Thromboprophylaxis in Traumatic Brain Injury

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Introduction

There is a well recognised relationship between trauma and venous thromboembolism (VTE). VTE consists of deep venous thrombosis and its much feared complication of pulmonary embolism (PE). Among hospitalised patients, those with major trauma have the highest risk of developing VTE without prophylaxis. Although the studies are few regarding incidence in isolated Traumatic brain injury (TBI) with small patient numbers they illustrate that the incidence is high around 20 - 50 % and hence warrants VTE prophylaxis to prevent the sequelae such as thrombophlebitis, venous ulcers, and the most detrimental a pulmonary embolus. The issue of pharmacological prophylaxis has been debated as many neurosurgeons are reluctant to start early (less 72 hours) intervention, especially in the patient with a TBI. The reluctance lies with the risk of intracranial haemorrhage in the patient on pharmacological prophylaxis and the detrimental effect of an intracranial bleed.¹

Traumatic Brain Injury

Traumatic brain injury (TBI) continues to be an enormous public health problem, even with modern medicine in the 21st century. Most patients with TBI (75-80%) have mild head injuries; the remaining injuries are divided equally between moderate and severe categories. The cost to society of TBI is staggering, from both an economic and an emotional standpoint.

Almost 100% of persons with severe head injury and as many as two thirds of those with moderate head injury will be permanently disabled in some fashion and will not return to their premorbid level of function. In the United States, the direct cost of care for patients with TBI, excluding inpatient care, is estimated at more than $25 billion annually. The impact is even greater when one considers that most severe head injuries occur in adolescents and young adults.²

Frequency

The annual incidence of TBI in the United States has been estimated to be 180-220 cases per 100,000 populations. In the United States, with a population of almost 300 million, approximately 600,000 new TBIs occur per year. As many as 10% of these injuries are fatal, resulting in almost 550,000 persons hospitalized annually in the United States with head injuries.²

Traumatic brain injury (TBI) is a serious neurodisorder commonly caused by car accidents, sports related events or violence. The primary injury to the brain initiates a secondary injury process that spreads via multiple molecular mechanisms in the pathogenesis of TBI.
The events leading to both neuro-degeneration and functional recovery after TBI are generalized into four categories:

(i) primary injury that disrupts brain tissues;
(ii) secondary injury that causes pathophysiology in the brain;
(iii) inflammatory response that adds to neuro-degeneration; and
(iv) repair-regeneration that may contribute to neuronal repair and regeneration to some extent following TBI.

**Primary Injury**

Generally, TBI is triggered by an external mechanical impact to the head. An impact load causes TBI through a combination of two injury mechanisms such as contact and inertial forces. Contact forces prevent the head from moving after the impact. Inertial forces set the head in acceleration (translational or rotational or both) with and without a contact force. The two main patterns of head trauma are focal and diffuse injuries. Contact forces cause focal injuries such as skull fracture, epidural hematoma, coup contusion, and subdural haematoma. Inertial forces with only pure translational acceleration cause focal injuries such as contracoup contusion, intracerebral hematoma, and subdural hematoma. The inertial forces cause diffuse injuries. The most common form of inertial forces is the angular acceleration, a combination of translational acceleration and rotational acceleration, which produces every type of head trauma except skull fracture and epidural hematoma. Rotational acceleration as a significant component of the injury mechanism produces concussion and Diffuse Axonal Injury (DAI).

**Secondary injury**

It develops over a period of hours or days after the initial impact to the head. Secondary injury is associated with synthesis and release of neurochemicals that alter cerebral blood flow, ion homeostasis, and metabolism. Most of the post-traumatic neurochemical mediators of secondary injury may act as neuro-destructive compounds. Identification of those neuro-destructive compounds and time of their pathological actions can help design therapeutic strategies to attenuate neuronal damage following TBI.
The Evolution of Thrombosis and Anticoagulants

The search for effective anticoagulation dates back to ancient times. Only during the previous century has medical conjecture been tested and proven through clinical practice.

It was as early as the 4th Century BC that Hippocrates proposed oral "blood thinners" in 10th Century AD medicinal leeches replaced venisection as a method of anticoagulation. In the 13th Century an illustrated manuscript depicts what is believed to be the first well-documented case of venous thromboembolism (VTE). Richard Wiseman provides the first detailed description of a VTE following childbirth in 1676.

Rudolph Virchow presents his observations on a triad of factors in the pathophysiology of clot formation in 1860. In 1866 Spencer Wells recognizes a link between VTE and surgery. In 1884 the anticoagulant compound hirudin is identified in the saliva of European medicinal leeches (the extract was proven to be too toxic for clinical use). It was in 1916 that the first clinically important anticoagulant, Heparin, was discovered by Jay McClean.

In 1935, a purified form of Heparin was developed. Carl Link, HA Campbell, and colleagues isolated and identified dicumarol in 1939. In 1948 the name of coumarin derivative No. 42 is coined as warfarin.

The 1950s saw Warfarin sodium being made available for clinical use. Low-molecular-weight heparin was developed and made available for clinical use in the 1980’s-1990. The 21st Century is the era for the development of Next-generation oral anticoagulants.
Pathophysiology and Pathogenesis of VTE

Rudolf Virchow’s 1856 interpretation of the pathogenesis of VTE remains the model for description of the pathophysiology of VTE. Virchow’s triad of venostasis, vascular injury and hypercoagulability is the underlying cause for the development of VTE in most trauma patients. In many instances, all three components of this triad are operative in combination with several other recognized risk factors for the development of VTE. Venous stasis associated with relative immobility caused by spinal cord injury or immobilization after long-bone injury is a relatively permissive factor.

The trauma patient often is incapacitated because of various factors including obtundation, chemical paralysis, and postoperative immobilization and coupled with other injuries for e.g. Long bone fractures or pelvic fractures. An absence of intermittent pulsatile blood flow is a correlate of immobilization and results in a collection of blood within the valve-pocket recesses of veins. This local stasis hypoxia serves as a pro-coagulative effect for the endothelium and subsequent activation of the coagulation cascade. Disruption of the endothelium physically through direct trauma or chemically through induced elevation of interleukin-1 can effect a change in the normally antithrombogenic endothelium, enabling prothrombotic conditions that favour thrombosis formation or propagation. Seriously injured patients exhibit an early activation of the coagulation cascade and the development of an underlying hypercoagulability.

In addition, a process of increased hypercoagulability have been identified in trauma patients. This process is reported to persist for at least 1 month after injury. Hypercoagulability is likely multifactorial, stemming from excessive activation of coagulation, a reduction in coagulation inhibitors and an increased fibrinolytic inhibition. This phenomenon of injury-induced hypercoagulability is not predictive of VTE; however, it must be considered when presented in a scenario of venostasis induced by immobilization. The activation of the coagulation cascade may be compounded by the systemic inflammatory response coincident with the physiologic response to traumatic injury.

Abnormalities of haemostasis can lead to haemorrhage, and on the other hand to thrombosis. Intracranial neoplasms, complex surgical procedures, and head injury have a specific impact on coagulation and fibrinolysis. The complex process of haemostasis is determined by the interaction of endothelial and sub endothelial cells, platelets, leukocytes, coagulation factors, and coagulation inhibitors. The three major steps of the coagulation process are the initiation, amplification, and propagation phases (Figure 1). Vascular injury leads to intravascular exposure of tissue factor (TF). TF binds circulating factor VII to form TFFVIIa complexes. This initial step results in activation of factor X and IX (Josso loop) on TF-bearing cells (initiation phase). It has to be considered that intravascular TF exposure can also be a result of invasive tumour growth or expression of TF on the surface of...
stimulated leukocytes in connection with acute or chronic inflammatory reactions. Platelets are localized to the site of injury by adhesion to the sub endothelial matrix mediated by interaction between collagen, von Willebrand factor (vWF) and GPIb receptors on the surface of platelets.

During the initiation phase, activated factor X (FXa) generates a small amount of thrombin, which is not high enough to produce a haemostatic sufficient fibrin clot, but leads to an activation of platelets and further enzymatic coagulation factors (factor XI, VIII and V) (amplification phase). Activated platelets release thromboxane and their granule contents (ADP, serotonin, vWF, PF4, calcium and coagulation factors), which results in activation and aggregation of further platelets. Furthermore, they alter their surface by expressing negative charged phospholipids (flip-flop-mechanism) to facilitate calcium-mediated coagulation factor binding. The further activation of coagulation factors and the subsequent thrombin generation takes place on the surface of activated platelets (propagation phase). Thrombin itself potentiates its generation by activation of factor XI, VIII and V, which results in a thrombin burst, sufficient to cleave fibrinogen and activate factor XIII (FXIII) as well as thrombin activatable fibrinolysis inhibitor (TAFI). Soluble fibrin monomers polymerize and are cross-linked by FXIII. Thereby fibrin and platelets form a stable clot that is anchored at the extracellular matrix due to the cross-linking of fibrin with adhesive proteins.

There is a growing body of evidence suggesting that normal brain parenchyma has a (local) influence on coagulation and fibrinolysis. Tissue factor (TF) or thromboplastin, the main initiator of the coagulation process, is abundantly expressed in normal brain tissue. Patients with severe head injury have significantly higher TF concentrations compared to patients with moderate head injury. The injured brain itself has a direct influence on coagulation and fibrinolysis. This could be (at least partially) an explanation for the high incidence of systemic thromboembolic complications such DVT or PE due to an associated procoagulatoric state in neurosurgical patients.
Figure 1: Coagulation Cascade$^{25}$

![Diagram of the coagulation cascade](image-url)
Incidence and Risk Factors of VTE in TBI

The incidence of VTE in the general trauma population has been well studied and is variable depending upon the type and severity of traumatic injury. VTE in trauma patients is a frequent, often life-threatening complication of major trauma. The reported incidence of deep venous thrombosis (DVT) in trauma patients varies from 20-90% according to study design, type of trauma population, and method of DVT prophylaxis and diagnosis\(^3\).

The prevalence of DVT has been estimated at 40 – 80% in major trauma patients not receiving prophylaxis\(^1\). The reported incidence of PE in these studies varies from 2.3-22%. Geerts\(^4\) et al found the incidence of lower extremity DVT to be as high as 58% in patients without prophylaxis\(^2\).

The reported incidence of DVT in untreated neurosurgical patients varies between 18 – 50%\(^5\)\(^,\)\(^2\). The incidence in patients with DVT is variously estimated at between 22% and 45%. DVT in Head injury is about 20%. The overall rate of PE in untreated neurosurgical patients is approximately 0.4%. An autopsy study of neurosurgical patients revealed a PE rate of 8-25% with a mortality rate of 5-60%\(^6\).

**Symptomatic** DVT and PE rates in traumatic brain injury reported in the literature range from 0 – 3.9% and 0-1.8% respectively, asymptomatic and symptomatic DVT rates are 4.8% - 16.9\(^7\).

Recent literature and incidence

A study by Khaldi\(^5\) et al looked at VTE in a mixed neurosurgical population of 555 high-risk patients in ICU. Only 8% of the cases were neuro-trauma cases. It was a retrospective study; all patients received mechanical DVT prophylaxis and subcutaneous Heparin (5000U twice daily) within 24 – 48hrs of a neuro-surgical procedure. They found the risk of developing DVT following a neurosurgical procedure while using only mechanical DVT prophylaxis was calculated at 16%. This risk was reduced to 9% with Heparin prophylaxis. This amounted to a 43% reduction in the lower extremity DVT rate with pharmacological prophylaxis. There was no significant difference in haemorrhagic complications between the group receiving heparin at 24 hours and 48 hours and the control group that did not receive heparin. 22 patients (0.8%) had radiological evidence of PE there was no correlation between pharmacological prophylaxis and PE. Some studies support that the addition of mechanical prophylaxis reduces the risk of DVT by 10-20% and this study by Khaldi found a similar risk reduction (16%).

A recent retrospective study by Ekeh\(^8\) et al which included a population of 677 patients with head injuries, 217 had isolated brain injuries and 460 had brain and
extra-cranial injuries (Figure 2). Again mechanical methods were routinely used, heparin was not used. Weekly duplex screening at 7 and 10 days were performed. They found that overall DVT was present in 31.6% of the patients fewer were found in patients with isolated brain injury (25.8%) and increased DVT rate was seen in patients with head and extra-cranial injuries (34.3%) – \( p = 0.026 \). PE occurred in 19 patients (2.8%) who were screened for DVT. The PE rate with isolated brain injuries was 0.92% and with mixed injuries 3.69% this difference was statistically significant \( (p < 0.05) \). Therefore DVT was shown to occur in one third of moderately to severely brain injured patients.

*Figure 2: Ekeh et al* Journal of Trauma Injury, Infection, and Critical Care. 2010

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**TABLE 2. Comparison of Patients Who Developed DVT With Those Who Did Not**

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>DVT</th>
<th>No DVT</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 677)</td>
<td>(n = 214)</td>
<td>(n = 463)</td>
<td></td>
</tr>
<tr>
<td>Head injury, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAH</td>
<td>328 (48.4)</td>
<td>120 (56.1)</td>
<td>208 (44.9)</td>
<td>0.007</td>
</tr>
<tr>
<td>SDH</td>
<td>302 (44.6)</td>
<td>94 (43.9)</td>
<td>208 (44.9)</td>
<td>0.81</td>
</tr>
<tr>
<td>EDH</td>
<td>52 (7.6)</td>
<td>16 (7.5)</td>
<td>36 (7.8)</td>
<td>0.89</td>
</tr>
<tr>
<td>IPH</td>
<td>233 (34.4)</td>
<td>78 (36.4)</td>
<td>155 (33.5)</td>
<td>0.45</td>
</tr>
<tr>
<td>Extracranial injury, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine</td>
<td>188 (27.8)</td>
<td>69 (32.2)</td>
<td>119 (25.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Thoracic</td>
<td>300 (44.3)</td>
<td>103 (48.1)</td>
<td>197 (42.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Intraabdominal</td>
<td>119 (17.6)</td>
<td>34 (15.9)</td>
<td>85 (18.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Pelvis</td>
<td>115 (17.0)</td>
<td>38 (15.4)</td>
<td>77 (16.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>143 (21.1)</td>
<td>44 (20.6)</td>
<td>99 (21.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>154 (22.7)</td>
<td>66 (30.8)</td>
<td>88 (19.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>ISS mean</td>
<td>NA</td>
<td>27 ± 9.8</td>
<td>25.1 ± 9.7</td>
<td>0.02</td>
</tr>
<tr>
<td>ICU LOS days</td>
<td>NA</td>
<td>18.1</td>
<td>10.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Patients who had higher ISS, SAH, or lower extremity injury were more likely to develop DVT. Patients with DVT also had significantly longer ICU length of stay. Chi-square test was used for categorical outcomes; \( t \) test for continuous outcomes.

SAH, subarachnoid hemorrhage; SDH, subdural hematoma; EDH, epidural hematoma; IPH, intraparenchymal hemorrhage; NA, not assayed.
Denson et al. demonstrated, in their analysis of 88 TBI patients who had weekly duplex Doppler imaging, a 25% incidence of VTE was found. All patients received knee-length compression stockings. They found that the incidence in isolated TBI is greatest in patients with intra-parenchymal haemorrhage. On diagnosis of DVT patients were treated with therapeutic dose of a LMWH an IVC filter was placed if LMWH was contra-indicated at time of diagnosis, only 3 IVC filters were placed.

Kim and Brophy studied the incidence of SYMPTOMATIC VTE in intracranial haemorrhage. This was a retrospective, single centre cohort study of 1195 patients of whom 500 had TBI 526 intracranial haemorrhage and 179 had aneurysmal SAH. All patients were on intermittent pneumatic compression device and low dose heparin or LMWH. The incidence of VTE in TBI patients was 3.8%. This was the first study to determine symptomatic VTE in non-tumour patients who were not routinely screened but on prophylaxis.

**Risk factors**

The risk of developing VTE is dependent upon a variety of individual patient risk factors (smoking, prior VTE, obesity, hypercoagulable states, etc.). Higher incidences of DVT have been associated with head injury, spinal cord injury; higher injury severity scores (ISS), the need for transfusions and fractures of the lower extremity or pelvis.

To assist clinicians in identifying at risk patients for development of VTE and for potentially improved cost effective treatment, a risk assessment profile for Thromboembolism (RAPT) score was established. (Figure 3) Using the RAPT scoring system, patients are then identified as either high-risk (score >5) or low risk (score<5) for development of DVT. Patients with a RAPT score of >5 are three times more likely to develop VTE than a patient with a score <5.

Knudson et al. identified 6 risk factors that were associated independently with the risk of VTE, including age over 40 years, lower extremity fracture, major head injury, more than 3 ventilator days, venous injury and major surgical procedure. Other risk factors include pelvic fractures and spinal cord injury with paralysis. TBI in itself is a significant independent risk factor for the development of VTE. For example in the National Trauma data Bank, a registry enrolling 450375 patients, the incidence of VTE was 0.36%. TBI was an independent risk factor for VTE with OR 2.59 (95% CI 2.31 -2.90). In another study, by far the most powerful predictor of VTE was > 3 days of ventilation, with OR 10.6 (95% CI 9.3 – 12.1).

The above mentioned study by Denson et al. revealed that intra-parenchymal haemorrhage was a risk factor for DVT. 12 patients out of 22 (55%) that developed DVT had IPH (p = 0.001). SAH was second with a 50% DVT rate however this wasn’t statistically significant.
The study by Ekeh et al confirmed that the DVT risk is higher in TBI associated with other injuries (Figure 4). Isolated TBI DVT incidence of 25.8% compared with head and extra-cranial injuries (34.3%) – p 0.026. Independent predictors for DVT were male gender (p=0.04), age >55(p=0.001), ISS >15(p=0.014), SAH (p = 0.006), lower extremity injury (p = 0.001).
TABLE 3. Independent Predictors of DVT Occurrence as Determined by Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>p</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity injury</td>
<td>0.001</td>
<td>2.05</td>
<td>1.39–3.03</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.04</td>
<td>1.7</td>
<td>1.16–2.5</td>
</tr>
<tr>
<td>SAH</td>
<td>0.006</td>
<td>1.52</td>
<td>1.08–2.14</td>
</tr>
<tr>
<td>Age &gt;55</td>
<td>&lt;0.001</td>
<td>2.37</td>
<td>1.67–3.36</td>
</tr>
<tr>
<td>ISS &gt;15</td>
<td>0.014</td>
<td>2.59</td>
<td>1.66–5.77</td>
</tr>
</tbody>
</table>

SAH, subarachnoid hemorrhage; CI, confidence interval.

Figure 5: Khaldi et al

**Fig. 2.** Graph comparing operative time estimated to within 1 hour of surgery (x axis) and percentage of positive lower-extremity DVT (y axis) based on positive duplex ultrasonography of the lower extremity in 555 high-risk patients.
The most commonly identified risk factors by Kim and Brophy were found to be age > 40 years, immobility due to paresis or restrictions for mechanical ventilation, presumed infection, and presence of an indwelling central venous catheter (see Figure 6 below).

**Figure 6: Kim and Brophy**

| Table 2 Frequency of risk factors for venous thromboembolism according to three types of intracranial hemorrhagic injuries$^a$ |
|-------------------------|----------------|----------------|----------------|----------------|
| Risk factors             | Total ($n = 37$) | SAH ($n = 10$) | ICH ($n = 11$) | TBI ($n = 16$) |
|                         | $n$          | (%)           | $n$           | (%)           | $n$           | (%)           | $n$           | (%)           |
| Age $\geq$40 years      | 25          | 67.6$^a$      | 8             | 80$^a$        | 10            | 90.9$^a$      | 7             | 43.8$^a$      |
| Obesity (>120% Ideal body weight) | 19          | 51.4          | 5             | 50$^a$        | 8             | 72.7$^a$      | 6             | 37.5$^a$      |
| Smoking                 | 10          | 27            | 2             | 20$^a$        | 3             | 27.3$^a$      | 5             | 31.3$^a$      |
| History of myocardial infarction | 1           | 2.7           | 0             | 0$^a$         | 0             | 0$^a$         | 1             | 6.3$^a$       |
| History of stroke       | 4           | 10.8          | 0             | 0$^a$         | 3             | 27.3$^a$      | 1             | 6.3$^a$       |
| Congestive heart failure | 2           | 5.4           | 1             | 10$^a$        | 0             | 0$^a$         | 1             | 6.3$^a$       |
| Central venous access   | 28          | 75.7$^a$      | 10            | 100$^a$       | 6             | 54.5$^a$      | 12            | 75$^a$        |
| Malignancy              | 3           | 8.1           | 2             | 20$^a$        | 1             | 9.1$^a$       | 0             | 0$^a$         |
| Hypercoagulable disease | 1           | 2.7           | 0             | 0$^a$         | 1             | 9.1$^a$       | 0             | 0$^a$         |
| Prior venous thromboembolism | 2           | 5.4           | 0             | 0$^a$         | 2             | 18.2$^a$      | 0             | 0$^a$         |
| Infection, presumed     | 33          | 89.2$^a$      | 10            | 100$^a$       | 8             | 72.7$^a$      | 15            | 93.8$^a$      |
| Major surgery           | 15          | 40.5$^a$      | 6             | 60$^a$        | 3             | 27.3$^a$      | 6             | 37.5$^a$      |
| Immobility ($>72$ h)    | 37          | 100$^a$       | 10            | 100$^a$       | 11            | 100$^a$       | 16            | 100$^a$       |

SAH = aneurysmal subarachnoid hemorrhage, ICH = intracerebral hemorrhage, TBI = traumatic brain injury

$^a$ A total of nine records were incomplete and therefore excluded; thus characteristics of 37 patients with VTE are presented.
Methods of VTE Prophylaxis

The primary prophylactic modalities are mechanical and pharmacologic methods and Inferior Vena Cava (IVC) filters have also been included where a contra-indication to other modalities exist.

Mechanical Methods\textsuperscript{3,6,14,15}

Mechanical methods include pneumatic compression boots, foot pumps, and graduated compression stockings. Multiple mechanical methods remain in use, according to the discretion of the surgeons and the intrinsic requirements of the surgical site.

Mechanical devices include graduated compression stockings (GCS), intermittent pneumatic compression (IPC) stockings and the venous foot pump (VFP). All three variations function by reducing the luminal diameter of a vein resulting in an increase in venous flow velocity. This increase in velocity theoretically reduces stasis and decreases the risk of thrombus formation. Compression devices are designed to apply pressure in either a uniform or graduated fashion. Graduated stockings offer a milking action to the leg and apply greatest compression at the ankles. GCS provide a slightly longer augmentation period, but there is no difference in peak venous flow velocity between GCS and uniform compression devices. Despite a suggestion that GCS may provide superior prophylaxis, they have not been reported in the trauma population. A randomized trial comparing IPC to VFP in injured patients demonstrated a statistically significant decrease in the incidence of DVT using stockings as compared to VFP (6.5\% versus 21\%).

As a result, VFP appears to play no role for DVT prophylaxis in trauma patients. Due to the lack of level one evidence, ACCP guidelines recommend against routine mechanical DVT prophylaxis in trauma patients. They may be considered in patients with a contraindication to anticoagulant VTE prophylaxis however, if mechanical devices are utilized, it is recommended that either IPC or GCS be applied, since VFP have demonstrated higher rates of associated DVT’s. Compression stockings are considered safer than pharmacologic DVT prophylaxis only because they minimize bleeding risks.

Risks associated with mechanical prophylaxis include skin irritation and local tissue injury, periods of non-compliance, device malfunction, nerve compression leading to neuropathy and rare incidences of allergies to the component materials. Benefits of mechanical prophylaxis include lack of interference with the clotting cascade, the ability to start and stop the intervention with ease, and constant visible evidence of compliance. The major benefit of this treatment is that there is no increased risk of postoperative ICH. Agnelli, et al. demonstrated a DVT incidence of 32\% after elective neurosurgical procedures when using compression stockings alone. In patients with head injuries, mechanical methods of
prophylaxis are attractive as DVT prophylactic agents because they lack the bleeding potential of anticoagulant-based prophylaxis.  

The Brain Trauma Foundation made a level 3 recommendation in 2007 that GCS or IPC stockings be used routinely unless lower extremity injuries prevent their use. These mechanical methods, however, have not been subjected to rigorously clinical studies and are considered inferior to anticoagulant-based prophylaxis. In addition, extremity injury may occasionally prohibit their utilization and furthermore, a high rate noncompliance and improper use have been described with these devices. The high rate of DVT that occurs despite GCS use in patients with head injuries demonstrates the need for further study of these devices in patients with head injuries as well as the unavoidable use of pharmacologic prophylaxis.

**Pharmacological methods**

The other main prophylactic option is pharmacologic, which primarily includes unfractionated heparin or low-molecular weight heparin.

**Unfractionated heparin (UH)**

Unfractionated heparin is a heterogeneous mixture of glycosaminoglycans with a molecular weight range of 4 to 30 kD. Its anticoagulation effect is mediated by the activation of antithrombin III, which then inactivates with relatively equal potency the coagulation enzymes thrombin (factor IIa) and factor Xa. Other antithrombotic effects include inhibition of platelet aggregation and additional antithrombin III–independent mechanisms. The partial thromboplastin time may be elevated because of inactivation of thrombin. Heparin has a short plasma half-life ($t_{1/2} = 1.5$ hours) and has variable and extensive binding to plasma proteins and cells. The dosage regimen of unfractionated heparin is typically 5000 U given subcutaneously twice daily for patients who weigh less than 90 kg and three times daily for patients who weigh more than 90 kg, starting 24 hours after the conclusion of surgery. With regard to TBI, timing of initiating Heparin prophylaxis is generally greater than 24 hours and made on an individual basis.

Studies have consistently shown a reduction in DVT risk after administration of subcutaneous heparin. Historically, in 1977 Barnett et al. were among the first to note the safety and efficacy of mini dose heparin administered in neurosurgical patients. Iorio and Agnelli in a meta-analysis published in 2000, suggested that the use of heparin (unfractionated and low-molecular weight heparin were combined in their analysis) resulted in a 45% relative risk reduction for the development of VTE in neuro-surgical patients. Frim et al., reported in 1992 that prophylaxis with pneumatic compression devices plus heparin significantly reduced the incidence of thromboembolic complications ($p = 0.02$). In their study none of the 138 patients treated with a pneumatic compression device plus
Heparin exhibited clinical evidence of PE or DVT (Figure 7). Overall, studies conducted in patients who have undergone neurosurgery, in whom the use of pneumatic compression devices alone has been compared with the use of heparin alone, show a clear reduction of the incidence of DVT and PE (by 40–50%) when heparin is used. The rate of major postoperative ICH, however, may rise from its baseline of 1 to 3.9% to as high as 10.9% when heparin is introduced.\textsuperscript{14}

**Figure 7: Browd\textsuperscript{14} et al literature review:**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Design</th>
<th>Medication</th>
<th>ICH Rate (%)</th>
<th>VTE Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>Study</td>
</tr>
<tr>
<td>Prophylactic treatment started preop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barnett, et al, 1977</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>NA</td>
<td>2/150 (1.3)</td>
</tr>
<tr>
<td>Dickinson, et al, 1988</td>
<td>P &amp; R</td>
<td>enoxaparin 30 mg BID</td>
<td>0/22 (0)</td>
<td>5/46 (10.9)</td>
</tr>
<tr>
<td>Macdonald, et al, 1999</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>2/68 (2.9)</td>
<td>4/106 (3.8)</td>
</tr>
<tr>
<td>Macdonald, et al, 2003</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>NA</td>
<td>1/49 (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dalteparin 2500 U QD</td>
<td>NA</td>
<td>2/51 (3.9)</td>
</tr>
<tr>
<td>Treatment started &lt;24 hrs postop</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frim, et al, 1992</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>1/473 (0.2)</td>
<td>0/138 (0)</td>
</tr>
<tr>
<td>Nurmohamed, et al, 1996</td>
<td>P &amp; R</td>
<td>fraxiparin 7500 U QD</td>
<td>2/244 (0.8)</td>
<td>6/241 (2.5)</td>
</tr>
<tr>
<td>Agnelli, et al, 1998</td>
<td>P &amp; R</td>
<td>enoxaparin 40 mg QD</td>
<td>3/154 (1.9)</td>
<td>4/153 (2.6)</td>
</tr>
<tr>
<td>Roabe, et al, 2001</td>
<td>R</td>
<td>UFH 5000 U TID</td>
<td>NA</td>
<td>28/1564 (1.8)</td>
</tr>
<tr>
<td>Goldhaber, et al, 2002</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>NA</td>
<td>0/75 (0)</td>
</tr>
<tr>
<td>Gerlach, et al, 2003</td>
<td>P</td>
<td>enoxaparin 40 mg QD</td>
<td>NA</td>
<td>1/75 (1.3)</td>
</tr>
</tbody>
</table>

\* NA = not applicable; P = prospective; P & R = prospective, randomized; R = retrospective; UFH = unfractionated heparin.

Benefits of heparin include ease of administration, improved patient compliance, and a lower risk of patient self-discontinuation.

Risks include injection site reaction, drug interaction, dosing errors, heparin-induced thrombocytopenia, risk of bleeding and risk of accumulation in renal failure.\textsuperscript{6}

**Heparin Induced Thrombocytopenia**

HIT is an immune-mediated aggregation of platelets leading to thrombocytopenia which has a high association with the development of arterial and venous thrombosis. HIT typically occurs between days 4 and 14 of heparin treatment.
Potentially fatal consequences, if not detected early, may include thromboembolism, PE and bleeding. The HIT mechanism involves the development of IgG class antibodies that bind heparin-platelet factor 4 (PF4) complexes. This antigen-antibody complex is thought to mediate new thrombi formation and platelet consumption. Consequently, the latest definition states that clinically significant HIT occurs with an unexplained platelet decrease of over 50%, even when the platelet count is greater than 150 x 10^9/L.\textsuperscript{15}

**Intracranial Haemorrhage**

The most important risk is that of Intracranial haemorrhage as this is the most feared risk as it can be detrimental.

The use of subcutaneous heparin in the setting of acute TBI’s remains more controversial. In 2001 Raabe\textsuperscript{16} et al reviewed several studies in which heparin was used for DVT prophylaxis (see below table) and several important findings were demonstrated. In studies in which patients were given 5000U heparin either two or three times daily in the immediate preoperative period the haemorrhage rate was 1.3 to 5.2 % compared to 2 to 4.3 % for patients in control groups without prophylaxis. For heparin administered in the post-operative period Raabe referenced a prospective study from 1992 by Frim et al in which no post op haematomas were demonstrated in 138 patients. In this protocol patients received 5000U heparin twice daily starting within 24 hours after surgery. However this was in a mixed neuro surgical population with few neuro-trauma cases.\textsuperscript{14}

Kim\textsuperscript{7} et al., demonstrated no increased risk of haemorrhage in patients admitted for traumatic head injury when subcutaneous heparin was initiated for prophylaxis within 72 hours of admission compared with patients in whom heparin therapy was started after 72 hours.

Khalid et al demonstrated that the use of Heparin at either 24 or 48 hours (mostly at 48 hours) was not associated with an increase in surgical site haemorrhage. However this was in a mixed neurosurgical population, 8 % of which were TBI patients.

Scudday\textsuperscript{17} et al studied 812 patients of which 402 (49.5%) patients received chemical prophylaxis. This study represents one of the larger series of patients with TBI in whom pharmacological prophylaxis was given and compared to a control group in which mechanical prophylaxis was only used. In this study heparin was the drug of choice and used in the majority of the patients (91%), particularly in patients requiring any type of operative intervention, however Enoxaparin was used twice daily in some patients (9%). All patients received mechanical prophylaxis. Heparin was given subcutaneously three times daily.\textsuperscript{3}
This use is in keeping with the American College of Chest Physicians recommendations for high-risk surgical patients. The group that received chemical prophylaxis were a higher risk group with increased age and ISS. 169 patients were started at 48 hours and 242 patients were started at 72 hours. The results demonstrated that patients with chemical prophylaxis had a lower incidence of VTE 1% vs. 3% (p = 0.019) and had a lower rate of progression of TBI.

Progression of TBI was defined as an evolution of intracranial haemorrhage seen on follow-up CT scan. 36 patients had progression of their head injury, 11 patients were on chemical prophylaxis and 25 were not on chemical prophylaxis however these findings were not statistically significant. The higher rate of progression in the group not on prophylaxis is the result of progression precluding administration of chemical prophylaxis. They concluded that the use of Chemical thromboprophylaxis in TBI with a stable or improved head CT scan after 24 hours substantially reduces the incidence of VTE and does not increase the progression of intracranial haemorrhage (Figure 8)\textsuperscript{17}.

\textbf{Figure 8: Scudday\textsuperscript{17} et al}

\begin{table}[h]
\centering
\caption{Multivariate Analysis of Traumatic Brain Injury Progression and Venous Thromboembolism Incidence}
\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & \textbf{No chemical prophylaxis} & & \textbf{Chemical prophylaxis} & & \\
 & \textbf{(n = 410)} & & \textbf{(n = 402)} & & \\
\hline
\textbf{n} & 25 & & 11 & & \\
\textbf{\%} & 6 & & 3 & & \\
\textbf{Progression} & & & & & \\
\hline
\textbf{VTE} & 11 & & 3 & & \\
\hline
\end{tabular}
\begin{tabular}{c}
\textbf{Risk ratio} \\
\textbf{95\% CI} \\
\textbf{p Value}
\end{tabular}
\begin{tabular}{c}
0.474 \\
0.221–1.015 \\
0.055
\end{tabular}
\begin{tabular}{c}
0.194 \\
0.049–0.760 \\
0.019
\end{tabular}
\end{table}

\textit{VTE, venous thromboembolism.}

\section*{Low Molecular Weight Heparins}

LMWHs are generated from the chemical depolymerisation of unfractionated heparin (UH). This reduces their size, charge, and weight. Both LMWHs and UHs inhibit thrombin (IIa), however LMWHs have significantly greater activity towards factor Xa secondary to their smaller size. LMWHs are also less likely to exhibit non-specific binding to endothelium, macrophages, and heparin-binding plasma proteins, hereby increasing their bioavailability and half-life.
In trauma patients with a minimal injury severity score (ISS) of 9, and without intracranial haemorrhage, on-going bleeding or coagulopathy, evidence supports the use of enoxaparin (LMWH) as the primary DVT prophylactic modality. In randomizing 265 patients to receive either enoxaparin or UH, Geerts et al. demonstrated a significant reduction in all DVT rates from 44% to 31%, as well as in proximal DVTs from 15% to 6%, with the use of enoxaparin. Current American College of Chest Physicians (ACCP) practice guidelines recommend LMWHs as soon as possible in the absence of intracranial haemorrhage, uncontrolled bleeding or incomplete spinal cord injury with an associated hematoma\textsuperscript{15}.

A large prospective observational study by Norwood\textsuperscript{22} et al examined 174 patients with TBI, prophylaxis with LMWH 5,000 U was initiated after patients were haemodynamically stable and CT 12–24 h after initial injury demonstrated no evidence of progression from initial scans. In patients with TBI there were no patients with extension of ICH.

LMWH prophylaxis is contraindicated in the case of active bleeding or expanding intracranial haematoma with surgical indication until the haematoma is evacuated and primary haemostasis is achieved. Severe TBI patients with no evidence of mass lesion should receive LMWH prophylaxis as soon as ongoing bleeding from other sources is firmly excluded and repeated brain CT scan within 12 to 24 hours after injury excludes intracranial haematomas\textsuperscript{1}.

A recent study by Levy\textsuperscript{19} et al retrospectively examined progression of haemorrhage in two populations, patients with a stable initial follow-up CT and patients with haemorrhage progression on initial follow-up CT. Timing of prophylaxis was defined as early(<72 hours) and late(>72 hours). In this study pharmacological prophylaxis (lovenox 30mg twice daily subcutaneously) was not associated with haemorrhage progression in patients with stable initial follow-up CT.

It concluded that those patients with ICH progression within 1 day of admission were at an increased risk of further haemorrhage progression and the pharmacological prophylaxis in this group further increased the odds of haemorrhage progression. This concludes that for patients with haemorrhage progression on initial CT it is best to err on the side of caution and delay the use of pharmacological prophylaxis. The predictors of haemorrhage progression found in this study are summarized in the table below (Figure 9)\textsuperscript{19}. 

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The advantages of using LMWH compared to other modalities are the ease of administration, increased efficacy, improved specificity compared to unfractionated heparin and no biochemical monitoring is required and decreased rate of Heparin-induced thrombocytopenia. There is no level 1 evidence to support LMWH over unfractionated Heparin however it is favoured because of the above advantages.

Pharmacological prophylaxis is contra-indicated in the case of active bleeding or expanding intracranial haematomas with surgical indication until the haematoma is evacuated and primary haemostasis is achieved. Severe TBI patients with no evidence of mass lesion should receive pharmacological prophylaxis as soon as on-going bleeding from other sources is firmly excluded, and repeated brain CT scan within 12 to 24 hours after injury excludes intracranial haematomas.
There is insufficient evidence to support recommendations regarding the preferred agent, dose or timing of pharmacological prophylaxis.

The risk of intracranial haemorrhage with pharmacological prophylaxis exists however depending on the patient selection and timing of initiation of prophylaxis this risk is low and the use of pharmacological prophylaxis is still warranted to reduce the risk of DVT.

**IVC Filters**

Pharmacologic and mechanical compression device DVT prophylaxis can infrequently be contraindicated in the trauma population. In 2004, ACCP guidelines recommended against the use of IVC filters as primary DVT prophylaxis. These recommendations suggested IVC filter placement only in patients with documented proximal DVT and an absolute contraindication to full dose anticoagulation therapy, or planned major surgery in the near future. The absence of a well powered, randomized clinical trial in the trauma population, as well as the unknown frequency of long term complications (i.e. filter migration, vena caval occlusion, and IVC penetration), have limited the use of permanent prophylactic IVC filters. There is increased interest in temporary and retrievable IVC filters. These devices offer the immediate benefits of caval filtration when patients are at their highest risk, but can be removed to prevent long-term complications. Although routine use is not indicated, a significant portion of trauma patients will still require placement of these devices when other forms of prophylaxis are contraindicated\(^\text{15}\).

Studies have shown VCF placement in patients with known lower extremity DVT and short-term contraindications to anticoagulation, and in patients considered to be at high risk of developing VTE who were unable to receive other forms of prophylaxis. Patients with major pelvic fractures associated with lower extremity long bone fractures, those with bilateral lower extremity long bone fractures or multiple long bone fractures, patients with spinal fractures and concomitant neurologic injury, and patients with multiple injuries including chest trauma and traumatic brain injuries have been considered for prophylactic VCF placement. These clinical situations have individually related contraindications to anticoagulation.

Although VCFs do not prevent DVT, they theoretically help to reduce the incidence of pulmonary embolism. However, these filters have inconsistent safety and efficacy records. VCF application is not without certain drawbacks\(^\text{20}\).

A recent observational study compared the VTE rates before and after the widespread use of retrievable filters in trauma patients at a single trauma centre. The groups were comprised of 5,042 patients before the common use of filters and 5,038 afterward. Filters were employed three times more frequently in the
second group, yet there was no change in the incidence of PE and filters could be successfully removed in only 21% of patients. Scepticism about a role for prophylactic IVC filter placement has been echoed by several experts\textsuperscript{3}.

Short-term temporary filters were designed to be left in place for 1--2 weeks but require percutaneous access and have been largely abandoned because of an increased risk of infection and mandated filter removal. Retrievable filters appear to be more versatile (they can be placed safely in the intensive care unit bedside under ultrasound guidance), and can be left in place permanently, should the clinical condition demand. Retrievable VCFs offer protection against pulmonary embolism during the early immediate injury and perioperative periods, when development of VTE risk is highest, while averting the potential long-term sequelae of permanent VCF. To date, only small prospective or retrospective studies have been conducted on their efficacy.

Complications related to IVC filter use fall into short and long-term groups. Short term complications occur during filter insertion, while long term complications arise from the filter itself, as well as its chronic effects on surrounding vasculature and blood flow (see Figure 10)\textsuperscript{15}.

Complications include filter migration, filter fragmentation, perforation of the vena cava or adjacent organs and caval occlusion. Permanent VCF have been shown to have an increased risk of recurrent DVT, and the protective effect of the filter is temporary\textsuperscript{20}.

\textit{Figure 10: Datta\textsuperscript{15} et al}

<table>
<thead>
<tr>
<th>Short Term Complications</th>
<th>Long Term Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to cannulate vein</td>
<td>Filter migration</td>
</tr>
<tr>
<td>Arterial Puncture</td>
<td>Filter tilting</td>
</tr>
<tr>
<td>Hematoma</td>
<td>Filter strut fracture</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>IVC perforation by struts</td>
</tr>
<tr>
<td>Air embolism</td>
<td>IVC thrombosis</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Lower extremity swelling from venostasis</td>
</tr>
<tr>
<td>Hemothorax</td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
</tr>
<tr>
<td>Insertion site thrombosis</td>
<td></td>
</tr>
<tr>
<td>Misplaced filter</td>
<td></td>
</tr>
<tr>
<td>IVC perforation</td>
<td></td>
</tr>
</tbody>
</table>
Timing of Pharmacological Prophylaxis

It has been proposed that early pharmaceutical prophylaxis is necessary because of the rapid development of VTE complications post-injury. The perceived risk for exacerbating intracranial haemorrhagic injury (IHI) has limited the use of early anticoagulation in the trauma patient with head injuries, based on several studies in the elective neurosurgical population illustrating this apparent risk when treating patients preoperatively or within 24 hours of surgery.\(^{21}\)

Taking the risk-benefit equation one step further, it is likely that the early administration of DVT prophylaxis in TBI may be less hazardous than the alternative of full-dose anticoagulation or an IVC filter when VTE actually develops.\(^{27}\)

Consequently, a recent study demonstrated that only 50% of high risk, multisystem trauma patients in the intensive care unit for 7 days or more received pharmaceutical prophylaxis within the first 4 days post injury. Delaying VTE prophylaxis from 48 hours to 96 hours post injury increases the risk of VTE by three times (risk ratio, 3.0; 95% CI, 1.4 – 6.5)\(^{21}\).

Studies by Norwood\(^{18,22}\) and colleagues (2002, 2008) were designed to explicitly evaluate the role of early LMWH prophylaxis in the TBI population. A prospective study treated 150 haemodynamically stable patients with acute intracranial haemorrhage 26.5 hours ± 11.5 hours post admission with enoxaparin. Only two DVTs (1.33%) and no PEs were diagnosed among the study population. Thirty-four patients (23%) had IHI progression as diagnosed by head CT, but only six (4.0%) of these patients progressed after administration of LMWH prophylaxis.

The second prospective study evaluated 525 patients who had sustained blunt TBI and were treated with enoxaparin prophylaxis at 36.2 hours ± 12.7 hours post admission. The VTE rates were still minimal at 1.14% and 0% for DVTs and PEs, respectively. By slightly delaying initiation of VTE prophylaxis compared with the previous study, the rate of IHI progression following enoxaparin administration was reduced to 3.4%. One patient (0.2%) death was attributed to pharmacologic prophylaxis. A significant limitation of this study was that 74% of patients who met the inclusion principles were not included in the study. Both of the above studies successfully defined the low incidence of venous thromboembolic complications for patients with TBIs treated with early VTE prophylaxis, neither one incorporated a control group to which the rates of IHI progression could be compared and the studies included patients with mild TBI who recover earlier (mobilise earlier) and have less risk of coagulopathy.\(^{18,22}\)

The recent study by Koehler et al.\(^{21}\) compared patients with TBIs treated with early (0-72 hours) versus late (> 72 hours) VTE prophylaxis and the rates of IHI
progression with the aim to determine whether early VTE prophylaxis is safe in haemodynamically stable trauma patients with intracranial haemorrhage. All subjects received VTE prophylaxis in the form of enoxaparin 30 mg subcutaneous injection 12 hourly. Follow-up head CT scans were preformed within 24 hours of admission and at variable intervals thereafter as determined by the attending trauma and neurosurgeons. Progression of IHI was monitored during the patient’s hospital course and was re-evaluated for the purpose of this study.

All scans were reviewed by an independent radiologist who was blinded to the results of the previous interpretations in the medical records to assess for IHI progression. Progression of an IHI was documented as (1) any expansion of a haemorrhagic lesion by radiologist report or (2) development of a new IHI on a follow-up head CT scan. Progression of IHI was documented both before and after initiation of VTE prophylaxis in all treatment groups. VTE complications were monitored throughout the patient’s hospital course. Upper and lower extremity Doppler duplex colour flow ultrasound examination was performed at any time during hospitalization when there was clinical suspicion for a DVT. The rates of IHI progression after VTE for each of the six TBI classifications are illustrated for early vs. late groups in the Table below (Figure 11).

Figure 11: Koehler et al

| TABLE 3. Intracranial Hemorrhagic Injury Progression Events After Venous Thromboembolism Prophylaxis Administration in the Early and Late Treatment Groups |
|---------------------------------|-----------------|---------------------------------|-----------------|-----------------|-----------------|
|                                | Early Prophylaxis |                                | Late Prophylaxis |                                |                  |
|                                | Total No.  | IHI Progression (%) | Total No.  | IHI Progression (%) | P                |
| Subarachnoid hemorrhage         | 157       | 3 (1.91)             | 258       | 3 (1.16)             | 0.536            |
| Subdural hematoma               | 92        | 1 (1.09)             | 159       | 2 (1.26)             | 0.904            |
| Epidural hematoma               | 23        | 0 (0.0)              | 49        | 1 (2.04)             | 0.490            |
| Axial shear injury              | 78        | 1 (1.28)             | 110       | 2 (1.82)             | 0.773            |
| Intraparenchymal contusion      | 102       | 1 (0.98)             | 142       | 3 (2.11)             | 0.492            |
| Intraventricular hemorrhage     | 28        | 1 (3.57)             | 63        | 1 (1.59)             | 0.551            |
| Total                           | 480*      | 7 (1.46)             | 781*      | 12 (1.54)            | 0.912            |

* Sum of traumatic brain injuries is greater than the number of patients in each study arm due to patients with multiple head injuries.

Test used: Pearson test.
Mean time to prophylaxis was 2.77 days and 5.3 days. IHI (intracranial haemorrhagic injury) progression before prophylaxis was 9.38% versus 17.4% and after prophylaxis was 1.46% versus 1.54%. They concluded that early VTE prophylaxis does not increase the rate of IHI progression in the haemodynamically stable patient with TBI. The outcomes were summarised in the table below (Figure 12).\(^{21}\)

**Figure 12 Koehler\(^{21}\) et al.**

<table>
<thead>
<tr>
<th>TABLE 4. Outcomes by Time of Venous Thromboembolism Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early (N = 268)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Proximal DVT</td>
</tr>
<tr>
<td>Distal DVT and superficial venous thrombosis</td>
</tr>
</tbody>
</table>

Test used: Pearson test.

A recent study by Dudley et al reviewed 287 patients with moderate-to-severe TBI. 187 patients had severe TBI with an initial GCS 3-8 and 100 patients had moderate TBI with an initial GCS of 9-12. Prophylaxis with enoxaparin and dalteparin were provided at 48-72 hours post trauma. No significant difference in VTE rates were seen between the two drug groups. This study did not assess ICH risk or other bleeding risk systematically. However, they confirmed that commencing at 48 hours – 72 hours with pharmacological prophylaxis provided a high level of VTE protection and a low risk of expanding ICH\(^{28}\).

The study by Khaldi\(^{5}\) et al used Heparin at 48 hours post-surgery for neuro-trauma and found no increase in surgical site haemorrhage. A decision analysis by Scales\(^{26}\) et al looked at the decision to commence LMWH at 24 hours post TBI. Their model favoured LMWH therapy if preventing DVT exceeded 80% and if the increased risk of ICH progression was no more than 5% above the baseline risk. A diagram of the results is included below (Figure 13).

This model showed no clear advantage to providing or withholding anticoagulation prophylaxis for VTE prevention at 24 hours after TBI associated ICH. In the context of such a toss-up they recommended against the routine use of anticoagulant prophylaxis at 24 hours post-injury. They concluded that randomised controlled trials are justifiable and needed to guide clinicians. There are no prospective studies or randomised controlled trials regarding the timing or choice of anticoagulant prophylaxis. From the literature it appears that initiating therapy at 48 hours post trauma or post-surgery seems acceptable as long as there is no coagulopathy or on-going bleeding\(^{26}\).
Figure 4 Results of decision analysis. The square node at the extreme left represents the decision node and the circles represent chance nodes. Numbers in boxes are the final calculated expected value at each chance node. The overall expected value associated with withholding anticoagulation prophylaxis (0.8961) is similar to that associated with the anticoagulant prophylaxis strategy (0.8862), indicating the choice is a toss-up. CNS Bleed: progression of intracranial hemorrhage; DVT: deep vein thrombosis; ICH: intracranial hemorrhage; PE: pulmonary embolism.
Recommendations

American College of Chest Physicians (ACCP) guidelines

The ACCP publishes guidelines on the use of anti-thrombotic therapy. The latest update, published in 2008, provides the most applicable and evidence-based recommendations for most surgeries. The recommendation for neurosurgery is that patients should receive routine thromboprophylaxis with optimal use of a mechanical method. They recommend the use of standard prophylaxis doses of LMWH or LDUH (5000IU twice daily subcutaneously). They also recommend a CT scan of the brain the day following surgery to rule out bleeding before initiating pharmacological prophylaxis. If patients are at particularly high risk for thrombosis, a mechanical method in combination with a pharmacological method is suggested.

Their recommendation in the trauma setting is to use LMWH prophylaxis (enoxaparin 40mg daily subcutaneously, or dalteparin 5000IU daily subcutaneously). If there is a risk for bleeding LMWH is contraindicated and a mechanical method should be used in the interim until the bleeding risk decreases. They recommend against the use of IVC filter for thromboprophylaxis. The ACCP points to the lack of direct evidence of the efficacy of filters.

Brain Trauma Foundation recommendations:

There is insufficient data to support a Level I and II recommendation. The level III recommendations are the use of graduated compression stockings or intermittent pneumatic compression stockings unless contra-indicated. Use should continue until patients are ambulatory. LMWH or low dose UH should be used in combination with mechanical prophylaxis. However, there is an increased risk for expansion of ICH. They conclude that there is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacological prophylaxis for DVT. They suggest that there is a need for randomised controlled trials of mechanical prophylaxis alone versus the addition of pharmacological prophylaxis of DVT in patients with severe TBI.

Conclusion

Mechanical methods are certainly the most widely used method of prophylaxis in the patient with TBI as there is usually a delay to start pharmacological prophylaxis. Most clinicians prefer to have some prophylaxis rather than none at all in the interim till safe institution of an anticoagulant is permissible.

Within IALCH hospital itself there are differing practices among units regarding institution of prophylaxis in TBI as was mimicked in a Canadian survey by Scales et al\textsuperscript{23} and a survey of practice in the UK by Gnanalingham et al\textsuperscript{29}.

The reluctance to use a pharmacological agent is understandable. The decision to provide anticoagulation prophylaxis to these patients therefore represents a balance between benefit and risk. The question is not whether to provide pharmacological prophylaxis; it is rather a question of when to start it.
Bibliography


