Venous Thromboembolism Following Spinal Cord Injury

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Key Points

Deep venous thrombosis is common in spinal cord injured patients not receiving prophylaxis.

5000 IU subcutaneously every 12 hours of unfractionated heparin does not prevent venous thrombosis post SCI while higher dose, adjusted unfractionated heparin is more effective, although risk of bleeding complications is higher.

Low-molecular-weight heparin reduces the risk of venous thromboembolism post SCI more effectively than standard or unfractionated heparin prophylaxis with fewer bleeding complications.

There appears to be no difference between enoxaparin and dalteparin, or enoxaparin and tinzaparin, in reducing the risk of venous thrombosis post-SCI.

Sequential pneumatic compression devices and gradient elastic stockings may reduce the incidence of venous thromboembolism post SCI. Rotating treatment tables may reduce the incidence of venous thromboembolism post SCI.

A combined regiment of pneumatic compression, pressure stockings and low-dose heparin or low molecular weight heparin given prophylactically may reduce the incidence of venous thrombosis and this effect is better in early post SCI.

Inferior vena cava filters significantly reduce the risk of pulmonary emboli in high-risk SCI patients.

Enoxaparin subcutaneously may be considered as an alternative to intravenous heparin for acute DVTs post SCI.
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Abbreviations

aPTT      Activated Partial Thromboplastin Time
ASA       Aspirin
AVV       Average Venous Velocity
CT        Computed Tomography
DIP       Dipyridamole
DVT       Deep Venous Thrombosis
ECG       Electrocardiogram
EPCC      External Pneumatic Calf Compression
ESPC      External Sequential Pneumatic Compression
GES       Gradient Elastic Stockings
IPC       Intermittent Pulsatile Compression
IVC       Inferior Vena Cava
LDUH      Low Dose Unfractionated Heparin
LMWH      Low Molecular Unfractionated Heparin
MVV       Maximum Venous Velocity
PE        Pulmonary Embolism
PIOPED    Prospective Investigation of Pulmonary Embolism Diagnosis
RBBB      Right Bundle Branch Block
SCD       Sequential Pneumatic Compression Devices
SCI       Spinal Cord Injury
V/Q       Ventilation/Perfusion
VFM       Venous Flow per Minute
VTE       Venous Thromboembolism
Venous Thromboembolism Following Spinal Cord Injury

1.0 Introduction

Deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE) remain a significant cause of morbidity and mortality in individuals with spinal cord injuries (SCI). The incidence of DVT has been reported by various authors to range between 9% to 100% during the acute stage of SCI, with most occurring in the first two-three weeks post-injury, sometimes leading to a pulmonary embolism which remains a common cause of death (Tribe 1963; Walsh & Tribe 1965; Watson 1968; Stover et al. 1983; Winchelli et al. 1996; Aito et al. 2000; Chiou-Tan et al. 2003).

2.0 Incidence

Incidence of DVT has been examined in-depth in the literature with the incidence in patients with acute SCI to be very high, more than 50% in early prospective studies (Joffe 1975; Todd et al. 1976; Brach et al. 1977; Rossi et al. 1980; Becker et al. 1987). More widespread reports, according to Aito et al. (2000), Li et al. (2012), and Sasa et al. (2012) place the incidence of DVTs at between 10% and 30%. This incidence has increased in the last years, ranging between 18 and 100% (De Campos Guerra et al. 2014), 5.4% and 90% (Chung et al. 2014). That is probably due to the utilization of more advanced diagnostic tools. Among multi-trauma patients, SCI patients have the highest rates of venous thromboembolism (9.07%) with a higher risk among cervical and thoracic SCI. The risk is highest in the first few days after the injury up to three months then falls at 6 months onward. At one year after SCI, the risk ranges from 0% to 0.31% (Godat et al. 2014; Hagen et al. 2012; Lo et al. 2013; Thumbikat et al. 2002).

Incidence rates have been shown to depend on the nature of the SCI. Verschueren et al. (2011) noted that 9.8% of non-traumatic SCI patients and 22.8% of traumatic SCI patients had DVTs. No significant difference has been noted in the incidence of DVT based on AIS scores (p=0.58; Sugimoto et al. 2009).

In an analysis by Cao et al. (2013) examining risk factors for mortality, the authors did not find that DVT was significantly associated with future mortality. The study was based on evidence from 22 studies and provides insight into the methodological issues noted by studies when reporting incidence rates. Current findings suggest that early recognition of DVT and successful treatment are necessary in reducing the likelihood of mortality.

Table 1 Incidence of DVT Post SCI

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Treatment (n size)</th>
<th>% of DVTs</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giorgi et al. (2013)</td>
<td>Low-Molecular-Weight Heparin and compression stockings (n=94)</td>
<td>23%</td>
<td>Compression Ultrasound or lower limb colour Doppler ultrasonography, perfusion lung scintigraphy (Q scan) matched with chest X-ray, or computed tomography pulmonary angiography</td>
</tr>
<tr>
<td>Germing et al. (2010)</td>
<td>(n=139)</td>
<td>45%</td>
<td>Serial color duplex sonography</td>
</tr>
<tr>
<td>Sugimoto et al. (2009)</td>
<td>(n=45)</td>
<td>21%</td>
<td>Doppler Ultrasonography</td>
</tr>
<tr>
<td>Colachs &amp; Clinchot (1993)</td>
<td>Prophylaxis Treatment (n=209)</td>
<td>14%</td>
<td>Contrast venography Ultrasound</td>
</tr>
</tbody>
</table>
The high risk of DVT in acute SCI patients is due to the simultaneous presence of three factors of Virchow’s triad: hypercoagulability, stasis, and intimal (inner vessel layer) injury (Aito et al. 2000). Venous thromboembolism usually begins with a calf DVT (Nicolaides et al. 1971; Philbrick et al. 1988; Cogo et al. 1998). Other contributing factors include partial or total limb paralysis and absence of spasticity which is a significant independent risk factor for DVT (Do et al. 2013). Venous thromboembolism affects blood flow, reduces the capacity of the vessels and increases the venous resistance. These as a result promote a cascade of metabolic derangements resulting in activation of the coagulation cascade and venous thrombosis (De Campos Guerra et al. 2014).

Approximately 20% of DVTs extend into the proximal veins (Kakkar et al. 1969; Lagestedt et al. 1985; Brandstater et al. 1992); over 80% of symptomatic DVTs involve the popliteal or more proximal veins (Kearon et al. 1998). Non-extending distal (i.e. calf) DVTs rarely cause PEs and as such are rarely worrisome (Kakkar et al. 1969), although they may account for over 80% of the incidence of DVT (Germing et al. 2010). Proximal (i.e. knee or above) DVTs often lead to PEs and are a cause for concern (Kakkar et al. 1969). Selassie et al. (2013) noted that patients who developed a pulmonary embolism had a twofold increase in the risk of in-hospital death compared to those who did not develop a DVT. Distal DVT, which is more common, is associated with post-thrombotic phlebitis and venous valvular insufficiency (Do et al. 2013).

Post SCI Pulmonary emboli incidence is 4.6-14% and is mostly asymptomatic or unrecognized. However in 1.7-4.7% of the cases, it is large and fatal (De Campos Guerra et al. 2014).

Conclusions

Deep venous thrombosis is common in SCI patients not receiving prophylactic treatment.

Deep venous thrombosis is common in spinal cord injured patients not receiving prophylaxis.
3.0 Diagnosis

3.1 Deep Venous Thrombosis Diagnostic Modalities

3.1.1 Clinical Presentation
The signs and symptoms of DVT are varied and depend on the severity. Generally DVTs can cause pain, swelling, tenderness, skin discolouration and increased warmth of the affected area. The signs and symptoms of PE are nonspecific and can include sudden chest pain, dyspnea, tachypnea, hemoptysis, and loss of consciousness (fainting), which often leads to difficulties with diagnosis. Several methods and techniques are currently used for diagnosis.

Although the various methods of DVT detection will be discussed, it is important for health care professionals, patients, family members and caregivers to be educated in the early signs and symptoms. Expert consensus, as noted by the PVA Consortium of Spinal Cord Medicine (2005) guideline for the prevention of thromboembolism, suggests that all extremities should be inspected twice daily for an increase in the calf or thigh venous pattern or circumference, low-grade fever of unknown origin and/or pain, tenderness, or heaviness of an affected extremity. Since patients can sometimes be asymptomatic, it is also suggested that health care providers, including family and caregivers, be familiarized with risk factors such as lower limb fractures, dehydration, obesity, age, malignancy, congestive heart failure, estrogen therapy, pregnancy, and a history of thrombosis.

Another measure, considered by expert consensus to be important and preventative, is the routine practice of active and passive range of motion exercises. Mobilization and movement of the extremities (with careful consideration of spinal stability in the acute phase) should be essential in the prevention of DVT after a SCI.

3.1.2 Venous Ultrasound
Venous ultrasound has become the primary noninvasive diagnostic test for DVTs (Furlan & Fehlings 2007). Furlan and Fehlings (2007) note that ultrasound is well recognized as an important tool in the initial workup of clinically suspected DVT; however, concern exists for ultrasound as a screening tool of asymptomatic DVTs because of relatively low sensitivities in other populations.

3.1.3 Venography
Venography is an invasive study whereby contrast dye is injected into the leg veins; it is considered a definitive test for DVT. Diagnosis of DVT is made if an intraluminal-filling defect is noted. Furlan and Fehlings (2007) note that, “Although contrast venography is considered as the gold standard for investigation of symptomatic or asymptomatic DVT, venography has been considered an unsuitable tool for routine assessment of asymptomatic DVT due to its invasive nature, potential complications, technical issues and costs (Kelly et al. 2001, Tapson et al. 1999, Zierler 2004).”

3.1.4 D-Dimer Assay
D-dimer assay tests are rapid, noninvasive and inexpensive (Gill & Nahum 2000). 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 but lacks specificity since d-dimers are found in other disease states including cancer, congestive heart failure and inflammatory conditions (Raimondi et al. 1993). D-dimer assays have a high negative predictive value, so that when it is negative it is unlikely that the patient has a DVT. However, it has poor positive
predictive value so that when it is positive the cause could be a condition other than DVT (i.e. false positive). To illustrate, Akman et al. (2004) reported that the sensitivity and negative predictive values of the D-dimer test were high, at 95.2% and 96.2% respectively, in a group of 68 rehabilitating patients admitted with a diagnosis of stroke, spinal cord injury (n=43%), hip arthroplasty or traumatic brain injury. The specificity and positive predictive value were low, at 55.3% and 48.7%. Therefore, the d-dimer test appears to be a useful and widely available screening test for venous thromboembolism. It has been utilized to screen for DVT at two weeks after the SCI (Masuda et al. 2015) or on admission to rehabilitation unit from acute care. If levels are high, further investigation is warranted (Wada et al. 2013).

3.1.5 Confirmation of Diagnosis of Deep Venous Thrombosis

A positive diagnosis of a DVT can only be made if the venogram is positive or there is a positive venous ultrasound at two or more sites of the proximal veins. A negative diagnosis for DVT can be made if there is a negative venogram, a negative d-dimer test or a normal venous ultrasound. A normal venous ultrasound requires one of the following findings to be considered negative: 1) low clinical suspicion for DVT, 2) normal d-dimer test, or 3) normal serial testing with the test interval being no greater than one week. Furlan and Fehlings (2007) noted that, “there is insufficient evidence to support (or refute) a recommendation for routine screening for DVT in adults with acute traumatic SCI under thromboprophylaxis.” The same authors note that, “The screening test of choice for asymptomatic DVT needs to be determined. A systematic review on noninvasive diagnosis of DVT from the McMaster Diagnosis of Deep Venous Thrombosis Working Group indicated that: 1) venography is the only reliable test for the diagnosis of asymptomatic DVT; 2) the role of surveillance testing with ultrasound in asymptomatic patients at high risk of DVT is uncertain; and 3) surveillance testing with impedance plethysmography is not recommended (Kearon et al. 1998).”

3.2 Pulmonary Embolism

3.2.1 Clinical Presentation

The clinical diagnosis of pulmonary emboli is unreliable, being both insensitive and nonspecific. Many cases are clinically silent with only 30% having the clinical features of a DVT and only 70% demonstrating a DVT on venography. Patients with a massive pulmonary embolus, who are compromised for more than 60% of pulmonary circulation, are considered critically ill. Right heart failure may progress to cardiovascular collapse with hypertension, coma and death. A sub-massive pulmonary embolus presents with tachycardia, tachypnea and signs of pulmonary infarction with consolidation, rales, hemoptyisis, pleuritic chest pain, pleural friction rub, pleural effusion and fever. In most cases patients often present with a few nonspecific clinical findings and the major clinical complaints of malaise and fever.

3.2.2 Ventilation/Perfusion Scanning

Nuclear ventilation/perfusion (V/Q) scans are often used to diagnose a PE. A normal perfusion scan usually excludes a PE but can be found in a minority of patients with a PE. Perfusion defects are non-specific; about one third of those with defects actually have a PE. The probability that a perfusion defect is a PE increases with the size, shape and number of defects as well as the presence of a normal ventilation scan. Mismatched perfusion defects (normal ventilation scan), which are segmental in size or larger are “high probability” defects and are associated with an approximately 80% prevalence of PE. Three or more mismatched defects are associated with a prevalence of approximately 90%. Patients should be treated if presenting with a positive V/Q scan and high clinical suspicion of a PE.
Table 2 Probability of Pulmonary Embolism Based on Ventilation-Perfusion Scan Results and Clinical Suspicion in Prospective Investigation of Pulmonary Embolism Study*

<table>
<thead>
<tr>
<th>Ventilation-Perfusion Scan Results</th>
<th>Clinical Suspicion of Pulmonary Embolism**</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Low</td>
</tr>
<tr>
<td>High probability</td>
<td>56%</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>16%</td>
</tr>
<tr>
<td>Low probability</td>
<td>4%</td>
</tr>
<tr>
<td>Normal/near-normal probability</td>
<td>2%</td>
</tr>
</tbody>
</table>

PIOPED (prospective investigation of pulmonary embolism diagnosis) investigators demonstrated that a low-probability or normal ventilation-perfusion scan with a low clinical suspicion of pulmonary embolism essentially excludes the diagnosis of pulmonary embolism (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 pulmonary embolism, the positive predictive value is 96% (Gill & Nahum 2000; PIOPED Investigators 1990).

3.2.3 Pulmonary Angiography

Pulmonary angiography is the definitive test for diagnosis of pulmonary embolism (Gill & Nahum 2000). It involves percutaneous catheterization and injection of contrast dye into a pulmonary artery branch (Gill & Nahum 2000). It is an expensive test and is associated with a significant risk of complications (e.g. hemorrhage, embolus, nerve injury). Relative contraindications include significant bleeding risk, allergy to contrast medium, and renal insufficiency (Gill & Nahum 2000). It is associated with a mortality rate of up to 0.5% (Newman 1989; Stein et al. 1992). Pulmonary angiography is most commonly used when ventilation-perfusion scanning is non-diagnostic but clinical suspicion remains high (Tapson et al. 1999). A negative pulmonary angiogram excludes clinically relevant pulmonary embolism (Tapson et al. 1999; Gill & Nahum 2000).

3.2.4 Spiral Computed Tomography Scan

A spiral Computed Tomography (CT) scan is a quick, less expensive CT scan which can scan the entire thorax in one breath-hold. It has a sensitivity ranging 64-93% with a specificity of 89-100%. Its accuracy increases with the size of the embolism. It directly visualizes the clot and has the added benefit of diagnosing other disease states in the differential diagnosis (e.g. lung cancer, vascular remodelling, and pleural effusion). Spiral CT is a useful adjunct to the majority of ventilation perfusion scans that have non-diagnostic results that require further testing (PIOPED Investigators 1990).

3.2.5 Right Bundle Branch Block

The electrocardiogram (ECG) abnormality of right bundle branch block is commonly associated with PE and heart conditions such as myocarditis, hypertension and ischaemis or congenital heart disease. Only one study examined its use in diagnosing PE post SCI (Frisbie & Sharma, 2009); however, its use in able-bodied individuals indicates there is a high PE specificity (Nielsen et al. 1989; Punukollu et al. 2005).

4.0 Prevention

4.1 Pharmacological Agents for DVT Prophylaxis

Anticoagulants can prevent thrombi from forming in the deep veins of the leg; however, they can also lead to serious complications such as excessive bleeding (e.g. intracerebral hemorrhaging,
The consortium for spinal cord medicine published clinical practice guidelines for the prevention of thromboembolism in SCI (2008). The clinical practice guidelines recommend to:

“Begin low molecular weight heparin, or unfractionated heparin plus intermittent pneumatic compression, in all patients when primary hemostasis becomes evident. Intracranial bleeding, perispinal hematoma, or hemothorax are potential contraindications to the administration of anticoagulants, but anticoagulants may be appropriate when bleeding has stabilized” (p. 38).

This recommendation is based on studies that showed that the risk of thromboembolism in SCI increases rapidly after injury and is maximal between days 7 and 10 (chiou-Tan et al. 2003; Green et al. 1982; Merli et al. 1988; Geerts et al. 1994).

4.1.1 Low-Dose Unfractionated Heparin as Prophylaxis

Heparin acts as an anticoagulant by forming a complex with anti-thrombin, catalyzing the inhibition of several activated blood coagulation factors: XIIa, XIa, IXa, Xa and thrombin. Heparin’s onset of action is immediate. It is most often used in acute conditions, and must be given parenterally. Although low-molecular-weight heparin has become more popular in the treatment of DVT, the effects of intravenous heparin can be reversed rapidly. Initiation of VTE prophylaxis within 72 hours is recommended and is continued for eight to 12 weeks in spinal cord injured patients as vast majority of thromboembolic events occur in the first two to three months. However, prophylaxis can be discontinued earlier if the patient gains functional motor control in the lower limbs (Dhall et al. 2013). Bleeding is the most common adverse effect of heparin. Osteoporosis is associated with the prolonged use of high doses of heparin, although its occurrence is infrequent. Thrombocytopenia, a decreased platelet level in the blood, is an uncommon but serious side-effect of heparin treatment (Pineo & Hull 2004).

### Table 3 Efficacy of Low-Dose Unfractionated Heparin as Prophylaxis

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Country</th>
<th>Research Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Population</th>
<th>Method(s)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwal &amp; Mathur 2009</td>
<td>India</td>
<td>RCT</td>
<td>PEDro=4</td>
<td>N=297</td>
<td>Mean age: 32yr; Gender: males=74%, females=26%</td>
<td>Patients were randomly allocated into the treatment group receiving 5000 IU low dose unfractionated heparin (LDUH) or the control group (no heparin).</td>
<td>Incidence of Deep Venous Thrombosis (DVT).</td>
</tr>
<tr>
<td>Merli et al. 1988</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=4</td>
<td>N_initial=53; N_final=48</td>
<td>Not available.</td>
<td>Randomly assigned to one of three groups: 5000 IU low dose unfractionated heparin (LDUH) alone, 5000 IU LDUH combined with electrical stimulation, or no treatment.</td>
<td>Incidence of Deep Venous Thrombosis (DVT).</td>
</tr>
</tbody>
</table>
| Kulkarni 1992 | England | Case Series | N=97 | | Level of injury: cervical=57, thoracic=34, lumbar=9; Type of injury: traumatic | 5000 IU LDUH every 8 hr. | Twenty six patients developed thromboembolic complications (17 DVT, 7 PE, and 2 DVT+PE). | 42% of delayed arrivals (>24hr post
Table 4 Fixed versus Adjusted Dose Heparin in Prophylaxis of Thromboembolism in SCI

<table>
<thead>
<tr>
<th>Author Year; Country Research Design PEDro Score Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al. 1988 USA RCT PEDro=7 N_initial=75; N_final=58</td>
<td>Population: Age=3-81yr; Gender: males=63, females=12; Severity of injury: complete=75. Intervention: Patients were randomized to one of two regimens of heparin treatment: fixed dose or adjusted dose heparin. Outcome Measures: Incidence of Deep Venous Thrombosis (DVT) and bleeding.</td>
<td>1. Patients on the adjusted-dose regimen received a mean of 13200±2200 U of heparin per dose and had an APTT 1.5 times higher than those on a fixed-dose regimen. 2. Thromboembolism was detected in 9/29 patients randomized to the fixed-dose regimen and 2/29 on the adjusted-dose regimen. 3. While no patient who received the adjusted-dose and whose APTT reached the target level had a thrombosis, bleeding occurred in 7 patients; no patient on the fixed-dose regimen bled.</td>
</tr>
</tbody>
</table>

Discussion

Unfractionated heparin has been the standard treatment for venous thromboembolism post SCI for years. Evidence for its effectiveness, however, is unclear. Using low-dose unfractionated heparin (LDUH) alone is not recommended as a prophylactic treatment (Dhall et al. 2013) and is associated with high rates of DVTs and PEs in acute SCI patients (Kulkarni et al. 1992). Three studies have examined the effect of treatment with LDUH versus placebo. Agarwal and Mathur (2009) randomly divided patients between treatment and control groups. The treatment group received 5000 IU of LDUH subcutaneously two times a day from admission to three months post injury while the control group received no treatment. The study found no significant difference in DVT incidence between the two groups (3.0% versus 1.8%, respectively).

Merli et al. (1988) evaluated 53 acute SCI patients who were randomly assigned to one of three groups: placebo saline (n=17), 5000 IU LDUH (n=16), or 5000 IU LDUH plus electrical stimulation of the tibialis anterior and gastrocnemius muscles (n=15) over 28 days. There was no difference between the placebo saline and heparin groups in the incidence of DVT while there was a significant improvement in the heparin and electrical stimulation group. The study
was prematurely discontinued because of the benefit of the heparin plus electrical stimulation group and lack of efficacy in the control group.

Frisbie and Sasahara (1981) conducted a non-randomized trial of 32 SCI patients receiving either no treatment or 5000 IU of LDUH until day 60 post SCI. Incidence of DVT was rare in both the control (1/17) and the LDUH group (1/15).

Green et al. (1988) studied 75 SCI patients who were randomized to receive either a fixed dose or an adjusted dose of unfractionated heparin. The fixed dose heparin was 5000 IU; the adjusted heparin group started off at 5000 IU and was adjusted according to aPTT (activated Partial Thromboplastin Time) to a maximum of 15000 IU (mean=13200 IU). Thromboembolism was detected in 9/29 on fixed-dose regimen with no bleeding complications while 2/29 on the adjusted-dose regimen developed thromboembolism and 7/29 had bleeding complications.

Typically prophylactic treatment involves 5000 IU of heparin. Two RCTs and one controlled study examining the efficacy of this dose and a placebo found no difference in the incidence of venous thrombosis in both the treatment and the placebo groups. Interestingly, Merli et al. (1988) found that heparin plus electrical muscle stimulation significantly reduced the incidence of venous thrombosis when compared to heparin alone. Finally, one RCT (Green et al. 1988) has shown that while 5000 IU of heparin was not an effective dose in reducing the incidence of thromboembolism, higher doses were more effective but had a higher risk of bleeding complications. In a recent systematic review and meta-analysis, Chen and Wang (2013) conclude that among patients with acute SCI, LDUH has no thromboprophylaxis effect compared with placebo or no treatment.

Conclusions

There is level 2 evidence (from two RCTs and one prospective controlled trial; Merli et al. 1988; Agarwal & Mathur 2009; Frisbie & Sasahara 1981) that 5000 IU of low-dose unfractionated heparin is no more effective than placebo in the prophylaxis of venous thrombosis post SCI.

There is level 1b evidence (from one RCT; Green et al. 1988) that adjusted (higher) dose unfractionated heparin is more effective in prophylaxis of venous thromboembolism than 5000 IU low-dose unfractionated heparin but has a higher incidence of bleeding complications.

5000 IU subcutaneously every 12 hours of unfractionated heparin does not prevent venous thrombosis post SCI while higher dose, adjusted unfractionated heparin is more effective, although risk of bleeding complications is higher.

4.1.2 Low-Molecular-Weight Heparin versus Low-Dose Unfractionated Heparin as Prophylaxis

Low-molecular-weight heparin (LMWH) is derived from standard heparin through either chemical or enzymatic depolymerization. Whereas standard heparin has a molecular weight of 5000 to 30 000 Daltons, LMWH ranges from 1000 to 10 000 Daltons. LMWH binds less strongly to protein, has enhanced bioavailability, interacts less with platelets and yields a very predictable dose response. The clinical advantages of LMWH include predictability, dose-
dependent plasma levels, a long half-life and less bleeding for a given antithrombotic effect. Thrombocytopenia is not associated with short-term use of MLWH. LMWH is administered once or twice daily, both during the high-risk period when prophylaxis for DVT is recommended and also while waiting for oral anticoagulation to take effect in the treatment of DVT. The activated partial thromboplastin time does not need to be monitored, and the dose does not need to be adjusted (Rydberg et al. 1999).

Danaparoid sodium (Orgaran) is an alternative anticoagulant for patients who develop heparin-induced thrombocytopenia from heparin therapy. Danaparoid is a low-molecular-weight heparinoid. Its active components consist of heparan sulfate, dermatan sulfate and chondroitin sulfate. The major difference between danaparoid and other LMWHs is that danaparoid is devoid of heparin or heparin fragments. However, it exerts effects similarly to other LMWHs; Danaparoid acts by inactivating thrombin.

Table 5 Generic and Trade-names of LMWH

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade-name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Orgaran</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Lovenox</td>
</tr>
<tr>
<td>Ardeparin</td>
<td>Normifilo</td>
</tr>
<tr>
<td>Parnaparin, Reviparin</td>
<td>Clivarine</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Logiparin, Innohep</td>
</tr>
<tr>
<td>Certoporain</td>
<td>Alphaparin, Sandoparin</td>
</tr>
</tbody>
</table>

The most commonly studied LMWH for the prophylaxis of venous thromboembolism post SCI is enoxaparin, which was the first used in the USA. The drug has a plasma half-life of 4.4 hours compared with 0.35 hours for LDUH and its subcutaneous bioavailability is 50%, compared to 20% for LDUH (Tomaio et al. 1998). In a meta-analysis, Paciaroni et al. (2008) compared the effectiveness of LDUH to that of LMWH in reducing DVT incidence in individuals post SCI. The study found no significant reduction in DVT between the LDUH group and the control group, or the LDUH group and the LMWH group. However, LMWH was reported to significantly reduce the rate of PE (p=0.04).

Table 6 LMWH versus LDUH as Prophylaxis

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Research Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>Spinal Cord Injury Thromboprophylaxis Investigators 2003a</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=9</td>
<td>N_initial=476; N_final=107</td>
<td>Population: Gender: males=389, females=87; Severity of injury: AIS A-D; Chronicity=acute. Intervention: Patients were assigned to receive thromboprophylaxis with either low dose unfractionated heparin (LDUH) (5000 IU subcutaneously every 8hr) plus intermittent pneumatic compression (IPC); used at least 22hr/day) or enoxaparin (30mg subcutaneously every 12hr). Outcome Measures: Incidence of Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), and major bleeding.</td>
<td>1. Incidence of DVT was 63.3% for LDUH-IPC group versus 65.5% for enoxaparin group (p=.81). 2. Incidence of PE was 18.4% for LDUH-IPC group versus 5.2% for enoxaparin group (p=.03). 3. Among all randomized patients, the incidence of major bleeding was 5.3% for LDUH-IPC group versus 2.6% for enoxaparin group (p=.14).</td>
</tr>
<tr>
<td>Green et al. 1990</td>
<td>USA</td>
<td></td>
<td></td>
<td>Population: Mean age=28yr; Gender: males=34, females=7; Severity of</td>
<td>1. 34.7% of the LDUH group had a DVT, and two individuals had</td>
<td></td>
</tr>
<tr>
<td>Author Year Country</td>
<td>Research Design</td>
<td>PEDro Score</td>
<td>Sample Size</td>
<td>Methods</td>
<td>Outcomes</td>
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<tr>
<td>Arnold 2010 USA Case Control</td>
<td>N=476</td>
<td>RCT</td>
<td>PEDro=8; N&lt;sub&gt;initial&lt;/sub&gt;=41; N&lt;sub&gt;final&lt;/sub&gt;=32</td>
<td>Injury: complete=41. <strong>Intervention:</strong> Patients were assigned to receive either low dose unfractionated heparin (LDUH) (5000 IU) or low molecular unfractionated heparin (LMWH) (3500 anti-Xa units). <strong>Outcome Measures:</strong> Incidence of Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), and major bleeding.</td>
<td>bleeding that necessitated discontinuation of therapy. 2. None of the patients treated with LMWH had DVT or bleeding. 3. The difference between the two groups was significant (p=0.006).</td>
<td></td>
</tr>
<tr>
<td>Worley et al. 2008 Canada Case Control</td>
<td>N=90</td>
<td>Population: SCI (n=24); Time post SCI&gt;72hr. <strong>Intervention:</strong> Retrospective review of patients who received either low dose unfractionated heparin (LDUH) (n=13) or enoxaparin (n=11). <strong>Outcome Measures:</strong> Incidence of Deep Venous Thrombosis/Pulmonary Embolism (DVT/PE) and bleeding.</td>
<td>1. There was no significant difference in incidence of DVT between the LDUH and LMWH groups (15.4% and 36.4%, respectively; p=.357).</td>
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<tr>
<td>Spinal Cord Injury Thromboprophylaxis Investigators 2003b USA Prospective Controlled Trial</td>
<td>N=172; N&lt;sub&gt;final&lt;/sub&gt;=119</td>
<td>Population: UFH group (n=60); Mean age=34yr; Gender: males=47, females=13; Level of injury: paraplegic=18, tetraplegic=32; Enoxaparin group (n=59); Mean age=30.5yr; Gender: males=53, females=634; Level of injury: paraplegic=15, tetraplegic=34. <strong>Intervention:</strong> Continuation of study 2003a above. Patients previously receiving low dose unfractionated heparin (LDUH) continued on this regimen. Those previously on the enoxaparin had an increase in dosage to 40mg. <strong>Outcome Measures:</strong> Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), major bleeding.</td>
<td>1. New DVT was demonstrated in 13/60 LDUH versus 5/59 enoxaparin patients (p=0.052).</td>
<td></td>
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</tr>
<tr>
<td>Maxwell et al. 2002</td>
<td>Population: Age range=15-91yr;</td>
<td>1. The total incidence rate for DVT and</td>
<td></td>
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<tr>
<td>Author Year</td>
<td>Country</td>
<td>Research Design</td>
<td>PEDro Score</td>
<td>Sample Size</td>
<td>Methods</td>
<td>Outcomes</td>
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<tr>
<td>Thumbikat et al. 2002</td>
<td>UK</td>
<td>Case Control</td>
<td>N=173</td>
<td></td>
<td>Population: Age range: 10-60yr; SCI; Severity of injury: complete/ incomplete; Chronicity=acute. Intervention: Patients received a combination of heparin followed by warfarin and mechanical treatments for thromboprophylaxis (n=101) or enoxaparin (n=72) started on the day of admission. Outcome Measures: Documentation of Deep Venous Thrombosis (DVT), Pulmonary Embolism (PE), complication and duration of anticoagulation, results of Doppler studies, Ventilation/Perfusion (V/Q) scans and unexplained decrease in hemoglobin and platelet levels.</td>
<td>1. No statistical results reported. 2. 4 patients in LDUH and 13 patients in LMWH developed venous thromboembolic episodes. 3. In the LDUH group, one of the thrombotic events occurred post-mobilization. 4. 6 of the 13 thrombotic events in LMWH occurred after the patients had been mobilized and anticoagulation stopped. 5. Two periods of peak incidence of venous thromboembolism were noticed in both groups-the first at 20-30 days following injury and the second at 90-100 days post-injury.</td>
</tr>
<tr>
<td>Winemiller et al. 1999</td>
<td>USA</td>
<td>Case Series</td>
<td>N=285</td>
<td></td>
<td>Population: Mean age=25yr; Severity of injury: Frankel scores: A-B; Chronicity=acute. Intervention: Review patients who presented with DVT or PE and were subsequently administered heparin prophylaxis for 42 days after injury. Outcome Measures: Risk of further Deep Venous Thrombosis (DVT).</td>
<td>1. Multivariate analysis suggested a decreased risk of thromboembolism in patients with SCI treated with heparin within the first 14 days or anytime within 42 days.</td>
</tr>
<tr>
<td>Green et al. 1994</td>
<td>USA</td>
<td>Pre-Post</td>
<td>N=48</td>
<td></td>
<td>Population: Age=14-83yr; Gender: males=39, females=9; Chronicity=acute. Intervention: Low molecular unfractionated heparin (LMWH) at a dose of 3500 anti-Xa U given subcutaneously once daily. All subjects received this medication at this dose for 8 wk, then discontinued if venous colour flow ultrasonography was negative. Outcome Measures: Incidence of Deep Venous Thrombosis (DVT), pulmonary embolism (PE), and bleeding compared to 20 individuals in the study by Green et al. 1990 (see above).</td>
<td>1. The differences in bleeding between the two forms of heparin were significant (p=0.04) favoring LMWH. 2. There was a trend toward fewer thrombotic events with LMWH (p=.15).</td>
</tr>
</tbody>
</table>
Table 7 Systematic Reviews comparing LMWH to LDUH

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>AMSTAR score</th>
<th>Methods</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen &amp; Wang 2013</td>
<td>China</td>
<td>Review of published articles up to February 2013</td>
<td>N=18</td>
<td>AMSTAR=9</td>
<td>Method: Comprehensive literature search of RCTs, quasi-RCTs, cohort studies, case control studies, and cross-sectional studies of acute SCI patients receiving heparin to prevent the risk venous thromboembolism (VTE) and major bleeding. Databases: MEDLINE. Level of evidence: High quality study designs such as RCTs, prospective cohort studies; moderate quality study designs such as case control studies were included. Cross-sectional observational studies were the only type of low quality study design included into the search. Low quality study designs such as case series, case reports, and reviews were excluded. Questions/measures/hypothesis: 1. Examine the effectiveness of low-dose unfractionated heparin (LDUH) in SCI in preventing venous thromboembolism (VTE). 2. To compare the effectiveness of low-dose unfractionated heparin (LDUH) with low-molecular-weight heparin (LMWH) in preventing venous thromboembolism (VTE) and major bleeding. 3. To compare the effectiveness of different types of low-molecular-weight heparin (LMWH) in preventing venous thromboembolism (VTE) and major bleeding. 1. Two RCTs and two case-control studies compared LDUH with a placebo or untreated condition but no significant differences were reported between the two conditions in the prevalence of VTE (p=.259). 2. Nine studies, including four case-control studies, three RCTs, one quasi-RCT, and one cohort study, compared LDUH and LMWH. No significant difference was reported between the two in regards to development of VTE (p=.162) but LMWH was associated with significantly lower instances of major bleeding (p=0.044). 3. One study compared fixed-dose LDUH with adjusted-dose LMWH and reported a significantly higher prevalence of VTE in the fixed-dose LDUH group (p=0.019). Major bleeding was also significantly higher in the fixed-dose LDUH group compared to the adjusted-dose LMWH group (p=0.0048). 4. Three studies compared three different types of LMWH (Enoxaparin, Tinzaparin, and Dalteparin) but no significant differences were found between Enoxaparin and Tinzaparin (p=.130), and Enoxaparin and Dalteparin (p=.866) in prevalence rates of VTE. 5. No significant differences were found between Enoxaparin and Dalteparin for major bleeding (p=.496). Prevalence of major bleeding was not investigated in the comparison between Enoxaparin and Tinzaparin.</td>
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</table>

Discussion

LMWH is the newest treatment for prophylaxis of venous thromboembolism. Given that LMWH appears to offer advantages (e.g. decreased incidence of DVT/PE and reduced costs; Spivack & Aisen 1997) over LDUH as the standard of care, it is not surprising that there are a number of trials comparing the two treatments.

There have been seven trials that have compared LDUH and LMWH. The SCI Thromboprophylaxis Investigators (2003a) conducted an RCT of 107 SCI patients who were assigned to receive thromboprophylaxis with either a combination of LDUH (5000 IU) plus intermittent pneumatic compression (IPC) 22 hr/day, or enoxaparin 30 mg s/c q12h. The incidence of DVT was 63.3% and 65.5% for the LDUH and enoxaparin groups, respectively
(p=0.81), whereas the incidence of PE was 18.4% and 5.2%, respectively (p=0.03). Among all the randomized patients, the incidence of major bleeding was 5.3% in the LDUH group versus 2.6% in the enoxaparin group (p=0.14). This may be the result of the added benefit of intermittent pneumatic compression. Nonetheless, the incidence of PEs was still significantly greater in the LDUH group. In their follow-up prospective controlled trial, the enoxaparin group increased their dosage to 40 mg once daily (SCI Thromboprophylaxis Investigators 2003b). A new DVT was detected in 21.7% of LDUH and 8.5% of enoxaparin patients (p=0.052). Enoxaparin appeared to be more effective in this population than LDUH (SCI Thromboprophylaxis Investigators 2003b).

The results by the SCI Thromboprophylaxis Investigators have been supported by earlier studies. In a case series by Maxwell et al. (2002), individuals with SCI using a combination of sequential compression devices and LMWH produced a fewer number of DVTs and PEs (7.4% and 0%, respectively) compared to those receiving sequential compression devices and LDUH. An RCT by Green et al. (1990) on 41 SCI subjects also compared LDUH to LMWH. Five patients in the standard heparin group had thrombotic events including two patients with fatal pulmonary embolism. Two other patients had bleeding severe enough to necessitate withdrawal of the heparin. The cumulative event rate was 34% in the LDUH group while the LMWH group had no thrombotic events or bleeding. The difference between the two groups was significant (p=0.006). In a follow-up study, Green et al. (1994) studied 48 acute SCI patients with complete motor paraplegia who all received LMWH (3500 IU). Treatment began within 72 hours of injury and continued for eight weeks. In total, eight suffered a thrombotic event which consisted of two pulmonary emboli, four proximal DVTs, and two distal calf DVTs. When combining data from a previous study (68 LMWH (20 from previous study) and 79 LDUH), the differences in bleeding and thrombotic events were significant (p=0.04 and p=0.015, respectively) favoring LMWH.

Interestingly, some studies (Arnold et al. 2010; Worley et al. 2008) report no difference in the incidence of DVT or bleeding complications among individuals with SCIs receiving LDUH or LMWH (enoxaparin and dalteparin, respectively). A systematic review by Chen and Wang (2015) examining 18 studies with 2578 patients compared the effect of different pharmacological VTE prophylactic options. It was concluded that LMWH is similar to LDUH in the VTE prevention but has less bleeding complications. There was no difference in VTE prophylaxis using various types and/or doses of LMWH, including enoxaparin, tinzaparin and dalteparin. Despite the conflicting results presented by Thubikat et al. (2002) and Chen and Wang (2015), there is still strong evidence based on five studies that LMWH is more effective than LDUH.

Table 8 Studies Evaluating Low-Molecular-Weight Heparin vs Low-Dose Unfractionated Heparin

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>N</th>
<th>Research Design</th>
<th>Treatment Group 1</th>
<th>Group 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCI Thromboprophylaxis Investigators 2003a</td>
<td>107</td>
<td>RCT</td>
<td>LDUH + mechanical methods</td>
<td>LMWH (Enoxaparin)</td>
<td>+</td>
</tr>
<tr>
<td>Green et al. 1990</td>
<td>32</td>
<td>RCT</td>
<td>LDUH</td>
<td>LMWH</td>
<td>+</td>
</tr>
<tr>
<td>Arnold et al. 2010</td>
<td>24</td>
<td>Case Control</td>
<td>LDUH</td>
<td>LMWH (Enoxaparin)</td>
<td>-</td>
</tr>
<tr>
<td>Worley et al. 2008</td>
<td>90</td>
<td>Case Control</td>
<td>LDUH</td>
<td>LMWH (Dalteparin)</td>
<td>-</td>
</tr>
<tr>
<td>SCI Thromboprophylaxis Investigators 2003b</td>
<td>119</td>
<td>Prospective Controlled Trial</td>
<td>LDUH</td>
<td>LMWH (Enoxaparin)</td>
<td>+</td>
</tr>
<tr>
<td>Maxwell et al. 2002</td>
<td>111</td>
<td>LDUH + mechanical</td>
<td>LMWH</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

There is level 1a evidence (from two RCTs, one prospective controlled trial, one pre-post, and one case series; SCI Thromboprophylaxis Investigators 2003a, 2003b; Green et al. 1990, 1994; Maxwell et al. 2002) that low-molecular-weight heparin, in particular enoxaparin, is more effective in reducing venous thromboembolic events, when compared to the standard subcutaneous heparin prophylaxis. Moreover, the incidence of bleeding complications was less in the LMWH group.

Low-molecular-weight heparin reduces the risk of venous thromboembolism post SCI more effectively than standard or unfractionated heparin prophylaxis with fewer bleeding complications.

### 4.1.3 Low Molecular Weight Heparin as Prophylaxis

Five studies have been found which examined LMWH alone, or compared different dosages or types of LMWHs.

#### Table 9 Low Molecular Weight Heparin Alone in Prophylaxis of Venous Thromboembolism Post SCI

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Research Design</th>
<th>Treatment Group 1</th>
<th>Treatment Group 2</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiou-Tan et al. 2003</td>
<td>Case Series</td>
<td>LDUH + warfarin</td>
<td>LMWH (Enoxaparin)</td>
<td>- -</td>
</tr>
<tr>
<td>Green et al. 1994</td>
<td>Pre-Post</td>
<td>LDUH</td>
<td>LMWH</td>
<td>+</td>
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</table>

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Total Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiou-Tan et al. 2003</td>
<td>USA</td>
<td>PEDro=6</td>
<td>Case Series</td>
<td>N=95</td>
<td>Population: Mean age=36yr; Severity of injury: complete/incomplete; Mean time since injury&lt;6wk. Intervention: Enrolled patients were randomized into two treatment groups. One group received 30mg of enoxaparin subcutaneously every 12hr and the other received 5000 IU of dalteparin subcutaneously once daily. Outcome Measures: Incidence of deep venous thrombosis (DVT) and bleeding.</td>
<td>1. 6% of the patients developed DVT while receiving enoxaparin and 4% while receiving dalteparin (p=.51). 2. 4% developed bleeding while receiving dalteparin and 2% while receiving enoxaparin (p=.72).</td>
</tr>
<tr>
<td>Marciniak et al. 2012</td>
<td>USA</td>
<td>Case Control</td>
<td>Case Series</td>
<td>N=140</td>
<td>Population: Enoxaparin (n=68) mean age=46.8±21.0; High-dose tinzaparin (n=58) mean age=48.4±19.6; Low-dose tinzaparin (n=14) mean age=32.9±16.1. Intervention: Patients received either enoxaparin (5000 IU), high-dose tinzaparin (4500 IU), or low-dose tinzaparin (3500). Outcome Measures: Incidence of Deep venous thrombosis (DVT) and bleeding.</td>
<td>1. 14 individuals developed a DVT and 4 developed a PE. 2. Compared with patients receiving low-dose tinzaparin, those receiving enoxaparin and high-dose tinzaparin had significantly reduced odds of DVT (OR=0.12 and OR=0.18, respectively). 3. After controlling for age, previous</td>
</tr>
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</table>
### Table 10 Timing of LMWH Prophylaxis on Venous Thromboembolism Post SCI

<table>
<thead>
<tr>
<th>Authors; Country Date included in the review Number of articles AMSTAR Score</th>
<th>Method; Level of evidence Questions</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Christie et al. 2011 Canada Date included in the review not stated N=5 AMSTAR: 5</td>
<td>Method: Comprehensive literature search of English RCT, Cohort studies, case series, and review articles of relating to prophylaxis low molecular unfractioned heparin (LMWH) for deep venous thrombosis (DVT) in traumatic SCI in adult age group (+18yr). Databases: PubMed. Questions/measures/hypothesis:</td>
<td>1. DVT prophylaxis should be instituted within 72hr post injury 2. LMWH should be held on the morning of surgery and resumed within 24hr following surgery.</td>
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</tbody>
</table>
Examine the ideal time for initiation of deep venous thrombosis (DVT) prophylaxis with low molecular unfractioned heparin (LMWH) after SCI or after surgery.

Discussion

In examining the LMWH enoxaparin, Harris et al. (1996) performed a case series with 105 subjects (66 with SCI). All patients received 30 mg of enoxaparin s/c q12h beginning at the time of admission. Patients scheduled for surgery withheld anticoagulation therapy on the morning of the operation, resumed 24 hours later, and continued until the patients’ discharge. No patient developed clinical or ultrasound evidence of a DVT.

The optimal dose of enoxaparin has not been established to date. Hebbeler et al. (2004) compared two dosing regimens of enoxaparin (40 mg daily or 30 mg twice daily) among 129 acute SCI patients. Symptomatic thromboembolism did not differ between the two groups with DVT occurring in only one patient in each group. Furthermore, there was no difference in bleeding complications between the two groups.

Since there are many new LMWHs available, studies have compared their efficacy. One RCT (Chiou-Tan et al. 2001) and one case control study (Slavik et al. 2007) compared acute SCI patients who received enoxaparin (30-40 mg s/c q12h) to those who received dalteparin (2000-5000 IU s/c daily). There were no significant group differences between the two groups in terms of incidence and location of DVTs or bleeding complications. A third study by Marciniak et al. (2012) compared enoxaparin to two different doses of tinzaparin (4500 IU and 3500 IU). After controlling for multiple variables they reported no differences in DVT incidence between the LMWHs.

One systematic review evaluated the ideal time for initiating DVT treatment with LMWH. Christie et al. (2011) concluded that LMWH prophylaxis for DVT should be administered within 72 hours post SCI. However, this conclusion should be interpreted with caution, as it was based on a single, small (N=5) systematic review.

Conclusion

There is level 4 evidence (from one case control study; Hebbeler et al. 2004) that 40 mg daily enoxaparin is no more effective than 30 mg twice daily enoxaparin in reducing the incidence of deep venous thrombosis or bleeding complications when used prophylactically.

There is level 1b evidence (from one RCT and one case control study; Chiou-Tan et al. 2003; Slavik et al. 2007) that enoxaparin is no more effective than dalteparin in reducing the risk of deep venous thrombosis or bleeding complications although enoxaparin is more expensive.

There is level 3 evidence (from one case control study; Marciniak et al. 2012) that enoxaparin is no more effective than tinzaparin in reducing the risk of deep venous thrombosis or bleeding complications.
There appears to be no difference between enoxaparin and dalteparin, or enoxaparin and tinzaparin, in reducing the risk of venous thrombosis post-SCI.

4.2 Mechanical Methods

4.2.1 Physical Methods for Prophylaxis

Although pharmacological measures have been generally the preferred treatment for venous thromboembolism prophylaxis post SCI, mechanical means of limiting venous stasis can also serve to reduce the incidence of DVT post SCI. Mechanical treatments are designed to limit stasis and increase fibrinolytic activity in the paralyzed lower extremities. However, it should be noted that use of these devices should be accompanied by twice daily inspection for skin discolouration or breakdown, and broken blood vessels. Pneumatic compression devices are not suitable for patients with severe arterial insufficiency.

Table 11 Evaluating Physical Methods for the Prevention of DVT

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Research Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nash et al. 2000</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=8</td>
<td>N=20</td>
<td>Population: Mean age=27.9yr; Gender: males=20; Level of injury: tetraplegic=20; Time since injury=2mo-17yr. Interventions: Patients were randomized into one of two groups: 1) Slow sequential pneumatic compression devices (SCD) - 15sec compression, 45sec relaxation at 35 mmHg (ankle), 30 mmHg (calf) or 20 mmHg (thigh); or 2) intermittent pulsatile compression (IPC) - 2sec compression, 18sec relaxation at 160mmHg. Outcome Measures: Venous flow/min (VFM); average venous velocity (AVV); maximum venous velocity (MVV); for bilateral popliteal and femoral veins at rest (baseline) and during compression.</td>
<td>1. Popliteal vein: no differences between devices. 2. Femoral vein: increase in VFM and MVV during IPC versus SCD (p&lt;0.05). 3. Rest versus compression: VFM, AVV and MVV, all increased during compression (p&lt;0.001).</td>
</tr>
<tr>
<td>Becker et al. 1987</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=6</td>
<td>N=15</td>
<td>Population: Age range=17-75yr; Gender: males=11, females=3; Severity of injury: complete/incomplete; Chronicity=acute. Intervention: Rotating treatment tables. Outcome Measures: Impedance blood plethysmography.</td>
<td>1. 4/5 control patients and only 1/10 treated patients developed positive fibrinogen leg scans.</td>
</tr>
<tr>
<td>Matsumoto et al. 2015</td>
<td>Japan</td>
<td>Observational</td>
<td></td>
<td>N=29</td>
<td>Population: Mean Age: 63.2yr; Gender: males=25, females=4; Injury etiology: High fall (n=11, 38%), Fall at ground level (n=8, 28%), Motor Vehicle Accident (n=4, 14%), Sports (n=3, 10%), Low fall (n=2, 7%), Stairs (n=1, 3%); Severity of Injury: AIS A=9, AIS B=2, AIS C=8, AIS D=10; Level of Injury: C3-4=11, C5-8=8, T1-12=6, L1-4=4. Intervention: All patients were monitored for the development of deep venous thrombosis (DVT) after surgery and after</td>
<td>1. DVT developed in 12 patients (41.4%), all of which were located distal to the popliteal vein. 2. The median length of time from surgery to detection of DVT was 7.5 days. 3. Seven of the 12 patients (58.3%) with DVT were classified as AIS A, one classified as AIS B (8.3%), three classified as AIS C (25.0%), and one classified as AIS D (8.3%). 4. Mean D-Dimer level in patients who</td>
</tr>
<tr>
<td>Author Year Country Research Design PEDro Score Sample Size</td>
<td>Methods</td>
<td>Outcomes</td>
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<tr>
<td>Do et al. 2013 Korea Observational N=185</td>
<td>they had received Intermittent pneumatic compression (IPC) with a calf pump and elastic stockings. The pump was attached throughout the day for at least 2wk after surgery and the elastic stockings were utilised after a median of 3 days post-surgery. Assessments were conducted 1, 3, 7, 14, and 28 days post-surgery. <strong>Outcome Measures:</strong> Development of deep venous thrombosis (DVT), D-Dimer levels.</td>
<td>developed DVT was 14.6+13.5ug-ml but this was not significantly different compared to patients who did not developed DVT (p&gt;0.05) at all assessment time-points except for 7 days after surgery (p=0.028). 5. Cutoff D-Dimer levels according to the receiver operator characteristic curve did not differ significantly between patients who developed DVT and those who did not except for 3 days after surgery (p=0.0287).</td>
<td></td>
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<tr>
<td>Chung et al. 2011 Korea Pre-Post N=37</td>
<td>Population: Mean age: 53yr; AIS: A=10, B=7, C=12, D=8. Cause: traumatic (n=19), non-traumatic injury (n=18). <strong>Intervention:</strong> Mechanical prophylaxis was provided to individuals admitted to SCI rehabilitation. <strong>Outcome Measures:</strong> Incidence of deep venous thrombosis (DVT).</td>
<td>1. The incidence of DVT after SCI was 27.6% (n=51) (CI: 21.1-34.0) at the time of initial presentation to the acute rehabilitation unit. 2. Age, sex, completeness of motor paralysis, AIS, level of injury, cause of injury, surgery, and active cancer were not significantly associated with occurrence of DVT (p&gt;0.05 for all). 3. Absence of surgery (p=0.025) and absence of spasticity (p=0.049) were significantly associated with occurrence of DVT. 4. Absence of spasticity was a significant independent risk factor (p=0.027) for occurrence of DVT (OR: 3.28; 95% CI 1.15-9.37).</td>
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<tr>
<td>Winemiller et al. 1999 USA Case Series N=285</td>
<td>Population: Mean age=25yr; Severity of injury: Frankel scores: A-B; Chronicity=acute. <strong>Intervention:</strong> Chart review of patients who presented with DVT or PE and were subsequently administered sequential pneumatic compression devices (SCD) or gradient elastic stockings (GES). <strong>Outcome Measures:</strong> Risk of further deep venous thrombosis (DVT).</td>
<td>1. Multivariate analysis showed that SCD and GES were associated with a reduced risk of venous thromboembolism.</td>
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</table>

**Discussion**

A variety of mechanical measures to reduce the incidence of DVT post SCI have been studied. Becker et al. (1987) studied whether rotating treatment tables would prevent the development and progression of DVT in acute SCI patients. The authors noted that rotating treatment tables had been used up to that time in acute SCI patients to maintain spinal cord alignment while facilitating nursing care, allowing even distribution of ventilation and preventing pressure sores.
It was hypothesized that because these appliances rotated continuously, they might serve to inhibit thrombosis formation by reducing venous stasis. This randomized trial involved 15 patients with acute SCIs. Four of the five control (nonrotated) patients developed distal and proximal thrombi, assessed by $^{125}$I fibrinogen scanning and impedance plethysmography while only one of the ten treated (rotated) SCI patients developed both distal and proximal venous thrombi ($p=0.007$).

Winemiller et al. (1999) examined the medical charts of 285 SCI patients and found that sequential pneumatic compression devices (SCD) or gradient elastic stockings (GES) were associated with a reduced risk of venous thromboembolism. Multivariate analysis also suggested a decreased risk of venous thromboembolism in SCI patients treated with heparin in the first 14 days or anytime within 42 days. Although this risk reduction was approximately twice that of SCD/GES it was not statistically significant. A pre-post study by Chung et al. (2011) also examined the use of GES, external SCD and early ambulation. To better examine the effectiveness of mechanical compression, individuals were not offered pharmacological prophylaxis which may have contributed to the high DVT incidence (43%) across the study.

More recent studies studying the prophylaxis using isolated compression devices is a study by (Do et al. 2013). The authors used only compression for VTE prophylaxis on 185 SCI patients. DVT was detected in 51 of the 185 patients and non-fatal PE was conformed in 13 patients in the first three months. No patients displayed thrombosis more than three months after SCI. Another similar study utilized only pneumatic compression and elastic stockings, but no anticoagulation. Patients were on compression devices all day except when they were out of bed. Elastic stockings were on most of the time except when bathing. DVT was diagnosed in 12 patients out of the 29 enrolled (Matsumoto et al. 2015). The Consortium for Spinal Cord Injury (2008) clinical practise guidelines, supports the application of mechanical compression devices early after injury since it is the period of highest VTE incidence (p. 38).

**Conclusion**

*There is level 4 evidence (from one pre-post study and one case series; Chung et al. 2011; Winemiller et al. 1999) that sequential pneumatic compression devices or gradient elastic stockings were associated with a reduced risk of venous thromboembolism post SCI.*

*There is level 1b evidence (from one RCT; Becker et al. 1987) that rotating treatment tables reduce the incidence of venous thrombi in acute SCI patients.*

Sequential pneumatic compression devices and gradient elastic stockings may reduce the incidence of venous thromboembolism post SCI.

Rotating treatment tables may reduce the incidence of venous thromboembolism post SCI.

### 4.2.2 Combined Physical and Pharmacological Methods for Prophylaxis

The combination of mechanical methods and pharmacological agents has been studied for their effect on DVT prophylaxis post SCI.
<table>
<thead>
<tr>
<th>Author Year</th>
<th>Country</th>
<th>Research Design</th>
<th>PEDro Score</th>
<th>Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halim et al. 2014</td>
<td>India</td>
<td>RCT</td>
<td>PEDro=7</td>
<td>N=74</td>
<td>Population: Experimental Group (n=37): Gender: males=25, females=12; Severity of Injury: AIS A=28, AIS B, C, D=9; Level of Injury: paraplegic=15, tetraplegic=22. Control Group (n=37): Gender: males=35, AIS B, C, D=7; Level of Injury: paraplegic=17, tetraplegic=20. <strong>Intervention:</strong> Patients were randomized into two groups; the experimental group received 40mg of Enoxaparin 1x/ay and for 8 wk as well as compression stockings, whilst patients in the control group received compression stockings only. Assessments were conducted at 2 wk post-injury. <strong>Outcome Measures:</strong> Development of deep venous thrombosis (DVT) according to Doppler venous ultrasonography scans.</td>
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<tr>
<td>Spinal Cord Injury Thromboprophylaxis Investigators 2003a</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=9</td>
<td>N_initial=476; N_final=107</td>
<td>Population: Gender: males=389, females=87; Severity of injury: AIS A-D; Chronicity=acute. <strong>Intervention:</strong> Patients were assigned to receive thromboprophylaxis with either low dose unfractionated heparin (LDUH) (5000 IU subcutaneously every 8 hr) plus intermittent pneumatic compression (IPC; used at least 22 hr/day) or enoxaparin (30 mg subcutaneously every 12 hr). <strong>Outcome Measures:</strong> Incidence of deep venous thrombosis (DVT), pulmonary embolism (PE), and major bleeding.</td>
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<tr>
<td>Green et al. 1982</td>
<td>USA</td>
<td>RCT</td>
<td>PEDro=7</td>
<td>N_initial=28; N_final=27</td>
<td>Population: Gender: males=24, females=4; Severity of injury: complete=28. <strong>Intervention:</strong> Subjects were randomized to one of two regimens: external pneumatic calf compression (EPCC) alone (n=15), or EPCC combined with aspirin (ASA) 300 mg bid and dipyridamole (Dip) 75 mg bid (n=13). <strong>Outcome Measures:</strong> Incidence of deep venous thrombosis (DVT); Factor VIII coagulant activity.</td>
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<tr>
<td>Giorgri et al. 2013</td>
<td></td>
<td></td>
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<td></td>
<td>Population: Mean age: 40.3 yr; Gender:</td>
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</table>

1. Eight patients in the control developed DVT (21.6%) compared to two patients in the experimental group (p=0.041).
2. Patients with paraplegia were significantly more likely to develop DVT in the control group compared to the experimental (p=0.05). However, rates of DVT among patients with Tetraplegia did not differ significantly between the experimental and control group (p=.86).
3. Patients with a complete SCI in the control group were significantly more likely to develop DVT compared to the experimental (p=0.05). However, rates of DVT among patients with an incomplete SCI did not differ significantly between the experimental and control group (p=0.99).
4. A greater number of patients in the control group were confirmed to have DVT according to Doppler venous ultrasonography scans but did not exhibit any symptoms. This finding was statistically significant compared to the experimental group (p=0.02).
<table>
<thead>
<tr>
<th>Author Year Country Research Design PEDro Score Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
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<tr>
<td>Italy Prospective Cohort Study N=94</td>
<td>males=80 males, females=14; Severity of injury: paraplegia=52, tetraplegia=42. <strong>Intervention:</strong> Retrospective review of patients who received prophylactic thigh length graduate compressive (18mmHg at the ankle) stockings plus LMWH (enoxaparin or dalteparin). <strong>Outcome Measures:</strong> Incidence of deep venous thrombosis (DVT).</td>
<td>during neurosurgical unit stay, 6 asymptomatic events were diagnosed by screening within one week after rehabilitation admission, 2 were diagnosed during the remaining rehabilitation stay and 1 was detected during follow-up after rehabilitation discharge.</td>
</tr>
<tr>
<td>Giorgi Pierfranceschi et al. 2013 Italy Observational N=94</td>
<td>Population: Mean age: 40.3yr; Gender: male=80, female=14; Level of injury: tetraplegic=42, paraplegic=52. <strong>Intervention:</strong> All patients received thromboprophylaxis with low-molecular-weight heparin combined with compressive stockings during hospitalization. This study prospectively evaluated short and long term risk of venous thromboembolism (VTE). <strong>Outcome Measures:</strong> Incidence of venous thromboembolism (VTE), timing of VTE event.</td>
<td>1. Cumulative incidence of VTE was 23.4% (22 events) over a median follow-up period of 36.3mo (IQR 4.4–48) after SCI. 2. VTE events were represented by isolated deep vein thrombosis (DVT) in 19 patients, isolated pulmonary embolism (PE) in two patients and concomitant DVT and PE in one patient. 3. Time of VTE events: 13 during neurosurgery unit (NSU) stay, 6 at rehabilitation unit (RU) admission (screening ultrasound), 2 during RU stay and 1 after RU discharge. 4. Age over 45yr (95% CI 3-23.3), previous VTE (95% CI 1.6-23.3) and paraplegia (95% CI 1.6-13.7) were independently associated with the occurrence of VTE.</td>
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<tr>
<td>Spinal Cord Injury Thromboprophylaxis Investigators 2003b USA Prospective Controlled Trial N_{Initial}=172; N_{Final}=119</td>
<td>Population: <strong>LDUH</strong> (n=60): Mean age=34 yr; Gender: males=47, females=13; Level of injury: paraplegic=18, tetraplegic=32; <strong>Enoxaparin</strong> (n=59): Mean age=30.5 yr; Gender: males=53, females=634; Level of injury: paraplegic=15, tetraplegic=34. <strong>Intervention:</strong> Continuation of study 2003a above. Patients previously receiving LDUH continued on this regimen. Those previously on the enoxaparin had an increase in dosage to 40mg. <strong>Outcome Measures:</strong> Deep venous thrombosis (DVT), pulmonary embolism (PE), major bleeding.</td>
<td>1. New DVT was demonstrated in 13/60 LDUH versus 5/59 enoxaparin patients (p=0.052).</td>
</tr>
<tr>
<td>Maxwell et al. 2002 USA Case Series N=111</td>
<td>Population: Age range=15-91yr; Mean hospital length of stay 23.5 days; Level of injury: paraplegic=41.4%, tetraplegia=58.6%; Mean time post SCI=23±20 days. <strong>Intervention:</strong> Retrospective review of patients using sequential compression devices alone or in combination with 5000 IU LDUH or LMWH. <strong>Outcome Measures:</strong> Incidence of deep venous thrombosis/pulmonary embolism (DVT/PE).</td>
<td>1. The total incidence rate for DVT and PE was 9.0% and 1.8%, respectively. 2. The incidence of DVT and PE in patients using compression only was 7.1% and 2.3%, respectively 3. The incidence of DVT and PE in patients using compression plus LDUH, the incidence was 11.1% and 2.8%, respectively 4. The incidence of DVT and PE in patients using compression LMWH was 7.4% and 0%, respectively.</td>
</tr>
<tr>
<td>Deep et al. 2001</td>
<td>Population: Level of injury: cervical=150,</td>
<td>1. 2.9% of patients developed clinical</td>
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<tr>
<td>Author Year</td>
<td>Country</td>
<td>Research Design</td>
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<tr>
<td>UK</td>
<td>Case Series</td>
<td>N=276</td>
</tr>
<tr>
<td>Aito et al. 2000</td>
<td>Italy</td>
<td>Pre-Post</td>
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<tr>
<td>Merli et al. 1992</td>
<td>USA</td>
<td>Case Control</td>
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</tbody>
</table>

**Discussion**

Various combinations of physical and pharmacological treatments to prevent DVTs post SCI have been studied. Three studies examined LDUH paired with mechanical methods. Merli et al. (1992) studied 36 SCI patients who received either prophylaxis (LDUH 5000 IU) combined with external pneumatic compression and gradient elastic stockings or no treatment for two weeks. The incidence of thrombosis was significantly lower in the treated group (p=0.04). Spinal Cord Injury Thromboprophylaxis Investigators conducted an RCT (2003a) and follow-up prospective controlled trial (2003b) both of which examined the effect of 5000 IU LDUH plus intermittent pneumatic compression versus enoxaparin alone. In the first study (2003a), the authors found no significant difference between the two groups in DVT incidence. However, in the second study the dosage of enoxaparin was increased and they found that high-dose enoxaparin resulted in fewer DVTs than the combined LDUH-IPC treatment (Spinal Cord Injury Thromboprophylaxis Investigators 2003b).

Three types of LMWH (enoxaparin, dalteparin, and Nadroparine) combined with physical methods have also been studied. In a prospective cohort study, Giorgi et al. (2013) found that
among 94 individuals receiving either dalteparin or enoxaparin in combination with physical methods, a high rate of DVTs (22%) still occurred. However, the rate of DVTs declined significantly after three months post rehabilitation stay. Aito et al. (2000) studied 275 SCI patients, 99 of who were treated within 72 hours of injury while 176 were treated 8-28 days post SCI. The treatment involved permanently dressed gradient elastic stockings, subcutaneous LMWH (Nadroparine), and external sequential pneumatic compression (ESPC) of the lower limbs. There was early mobilization of the lower limbs. The complete prophylactic treatment lasted at least 30 days post SCI; LMWH and ESPC were continued for two more months depending on the patient's progress. A 2% DVT incidence in the early treatment group compared to a 26% incidence in the later treatment group demonstrated that early treatment was clearly important. In a retrospective study by Deep et al. (2001), the authors reported that just 2.9% of patients developed a DVT/PE between admission and discharge from rehabilitation after being treated with anti-thromboembolic stockings and 40 mg of enoxaparin.

Finally, Green et al. (1982) randomized 27 SCI patients to either external pneumatic calf compression alone, or in combination with 300 mg acetylsalicylic acid twice daily plus 75 mg dipyridamole twice daily. Thrombi developed in 6/15 patients treated solely with external calf compression (EPCC) and in 3/12 receiving ASA/Dipyridamole as well as EPCC (p<0.100).

Early application of pharmacological agents, along with mechanical treatments, has been shown to reduce the risk of DVT complications. Maxwell et al. (2002) demonstrated that in comparison to individuals receiving only sequential compression devices, those using compression combined with LMWH developed fewer DVTs and PEs. Given the results by the Spinal Cord Injury Thromboprophylaxis Investigators (2003b) showing better outcomes with high-dose Enoxaparin (alone), future studies comparing LMWH to LMWH plus mechanical methods are warranted. In a recent RCT, Halim et al. (2014) compared individuals using only compression stockings to another group receiving prophylactic LMWH with the physical compression. Patients were screened at a two week intervals for DVT using Doppler ultrasound. The incidence of DVT was significantly lower in the group receiving both prophylactic LMWH and physical compression compared to the compression-only group.

Conclusions

There is level 3 evidence (from one case control study and one case series study; Merli et al. 1992; Maxwell et al. 2002) that a comprehensive prophylactic treatment of external pneumatic compression, gradient pressure stockings and low dose unfractionated heparin reduces venous thrombosis post SCI.

There is level 4 evidence (from one pre-post study; Aito et al. 2000) that a comprehensive prophylactic regimen of pharmacological and physical measures is more effective in preventing venous thrombosis post SCI when instituted earlier rather than later.

There is level 1b evidence (from one RCT; Halim et al. 2014) that a comprehensive prophylactic treatment of gradient pressure stockings and low molecular weight heparin is more effective than pressure stockings alone in reducing venous thrombosis post SCI.

A combined regiment of pneumatic compression, pressure stockings and low-dose heparin or low molecular weight heparin given prophylactically may reduce the incidence of venous thrombosis and this effect is better in early post SCI.
4.3 Vena Cava Filtration

A vena cava filter is a cone shaped medical device that is inserted into the inferior vena cava (IVC), the largest vein in the body, to prevent devastating pulmonary embolisms. The filters are inserted into easily accessible blood vessels (e.g. femoral vein, internal jugular vein) using a catheter and guided fluoroscopically to the inferior vena cava just below the kidneys. The IVC filter is designed to capture blood clots from deep veins (mostly commonly from the leg) that would otherwise travel to the heart and lungs. The device is safe and cost effective if inserted percutaneously in the intensive care unit rather than in the operating room or radiology suite (Dhall et al. 2013).

Table 13 Prophylactic Vena Cava Insertion in Patients with Traumatic SCI

<table>
<thead>
<tr>
<th>Author Year Country</th>
<th>PEDro Score Research Design Sample Size</th>
<th>Methods</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Roberts et al. 2011 USA Case Series N=45</td>
<td>Population: Mean age: 39.7 yr (17-67); Gender: males=37, females=8; Injury severity: Injury Severity Score: 34.2; Chronicity: acute (&lt;72 hr post SCI). Intervention: Prophylactic IVC filter insertion. Outcome Measures: Incidence of pulmonary embolism (PE) and complications related to insertion.</td>
<td>1. Not one patient sustained a PE. 2. No complications related to IVCF insertion were observed.</td>
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<tr>
<td>Gorman et al. 2009 USA Case Control N=114</td>
<td>Population: Inferior vena cava (IVC) filter (N=54): Mean age=37.1 yr; Gender: males=52%, females=48%; Level of injury: tetraplegic=38.8%; No IVC filter (N=58): Mean age=48.1 yr; Gender: males=40%, females=60%; Level of injury: tetraplegic=51.7%. Intervention: Charts were reviewed of SCI patients who received a prophylactic IVC filter. Outcome Measures: Incidence of deep venous thrombosis (DVT).</td>
<td>1. IVC filters were more likely to be inserted in individuals with major trauma than those without. 2. Patients without IVC filter had fewer DVTs than those with an IVC filter (5.2% versus 20.4%, p=0.021). 3. Incidence of DVT was not related to AIS score although individuals with an Injury Severity Score &gt;30 were more likely to have DVT (p=0.007) and more likely to have received an IVC filter (p=0.001).</td>
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<tr>
<td>Kinney et al. 1996 USA Case Control N=27</td>
<td>Population: Cervical (n=11): Mean age=38.8 yr; Control (non-cervical, n=16): Mean age=48.6 yr; Gender: males=62%, females=38%. Intervention: Charts of SCI patients who received prophylactic Greenfield filter insertion were reviewed and compared to non-SCI patients who received the filter. Outcome Measures: Complications.</td>
<td>1. The most common complication (45.5%) in cervical patients with filter insertions was migration. 2. The mean migration distance was significantly higher in cervical patients than non-cervical patients (13.3 mm versus 2.3 mm; p&lt;0.05). 3. The SCI population had higher rates of PE (9-18%) than the non-SCI control group.</td>
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<tr>
<td>Balshi et al. 1989</td>
<td>Population: Age range=17-48 yr; Gender:</td>
<td>1. Twelve patients experienced a...</td>
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<tr>
<td>Author Year Country</td>
<td>PEDro Score Research Design</td>
<td>Sample Size</td>
<td>Methods</td>
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<tr>
<td>Jarrell et al. 1983 USA Case Series</td>
<td></td>
<td>N=21</td>
<td>Population: Chronicity=acute. Intervention: Prophylactic Greenfield inferior vena cava (IVC) filter insertion.</td>
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</table>

**Discussion**

Six studies have examined the effect of prophylactic IVC filter insertion on the incidence of PE after SCI. Gorman et al. (2009) conducted a retrospective chart review of individuals admitted to SCI rehabilitation receiving IVC filters compared to those that did not. The authors found that individuals with IVC filters had significantly lower DVT incidence rates compared to those without a filter (p=0.021). These results were supported by a case series study by Roberts et al. (2011) and a pre-post study by Wilson et al. (1994) who both demonstrated that retrievable IVC filters were effective in reducing incidence of PE without causing any insertion-related complications.

Three studies have specifically studied the insertion of Greenfield IVC filters. Jarrell et al. (1983) studied 21 acute SCI patients who had received a Greenfield filter and reported that one patient developed a PE. On follow-up, no other PEs were noted although two individuals developed thrombosis of the inferior vena cava. Balshi et al. (1989) reported on patients with SCI who received this filter and found that 12 of the 13 patients had a DVT; distal migration of the filter was a common complication. Kinney et al. (1996) also studied Greenfield filter placement among 27 individuals with SCI and noted that filters migrated frequently in patients with cervical injuries (45.5%). The mean migration distance was significantly higher than individuals with non-cervical injuries (p<0.05). Overall, there was a greater number of PEs sustained in the SCI population compared to the non-SCI control group.

The literature has shown that IVC filters significantly reduce PE in SCI patients; however, this form of prophylaxis is invasive and therefore, should only be considered for high-risk patients. According to the Consortium for Spinal Cord Injury (2008) clinical practise guidelines, it is recommended that health care providers should "consider placing a vena cava filter only in those patients with active bleeding anticipated to persist for more than 72 hours and begin anticoagulants as soon as feasible" (p. 38).

**Conclusion**

*There is level 3 evidence (from two case control studies, two case series studies, and one pre-post study; Roberts et al. 2011; Gorman et al. 2009; Kinny et al. 1996; Wilson et al. 1994; Jarrell et al. 1983) that inferior vena cava filters significantly reduce the risk of pulmonary emboli in high-risk SCI patients.*
Inferior vena cava filters significantly reduce the risk of pulmonary emboli in high-risk SCI patients.

5.0 Treatment

Virtually all research to date on thromboembolism in SCI has focused on prevention rather than treatment. The standard treatment is anticoagulation, generally with intravenous unfractionated heparin immediately followed by a gradual transition to Coumadin which is generally maintained for three to six months. A single study compares the cost effectiveness of unfractionated heparin to enoxaparin in the treatment of DVT post SCI.

Table 14 Unfractionated Heparin versus Low Molecular Weight Heparin

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<tr>
<th>Author Year</th>
<th>Country</th>
<th>Score</th>
<th>Research Design</th>
<th>Sample Size</th>
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<tbody>
<tr>
<td>Tomaio et al. 1998</td>
<td>USA</td>
<td></td>
<td>Case Series</td>
<td>N=6</td>
</tr>
</tbody>
</table>

Methods

Population: Age range=33-60yr; Severity of injury: AIS A-D.

Intervention: Three patients were given IV heparin followed by warfarin, while the remaining three were treated with subcutaneous enoxaparin followed by warfarin.

Outcome Measures: Cost analysis.

Outcomes

1. The average cost of initial anticoagulation of Group 1 (IV heparin) was $413.33 ($331.20-$502.80), which included the cost of heparin, IV pump and tubing, and laboratory monitoring of partial thrombin time whereas the average cost in Group 2 (enoxaparin) was $362.27 ($197.60-$617.50), which included only the cost of medication.

2. Enoxaparin was slightly less expensive when peripheral costs were taken into account.

Discussion

Again, there are remarkably few studies examining treatment of venous thromboembolism post SCI with most of the research focus to date on prophylaxis. Tomaio et al. (1988) studied six SCI patients with acute DVT, half of whom were treated with IV heparin followed by warfarin and half who were treated with subcutaneous enoxaparin followed by warfarin. Though the study was extremely small, the author did a careful cost analysis. Subcutaneous enoxaparin was regarded as a safe, cost-effective and simple treatment that could be of substantial benefit in the treatment of DVT in SCI patients.

Conclusions

There is level 4 evidence (from one case series study; Tomaio et al. 1998) that subcutaneous enoxaparin is a safe, cost-effective and less labour-intensive compared to intravenous heparin for acute DVTs post SCI.

Enoxaparin subcutaneously may be considered as an alternative to intravenous heparin for acute DVTs post SCI.
6.0 Summary

Venous thromboembolism following SCI is a source of significant morbidity and mortality. The majority of the research is focused on prophylaxis of venous thromboembolism in this very high-risk population. Guidelines, based on best available evidence for DVT prophylaxis in SCI, include use of sequential compression devices for two weeks and anticoagulant for eight to 12 weeks after injury (Maxwell et al. 2002). There is evidence in the literature that 5000 IU subcutaneously of unfractionated heparin delivered every 12 hours in this population may not be sufficient to provide adequate protection. LMWH with enoxaparin (primary drug studied), appears to be more effective and should be considered the new standard of care, given the added benefit of lower risk of bleeding complications. Physical or mechanical prevention methods, in particular gradient pressure stockings and intermittent pneumatic compression, are designed to reduce the impact of stasis due to prolonged immobilization of the lower extremities and have been shown to have a limited impact. There is an intuitive benefit to combining treatment (i.e. pharmacological with mechanical treatment) although the evidence suggests pharmacological measures are the more important of the two for the purpose of prophylaxis.

**Deep venous thrombosis is common in SCI patients not receiving prophylactic treatment.**

*There is level 2 evidence (from two RCTs and one prospective controlled trial; Merli et al. 1988; Agarwal & Mathur 2009; Frisbie & Sasahara 1981) that 5000 IU of low-dose unfractionated heparin is no more effective than placebo in the prophylaxis of venous thrombosis post SCI.*

*There is level 1b evidence (from one RCT; Green et al. 1988) that adjusted (higher) dose unfractionated heparin is more effective in prophylaxis of venous thromboembolism than 5000 IU low-dose unfractionated heparin but has a higher incidence of bleeding complications.*

*There is level 1a evidence (from two RCTs, one prospective controlled trial, one pre-post, and one case series; SCI Thromboprophylaxis Investigators 2003a, 2003b; Green et al. 1990, 1994; Maxwell et al. 2002) that low-molecular-weight heparin, in particular enoxaparin, is more effective in reducing venous thromboembolic events, when compared to the standard subcutaneous heparin prophylaxis. Moreover, the incidence of bleeding complications was less in the LMWH group.*

*There is level 4 evidence (from one case control study; Hebbeler et al. 2004) that 40 mg daily enoxaparin is no more effective than 30 mg twice daily enoxaparin in reducing the incidence of deep venous thrombosis or bleeding complications when used prophylactically.*

*There is level 1b evidence (from one RCT and one case control study; Chiou-Tan et al. 2003; Slavik et al. 2007) that enoxaparin is no more effective than dalteparin in reducing the risk of deep venous thrombosis or bleeding complications although enoxaparin is more expensive.*

*There is level 3 evidence (from one case control study; Marciniak et al. 2012) that enoxaparin is no more effective than tinzaparin in reducing the risk of deep venous thrombosis or bleeding complications.*
There is level 4 evidence (from one pre-post study and one case series; Chung et al. 2011; Winemiller et al. 1999) that sequential pneumatic compression devices or gradient elastic stockings were associated with a reduced risk of venous thromboembolism post SCI.

There is level 1b evidence (from one RCT; Becker et al. 1987) that rotating treatment tables reduce the incidence of venous thrombi in acute SCI patients.

There is level 3 evidence (from one case control study and one case series study; Merli et al. 1992; Maxwell et al. 2002) that a comprehensive prophylactic treatment of external pneumatic compression, gradient pressure stockings and low dose unfractionated heparin reduces venous thrombosis post SCI.

There is level 4 evidence (from one pre-post study; Aito et al. 2000) that a comprehensive prophylactic regimen of pharmacological and physical measures is more effective in preventing venous thrombosis post SCI when instituted earlier rather than later.

There is level 1b evidence (from one RCT; Halim et al. 2014) that a comprehensive prophylactic treatment of gradient pressure stockings and low molecular weight heparin is more effective than pressure stockings alone in reducing venous thrombosis post SCI.

There is level 3 evidence (from two case control studies, two case series studies, and one pre-post study; Roberts et al. 2011; Gorman et al. 2009; Kinny et al. 1996; Wilson et al. 1994; Jarrell et al. 1983) that inferior vena cava filters significantly reduce the risk of pulmonary emboli in high-risk SCI patients.

There is level 4 (from one case series study; Tomaio et al. 1998) evidence that subcutaneous enoxaparin is a safe, cost-effective and less labour-intensive compared to intravenous heparin for acute DVTs post SCI.
References


