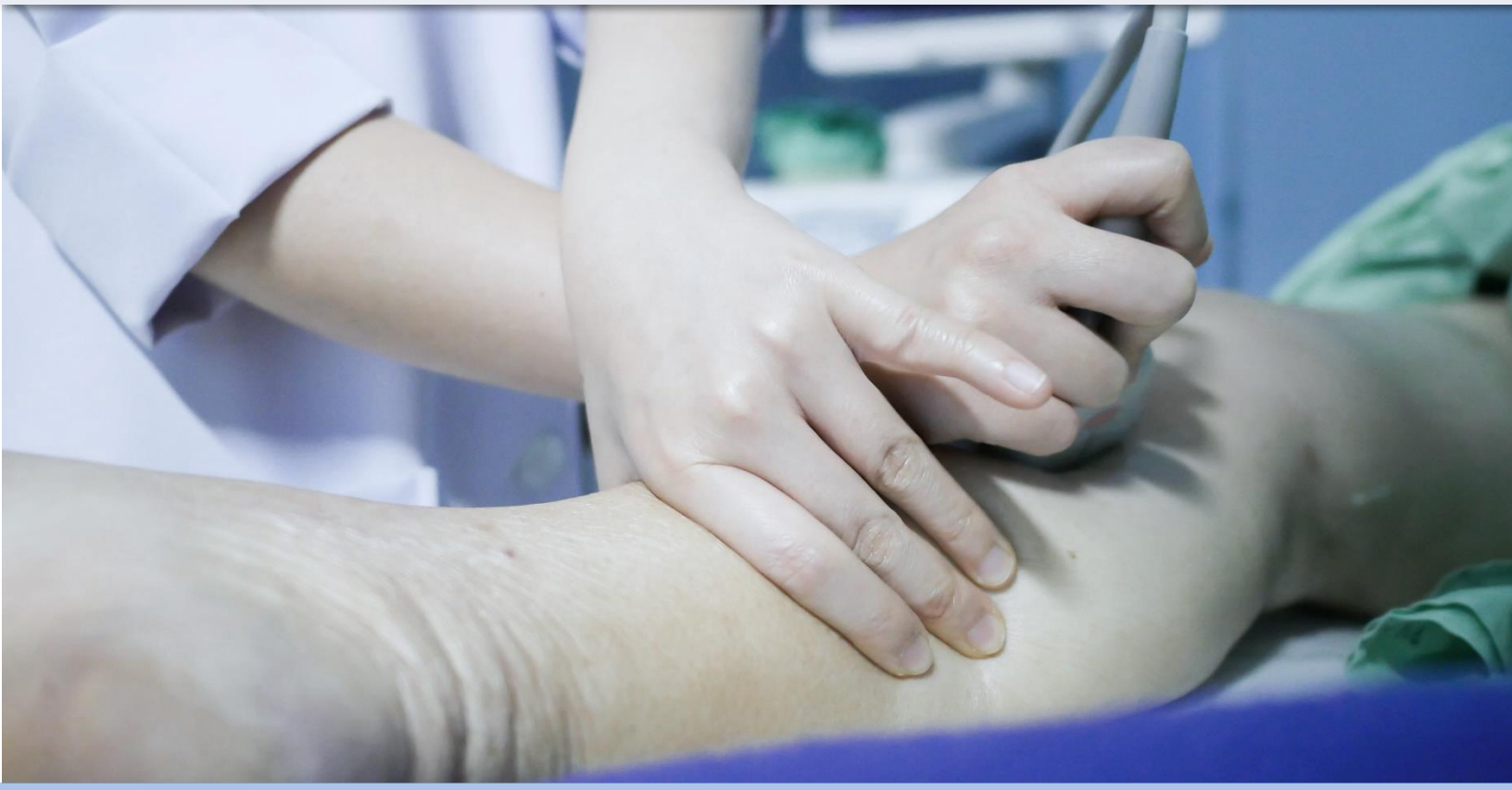
ERABI
EVIDENCE-BASED REVIEW
of moderate to severe
ACQUIRED BRAIN INJURY



VENOUS THROMBOEMBOLISM

POST ACQUIRED BRAN INJURY

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Conflict of Interest

In the context of ERABI development, the term “conflict of interest” (COI) refers to situations in which an author or ERABI staff member’s financial, professional, intellectual, personal, organizational or other relationships may compromise their ability to independently conduct this evidence-based review. No limiting conflicts were identified.

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Greetings from Dr. Robert Teasell,

Professor and Chair-Chief of Physical Medicine and Rehabilitation

The Collaboration of Rehabilitation Research Evidence (CORRE) team is delighted to present the Evidence-Based Review of Moderate to Severe Acquired Brain Injury (ERABI) *Venous Thromboembolism post Acquired Brain Injury.* Through the collaboration of researchers and clinicians and supported by the Ontario Neurotrauma Foundation/Ontario Ministry of Health, ERABI provides an up-to-date review of the current evidence in brain injury rehabilitation. ERABI synthesizes the research literature into a utilizable format, laying the foundation for effective knowledge transfer to improve healthcare programs and services.

We offer our heartfelt thanks to the many stakeholders who are able to make our vision a reality. Firstly, we would like to thank the Ontario Neurotrauma Foundation, which recognizes ERABI's capacity to lead in the field of brain injury evidence-based reviews and has been committed to funding it. We would also like to thank the co-chairs of ERABI, Dr. Mark Bayley (University of Toronto), Dr. Shawn Marshall (University of Ottawa) and Dr. Nora Cullen (McMaster University) for their invaluable expertise and stewardship of this review. Special thanks to the authors for generously providing their time, knowledge and perspectives to deliver a rigorous and robust review that will guide research, education and practice for a variety of healthcare professionals. We couldn't have done it without you! Together, we are building a culture of evidence-based practice that benefits everyone.

We invite you to share this evidence-based review with your colleagues, patient advisors that are partnering within organizations, and with the government agencies with which you work. We have much to learn from one another. Together, we must ensure that patients with brain injuries receive the best possible care every time they require rehabilitative care – making them the real winners of this great effort!

Robert Teasell, MD FRCPC

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Preface

About the Authors

ERABI is internationally recognized and led by a team of clinicians and researchers with the goal of improving patient outcomes through research evidence. Each ERABI module is developed through the collaboration of many healthcare professionals and researchers.

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Dr. Robert Teasell is Professor of Physical Medicine and Rehabilitation, Schulich School of Medicine and Dentistry, Western University and a Clinical Researcher at Lawson Research Institute in London, Ontario. He is a clinician at Parkwood Institute, St. Joseph's Health Care London.

Purpose

The Evidence-Based Review of Acquired Brain Injury (ERABI) is a systematic review of the rehabilitation literature of moderate to severe acquired brain injuries (ABI). It is an annually updated, freely accessible online resource that provides level of evidence statements regarding the strength of various rehabilitation interventions based on research studies. The ERABI is a collaboration of researchers in London, Toronto and Ottawa. Our mission is to improve outcomes and efficiencies of the rehabilitation system through research synthesis, as well as from providing the foundational research evidence for guideline development, knowledge translation, and education initiatives to maximize the real-world applications of rehabilitation research evidence.

Key Concepts

Acquired Brain Injury

For the purposes of this evidence-based review, we used the definition of ABI employed by the Toronto Acquired Brain Injury Network (2005). ABI is defined as damage to the brain that occurs after birth and is not related to congenital disorders, developmental disabilities, or processes that progressively damage the brain. ABI is an umbrella term that encompasses traumatic and non-traumatic etiologies (Table 1).

TABLE 1 | Defining Acquired Brain Injury

Included in ABI definition	Excluded from ABI definition
Traumatic Causes • Motor vehicle accidents • Falls • Assaults • Gunshot wounds • Sport Injuries **Non-traumatic Causes** • Tumours (benign/meningioma only) • Anoxia • Subarachnoid hemorrhage (non-focal) • Meningitis • Encephalitis/encephalopathy (viral, bacterial, drug, hepatic) • Subdural Hematoma	**Vascular and Pathological Incidents** • Intracerebral hemorrhage (focal) • Cerebrovascular accident (i.e., stroke) • Vascular accidents • Malignant/metastatic tumours **Congenital and Developmental Problems** • Cerebral Palsy • Autism • Developmental delay • Down's syndrome • Spina bifida with hydrocephalus **Progressive Processes** • Alzheimer's disease • Pick's disease • Dementia • Amytrophic Lateral Sclerosis • Multiple Sclerosis • Parkinson's disease • Huntington's disease

Given that 'ABI' can have multiple definitions, studies with an 'ABI' population can be equally heterogeneous in terms of the sample composition. Such studies may include any combination of persons with TBI, diffuse cerebrovascular events (i.e., subarachnoid hemorrhage) or diffuse infectious disorders (i.e., encephalitis or meningitis). The vast majority of individuals with ABI have a traumatic etiology; therefore, much of the brain injury literature is specific to TBI. The terms ABI and TBI have been used intentionally throughout ERABI to provide more information about populations where relevant.

Moderate to Severe Injury

ABI severity is usually classified according to the level of altered consciousness experienced by the patient following injury (Table 2). The use of level of consciousness as a measurement arose because the primary outcome to understand the severity of an injury is the Glasgow Coma Scale. Consciousness levels following ABI can range from transient disorientation to deep coma. Patients are classified as having a mild, moderate or severe ABI according to their level of consciousness at the time of initial assessment. Various measures of altered consciousness are used in practice to determine injury severity. Common measures include the Glasgow Coma Scale (GCS), the duration of loss of consciousness (LOC), and the duration of post-traumatic amnesia (PTA).

TABLE 2 | Defining Severity of Traumatic Brain Injury, adapted from Veterans Affairs Taskforce (2008) and Campbell (2000)

Criteria	Mild	Moderate	Severe	Very Severe
Initial GCS	13-15	9-12	3-8	Not defined
Duration LOC	< 15minutes*	<6 hours	6-48 hours	>48 hours
Duration PTA	< 1hour*	1-24 hours	1-7 days	>7 days
	*This is the upper limit for mild traumatic brain injury; the lower limit is any alteration in mental status (dazed, confused, etc.).			

Methods

An extensive literature search using multiple databases (CINAHL, PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO) was conducted for articles published in the English language between 1980–April 2022 that evaluate the effectiveness of any intervention/treatment related to ABI. The references from key review articles, meta-analyses, and systematic reviews were reviewed to ensure no articles had been overlooked. For certain modules that lacked research evidence the gray literature, as well as additional databases, were searched in order to ensure the topic was covered as comprehensively as possible.

Specific subject headings related to ABI were used as the search terms for each database. The search was broadened by using each specific database's subject headings, this allowed for all other terms in the database's subject heading hierarchy related to ABI to also be included. The consistent search terms used were "head injur*", "brain injur*", and "traumatic brain injur*". Additional keywords were used

specific to each module. A medical staff librarian was consulted to ensure the searches were as comprehensive as possible.

Every effort was made to identify all relevant articles that evaluated rehabilitation interventions/ treatments, with no restrictions as to the stage of recovery or the outcome assessed. For each module, the individual database searches were pooled, and all duplicate references were removed. Each article title/abstract was then reviewed; titles that appeared to involve ABI and a treatment/intervention were selected. The remaining articles were reviewed in full.

Studies meeting the following criteria were included: (1) published in the English language, (2) at least 50% of the population included participants with ABI (as defined in Table 1) or the study independently reported on a subset of participants with ABI, (3) at least three participants, (4) ≥50% participants had a moderate to severe brain injury, and (5) involved the evaluation of a treatment/intervention with a measurable outcome. Both prospective and retrospective studies were considered. Articles that did not meet our definition of ABI were excluded.

Interpretation of the Evidence

The levels of evidence (Table 3) used to summarize the findings are based on the levels of evidence developed by Sackett et al. (2000). The levels proposed by Sackett et al. (2000) have been modified; specifically, the original ten categories have been reduced to five levels. Level 1 evidence pertains to high quality RCTs (PEDro ≥6) and has been divided into two subcategories, level 1a and level 1b, based on whether there was one, or more than one, RCT supporting the evidence statement.

The evidence statements made in evidence-based reviews are based on the treatment of groups rather than individuals. There are times when the evidence will not apply to a specific case; however, the majority of patients should be managed according to the evidence. Ultimately, the healthcare professional providing care should determine whether an intervention is appropriate, and the intensity in which it should be provided, based on their assessment of the patient. Furthermore, readers are asked to interpret the findings of studies with caution as evidence can be misinterpreted. The most common scenario occurs when results of a trial are generalized to a wider group than the evidence allows. Evidence is a tool, and as such, the interpretation and implementation of it must always be done with these limitations in mind.

TABLE 3 | Levels of Evidence

Level	Research Design	Description
1A	Randomized Controlled Trial (RCT)	More than one RCT with PEDro score ≥6. Includes within subject comparisons, with randomized conditions and crossover designs
1B	RCT	One RCT with PEDro ≥6
2	RCT	One RCT with PEDro <6
	PCT	Prospective controlled trial (not randomized)

	Cohort	Prospective longitudinal study using at least two similar groups with one exposed to a particular condition
3	Case Control	A retrospective study comparing conditions including historical controls
4	Pre-Post test	A prospective trial with a baseline measure, intervention, and a post-test using a single group of subjects
	Post-test	A prospective intervention study using a post intervention measure only (no pre-test or baseline measurement) with one or more groups
	Case Series	A retrospective study usually collecting variables from a chart review
5	Observational study	Using cross sectional analysis to interpret relations
	Clinical Consensus	Expert opinion without explicit critical appraisal, or based on physiology, biomechanics or “first principles”
	Case Reports	Pre-post or case series involving one subject

Strength of the Evidence

The methodological quality of each randomized controlled trial (RCT) was assessed using the Physiotherapy Evidence Database (PEDro) rating scale developed by the Centre for Evidence-Based Physiotherapy in Australia (Moseley et al., 2002). The PEDro is an 11-item scale; a point is awarded for ten satisfied criterion yielding a score out of ten. The first criterion relates to external validity, with the remaining ten items relating to the internal validity of the clinical trial. The first criterion, eligibility criteria, is not included in the final score. A higher score is representative of a study with higher methodological quality.

VENOUS THROMBOEMBOLISM

POST ACQUIRED BRAIN INJURY

SUMMARY OF THE EVIDENCE

Intervention	Key Point Level of Evidence
Non-Pharmacological Interventions	
Mechanical Interventions	Intermittent pneumatic compression devices alone may be inferior to low molecular weight heparin for the prevention of venous thromboembolism (VTE) post ABI. - *There is conflicting level 2 (Kurtoglu et al., 2004; Gersin et al., 1994) and level 4 evidence (Minshall et al., 2011) regarding the effectiveness of intermittent pneumatic compression devices compared to low-molecular-weight heparin for the prophylaxis of DVT and PE. In one level 4 study (Minshall et al., 2011), LMWH was superior to unfractionated heparin and intermittent pneumatic compression alone for preventing VTE and death; in two level 2 studies (Kurtoglu et al., 2004; Gersin et al., 1994), there was no statistically significant difference between LMWH and intermittent pneumatic compression for VTE or death.* Intermittent compression devices may not aggravate intracranial hemodynamics in patients with severe ABI. - *There is level 4 evidence (Davidson et al., 1993) that intermittent compression devices may not cause acute elevations in intracranial pressure in individuals with ABI.* When compared to VTE chemoprophylaxis, prophylactic inferior vena cava filter (IVCF) may be associated with higher incidence of DVT and non-fatal PE, as well as longer hospital stays. Early placement of IVCF (0-48hr) may shorten ICU and hospital length of stay. - *There is level 2 evidence (Elkbuli et al., 2021) that prophylactic IVCF may be associated with higher rates of DVT, nonfatal PE and longer hospital stays when compared to VTE chemoprophylaxis following TBI.* - *There is level 2 evidence (Elkbuli et al., 2020) that IVCF placement within 48hrs of admission may shorten ICU and hospital length of stay post TBI.*
Pharmacological Interventions	
Low-Molecular-Weight Heparin (LMWH)	VTE prophylaxis with LMWH, such as enoxaparin, may be safe and effective for individuals post ABI. Enoxaparin and compression stockings combined may be more effective than compression stockings alone. Early administration of enoxaparin may reduce the number of days spent on ventilator and length of stay in ICU and hospital. - *There is level 1b evidence (Baharvahdat et al., 2019; Jamous et al., 2020; Phelan et al., 2012; Störmann et al. 2019;) that enoxaparin may improve outcomes for individuals with TBI without increasing the risk for progression of intracranial bleeding.* - *There is level 1b evidence (Agnelli et al., 1998) the combination of enoxaparin and compression stockings is more effective than compression stockings alone for the prevention of VTE.*

	- *There is level 2 evidence (Koehler et al., 2011) that early administration of enoxaparin may reduce the days spent on a ventilator, as well as the length of stay in the ICU and hospital.* - *There is level 2 evidence (Dudley et al., 2010) that there may be no difference in effectiveness between VTE prophylaxis with enoxaparin or dalteparin.* - *There is level 3 evidence (Daley et al., 2015; Hachem et al., 2018) that enoxaparin may reduce in-hospital mortality.* - *There is level 4 evidence that (Kleindienst et al., 2003) certoparin may be safe for individuals undergoing neurosurgery.*
Unfractionated Heparin (UH)	Unfractionated Heparin (UFH) may be safe for individuals with severe ABI. However, it may not be effective for reducing risk of DVT or PE. Delaying the initiation of UFH prophylaxis may result in a higher risk of VTE. - *There is level 3 evidence (Brandi et al., 2020) that a delay in the initiation of UFH therapy post TBI may result in a higher risk of VTE.* - *There is level 3 evidence (Kim et al., 2002) that UFH may be safe in individuals with severe head injuries.* - *There is level 4 evidence (Lin et al., 2013) that UFH may not be effective in reducing risk of DVT and PE post TBI.*
Low-Molecular-Weight Heparin (LMWH) versus Unfractionated Heparin (UH)	There is conflicting evidence on the effectiveness of Low-Molecular-Weight Heparin (LMWH) and Unfractionated Heparin (UFH) for the prophylaxis of VTE, when compared to each other. - *There is conflicting evidence regarding the effectiveness of LMWH and UH when compared to each other for the prevention of VTE post ABI.*
Propranolol	Early administration of propranolol may reduce rates of VTE in individuals with TBI. - *There is level 2 evidence (Dhillon et al., 2021) that early use of propranolol may decrease rates of VTE and mortality post TBI.*

Introduction

Venous thromboembolism (VTE) refers to the formation of blood clots within veins and includes deep vein thrombosis (DVT) and pulmonary embolism (PE) (Khan et al., 2021). DVT occurs when one or more thrombi form in the veins, frequently in the large veins of the legs or pelvis; PE occurs when one or more thrombi travel to the pulmonary arteries through the heart (Phillippe, 2017). Together, DVT and PE are referred to as VTE. VTE is a common and potentially life-threatening complication in patients who have sustained an ABI (Raslan et al., 2010; Scudday et al., 2011); however the scientific literature specific to VTE in ABI is quite limited.

The following section presents ABI specific research regarding the prevention and treatment of VTE. All studies cited in the evidence summary tables meet the ERABI ABI inclusion criteria. Additional information on clinical presentation and testing practices is presented; however, it should be noted that not all in-text citations refer to research that meets the specific ERABI ABI inclusion criteria (mixed populations, age, mixed ABI severity, etc.) and therefore should be interpreted with caution when considering the application of any tests or indicators of VTE to an ABI population.

Incidence of Venous Thromboembolism Post Head Injury

The reported incidence of VTE among patients with TBI ranges from 11% to 54% (Carlile et al., 2010; Cifu et al., 1996; Denson et al., 2007; Geerts et al., 1994). The risk of developing a DVT or PE post TBI, in the absence of VTE prophylaxis, is estimated to be 20-30% (Haddad & Arabi, 2012). Hachem et al. (2018) found rates of VTE in patients with severe TBI not receiving anticoagulation prophylaxis were near 30%, compared to 5-10% of patients who received prophylaxis. In a large sample study consisting of 38,984 individuals with TBI, Olufajo et al. (2016) reported that the incidence of VTE at the time of admission was 1.31%; and at 1-month post injury, the incidence of VTE had increased to 1.87% and by 1-year it was 2.83%. It should be noted that this study did not assess whether or not patients were receiving VTE prophylaxis before or after sustaining their injuries or if inferior vena cava filters were in place before or after patients developed VTE (Olufajo et al., 2016). A smaller Australian study in which patients admitted to ICU with moderate to severe TBI received mechanical thromboprophylaxis and/or low molecular weight heparin as soon as medically safe found the overall incidence of VTE was 11%, and the incidence of DVT and PE were 6% and 6%, respectively (Praeger et al., 2012). Increased injury severity was found to be associated with a higher incidence of VTE in patients with TBI (Praeger et al., 2012; Van Gent et al., 2014).

Due to the high incidence of VTE in persons with ABI and in hospitalized patients generally, VTE prophylaxis is routinely administered. Experts recommend beginning pharmacological prophylaxis as early as is medically safe, and within 48 to 72 hours post injury (INESSS-ONF, 2017; Norwood et al., 2001). Unless contraindicated, interventions such as mechanical thromboprophlaxis and low-molecular-weight

heparin (LMWH) are often recommened in the acute phase of recovery to prevent VTE (Haddad & Arabi, 2012). If VTE develops, decisions regarding type and timing of treatment are often made on a case-by-case basis due to the need to balance the risks of untreated VTE with the risks of anticoagulation (Tang & Lobel, 2009).

Risk Factors for Venous Thromboembolism

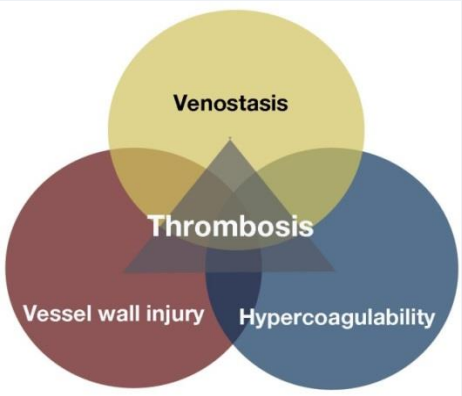

Figure 1 | Virchow's Triad

The most recognized risk factors for VTE are venostasis, intimal damage of the blood vessel wall, and a hypercoagulable state (Virchow's triad; see Figure 1) (Watanabe & Sant, 2001). Significant risk factors for venous thromboembolism include undergoing surgical procedures, immobilisation for long periods of time, and the presence of cancer (Di Nisio et al., 2016). Those at highest risk of developing VTE post ABI are those who remain on a ventilator longer than 3 days (Olufajo et al., 2016; Raslan et al., 2010). Individuals who have sustained a TBI may be at increased risk of developing VTE due to factors such as age, lower extremity fractures, blood product transfusions, and hypercoagulability (Valle et al., 2014). There is conflicting evidence for the impact of severity of injury on the risk of developing VTE. Some studies note a correlation between greater injury severity and risk of VTE (Praeger et al., 2012; Van Gent et al., 2014); others note no correlation between VTE incidence and initial Glasgow Coma Scale (GCS) scores, Injury Severity Scale scores, or the Abbreviated Injury Scale score (Denson et al., 2007). At 1-year post injury, risk of VTE is greatest for those discharged to extended care facilities compared to home, and for individuals who undergo an operation (Olufajo et al., 2016).

Clinical Presentation of Deep Vein Thrombosis and Pulmonary Embolism

The most common symptoms associated with DVT are pain, swelling of the legs, and discoloration of the region (Collins, 2009). Other symptoms include redness and tenderness and the area, as well as collateral superficial veins (Di Nisio et al., 2016). Up to 91% of thrombi form below the iliac level (De Maeseneer et al., 2016). Asymptomatic PE has been discovered in 70% of patients with confirmed clinically symptomatic DVT (Browse, 1974; Corrigan et al., 1974; Hull & Hirsh, 1983).

Clinically, symptomatic PE presents with tachycardia, tachypnea, and/or pleuritic chest pain (Doherty, 2017). Individuals with PE may also experience sudden dyspnoea, syncope, and dizziness due to hypotension or shock (Di Nisio et al., 2016). However, the clinical presentation of PE can be challenging,

as not all PEs are symptomatic. Many cases are clinically silent (66%) with no overt symptoms, and only 30% will have concurrent clinical features of a DVT (Garcia-Fuster et al., 2014).

Diagnostic Testing for Deep Vein Thrombosis

A positive diagnosis of DVT is made if a venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal leg veins. The diagnosis of DVT can be ruled out if there is a negative venogram, a negative D-dimer test, or a normal venous ultrasound in patients with low clinical suspicion of DVT (Carlile et al., 2006). D-dimer is a fibrin degradation product that can be detectable in the blood after the blood clot has degraded by fibrinolysis, and cannot be used to diagnose VTE (Wilbur & Shian, 2012).

Venous Ultrasound

Venous ultrasound is the diagnostic test most frequently used to diagnose a DVT. There are several types of venous ultrasonography. They include compression ultrasound, duplex ultrasound, and color Doppler imaging. Although these types of venous ultrasonography are sometimes used interchangeably, their sensitivities and specificities for detecting acute DVT vary (Zierler, 2004). The sensitivity and specificity of compression ultrasonography for detecting DVTs is 43% and 85%, respectively (Girard et al., 2005). The weighted mean sensitivity and specificity of venous ultrasonography for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively; the sensitivity falls to 73% for distal DVT (Kearon et al., 1998; Zierler, 2004). Importantly, distal DVTs do not confer the same risk of embolization to PE as do proximal DVTs. Typically, if a distal clot is going to extend into proximal leg veins, this occurs within one week of its development. Consequently, serial ultrasound could be used in symptomatic patients in whom the test is initially negative as the test would become positive with clot extension. While ultrasonography is considered a highly sensitive test to determine the presence of DVT, there are some limitations such as low reliability when distinguishing between old and new clots, as well as the possibility of a false-positive result if the patient presents with a tumor or abscess in the pelvis (Wilbur & Shian, 2012).

Venography

Venography has been considered a standard test for the diagnosis of DVT; however, it is not recommended when performing an initial evaluation of the patient given its invasiveness and risks, including pain, vessel damage, hematoma and a potential allergic reaction to the agent used to achieve contrast (Wilbur & Shian, 2012).

D-Dimer Assay

D-dimer assay is a rapid, non-invasive, and cost-effective test in selected patients. Fibrin is the main component of thrombus formation and fibrin degradation products include D-dimers (Gill & Nahum, 2000). A positive D-dimer test is highly sensitive for the presence of a thrombus but lacks specificity since D-dimers are found in other disease states, including trauma, cancer, congestive heart failure, and

inflammatory conditions (Raimondi et al., 1993). As a result, D-dimer assays have a high negative predictive value but a poor positive predictive value. To illustrate, in a group of 68 rehabilitation patients (stroke, spinal cord injury, TBI, hip arthroplasty), Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-dimer test were high (95.2% and 96.2%, respectively), whereas the specificity and positive predictive values were low (55.3% and 48.7%, respectively). Therefore, a normal D-dimer assay is useful to rule out DVT (high negative predictive value), but a high D-dimer assay cannot be used to rule in or diagnose a DVT.

Diagnostic Testing for Pulmonary Embolism

The diagnostic work-up for a suspected PE often follows a step-wise decision algorithm (Di Nisio et al., 2016; Moore et al., 2018). Patients with a low clinical suspicion of PE may be appropriate for D-dimer testing. In this group of patients, if the D-dimer is negative, PE can be ruled out; however, if the D-dimer is positive, this neither rules in nor rules out PE and patients will require imaging to diagnose or exclude PE. Patients with a high clinical suspicion of PE are not appropriate for D-dimer testing and should undergo imaging. Computed Tomography Pulmonary Angiogram (CTPA) is the preferred imaging modality for diagnosis of PE (Di Nisio et al., 2016; Moore et al., 2018). Patients with ABI are most often considered high-risk for PE.

Computed Tomography Pulmonary Angiogram

Computed Tomography Pulmonary Angiogram (CTPA) is the preferred imaging modality for diagnosing PE (Di Nisio et al., 2016; Moore et al., 2018). It has become first line at most centers because it is fast, highly sensitive and specific, and can detect other causes of chest pain such as pneumonia, musculoskeletal injuries, or pericardial abnormalities (Di Nisio et al., 2016). Combined with clinical probability rules, this test has very high positive predictive value (Gottschalk et al., 2002; Stein et al., 2006). CTPA carries risks associated with radiation exposure, bleeding, adverse reaction to contrast medium, and is contraindicated in some patients with renal insufficiency and in pregnant women (Di Nisio et al., 2016).

Ventilation/Perfusion Scanning

Ventilation/Perfusion Scanning (V/Q Scan) can be used when other forms of imaging, such as CTPA, are contraindicated, such as to avoid exposing pregnant women to radiation (Di Nisio et al., 2016). Palmowski et al. (2014) reported the sensitivity and specificity of V/Q scanning as 95.8% and 82.6%, respectively, with false negative rates of 4.2% and false positive rates of 17.3%; hence, a normal scan virtually excludes a PE (high negative predictive value).

TABLE 4 | Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Clinical Suspicion in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) Study

Ventilation-Perfusion Scan Results	Clinical Suspicion of Pulmonary Embolism*		
	Low	Intermediate	High

High Probability	56%	88%	96%
Intermediate Probability	16%	28%	66%
Low Probability	4%	16%	40%
Normal/Near-Normal Probability	2%	6%	0%

*Percentage of patients with pulmonary embolism; adapted from the PIOPED Investigators (Gill & Nahum, 2000; PIOPED Investigators, 1990).

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED Investigators) Study demonstrated that a low-probability or normal V/Q Scan with a low clinical suspicion of PE essentially excludes the diagnosis of PE (negative predictive values of 96% and 98% respectively) (Gill & Nahum, 2000; PIOPED Investigators, 1990). When clinical suspicion is high and the scan indicates a high probability of PE, the positive predictive value is 96% (Gill & Nahum, 2000; PIOPED Investigators, 1990), and these patients should be treated. However, the majority of V/Q Scans have non-diagnostic results, and thus those patients require further testing (PIOPED Investigators, 1990). Accordingly, with the availability of more accurate tests, there has been a decline in the use of the V/Q scan (Wilbur & Shian, 2012).

PROPHYLAXIS OF VENOUS THROMBOEMBOLISM

Several interventions have been examined for the prevention of DVT after an ABI, including mechanical interventions, pharmaceuticals, or a combination of both. In a systematic review, Hachem et al. (2018) found rates of VTE in patients with severe TBI not receiving anticoagulation prophylaxis were nearly 30%, compared to 5-10% of patients with prophylaxis. However, there is no agreement on the use of these medications in terms of type, timing and dose (Hachem et al., 2018).

Non-Pharmacological Interventions

Mechanical Interventions

There are two categories of mechanical interventions: those that prevent deep vein thrombosis (DVT) and those that prevent pulmonary embolism (PE). Mechanical interventions used to prevent the development of DVT include thromboembolism-deterrent stockings and intermittent pneumatic compression devices including arteriovenous foot pumps and sequential compression devices (SCDs) (Macatangay et al., 2008). These mechanical compression devices operate primarily through two mechanisms of action. The first is mechanical, in which the device increases the velocity of venous return to decrease venous stasis, thus reducing the opportunity for clot formation. The second, and perhaps more important mechanism, involves the activation of the fibrinolytic system which, during

compression, leads to the breakdown of fibrin clots associated with thromboembolism (Macatangay et al., 2008).

A separate category of mechanical intervention is the insertion of inferior vena cava filters (IVCFs), which prevent PEs. IVCFs are distinct from other mechanical interventions because they are invasive, requiring the insertion of a device within the inferior vena cava, and they only prevent pulmonary embolism and not deep vein clot formation (Watanabe & Sant, 2001). Inferior vena cava filters were first designed in the 1970s to trap emboli traveling from the lower extremities to the lungs via the inferior vena cava, thereby preventing them from causing PE. Due to the invasive nature of IVCFs, there are several risks associated with this intervention including perforation, filter migration, filter fracture and thrombotic occlusion (Duffett & Carrier, 2017).

TABLE 5 | Mechanical Interventions for Venous Thromboembolism Prophylaxis post ABI

Author, Year Country Study Design Sample Size	Methods	Outcome
Compression Devices		
Minshall et al. (2011) USA Cohort N=386	**Population**: TBI; *LMWH* (n=158); Mean Age= 41.2yr; Gender: Male=119; Female=39; *UFH* (n=171); Mean Age=42yr; Gender: Male=134, Female=37; Mean Time Post Injury=Not Reported. **Intervention:** Chart review of patients receiving sequential compression devices alone (n=57), or with LMWH (enoxaparin 30 mg, 2x/day; n=158) or with unfractionated heparin (UFH; 5000 IU 3x/day; n=171). **Outcome Measures:** Rate of DVT, PE, and intracranial hemorrhage complications.	1. Mortality in the sequential compression devices alone group was significantly higher (47%) compared to the LMWH (5%) and UFH (16%) groups. 2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group ($p<0.05$). 3. 25% of those treated with sequential compression devices alone had progression of their intracranial hemorrhage, compared to 5% in the LMWH group and 12% in the UFH group.
Kurtoglu et al. (2004) Turkey PCT N=120	**Population:** TBI=103, Other=17; Median Age=37.1yr; Gender: Male=47, Female=73. **Intervention:** Patients admitted to the Intensive Care Unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or Low-Molecular-Weight Heparin (LMWH) (n=60) (enoxaparin sodium 40 mg/day) for VTE prophylaxis. Follow-up head CT scans were obtained at 24hr. **Outcome Measures:** Rate of DVT, PE and mortality.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. This difference was not statistically significant. 2. 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH groups, respectively. 3. There were no significant differences between groups in rates of DVT ($p=0.04$), PE ($p=0.07$), or mortality ($p=0.08$).
Gersin et al. (1994) USA Cohort N=32	**Population:** TBI; *Group 1 (n=14)*: Mean Age=38.3yr; Gender: Male=10, Female=4; Mean GCS Score=7.1. *Group 2 (n=18)*: Mean Age=36.1yr; Gender: Male=14, Female=4; Mean GCS Score=6.8. **Intervention:** Patients admitted to the surgical Intensive care unit (ICU) either received or did not receive prophylactic sequential	1. Of those who were given SCD prophylaxis, four developed PE and none developed DVT. 2. Of those who did not receive prophylactic SCD, two developed PE and two developed DVT. 3. The groups did not differ significantly in the development of DVT and PE ($p=0.7$).

Author, Year Country Study Design Sample Size	Methods	Outcome
	compression devices (SCDs). Technetium venoscans were conducted along with ventilation/perfusion (V/Q) lung scans within 6 days of admission and repeated weekly for 1 mo. to identify DVT and/or PE. **Outcome Measure:** Incidence of DVT/PE.	
Davidson et al. (1993) USA Pre-Post N=24	**Population:** TBI=22, Other=2; Gender: Male=20, Female=4; Mean GCS Score=6. **Intervention:** Patients admitted to the surgical or trauma intensive care unit received intermittent sequential pneumatic leg compressions (11s compression phase, 60 sec of deflation). **Outcome Measures:** Mean Arterial Pressure (MAP), heart rate, central venous pressure, intracranial pressure, cerebral perfusion pressure. Measurements were obtained when the compression was initiated (time 0) and at 10, 20, and 30 min into therapy.	1. No significant changes in MAP, central venous pressure, intracranial pressure, or cerebral perfusion pressure occurred during the study period.
IVC Filters		
Elkbuli et al., (2021) USA Cohort N=2900	**Population:** TBI=481; *Inferior Vena Cava Filter (IVCF; n=413); M*ean Age=51.9±22.3yr; Gender: Male=310, Female=103; Time Post Injury=Not Reported; Mean GCS=10.0±4.8. *VTE Chemoprophylaxis (unfractionated heparin or enoxaparin, VTEC; n=2487);* Mean Age=51.3±23.4yr; Gender: Male=1714, Female=733; Time Post Injury=Not Reported; Mean GCS=11.8±4.7. **Intervention:** Retrospective analysis of outcomes related to prophylactic IVCFs or VTE chemoprophylaxis. **Outcome Measures:** Intensive care unit (ICU) length of stay (LOS), total hospitalization LOS, incidence of pulmonary embolism (PE), incidence of deep vein thrombosis (DVT), in-hospital mortality, home mortality.	1. IVCF placement was associated with higher injury severities (p<.001). 2. Patients with IVCFs had significantly increased ICU LOS. 3. Incidence of DVT and PE for patients with an injury severity score <35 was greater in the IVCF group (p<.001); there was no difference between groups for patients with injury severity score ≥35 (p>.05). 4. In a subgroup analysis, patients with injury severity scores >15 and AIS head injury scores ≥3, IVCF was associated with longer ICU LOS (p<.001), higher incidence of DVT and PE (p<.001), but lower in-hospital mortality (p=.001).
Elkbuli et al., (2020) USA Cohort N=513	**Population:** TBI=390; *Early IVCF 0-48hr* (n=119); Mean Age=49.9±22.9yr; Gender: Male=81, Female=38; Time Post Injury=Not Reported; Mean GCS=10.5±4.9; *Late IVCF (>48hr);* (n=394); Mean Age=54.6±22.6yr; Gender: Male=275, Female=119; Time Post Injury=Not Reported; Mean GCS=10.4±4.8. **Intervention:** Adult trauma patients underwent prophylactic inferior vena cava filter (IVCF) placement. Patients were stratified by admission time to IVCF placement: early (0-48hr) and late (>48hr) and the two groups were	1. Early placement of IVCF (first 48hrs) was associated with shorter ICU LOS (p=.005) and hospital LOS (p=.022). 2. No significant differences in rate of VTE, hemorrhagic complications, or mortality were observed between early and late IVCF placement (p>.05).

Author, Year Country Study Design Sample Size	Methods	Outcome
	compared. Outcomes were measured throughout their hospitalization. **Outcome Measures:** Venous thromboembolism (VTE), hemorrhagic complications, intensive care unit (ICU) length of stay (LOS), hospital LOS.	

Discussion

In a pre-post study, Davidson et al. (1993) examined the effectiveness of intermittent pneumatic compression in patients with severe brain injury. The authors reported that the use of intermittent compression devices to prevent the occurrence of DVT was not associated with any significant changes in intracranial pressure or cerebral perfusion pressure in stable patients in whom intracranial pressure was controlled by conventional measures (Davidson et al., 1993).

In a cohort study, Gersin et al. (1994) investigated the effectiveness of sequential compression devices (SCDs); and found no significant difference in the incidence of VTE between those who used SCDs and those who received no intervention. In a PCT study, Kurtoglu et al. (2004) found no significant differences in rates of DVT or PE when comparing patients who used intermittent pneumatic compression devices, and those who received Low-Molecular-Weight Heparin (LMWH) for the prevention of VTE. However, in a cohort study, Minshall et al. (2011) found that mortality was higher in the group of patients receiving sequential compression devices alone compared to those receiving Low-Molecular-Weight Heparin (LMWH) or unfractionated heparin (UFH).

Two cohort studies examined the use of vena cava filters (IVCF). Elkbuli et al. (2021) found that the use of IVCF was more common in patients with more severe injuries, associated with higher rates of DVT and nonfatal PE, and prolonged length of stay in the ICU, when compared to chemoprophylaxis. Elkbuli et al. (2020) examined the timing of IVCF placement, either placed early (0-48hr) or late (>48hr) relative to the time of the TBI. The authors found that early placement of IVCF was associated with shorter lengths of stay in the ICU.

Conclusions

There is conflicting level 2 (Kurtoglu et al., 2004; Gersin et al., 1994) and level 4 evidence (Minshall et al., 2011) regarding the effectiveness of intermittent pneumatic compression devices compared to low-molecular-weight heparin for the prophylaxis of DVT and PE. In one level 4 study (Minshall et al., 2011), LMWH was superior to unfractionated heparin and intermittent pneumatic compression alone for preventing VTE and death; in two level 2 studies (Kurtoglu et al., 2004; Gersin et al., 1994), there was no statistically significant difference between LMWH and intermittent pneumatic compression for VTE or death.

There is level 4 evidence (Davidson et al., 1993) that intermittent compression devices may not cause acute elevations in intracranial pressure in individuals with severe ABI.

There is level 2 evidence (Elkbuli et al., 2021) that prophylactic IVCF may be associated with higher rates of DVT, nonfatal PE and longer hospital stays when compared to VTE chemoprophylaxis following TBI.

There is level 2 evidence (Elkbuli et al., 2020) that IVCF placement within 48hrs of admission may shorten ICU and hospital length of stay post TBI.

KEY POINTS

- Intermittent compression devices alone may not be inferior to low molecular weight heparin for the prevention of venous thromboembolism (VTE) post ABI.
- Intermittent compression devices alone may not aggravate intracranial hemodynamics in patients with severe ABI.
- When compared to VTE chemoprophylaxis, prophylactic IVCF may be associated with higher incidence of DVT and non-fatal PE, as well as longer hospital stays.
- Early placement of IVCF (0-48hr) may shorten ICU and hospital length of stay.

Pharmacological Interventions

The *Institut national d'excellence en santé et en services sociaux* (INESSS) and Ontario Neurotrauma Foundation clinical practice guidelines (2017) for the rehabilitation of moderate to severe TBI recommend initiating thromboprophylaxis as soon as medically appropriate (level B evidence), and using physical methods of thromboprophylaxis (i.e., compression stockings) when pharmacological prophylaxis is delayed or contraindicated (level B evidence).

Several pharmacological interventions have been used for preventing or treating DVT and/or PE, including unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), selective factor X inhibitors, and vitamin K antagonists (VKA) (Long, 2009). Deciding which anticoagulant to use may depend on institutional practices and patient factors, such as the risks of bleeding, patient preference, and underlying conditions that may be exacerbated by this therapy. Some risks factors for bleeding while on anticoagulation include age (over 65yrs), anemia, antiplatelet therapy, cancer, diabetes, liver failure, renal failure, and recent surgery (Bartholomew, 2017). Some clinicians may be hesitant to use chemoprophylaxis in individuals who sustained a TBI, due to the risks of a new or worsening hemorrhage,

In addition to anticoagulants, this section also reviews beta-blockers, which have been investigated as agents for VTE prophylaxis.

Anticoagulants

Low-Molecular-Weight Heparin (LMWH)

Low-Molecular-Weight Heparin (LMWH), including enoxaparin, dalteparin, and certoparin, act by inhibiting the coagulation cascade, thus preventing clots from forming (Solari & Varacallo, 2022). The use of LMWH for VTE prophylaxis has been considered the standard of care for trauma patients; however, its use in individuals who have sustained a TBI has been widely debated given the potential for intracranial hemorrhage exacerbation (Thier et al., 2022).

TABLE 6 | Low-Molecular-Weight Heparin for the Prophylaxis of Venous Thromboembolism Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Baharvahdat et al., (2019) Iran RCT PEDro=9 $N_{Initial}$=54, N_{Final}=53	**Population:** TBI=54; *Enoxaparin* (n=26); Mean Age=27.2±13.2yr; Gender: Male=22, Female=4; Time Post Injury=<5h; Median GCS=7; *Placebo* (n=27); Mean Age=25.9±0.9yr; Gender: Male=22, Female=5; Time Post Injury=<5h; Median GCS=7. **Intervention:** Participants were randomly allocated to receive enoxaparin (0.5mg/kg subcutaneous) or placebo (2mL sterile water subcutaneous) every 6h for a total of six doses. Outcome measures were assessed at baseline and discharge. **Outcome Measures:** Incidence of intracranial hematoma (ICH), Glasgow Outcome Scale (GOS), hospital length of stay, intensive care unit length of stay.	1. There were no significant between group differences in the incidence of new ICH or ICH size increase (p>.05). 2. Enoxaparin significantly improved favorable outcomes (GOS, p=.019) compared to the placebo group. 3. No significant differences in hospital or ICU length of stay were observed between groups (p>.05).
Phelan et al. (2012) USA RCT PEDro=8 N=62	**Population:** TBI; *Intervention Group* (n=34); Mean Age=40.7yr; Gender: Male=22, Female=12; *Control Group* (n=28); Mean Age=42.6yr; Gender: Male=16, Female=12. **Intervention:** The intervention group received enoxaparin (30 mg, 2x/day) within 24-96hr after injury, whereas the control group received a placebo. **Outcome Measures:** Radiographic worsening of TBI, VTE, and extracranial hemorrhagic complications.	1. One DVT occurred in the control group; however, no mention of DVT occurrence was reported for the intervention group. 2. No radiographic worsening of TBI was found.
Agnelli et al. (1998) USA RCT PEDro=6 N=307	**Population:** TBI=261, Other=46; *Intervention Group (n=153)*: Mean Age=55.1yr; Gender: Male=69, Female=84. *Placebo Group (n=154)*: Mean Age=57.5yr; Gender: Male=84, Female=70. **Intervention:** Patients received either enoxaparin (40 mg/day) or placebo administered subcutaneously for no less than 7 days, beginning within 24 hr following elective neurosurgery. All patients were fitted with thigh-length compression stockings, which were worn from the morning of surgery until discharge.	1. 84% of patients receiving placebo and 85% of the patients receiving enoxaparin had venographic studies sufficient for analysis. 2. 32% of patients in the placebo group and 17% in the intervention group had DVT, with a relative risk of 0.52 (p=0.004). 3. 6% of patients in the placebo group had a clinically overt thromboembolic event compared to only 1% in the enoxaparin group.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: Symptomatic, objectively documented VTE (DVT or PE) or DVT detected by bilateral venography performed at the end of the treatment period.	4. The rates of proximal DVT were 13% in the placebo and 5% in the enoxaparin groups (p=0.04).
Jamous et al. (2020) Jordan Pre-Post N=46	**Population:** TBI patients with traumatic ICH; Mean Age=43.9±25.8yr; Gender: Male=36, Female=10; Mean GCS=9.9±4.7. **Intervention:** Forty-six patients with closed traumatic intracranial bleeding received early (i.e., within 72 hours) venous thromboembolic prophylaxis with 40 mg of enoxaparin. **Outcome Measures:** Propagation of ICH (increase in hemorrhage size on CT scan, recurrence of ICH or occurrence of new ICH). GCS after VTEp	1. Neither the non-surgical patients (n=18) nor the surgical patients (n=28) showed significant progression of baseline ICH or development of new ICH. 2. 8 patients had poor outcome (vegetative state or severe disability); 38 had a good outcome (full recovery or mild disability).
Störmann et al., (2019) Germany Cohort N=292	**Population:** TBI=292; Intervention Groups (time to chemical VTE prophylaxis): *Early* (<24hr after hospitalization) (n=93*);* Mean Age=62.1±19.1yr; Gender: Male=61.3%; Mean AIS=3.7±0.8. *Intermediate* (24-48hr) (n=90); Mean Age=60.8±21.6yr; Gender: Male=66.7%; Mean AIS=3.6±0.7; *Late* (>48hr) (n=74); Mean Age=62.1±21.7yr; Gender: Male=71.6%; Mean AIS=3.4±0.6. *No Therapy* (n=35); Mean Age=64.5±19.3yr; Gender: Male=60.0%; Mean AIS=3.9±0.9. **Intervention:** Participants with severe TBI were given VTE prophylaxis (LMWH,) at different times. Outcomes were monitored over the first 7 days of recovery. **Outcome Measures:** Intracranial bleeding progression, venous thromboembolism (VTE), mortality.	1. Early administration of LMWH within 24hr after admission did not significantly increase the risk of intracranial bleeding progression (p>.05) in patients with severe blunt TBI. 2. The in-hospital mortality rate did not differ significantly between the ‘‘early,’’ ‘‘intermediate’’ and ‘‘late’’ groups. 3. Thromboembolic events were observed in patients that received LMWH.
Hachem et al. (2018) Canada PCT N=64	**Population:** TBI; Mean Age=44yr; Gender: Male=45, Female=19; Mean GCS=5. **Intervention:** Prospective evaluation of patients who received enoxaparin within 3 days of admission (Early group), after 3 days (Late group), and no enoxaparin (No treatment group). Doppler ultrasounds (DUS) 7 days (+/- 3d) post admission were used to evaluate DVTs, in addition to care and investigations ordered by the treating clinicians. **Outcome Measures**: VTE events, Intracranial Hemorrhage (ICH) progression, Mortality.	1. Patients receiving early or late LMWH had lower in-hospital mortality than patients who did not receive any VTE chemoprophylaxis (p<0.0001) 2. Progression of ICH after initiation of enoxaparin was similar between the early (0%) and late (7%) groups. 3. VTE incidence was not significantly different between the early (10%) and late (16%) groups (p=0.99). 4. Patients that did not receive anticoagulant prophylaxis were significantly older and had a higher incidence of incidence of death.
Daley et al. (2015) USA Case Control N=271	**Population:** TBI; *Intervention Group (n=45):* Mean Age=42yr; Gender: Male=38, Female=7; Mean GCS=10. *Control Group (n=226):* Mean Age=47yr; Gender: Male=173, Female=53; Mean GCS=10. **Intervention:** Participants were categorized based on exposure (intervention) or lack of exposure (control) to	1. No significant differences between groups (intervention and control) were found in terms of rate of DVT (2% vs 3%, p=0.87), rate of PE (0% versus 1%, p=0.99), LOS or DOV.

Author Year Country Study Design Sample Size	Methods	Outcome
	enoxaparin during the acute phase after undergoing an emergency craniotomy, post-TBI. **Outcome Measures:** Rate of DVT and PE, Days on ventilation (DOV), Length of stay (LOS), Mortality rate.	2. The intervention group had significantly lower mortality in hospital compared to the control group (4% vs 24%, p=0.01).
Kwiatt et al. (2012) USA Case Series N=1215	**Population:** TBI; Gender: Male=836, Female=379; *Control Group* (n=995); Mean Age=52.9yr; Mean GCS=11.4. *Treatment Group* (n=220); Mean Age=46.2yr; Mean GCS=8. **Intervention:** Retrospective comparison of patients who received low-molecular-weight heparin (LMWH, *treatment group*) for VTE prophylaxis and those who did not. **Outcome Measure:** Progression of intracranial hemorrhage.	1. Patients receiving LMWH were significantly older and had more severe injuries (p<0.001) than those who did not. 2. Patients receiving LMWH compared to controls had greater hemorrhage progression (42% versus 24%, p<0.001). 3. For those receiving LMWH, timing did not impact the rate of hemorrhage progression. 4. The LMWH group compared to the controls had a greater number of VTE episodes (9.1% versus 3.1%, p<0.001).
Koehler et al. (2011) USA Cohort N=669	**Population:** TBI; Gender: Male=487, Female=182. *Early Group* (n=268); Mean Age=39.8yr. *Late Group* (n=401); Mean Age=40.2yr. **Intervention:** Enoxaparin (30 mg 2x/day) was administered to all patients. The early group received the VTE prophylaxis within 0-72 hr and the late group at 73 hr or later post injury. **Outcome Measure:** Incidence of DVT and PE.	1. Those in the early group compared to the late group spent significantly fewer days on a ventilator (p<0.001), fewer days in ICU (p<0.002) and hospital (p<0.004). 2. Intracranial hemorrhage progression for the early vs late groups was 9.38% vs 17.41% (p<0.001) before prophylaxis and 1.46% vs 1.54% after (p=0.912). 3. The proportion of DVTs and PEs were not significantly different (p=0.117 and p=0.49, respectively).
Dudley et al., (2010) Canada Cohort N=287	**Population:** TBI; Mean Age=46.5± 20.5yr; Gender: Male=214, Female=73; Average initial GCS=7.4±3.0; Moderate: n=100, Severe: n=187; No VTE=266, VTE=21; Dalteparin: N=159, Enoxaparin: N=128. **Intervention:** Routine treatment with dalteparin and enoxaparin. **Outcome Measures:** Rate of VTE and timing of VTE diagnosis.	1. 21 patients (7.3%) developed VTEs (11 were severe TBI and ten were moderate). 2. Nine patients (3.1%) developed proximal VTE. 3. In the dalteparin group, 7.5% experienced VTEs, compared to 7.0% in the enoxaparin group, which was not statistically significant (p=0.868). 4. In total, 6 (3.8%) patients treated with dalteparin developed a proximal VTE, while 3 (2.3%) patients treated with enoxaparin developed a proximal VTE. This was not statistically significant (p =0.380). 5. Difference in timing of the VTE diagnosis between the dalteparin and enoxaparin groups (mean ± standard deviation, 20.1 ± 24.8 days and 15.6 ±7.9 days, respectively) was not statistically significant (p=0.464).
Norwood et al. (2008) USA Case Series N=525	**Population:** TBI; Mean Age=39.6yr; Gender: Male=387, Female=138; Abbreviated Injury Scale ≥2; Mean Time Post-Injury=36.2hr. **Intervention:** Patients were given Enoxaparin sodium (30 mg, 2x/day).	1. 4% of patients died. 2. Of 151 patients who underwent a lower extremity venous Doppler ultrasound, 6 patients were diagnosed with a DVT. 3. No patients within the study group were diagnosed with a PE.

Author Year Country Study Design Sample Size	Methods	Outcome
	Outcome Measures: Incidence of DVT and PE, mortality rates.	
Kurtoglu et al. (2004) Turkey PCT N=120	**Population:** TBI=103, Other=17; Median Age=37.1yr; Gender: Male=47, Female=73. **Intervention:** Patients admitted to the Intensive Care Unit (ICU) were allocated to receive either Intermittent Pneumatic Compression devices (IPC; n=60) placed below the knee or Low-Molecular-Weight Heparin (LMWH) (n=60) (40 mg/day, enoxaparin sodium) for VTE prophylaxis. CT scans were obtained at 24hr. **Outcome Measures:** Rate of DVT, PE and mortality.	1. In the IPC group, there were 4 (6.6%) and 2 (3.3%) cases of DVT and PE, respectively. 2. In the LMWH group, there were 3 (5%) and 4 (6.6%) cases of DVT and PE, respectively. This difference was not statistically significant. 3. Overall, 7 (11.6%) and 8 (13.3%) patients died in the IPC and the LMWH group, respectively. 4. There were no significant differences between groups in rates of DVT (p=0.04), PE (p=0.07), or mortality (p=0.08).
Kleindienst et al. (2003) USA Case Series N=940	**Population:** Head Injury=344, Elective Surgery (tumors)=294, Intracranial Hemorrhage (ICH)=302; Mean Age=57.3yr; Gender: Not Reported. **Intervention:** A retrospective review of patients either receiving 18 mg/day of Certoparin-sodium (3000 U anti-factor Xa) for prophylaxis on the evening prior to elective neurosurgery (ES) and within 24 hours after surgery, or admission whenever a CT showed an absence of a progressive haematoma. **Outcome Measures:** Incidence of bleeding complications, VTE events, and morbidity/mortality rates.	1. 155 patients were excluded due to coagulation abnormalities or significant bleeding. 2. Intracranial bleeding was found in 1.5% of the total sample. 3. The incidence of VTE and PE was 0.2% and 0.1% of patients respectively, with no associated mortality. 4. No heparin induced thrombocytopenia was observed.
Norwood et al. (2002) USA Pre-Post N=150	**Population:** Traumatic Intracranial Hemorrhagic injuries (IHI); Mean Age=39.5yr; Mean GCS=10; Gender: Not Reported. **Intervention:** Patients received Enoxaparin-sodium (30 mg, 2x/day) beginning 24 hr after initial evaluation. **Outcome Measures:** Incidence of DVT or PE, Progression of IHI, mortality, Glasgow Outcome Scale (GOS).	1. At discharge (n=106), 2% of patients had a DVT and no PE were recorded. 2. 23% of patients had CT progression of IHI pre-treatment. Rate of progression of IHI significantly decreased after initiation of the intervention (p=0.002). 3. Mortality was 7%. 4. On the GOS, the majority (76%) of patients showed good recovery.

Discussion

In an RCT, Agnelli et al. (1998) found that the combination of enoxaparin and compression stockings was more effective than compression stoking alone in individuals who underwent neurosurgery. While a combination of LMWH with or without intermittent pneumatic compression was found to be effective, there were no significant differences between groups in terms of reduced DVT, PE or mortality in a PCT study by Kurtoglu et al. (2004). In the RCT by Phelan et al. (2012), rates of progression of intracranial hemorrhage after starting enoxaparin in small, stable injuries were reported to be similar to what was seen with placebo.

In an RCT, Baharvahdat et al. (2019) found that early administration of enoxaparin was associated with improved outcomes for individuals with TBI, without increasing the risk of intracranial hematoma. Similarly, in a cohort study, Störmann et al. (2019) found that early administration of chemoprophylaxis with LWMH within 24 hours of admission did not increase the risk of intracranial bleeding progression. Furthermore, in a pre-post study, the authors found that prophylaxis with enoxaparin did not result in deterioration and or progression of intracranial bleeding (Jamous et al., 2020). However, in the PCT by Hachem (2018), there was no difference between those who received LMWH early or late post innury in terms of rates of intracranial hemorrhage progression, but in-hospital mortality was higher in patients who did not receive any VTE chemoprophylaxis with LMWH. Similar findings regarding timing of LMWH were reported in a case series study by Kwiatt et al. (2012).

In a case control study by Daley et al. (2015), no significant differences in rates of DVT or PE were observed between those given enoxaparin and those who received no prophylaxis; however, those who received enoxaparin showed a significantly lower rate of in-hospital mortality. In a cohort study, Koehler et al. (2011) reported that early timing of enoxaparin administration was associated with fewer days spent on a ventilator, and shorter length of stay in the ICU and hospital. Findings supporting the early use of enoxaparin for VTE prophylaxis were also reported by Norwood et al. (2008) in a case series study and by Norwood et al. (2002) in a pre-post study.

In a cohort study, Dudley et al. (2010) found that, while VTE prophylaxis offered a relatively high level of proception against VTE, there were no statistically significant differences between the enoxaparin and dalteparin groups. Only one study examined the use of certoparin for prophylaxis before surgery; in a case series, Kleindienst et al. (2003) found that the early administration of certoparin was safe and effective in individuals undergoing neurosurgery.

Conclusions

There is level 1b evidence (Baharvahdat et al., 2019; Jamous et al., 2020; Phelan et al., 2012; Störmann et al. 2019;) that enoxaparin may improve outcomes for individuals with TBI without increasing the risk for progression of intracranial bleeding.

There is level 1b evidence (Agnelli et al., 1998) the combination of enoxaparin and compression stockings is more effective than compression stockings alone for the prevention of VTE.

There is level 2 evidence (Koehler et al., 2011) that early administration of enoxaparin may reduce the days spent on a ventilator, as well as the length of stay in the ICU and hospital.

There is level 2 evidence (Dudley et al., 2010) that there may be no difference in effectiveness between VTE prophylaxis with enoxaparin or dalteparin.

There is level 3 evidence (Daley et al., 2015; Hachem et al., 2018) that enoxaparin may reduce in-hospital mortality.

There is level 4 evidence that (Kleindienst et al., 2003) certoparin may be safe for individuals undergoing neurosurgery.

KEY POINTS

- VTE prophylaxis with LMWH, such as enoxaparin, may be safe and effective for individuals post ABI.
- Enoxaparin and compression stockings combined may be more effective than compression stockings alone.
- Early administration of enoxaparin may reduce the number of days spent on ventilator and length of stay in ICU and hospital.

Unfractionated Heparin (UFH)

Unfractionated heparin (UFH) is an anticoagulant drug used for the prophylaxis of VTE, it prevents clots from forming by prolonging the time needed for the blood to clot (Warnock & Huang, 2022).

TABLE 7 | Unfractionated Heparin for the Prophylaxis of Venous Thromboembolism Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Brandi et al., (2020) Switzerland Case Control N=177	**Population:** TBI=177; *Patients with VTE* (n=23); Mean Age=51±20yr; Gender: Male=16, Female=7; Time Post Injury=Not Reported; *Patients without VTE* (n=154); Mean Age=50±22yr; Gender: Male=114, Female=40; Time Post Injury=Not Reported. **Intervention:** Retrospective analysis of timing and exposure with a continuous infusion of unfractionated heparin (UFH) on VTE, and the risk factors associated with developing VTE following moderate to severe TBI. **Outcome Measures:** Hypotension, intensive care unit length of stay, number of days on mechanical ventilation, timing of UFH initiation.	1. Delayed onset of administration of UFH was the only independent predictor of VTE ($p<.05$). 2. No other measures significantly predicted the incidence of VTE ($p>.05$).
Lin et al. (2013) USA Case Series N=3812	**Population:** TBI, Abbreviated Injury Severity Scale>3. **Intervention:** Patient records were retrospectively reviewed. Participants were analyzed based on whether they received care before the initiation of heparin (UFH) prophylaxis protocol (n=1970) or after the implementation of a heparin prophylaxis protocol (n=1842). **Outcome Measures:** Rate of DVT and PE.	1. Rate of DVT was 0.97% before and 1.21% after heparin prophylaxis protocol. 2. A single patient had a PE in each group.

Author Year Country Study Design Sample Size	Methods	Outcome
Kim et al. (2002) USA Case Control N=64	**Population:** ABI; Gender: Male=49, Female=15. *Early Group (n=47):* Mean Age=37.7yr; Mean GCS=9.1. *Late Group (n=17):* Mean Age=44yr; Mean GCS=9.4. **Intervention:** Retrospective review of patients who received unfractionated heparin (UFH) within 72 hours of admission (Early Group) and those who received it after the third day (Late Group). **Outcome Measures:** VTE events, bleeding complications.	1. There was no increase in intracranial bleeding or deterioration on neurological examination due to early UFH administration. 2. There was no statistical difference in VTE events between groups.

Discussion

Prophylaxis of VTE using unfractionated heparin (UFH) was examined by three studies. In a case control study, Brandi et al. (2020) found that a delay in the initiation of VTE prophylaxis with UFH was associated with higher risk of developing VTE. In contrast, in a case series study, Lin et al. (2013) found that the initiation of a VTE prophylaxis protocol using UFH did not have a significant effect on rates of DVT and PE in individuals with moderate to severe TBI.

As for intracranial bleeding, Kim et al. (2002) found that individuals who received UFH early (within 72 hrs of admission) had no increase in intracranial bleeding as a result of UFH administration; furthermore, no statistical differences were found when comparing rates of VTE among those who received early versus late (after 3 days of hospitalization) UFH.

Conclusions

There is level 3 evidence (Brandi et al., 2020) that a delay in the initiation of UFH therapy post TBI may result in higher risk of VTE.

There is level 3 evidence (Kim et al., 2002) that UFH may be safe in individuals with severe head injuries.

There is level 4 evidence (Lin et al., 2013) that UFH may not be effective in reducing risk of DVT and PE post TBI.

KEY POINTS

- Unfractionated Heparin (UFH) may be safe for individuals with severe ABI. However, it may not be effective for reducing risk of DVT or PE.
- Delaying the initiation of UFH prophylaxis may result in a higher risk of VTE.

Low-Molecular-Weight Heparin and/or Unfractionated Heparin

Several studies have investigated VTE chemoprophylaxis post ABI by examining the use of different regiments of anticoagulation therapy, such as comparing LMWH to UFH, or administering them in combination.

TABLE 8 | LMWH and/or UH for the Prophylaxis of Venous Thromboembolism Post ABI

Author Year Country Study Design Sample Size	Methods	Outcome
Byrne et al. (2022) USA Cohort N=4951	**Population:** TBI; Median Age=50yr; Gender: Male=3676, Female=1275; Median head AIS=5; Mean GCS on Arrival=7. **Intervention:** Retrospective review of patients who received pharmacologic VTE prophylaxis (LMWH or UH). **Outcome Measures:** Incidence of VTE (PE or VTE) after urgent neurosurgical intervention.	1. A longer prophylaxis delay was associated with increased risk of VTE. Each additional day was associated with an 8% increase in the odds of VTE (adjusted odds ratio [aOR], 1.08 per day; 95% CI, 1.04-1.12). 2. LMWH was associated with lower odds of VTE than UFH (aOR, 0.64; 95% CI, 0.49-0.84). 3. Interaction between prophylaxis delay and the type of urgent neurosurgical intervention were not significant in the models for VTE or repeated neurosurgery. 4. Interaction between prophylaxis delay and type of urgent neurosurgical intervention (craniotomy/craniectomy) was significant in the model for mortality (p=.049).
Jakob et al. (2022) USA Cohort N=4304	**Population**: TBI; Early prophylaxis group (<48 hours): n=2152; Mean Age=55 years; Gender: Male=1485; AIS head: < 3= 2152; ISS=16; UH: n=1101; LMWH: n=1051. Late prophylaxis group (>48 hours): n=2152; Mean Age=56 years; Gender: Male=1485; AIS head: < 3= 2152; ISS=16; UH: n=1101; LMWH: n=1051. **Intervention**: LMWH and UH administered within 48 hours and after 48 hours of admission. **Outcome Measures**: Effectiveness of LMWH vs UH in patients with severe TBI and combined SAH and SDH.	1. Overall VTE complications (2.6% vs 1.3%, p = 0.002) including DVT (2.1% vs 1.0%, p = 0.006) were more common in the late compared to the early group. 2. The rate of PE was 0.7% in the late group vs 0.4% in the early group, p = 0.228. 3. ICU admission rate was higher in the late group (87.1% vs 80.8%, p < 0.001), including longer ICU LOS [5 vs 3 days, p < 0.001] and hospital LOS [10 vs 6 days, p < 0.001] compared to the early group. 4. The type of VTEp (UFH vs LMWH) was not independently associated with thromboembolic events, mortality or craniectomies after the initiation of the VTE prophylaxis.
Coleman et al., (2021) United States Cohort N=1803	**Population:** TBI; Median Age=55yr; Gender: Male= 69% (n=1247); Median ISS=22; Median Head AIS=4; Median GCS=14; Isolated Head Injury=91% (n=1644), Polytrauma (Spinal cord, pelvis, tibia, femur injury) =9%. **Intervention:** Participants were given VTE chemoprophylaxis (LMWH or UH) early (within 48 hrs of admission) or late (after 48 hrs post admission). **Outcome Measures:** Incidence and timing of VTE in patients with TBI.	1. 29 patients (2%) developed PE, and 118 patients (7%) developed DVT resulting in 137 VTE event (8%) overall. 2. No significant differences were observed in rates of radiographic TBI progression in the early vs late VTE chemoprophylaxis initiation timing groups (P=0.59). 3. Early administration of VTE-chemoprophylaxis was associated with decreased VTE.

Author Year Country Study Design Sample Size	Methods	Outcome
Gunning et al. (2021) Netherland Cohort N=1253	**Population:** TBI; *UMCU Hospital* (n=279); TBI=93%; Mean Age=53yr; Gender: Male=199; Mean ISS=24.2. *HMC Hospital* (n=974); TBI=84%; Mean Age=52; Gender: Male=709; Mean ISS=26.6. **Intervention:** Patients in UMCU group were administered dalteparin (LMWH). Patients in HMC group were administered enoxaparin (LMWH) every 24 hours or unfractionated heparin (UH) every 8 hours. **Outcome Measures:** Rates of VTE (DVT), PE, and hemorrhagic complications.	1. Four patients (1.4%) at UMCU developed a VTE [pulmonary embolism (PE)=3, deep venous thrombosis (DVT)=1], compared to 37 patients (3.8%) at HMC (PE=22, DVT=16; p=0.06). 2. Hemorrhagic complications occurred, respectively, in four (1.4%) and ten (1%) of patients at UMCU and HMC (p=0.570). 3. Although the number of patients who received thromboprophylaxis within 48 h after admission was significantly higher at UMCU, no significant difference was demonstrated in either the number of VTEs or the number o hemorrhagic complications between the two populations. 4. Early initiation of therapy appears to be safe, with respect to the risk of bleeding complications even in patients with TBI. 5. One site used LMWH (dalteparin) exclusively and the other used LMWH (enoxaparin) or UFH; there were no statistically significant differences between the sites.
Hecht et al. (2021) United States Cohort N=79,386	**Population:** TBI; VTE prophylaxis <24 hours: n=39,432; Mean Age: 61.7yr; Gender: Male=51.1%; GCS ≤ 6: 91.1%. VTE prophylaxis 24 to <48 hours: 23,949; Mean Age: 63.5yr; Gender: Male=47.7%; GCS ≤ 6: 90.0%. VTE prophylaxis ≥48 hours: 16,005; Mean Age: 58.2yr; Gender: Male=58.5%; GCS ≤ 6: 92.2%. **Intervention:** VTE prophylaxis (low molecular weight heparin, subcutaneous heparin, oral warfarin and direct oral anticoagulant) were administered. **Outcome Measures:** Occurrence of VTE (DVT and PE) and mortality.	1. VTE events were significantly increased among those who received VTE prophylaxis at 24 to <48 hours and ≥48 hours compared with patients who received VTE prophylaxis <24 hours after admission. 2. Mortality was significantly increased if VTE prophylaxis was delayed until ≥48 hours after admission (p=0.001). 3. The results for mortality, VTE, pulmonary embolism, and deep venous thrombosis demonstrated that there was a significantly higher rate of occurrence for each outcome analyzed as time to VTE prophylaxis increased between groups.
Saadi et al., (2021) USA Case Series N=96	**Population:** *No Prophylaxis* (n=14); Mean Age=58.3±21.7yr; Gender: Male=7, Female=7; Time Post Injury=Not Reported; Mean GCS=7.7±3.7. *Prophylaxis within 24h* (n=7); Mean Age=62.1±27.6yr; Gender: Male=4, Female=3; Time Post Injury=Not Reported; Mean GCS=7.3±4.0. *Prophylaxis within 48h* (n=14); Mean Age=48.8±19.0yr; Gender: Male=13, Female=1; Time Post Injury=Not Reported; Mean GCS=5.6±3.6. *Prophylaxis after 48h* (n=61); Mean Age=54.5±20.5yr; Gender: Male=48, Female=13; Time Post Injury=Not Reported; Mean GCS=5.1±3.3.	1. Of the patients included, 14.6% did not receive VTE prophylaxis, 7.3% initiated therapy within 24h, 14.6% within 48h and 63.5% after 48h. 2. Delayed prophylaxis significantly increased the incidence of VTE (p=.038). 3. No significant differences between VTE prophylaxis regimens and incidence of VTE were observed (p>.05). 4. Lack of VTE prophylaxis resulted in significantly higher rates of mortality (p=.006).

Author Year Country Study Design Sample Size	Methods	Outcome
	Intervention: Retrospective chart review of patients that received pharmacological VTE prophylaxis (LMWH or UFH) following severe TBI. **Outcome Measures:** Time to prophylaxis initiation, prophylaxis regimen, incidence of VTE, adverse effects.	5. Earlier VTE prophylaxis was associated with increased minor bleeds (p=.042) but not major bleeds (p>.05).
Seifi et al. (2018) USA Case Control N=155	**Population:** TBI; Gender: Male=119, Female=36. Mean Age=41.6yr. **Intervention:** Retrospective review of patients to evaluate the effectiveness of chemoprophylaxis (on PE prevention. Only patients with clinical suspicion of PE had diagnostic investigations, there was no surveillance for PE. **Outcome Measure:** Incidence of PE.	1. 33 patients did not receive chemical thromboprophylaxis. 2. 60 patients had an IVC filter. 3. 4 patients developed a clinically significant PE. They were all in the group of patients that received chemical thromboprophylaxis. 4. There was no significant difference between incidence of PE between patients that received chemical thromboprophylaxis and those who did not (p=0.58). 5. There was no correlation between the prophylaxis regimen and incidence of VTE or bleeding.
Meyer et al. (2017) USA Case Series N=67	**Population:** TBI=67; *No Early Chemoprophylaxis (n=35):* Mean Age=25.2yr; Gender: Male=35; Mean GCS=8.3. *Early Chemoprophylaxis (n=32):* Mean Age=24.9yr; Gender: Male=32; Mean GCS=10.3. **Intervention:** A retrospective analysis of patients with penetrating brain injury (PBI) was conducted. Patients were grouped based on if they received VTE chemoprophylaxis (UFH or Enoxaparin), within 48hr of injury status or not. **Outcome Measures:** Intracranial hemorrhage (ICH) incidence of PE and DVT; 30-day mortality, emergent reoperation; chemoprophylaxis timing, chemoprophylaxis agents used.	1. 91% of patients receiving early VTE prophylaxis were given enoxaparin (LMWH). 2. The incidence of worsened ICH, DVT or PE, 30-day mortality, or non-elective reoperation were not significantly different between the treatment groups. 3. The mean time of first VTE prophylaxis dose was 24hr from admission.
Byrne et al. (2016) USA Cohort N=3634	**Population**: Severe TBI; Median Age=43yr; Gender: Male=2798, Female=836; Median Time Post Injury=84hr; Median GCS=3. **Intervention**: Participants were included in retrospective analysis after having received either unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) as either early prophylaxis (<72 hr) or late prophylaxis (≥72 hr) for VTE. **Outcome Measures**: Risk of DVT, PE, late neurosurgical intervention, and mortality; abbreviated head injury scale (AIS) and incidence of ischemic stroke.	1. PE occurred in 1.7% of participants, and DVT in 6.5%. 2. Early prophylaxis was associated with lower odds of PE (OR=0.48) and DVT (OR=0.51) than late prophylaxis. 3. There was no significant difference in risk of late neurosurgical intervention or death between the early and late prophylaxis groups. 4. LMWH was associated with lower odds of VTE (OR=0.6) and mortality (OR=0.59) than UFH. 5. The late prophylaxis group had significantly higher AIS scores, rates of ischemic stroke, rates of early neurosurgical intervention than the early prophylaxis group. 6. The late group most commonly received LMWH and the early group most commonly received UFH.

Author Year Country Study Design Sample Size	Methods	Outcome
Dengler et al. (2016) USA Case Series N=155	**Population:** Gender: Male=119, Female=36. **Intervention:** Patients with severe TBI, intracranial hemorrhage (ICH), and invasive intracranial monitoring were retrospectively reviewed. Patient outcomes were correlated with the prophylactic treatment (UFH or LMWH) for DVT that patients received. **Outcome Measures:** DVT: incidence, time to detection, time to starting prophylaxis; time to stable head computed tomography (CT); in-hospital mortality.	1. 12% of the cohort experienced at least one DVT during the course of the study. 2. Following admission, median time to stable head CT was 2 days. 3. Following admission, median time to initiation of DVT prophylaxis was 4 days, and median time to DVT detection was 8 days. 4. Among patients who did not receive anticoagulation, the incidence of DVT (30.3%) was significantly greater than that of patients who received anticoagulation (8.0%, p<0.01). 5. 28 patients (18%) experienced in-hospital mortality. 6. Those who did not receive anticoagulation treatment had a significantly increased risk of DVT and in-hospital death. 7. No significant association was observed between DVT formation, and the various doses of unfractionated heparin and low-molecular-weight heparin.
Kim et al. (2014) USA Case Control N=75	**Population:** TBI; Mean Age=44yr; Gender: Male=59, Female=16; Mean GCS=4. **Intervention:** Participants received heparin prophylaxis at early (<3 days, n=22), intermediate (3-5 days, n=34), or late (>5 days, n=19) time intervals post injury. **Outcome Measures:** Rate of DVT, PE, and morality, number of ventilator and Intensive care unit (ICU) days, Glasgow Coma Scale (GCS), Abbreviated Injury Scale (AIS), Injury Severity Score, Marshall CT score, neurological improvement.	1. There was no significant difference between groups in mean rates of DVT, PE, or mortality; mean days on ventilator or in ICU; or mean scores on GCS, AIS, or Marshall CT score. 2. There was a significant difference in mean ISS score between the early and intermediate groups (28 versus 35, p=0.02) and between the early and late groups (28 versus 36, p=0.007). 3. There was a significant difference in cumulative neurological improvement between the early and late groups (p<0.05), with greater improvement in the early group.
Farooqui et al. (2013) USA Case Control N=236	**Population:** TBI; Gender: Male=146, Female=90. *Group A* (n=107)*:* Mean Age=53.3yr. *Group B* (n=129): Mean Age=57.4yr. **Intervention:** Group A had no routine administration of chemoprophylaxis and Group B received either Lovenox (LMWH) (30 mg, 2x/day) or Heparin (UH) (5000 U, 3x/day) 24 hr after stable computed tomography (CT). **Outcome Measures:** Rate of DVT and PE.	1. DVT rate was higher in patients who did not receive VTE prophylaxis than in patients who did (5.6% versus 0%, p=0.008). 2. PE rate was 3.74% in patients who did not receive VTE prophylaxis and 0.78% in those who did (p=0.18). 3. Progression of intracranial hemorrhage did not differ significantly between groups (p=0.33).
Nickele et al. (2013)	**Population:** TBI; Protocol no PTP group (n=24): Mean Age=59.2±23.1yr; Gender: Male=15, Female=9; Mean GCS=9.9±4.1. Protocol PTP group (n=63): Mean Age=52.1±19.4yr; Gender: Male=49, Female=14; Mean	1. The rate of DVT in the protocol period trauma patients (n=87) was 6.9%. The rate of DVT in the control period (n=48) was 4.2%.

Author Year Country Study Design Sample Size	Methods	Outcome
USA Case Series N= 135	GCS=10.9±4.4. Control no PTP group (n=26): Mean Age=56.6±17.9y; Gender: Male=17, Female=9; Mean GCS=12.2±3.8. Control PTP group (n=22): Mean Age=53.8±21.4yr; Gender: Male=16, Female=6; Mean GCS=8.1±4.2. **Intervention:** Retrospective before and after trial design of patients who underwent treatment with a pharmacological thromboembolism prophylaxis (PTP) protocol. Patients discharged during the 6 months before July 1st and December 1st, 2008, served as the before group in the control period (n=48); all patients discharged between January 1st and December 31st, 2009, served as the after group in the protocol period (n=87). Patients in the protocol period received prophylaxis in the form of unfractionated heparin (UFH; 5000 units subcutaneously twice/day) or dalteparin (LMWH; 5000 units daily) or no prophylaxis. **Outcome Measures:** incidence of DVT, PE	There was no significant change in DVT from the protocol (p=0.20). 2. The change in percentage of patients receiving PTP was significantly increased by the protocol (p<0.0001). 3. Five of 87 patients in the protocol group developed PE (5.75%) whereas 2 of 48 patients in the control group developed PE (4.2%); this was not a significant change from the protocol (p=0.45).
Minshall et al. (2011) USA Case Series N=386	**Population**: TBI; Gender: Male=293, Female=93. **Intervention:** Chart review of patients receiving LMWH (30 mg, 2x/day; n=158), unfractionated heparin (UFH; 5000 IU 3x/day; n=171) or sequential compression devices alone (n=57). **Outcome Measures:** Rate of DVT, PE, and intracranial hemorrhage complications.	1. Mortality in the sequential compression devices alone group was higher (47%) compared to the LMWH (5%) and UFH (16%) groups. 2. Those in the UFH group had a significantly higher rate of DVT and PE than those in the LMWH group (p<0.05). 3. Five percent of those in the LMWH group and 12% in the UFH group had progression of their intracranial hemorrhage, compared to 25% in the untreated group.
Scudday et al. (2011) USA Case Control N=812	**Population:** TBI; Gender: Male=560, Female=252. *Intervention Group (n=402):* Mean Age=45.2yr. *Control Group (n=410):* Mean Age=51.5yr. **Intervention:** Retrospective review comparing patients that received chemical thromboprophylaxis (91% Heparin (UFH), 9% Enoxaparin (LMWH)) to an untreated control group. **Outcome Measure:** Incidence of VTE.	1. A lower incidence of VTE was found in the treated group compared to the untreated group (1% versus 3%, p=0.019).
Salottolo et al. (2011) USA Case Series N=480	**Population:** TBI; Mean Age=53yr; Gender: Male=296, Female=184; Mean GCS=12.2. **Intervention:** Retrospective review of patients considered for thrombus prophylaxis (Lovenox (LMWH) 30 mg 2x/day or heparin (UH) 5000 U, 2x/day), timing of administration, and whether or not the intervention was interrupted. **Outcome Measures:** Development of VTE or DVT.	1. 53% of patients received pharmacological thromboprophylaxis (PTP); median time to start was 3d and it was continuous in 73.7%. 2. Medications began <72 hr post injury in 108 patients and >72 hr post injury in 147. 3. The group that did not receive VTE prophylaxis had 4 DVTs and 2 PEs compared to the VTE prophylaxis group which had 8 DVTs and 3 PEs. 4. Neither the administration of these medications (p=0.29) or the timing of

Author Year Country Study Design Sample Size	Methods	Outcome
		administration (p=0.26) had any correlation with the development of VTE. 5. Patients with interrupted VTE prophylaxis had significantly increased odds of developing VTE compared with patients with continuous treatment (OR=7.07, p=0.04).
Depew et al. (2008) USA Cohort N=124	**Population:** TBI; Mean Age=47yr; Gender: Male=83, Female=41; Mean ISS=26; Enoxaparin Group=62, Heparin=20, No Prophylaxis=42. **Intervention:** Pharmacological VTE prophylaxis with either enoxaparin (LMWH) or heparin (UH). Patients divided into early (within 72 hrs of admission) and late (after 72 hours of admission) groups. **Outcome Measures:** Incidence of VTE and PE.	1. The group had a DVT rate of 14% DVT, one PE, and 3% progression to ICH. 2. The late group had a DVT rate of 11%, no PE, and 3% progression to ICH. 3. The no prophylaxis group had no DVT, PE or progression to ICH. 4. Three patients developed progression of ICH, with one belonging to the early group and two belonging to late group. 5. Of the 124 patients, nine patients developed DVT and one developed PE. 6. Overall mortality (n=17) was deemed attributed to their injury and disease process and not due to DVT or PE.

Discussion

Few studies exist comparing LMWH to UFH for VTE prophylaxis post ABI. However, more commonly studies have looked at early versus late initiation of prophylaxis and have compared VTE prophylaxis to no therapy.

In a cohort study, Byrne et al. (2022) found that the use of LMWH was associated with lower odds of developing VTE when compared to UH and that late pharmacological prophylaxis increased the risk of VTE in individuals who underwent urgent neurosurgical intervention. Byrne et al. (2016) also found that LMWH was associated with lower mortality when compared to UFH. In a case series, Nickele et al. (2013) found that LMWH was more effective for the prophylaxis of DVT in individuals with trauma injuries. Similar findings favoring the use of LMWH, were reported in a case series by Minshall et al. (2011). In a cohort study, Jakob et al. (2022) found that the type of VTE prophylaxis (LMWH versus UFH) was not independently associated with the development of VTE, mortality, or craniectomies after initiation of therapy. In the case series study by Saadi et al. (2021), no correlation was found between the prophylaxis regimen (LMWH or UFH) and the incidence of VTE or bleeding. Similarly, in a case series study, Dengler et al (2016) found no association between type (LMWH or UFH) or dose of VTE prophylaxis given subsequent rates of DVT or hemorrhage expansion.

Some studies reported the use of both LMWH and UFH but reported results considering chemoprophylaxis in general. In the cohort study by Coleman et al. (2021), early prophylaxis (within 48 hours of admission) may be beneficial. Similarly, several studies found that early VTE prophylaxis was

safe and favorable among persons with ABI (Depew et al., 2008; Farooqui et al., 2013; Gunning et al., 2021; Hecht et al., 2021; Kim et al., 2014; Meyer et al., 2017; Salottolo et al., 2011; Scudday et al., 2011). In a case control study, Seifi et al. (2018) reported that the type of heparin that should be used for PE prophylaxis remains controversial.

Conclusions

There is conflicting evidence regarding the effectiveness of LMWH and UFH when compared to each other for the prevention of VTE post ABI.

KEY POINTS

- There is conflicting evidence on the effectiveness of Low-Molecular-Weight Heparin (LMWH) and Unfractionated Heparin (UFH) for the prophylaxis of VTE, when compared to each other.

Beta blockers

Propranolol

Propranolol is a beta blocker that is often used to manage conditions such as hypertension, myocardial infarction and cardiac arrhythmias (Al-Majed et al., 2017). It has been hypothesized that, through attenuation of the catecholamine response, beta blockers may reduce hypercoagulability post TBI (Dhillon et al., 2021).

TABLE 9 | Propranolol for the Prophylaxis of Venous Thromboembolism Post TBI

Author Year Country Study Design Sample Size	Methods	Outcome
Dhillon et al. (2021) USA Cohort N=131	**Population:** TBI; *Propranolol Group*=31; Mean Age= 50.4 ± 21.6; Gender: Male=31, Female=10; Mean GCS= 9.3 ± 5.0; *No propranolol Group*=100; Mean Age= 57.2 ± 23.7yr; Gender: Male=70, Female=30; Mean GCS= 9.8 ± 5.1. **Intervention:** Administration of propanol. **Outcome Measures:** Incidence of lower VTE in TBI patients.	1. Patients in the propranolol group were more likely to be placed on VTE chemoprophylaxis at some point during their hospitalization (83.9% vs 46.0%, p<.01). 2. No differences were observed in the proportion of patients started on VTE chemoprophylaxis within 2 days of their admission (3.2% vs 7.0%, p=.68) or 5 days after admission (41.9% vs 35.0%, p=.48). 3. Mortality rate was significantly lower in the propranolol group (p=.02). 4. After adjusting for confounders (head AIS, ISS, receiving VTE chemoprophylaxis within 2 days of admission, ventilator days, and hospital LOS), patients

		receiving early propranolol had a lower risk of VTE (AOR 0.20).

Discussion

One cohort study examined the use of propranolol on VTE post TBI. Dhillon et al. (2021) found that those who received early propranolol had significantly lower rates of mortality and VTE.

Conclusions

There is level 2 evidence (Dhillon et al., 2021) that early use of propranolol may decrease rates of VTE and mortality post TBI.

KEY POINTS

- Early administration of propranolol may reduce rates of VTE in individuals with TBI.

Conclusion

The available evidence supports the use of VTE chemoprophylaxis with LMWH in acute settings. However, clinicians should use careful consideration for patients' characteristics and clinical status to determine if the use of non-pharmacological and/or pharmacological prophylaxis is most appropriate for a given patient at a given time. In a systematic review, Margolick et al. (2018) found that early prophylaxis with anticoagulants may be safe for individuals with TBI; however, those with unstable injuries or increased hemorrhagic risk may benefit from mechanical prophylaxis instead. In another systematic review, Spano et al. (2020) reported that early pharmacological prophylaxis may be associated with reduced rates of VTE, without increase or exacerbation of existing intracranial hemorrhage. Several studies examined the use of anticoagulants such as LMWH and UH; however, there is insufficient evidence regarding effectiveness of different drug types to conclusively recommend one over others. More research, particularly RCT studies, is required to determine if different anticoagulants may result in different outcomes for the incidence of VTE or mortality post ABI. There is insufficient research to establish optimal timing for initiating VTE chemoprophylaxis, the optimal duration of treatment, and the optimal medication.

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