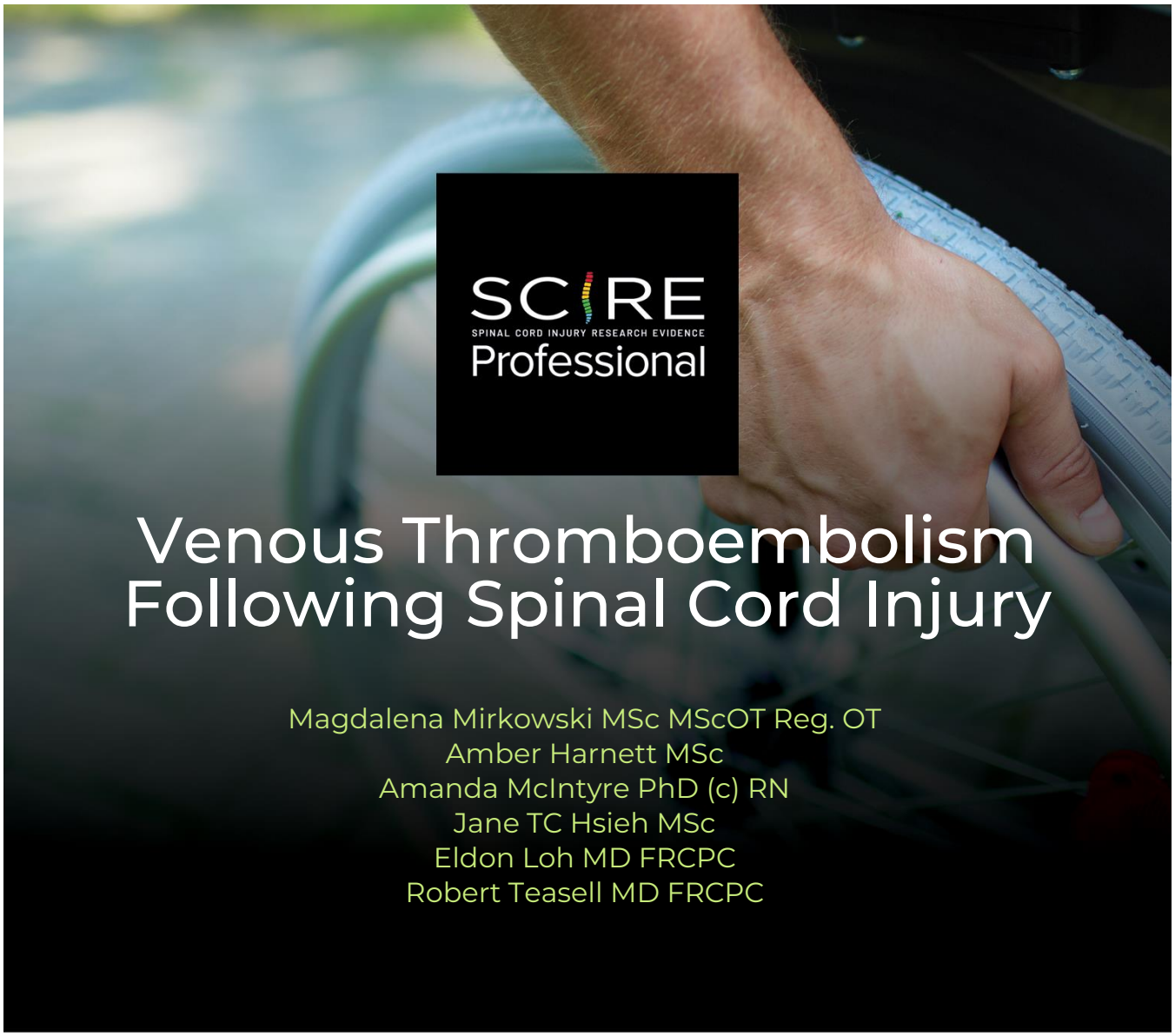

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Venous Thromboembolism Following Spinal Cord Injury

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Key Points

Deep venous thrombosis is common among individuals with SCI who are receiving or not receiving prophylaxis.

Low-dose unfractionated heparin may effectively prevent the risk of developing venous thromboembolic events during the acute phase post SCI if provided early after injury.

The use of Enoxaparin and Dalteparin (low molecular weight heparin), alone, are effective in reducing the risk of venous thromboembolism during the acute SCI and their effects are comparable.

Logiparin may be more effective than low-dose unfractionated heparin as venous thromboembolism prophylaxis during the acute phase post SCI.

Enoxaparin may be more effective than low dose unfractionated heparin in reducing pulmonary embolism and equally effective in reducing deep vein thrombosis in acute SCI.

Dalteparin appears to be as effective as low-dose unfractionated heparin in reducing risk of venous thromboembolism during acute SCI.

Sequential compression and gradient elastic stockings may reduce the incidence of venous thromboembolism during the acute phase post SCI.

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

Rapid intermittent pulsatile compression devices may stimulate venous blood flow more effectively than sequential compression devices during the chronic phase post SCI.

Inferior vena cava filters reduce the risk of pulmonary embolism in acute SCI.

A combination of low-dose unfractionated heparin with intermittent pneumatic compression seems equally as effective as low-molecular-weight heparin alone at reducing this risk.

There is conflicting evidence regarding the effectiveness of the combination of low-molecular-weight heparin with physical measures at reducing the risk of venous thromboembolism compared to physical measures alone during the acute phase post SCI.

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1 Executive Summary

2 Introduction

Deep vein thrombosis (DVT) is defined as a blood clot, or thrombus, which forms within the deep veins of the body causing an interruption in blood flow. The coagulation cascade is the process responsible for thrombus formation, involving a complex set of reactions by which fibrinogen, a soluble plasma protein, is converted into insoluble fibrin (S.-B. Chung, Lee, Kim, & Eoh, 2011; Freedman & Loscalzo, 2012).

DVT is considered to be a major acute complication that occurs after a spinal cord injury (SCI). Importantly, managing this condition in terms of prevention is crucial as it may lead to fatal pulmonary embolism (PE). A PE occurs when a portion of the thrombus travels through the bloodstream to the lung, blocking blood flow; together DVT and PE are collectively considered venous thromboembolism (VTE). Individuals with SCI are at an increased risk of having a thromboembolic event occur during the acute phase following injury (Aito, Pieri, D'Andrea, Marcelli, & Cominelli, 2002; Chen & Wang, 2013; S.-B. Chung et al. 2011; Lo, Esquenazi, Han, & Lee, 2013; G. Merli, Crabbe, Paluzzi, & Fritz, 1993).

The etiology for DVT after SCI is related to immobilization, secondary to stabilization or functional impairment following injury, which contributes to venous stasis. This insufficiency, together with endothelial damage and hypercoagulability, are the three main etiological factors that simultaneously lead to the development of venous thrombosis and are known as the Virchow Triad (Aito et al. 2002; Anaya & Nathens, 2005; G. Merli et al. 1993; Tai, Buddhdev, Baskaradas, Sivarasan, & Tai, 2013). A recent study reported the effect of Vitamin D supplementation on DVT incidence among individuals with SCI (Ehsanian et al. 2019). In a large (n=282) cohort study, Ehsanian et al. (2019) found that, compared to individuals receiving Vitamin D supplementation, those who did not receive supplementation had a significantly greater incidence of DVTs (24% versus 2%, $p<0.001$) suggesting that Vitamin D may be an important mediator of DVTs. Alternatively, it may act as a marker of immobility among individuals with SCI which may highlight those at greater risk of DVTs.

Characteristics of individuals with acute SCI that may be important for predicting the occurrence of fatal PE have been identified, which include injury leve l (specifically cervical injury), obesity and absence of spasticity (Green, Twardowski, Wei, & Rademaker, 1994). Additionally, PE is more common in individuals with tetraplegia compared to those with paraplegia, and in complete rather than incomplete injuries (DeVivo, Black, & Stover, 1993).

3 Incidence

Overall, DVT is considered to be a complication occurring at a variable rate in acute SCI, with incidence rates depending on several factors including diagnostic methods used, study population, characteristics (e.g., age, acuity of injury, location of SCI), associated risk factors, and modality of thromboprophylaxis (W.-S. Chung et al. 2014; G. Merli et al. 1993). There are

inconsistencies in the scientific literature regarding the incidence of this complication as most occurrences of DVT are asymptomatic. Thus, the use of various diagnostic imaging screening methods is of utmost importance as clinical criteria alone are insufficient (Meissner, 1998). However, the incidence of DVT varies even with the use of non-clinical methods of detection (Winemiller, Stolp-Smith, Silverstein, & Therneau, 1999). Nevertheless, DVT in acute SCI has been reported as having the highest rate of incidence within the first 3 months following injury (W.-S. Chung et al. 2014), with a variable incidence rate reported in older studies ranging from 49% to 100% during the first 12 weeks (G. Merli et al. 1993); however, most DVT events occur within the first 2 weeks (Chen & Wang, 2013; G. Merli et al. 1993). Table 1 shows the incidence of DVT among individuals with SCI; between 2010 and 2019, reports place the incidence of DVT between 1.6% and 45%; this range is based on studies in which individuals with SCI did or did not use thromboprophylaxis methods.

The formation of venous thrombosis has been reported to occur as early as 72 hours post injury, peaking between day 7 and 10, as detected by impedance plethysmography, venous flow dopplers, and lung scanning. However, this statistic is also based on some studies which did not indicate a specific method of assessment, and as such should be interpreted with caution (G. Merli et al. 1993). Using color duplex sonography, Germing et al. (2010) detected the formation of DVT even sooner, reporting that 38% of individuals in their study developed DVT within the first 36 hours after hospitalization following injury. However, the occurrence of DVT and PE is rare within the first three days after injury (Raslan, Fields, & Bhardwaj, 2010). PE has also been reported to have the highest likelihood of occurrence within the first 3 months following SCI (W.-S. Chung et al. 2014); however, fatal PE has been found to be a rare occurrence after the initial 3-month duration following SCI (Sugimoto et al. 2009). Interestingly, some studies have shown that the incidence of DVT seems to be lower in Eastern (e.g., India and Pakistan) SCI populations compared to those in the West, possibly due to a difference in diet and genetic risk factors (Rathore et al. 2008; Saraf, Rana, & Sharma, 2007). Despite prophylaxis being widely used since the 1980s to prevent and treat occurrences of VTE, it remains a major health complication for acute SCI individuals that results in significant morbidity and mortality (Furlan & Fehlings, 2007).

Table 1. Incidence of DVT Post SCI

Author/Year	Treatment (n size)	% of DVTs	Test
Hon et al. (2019)	(n=189)	16.4%	Duplex scan
Morita et al. (2018)	(n=75)	35.7%	Doppler Ultrasonography
Passias et al. (2018)	(n=488,262)	32-36%	
Eichinger et al. (2018)	Prophylactic anticoagulant therapy (n=185)	4%	D-dimer
Clements et al. (2017)	(n=222)	21%	
Marion et al. (2017)	(n=444)	1.6%	
Mackiewicz et al. (2016)	(n=63)	7.9%	D-dimer and venous duplex scans
Piran et al. (2016)	(n=151)	11%	
Dietch et al. (2015)	(n=8,238)	3.5-4.4%	Ultrasonography

Masuda et al. (2015)	(n=268)	10.4%	Ultrasonography
Halim et al. (2014)	LMWH + compression stockings or LMWH only (n=37)	LMWH only=5.4% LMWH + compression stockings=21.6%	Doppler Venous Ultrasonography
Giorgi Pierfranceschi et al. (2013)	LMWH and compression stockings (n=94)	23%	Compression Ultrasound or lower limb colour Doppler ultrasonography, perfusion lung scintigraphy (Q scan) matched with chest X-ray, or computed tomography pulmonary angiography
Germing et al. (2010)	(n=139)	45%	Serial color duplex sonography
Sugimoto et al. (2009)	(n=45)	21%	Doppler Ultrasonography
Colachis & Clinchot (1993)	Prophylaxis Treatment (n=209)	14%	Contrast venography Ultrasound
Gunduz et al. (1993)	Low-dose Heparin (n=31)	53%	Venography
Kulkarni et al. (1992)	Low-dose unfractionated heparin (n=97)	27%	
Merli et al. (1988)	Untreated (n=17)	47%	I^{125} fibrinogen scan Impedance Plethysmography Venography
Myllynen et al. (1985)	Anticoagulant therapy (n=37)	100%	I^{125} fibrinogen scan Venography
Green et al. (1982)	External pneumatic calf compression (ENCP) or ENCP + aspirin + dipyrid (n=28)	78% untreated 33% treated	Platelet aggregation studies
Rossi et al. (1980)	N/A (n=18)	72%	I^{125} fibrinogen scan

The high risk of DVT in acute individuals with SCI 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). VTE usually begins with a calf DVT (Cogo et al. 1998; Nicolaides, Kakkar, Field, & Renney, 1971; Philbrick & Becker, 1988). Other contributing factors include partial or total limb paralysis and absence of spasticity which is a significant independent risk factor for DVT (Do, Kim, & Sung, 2013). VTE 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, Mourao, França, Da Rosa, & Burattini, 2014)

Approximately 20% of DVTs extend into the proximal veins (Brandstater, Roth, & Siebens, 1992; Kakkar, Howe, Flanc, & Clarke, 1969; Lagerstedt, Fagher, Olsson, Öqvist, & Albrechtsson, 1985); over 80% of symptomatic DVTs involve the popliteal or more proximal

veins. 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. (2011) noted that individuals who developed a PE 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).

Conclusion

Deep venous thrombosis is common among individuals with SCI who are receiving or not receiving prophylactic treatment.

Key Points

Deep venous thrombosis is common among individuals with SCI who are receiving or not receiving prophylaxis.

4 Diagnosis

4.1 Deep Venous Thrombosis Diagnostic Modalities

4.1.1 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 individuals 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.

4.1.2 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.

4.1.3 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, Rudd, Lewis, & Hunt, 2001; Tapson et al. 1999; Zierler, 2004)."*

4.1.4 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, 1993). For example, Masuda et al. (2015) report sensitivity and specificity at 77.3% and 69.2%, respectively, among a sample of 268 individuals with acute traumatic SCI. D-dimer assays have a high negative predictive value, so that when it is negative it is unlikely that the individual 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 individuals admitted with a diagnosis of stroke, SCI (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 VTE. 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 (Eichinger et al. 2018). If levels are high, further investigation is warranted (Wada et al. 2013).

4.1.5 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 individuals at high risk of DVT is uncertain; and 3) surveillance testing with impedance plethysmography is not recommended.*"

4.2 Pulmonary Embolism

4.2.1 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. Individuals 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, hemoptysis, pleuritic chest pain, pleural friction rub, pleural effusion and fever. In most cases individuals often present with a few nonspecific clinical findings and the major clinical complaints of malaise and fever.

4.2.2 Ventilation/Perfusion Scanning

Nuclear ventilation/perfusion scans are often used to diagnose a PE. A normal perfusion scan usually excludes a PE but can be found in a minority of individuals with a PE. Perfusion defects are non-specific; about one third of those with defects 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%. Individuals should be treated if presenting with a positive ventilation/perfusion scan and high clinical suspicion of a PE.

4.2.3 Pulmonary Angiography

Pulmonary angiography is the definitive test for diagnosis of PE (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 PE (Gill & Nahum, 2000; Tapson et al. 1999).

4.2.4 Spiral Computed Tomography Scan

A spiral computed tomograpy scan is a quick, less expensive computed tomography 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 computed tomography is a useful adjunct to the majority of ventilation perfusion scans that have non-diagnostic results that require further testing (Investigators, 1990).

5 DVT Prophylaxis

Currently, modalities of DVT and PE prophylaxis include the use of pharmacological, mechanical and surgical methods. Pharmacological methods include low-dose unfractionated heparin (LDUH) and low-molecular-weight heparin (LMWH), as well as oral anticoagulants such as aspirin and warfarin. Mechanical modalities include intermittent pneumatic compression (IPC)/sequential compression devices (SCD) and graduated compression stockings. Surgical methods refer to the use of inferior vena cava (IVC) filter implantation, specifically used in the prevention of PE for high risk individuals (Chen & Wang, 2013; Tai et al. 2013). Effective prophylaxis can prevent thromboembolic events during both hospitalization and in the months and years after discharge as well. (Spinal Cord Injury Thromboprophylaxis Investigators, 2003b).

5.1 Pharmacological Agents

Pharmacological methods are the most widely used form of thromboprophylaxis (Chen & Wang, 2013). Pharmacological prophylaxis aims to inhibit the formation of the clot itself, or to prevent the progress of the coagulation cascade which ultimately leads to venous thrombi (Tai et al. 2013). Antithrombotic prophylaxis is given to individuals with acute SCI in an effort to lower the coagulability of the blood by maintaining the concentration of factor Xa, a key factor in the coagulation cascade, below the critical level. High levels of factor Xa result in thrombus formation, leading to thromboembolic complications such as excessive bleeding (Kulkarni et al. 1992).

5.1.1 Low-Dose Unfractionated Heparin

Heparin is a naturally occurring anticoagulant that is produced by basophils and mast cells. Two types of heparins are commonly used as anticoagulants to prevent thrombosis: LDUH and LMWH. The mechanism of action of LDUH includes binding to antithrombin III, and together this heparin/antithrombin complex then binds to factor Xa, causing inactivation. LMWH is synthesized from unfractionated heparin (UFH) by depolymerization, and thus has a reduced size and molecular weight (3000-7000 daltons) in comparison to LDUH (3000-30000 daltons). LDUH also binds to and inactivates thrombin (factor II), although this process requires larger heparin molecules (at least 18 saccharide units in length). Therefore, LMWH has a reduced ability to inhibit thrombin due to the smaller molecular structure not being able to simultaneously bind antithrombin and thrombin. However, this reduced binding to plasma proteins contributes to a more predictable dose-dependent response for LMWH. Pharmacokinetically, LMWH has a higher and more efficient bioavailability compared to LDUH, although LMWHs are themselves a heterogeneous class of compounds that differ in weight, anticoagulant activity and pharmacokinetic properties. Various LMWHs exist including Enoxaparin, Dalteparin, Ardeparin, Nadroparin, Parnaparin, Reviparin, and Tinzaparin. A major complication associated with the use of heparin for thromboprophylaxis is the risk of hemorrhaging, although LMWH is associated with a lower incidence of hemorrhaging as a result of reduced binding to platelets and endothelium (Hirsh & Raschke, 2004; Quader, Stump, & Sumpio, 1998). Additionally, spinal epidural hematoma is a rare but devastating complication that has been reported to occur after spinal surgery; this may potentially be associated with pre-operative use of chemical thromboprophylaxis although evidence has shown this to be a rare occurrence. Nevertheless, the benefits of thromboprophylaxis must be weighed against the risk of potential hematoma formation (Al-Dujaili, Majer, Madhoun, Kassis, & Saleh, 2012; Awad, Kebaish, Donigan, Cohen, & Kostuik, 2005; Cunningham, Swamy, & Thomas, 2011).

Table 2. Efficacy of Low-Dose Unfractionated Heparin as Prophylaxis

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
Agarwal & Mathur (2009) India RCT PEDro=4 N=297	**Population:** Mean age=32 yr; Gender: males=87% (study group), males=74% (control group); Level of injury: not specified; Severity of injury: AIS A-E. **Chronicity:** Individuals studied were within an average of 8 days (range: 3-40 days) after injury; 80% and 77% individuals in the study and control groups entered the study within 10 days after injury, respectively. **Intervention:** Individuals were randomly allocated into the treatment group receiving 5000 IU low dose	**Timing of DVT onset:** DVT was detected within 6-10 days after injury in the study group, and within 5-28 days after injury in the control group. **Incidence of DVT:** 1. 1.8% of individuals in the treatment group and 3% of individuals in the control group developed DVT (>0.05). 2. Heparin prophylaxis was found to have no significant correlation with DVT incidence (p<0.05).

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
	unfractionated heparin (LDUH) every 12 hr for 3 mo from time of admission, or the control group (no heparin). Physical therapy measures were advised for both groups. **Outcome Measures:** Incidence of Deep Vein Thrombosis (DVT). **Method of Diagnosis:** Color Doppler studies.	
Green et al. (1988) USA RCT PEDro=7 $N_{Initial}$=75; N_{Final}=58	**Population:** Age=3-81yr; Gender: males=63, females=12; Severity of injury: complete=75. **Chronicity:** Unknown **Intervention:** Individuals 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.	1. Individuals on the adjusted-dose regimen received a mean of 13200±2200 U of heparin per dose and had an activated partial thromboplastin time 1.5 times higher than those on a fixed-dose regimen. 2. Thromboembolism was detected in 9/29 individuals randomized to the fixed-dose regimen and 2/29 on the adjusted-dose regimen. 3. While no individual who received the adjusted-dose and whose activated partial thromboplastin time reached the target level had a thrombosis, bleeding occurred in 7 individuals; no individual on the fixed-dose regimen bled.
Merli et al. (1988) USA RCT PEDro=4 $N_{Initial}$=53; N_{Final}=48	**Population:** Not available. **Chronicity:**<2 weeks post SCI **Intervention:** 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. **Outcome Measures:** Incidence of Deep Venous Thrombosis (DVT).	1. Electric stimulation plus heparin significantly lowered ($p<0.05$) the incidence of DVT. 2. No differences were noted between the heparin and placebo group.
Frisbie & Sasahara (1981) USA Prospective Controlled Trial N=32	**Population:** Mean age=27yr (treatment), 28yr (control); Level of injury: cervical-lumbar; paraplegic=8, tetraplegic=24. **Chronicity:**<1 week post SCI	1. DVT incidence was unexpectedly low in both the control (1/17) and treatment (1/15).

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
	Intervention: Individuals were assigned to receive 5000 IU low dose unfractionated heparin (LDUH) every 12hr until 60 days post SCI or no treatment. **Outcome Measures:** Incidence of Deep Venous Thrombosis (DVT).	
et al. (1999) USA Case Series N=285	**Population:** Mean age=26 yr (VTE), mean age=25 yr (no VTE); Gender: males=88% (VTE), males=72% (no VTE); Level of injury: cervical-lumbar; Severity of injury: Frankel scores A-B. **Chronicity:** All individuals were studied for the initial 6 week duration following injury. **Intervention:** Retrospective review of individuals who were administered antithrombotic prophylaxis (sequential compression devices (SCD)/gradient elastic stockings (GES)) or unfractionated heparin (UFH) for 42 days-6 weeks after injury. **Outcome Measures:** Incidence of DVT/PE. **Method of Diagnosis:** Fibrinogen scans, impedance plethysmography, Doppler studies, venography, and ventilation-perfusion scanning.	**Timing of DVT onset:** DVT/PE was first detected at a median of 14.5 days after injury; 63% of initial DVT/PE events occurred within the first 3 weeks. **Incidence of DVT:** 1. Overall incidence of DVT/PE was 84/428 (19.6%); 59 DVT and 25 PE. 2. A multivariate analysis suggested a reduced risk of thromboembolism in individuals with SCI treated with heparin within the first 14 to 42 days after injury. 3. The effect of heparin may be most effective within the first 14 days after injury.
Gunduz et al. (1993) Turkey Post-Test N=31	**Population:** Mean age=27 yr; Gender: males=27, females=4; Level of injury: cervical-lumbar; Severity of injury: Frankel complete=24, Frankel partial=6. **Chronicity:** Individuals were admitted within an average of 27 days post injury; 12 individuals were admitted within the first 2 weeks (mean=12.25 days ± 2.2 days), 18 individuals were admitted within the first 2 mo (mean=40.98 ± 3.75 days). **Intervention:** All individuals received 5000 IU low dose unfractionated heparin (LDUH) every 12h for 12 weeks from time of admission. **Outcome Measures:** Incidence of deep vein thrombosis (DVT). **Method of Diagnosis:** Venography.	**Timing of DVT onset**: Not indicated. **Incidence of DVT**: 1. Incidence of DVT was 53.3%.

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
Kulkarni et al. (1992) England Case Series N=97	**Population:** Mean age: not specified; Gender: males=80, females=20; Level of injury: cervical-lumbar; Severity of injury: not specified. **Chronicity:** Most individuals studied were admitted<24 hr following injury; 33 individuals were admitted within 2-87 days following injury. **Intervention:** All individuals received 5000 IU low dose unfractionated heparin (LDUH) every 8 hr from time of admission. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Clinical examination.	**Timing of DVT onset**: Not indicated. **Incidence of DVT:** 1. 26 individuals developed thromboembolic complications (17 DVT, 7 PE, 2 DVT + PE). 2. Delayed arrivals (>24 hr post SCI) were more at risk of developing thromboembolic complications.

Table 3. Systematic Reviews and Guidelines on Low Dose Unfractionated Heparin

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
Arnold et al. (2017) USA Review of published articles up to February 2015 N=9	**Method:** A comprehensive literature search was conducted to identify randomized controlled trials (RCT) evaluating the efficacy and safety of antithrombotic strategies. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** MEDLINE; Cochrane Collaboration Library. **Level of evidence:** High quality study designs such as RCTs and one prospective controlled trial, were the only studies included. **Questions/measures/hypothesis:** 1. What is the effectiveness and safety of	Question one: 1. Seven RCTs reported on the efficacy and/or safety of anticoagulant drug interventions. 2. A single RCT reported the efficacy of LMWH versus no prophylaxis. Individuals treated with enoxaparin has a lower rate of DVT (5.4%) than those who received no LMWH prophylaxis (21.6%). 3. Two RCTs assessed the risk of DVT in individuals receiving unfractionated heparin versus no treatment or placebo and found no significant difference between groups. 4. A single RCT compared the efficacy and safety of two different LMWH drugs (enoxaparin or dalteparin). There was no significant difference in the rate of DVT or PE between groups.

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	anticoagulant thromboprophylaxis compared to no prophylaxis, placebo, or another anticoagulant strategy for preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) after acute SCI? 2. What is the comparative effectiveness and safety of mechanical prophylaxis strategies alone or in combination with other prophylactic strategies for preventing DVT and PE after acute SCI? 3. What is the comparative effectiveness and safety of prophylactic inferior vena cava (IVC) filter insertion alone or in combination with other prophylactic strategies for preventing DVT and PE after acute SCI? 4. What is the optimal timing to initiate and/or discontinue anticoagulant, mechanical, and/or prophylactic IVC filter following acute SCI? What is the cost-effectiveness of the treatment options mentioned above?	5. One RCT evaluated the efficacy and safety of fixed, low-dose versus adjusted-dose UFH. DVT and PE were observed in 9/29 (31%) and 2/29 (6.9%). The risk of DVT in the fixed, low-dose group was three times greater than the adjusted-dose group (RD=13.8, 95% CI=-3.6-31.2, RR=3.0, 95% CI=0.66-13.7, p=0.25). 6. Two RCTs evaluated the efficacy and safety of LMWH versus UFH and found no statistically significant difference in the rate of DVT or PE between groups. Question two: 1. One RCT compared the efficacy and safety of mechanical prophylaxis versus mechanical prophylaxis plus antithrombotic drugs. No significant difference in safety or efficacy was observed between groups. 2. Two RCTs compared outcomes between anticoagulant thromboprophylaxis and anticoagulant plus mechanical prophylaxis. Both studies reported significantly higher risk of DVT in the group that received anticoagulant prophylaxis only (50% and 60.3% versus 6.7% and 44.9%). Question three: 1. No RCTs were identified that met inclusion criteria. Question four: 1. One prospective controlled trial examined the timing of initiation of anticoagulant thromoboprophylaxis in individuals with acute SCI. Combined anticoagulant and mechanical prophylaxis initiated within 72 hr of SCI resulted in significantly lower risk of DVT than treatment commenced 72 hr after injury. Question five:

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
		1. No RCTs were identified that met inclusion criteria.
Fehlings et al. (2017) Canada Clinical Practice Guideline	**Method:** A comprehensive literature search was conducted to address key questions relating to thromboprophylaxis in SCI. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** Not reported. **Level of evidence: ...** **Questions/measures/hypothesis:** 1. Should anticoagulant thromboprophylaxis be employed to reduce the risk of thromboembolic events in the acute period after SCI? 2. What anticoagulant thromboprophylaxis should be employed to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 3. Should enoxaparin versus dalteparin be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 4. Should fixed, low-dose, versus adjusted-dose unfractionated heparin (UFH) be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 5. Should low dose unfractionated heparin (LWMH) versus UFH be used to reduce the risk of thromboembolic events	1. Three RCTs compared the risk of DVT in individuals treated with LMWH or UFH to those receiving no prophylaxis or placebo. Individuals treated with enoxaparin have a lower rate of DVT (5.45%) than those who received no anticoagulant prophylaxis (21.6%) (p=0.09). 2. Rates of DVT did not significantly differ between the UFH and the placebo/no prophylaxis group (1.8% and 3% in one trial and 50% and 74% in another). 3. Anticoagulant thromboprophylaxis should be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI. 4. There is little to no difference in the rate of DVT, PE, bleeding and mortality between individuals treated with enoxaparin versus dalteparin. 5. There is low quality evidence that the risk of DVT is three times higher in individuals who received fixed, low-dose UFH compared to adjusted-dose heparin (RD=13.8, 95% CI=-3.6-31.2; RR=3.0, 95% CI=0.66 to 13.7; p=0.25). 6. The rate of bleeding is significantly higher in individuals treated with adjusted-dose heparin (24.1%) than in those receiving low-dose (0%) (RD=24.1, 95% CI=8.6-39.7; p=0.01). 7. Anticoagulant thromboprophylaxis, consisting of either subcutaneous LMWH or fixed, low-dose UFH, should be offered to reduce the risk of thromboembolic events in the acute period after SCI. 8. The authors caution against use of adjusted-dose UFH, due to the potential pf increased bleeding events. 9. One prospective observational study evaluated the risks of DVT and PE in individuals who received prophylaxis initiated within or after 72 hr of injury. Based on low quality evidence, the rate

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	in the acute period after traumatic SCI? 6. Should thromboprophylaxis be initiated within 72 hr (vs after 72 hr) of SCI? Should mechanical or anticoagulant thromboprophylaxis be used in combination or alone?	of DVT was significantly lower in individuals treated early (n=2) compared with late (n=46). There was insufficient evidence to compare the groups. 10. Anticoagulant thromboprophylaxis should be commenced within the first 72 hr after injury, if possible, to minimize the risk of VTE complications during acute hospitalization. 11. Individuals who received a combination of UFH and electronic calf stimulation had a lower risk of DVT than individuals treated with UFH alone (RD=43.3, 95% CI=15.8-70.9; RR=7.5, 95% CI=1.06-53.03, p=0.02). 12. Individuals treated with LMWH alone have a lower risk of PE compared with individuals who receive UFH plus IPC (RD=13.2, 95% CI=0.9-25.4; RR=0.28, 95% CI=0.08-0.98; p=0.06). 13. A higher percentage of individuals experienced a DVT when treated with IPC alone (40%) compared with IPC plus aspirin and dipyridamole (25%); however, this difference was not statistically significant.

Unfractionated heparin has been the standard treatment for VTE post SCI for years. Evidence for its effectiveness, however, is unclear. Using LDUH alone is not recommended as a prophylactic treatment (Dhall et al. 2013) and is associated with high rates of DVTs and PEs in individuals with acute SCI (Kulkarni et al. 1992). Seven studies examined the independent prophylactic effectiveness on the incidence of DVT and PE in acute SCI individuals.

Agarwal and Mathur (2009) conducted a randomized controlled trial (RCT) in which acute SCI individuals who had sustained injury within an average of 8 days were randomly allocated into either the experimental group receiving 5000 IU LDUH every 12 hours for 3 months, or the control group (receiving no intervention). The results showed that 1.8% of participants who received LDUH developed DVT (within 6-10 days after injury), while 3% of participants in the control group developed DVT (within 5-28 days after injury); the two groups were not significantly different in terms of DVT incidence ($p>0.05$). This low incidence rate in the control group can perhaps be attributed to the study being conducted within an Asian population, where it is believed that Eastern populations have lower incidence rates of DVT compared to Western populations (Rathore et al. 2008).

Green et al. (1988) studied 75 individuals with SCI 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 (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 individuals with acute SCI, LDUH has no thromboprophylaxis effect compared with placebo or no treatment.

Merli et al. (1988) evaluated 53 individuals with acute SCI 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 individuals with SCI 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).

A case series by Winemiller et al. (1999) retrospectively reviewed individuals who were administered LDUH for the initial 42 days to 6 weeks after injury (dosage unspecified). VTE events were first detected at a median of 14.5 days after injury. A multivariate analysis suggested that these individuals had a reduced risk of thromboembolism when treated with LDUH within the first 14 to 42 days after injury, suggesting that LDUH may be most effective within the first 14 days after injury in preventing thromboembolic events.

In a post-test study conducted by Gunduz et al. (1993), all SCI individuals also received 5000 IU LDUH every 12 hours, administered for 12 weeks from the time of admission. All participants were admitted within an average of 27 days after injury. The incidence of DVT was 53.3% but the onset timing was not indicated.

In a case series study, Kulkarni et al. (1992) examined SCI individuals who were admitted<24 hours following injury. Participants received 5000 IU LDUH every 8 hours. The researchers noted that 27% of individuals still developed thromboembolic complications, including 17 DVT, 7 PE and 2 DVT + PE events.

According to the most recent clinical practice guidelines (Fehlings et al. 2017)213S, the following conclusions and recommendations have been made:

We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin, be offered to reduce the risk of thromboembolic events in the acute period after SCI. Given the potential for increased bleeding events with the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.
Quality of Evidence: Low
Strength of Recommendation: Weak

Conclusion

There is level 2 evidence (from one RCT; (Agarwal & Mathur, 2009)) that low-dose unfractionated heparin is not effective as prophylaxis for venous thromboembolism in acute SCI individuals; However, there is level 4 evidence (from one case series; (Winemiller et al. 1999) that low-dose unfractionated heparin is effective as prophylaxis for venous thromboembolism if provided early (within 14 days after injury).

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

Key Points

Low-dose unfractionated heparin may effectively prevent the risk of developing venous thromboembolic events during the acute phase post SCI if provided early after injury.

5.1.2 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, Westfall, & Nicholas, 1999). Several types of LMWH are available (Table 5).

Table 4. Generic and Trade-names of Low Molecular Weight Heparin

Generic Name	Trade-name
Dalteparin	Fragmin
Danaparoid	Orgaran
Enoxaparin	Lovenox
Ardeparin	Normiflo
Parnaparin, Reviparin	Clivarine
Tinzaparin	Logiparin, Innohep
Certoporain	Alphaparin, Sandoparin

Danaparoid sodium (Orgaran) is an alternative anticoagulant for individuals 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.

The most commonly studied LMWH for the prophylaxis of VTE post SCI is enoxaparin, which was the first used in the United States. 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, Kirshblum, O'Connor, & Johnston, 1998).

Table 5. Low Molecular Weight Heparin Alone in Prophylaxis of Venous Thromboembolism Post SCI

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
Chiou-Tan et al. (2003) USA RCT PEDro=6 N=95	**Population:** Mean age=37 yr (Enoxaparin group), mean age=35 yr (Dalteparin group); Gender: males=72%, females=28% (Enoxaparin group), males=80%, females=20% (Dalteparin group); Level of injury: not specified; Severity of injury: complete=53, incomplete=42. **Chronicity:** All individuals had sustained acute SCI within 3 mo time; Individuals in the Enoxaparin group were enrolled 1-99 days after injury, and individuals in the Dalteparin group were enrolled 1-84 days after injury. The majority of participants were recruited within 4 weeks of injury, and more than ¾ of individuals were recruited within 6 weeks of injury. **Intervention:** Individuals were randomized to either receive 30 mg Enoxaparin subcutaneously every 12 hr (Enoxaparin group), or 5000 IU Dalteparin subcutaneously once daily (Dalteparin group). **Outcome Measures:** Incidence of deep vein thromobis (DVT) or pulmonary embolism (PE) and bleeding. **Method of Diagnosis:** Duplex ultrasonography.	**Timing of DVT onset:** Not indicated. **Incidence of DVT:** 1. 6% of individuals (Enoxaparin group) and 4% of individuals (Dalteparin group) developed DVT (p=0.51). 2. No individuals developed PE overall. 3. 4% developed bleeding while receiving Dalteparin and 2% while receiving Enoxaparin (p=0.72). 4. Similar rates of DVT were found between Enoxaparin and Dalteparin.
DiGiorgio et al. (2017) USA Observational N=49	**Population:** Mean age=53.5 yr; Gender: males=65.3%, females=34.7%; Level of injury: not reported; Severity of injury: not reported. **Chronicity:**<24 hr post SCI. **Intervention:** A retrospective review of individuals with SCI at the UCSF Brain and Spinal Injury Center to determine if administration of enoxaparin (40 mg/day) low-molecular-weight heparin (LMWH) within 24 hr after injury is safe and effective in preventing the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE).	1. There were three DVTs (6.1%) and two PEs (4.1%), with no hemorrhagic complications. 2. No association was observed between DVT and/or PE and age, ASIA grade, sec, race, or having undergone a neurosurgical procedure.

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
	Outcome Measures: Incidence of DVT and PE.	
Marciniak et al. (2012) USA Case Control N=140	**Population:** Mean age=46.8 yr (Enoxaparin), mean age=48.4 yr (4500 Tinzaparin), mean age=32.9 yr (3500 Tinzaparin); Gender: males=64.7%, females=35.3% (Enoxaparin), males=74.1%, females=25.9% (4500 Tinzaparin), males=71.4%, females=28.6% (3500 Tinzaparin); Level of injury: not specified; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-C, D. **Chronicity:** Individuals studied were within 3 mo of sustaining SCI; individuals were admitted at a median of 15 days after injury. **Intervention:** Individuals received either Enoxaparin (5000 IU), Tinzaparin (4500 IU), or Tinzaparin (3500 IU). The majority of individuals were on some form of pharmacological prophylaxis before admission. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) and bleeding. **Method of Diagnosis:** Clinical examination, venous duplex scans and computed tomography.	**Timing of DVT onset**: Individuals developed VTE symptoms at median of 12 days after admission. **Incidence of DVT:** 1. 14 individuals developed a DVT and 4 developed a PE. 2. Individuals receiving Enoxaparin and 4500 IU Tinzaparin had significantly reduced odds of VTE compared with individuals receiving 3500 IU Tinzaparin (OR=0.12 and OR 0.18, respectively); uncontrolled factors may have affected this result. 3. Bleeding events were low and equivalent in all 3 treatment groups.
Slavik et al. (2007) Canada Case Control N=135	**Population:** Mean age=40.6 yr (Enoxaparin), mean age=45.4 yr (Dalteparin); Gender: males=71.4% (Enoxaparin), males=80.6% (Dalteparin); Level of injury: cervical-thoracic (Enoxaparin), cervical-lumbar (Dalteparin); Severity of injury: American Spinal Injury Association Impairment Scale (AIS A-E) (Enoxaparin), AIS A-C, E (Dalteparin). **Chronicity:** Individuals were studied beginning within 72 hr after injury. Hospital length of stay was a median of 42.8 days (Enoxaparin group) and a median of 48.9 days (Dalteparin group).	**Timing of DVT onset:** Not indicated. **Incidence of DVT:** 1. 1.6% of individuals (Enoxaparin) and 9.7% of individuals (Dalteparin) developed DVT/PE, p=NS. 2. No significant difference between the two groups in major or minor bleeding was found.

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
	Intervention: Individuals received either Enoxaparin (30 mg subcutaneously twice daily, n=63, beginning at a median of 4 days after injury) or Dalteparin (5000 IU subcutaneously once daily, n=72, beginning at a median of 3.2 days after injury). **Outcome Measures:** Incidence of deep vein thrombosis (DVT) pulmonary embolism (PE) and bleeding. **Method of Diagnosis:** Contrast venography, duplex ultrasonography, ventilation-perfusion lung scanning, high-resolution chest tomography, and pulmonary angiography.	
Hebbeler et al. (2004) USA Case Control N=129	**Population:** No demographical information was provided. **Chronicity:** Individuals studied were within 2 mo after sustaining injury. **Intervention:** Individuals received either Enoxaparin 40 mg once daily or Enoxaparin 30 mg twice daily. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Venous duplex scans and spiral computed tomography imaging.	**Timing of DVT onset**: Individuals were screened for clinical symptoms of DVT daily. No information was provided specifying when screening was performed. **Incidence of DVT:** 1. DVT occurred in 2.0% of individuals receiving twice daily Enoxaparin, and in 1.25% of individuals receiving once daily Enoxaparin (not significant). 2. PE only occurred in 2.0% of individuals receiving twice daily Enoxaparin, no individuals in the twice daily Enoxaparin group sustained PE (not significant). 3. No significant differences were found in bleeding complications between the two groups. 4. Efficacy of prophylaxis was deemed equivalent between groups. 5. Individuals who received twice daily Enoxaparin were more likely to have been given Enoxaparin or low dose unfractionated heparin prior to admission ($p<0.001$).

Author Year Country Score Research Design Total Sample Size	Methods	Outcomes
Harris et al. (1996) USA Case Series N=105	**Population:** Mean age=42 yr; Gender: males=58, females=47; Level of injury: not specified; Severity of injury: complete/incomplete, tetraplegia=35, paraplegia=26. **Chronicity:** All individuals were hospitalized 6-104 days (mean=19) after injury. **Intervention:** All individuals received 30 mg of Enoxaparin subcutaneously every 12 hr from the time of admission. **Outcome Measures:** Incidence of deep vein thrombosis (DVT). **Method of Diagnosis:** Clinical examination and venous ultrasonography.	**Timing of DVT onset**: Not indicated. **Incidence of DVT:** 1. No clinical or ultrasound evidence of DVT.

Table 6. Systematic Reviews and Guidelines on Low-Molecular-Weight Heparin

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
Arnold et al. (2017) USA Review of published articles up to February 2015 N=9	**Method:** A comprehensive literature search was conducted to identify randomized controlled trials (RCT) evaluating the efficacy and safety of antithrombotic strategies. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** MEDLINE; Cochrane Collaboration Library. **Level of evidence:** High quality study designs such as RCTs and one prospective controlled trial, were the only studies included. **Questions/measures/hypothesis:** 1. What is the effectiveness and safety of anticoagulant thromboprophylaxis compared to no prophylaxis, placebo, or	Question one: 1. Seven RCTs reported on the efficacy and/or safety of anticoagulant drug interventions. 2. A single RCT reported the efficacy of LMWH versus no prophylaxis. Individuals treated with enoxaparin has a lower rate of DVT (5.4%) than those who received no LMWH prophylaxis (21.6%). 3. Two RCTs assessed the risk of DVT in individuals receiving unfractionated heparin versus no treatment or placebo and found no significant difference between groups. 4. A single RCT compared the efficacy and safety of two different LMWH drugs (enoxaparin or dalteparin). There was no significant difference in the rate of DVT or PE between groups. 5. One RCT evaluated the efficacy and safety of fixed, low-dose versus

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	another anticoagulant strategy for preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) after acute SCI? 2. What is the comparative effectiveness and safety of mechanical prophylaxis strategies alone or in combination with other prophylactic strategies for preventing DVT and PE after acute SCI? 3. What is the comparative effectiveness and safety of prophylactic inferior vena cava (IVC) filter insertion alone or in combination with other prophylactic strategies for preventing DVT and PE after acute SCI? 4. What is the optimal timing to initiate and/or discontinue anticoagulant, mechanical, and/or prophylactic IVC filter following acute SCI? What is the cost-effectiveness of the treatment options mentioned above?	adjusted-dose UFH. DVT and PE were observed in 9/29 (31%) and 2/29 (6.9%). The risk of DVT in the fixed, low-dose group was three times greater than the adjusted-dose group (RD=13.8, 95% CI=-3.6-31.2, RR=3.0, 95% CI=0.66-13.7, p=0.25). 6. Two RCTs evaluated the efficacy and safety of LMWH versus UFH and found no statistically significant difference in the rate of DVT or PE between groups. Question two: 3. One RCT compared the efficacy and safety of mechanical prophylaxis versus mechanical prophylaxis plus antithrombotic drugs. No significant difference in safety or efficacy was observed between groups. 4. Two RCTs compared outcomes between anticoagulant thromboprophylaxis and anticoagulant plus mechanical prophylaxis. Both studies reported significantly higher risk of DVT in the group that received anticoagulant prophylaxis only (50% and 60.3% versus 6.7% and 44.9%). Question three: 1. No RCTs were identified that met inclusion criteria. Question four: 1. One prospective controlled trial examined the timing of initiation of anticoagulant thromboprophylaxis in individuals with acute SCI. Combined anticoagulant and mechanical prophylaxis initiated within 72 hr of SCI resulted in significantly lower risk of DVT than treatment commenced 72 hr after injury. Question five: 1. No RCTs were identified that met inclusion criteria.

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
Fehlings et al. (2017) Canada Clinical Practice Guideline	**Method:** A comprehensive literature search was conducted to address key questions relating to thromboprophylaxis in SCI. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** Not reported. **Level of evidence: …** **Questions/measures/hypothesis:** 1. Should anticoagulant thromboprophylaxis be employed to reduce the risk of thromboembolic events in the acute period after SCI? 2. What anticoagulant thromboprophylaxis should be employed to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 3. Should enoxaparin versus dalteparin be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 4. Should fixed, low-dose, versus adjusted-dose unfractionated heparin (UFH) be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 5. Should low weight molecular heparin (LWMH) versus UFH be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 6. Should thromboprophylaxis be initiated within 72 hr (vs after 72 hr) of SCI?	1. Three RCTs compared the risk of DVT in individuals treated with LMWH or UFH to those receiving no prophylaxis or placebo. Individuals treated with enoxaparin have a lower rate of DVT (5.45%) than those who received no anticoagulant prophylaxis (21.6%) (p=0.09). 2. Rates of DVT did not significantly differ between the UFH and the placebo/no prophylaxis group (1.8% and 3% in one trial and 50% and 74% in another). 3. Anticoagulant thromboprophylaxis should be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI. 4. There is little to no difference in the rate of DVT, PE, bleeding and mortality between individuals treated with enoxaparin versus dalteparin. 5. There is low quality evidence that the risk of DVT is three times higher in individuals who received fixed, low-dose UFH compared to adjusted-dose heparin (RD=13.8, 95% CI=-3.6-31.2; RR=3.0, 95% CI=0.66 to 13.7; p=0.25). 6. The rate of bleeding is significantly higher in individuals treated with adjusted-dose heparin (24.1%) than in those receiving low-dose (0%) (RD=24.1, 95% CI=8.6-39.7; p=0.01). 7. Anticoagulant thromboprophylaxis, consisting of either subcutaneous LMWH or fixed, low-dose UFH, should be offered to reduce the risk of thromboembolic events in the acute period after SCI. 8. The authors caution against use of adjusted-dose UFH, due to the potential pf increased bleeding events. 9. One prospective observational study evaluated the risks of DVT and PE in individuals who received prophylaxis initiated within or after 72 hr of

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	Should mechanical or anticoagulant thromboprophylaxis be used in combination or alone?	injury. Based on low quality evidence, the rate of DVT was significantly lower in individuals treated early (n=2) compared with late (n=46). There was insufficient evidence to compare the groups. 10. Anticoagulant thromboprophylaxis should be commenced within the first 72 hr after injury, if possible, to minimize the risk of VTE complications during acute hospitalization. 11. Individuals who received a combination of UFH and electronic calf stimulation had a lower risk of DVT than individuals treated with UFH alone (RD=43.3, 95% CI=15.8-70.9; RR=7.5, 95% CI=1.06-53.03, p=0.02). 12. Individuals treated with LMWH alone have a lower risk of PE compared with individuals who receive UFH plus IPC (RD=13.2, 95% CI=0.9-25.4; RR=0.28, 95% CI=0.08-0.98; p=0.06). 13. A higher percentage of individuals experienced a DVT when treated with IPC alone (40%) compared with IPC plus aspirin and dipyridamole (25%); however, this difference was not statistically significant.
Christie et al. (2011) Canada Date included in the review not stated N=5 AMSTAR=5	**Method:** Comprehensive literature search of English RCT, Cohort studies, case series, and review articles of relating to prophylaxis low molecular unfractionated heparin (LMWH) for deep venous thrombosis (DVT) in traumatic SCI in adult age group (+18yr). **Databases:** PubMed. **Questions/measures/hypothesis:** Examine the ideal time for initiation of deep venous thrombosis (DVT) prophylaxis with LMWH after SCI or after surgery.	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.

Discussion

Several studies have examined the independent thromboprophylactic effectiveness of LMWH on the incidence of DVT and PE in acute SCI. Various forms of LMWH have been investigated including Enoxaparin, Dalteparin and Tinzaparin.

Two studies compared the effectiveness of Enoxaparin versus Dalteparin in preventing VTEs. Chiou-Tan et al. (2003) conducted an RCT in which acute SCI individuals (<3 months post SCI) were randomized to receive either 30 mg Enoxaparin every 12 hours or 5000 IU Dalteparin once daily. The authors found that 6% of individuals receiving Enoxaparin and 4% of individuals receiving Dalteparin developed DVTs ($p=0.51$); however, no individuals developed PE. A case control study conducted by Slavik et al. (2007) also compared the efficacy of Enoxaparin and Dalteparin. Individuals were studied within 72 hours post SCI and received either 30 mg Enoxaparin twice daily or 5000 IU Dalteparin once daily. No significant difference regarding the incidence rate of DVT or PE was found between these groups, indicating equivalent prophylactic efficacy.

A case control study by Marciniak et al. (2012) compared the effect of Enoxaparin versus Tinzaparin on incidence of VTE events. All individuals were within 3 months of sustaining a SCI and were admitted to inpatient rehabilitation at a median of 15 days after injury. Individuals received either 5000 IU Enoxaparin, 4500 IU Tinzaparin (high-dose), or 3500 IU Tinzaparin (low-dose). The results revealed that individuals who received either Enoxaparin or the high dose of Tinzaparin had a significantly reduced risk of developing VTE complications compared with individuals receiving 3500 IU Tinzaparin. The authors indicated that uncontrolled factors may have affected this result, although these were not specified. The findings suggested an association between developing VTE and having had no prophylaxis prior to admission to inpatient rehabilitation, despite using prophylaxis after admission. Prophylaxis prior to admission may be protective of VTE, with no particular type of prophylaxis being significantly different in terms of protective efficacy.

A case control study by Hebbeler et al. (2004) compared two dosages of Enoxaparin. Individuals were within 2 months of sustaining SCI and received either 40 mg once daily or 30 mg twice daily of Enoxaparin. There were no significant differences found in DVT or PE incidence between groups and therefore the prophylactic efficacy of Enoxaparin was equivalent between the two dosages studied.

In a case series by Harris et al. (1996), individuals who were hospitalized for an average of 19 days following injury received 30 mg of Enoxaparin every 12 hours from admission. No individuals developed DVT in this study population. In a recent observational study, DiGiorgi et al. (2017) found that just 6.1% of their sample experienced a DVT and 4.1% a PE after 40 mg daily enoxaparin administration.

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.

According to the most recent clinical practice guidelines (Fehlings et al. 2017)213S, the following conclusions and recommendations have been made:

We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin, be offered to reduce the risk of thromboembolic events in the acute period after SCI. Given the potential for increased bleeding events with the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.
Quality of Evidence: Low
Strength of Recommendation: Weak

Conclusion

There is level 1b evidence (from one RCT and one case control; (Chiou-Tan et al. 2003; Slavik et al. 2007) that 30 mg twice daily Enoxaparin and 5000 IU daily Dalteparin are equally effective as prophylaxis for venous thromboembolism in acute SCI individuals.

There is level 4 evidence (from one case control; (Hebbeler et al. 2004) that twice daily 30 mg Enoxaparin is equally as effective as 40 mg daily Enoxaparin as prophylaxis for venous thromboembolism in acute SCI individuals.

There is level 4 evidence (from two observational studies; (DiGiorgio et al. 2017; Harris et al. 1996) that 40 mg daily enoxaparin is effective in reducing risk of thromboembolism.

Key Points

The use of Enoxaparin and Dalteparin (low molecular weight heparin), alone, are effective in reducing the risk of venous thromboembolism during the acute SCI and their effects are comparable.

5.1.3 Low-Molecular-Weight Heparin VS. Low-Dose Unfractionated Heparin

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

Table 7. Low-Molecular-Weight Heparin versus Low-Dose Unfractionated Heparin as Prophylaxis

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
Spinal Cord Injury Thromboprophylaxis Investigators (2003a) USA RCT PEDro=9 N=107	**Population:** Mean age=40.6 yr (unfractionated heparin (UFH)-intermittent pneumatic compression (IPC) group), mean age=38.5 yr (Enoxaparin group); Gender: males=79.6% (UFH-IPC group), males=89.7% (Enoxaparin group); Level of injury: not specified; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-D. **Chronicity**: All individuals were studied beginning within 72 hr of sustaining injury and monitored for approximately 2 weeks during acute treatment (mean=13.4 days for UFH-IPC group, mean=14 days for Enoxaparin group). **Intervention:** Individuals were assigned to receive either low-dose UFH (5000 IU subcutaneously every 8 hr) plus IPC (used at least 22hr/day), or only Enoxaparin (30 mg subcutaneously every 12 hr). **Outcome Measures:** Incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), and major bleeding. **Method of Diagnosis:** Doppler ultrasonography, venography, ventilation-perfusion lung scanning, spiral computed tomographic scanning, and pulmonary angiography.	**Timing of DVT onset**: DVT/PE screening/data collection was performed at the end of the 2-week acute treatment phase or within 2 days of the last dose of acute-phase medication. **Incidence of DVT:** 1. Incidence of DVT was 44.9% for UFH-IPC group versus 60.3% for Enoxaparin group; nonsignificant difference (p=0.11). 2. Incidence of PE was 18.4% for UFH-IPC group, significantly higher than 5.2% of individuals in the Enoxaparin group (p=0.03). 3. Among all randomized individuals, the incidence of major bleeding was 5.3% for low dose unfractionated heparin IPC group versus 2.6% for Enoxaparin group (p=0.14).
Green et al. (1990) USA RCT PEDro=8 $N_{Initial}$=41; N_{Final}=32	**Population:** Mean age=31 yr (LDUH group), mean age=28 yr (LMWH group); Gender: males=4, females=17 (LDUH group), males=3, females=17 (LMWH group); Level of injury: cervical-lumbar; Severity of injury: not specified.	**Timing of DVT onset**: DVT events occurred on days 4, 7, and 32 after admission; PE events occurred on days 21 and 38 after admission. **Incidence of DVT:**

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
	Chronicity: All individuals were studied beginning within 72 hr of sustaining injury and monitored for 8 weeks. **Intervention:** Individuals were randomly assigned to receive either low dose unfractionated heparin (LDUH) (5000 IU) subcutaneously every 8 hr or low molecular unfractionated heparin (LMWH) (Logiparin, 3500 anti-Xa units) subcutaneously once daily. **Outcome Measures:** Incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), and major bleeding. **Method of Diagnosis:** Impedance plethysmography, Doppler flow measurements and duplex ultrasonography.	1. 33% of the LDUH group had thrombosis or hemorrhage; 24% (5/21) of individuals in this group had DVT/PE. 2. No individuals treated with LMWH had a documented thrombotic event. 3. The difference between the two groups in terms of frequency of developing thrombosis was significant (p=0.02).
Arnold et al. (2010) USA Case Control N=476	**Population:** Acute SCI individuals were a subset of the study population (n=24); no further information was provided. **Chronicity:** Individuals studied were admitted after>72 hr post injury. **Intervention:** Retrospective review of individuals who received either 5000 U low dose unfractionated heparin (LDUH) three times a day or low molecular unfractionated heparin (LMWH) (Enoxaparin, 30 mg twice daily or 40 mg once daily). **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Duplex ultrasonography.	**Timing of DVT onset**: Not indicated. **Incidence of DVT:** 1. 15.4% of the LDUH and 36.4% of the LMWH groups developed DVT (NS, p=0.357).
Worley et al. (2008) Canada Case Control N=90	**Population:** Mean age=46yr (LDUH group), mean age=38 yr (LMWH group); Gender: males=40, females=7 (LDUH group), males=39, females=4 (LMWH group); Level of injury: cervical-sacral; Severity of injury: tetraplegia=35, paraplegia=12, American Spinal Injury Association Impairment Scale (AIS) A-D. **Chronicity**: Individuals studied were under acute care following acute SCI. No other information was provided.	**Timing of DVT onset**: Not indicated. **Incidence of DVT:** 1. 7.8% of all individuals developed DVT/PE: 3 in LDUH group, and 4 in LMWH group. 2. No significant difference was found in terms of incidence of DVT and type of prophylaxis received (p=0.7054).

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
	Intervention: Individuals reviewed received either 5000 U low molecular unfractionated heparin (LMWH) (Dalteparin) subcutaneously daily or 5000 U low dose unfractionated heparin (LDUH) subcutaneously twice daily. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Compression ultrasonography, ventilation-perfusion lung scanning, computed tomography, and pulmonary angiography.	3. No association was found between type of prophylaxis used and localization of DVT.
Spinal Cord Injury Thromboprophylaxis Investigators (2003b) USA Prospective Controlled Trial N=119	**Population:** Mean age=34 yr (unfractionated heparin (UFH) group), mean age=30.5 yr (Enoxaparin group); Gender: males=78.3% (UFH group), males=89.8% (Enoxaparin group); Level of injury: not specified; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-D. **Chronicity:** All individuals were studied from 2-8 weeks following injury (in continuation of study 2003a, above). **Intervention:** Continuation of study 2003a (above): Individuals previously receiving unfractionated heparin (UFH) continued on this regimen (5000 IU subcutaneously every 8 hr), but intermittent pneumatic compression (IPC) was discontinued. Those previously receiving Enoxaparin continued this regimen, but at a dose of 40mg once daily (instead of 30 mg twice daily). **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Doppler ultrasonography, venography, ventilation-perfusion lung scanning, spiral computed tomographic scanning, and pulmonary angiography.	**Timing of DVT onset**: DVT/PE screening/data collection was performed at the end of the 6-week rehabilitation treatment phase (8 weeks following injury). **Incidence of DVT:** 1. Incidence of DVT was 18.3% in the UFH group versus 6.8% in the Enoxaparin group; (p=0.067). 2. Incidence of PE was 3.3% in the UFH group versus 1.7% of individuals in the Enoxaparin group (p=0.576).
et al. (2002) UK Case Control N=173	**Population:** Age range=10-60 yr (27 individuals were over 60); Gender: males=129, females=44; Level of injury:	**Timing of DVT onset**: Peak incidences of VTE occurred at 20-30 and 90-100 days

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
	cervical-lumbar; Severity of injury: not specified. **Chronicity**: Individuals in the heparin group commenced treatment "soon after admission," and individuals in the Enoxaparin group received treatment on the day of admission. Individuals were studied beginning within an average of 12 days following injury (range 0-80). Average period of anticoagulation was 57 days for individuals in the heparin group and 52 days for individuals in the Enoxaparin group. **Intervention:** Individuals received either a combination of heparin 5000 IU twice daily followed by warfarin, or only Enoxaparin 20 mg (n=40) or 40 mg (n=32). **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE) and other complications. **Method of Diagnosis:** Doppler ultrasonography and ventilation-perfusion scanning.	following injury for both groups studied. **Incidence of DVT:** 1. 13% of individuals in the heparin group and 18% of individuals in the Enoxaparin group developed VTE episodes, respectively. 2. 25% of individuals receiving 20 mg Enoxaparin and 9.4% of individuals receiving 40 mg Enoxaparin developed DVT/PE, respectively. 3. 6 of the 13 thrombotic events in the Enoxaparin group occurred after the individuals had been mobilized and anticoagulation stopped.
Green et al. (1994) USA Pre-post N=48	**Population:** No demographical information was provided. **Chronicity:** Individuals were studied beginning within 72 hr post injury and monitored for 8 weeks. **Intervention:** All individuals received low molecular unfractionated heparin (LMWH) (Logiparin) at a dose of 3500 anti-Xa U subcutaneously once daily, beginning within 72 hr of injury for 8 weeks. **Outcome Measures**: Incidence of deep vein thrombosis (DVT), pulmonary embolism (PE), and bleeding in these 48 individuals combined with 20 individuals receiving LMWH in the study by Green et al. 1990 (above) were compared to previously studied individuals treated with standard heparin. **Method of Diagnosis:** Impedance plethysmography Doppler flow measurements and duplex ultrasonography.	**Timing of DVT onset**: DVT screening was done at the conclusion of the 8 week timeframe post injury. **Incidence of DVT:** 1. A trend toward less thrombotic events was reported for LMWH (p=0.15). 2. LMWH and standard heparin were significantly different in terms of bleeding, favouring LMWH (p=0.04). 3. LMWH compares favourably with low dose unfractionated heparin as VTE prophylaxis.

Table 8. Systematic Reviews and Guidelines comparing Low-Molecular-Weight Heparin to Low-Dose Unfractionated Heparin

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
Arnold et al. (2017) USA Review of published articles up to February 2015 N=9	**Method:** A comprehensive literature search was conducted to identify randomized controlled trials (RCT) evaluating the efficacy and safety of antithrombotic strategies. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** MEDLINE; Cochrane Collaboration Library. **Level of evidence:** High quality study designs such as RCTs and one prospective controlled trial, were the only studies included. **Questions/measures/ hypothesis:** 1. What is the effectiveness and safety of anticoagulant thromboprophylaxis compared to no prophylaxis, placebo, or another anticoagulant strategy for preventing deep vein thrombosis (DVT) and pulmonary embolism (PE) after acute SCI? 2. What is the comparative effectiveness and safety of mechanical prophylaxis strategies alone or in combination with other prophylactic strategies for preventing DVT and PE after acute SCI? 3. What is the comparative effectiveness and safety of prophylactic inferior vena cava (IVC) filter insertion alone or in combination with other prophylactic	**Question one:** 1. Seven RCTs reported on the efficacy and/or safety of anticoagulant drug interventions. 2. A single RCT reported the efficacy of LMWH versus no prophylaxis. Individuals treated with enoxaparin has a lower rate of DVT (5.4%) than those who received no LMWH prophylaxis (21.6%). 3. Two RCTs assessed the risk of DVT in individuals receiving unfractionated heparin versus no treatment or placebo and found no significant difference between groups. 4. A single RCT compared the efficacy and safety of two different LMWH drugs (enoxaparin or dalteparin). There was no significant difference in the rate of DVT or PE between groups. 5. One RCT evaluated the efficacy and safety of fixed, low-dose versus adjusted-dose UFH. DVT and PE were observed in 9/29 (31%) and 2/29 (6.9%). The risk of DVT in the fixed, low-dose group was three times greater than the adjusted-dose group (RD=13.8, 95% CI=-3.6-31.2, RR=3.0, 95% CI=0.66-13.7, p=0.25). 6. Two RCTs evaluated the efficacy and safety of LMWH versus UFH and found no statistically significant difference in the rate of DVT or PE between groups. **Question two:** 7. One RCT compared the efficacy and safety of mechanical prophylaxis versus mechanical prophylaxis plus antithrombotic drugs. No significant difference in safety or efficacy was observed between groups. 8. Two RCTs compared outcomes between anticoagulant thromboprophylaxis and anticoagulant plus mechanical prophylaxis. Both studies reported significantly higher

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	strategies for preventing DVT and PE after acute SCI? 4. What is the optimal timing to initiate and/or discontinue anticoagulant, mechanical, and/or prophylactic IVC filter following acute SCI? 5. What is the cost-effectiveness of the treatment options mentioned above?	risk of DVT in the group that received anticoagulant prophylaxis only (50% and 60.3% versus 6.7% and 44.9%). **Question three:** 9. No RCTs were identified that met inclusion criteria. **Question four:** 10. One prospective controlled trial examined the timing of initiation of anticoagulant thromoboprophylaxis in individuals with acute SCI. Combined anticoagulant and mechanical prophylaxis initiated within 72 hr of SCI resulted in significantly lower risk of DVT than treatment commenced 72 hr after injury. **Question five:** 11. No RCTs were identified that met inclusion criteria.
Fehlings et al. (2017) Canada Clinical Practice Guideline	**Method:** A comprehensive literature search was conducted to address key questions relating to thromboprophylaxis in SCI. The strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. **Databases:** Not reported. **Level of evidence:** Weak, Moderate, Strong **Questions/measures/ hypothesis:** 1. Should anticoagulant thromboprophylaxis be employed to reduce the risk of thromboembolic events in the acute period after SCI? 2. What anticoagulant thromboprophylaxis should be employed to reduce the risk of thromboembolic events in the acute period after traumatic SCI?	1. Three RCTs compared the risk of DVT in individuals treated with LMWH or UFH to those receiving no prophylaxis or placebo. Individuals treated with enoxaparin have a lower rate of DVT (5.45%) than those who received no anticoagulant prophylaxis (21.6%) (p=0.09). 2. Rates of DVT did not significantly differ between the UFH and the placebo/no prophylaxis group (1.8% and 3% in one trial and 50% and 74% in another). 3. Anticoagulant thromboprophylaxis should be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI. 4. There is little to no difference in the rate of DVT, PE, bleeding and mortality between individuals treated with enoxaparin versus dalteparin. 5. There is low quality evidence that the risk of DVT is three times higher in individuals who received fixed, low-dose UFH compared to adjusted-dose heparin (RD=13.8, 95% CI=-3.6-31.2; RR=3.0, 95% CI=0.66 to 13.7; p=0.25). 6. The rate of bleeding is significantly higher in individuals treated with

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
	3. Should enoxaparin versus dalteparin be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 4. Should fixed, low-dose, versus adjusted-dose unfractionated heparin (UFH) be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 5. Should low molecular weight heparin (LWMH) versus UFH be used to reduce the risk of thromboembolic events in the acute period after traumatic SCI? 6. Should thromboprophylaxis be initiated within 72 hr (vs after 72 hr) of SCI? 7. Should mechanical or anticoagulant thromboprophylaxis be used in combination or alone?	adjusted-dose heparin (24.1%) than in those receiving low-dose (0%) (RD=24.1, 95% CI=8.6-39.7; p=0.01). 7. Anticoagulant thromboprophylaxis, consisting of either subcutaneous LMWH or fixed, low-dose UFH, should be offered to reduce the risk of thromboembolic events in the acute period after SCI. 8. The authors caution against use of adjusted-dose UFH, due to the potential pf increased bleeding events. 9. One prospective observational study evaluated the risks of DVT and PE in individuals who received prophylaxis initiated within or after 72 hr of injury. Based on low quality evidence, the rate of DVT was significantly lower in individuals treated early (n=2) compared with late (n=46). There was insufficient evidence to compare the groups. 10. Anticoagulant thromboprophylaxis should be commenced within the first 72 hr after injury, if possible, to minimize the risk of VTE complications during acute hospitalization. 11. Individuals who received a combination of UFH and electronic calf stimulation had a lower risk of DVT than individuals treated with UFH alone (RD=43.3, 95% CI=15.8-70.9; RR=7.5, 95% CI=1.06-53.03, p=0.02). 12. Individuals treated with LMWH alone have a lower risk of PE compared with individuals who receive UFH plus IPC (RD=13.2, 95% CI=0.9-25.4; RR=0.28, 95% CI=0.08-0.98; p=0.06). 13. A higher percentage of individuals experienced a DVT when treated with IPC alone (40%) compared with IPC plus aspirin and dipyridamole (25%); however, this difference was not statistically significant.
Chen & Wang (2013) China	**Method:** Comprehensive literature search of randomized controlled trials (RCT), quasi-	1. Two RCTs and two case-control studies compared LDUH with a placebo or untreated condition but no significant

Author Year Country Research Design Total Sample Size AMSTAR Score	Methods	Outcome
Review of published articles up to February 2013 N=18 AMSTAR=9	RCTs, cohort studies, case control studies, and cross-sectional studies of individuals with acute SCI 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 VTE. 2. To compare the effectiveness of LDUH with low-molecular-weight heparin (LMWH) in preventing VTE and major bleeding. 3. To compare the effectiveness of different types of LMWH in preventing VTE and major bleeding.	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.

Discussion

Several studies have examined the thromboprophylactic effectiveness of LMWH compared to that of LDUH on the incidence of DVT and PE in the acute phase (<3 months) of SCI. Two studies evaluated the efficacy of Logiparin compared to LDUH. One RCT by Green et al. (1990) included individuals who were within 72 hours of sustaining SCI, and who were randomly assigned to receive 5000 IU LDUH every 8 hours or 3500 anti-Xa U Logiparin once daily. Significantly more individuals receiving LDUH (24%) developed DVT/PE compared to

individuals receiving LMWH (0%, p=0.02). Green et al. (1994) studied 48 individuals who were given 3500 anti-Xa U Logiparin once daily for 8 weeks, beginning within 72 hours of injury. These individuals, combined with 20 individuals receiving the same regimen in the previously mentioned study (1990), were compared to individuals receiving LDUH (also from the previously mentioned study by Green et al. (1990)). Although not significant, a trend was reported in terms of fewer thrombotic events occurring for LMWH, which compared favourably to LDUH for VTE prophylaxis.

Several studies evaluated the efficacy of Enoxaparin compared to LDUH. In a case control study, Arnold et al. (2010) retrospectively reviewed individuals who were admitted greater than 72 hours post SCI, and who received either 5000 U LDUH three times a day or Enoxaparin (30 mg twice daily or 40 mg once daily). A significant difference between groups in incidence of DVT was not observed (p=0.357). Thumbikat et al. (2002) also conducted a case control study in which individuals were studied, on average, 12 days post injury. Participants received either 5000 IU LDUH twice daily, or 20 or 40 mg Enoxaparin. The authors reported that 13% of individuals receiving LDUH and 18% of individuals receiving Enoxaparin developed VTE, with peak incidences occurring at 20 to 30 days and 90 to 100 days following injury for both groups overall; however, no statistical analyses were reported.

In an RCT by the Spinal Cord Injury Thromboprophylaxis Investigators (2003a), individuals were randomly assigned to receive either 5000 IU LDUH every 8 hours along with IPC, or 40 mg of Enoxaparin every 12 hours without IPC. All individuals studied had sustained a SCI within 72 hours, were monitored for approximately two weeks and were screened for DVT/PE. In individuals receiving LDUH, the incidence of DVT was 44.9%, which was not significantly different from 60.3% of individuals receiving Enoxaparin (p=0.11). The incidence of PE was significantly higher (18.4%) in individuals receiving LDUH compared to Enoxaparin (5.2%, p=0.03). Further to the previous study, the Spinal Cord Injury Thromboprophylaxis Investigators (2003b) investigated the effect of 6 more weeks of pharmacological prophylaxis following the initial 2-week protocol. Individuals previously receiving 5000 IU LDUH every 8 hours continued to do so, but without concurrent IPC. Individuals previously receiving Enoxaparin continued this regimen, but at a dose of 40 mg once daily. Screening for DVT and PE was performed at the conclusion of the additional 6-week protocol. In individuals receiving LDUH, the incidence of DVT was 18.3% which was not significantly different from 6.8% of individuals receiving Enoxaparin (p=0.067). The incidence of PE was also not significantly different between groups (3.3% and 1.7% of individuals receiving LDUH and Enoxaparin, respectively, p=0.576).

Finally, a case control by Worley et al. (2008) evaluated the efficacy of Dalteparin compared to LDUH. Individuals in acute care (time post injury otherwise not specified) were retrospectively reviewed; individuals received either 5000 U LDUH twice daily or 5000 U Dalteparin daily. No significant difference in DVT incidence was found between the groups (p=0.7054).

A systematic review by Chen and Wang (2013) examining 18 studies with 2578 individuals 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 Chen and Wang (2013), there is still strong evidence based on five studies that LMWH is more effective than LDUH.

According to the most recent clinical practice guidelines (Fehlings et al. 2017)213S, the following conclusions and recommendations have been made:

We suggest that anticoagulant thromboprophylaxis be offered routinely to reduce the risk of thromboembolic events in the acute period after SCI.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest that anticoagulant thromboprophylaxis, consisting of either subcutaneous low-molecular-weight heparin or fixed, low-dose unfractionated heparin, be offered to reduce the risk of thromboembolic events in the acute period after SCI. Given the potential for increased bleeding events with the use of adjusted-dose unfractionated heparin, we suggest against this treatment option.
Quality of Evidence: Low
Strength of Recommendation: Weak

We suggest commencing anticoagulant thromboprophylaxis within the first 72 hours after injury, if possible, in order to minimize the risk of venous thromboembolic complications during the period of acute hospitalization.
Quality of Evidence: Low
Strength of Recommendation: Weak

Conclusion

There is level 1b evidence (from one RCT; (Green et al. 1990) that Logiparin (low molecular weight heparin) is more effective than low-dose unfractionated heparin as prophylaxis for venous thromboembolism in acute SCI individuals.

There is level 1b evidence (from one RCT; (Spinal Cord Injury Thromboprophylaxis Investigators, 2003a) that Enoxaparin (low molecular weight heparin) is more effective than low-dose unfractionated heparin as prophylaxis for pulmonary emboli in acute SCI.

There is level 1b evidence (from one RCT (Spinal Cord Injury Thromboprophylaxis Investigators, 2003a), one prospective controlled trial(Spinal Cord Injury Thromboprophylaxis Investigators, 2003b), and two case controls (J. D. Arnold et al. 2010; Thumbikat et al. 2002)) that Enoxaparin (low molecular weight heparin) is equally as effective as low-dose unfractionated heparin as prophylaxis for deep venous thrombosis in acute SCI.

There is level 3 evidence (from one case control; (Worley et al. 2008) that Dalteparin (low molecular weight heparin) is equally as effective as low-dose unfractionated heparin as prophylaxis for venous thromboembolism in acute SCI individuals.

Key Points

Logiparin may be more effective than low-dose unfractionated heparin as venous thromboembolism prophylaxis during the acute phase post SCI.

Enoxaparin may be more effective than low dose unfractionated heparin in reducing pulmonary embolism and equally effective in reducing deep vein thrombosis in acute SCI.

5.2 Mechanical Methods

5.2.1 External Methods

Although pharmacological measures have been generally the preferred treatment for VTE prophylaxis post SCI, mechanical means of limiting venous stasis can also serve to reduce the incidence of DVT post SCI. Mechanical methods of prophylaxis for venous thrombosis include the use of compression devices. These are generally considered safer forms of prophylaxis than pharmacological methods since there is no risk for bleeding. Compression devices include graduated compression stockings and gradient elastic stockings, as well as IPC/SCD. Compression stockings exert a graded pressure along the lower extremities and are postulated to increase blood flow velocity as well as volume, thereby preventing thrombus formation. IPC and SCD involve an air pump that intermittently and/or sequentially inflates a sleeve fitted around the extremity, and likely involves a mechanism of action that increases femoral vein blood flow. 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 individuals with severe arterial insufficiency.

Table 9. Evaluating Physical Methods for the Prevention of DVT

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
Becker et al. (1987) USA RCT PEDro=6 N=15	**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.	1. 4/5 control individuals and only 1/10 treated individuals developed positive fibrinogen leg scans.
Matsumoto et al. (2015) Japan Observational	**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%),	1. DVT developed in 12 individuals (41.4%), all of which were located distal to the popliteal vein.

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
N=29	Sports (n=3, 10%), Low fall (n=2, 7%), Stairs (n=1, 3%); Severity of Injury: American Spinal Injury Association Impairment Scale (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. **Chronicity:**<24 hr post SCI. **Intervention:** All individuals were monitored for the development of deep venous thrombosis (DVT) after surgery and after 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. **Outcome Measures:** Development of deep venous thrombosis (DVT), D-Dimer levels.	2. The median length of time from surgery to detection of DVT was 7.5 days. 3. Seven of the 12 individuals (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 individuals who developed DVT was 14.6+13.5ug-ml but this was not significantly different compared to individuals who did not developed DVT (p>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 individuals who developed DVT and those who did not except for 3 days after surgery (p=0.0287).
Chung et al. (2011) Korea Pre-Post N=37	**Population:** Mean age=53 yr; Gender: Males=26, females=11; Level of injury: cervical-lumbar; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-D. **Chronicity**: All individuals were studied beginning within 1 week of injury. **Intervention:** Only routine mechanical prophylaxis was administered to all individuals in the form of gradient elastic stockings (GES), external sequential pneumatic compression, and early ambulation. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Doppler ultrasonography.	**Timing of DVT onset**: Routine checks for DVT were performed every 2 weeks beginning usually within 1 week of injury. 27% of individuals developed DVT within 7 days after injury, 8% developed DVT within 2-3 weeks after injury, and 8% developed DVT>1 month after injury. **Incidence of DVT:** 1. 43% of individuals developed DVT. 2. 2 individuals (5%) developed a PE. 3. Incidence of DVT in individuals in the present study was higher when compared to studies using pharmacological forms of prophylaxis.

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
Maxwell et al. (2002) USA Case Series N=111	**Population**: Mean age=37.5 yr; Gender: males=81%, females=19%; Level of injury: not specified; Severity of injury: paraplegia=41.4%, tetraplegia=58.6%. **Chronicity**: Individuals were hospitalized and monitored for an average of 23 ± 20 days following injury. **Intervention**: Retrospective review of individuals using sequential compression devices alone or in combination with 5000 IU low dose unfractionated heparin (LDUH) subcutaneously every 12 hr or low molecular unfractionated heparin (LMWH) (Enoxaparin) 30 mg subcutaneously every 12 hr. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Venous duplex ultrasonography.	**Timing of DVT onset**: Screening for DVT was performed on average 2.3 times during each admission. No other information was provided. **Incidence of DVT:** 1. The overall incidence rate for DVT and PE in SCI individuals was 9.0% and 1.8%, respectively, which was not significantly different. 2. The incidence of DVT and PE in individuals using compression only was 7.1% and 2.4%, respectively.
Winemiller et al. (1999) USA Case Series N=285	**Population:** Mean age=26 yr (VTE), mean age=25 yr (no VTE); Gender: males=88% (VTE), males=72% (no VTE); Level of injury: cervical-lumbar/sacral; Severity of injury: Frankel scores: A-B. **Chronicity:** All individuals were studied for the initial 6 week duration following injury. **Intervention:** Retrospective review of individuals who were administered antithrombotic prophylaxis (sequential compression devices (SCD)/gradient elastic stockings (GES)) or unfractionated heparin (UFH)) for 42 days-6 weeks after injury. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Fibrinogen scans, impedance plethysmography, Doppler studies, venograms, and ventilation-perfusion scanning.	**Timing of DVT onset:** DVT/PE first detected at a median of 14.5 days after injury. 63% of initial DVT/PE events occurred within the first 3 weeks. **Incidence of DVT:** 1. Overall Incidence of DVT/PE was 19.6%. 2. Multivariate analysis showed that SCD and GES were associated with a reduced risk of venous thromboembolism. 3. The risk reduction for heparin compared to SCD/GES was not significant (p=0.06 (95% CI, 0.05-1.08) for the first 14 days, p=0.13 for anytime); SCD/GES and heparin seemed to each be effective. 4. SCD/GES should be continued after 2 weeks post injury.
CHRONIC		
Nash et al. (2000) USA RCT PEDro=8	**Population:** Mean age=27.9yr; Gender: males=20; Level of injury: tetraplegic=20; **Chronicity:** 2mo-17yr post SCI. **Intervention:** Individuals were randomized into one of two groups: 1) Slow sequential	1. Popliteal vein: no differences between devices. 2. Femoral vein: increase in VFM and MVV during IPC versus SCD ($p<0.05$).

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
N=20	pneumatic compression devices (SCD)- 15sec compression, 45sec relaxation at 35 mmHg (ankle), 30 mmHg (calf) or 20 mmHh (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.	3. Rest versus compression: VFM, AVV and MVV, all increased during compression ($p<0.001$).

Of the studies evaluating physical methods for the prevention of DVT, five studies evaluated individuals during the acute phase (<3 months), while one study evaluated individuals during the chronic phase (>3 months) of SCI.

Acute Studies

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 individuals with acute SCI. The authors noted that rotating treatment tables had been used up to that time in individuals with acute SCI 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 individuals with acute SCIs. Four of the five control (non-rotated) individuals developed distal and proximal thrombi, assessed by I^{125} fibrinogen scanning and impedance plethysmography while only one of the ten treated (rotated) individuals with SCI developed both distal and proximal venous thrombi ($p=0.007$).

Matsumoto et al. (2015) examined the use of prophylactic pneumatic compression and elastic stockings without anticoagulation. Individuals 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 individuals 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).

Winemiller et al. (1999) examined the medical charts of 285 individuals with SCI and found that sequential pneumatic compression devices (SCD) or gradient elastic stockings were associated with a reduced risk of VTE. Multivariate analysis also suggested a decreased risk of VTE in individuals with SCI treated with heparin in the first 14 days or anytime within 42 days. Although this risk reduction was approximately twice that of SCD/gradient elastic stockings it was not statistically significant. A pre-post study by Chung et al. (2011) also examined the use of gradient elastic stockings, 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.

Maxwell et al. (2002) retrospectively reviewed individuals with acute SCI for an average of 23 days following injury, who used SCD as thromboprophylaxis. The authors found the incidence of DVT and PE to be 7.1% and 2.4%, respectively.

Chronic Studies

In a small randomized controlled trial, Nash et al. (2000) compared the effects of slow SCD and rapid intermittent pulsatile pneumatic compression devices (IPC) on venous hemodynamics in subjects with complete tetraplegia. Doppler examination of the popliteal and femoral veins in each compression condition revealed significant improvements in hemodynamic parameters in both treatment groups from rest. However, resting volume flow per minute and maximal venous velocity was significantly enhanced in the IPC group. As maximal venous velocity is considered a key measure to evaluate the effectiveness of compression devices used for DVT prevention, the authors suggest that IPC is more effective than SCD. It is important to note that incidence of DVT was not recorded in this study. Therefore, further research regarding the incidence of DVT is necessary to truly determine the superiority of one method over the other.

Conclusion

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

There is level 4 evidence (from one pre-post and two case series; (S.-B. Chung et al. 2011; Maxwell et al. 2002; Winemiller et al. 1999) that sequential compression or gradient elastic stockings are associated with a reduced the risk of venous thromboembolism in acute SCI individuals.

There is level 1b evidence (from one RCT; (Nash et al. 2000) that rapid intermittent pulsatile compression devices are more effective than slow sequential compression devices for stimulating venous blood flow in chronic SCI individuals.

Key Points

Sequential compression and gradient elastic stockings may reduce the incidence of venous thromboembolism during the acute phase post SCI.

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

Rapid intermittent pulsatile compression devices may stimulate venous blood flow more effectively than sequential compression devices during the chronic phase post SCI.

5.2.2 Internal Methods

5.2.2.1 Inferior Vena Cava Filtration

Vena Cava Filters are an invasive form of thromboembolic prophylaxis that primarily function to prevent clots from travelling to the heart and lungs while still allowing venous blood flow to flow. Earlier, these cone-shaped filters were placed surgically through the femoral vein; currently, less invasive techniques exist, allowing for filter placement through femoral, internal jugular, or small peripheral veins under fluoroscopic or ultrasound guidance (Jundt, Liem, & Moneta, 2014; Tai et al. 2013).

While pharmacological and mechanical methods remain the primary forms of thromboprophylaxis used in acute SCI, the use of vena cava filters is indicated in trauma individuals who are considered to be at high risk for developing DVT, specifically when there are contraindications to using anticoagulation (e.g., bleeding risk) or mechanical prophylaxis (e.g., external fixators or immobilizers are present). The ability to retrieve IVC filters offers the benefit of the filter during periods when PE risk is high, without long-term complications associated with their use (Lo et al. 2013; Rogers, Shackford, Wilson, Ricci, & Morris, 1993; Shackford, Cook, Rogers, Littenberg, & Osler, 2007). Routine implementation of IVC filters is not recommended as prophylaxis in SCI individuals (Maxwell et al. 2002).

Table 10. Prophylactic Vena Cava Insertion in Individuals with Traumatic SCI

Author Year Country PEDro Score Research Design Sample Size	Methods	Outcomes
Roberts & Young (2010) USA Case Series N=45	**Population:** Mean age=39.7 yr; Gender: males=37, females=8; Level of injury: cervical; Severity of injury: injury severity score (ISS)>20 (mean score=34.2). **Chronicity:** Filters were placed in all individuals within 72 hr of admission. **Intervention:** Placement of a prophylactic inferior vena cava (IVC) filter. Individuals were placed on prophylactic anticoagulant therapy 1 week after injury (Lovenox or Heparin). **Outcome Measures:** Incidence of pulmonary embolism (PE) and complications related to insertion. **Method of Diagnosis:** Not indicated.	**Timing of DVT onset**: Not indicated. **Incidence of PE:** 1. No individuals sustained a PE. 2. No complications related to IVC filter insertion were observed. 3. IVC filters are suggested as safe and perhaps add preventative value against thrombotic complications.
Gorman et al. (2009) USA Case Control	**Population:** Mean age=37.1 yr (inferior vena cava (IVC) filter), Mean age=48.1 yr (no filter); Gender: males=96% (IVC filter), males=69% (no filter); Level of injury: C3-L3; Severity of injury: not specified.	**Timing of DVT onset**: Average length of stay for individuals was 39 days (IVC filter) and 27 days (no filter) after acute hospitalization. No information was

Author Year Country PEDro Score Research Design Sample Size	Methods	Outcomes
N=112	**Chronicity**: Individuals either received or did not receive an IVC filter during their acute hospitalization before admission to the rehabilitation centres. No other information was provided. **Intervention:** Retrospective review of SCI individuals who had received a prophylactic IVC filter, compared to those that had not. All individuals were also treated with another form of prophylaxis, "usually low molecular unfractionated heparin (LMWH) and compression stockings." **Outcome Measures:** Incidence of deep vein thrombosis (DVT). **Method of Diagnosis:** Clinical examination and duplex ultrasonography.	provided specifying when screening was performed. **Incidence of DVT:** 1. Individuals without IVC filter had fewer DVTs than those with an IVC filter (5.2% and 20.4% respectively, p=0.021). 2. IVC filter placement resulted in significantly increased risk of DVT development.
Kinney et al. (1996) USA Case Control N=11	**Population:** Mean age=33.8 yr; Gender: males=100% (SCI group); Level of injury: cervical; Severity of injury: not specified. **Chronicity:** The mean acute hospitalization after injury was 27.5 days (SCI group). Timing of filter insertion was not described. **Intervention:** Retrospective review of SCI individuals who received prophylactic inferior vena cava (IVC) filters, compared to non-SCI individuals (historical controls) who received the filter. **Outcome Measures:** Incidence of pulmonary embolism (PE). **Method of Diagnosis:** Computed tomography and ventilation-perfusion lung scanning.	**Timing of PE onset**: No information was provided specifying when screening was performed. **Incidence of PE:** 1. The SCI population had an 18.2% incidence rate of PE, which was higher compared to rates in historical controls.
Rogers et al. (1995) USA Pre-Post N=63	**Population:** Mean age=38.9 yr; Gender: males=73%, females=27%; Level of injury: not specified; Severity of injury: not specified. **Chronicity**: The mean time from admission to filter insertion was 4.3 days. **Intervention:** A subset of high-risk trauma individuals (SCI=25) received prophylactic vena cava filter (VCF) insertion. Forms of standard prophylaxis were contraindicated. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Impedance plethysmography, venous duplex	**Timing of DVT onset**: Screening was done within 48 hr of filter insertion and on a weekly basis afterwards until death/discharge. No other information specifying timing of DVT onset was described. **Incidence of DVT:** 1. 3 individuals developed DVT. 2. No individuals developed PE.

Author Year Country PEDro Score Research Design Sample Size	Methods	Outcomes
	ultrasonography, ventilation-perfusion scanning, and pulmonary angiography.	
Wilson et al. (1994) USA Pre-Post N=15	**Population:** Mean age=31.4 yr; Gender: males=12, females=3; Level of injury: cervical-lumbar; Severity of injury: injury severity score (ISS)>20. **Chronicity:** Individuals were hospitalized for a median of 22 days. Timing of filter insertion was done "as soon as clinically feasible." **Intervention:** Prophylactic inferior vena cava (IVC) filter insertion. All individuals also received either low-dose subcutaneous heparin or venous compression devices while hospitalized. These individuals were compared to historic controls who did not receive filters. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Impedance plethysmography and venous duplex ultrasonography.	**Timing of DVT/PE onset**: No PE was observed in up to 24 mo of follow-up. **Incidence of DVT:** 1. No individuals developed DVT during acute hospitalization. 2. No individuals developed PE after filter insertion.
Balshi et al. 1989 USA Case Series N=13	**Population:** Age range=17-48yr; Gender: males=11, females=2; Severity of Injury: quadriplegia. **Chronicity:** 2 weeks-4 yr post SCI. **Intervention:** Prophylactic Greenfield inferior vena cava (IVC) filter insertion. **Outcome Measures:** Incidence of deep venous thrombosis (DVT) or pulmonary embolism (PE).	1. Twelve individuals experienced a DVT while one had a PE. 2. Two individuals experienced recurrent DVT. 3. Distal migration of the filter occurred in two individuals.
Jarrell et al. (1983) USA Case Series N=21	**Population:** Not clear. **Chronicity:** Acute. **Intervention:** Prophylactic Greenfield inferior vena cava (IVC) filter insertion. **Outcome Measures:** Incidence of pulmonary embolism (PE).	1. There was one PE-related fatality. 2. There was no other instance of suspected or proved PE after insertion of the filter. 3. Follow-up revealed two instances of thrombosis.

Discussion

Several studies have examined the prophylactic effect of IVC filter insertion on the incidence of DVT and/or PE after acute SCI. Roberts and Young (2010) conducted a case series study of individuals who received IVC filters within 72 hours of admission. The authors observed no occurrences of PE or other complications. These findings were supported by two pre-post studies by Wilson et al. (1994) and Rogers et al. (1995). In the latter studies the authors observed

that inferior vena cava filter insertion "as soon as clinically feasible" and on average 4.3 days after admission, respectively, did not result in any occurrences of PE. However, it should be noted that, in the latter study, individuals were not on any other forms of prophylaxis concurrently and as a result three individuals developed DVT.

Interestingly, a retrospective case control study by Gorman et al. (2009) compared SCI individuals who had received IVC filters during acute hospitalization with SCI individuals who had not received filters. The authors found that the incidence of DVT was significantly higher in individuals with implanted filters ($p=0.021$).

Three studies have specifically studied the insertion of Greenfield IVC filters. Jarrell et al. (1983) studied 21 individuals with acute SCI who had received a Greenfield filter and reported that one individual 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 individuals with SCI who received this filter and found that 12 of the 13 individuals 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 individuals 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 individuals with SCI; however, this form of prophylaxis is invasive and therefore, should only be considered for high-risk individuals. 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 individuals with active bleeding anticipated to persist for more than 72 hours and begin anticoagulants as soon as feasible" (p. 38).

Conclusion

There is conflicting level 3 evidence (from two case control studies, two case series studies, and one pre-post study; (Gorman et al. 2009; Jarrell et al. 1983; Kinney et al. 1996; Roberts & Young, 2010; Wilson et al. 1994) that inferior vena cava filters significantly reduce the risk of pulmonary emboli in high-risk individuals with SCI.

Key Points

Inferior vena cava filters reduce the risk of pulmonary embolism in acute SCI.

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

5.3 Combined Pharmacological Agents and Mechanical Methods

The combination of mechanical methods and pharmacological agents has been studied for their effect on DVT prophylaxis post SCI.

Table 11. Combined Pharmacological and Physical Measures for the Prophylaxis of Venous Thromboembolism Post SCI

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
Halim et al. (2014) India RCT PEDro=7 N=74	**Population:** Mean age: not specified; Gender: males=35, females=2 (group I), males=25, females=12 (group II); Level of injury: not specified; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-D. paraplegia=32, tetraplegia=42. **Chronicity**: Only individuals with acute SCI (≤ 5 days) were studied for a 2-week duration following injury. **Chronicity:**<7 days post SCI. **Intervention:** Individuals were randomly allocated to receive only physical measures "like compression stockings" (group I), or low molecular unfractionated heparin (LMWH) (Enoxaparin) 40 mg subcutaneously once daily starting from the day of admission along with physical measures as in group I (group II). **Outcome Measures**: Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Clinical examination and color Doppler venous ultrasonography.	**Timing of DVT onset:** Screening for DVT was done in all subjects at the end of 2 weeks +/-2 days following injury (earlier or later if symptoms arose). **Incidence of DVT:** 1. Incidence of DVT was 21.6% in group I and 5.4% in group II; this difference was significant (p=0.041). 2. 6/8 individuals in group I had asymptomatic DVT, whereas no asymptomatic DVT events occurred in group II. 3. No PE events occurred overall. 4. Pharmacological prophylaxis decreases the incidence of DVT in acute SCI individuals.
Spinal Cord Injury Thromboprophylaxis Investigators (2003a) USA	**Population:** Mean age=40.6 yr (unfractionated heparin (UFH)-intermittent pneumatic compression (IPC) group), mean age=38.5 yr (Enoxaparin group); Gender: males=79.6% (UFH-IPC group), males=89.7% (Enoxaparin group); Level of injury: not specified; Severity of injury: American Spinal Injury Association Impairment Scale (AIS) A-D.	**Timing of DVT onset**: DVT/PE screening/data collection was performed at the end of the 2-week acute treatment phase or within 2 days of the last dose of acute-phase medication. **Incidence of DVT:** 1. Incidence of DVT was 44.9% for UFH-IPC group versus 60.3% for

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
RCT PEDro=9 $N_{Initial}$=476; N_{Final}=107	**Chronicity**: All individuals were studied beginning within 72 hr of sustaining injury and monitored for approximately 2 weeks during acute treatment (mean=13.4 days for UFH-IPC group, mean=14 days for Enoxaparin group). **Intervention:** Individuals were assigned to receive either low-dose UFH (5000 IU subcutaneously every 8 hr) plus IPC (used at least 22h/day), or only Enoxaparin (30 mg subcutaneously every 12 hr). **Outcome Measures:** Incidence of deep vein thrombosis (DVT), pulmonary embolism (PE) and major bleeding. **Method of Diagnosis:** Doppler ultrasonography, venography, ventilation-perfusion lung scanning, spiral computed tomographic scanning, and pulmonary angiography.	Enoxaparin group; non-significant difference (p=0.11). 2. Incidence of PE was 18.4% for UFH-IPC group, significantly higher than 5.2% of individuals in the Enoxaparin group (p=0.03). 3. Among all randomized individuals, the incidence of major bleeding was 5.3% for low dose unfractionated heparin-IPC group versus 2.6% for Enoxaparin group (p=0.14).
Spinal Cord Injury Thromboprophylaxis Investigators (2003b) USA Prospective Controlled Trial $N_{Initial}$=172; N_{Final}=119	**Population:** *LDUH* (n=60): Mean age=34 yr; Gender: males=47, females=13; Level of injury: paraplegic=18, tetraplegic=32; *Enoxaparin* (n=59): Mean age=30.5 yr; Gender: males=53, females=634; Level of injury: paraplegic=15, tetraplegic=34. **Chronicity:** 2 weeks post SCI. **Intervention:** Continuation of study 2003a above. Individuals previously receiving low dose unfractionated heparin (LDUH) continued on this regimen. Those previously on the enoxaparin had an increase in dosage to 40mg. **Outcome Measures:** Deep venous thrombosis (DVT), pulmonary embolism (PE), major bleeding.	1. New DVT was demonstrated in 13/60 LDUH versus 5/59 enoxaparin individuals (p=0.052).
Green et al. (1982) USA RCT PEDro=7 $N_{Initial}$=28; N_{Final}=27	**Population:** Gender: males=24, females=4; Severity of injury: complete=28. **Chronicity:**<1 mo post SCI. **Intervention:** 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) 75mg bid (n=13).	1. Thrombi developed in 6/15 individuals treated solely with EPCC, and in 3/12 receiving EPCC+ASA/Dip (p<.100). 2. Factor VIII levels of individuals treated with EPCC alone as compared to EPCC+ASA/Dip were higher.

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
	Outcome Measures: Incidence of deep venous thrombosis (DVT); Factor VIII coagulant activity.	
Giorgi Pierfranceschi et al. (2013) Italy Cohort N=94	**Population:** Mean age=40.3 yr; Gender: males=80, females=14; Level of injury: not specified; Severity of injury: paraplegia=52, tetraplegia=42. **Chronicity:** Individuals were monitored during their stay in the neurosurgery unit (NSU, median=20 days after injury) and rehabilitation unit (RU, median=6 mo, admitted after NSU discharge). **Intervention:** Individuals received prophylactic thigh-length graduate compressive stockings plus low molecular unfractionated heparin (LMWH) (Enoxaparin 4000 U daily or Dalteparin 5000 U daily) within 72 hr upon admission to the RU after neurosurgery (which occurred 48-72 hr after trauma). **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Compression ultrasonography, color Doppler ultrasonography, perfusion lung scintigraphy, and computed tomography pulmonary angiography.	**Timing of DVT onset**: All VTE events occurred after a median of 15 days from SCI; 90.9% of VTE events occurred during the first 3 mo after SCI. Of 22 VTE events, 59.1% were diagnosed during NSU stay, 27.3% were diagnosed within one week of RU admission, 9% were diagnosed during RU stay, and 5% were detected during follow-up after rehabilitation discharge (>6mo). **Incidence of DVT:** 1. 23.4% of individuals had VTE events (22 individuals; 19 DVT, 2 PE, 1 DVT/PE).
Germing et al. (2010) Germany Pre-Post N=139	**Population:** Age range=19-90 yr; Gender: Males=63.5%; Level of injury: not specified; Severity of injury: tetraplegia=68, paraplegia=71. **Chronicity:** All individuals were studied beginning within the first 36 hr of admission and monitored for 21 days. **Intervention:** All individuals received low molecular unfractionated heparin (LMWH) (Enoxaparin) 40 mg subcutaneously and compression stockings. **Outcome Measures:** Incidence of and localization of deep vein thrombosis (DVT). **Method of Diagnosis:** Color duplex ultrasonography.	**Timing of DVT onset**: DVT screening was performed within the first 36 hr after admission, and after 7 and 21 days. DVT occurred in 38.1% of individuals within the first 36 hr, in 5% of individuals after 7 days, and in 2% of individuals after 21 days. **Incidence of DVT:** 1. The cumulative incidence of DVT was 45.3%. 2. 71.4% of DVTs were localized below the knee. 3. 84.5% of distal vein thromboses were in the Vena tibialis. 4. Recanalization occurred in 33.3% of individuals after 3 weeks of prophylaxis, no change

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
		in 30.2%, and residual thrombi in 36.5%.
Maxwell et al. (2002) USA Case Series N=111	**Population**: Mean age=37.5 yr; Gender: males=81%, females=19%; Level of injury: not specified; Severity of injury: paraplegia=41.4%, tetraplegia=58.6%. **Chronicity**: Individuals were hospitalized and monitored for an average of 23 days following injury. **Intervention**: Retrospective review of individuals using sequential compression devices alone or in combination with 5000 IU low dose unfractionated heparin (LDUH) subcutaneously every 12 hr or low molecular unfractionated heparin (LMWH) (Enoxaparin) 30 mg subcutaneously every 12 hr. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Venous duplex ultrasonography.	**Timing of DVT onset**: Screening for DVT was performed on average 2.3 times during each admission. No other information was provided. **Incidence of DVT:** 1. The incidence of DVT and PE in individuals using compression alone was 7.1% and 2.4%, respectively. 2. The incidence of DVT and PE in individuals using compression and LDUH was 11.1% and 2.8%, respectively. 3. The incidence of DVT and PE in individuals using compression and LMWH was 6.9% and 0%, respectively. 4. No significant difference was found among these groups ($p>0.05$).
Aito et al. (2002) Italy Pre-Post N=275	**Population:** Mean age=41.3 yr (early admitted individuals (EAP)), mean age=42.3 yr (late admitted individuals (LAP)); Gender: males=81, females=20 (EAP), males=185, females=37 (LAP); Level of injury: not specified; Severity of injury: AIS A-D. **Chronicity:** Individuals were either EAP (within 72 hr from injury) or LAP (on average 12 days after injury, range=8-28 days). **Intervention:** All individuals received permanently dressed gradient elastic stockings (GES), external sequential pneumatic compression and low molecular unfractionated heparin (LMWH) (Nadroparine) beginning within 72 hr post injury for EAP and upon admission for LAP, lasting for at least 30 days from injury. **Outcome Measures**: Incidence of deep vein thrombosis (DVT). **Method of Diagnosis:** Color Doppler ultrasonography.	**Timing of DVT onset**: Examinations to detect the presence of DVT were performed immediately on admission, after 45-60 days and when requested. DVT was detected 25 and 29 days after injury in EAP; 60% of LAP had DVT detected on admission, 40% developed DVT within 6 weeks. **Incidence of DVT:** 1. DVT incidence was 2% for EAP. 2. DVT incidence was 26% for LAP. 3. 65% of detected DVTs had no clinical signs evident. 4. Individuals with ASIA A SCIs were more likely to develop DVTs (36%). 5. No comparisons between the two groups were done due to lack of homogeneity of treatment, however a dramatic reduction in thromboembolic events was observed in the EAP group, supporting the use of

Author Year Country Research Design PEDro Score Sample Size	Methods	Outcomes
		pharmacological and mechanical treatment early after injury.
Deep et al. (2001) UK Case Series N=276	**Population:** Mean age=39.8 yr; Gender: not specified; Level of injury: cervical=150, thoracic and lumbar=126; Severity of injury: not specified. **Chronicity:** All individuals were studied beginning upon admission to the spinal injuries unit. **Intervention:** A retrospective review of SCI individuals receiving full length anti-thromboembolic stockings (up to mid-thigh) from admission to discharge and 40mg of Enoxaparin once daily beginning the day of injury or admission. **Outcome Measures:** Incidence of deep vein thrombosis (DVT) or pulmonary embolism (PE). **Method of Diagnosis:** Venous ultrasonography, venography, ventilation-perfusion scanning, and computed tomography angiography.	**Timing of DVT onset:** DVT developed 8-30 days after discontinuing Enoxaparin in 6 individuals (which was stopped after 26-46 days); 1 episode of PE developed 33 days after discontinuing Enoxaparin (which was stopped after 56 days). **Incidence of DVT:** 1. 6 (2.2%) individuals developed DVT, 2 (0.7%) individuals developed DVT while still receiving Enoxaparin. 2. 2 (0.7%) of individuals developed PE (1 individual developed PE while still receiving Enoxaparin).
Merli et al. (1992) USA Case Control $N_{Initial}$=38; N_{Final}=36	**Population:** Age range=15-69 yr (control), age range=18-70 yr (treatment); Gender: males=11, females=6 (control), males=14, females=5 (treatment); Level of injury: not specified; Severity of injury: Frankel A-B. **Chronicity:** Individuals were studied beginning within 48 hr of acute SCI for the duration of the first 2 weeks following injury. **Intervention:** Individuals received external pneumatic compression with gradient elastic stockings (GES) and low dose unfractionated heparin (LDUH) 5000 U subcutaneously every 12 hr (treatment group, n=19), and were compared to a group of individuals from a previous study receiving no treatment (control group, n=17). **Outcome Measures:** Incidence of deep vein thrombosis (DVT). **Method of Diagnosis:** 125 I fibrinogen scanning and venography.	**Timing of DVT onset**: Screening was performed beginning within 18 hr of admission and daily thereafter for 2 weeks. **Incidence of DVT:** 1. 2 individuals (11%) in the treatment group developed a positive fibrinogen scan on days 6 and 8 of the study, only 1 individual (5.2%) was confirmed to have DVT by venography. 2. 6 individuals (35%) in the control group had positive fibrinogen scans for DVT, all of which were confirmed by venography. 3. The incidence of thrombosis was significantly lower in the treatment group compared to the control group (p=0.04). 4. A significant difference favouring the treatment group was found in terms of the extent of the clot (p=0.02).

Discussion

Several studies have examined the prophylactic effectiveness of various combinations of mechanical and pharmacological methods on the incidence of DVT and PE in acute SCI. Two studies investigated the combined effect of LDUH with mechanical methods for VTE prophylaxis. In an RCT by the Spinal Cord Injury Thromboprophylaxis Investigators (2003a), individuals were randomly assigned to either receive 5000 IU LDUH every 8 hours along with IPC, or 40 mg of Enoxaparin every 12 hours. All individuals studied had sustained SCI within 72 hours and were monitored for a duration of approximately 2 weeks of acute treatment, at the end of which screening for DVT and PE was performed. In individuals receiving LDUH, the incidence of DVT was 44.9%, which was not significantly different from 60.3% of individuals receiving Enoxaparin ($p=0.11$). The incidence of PE was significantly higher (18.4%) in individuals receiving LDUH compared to Enoxaparin (5.2%, $p=0.03$). Merli et al. (1992) conducted a case control study in which individuals received external pneumatic compression with gradient elastic stockings and 5000 U LDUH every 12 hours and were compared to a control group of individuals receiving no intervention. All individuals were studied beginning within 48 hours of injury for the initial 2-week duration following injury. The incidence of DVT was found to be significantly lower in individuals receiving mechanical and pharmacological prophylaxis as compared to the group of control individuals ($p=0.04$). However, in the second study by The Spinal Cord Injury Thromboprophylaxis Investigators (2003b) dosage of enoxaparin was increased, and they found that high-dose enoxaparin resulted in fewer DVTs than the combined LDUH-IPC treatment.

One study by Maxwell et al. (2002) compared LDUH and LMWH, each in combination with mechanical methods of prophylaxis. Individuals hospitalized for an average of 23 days after injury were retrospectively reviewed in terms of their use of SCD in combination with either 5000 IU LDUH every 12 hours or 30 mg Enoxaparin every 12 hours. The incidence of DVT and PE in individuals using SCD and LDUH was 11.1% and 2.8%, respectively. The incidence of DVT in individuals using SCD and Enoxaparin was 6.9%; no PE was observed in this group of individuals. There were no significant differences in incidence rates for DVT or PE between groups.

Five studies investigated LMWH in combination with mechanical methods of prophylaxis. Giorgi Pierfranceschi et al. (2013) studied individuals who had received graduate compressive stockings in combination with either 4000 U Enoxaparin daily or 5000 U Dalteparin daily. Treatment was administered within 72 hours of admission after surgery, which occurred 48-72 hours after injury. The authors found that 23.4% of individuals developed VTE events, 90.9% of which occurred within the first 3 months after SCI. Halim et al. (2014) conducted an RCT in which individuals were randomly assigned to receive either only physical modalities of prophylaxis (not specified further), or 40 mg Enoxaparin once daily along with the same form of physical prophylaxis. Individuals enrolled in this study had sustained a SCI no more than 5 days prior to entering the study and were monitored for the initial 2-week duration following injury. The incidence of DVT was significantly higher in individuals receiving only mechanical prophylaxis (21.6%) compared to individuals receiving a combination of mechanical and pharmacological prophylaxis (5.4%, $p=0.041$). PE occurrences were nonexistent. Germing et al. (2010) enrolled individuals within the first 36 hours of admission in a pre-post study; all individuals received 40 mg Enoxaparin together with compression stockings. The cumulative

incidence of DVT was reported to be 45.3%, with 38% of DVT events occurring within the first 36 hours of admission; no statistical analysis was reported. A case series by Deep et al. (2001) retrospectively investigated individuals on admission to a spinal injury's unit. On admission or at the time of injury, individuals received anti-thromboembolic stockings and 40 mg Enoxaparin once daily. Of this study population, 2.2% and 0.7% of individuals developed DVT and PE, respectively. Finally, in a pre-post study by Aito et al. (2002), individuals, who were classified as either early admitted (i.e., 72 hours post injury) or late admitted (mean=12 days post injury), received a combination of permanently dressed gradient elastic stockings, external sequential pneumatic compression, as well as Nadroparine. The incidence of DVT was 2% and 26% for early admitted and late admitted individuals, respectively; no statistical analysis was reported.

Conclusion

There is level 1b evidence (from one RCT; (Spinal Cord Injury Thromboprophylaxis Investigators, 2003a) that low-dose unfractionated heparin in combination with intermittent pneumatic compression is as effective as Enoxaparin as prophylaxis for deep vein thrombosis in acute SCI individuals.

There is level 3 evidence (from one case control; (G. J. Merli et al. 1992) that pneumatic compression in combination with gradient elastic stockings and low-dose unfractionated heparin is effective in reducing the incidence of deep vein thrombosis in acute SCI individuals.

There is level 1b evidence (from one RCT; (Halim et al. 2014) that Enoxaparin in combination with physical measures is more effective than physical measures alone as prophylaxis for deep venous thrombosis in acute SCI individuals; However, there is level 4 evidence (from one case series; (Maxwell et al. 2002) that Enoxaparin plus sequential compression devices, low-dose unfractionated heparin plus sequential compression devices, and sequential compression devices alone are similarly effective as venous thromboembolism prophylaxis in acute SCI individuals.

Key Points

A combination of low-dose unfractionated heparin with intermittent pneumatic compression seems equally as effective as low-molecular-weight heparin alone at reducing this risk.

There is conflicting evidence regarding the effectiveness of the combination of low- molecular-weight heparin with physical measures at reducing the risk of venous thromboembolism compared to physical measures alone during the acute phase post SCI.

6 Summary

VTE following SCI is a source of significant morbidity and mortality. Most research is focused on prophylaxis of VTE 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 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.

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Abbreviations

DVT	Deep Venous Thrombosis
IPC	Intermittent Pulsatile Compression
IVC	Inferior Vena Cava
LDUH	Low Dose Unfractionated Heparin
LMWH	Low Molecular Unfractionated Heparin
PE	Pulmonary Embolism
RCT	Randomized Controlled Trial
SCD	Sequential Pneumatic Compression Devices
SCI	Spinal Cord Injury
VTE	Venous Thromboembolism