

# Venous Thromboembolic Sequel of Head Injury: A Narrative Review

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## Abstract

In this systematic review, we detailed the current understanding and controversies on venous thromboembolism as the sequel following traumatic brain injury (TBI). The review was conducted on the literature survey to find the thromboembolic morbidities in TBI patients. This review presented the thromboembolic sequel of patients with TBI by a comprehensive focused assembly of research publications by searching various resources. A search strategy with specific inclusion criteria was performed in PubMed, Cochrane, Web of Science, and the WHO Global Health Library. TBI is related with the incremental presence of spectrum of thromboembolic disorders from primary and secondary injuries by the significant increases in the concentrations of the initiating factors of the coagulation cascade. The incidences of thromboembolism vary on factors like the severity of TBI, methods of prophylaxis used or the processes to diagnose embolic involvement. The most effective time for the initiation of antithrombotic therapy chemoprophylaxis should be initiated after 24 h or after 72 h in patients with brain trauma is still a controversial issue. Patients with brain injury are at increased risk for thromboembolism for which prophylaxis and timely management are highly recommended, and this should be available in all levels of care.

**Keywords:** Sequel, traumatic brain injury, venous thromboembolism

## INTRODUCTION

Trauma increases the possibility of venous thromboembolism (VTE), leading to higher mortality in the hospitalized population.<sup>[1-3]</sup> Traumatic brain injury (TBI) is considered a global public health issue; About 75%–80% are minor injuries and more frequent among adolescents and young adults.<sup>[4,5]</sup> The Centers for Disease Control and Prevention estimated 1.7 million persons as annual victims TBI, 275,000 are hospitalized, and 52,000 die inclusive of different postinjury

complications.<sup>[6]</sup> This manuscript presents a narrative review of the VTE reported in the published literature of patients with TBI.

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## METHODS

We explored a comprehensive, focused collection of research publications by searching various resources; University publications, hospital-based studies, retrospective data mining, surveys, presentations, meeting, and personal communications about recent surveys not included in previous analyses in which long-term thromboembolic sequel of traumatic brain injuries were reported. A search strategy with specific inclusion criteria was performed in PubMed, Cochrane, Web of Science, and the WHO Global Health Library. The literature search for “TBI” and downstream “VTE” in PubMed with specific subject headings related to “TBI” (medical subject heading [MeSH] Terms) OR AND “VTE” (complete fields), OR AND “injury” (complete fields), “head injury” (complete fields) AND “thromboembolism” (MeSH Terms) was used as the search terms for each database. All the crucial items were identified for inclusion in this review that reported on “TBI” and “VTE” from 1966 to 2017. Any other published reports relating “TBI” and “VTE” in South-east Asia including India, were also explored. The research works were further classified into clinical and epidemiological studies for better internalization. The main outcome variables were specific patterns of TBI and associated thromboembolism from published reports.

## EPIDEMIOLOGY

Worldwide, the new cases of VTE are 1–2/1000 patients/year<sup>[1]</sup> and the incidence of deep-vein thrombosis (DVT) after trauma is approximately between 6% and 58%.<sup>[2]</sup> The United States researchers reported nearly 300,000 deaths/year from VTE.<sup>[3]</sup> VTE occurs in approximately 25% of persons with isolated brain lesions and up to 50% of polytraumatized individuals with brain injuries.<sup>[7]</sup> The TBI is an independent risk factor to develop thromboembolic complications,<sup>[8]</sup> due to prolonged immobilization, systemic hypercoagulability,<sup>[3,9,10]</sup> and delay in the onset of prophylaxis.<sup>[7]</sup> Out of the hospitalized patients with TBI, 54% are at risk of VTE.<sup>[11]</sup> Despite this incidence of VTE in neurosurgical patients varies between 19% and 54% taking into account the prophylactic measures, timely diagnosis, and prolonged stay (preoperative and postoperative).<sup>[12]</sup>

## PATHOPHYSIOLOGY

TBI is classified as primary and secondary lesions. The primary lesions occur due to an external mechanical impact on the head<sup>[4]</sup> that causes damage to blood vessels and brain tissue,<sup>[13]</sup> and their severity depends on the force exerted on the brain. Subsequently, an alteration of the blood–brain barrier, hemodynamic instability, and activation of the immune system are observed, triggering greater neurological damage that corresponds to a secondary cerebral injury.<sup>[14]</sup> The secondary lesions also include excesses of the free radicals, excessive release of neurotransmitters, and mitochondrial dysfunction among other organic alterations that seek to compensate for the instability caused by the impact.<sup>[13]</sup>

Excessive synthesis and neurochemical releases alter blood flow, ion homeostasis, and downstream metabolic effects.<sup>[4]</sup> Secondary injuries may occur due to emboli production or hemorrhagic progression, probably due to mechanisms such as tissue factor release, hypoperfusion, platelet dysfunction, and disseminated intravascular coagulation.<sup>[15]</sup> The disruptions of the neuronal and axonal cell membranes lead to the release of neurotransmitters and ionic changes.<sup>[16,17]</sup>

## INCIDENCE AND RISK FACTORS BETWEEN TRAUMATIC BRAIN INJURY AND VENOUS THROMBOEMBOLISM

Venous thromboembolic complications occur more frequently in patients with trauma and may cause an increase in the mortality rate.<sup>[1,4]</sup> Approximately 25% of people suffering from isolated brain injuries and 50% of polytraumatized patients with brain injuries can present with VTE.<sup>[7]</sup> Specifically, in the cases of injured patients, of DVT reported among 20%–25% of the new cases.<sup>[4]</sup> However, the incidence of VTE can be very variable because factors such as the severity of the trauma, methods of prophylaxis used or the processes to diagnose embolic involvement must be taken into account.<sup>[2,4]</sup> There are several risk factors and risk correlates to develop VTE viz. Obesity, hypercoagulable states, smoking, having previously presented a VTE, among others.<sup>[4,18]</sup> However, most cases of VTE have been related to spinal cord injuries with paralysis, head injuries, and fractures of the hip, pelvis, or lower limb, with TBI being the criterion that most frequently causes VTE. This may be due to three aspects: (a) the extensive state of immobility presented by patients with TBI, a consequence of their poor state of consciousness; (b) the late start of prophylactic treatment of VTE, seeking to avoid the consequences such as the expansion of intracranial haemorrhage (ICH); and (c) hypercoagulability thanks to the activation of tissue factor, platelets, and other procoagulant agents such as the Von Willebrand factor.<sup>[2,7,12]</sup>

## RELATIONSHIP BETWEEN TRAUMATIC BRAIN INJURY AND VENOUS THROMBOEMBOLISM

For the evolution of VTE, in the majority of the injury cases, the appearance of the Virchow Triad (vascular injury, venostasis, and hypercoagulability) is the main cause. This triad, accompanied by other risk factors, such as immobility, promotes this condition.<sup>[1,4]</sup> Immobilization of patients causes an absence of pulsatile blood flow, generating an accumulation of venous blood promoting local hypoxia, which activates the coagulation cascade.<sup>[19]</sup> After the TBIs, endothelial functionality is affected, promoting the prothrombotic environment that increases the risk of thrombosis. Subsequently, there is a hypercoagulability due to excessive coagulation, increased fibrinolytic inhibition, and decreased inhibition of coagulation.<sup>[4]</sup> On the other hand, in the TBI, there is a significant increase in the concentrations of the initiating factor of the coagulation process, tissue factor, or thromboplastin. This could partially explain the high incidence

of systemic thromboembolic problems in this type of patients due to the procoagulant state generated by their organism.<sup>[4,18]</sup>

## MANAGEMENT

The thrombo-prophylactic interventions are organized into pharmacotherapy with anticoagulants, mechanical prophylaxis, and use of inferior vena cava (IVC) filters.<sup>[18]</sup> The use of subcutaneous heparin as a prophylactic measure has shown that it decreases the risk of DVT without generating complications in neurosurgical patients when administered between 24 and 48 h after surgery.<sup>[8]</sup> In addition, research groups reported the superiority of low-molecular-weight and low doses of unfractionated heparin (UFH) decreases VTE without the higher probability of bleeds in neurosurgical cases. Judicious use of intermittent pneumatic compression devices and graduated compression stockings has shown promising results in reducing VTE, though these failed to show greater effectiveness and better prophylaxis.<sup>[12]</sup>

## PROPHYLACTIC AGENTS FOR VENOUS THROMBOEMBOLISM AFTER ACUTE CEREBRAL INJURY

Among the main primary prophylactic options are mechanical and pharmacological options.<sup>[4,18]</sup> The mechanical modalities and pharmacological prophylaxis have been related with an elevated risk of bleeding.<sup>[18]</sup>

## MECHANICAL ANTI-THROMBOTIC PROPHYLAXIS

This type of prophylactic modality has as the main purpose to avoid stasis and ignite the fibrinolytic pathway, thus reducing the incidence of DVT.<sup>[3]</sup> These can act as monotherapy, in cases where there is a contraindication for the pharmacological option, or contributing in a complementary way to it.<sup>[15,18]</sup> The main advantage of the use of mechanical prophylaxis is the lack of action on coagulation, greatly reducing the risk of hemorrhage.<sup>[18]</sup> However, there are several disadvantages such as costefficiency, which alone may be insufficient to counteract the death and illness associated with DVT, despite the economic costs that this prophylactic treatment can cause.<sup>[15,18]</sup>

## CHALLENGES

Usually, DVT is not clinically evident. The absence of signs and symptoms, higher incidence, mortality of DVT, and the cost of management increase the importance for the realization of prophylaxis for DVT and pulmonary embolism.<sup>[3]</sup> Most neurosurgeons are scared for anticoagulant use for the management of VTE in TBI cases to circumvent ICH, yet keeping in mind about the risk of ICH, chemoprophylaxis is used to avoid VTE.<sup>[8,9,15,20]</sup> In 45% of patients with TBI ICH is present, this means that medical personnel must balance the risk of hemorrhage progression and DVT before starting pharmacological prophylaxis.<sup>[9]</sup>

## ANTI-THROMBOTIC CHEMO-PROPHYLAXIS

The question about the use of anticoagulation prophylaxis drugs in TBI has been debated for decades. Some neurosurgeons approach the concept with hesitation based on the precept that anticoagulation will increase the risk of cerebral hemorrhage or expand an already established one.<sup>[15,21]</sup> The management guidelines for patients with TBI address positive role of chemotherapy for optimal prophylaxis with specific precautions. However, multiple studies promote the use of this prophylactic method in humans with TBI.<sup>[15]</sup> Another proposed mechanism for antithrombotic prophylaxis in patients with TBI, apart from mechanical mechanisms, is the use of medications, this process being known as chemoprophylaxis. Among the proposed medications are UFHs; these drugs have been evaluated in various studies.<sup>[3,22]</sup> Heit *et al.*, in their study, on survival predictors, after a thromboembolism, the effect of the use of 5000 units of heparin every 8 h was evaluated subcutaneously in patients with high thromboembolic risk, with guidelines of 2 h before surgery and 7 days postoperatively; in which they found a three-fold decrease in DVT incidence.<sup>[23]</sup> For Geerts *et al.*, in their study, low doses of UFH are not effective when performed in trauma patients, and their effectiveness is reduced in patients with high-risk trauma.<sup>[24]</sup> Consequently, low doses of UFH should not be used unless it is of low-molecular-weight heparin (LMWH), namely enoxaparin 30 mg 12 hourly, decreasing risk of DVT by 58%. As a result, LMWH used initially when primary hemostasis was promoted as the predilection technique promoted for DVT in major trauma.<sup>[25]</sup> With regard to low-molecular-weight heparins, the literature raises many issues on their clinical use. Among these, enoxaparina, dalteparina, enoxaparin have the advantage as their dosage are based on units of measurement viz. Milligrams or milligrams per kilogram body weight, compared to the other heparins whose dosages are based on international units or international units per kilo per kilogram body weight.<sup>[26]</sup>

Currently, studies are underway with another drug whose mechanism of action is to act as an anti-factor X inhibitor, whose indication is based on DVT prophylaxis 2.5 mg daily in postoperative hip and knee replacement; even though Lu *et al.*, in their study, of DVT prevention in cases with trauma and higher thromboembolism risk, concluded that fondaparinux was effective for DVT, in trauma patients, yet it has no indication at present for this type of patients.<sup>[27]</sup>

## MONITORING OF ANTI-Xa FACTOR IN TRAUMATIZED PATIENTS WITH HIGH RISK OF THROMBOEMBOLISM

Currently, multiple investigations have suggested that the standard dosage of LMWH, in patients with brain injury or any type of trauma (30 mg subcutaneous 12 hourly), may not be able to impart prophylaxis, in high-risk trauma cases.<sup>[3,28,29]</sup> In the patients described above, the doses of LMWHs should be adjusted taking into account the level of anti-factor Xa. Because <0.1 is the value that is considered normal for the

anti-factor Xa, its measurement is indicated before the number 4 dose of these heparins; in the case that the anti-factor Xa is normal ( $<0.1$ ), it is considered that enoxaparin should be adjusted to a dose of 40 mg subcutaneous 12 hourly; it is necessary to take as a point of reference that a patient with an anti-factor value Xa  $>0.5$  is considered therapeutically anticoagulant and the objectives will be to maintain the anti-factor Xa values between 0.2 and 0.5.<sup>[30]</sup> In case the sub-therapeutic value continues, it is considered to adjust the dose to 50 mg every 12 h of enoxaparin. This approach promotes effective prophylaxis and decreases subtherapeutic therapies that would raise the probability of thromboembolism in injury victims.<sup>[31]</sup>

## TIME FOR THE CHEMO-PROPHYLAXIS OF DEEP VEIN THROMBOSIS IN ACUTE CEREBRAL INJURY

Current literature based on determining the most effective time for the initiation of antithrombotic therapy, has investigated whether this chemoprophylaxis should be initiated after 24 h or after 72 h in TBI. LMWH (enoxaparin, 30 mg 12 hourly.) or UFH (5000 IU 12 hourly) was used in severe TBI.<sup>[16,17,20]</sup> It was evidenced that the rate of ICH does not increase if it is applied before 72 h; On the contrary, the efficacy of chemoprophylaxis decreased from 3.6% to 15.4%.<sup>[25,32,33]</sup>

## RISK OF POSTCHEMOPROPHYLAXIS CEREBRAL HEMORRHAGE

One of the problems associated with antithrombotic chemoprophylaxis in brain trauma is the appearance of de novo cerebral hemorrhage or the exacerbation of an already established TBI. Taking into account retrospective studies of progression of cerebral hemorrhages in patients who were followed up with computed tomography (CT) scans, it was demonstrated that antithrombotic chemoprophylaxis can increase the rate of cerebral hemorrhages.<sup>[33,34]</sup> It was established that bleeding rates increased in susceptible patients with higher criteria of pre-established risk factors.<sup>[19,33]</sup> That is why you should identify posttraumatic patients with an increased risk of these conditions. Literature reports that several criteria are proposed to classify these patients, namely, Parkland protocol or Berne-Norwood criteria, categorizing them into high-, moderate-, and low-risk for cerebral hemorrhage. The modification of the Parkland protocol, which was first, proposed by Berne and Norwood and thus is now called the Berne-Norwood criteria or new Parkland protocol advised to initiate LMWH within 24 h for low-risk TBI, within 72 h for moderate risk TBI and consider placing an IVC filter in case of high-risk TBI. Phelan *et al.* in their study of stratification of the risk of bleeding in brain trauma, showed that antithrombotic chemoprophylaxis after 24 h did not cause an increase in cerebral hemorrhage rates.<sup>[33,35]</sup> Further, in an internal validation study, Pastorek *et al.*<sup>[36]</sup> modified the moderate and high-risk category recommendations to either LMWH initiation at 72 h if the CT scan is table at that time or to delay the same until the hemorrhage pattern stabilizes.

## CONCLUSIONS

VTE is a common sequel in medical and surgical emergencies. Trauma cases usually face the Virchow's Triad comprising stasis, injury, and thrombophilia, following TBI. The rationale toward prophylactic interventions are targeted on the spectrum, the diagnostic dilemma, the fatality as well as disability as well and last but not the least, cost reduction for the holistic approach of thromboembolism intervention.

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## Conflicts of interest

There are no conflicts of interest.

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