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Review Article

Trauma-induced pulmonary thromboembolism: What's update?

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ABSTRACT

Trauma-induced pulmonary thromboembolism is the second leading cause of death in severe trauma patients. Primary fibrinolytic hyperactivity combined with hemorrhage and consequential hypercoagulability in severe trauma patients create a huge challenge for clinicians. It is crucial to ensure a safe anticoagulant therapy for trauma patients, but a series of clinical issues need to be answered first, for example, what are the risk factors for traumatic venous thromboembolism? How to assess and determine the status of coagulation dysfunction of patients? When is the optimal timing to initiate pharmacologic prophylaxis for venous thromboembolism? What types of prophylactic agents should be used? How to manage the anticoagulation-related hemorrhage and to determine the optimal timing of restarting chemoprophylaxis? The present review attempts to answer the above questions.

Introduction

Trauma patients who survive the initial injury are at a high risk of secondary multiple organ dysfunction and thromboembolic events, both of which are major contributors to subsequent morbidity and mortality.[1–3] Venous thromboembolism (VTE), clinically presenting as pulmonary thromboembolism (PTE) and deep venous thrombosis (DVT), is a life-threatening but potentially preventable complication after trauma. Trauma as a strong trigger factor for VTE is a leading cause of global death and disability.[4–7] Severe trauma patients faced a double threat of post-traumatic bleeding and post-traumatic thrombotic events, as pulmonary embolism (PE) is commonly PTE, which will be focused in this review.

Acute trauma-induced coagulopathy is inevitable following severe trauma such as shock, low perfusion and vascular injury.[8–10] Fröhlich et al.[11] reported that one in every four patients with severe trauma at admission had abnormal blood clotting with laboratory defined signs of coagulopathy. The therapeutic focus is to identify bleeding and hypercoagulability as soon as possible and give targeted treatment.[8,12]

Base on that trauma-induced coagulopathy is a potentially preventable and controllable disease,[13] this review focuses on the pathogenesis, risk factors, diagnosis and preventative strategies for post-traumatic VTE, so as to reduce the incidence of trauma-related thromboembolic events. Patients who survive the initial injury are thought to emerge from dysfunctional or exaggerated responses to major tissue damage and shock, exacerbated by iatrogenic factors such as transfusion and surgical intervention.[14,15]

Epidemiological characteristics of post-traumatic VTE

Incidence of post-traumatic VTE

The incidence of post-traumatic VTE can be up to 13 times more than that of non-traumatic patients.[16] Base on the sample size, types of trauma, diagnostic methods, and means of VTE prevention during trauma treatment, the incidence of post-traumatic VTE varies greatly among different study designs: from 0.27% to 65% and remains high after major traumas even with the initiation of prophylactic antithrombotic therapy within 48 h. Study of Bahloul et al.[17] showed that 60% of patients with an injury severity score ≥45 developed hypercoagulability within 1 h of injury and these patients were four times more likely to die than those without clotting abnormalities (46.0% *vs.* 10.9%). Once post-traumatic PTE occurs, the mortality will be greatly increased.[18] VTE can occur in hospitalized patients with acute

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trauma as well as in the community where the incidence of VTE following trauma is 12%.[19]

Characteristics of post-traumatic VTE

The peak period and duration of traumatic VTE

Patients are at a risk of hypercoagulability early after traumatic injury, although the highest risk appears at one week after trauma. Lots of PTE is diagnosed within the first few days, and a significant number of PTE is found as early as the first 24 h after injury; and the hypercoagulable state persisted even after patient discharge.[20,21] A recent study shows that the occurrence of PTE in trauma patients within 72 h accounts for 41.5% of total PTE, and the mortality rate of PTE patients are significantly higher than that of non-PTE patients after 72 h.[22] A retrospective study[23] enrolled 267,743 trauma patients including pelvic fractures, vertebral fractures, and spinal cord injuries (SCIs) showed that the incidence of VTE was the highest within 3 months and decreased to normal after 12–15 months. This study also found that the decrease of VTE risks differs over time based on the types of trauma. It is showed that the VTE risk decreases more rapidly in patients with pelvic fractures and vertebral fractures than in those with spinal cord injuries. The recurrence of VTE occurred mostly in 6–12 months, and the recurrence risk lasted for at least 10 years for previous VTE. The patients with neurological disease, local paralysis, or malignancy are at a higher risk of recurrence than others. It is worth mentioning that regardless of the types of injury, trauma-induced coagulopathy generally resolves within 24 h of trauma, and hypercoagulability becomes more common.

The features of traumatic DVT

Traumatic DVT can occur on either injured extremity or uninvolved lower extremity, preoperatively or postoperatively. A study[24] enrolled 1454 patients with lower extremity fractures found that the incidence of preoperative DVT in the uninjured lower extremity was 9.63% whereas the postoperative incidence was 20.29%. Age and female were independent risk factors for preoperative DVT in the uninjured lower extremity. They found that 5.39% of patients with preoperative peripheral DVT presented no thrombosis postoperatively; conversely, 34.73% of patients with no preoperative thrombosis developed postoperative peripheral (33.83%), central (0.30%), or mixed DVT (0.60%), respectively. Another study[25] enrolled 1179 patients with tibial plateau fractures and showed that 192 of them (16.3%) had a preoperative DVT, with the incidence rate of proximal DVT being 1.0% and distal DVT being 15.3%. The average interval between fracture occurrence and diagnosis of DVT was 3.5 days (median, 2 days), range 0–19 days. DVT involved the injured extremity in 166 (86.4%) patients, both extremities (injured and uninjured) in 14 patients (7.3%) and the uninjured extremity alone in 12 patients (6.3%). This study also identified six risk factors to be associated with DVT, respectively gender (male *vs.* female), hypertension, open fracture, alkaline phosphatase >100 u/L, sodium concentration <135 mmol/L, and D-dimer > 0.5 mg/L.

The relation between types of trauma and risk of VTE

Compared with the severity of trauma, the types of trauma have greater influence on VTE although Tan et al.'s[26] meta-analysis did not support the same conclusion. Major orthopedic trauma has the highest incidence of VTE. The incidence of VTE in pelvic fracture, traumatic brain injury (TBI), SCI, and lower limb fracture was 32.7%, 25.0%, 11.0%, and 9.2%, respectively.[11,27–29] The onset of thrombotic events is more common after TBI because of the rich tissue factors (TF) in the brain. The risk of VTE is further increased when TBI patients have intracranial hemorrhage or multiple craniocerebral injury.[30] Patients with multiple fractures have a higher risk of VTE than those with single fractures, meanwhile pelvic fracture patients are more likely to develop PTE than those with single tibial or femoral fractures.[31] Blunt injuries are accompanied with a higher incidence of VTE than sharp injuries. Patients with severe abdominal injuries, vascular injuries, and younger patients are at higher risks for VTE, and those with neurological diseases, local paralysis, or malignancy are at higher risks of recurrent VTE than others.[32]

The relation between pathophysiology of acute traumatic coagulopathy and the mechanisms of traumatic VTE

Pathophysiology of acute traumatic coagulopathy

Acute traumatic coagulopathy consists of traumatic coagulopathy caused by primary endogenous immediately after trauma such as hypoperfusion, shock, tissue injury, trauma, etc. and iatrogenic coagulopathy, which is aggravated in further sequalae, such as dilution (hemodilution) or anticoagulants.[33,34] In recent years, however, experts have pointed out that activation of the protein C pathway is associated with tissue hypoperfusion/shock. Combined trauma and hypoperfusion/shock may lead to a hypocoagulable state via formation of an anticoagulant complex (thrombomodulin complex), which converts protein C into activated protein C, leading to an inactivation of the coagulation factors V and VIII. The activated protein C in surplus also consumes plasminogen activator inhibitor-1, which may lead to an increase in tissue plasminogen in the context of severe trauma.[35,36]

Acute traumatic coagulopathy is divided into three stages. In the first stage, multiple hemostasis pathways are activated immediately after trauma, with fibrinolytic hyperactivity associated with tissue damage and/or tissue hypoperfusion. The second phase deals with factors related to resuscitation therapy. The third stage is the pre-thrombosis state associated with the acute phase reaction.[37] The consumption of protein C associated with tissue injury, the increase of thromboregulatory protein level and the decrease of factor V level indicate the important role of protein C pathway in acute traumatic coagulopathy. The hypoperfusion of tissue in the early stage of trauma may change the function of thrombin from promoting fibrin formation to activating the protein C system and generating systemic anticoagulant response. Hypoxia, acidosis, low temperature and other factors affect the function of platelets and thrombin, and then aggravate fibrinolytic hyperactivity. Tissue damage itself activates the immune system and further activates the clotting pathway through protein degradation and oxidative stress, which aggravates tissue damage. Non-standard resuscitation and traumatic bleeding can lead to dilution of coagulation factors and aggravate acute traumatic coagulopathy.[9,10]

Mechanisms of traumatic VTE

Clinically VTE is the result of multifactorial interactions (gene-gene and/or gene-environment). When the threshold is exceeded, the onset of VTE will be triggerred.[32,38] Venous stasis following injury was already described by Rudolf Virchow in 1856 as one of the main etiologic factors for VTE.[39] The occurrence of VTE is closely related to three aspects: blood stasis, vascular endothelial injury and onset of blood hypercoagulability rapidly after trauma. Immobilization was required for all the trauma patients with TBI, SCI, pelvic fracture/long bone fracture, etc., which results in venous blood stasis. In addition, the significantly reduced capability of calf muscle pump further slows down the rate of venous return in the lower extremities. For trauma patients, the exogenous coagulation pathway will be initiated by TFs released after tissue injury. TFs

bind to activated factor VII and further activates factor X, to promote the activation of prothrombin into thrombin, which converts fibrinogen into fibrin and activates platelets to promote thrombosis. In general, TFs are expressed in cardiomyocytes, bronchial and alveolar epithelial cells, brain astrocytes, etc., and are separated from blood circulation. Inflammation and hypoxia after vascular endothelial injury in trauma patients can promote the expression of TFs released by neutrophils and macrophages. Once these organs are injured, TFs will be released into the blood and trigger clotting. It has been found that progressive trauma-induced coagulopathy is often associated with microparticles and increased thrombin production, in addition to TFs. Cheng et al.[40] reported that the TF pathway inhibitor, thrombin, Xa-TF pathway inhibitor were involved in the occurrence of hypercoagulability in trauma patients. Interestingly, platelets are involved in the thrombus of trauma patients (both hemostatic and innate immune responses against injured tissue), such as offering a wide array of cell surface receptors at a high density, enabling rapid reaction to a range of stimuli, making sure close endothelial contact and can be deployed rapidly and simultaneously by possessing a diverse toolkit of molecular effectors. This dual regulation of inflammation and thrombosis, known as immunothrombosis, plays a key role in understanding the response to injury.[41–44] Cardenas et al.'s study[45] has indicated similar associations between trauma-induced impairment in platelet aggregation and fibrinolytic shutdown phenotypes. Obviously, acute trauma coagulopathy creates favorable conditions for thrombotic events which involve multiple factors.

Risk factors for traumatic VTE

There are several risk factors that affect the occurrence of VTE in trauma patients. Obesity and advanced age were found to be independent risk factors for VTE after discharge.[46] Age and smoking can increase the risk of VTE,[46] and a meta-analysis[47] showed that the risk of VTE was nearly doubled in people over 60 years old. The acute physiology and chronic health evaluation II score on intensive care unit admission, ventilator-acquired pneumonia, heart failure, history of hypertension, duration of surgery and bed rest, cancer, diabetes, varicose veins, obesity, or blood transfusion of more than 5 units can all contribute to VTE. Patients with a history of VTE had a more than 5-fold increased risk of developing post-traumatic VTE. A 5-year study[48] of the incidence of trauma-related VTE on 662 patients diagnosed with DVT and 258 with acute PTE found that 84 of these patients were trauma-related, i.e. 56 (8.5%) with DVT and 29 (10.9%) with PTE. The majority were diagnosed as inpatients (64.3% *vs.* 28.6%; $p = 0.002$), compared to DVT where a significantly higher proportion was constituted by outpatient diagnosis (71.4% *vs.* 35.7%; $p = 0.002$). Patients diagnosed with PTE were more likely to have a history of recent surgery (51.9% *vs.* 28.6%; $p = 0.03$), immobilization (25.0% *vs.* 8.9%; $p = 0.04$), and a prior PTE (7.4% *vs.* 0.0%; $p = 0.03$) as compared to those with DVT. Studies also found that the comorbidity of obesity, hypertension, diabetes mellitus, and hypercholesterolemia in VTE patients (52.9%, 25.0%, 17.9% and 17.9%, respectively) was high than that in non-VTE group, despite no significant difference was observed between the two groups.[48,49]

Diagnosis of traumatic VTE

Clinical manifestations and probability assessment system

Up to now, there are not any ideal scoring systems for traumatic VTE patients. The Wells score is important in the differential diagnosis of non-high-risk PTE patients,[50,51] but its predictive value in trauma patients is limited.[52] The trauma embolic scoring system (TESS) for VTE may be an objective measure of classifying VTE risk for patients with trauma. Studies suggest that an optimal high-risk cut-off value of TESS ≥ 7 demonstrates a high sensitivity in predicting VTE.[53,54]

Laboratory tests

PT/INR ratio

Although a prolonged PT alone may indicate the presence of traumatic coagulopathy, studies showed that PT/INR >1.2 was clearly associated with not only traumatic hemorrhagic shock-related mortality, but also VTE and all-cause mortality.[55,56]

D-dimer level

D-dimer has an important value of excluding VTE, whose level is closely related to the occurrence of traumatic VTE.[57] Masuda et al.[58] indicated the best time to detect D-dimer was 2 weeks after SCI, with a cutoff value of 0.016 mg/L (sensitivity 77.3%, specificity 69.2%). Whereas other studies showed that the highest value of D-dimer should be detected within 2 days or 1 week after trauma.[59,60] Due to the presence of injury and bleeding in trauma itself, the predictive value of D-dimer is limited.[61] A new study showed that the measurement of D-dimer level should be complemented by routine color doppler ultrasound for detecting DVT within 6 months post-SCI. D-dimer screening alone for DVT detection revealed a better effect with the during of >6 months, compared with that within the periods of 3 weeks–3 months and 3–6 months.[62]

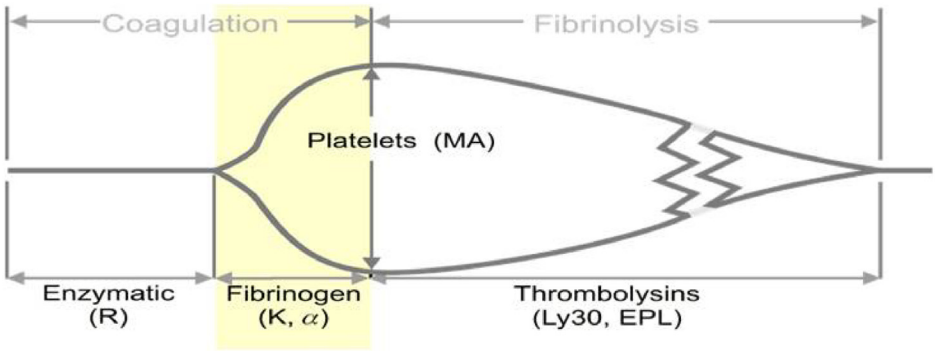

Fig. 1. The comprehensive view of thromboelastogram.

Soluble fibrin monomer complex (SFMC)

SFMC can reflect the early changes of thrombus formation and can be increased within 1 day after the occurrence of trauma or even increased before the formation of thrombus. SFMC level will decline the first day after thrombus formation. Studies have shown that the combination of SFMC and D-dimer will improve the sensitivity of VTE diagnosis.[63]

Platelet monitoring

As a sensitive and reversible indicator of bleeding, coagulation and inflammation, platelet has obtained great attention. Dynamic monitoring of both the count and function of platelets plays an important guiding role in understanding the overall changes of patients and helping clinicians to make treatment decisions timely.[42,64,65]

Thromboelastogram (TEG)

TEG have been proved to be useful in many studies because it can reflect the complete changes of coagulation and fibrinolysis system in the process of blood clot formation, and can reflect the function of coagulation factors, fibrin, platelet and fibrinolysis. TEG can help clinicians to estimate the clotting status of trauma patients: the more complex the clotting status, the more detailed information TEG can offer.[66–69] Unfortunately, TEG has limited guidance in the presence of shock, hypothermia, and coagulation disorders in patients with severe trauma. The comprehensive view of TEG (Fig. 1) and the main parameters of TEG such as reaction time (R), coagulation time (K)/(α), platelet function and fibrinolytic function and its significance have been shown in Table 1.

Imageological diagnosis

Venous ultrasound of lower limbs

Venous ultrasound has been widely used as a diagnosis method for DVT in trauma patients for its non-invasive, repeatable and bedside property. At the same time, venous ultrasound can identify the nature of lower limb thrombus, i.e. fresh thrombus, old thrombus, etc. It is worth noting that ultrasound diagnosis is more sensitive to embolisms in the femoral and popliteal veins, but less sensitive to those in the proximal iliac and distal intermuscular veins. Weekly venous compression duplex should be considered in patients at a high risk of VTE who is unable to start or maintain on pharmacologic prophylaxis as this is associated with a reduced PE rate.[62]

Computed tomography pulmonary angiogram (CTPA) and lung perfusion/ventilation scan

Intravenous pulmonary angiography used to be a gold standard for the diagnosis of DVT, but it has been rarely used now because of its several disadvantages, such as high price, many contraindications, and invasion, etc. CTPA or lung perfusion/ventilation scan has become an alternative to pulmonary angiography for the diagnosis of PTE.[70] Low doses of CTPA can be safely used in trauma patients even in pregnancy. CTPA is more sensitive to the main and subsegmental parts of pulmonary artery, whereas lung perfusion/ventilation scan is more suitable and meaningful for the diagnosis of PTE below the subsegment level of pulmonary artery.

The machine learning predictors

Improved risk stratification may not only prevent unnecessary invasive testing in patients for whom DVT cannot be ruled out using the existing methods, but also allow for more targeted use of prophylactic anticoagulants, as well as earlier diagnosis and treatment, preventing the development of pulmonary emboli and other sequelae of DVT. The machine learning predictors can be obtained for DVT risk prediction on hospitalized patients at 12-h and 24-h windows.[71]

Treatment and prevention of trauma VTE

The treatment of trauma-induced VTE is the same as other causes. A therapeutic dose of anticoagulants should be used timely if there is no anticoagulant contraindication (Table 2).[72–77] Systematic thrombolytic therapy, such as, recombinant tissue type plasminogen activator (r-tPA), 50 mg intravenous infusion for 2 h, is recommended only for patients at a high risk of PTE.[70] For trauma patients with contraindications to systemic thrombolysis, pulmonary interventional thrombolysis, or thrombus aspiration can be considered, even under the condition that extracorporeal membrane oxygenation was needed for help. While unfractionated heparin and the low molecular weight heparin (LMWH), enoxaparin, is most commonly dosed at 5000 units every 8 h and 30 mg every 12 h, respectively. In TBI evaluation, the anti-factor Xa assay allows for assessment of LMWH within a targeted range without increased risk of intracranial hemorrhage progression.[78]

The prevention methods of VTE include mechanical prophylaxis and chemical prophylaxis. This review focuses on primary prophylactic anticoagulation for trauma patients, such as (1) how to assess? (2) The means of prophylaxis? (3) The optimal timing, frequency, and duration of prophylaxis? (4) Who should be delayed in pharmacologic prophylaxis? (5) The initial dose, etc.

Relevant guidelines[79,80] suggest an important basis for active assessment of patients' blood coagulation state and early prophylaxis. However, patients with intracranial injury tend to receive a delayed chemoprophylaxis. Severe trauma patients face the dual threat of traumatic bleeding and hypercoagulable thrombus

Table 1
The parameters of thromboelastogram and its significance.

Parameters	Normal range	Significance
Reaction time (R)	4–9 min	It indicates that there is no fibrin formation in the sample, which reflects the coagulation state. An increase in R indicates a prolonged clotting time, which can be corrected by fresh frozen plasma. Whereas, the decline in R shows hypercoagulability, and thus anticoagulant therapy is need.
Coagulation time (K)/(α)	1–3 min/53°–73°	It indicates that fibrin begins to form in the tested sample. Decline in K or increase in α indicates a high fibrinogen level and the need for anticoagulant therapy. An increase in K or a decrease in α indicates a low fibrinogen level, which can be treated with fresh frozen plasma or cryoprecipitation.
Platelet function (MA)	50–70 mm	MA suggests the maximum size of thrombosis. A decrease in MA indicates low platelet function and the need for platelet transfusion. An elevated MA indicates the use of antiplatelet drugs.
Fibrinolytic function (LY30/EPL)	0–8%/0–15%	It shows the fibrinolytic function. Elevated LY30 and/or EPL both indicate fibrinolytic hyperactivity, which requires the combination of MA (MA > 70 mm, secondary fibrinolytic hyperactivity; MA < 50 mm, primary fibrinolytic hyperactivity). Hyperfibrinolysis occurs within 24 h in patients with severe trauma, and LY30 > 3% is usually used as an important basis for tranexamic acid in patients with traumatic bleeding.

MA: maximum amplitude.

Table 2
Anticoagulant, dosage (prophylactic/therapeutic) and special considerations for trauma patients.

Anticoagulant	Therapeutic dose	Prophylactic dose	Special considerations
UFH	80 unit/kg IV bolus, followed by an 18-unit/kg/h infusion	5000 units every 8 h	Caution of heparin-induced thrombocytopenia
Enoxaparin	1 mg/kg subQ BID	30 mg every 12 h	Caution of heparin-induced thrombocytopenia
Fondaparinux	<50 kg: 5 mg subQ daily 50–100 mg: 7.5 mg subQ daily >100 kg: 10 mg subQ daily	–	Initiate warfarin within 72 h and give concomitantly for at least 5 days.
Edoxaban	60 mg po once daily; 30 mg once daily if body weight ≤60 kg	–	Not for use in patients with CrCl >95 mL/min. Dose after 5–10 days of initial therapy with a parenteral anticoagulant
Rivaroxaban	15 mg po twice daily for 3 weeks, then 20 mg once daily at least 6 months	–	Take with food to improve absorption. Dose after 5–10 days of initial therapy with a parenteral anticoagulant
Dabigatran	150 mg po BID; 110 mg BID for patients ≥80 years old	–	Reduce dose to 110 mg BID for patients ≥80 years or ≥75 years with at least one bleeding risk factor.

UFH: unfractionated heparin; subQ: subcutaneously; BID: twice a day; CrCL: creatinine clearance; IV: intravenous injection; po: profess to convinced.

events.[81] Unfortunately, there are still many uncertainties about how to safely and effectively use the thromboprophylaxis in severe trauma patients, even with the updated medical progress.[82,83] It is difficult to decide the optimal strategy for VTE prevention because trauma patients may have real or perceived contraindications to prophylaxis, which affects the timing of preventive measures. A meta-analysis[84] showed that the optimal plan for the prevention of traumatic VTE has not been reached, due to many factors such as the poor study quality, study design, population characteristics, outcome definition, etc. Chemical anticoagulation has clear therapeutic effects, but there is an unavoidable risk of bleeding. Therefore, although hypercoagulability may appear in severe trauma patients within 24 h, how to prevent its development safely and effectively still needs to be further explored, due to each trauma modality has different complications. A recent study from the Netherlands and USA[85] indicated that more early commencement protocol (chemical prophylaxis started within 48 h after arrival) resulted in reduced thrombosis events almost twice as much compared with a delayed initiation of treatment. However, most episodes of VTE developed while receiving recommended prophylaxis. Early chemical thromboprophylaxis appears to be safe if started early, not significantly increasing the bleeding complications.[86] Studies also indicated that except for spine and intracranial surgery, almost no existing data demonstrate that continuing chemoprophylaxis without interruption leads to increased bleeding complications. In patients with a low risk of bleeding complications and a high risk of VTE, chemoprophylaxis should be continuously used.[87–89]

Mechanical prophylaxis

Mechanical prophylaxis is recommended for patients with moderate to high risks of VTE no matter concurrent pharmacologic prophylaxis or not. Mechanical prophylaxis includes stretch socks, intermittent pneumatic compression, and inferior vena cava (IVC) filters, which can be used alone or combined with chemoprophylaxis. Indications and contraindications for mechanical prophylaxis need to be carefully evaluated in order to avoid the occurrence of complications,[90] e.g. mechanical compression devices may lead to local soft tissue injury, bleeding and patient non-compliance. IVC filters may migrate, causing IVC occlusion or penetrating the vessel wall. Application of these techniques must be appropriately utilized even if it can be life-saving. Intermittent pneumatic compression lowers the DVT incidence if no pharmacologic prophylaxis is initiated and therefore is recommended for patients with contraindication to pharmacologic prophylaxis.[91–93] But intermittent pneumatic compression in critically ill patients who received pharmacologic prophylaxis failed to effectively reduce the incidence of DVT, although the DVT rate in this study was low and only 8% of the population were trauma patients.[94] It was found that a mobility protocol is safe in trauma patients and may reduce the rate of traumatic VTE.[95] On the contrary, prolonged maintenance of spinal precautions (>72 h) is associated with an increased immobility-associated DVT rate and physicians should focus on prompt, definitive care and early mobilization.[96]

Chemoprophylaxis

Geerts et al.[97] determined that the DVT rate without pharmacologic prophylaxis was 58% in severely injured trauma patients who undergo serial impedance plethysmography with lower extremity contrast venography. More recently, a systematic review[86] from 2020 evaluated 17 studies, and concluded that early chemoprophylaxis between 24 h and 72 h after injury is associated with a reduced VTE incidence without increasing intracranial hemorrhage in TBI patients, confirmed by a stable repeat head CT.

How to assess VTE risk?

An appropriate assessment of VTE risk will assist in determining which patients require pharmacologic prophylaxis. Patients with a TESS ≥7 is at a high risk of VTE and should receive prophylaxis earlier.[53,54] Studies have shown that an ISS ≥10 suggests that pharmacologic prophylaxis should be initiated as soon as possible, whereas patients with an ISS<10 are at a lower VTE risk and may not require pharmacologic prophylaxis.[46,53] Patients with minor trauma may not require pharmacologic prophylaxis. Pharmacologic prophylaxismay needs to be appropriately delayed for those patients with an active bleeding, coagulopathy, hemodynamic instability, solid organ injury, TBI, or spinal trauma.[86,98,99]

Optimal timing to initiate VTE prophylaxis and types of prophylactic agents

What needs to be emphasized is that a continuous prophylaxis therapy is crucial once initiated. Interruption of VTE prophylaxis for a period of 24 h or even missing a single dose is closely related to an increased risk of VTE.[100] Pharmacological prophylaxis should be continued or only stopped for significant or potentially significant bleeding events, development of heparin-induced thrombocytopenia, active hemorrhage and recent spine or intracranial surgery.

Optimal timing of VTE prophylaxis. VTE prophylaxis should be given to trauma patients at medium to high risks. Anticoagulant therapy should be synchronized with surgery in patients with pelvic fractures. Due to the rich TFs and other factors in the brain tissue of TBI

patients, the risk of VTE greatly increases. Therefore, anticoagulant therapy should be started within 24–48 h after cerebral hemorrhage event has been excluded, and chemoprophylaxis is the first choice for patients without contraindications. Additional stratification of TBI patients into moderate-risk and high-risk groups follows with a 72-h delay in VTE prophylaxis initiation and consideration of an IVC filter, respectively.[101]

Pharmacologic prophylaxis. Patients with severe trauma have a high risk of both hemorrhage and thrombus; it is a key issue to ensure the safety of anticoagulant therapy.[102] After deciding to start pharmacologic prophylaxis, the non-oral anticoagulants and initial dose should be determined individually. Many trauma patients require dose adjustment after initiating enoxaparin. Compared with LMWH may be superior for its more specific inhibitor of Xa. Both low dose unfractionated heparin (5000U Q12H) and LMWH (30 mg Q12H) enoxaparin administered after trauma can effectively prevent the occurrence of VTE and be safely adjusted based on the anti-Xa levels.[72,103] Weight-based and blood for the anti-Xa testing should be typically drawn 4 h after the third dose of enoxaparin, that with the target prophylactic levels falling in the range of 0.2–0.4 IU/mL (the target for therapeutic full anticoagulation is > 0.5 IU/mL) is recommended. But one larger retrospective study[104] reported no decrease in VTE rates with an anti-Xa-based regimen. As an inhibitor of the factor Xa, fondaparinux has been shown to be more effective in preventing VTE than LMWH in trauma patients.[105] Other studies have shown that fondaparinux is not inferior to LMWH in preventing post-traumatic VTE and does not increase the risk of bleeding.[106] However, fondaparinux has a long half-life and is metabolically cleared by the kidney, and once dose accumulation occurs, the risk of bleeding will be increased.[91] A multicenter, double-blind, randomized, controlled trial involved 3424 patients experienced total hip or knee arthroplasty shown that after received 5 days of rivaroxaban prophylaxis, extended prophylaxis with aspirin was not significantly different from rivaroxaban in the prevention of symptomatic venous thromboembolism.[107]

Duration of prophylactic anticoagulant therapy

The optimal postdischarge dose and duration of pharmacologic prophylaxis after trauma are not well defined. By now, the duration of pharmacologic prophylaxis may be considered for up to 4 weeks after the date of admission. For those who undergo major orthopedic surgery, pharmacologic prophylaxis may be extended up to 35 days from the date of surgery.[91] Trauma patients with TBI, orthopedic or spinal injuries, and those who undergo major surgeries are at a particular VTE risk and should be considered for post-discharge pharmacologic prophylaxis. A recent study[108] show that prolonged thromboprophylaxis for more than 28 days with LMWH significantly reduces the risk of VTE compared to thromboprophylaxis during hospital stay only, without increasing bleeding complications or mortality after major abdominal or pelvic surgery. The highest VTE risk occurs during the first 3 months after injury with approximately 1 year required until the VTE risk rate returns to that of general population.[109,110] Direct oral anticoagulants may also be considered for post discharge pharmacologic prophylaxis after isolated orthopedic injury.[107] Prophylactic anticoagulant therapy for SCI patients should be extended or even continued into the recovery period. Once VTE is present, anticoagulant therapy should be performed for at least 3 months.[70] Severe trauma patients with risk assessment profile score >10 have a ≥25% rate of VTE despite receiving prophylactic anticoagulation.[111] Studies show that the patients received tranexamic acid can significantly reduce the fibrinolytic activity and not increase the risk of VTE, even TEG, or other blood coagulation indexes within 24 h of admission shows the coming state of hypercoagulation status.[3,112] But a recent systemic review[113] indicated the use of tranexamic acid and fibrinogen concentrate was associated with the development of thromboembolic complications.

Management of anticoagulation-related bleeding

Determination of major bleeding and minor bleeding

The classification of bleeding has been simplified as major or nonmajor.[114] The former refers to bleeding that is associated with hemodynamic instability, requires transfusion (≥2 units of packed red blood cells) or results in a hemoglobin drop ≥20 g/L, occurs in an anatomically critical site such as intracranial hemorrhage and other central nervous system bleeds (e.g., intraocular, spinal). Thoracic, airway, pericardial, intra-abdominal, retroperitoneal, intra-articular, and intramuscular bleedings are considered critical as they may cause severe disability and necessitate surgical procedures for hemostasis. Intraluminal gastrointestinal bleeding is not considered a critical site bleeding; however, it can result in hemodynamic compromise. All the other bleedings are classified as minor bleeding.[115,116]

Management of major bleeding and minor bleeding

There is no indication to discontinue medication for minor bleeding, and studies have shown that minor bleeding during anticoagulation has no predictive value for major bleeding.[115–117] Stop the chemoprophylaxis once major bleeding is confirmed, maintain vital signs, and blood transfusion or specific reversal agents are recommended if necessary (Table 3).[118–123]

The optimal timing of restarting anticoagulation

The timing to restart anticoagulation is different, depending on the exact sites of anticoagulation-related bleeding, for example, 4–7 days after the stop of gastrointestinal bleeding (a multidisciplinary decision is required to restart anticoagulation), whereas, 4–8 weeks for intracranial hemorrhage and recheck by cranial CT.

Table 3
Recommended reversal agents for anticoagulant therapy.

Anticoagulant	First line reversal agent	Alternative reversal agent(s)
UFH	Protamine sulfate	
LMWH	Protamine sulfate	
VKA	4F-PCC	FFP
Dabigatran	Idarucizumab	PCC, aPCC
Direct oral factor-Xa inhibitors	Andexanet alfa PCC	aPCC
Fondaparinux factor	VIIa aPCC	Andexanet alfa

UFH: Unfractionated heparin; LMWH: low molecular weight heparin; VKA: vitamin K antagonist; 4F-PCC: 4-factor prothrombin complex concentrate; FFP: fresh frozen plasma; PCC: prothrombin complex concentrate.
aPCC: activated prothrombin complex concentrate.

The optimal timing of restarting chemoprophylaxis in trauma patient remains uncertain and ranges between 24 h and 72 h. There are no clear data to guide the decision making until now.[124]

Vena cava filter

IVC filters may be considered in the setting of proximal DVT or PE when there is a contraindication to appropriate therapeutic anticoagulation. The use of prophylactic IVC filters in trauma patients is controversial, but should be considered in trauma patients at a very high-risk of VTE who cannot receive chemoprophylaxis for a long period because of the increased bleeding risk.[123–125] The IVC filters should be removed as soon as protection is no longer needed or the patient can safely receive chemoprophylaxis or therapeutic anticoagulation, to avoid long-term complications related to IVC filters.[126,127]

But there is study showed that a prophylactic IVC filter did not lower the incidence of PE or mortality, which established the lack of utility of early prophylactic placement of an IVC filter in this population.[128]

Take home messages

(1) The mechanisms of traumatic coagulopathy are complex, severe trauma patients faced a double threat of post-traumatic bleeding and post-traumatic thrombotic events soon after injury.
(2) Hypercoagulability exists early after the traumatic injury, although one week after trauma is the time-point with a higher risk of VTE. A significant number of VTE cases have been reported to be diagnosed as early as the first 24 h after injury and the hypercoagulable state persisted even after discharged.
(3) TESS $\geq$ 7 or ISS $\geq$ 10 suggests that pharmacologic prophylaxis should be initiated as soon as possible. Patients with higher acute physiology and chronic health evaluation II score on intensive care unit admission, ventilator-acquired pneumonia, heart failure, history of hypertension, duration of surgery and bed rest, cancer, diabetes, varicose veins, obesity, or blood transfusion of more than 5 units may all contribute to VTE incidence. A rapid and timely diagnosis and treatment is necessary.
(4) Effective monitoring (such as TEG and anti-Xa levels) and the optimal timing for mechanical and/or chemoprophylaxis are the most effective means to prevent venous thrombus events. Non-oral anticoagulants are routinely recommended for primary prophylaxis, whereas oral anticoagulants were used for secondary prevention if there are no anticoagulation contraindications and should not be interrupted within 3 months.
(5) Pharmacological prophylaxis should only be held or stopped for significant or potentially significant bleeding events. The optimal timing of restarting anticoagulants depends on the specific condition of the patient.

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Declaration of competing interest

The authors declare no conflicts of interest or financial interests.

Author contributions

Yu-Hong Mi is responsible for data analysis and manuscript composition. Ming-Ying Xu did data collection. Both the two authors approved the drafting, editing and publication of this article.

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