauma, VTEp initiation <48h appears to be safe in terms of bleeding risk and effective in terms of mitigating VTE[41–42]. Existing studies are largely single-center retrospective endeavors and will necessitate validation with prospective multicenter evaluation. Key studies on the optimal time to VTEp initiation after spine injury are summarized in Table 3.

The evidence surrounding VTEp agent selection for patients with SCI is also sparse, with one study demonstrating comparable VTE rates after SCI when prophylaxis was achieved with UH versus LMWH[37]. Conversely, others have shown improved VTE rates and lower or comparable risk of bleeding complications with the use of LMWH instead of UH for VTEp after SCI[43–44].

Part of the challenge in the rigorous scientific examination of this topic is the heterogeneity of these injuries. For example, patients with vertebral column fractures and no neurologic deficit are likely to differ in VTE risk from patients with true SCI due to degree of hindered mobility. The motor level and completeness of SCI may affect VTE risk as well. For instance, a patient with a complete SCI (i.e. ASIA A) SCI in the mid cervical cord will have a greater degree of immobility than a patient with similarly severe SCI in the distal thoracic spinal cord. These nuances may impart different degrees of VTE risk and therefore there may be subsets of spine-injured patients who require more or less aggressive approaches to early VTEp initiation. The ASIA classification is summarized in Supplemental Digital Content Table 1[45].

Moving forward, it will be important to delineate subsets of spine injury patients and an optimal approach to VTEp for each based upon the level and completeness of injury. Specifically, patients with vertebral fractures both with and without SCI need to be investigated and analyzed separately. The impact of spine injury level (cervical, thoracic, or lumbar) on VTE risk should also be examined to determine whether the optimal time to VTEp initiation should take motor injury level into consideration. Further subtleties will also need to be established, including the need for routine follow-up imaging to check for hematoma expansion after initiation of VTEp and/or the role for MRI in the diagnosis or exclusion of epidural hematoma prior to commencing VTEp.

Conclusions

In general for trauma patients with high-risk injuries including abdominal solid organs, TBI, and spinal cord/column, VTEp initiation can and should be pursued early after trauma once clinical and/or radiographic injury stability has been confirmed. Early VTEp commencement, typically <48h from time of admission or, in the case of TBI, from time of stable CT Head is safe and effective in the prevention of VTE. Further research, particularly prospective multicenter clinical trials, is needed to more completely delineate the optimal time for VTEp initiation after solid organ, TBI, and spine injuries[46].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest

Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R13HL158206 (“Consensus Conference to Implement Optimal VTE Prophylaxis in Trauma”). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Author ERH reports research funding from The Patient-Centered Outcomes Research Institute (PCORI), the Agency for Healthcare Research and Quality (AHRQ), the NIH/NHLBI, and the DOD/Army Medical Research Acquisition Activity. Otherwise, the study authors have no conflicts of interest or disclosures of funding to declare.

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Table 1.

Key Studies on the Optimal Time to VTEp among Patients with Solid Organ Injury.

First Author	Senior Author	Journal	Year	Study Design	Number of Patients	Study Population	Early VTEp Definition	Important Findings - Early VTEp Is Associated with:
Joseph	Rhee	*Am J Surg*	2015	Retrospective Cohort	n=116	Nonoperative blunt solid organ injuries	≤48h	= Bleeding complications = VTE
Khatsilouskaya	Schnuriger	*World J Surg*	2017	Retrospective Cohort	n=179	Nonoperative blunt solid organ injuries	<72h	= Bleeding complications = VTE
Murphy	Vogt	*Can J Surg*	2016	Retrospective Cohort	n=162	Nonoperative blunt solid organ injuries	<48h	= Bleeding complications = VTE
Schellenberg	Demetriades	*World J Surg*	2019	Prospective Cohort	n=118	Nonoperative blunt solid organ injuries	≤48h	= Bleeding complications ↓ DVT = PE
Skarupa	Joseph	*J Trauma Acute Care Surg*	2019	Retrospective Cohort (TQIP)	n=36,187	Nonoperative blunt solid organ injuries	≤48h	= Bleeding complications ↓ DVT ↓ PE

VTEp, venous thromboembolism prophylaxis. VTE, venous thromboembolic events. DVT, deep vein thromboses. PE, pulmonary emboli. TQIP, Trauma Quality Improvement Program. =, comparable. ↓, reduced.

Table 2.

Key Studies on the Optimal Time to VTEp among Patients with Traumatic Brain Injury.

First Author	Senior Author	Journal	Year	Study Design	Number of Patients	Study Population	Early VTEp Definition	Important Findings - Early VTEp Is Associated with:
Byrne	Nathens	*J Am Coll Surg*	2016	Retrospective Cohort	n=3,634	TBI with Head AIS ≥3 and GCS ≤8	<72h	↓ DVT ↓ PE = delayed neurosurgical intervention = mortality
Byrne	Seamon	*JAMA Surg*	2022	Retrospective Cohort (TQIP)	n=4,951	TBI with neurosurgical intervention <24h	24h periods*	↓ VTE ↑ delayed neurosurgical intervention ↑ mortality
Farooqui	Litofsky	*J Neurosurg*	2013	Retrospective Cohort	n=236	TBI with ICH	24h after stable CTH	↓ DVT = PE = ICH progression
Phelan	Minei	*J Trauma Acute Care Surg*	2012	Randomized Controlled Trial	n=62	Small TBI with stable CTH at 24h	At 24h	= VTE = ICH progression = mortality

* instead of Early vs. Late groups, this study utilized 24-hour periods (days).

VTEp, venous thromboembolism prophylaxis. VTE, venous thromboembolic events. DVT, deep vein thromboses. PE, pulmonary emboli. TQIP, Trauma Quality Improvement Program. ICH, intracranial hemorrhage. =, comparable. ↓, reduced, ↑, increased.

Table 3.

Key Studies on the Optimal Time to VTEp among Patients with Spine Injury.

First Author	Senior Author	Journal	Year	Study Design	Number of Patients	Study Population	Early VTEp Definition	Important Findings - Early VTEp Is Associated with:
Aito	Cominelli	*Spinal Cord*	2002	Prospective Cohort	n=275	Traumatic SCI (ASIA A-D)	<72h	↓ DVT = PE
Chang	Holcomb	*J Trauma Acute Care Surg*	2011	Retrospective Cohort	n=501	Traumatic SCI	≤48h	↓ DVT = intraspinal hematoma expansion
Hamidi	Joseph	*J Surg Res*	2021	Retrospective Cohort	n=526	Isolated operative traumatic spine fractures	≤48h	↓ DVT = PE = intraspinal hematoma expansion
Khan	Joseph	*J Am Coll Surg*	2018	Retrospective Cohort (TQIP)	n=8,552	Nonoperative spine trauma	<48h	↓ DVT ↓ PE
Kim	Coimbra	*Spine*	2015	Retrospective Cohort	n=206	Operative traumatic spine fractures	<48h	= DVT = PE = neurologic progression

VTEp, venous thromboembolism prophylaxis. SCI, spinal cord injury. ASIA, American Spinal Injury Association impairment scale. DVT, deep vein thromboses. PE, pulmonary emboli. TQIP, Trauma Quality Improvement Program. =, comparable. ↓, reduced, ↑, increased.