Deep Venous Thrombosis and Thromboembolism in Patients With Cervical Spinal Cord Injuries

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RECOMMENDATIONS

Prophylaxis:

Level I

- Prophylactic treatment of venous thromboembolism (VTE) in patients with severe motor deficits due to spinal cord injury is recommended.
- The use of low molecular weight heparins, rotating beds, or a combination of modalities is recommended as a prophylactic treatment strategy.
- Low dose heparin in combination with pneumatic compression stockings or electrical stimulation is recommended as a prophylactic treatment strategy.

Level II

- Low dose heparin therapy alone is not recommended as a prophylactic treatment strategy.
- Oral anticoagulation alone is not recommended as a prophylactic treatment strategy.
- Early administration of VTE prophylaxis (within 72 hours) is recommended.
- A 3-month duration of prophylactic treatment for deep vein thrombosis (DVT) and pulmonary embolism (PE) is recommended.

ABBREVIATIONS: ASCI, acute spinal cord injury; **DVT,** deep venous thrombosis; **IVC,** inferior vena cava; **IV,** intravenous; **LMWH,** low molecular weight heparins; **PE,** pulmonary embolism; **SCI,** spinal cord injury; **UFH,** unfractionated heparin; **VOP,** venous occlusion plethysmography; **VTE,** venous thromboembolism

Level III

- Vena cava filters are not recommended as a routine prophylactic measure, but are recommended for select patients who fail anticoagulation or who are not candidates for anticoagulation and/or mechanical devices.

Diagnosis:

Level III

- Duplex Doppler ultrasound, impedance plethysmography, venous occlusion plethysmography, venography, and the clinical examination are recommended for use as diagnostic tests for DVT in the spinal cord injured population.

RATIONALE

DVT and PE collectively considered as VTE are problems frequently encountered in patients who have sustained cervical spinal cord injuries. Several means of prophylaxis and treatment are available, including anticoagulation, pneumatic compression devices, and vena cava filters. In 2002, the guidelines author group of the Joint Section on Disorders of the Spine and Peripheral Nerves of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS) produced a medical evidence-based guideline on this important topic.[1] The purpose of this current evidence-based review is to update, evaluate, and rank the literature on the methods of prevention, identification, and treatment of VTE complications in patients following acute cervical spinal cord injury published since 2002.

SEARCH CRITERIA

A National Library of Medicine (PubMed) computerized literature search from 1966

through 2011 was performed using Medical Subject Headings in combination with "spinal cord injury": "deep venous thrombosis" "pulmonary embolism" and "thromboembolism." The search was limited to human studies reported in the English language. This resulted in 599 citations. Duplicate references, reviews, letters, and tangential reports were discarded. The bibliographies of these citations were analyzed for additional potential contributions. Finally, the author group found 45 citations describing the diagnosis, prophylaxis or treatment of thromboembolic disease in adult spinal cord injured patients make up the basis for this guideline and are summarized in Evidentiary Table format (Table). Supporting references included 4 evidence-based reviews on VTE prophylaxis and treatment in a variety of patient populations. Finally, several series dealing with VTE in general trauma patients with results germane to a discussion of spinal cord injured patients are included in the bibliography as supporting documents.

SCIENTIFIC FOUNDATION

The incidence of thromboembolic complications in the untreated spinal cord injury (SCI) population is high. Depending upon injury severity, patient age, and the methods used to diagnose a thromboembolism, the incidence of thromboembolic events ranges from 7% to 100% in reported series of patients receiving either no prophylaxis or inadequate prophylaxis.[2-14] Substantial morbidity and mortality has been associated with the occurrence of DVT and PE events in the SCI population.[15,16,55-57]

Prophylaxis

Prophylactic therapy has been shown to be effective for the prevention of DVT and PE. In a small randomized study, Becker et al[17] demonstrated that the use of rotating beds during the first 10 days following SCI decreased the incidence of DVT and provided Class I medical evidence on this subject. Four of 5 control patients were diagnosed with DVT (by fibrinogen screening) compared to 1 of 10 treated patients. The use of low dose heparin (5000 units given via subcutaneous injection twice or 3 times daily) has been described by several authors.[3,6,7,12,18-20] Hachen[19] published the results of a retrospective historical comparison of low dose heparin vs oral anticoagulation in a group of 120 SCI patients. He found a lower incidence of thromboembolic events in the low dose heparin group compared to the oral anticoagulation group. In 1977, Casas et al[18] reported the results of a prospective assessment of low dose heparin in SCI patients. They administered heparin for a mean period of 66 days in 18 SCI patients and noted no thromboembolic events as detected by clinical examination. Watson reported a lower incidence of thromboembolic events with the use of low dose heparin when compared to no prophylaxis in a retrospective historical cohort study.[20] Frisbie and Sasahara, however, found that low dose heparin did not affect the incidence of DVT in a prospective study of 32 SCI patients compared to treatment with twice daily physical therapy alone. These authors felt that the lack of effect was due to the very low incidence of DVT in their control group compared to other series because of the aggressive physical therapy paradigm employed in their patients. Although they performed screening venous occlusion plethysmography (VOP) with confirmatory venography weekly, the incidence of DVT was only 7% in both groups, suggesting that the treatments were equivalent in their study.[4] This low incidence of DVT is substantially lower than that reported by 2 separate groups of investigators a decade later.[6,7] In 1992, Kulkarni et al reported the much higher incidence of DVT (26%) and of PE (9%) in a group of 100 SCI patients prospectively treated with low-dose heparin.[7] In 1993, Gunduz et al reported a 53% incidence of DVT confirmed by venography in 31 patients they managed with SCI treated with low dose heparin.[6] In a study published in 1999, Powell et al noted that the incidence of DVT in 189 SCI patients receiving prophylaxis was significantly lower than that identified in SCI patients who did not receive prophylaxis, 4.1% vs 16.4%, respectively. Their comparative study provides supportive Class II medical evidence in favor of DVT prophylaxis. They reported that DVT in the prophylaxis group occurred in patients who received low dose heparin alone.[12]

Several studies have demonstrated that better prophylactic therapies than low dose heparin exist.[5,9,21] Green et al[5] published a randomized controlled study comparing low dose vs adjusted dose heparin (dose adjusted to APTT 1.5 times normal) in SCI patients. They found that patients treated with adjusted dose heparin had fewer thromboembolic events (7% vs 31%) during the course of their 10-week study, but had a higher incidence of bleeding complications. Merli et al[21] in 1988 reported their findings of the additive protective effects of electrical stimulation in combination with low dose heparin, heparin alone, and placebo in 48 SCI patients treated for 4 weeks duration. In this Class I prospective, randomized medical evidence trial, they found that the heparin therapy alone group had a similar incidence of DVT compared to the placebo group. The combination of low dose heparin and electrical stimulation significantly decreased the incidence of DVT (1 of 15 patients compared to the other 2 treatment groups (8/16 low dose heparin alone, and 8/17 placebo, $P < .05$), providing Class I medical evidence on this issue.[21] In 1992, this same group reported that heparin in combination with pneumatic stockings was equal to the effectiveness of heparin plus electrical stimulation.[9] The heparin in combination with electrical stimulation group and the placebo group for this comparison were a historical cohort, rendering the medical evidence provided Class III. Winemiller et al[22] studied a large series of 428 SCI patients with a multivariate analysis and found that the use of pneumatic compression devices for 6 weeks duration was associated with a significant decrease in thromboembolic events (odds ratio of 0.5 [95% CI 0.28-0.90]). Low dose heparin treatment seemed to have a protective effect as well; however, the effect of heparin alone was not statistically significant.

Recently, low molecular weight heparins (LMWH) have been studied as prophylactic therapy for thromboembolism in SCI

patients. Green et al[23] treated a series of SCI patients with 8 weeks of LMWH (tinzaparin) and compared the results with a historical cohort of patients treated with low dose or adjusted dose heparin. They found that the use of LMWH compared favorably with the use of either heparin dosing regimen in terms of fewer thromboembolic events, (16 events in 79 patients in the heparin group vs 7 events among 68 patients in the LMWH group, $P = .15$). Patients treated with LMWH had a significant decrease in bleeding complications (9 of 79 in the heparin group vs 1 of 68 in the LMWH group, $P = .04$).[23] More recently, Harris et al[24] performed a retrospective study of LMWH (enoxaparin) administration in a series of 105 patients with spinal injuries. Forty of their 105 patients suffered neurologically complete injuries. No patient exhibited clinical or ultrasound evidence of DVT and no patient suffered a PE treated with LMWH.[24] Roussi et al[25] reported a 9% incidence of DVT in a study involving 69 SCI patients receiving LMWH, testimony to the fact that no prophylactic therapy is 100% effective.

In 2003, the Spinal Cord Injury Thromboprophylaxis Investigators reported their study that randomized 476 acute SCI patients to unfractionated heparin (UFH) plus intermittent pneumatic compression or to enoxeparin as VTE prophylaxis strategies. The study was sponsored by the enoxeparin manufacturer. All but 107 patients were excluded from analysis due to "protocol deviations, bleeding and/or other adverse clinical events, thrombocytopenia and/or other adverse laboratory findings, withdrawal of consent, and intercurrent illness." Though they found no significant difference in the incidence of thromboembolism between the treatment groups (63.3% vs 65.5%, respectively), they did note a significantly lower incidence of PE in the enoxaparin group (5.2%) vs the UFH + IPC group (18.4%). Due to the high exclusion rate, the medical evidence provided by this study is downgraded to Class III.[26]

In 2003, this same group prospectively examined the incidence of VTE in SCI patients in the rehabilitation phase (2 weeks after injury) who received either enoxaparin or UFH for 6 weeks. Of the 172 patients in their study, they excluded 53 due to "protocol deviations, bleeding and/or other adverse clinical events, thrombocytopenia and/or other adverse laboratory findings, withdrawal of consent, and intercurrent illness." In the remaining patients, they found a lower incidence of thromboembolic complications in patients treated with enoxeparin (21.7% vs 8.5%; $P = .052$). Due to the high exclusion rate, the medical evidence provided by this study is downgraded to Class III.[27]

In 2004, Hebbeler and colleagues[28] compared once daily dosing (40 mg) of enoxaparin to twice daily (30 mg each) dosing and found no significant difference in the incidence of thromboembolic complications among SCI patients in the rehabilitation setting. In 2005, Green et al[29] compared the incidence of DVT in SCI patients treated from 1992 to 1995 to SCI patients they treated from 1999 to 2003, and found a significant decrease from 21% in the group of patients treated in the early 1990s compared to 7.9% in the latter series managed in the early 2000s. They concluded that the decline in the incidence of venous thromboembolism in their 2 patient series coincided with their transition from unfractionated heparin to LMWH used for prophylaxis. In 2007, Slavik et al[30] performed a retrospective cohort study comparing enoxaparin to dalteparin in 135 patients with orthopedic trauma and/or spinal cord injury (73 with SCI). They found that the incidence of VTE was 1.8% and 9.7% in the enoxaparin and dalteparin patients, respectively, but reported that this difference was not statistically significant ($P = .103$).[30] In 2010, Arnold et al[31] performed a retrospective cohort study comparing unfractionated heparin to enoxeparin in 476 trauma patients, including 24 with spinal cord injury. Proximal lower extremity DVTs were detected in 16 patients in the enoxaparin group (6.75%) and in 17 patients in the UFH group (7.11%). Among the 24 SCI patients, however, the authors found the incidence of DVT in the enoxeparin group to be 36.4% compared to 15.4% in the UFH treated group ($P = .357$). The authors concluded that UFH was equally effective as enoxeparin as prophylaxis against DVT in their study, and far less expensive.[31] These 4 retrospective studies offer Class III medical evidence on the use of UFH, dalteparin and enoxeparin as prophylaxis for DVT[28-31]; however, the study populations were heterogeneous and difficult to compare. Many patients in these various studies were managed with chemical prophylaxis and other prophylactic modalities, yet others were managed with chemical prophylaxis alone; therefore, conclusions regarding these agents as stand-alone therapy cannot be made.

Prophylaxis: Inferior Vena Cava Filters

The use of inferior vena cava (IVC) filters as prophylactic devices for thromboembolism has been advocated.[32-35] Wilson et al[35] placed caval filters in 15 SCI patients who were concurrently treated with either low dose heparin or pneumatic stockings. None suffered a PE during a 1-year follow-up period. The reported 1-year patency rate of the IVC was 81%. The authors noted that their results are superior to those from a historical cohort of 111 patients treated without IVC filters.[35] Seven of the cohort patients suffered a PE; however, 6 of the 7 were not receiving any prophylaxis at the time of their PE. The single patient they described who had a PE while receiving DVT prophylaxis suffered a gunshot blast injury to the spine.[35] Khansarinia and colleagues[33] described a historical cohort study of 108 general trauma patients treated with prophylactic IVC filters. None of these patients suffered a PE. They compared this group to another historical cohort of 216 patients treated (apparently) with either low dose heparin or pneumatic compression devices prior to the use of IVC filters. Thirteen of these 216 suffered a PE, 9 of which were fatal.[33] The mortality among the filter treatment group was lower than the mortality of the control group, but the difference was not significant (16% vs 22%).[33] Tola et al[36] have shown that percutaneous IVC filter placement in the intensive care unit setting is safe and is less costly than IVC filter placement in the operating room or the radiology suite. These authors suggest that IVC interruption is an effective means to prevent PE.

The placement of IVC filters is not without complications. Balshi et al, Kinney et al, and others have described distal migration, intraperitoneal erosion, and symptomatic IVC occlusion in patients with SCI treated with IVC filters.[37-39] Balshi et al[37] have hypothesized that quadriplegic patients are at higher risk for complications from IVC filter placement due to loss of abdominal muscle tone, as well as their requisite use of the "quad cough" maneuver.

In 2009, Gorman and colleagues[40] performed a retrospective chart review of 114 patients with SCI, 47% of whom were treated with prophylactic IVC filter placement. All SCI patients received either LMWH or heparin prophylaxis. The IVC filter group had significantly more DVTs (20.4%) when compared to the group without filters (5.4%). Interestingly, only 1 patient suffered from PE; that patient had received a prophylactic IVC filter.

Timing and Duration of Prophylaxis

The vast majority of VTE events appear to occur within the first 2 to 3 months following injury. Naso described his experience with 4 patients with PE in a group of 43 SCI patients. All 4 PE events were documented within 3 months of injury.[41] Perkash et al reported an 18% incidence of thromboembolism in a series of 48 patients with acute spinal cord injury and 2 patients with transverse myelitis. Only 1 patient had a new onset PE 3 months after injury; 2 other patients had recurrent PE 3 months after injury due to existing DVT.[11] Lamb et al[8] determined that the risk of thromboembolic events in their series of 287 SCI patients was 10%. The vast majority of events occurred within the first 6 months following injury. Twenty-two of 28 events they documented occurred within the first 3 months of injury. El Masri and Silver[3] reported 21 documented events of PE in a series of 102 spinal injured patients. Twenty of 21 events occurred within the first 3 months following SCI. A pulmonary embolism occurred in a patient with a history of PE whose therapeutic anticoagulation was discontinued for gallbladder surgery.[3] DeVivo et al[42] described a 500-fold risk of dying from PE in the first month following acute SCI, compared to age- and gender-matched non-injured patients. This risk decreased with time, but remained approximately 20 times greater than that for normative controls 6 months following SCI.[42] McKinley et al[43] studied chronic spinal injured patients in a rehabilitation center setting and found an incidence of DVT of 2.1% in the first year following injury. This incidence dropped to between 0.5% and 1% per year thereafter.[43] The collective data from these 6 studies provide confirming evidence that the great majority of thromboembolic events (DVT and PE) occur within the first 3 months after acute SCI and is considered Class II medical evidence.[3,8,11,41-43] Prolonged prophylactic anticoagulation therapy is not without risk, and is associated with bleeding complications.[5,23] The vast majority of studies addressing prophylactic treatment for DVT and PE have utilized treatment courses of 8 to 12 weeks duration with success. In 2002, Aito and colleagues[44] studied 275 patients admitted to their institution with acute SCI (ASCI) who were screened for DVT with color Doppler ultrasonography at admission and at 30 to 45 days, or when clinically indicated. They found only 2% of patients admitted within 72 hours had DVT compared to 26% among patients admitted between 8 and 28 days after injury. Remarkably, none of the delayed admission group patients were prophylactically treated with sequential compression devices prior to admission. These authors provide Class II medical evidence that the early application of both chemical and mechanical prophylaxis reduces the incidence of DVT in patients with acute SCI.[44]

In 2009, Ploumis et al[45] surveyed 25 spine surgeons to obtain a consensus on the use of pharmacologic thromboprophylaxis following spinal injury. The consensus was that postoperative pharmacologic thromboprophylaxis was unnecessary in patients with cervical spinal injuries without SCI; however, it was recommended in instances of cervical spine trauma with SCI or patients treated with anterior thoracolumbar procedures, irrespective of SCI. It was recommended that pharmacologic thromboprophylaxis be initiated preoperatively as soon as possible in patients with SCI and in cases requiring a delay in surgical treatment. Pharmacologic prophylaxis was recommended to be administered for at least 3 months post-injury.[45]

For these reasons, it is recommended that prophylactic treatment be continued for 8 to 12 weeks in spinal cord injury patients without other major risk factors for DVT and PE. Prophylactic treatment may be discontinued earlier in patients with useful motor function in the lower extremities, as these patients appear to be at less risk for DVT and PE.[10,16]

Diagnosis

The diagnosis of DVT in various studies has been made based on the clinical examination, Doppler ultrasound examination, impedence plethysmography, venous occlusion plethysmography (VOP), venography, fibrinogen scanning, or by D-Dimer measurement.[2-7,10,11,17,19,21,41,42,46-50] There is no established "gold standard" examination for DVT. Venography has been considered the best test, but is too inaccurate, is not possible in all patients, is invasive, and expensive.[51] Gunduz et al[6] report a 10% incidence of adverse effects from venography including post-venographic phlebitis and allergic reactions. Doppler ultrasound examination and VOP are both less invasive, less expensive, and more broadly applicable.[12,51] The sensitivity and specificity of these examinations when compared with venography has been generally reported to range from 80% to 100%. Chu et al[52] compared Doppler ultrasound and VOP with the clinical examination and found all 3 to agree 100% of the time in a small series of 21 patients. Perkash and colleagues[11] studied a series of 48 SCI patients with daily physical examinations and weekly VOP. They found that the sensitivity of the clinical examination compared to VOP was 89%. The specificity was 88%, the negative predictive value was 97%, and the positive predictive value was 62% in their study. Other authors have described the increased sensitivity of fibrinogen scanning and the use of D-Dimer measurements for the diagnosis of DVT.[25,53]

TABLE. Evidentiary Table: Deep Vein Thrombosis and Venous Thromboembolism

Citation	Description of Study	Evidence Class	Conclusions
Arnold et al,[31] *Am Surg*, 2010	Retrospective chart review comparing UFH to LMWH in 476 trauma patients, 24 with SCI.	III	Overall risk of DVT in enoxaparin group was 6.75% compared to 7.11% in UFH group. In SCI patients, risk of DVT 36.4% with enoxaparin vs 15.4% with UFH.
Gorman et al,[40] *J Trauma*, 2009	Retrospective chart review comparing prophylactic IVC filter in 47% of 114 patients.	III	Higher incidence (20.4% vs 5.2%) of DVT in IVC filter group; only PE case in filter group.
Slavik et al,[30] *J Trauma*, 2007	Retrospective cohort study comparing dalteparin (LMWH) qday to enoxaparin BID in acute SCI and major orthopedic trauma.	III	Incident VTE in dalteparin 9.7% vs 1.6% for enoxaparin ($P = 0.103$).
Green et al, [29] *Am J Phys Med Rehabil*, 2005	Comparison of DVT rates in ASCI populations from 1992 to 1995 vs 1999 to 2003.	III	Drop from 21% to 7.9% DVT rate, coincided with transition to LMWH from UFH.
Hebbeler et al,[28] *J Spinal Cord Med*, 2004	Retrospective chart review comparing once-daily to twice daily enoxaparin during rehabilitation after SCI.	III	Equal effectiveness.
Spinal Cord Injury Thromboprophylaxis Investigators,[26] 2003	Prospective multicenter comparison of UFH to LMWH in rehabilitation phase (2 weeks post SCI).	III	21.7% VTE in UFH group vs 8.5% in LMWH group ($P = .052$).
			High exclusion rate.
Spinal Cord Injury Thromboprophylaxis Investigators,[27] 2003	Prospective multicenter randomization of 476 acute SCI patients to either UFH + SCDs or enoxaparin. Only 107 "assessable" patients.	III	Similar incidence of DVT, but significantly lower PE in enoxaparin (*study funded by enoxeparin manufacturer).*
			High exclusion rate.
Aito et al,[44] *Spinal Cord*, 2002	Prospective observation of early (<72 hr) vs late (mean 12 days) initiation of mechanical and chemical DVT prophylaxis in 275 patients.	II	26% DVTs in delayed group compared to 2% in early group.
Chen et al,[55] *Arch Phys Med and Rehab*, 1999	Huge population of SCI patients (1649) studied from admission to rehab (mean 19 days) to discharge (mean 50 days). Incidence of DVT + PE declining over time but remains 6.1% despite prophylaxis.	III	DVT/PE still problems despite prophylaxis. (See McKinley for follow-up).
McKinley et al,[43] *Arch Phys Med Rehabil*, 1999	Chronic SCI population studied. Incidence of DVT highest during first year (2.1%) but then drops off to 0.5-1% per year thereafter.	III	Risk of DVT/PE highest during first year following injury and then risk drops significantly.
Powell et al,[12] *Arch Phys Med Rehab*, 1999	Incidence of DVT in SCI population (n = 189) on transfer to rehab dx with ultrasound was 4.1% in group who received prophylaxis vs 16.4% in group without prophylaxis. In prophylaxis group, DVTs only occurred in pts receiving heparin alone.	II	Prophylaxis decreases incidence of DVT in SCI population. Heparin alone was the least effective treatment measure.
Roussi et al,[25] *Spinal Cord*, 1999	6 of 67 (9%) of SCI patients developed DVT despite prophylaxis with LMWH.	III	Incidence of DVT despite prophylaxis with LMWH 9%.
	D-Dimer had 100% negative predictive value compared to duplex Doppler. (However, specificity only 34% and PPV 13%).		D-Dimer is sensitive but not specific test for DVT.
Winemiller et al,[22] *Journal of Spinal Cord Medicine*, 1999	Retrospective case-cohort study of 428 patients. TE occurred in 19.6%. Compression stockings and sequential compression devices lowered risk of TE. Effects of low dose heparin were seen in first 14 days but were not significant. TEs all occurred in first 150 days.	III	SCD and stockings reduce risk of thromboembolism. Low dose heparin may be effective in first 14 days following injury.

(Continues)

TABLE. ***Continued***

Citation	Description of Study	Evidence Class	Conclusions
Tomaio et al,[56] *Journal of Spinal Cord Medicine*, 1998	Enoxaprin (LMWH) vs heparin use for initial DVT treatment in group of 6 SCI patients.	III	Enoxaprin was cost effective alternative to IV heparin for initial treatment of DVT.
Harris et al,[24] *Am J of Phys Med and Rehab*, 1996	Retrospective study of enoxaparin (LMWH) in 105 SCI pts. (one third intact, 40 complete). No clinical DVT/PE in 105, no ultrasound evidence in 60.	III	Enoxaparin is safe and effective for DVT prophylaxis in the SCI patient.
Khansarinia et al,[33] *Journal of Vascular Surgery*, 1995	Retrospective historical cohort comparison of prophylactic PGF in 324 general trauma patients. PGF group had fewer PE than control group.	III	Greenfield filter safe and effective for PE prophylaxis in general trauma population.
Geerts et al,[16] *New England Journal of Medicine*, 1994	Prospective evaluation of 716 trauma patients (no prophylaxis) with VOP and venography. Incidence of DVT in SCI population (n = 66) was 62%.	III	DVT is very common in SCI patients if no prophylaxis used.
Wilson et al,[35] *Neurosurgery*, 1994	Inserted Caval filters in 15 SCI patients. None had DVT or PE in 1 year. Claims this result superior to historical controls (No evidence presented to support this claim). One-year patency rate was 81%.	III	Insertion of caval filters appears to be safe in SCI patients.
Green et al,[23] *Archives of Physical Medicine and Rehabilitation*, 1994	Historical cohort comparison of LMWH and standard and adjusted dose heparin prophylaxis. Trauma patients treated with 8 week course of LMWH had fewer thromboembolic complications than those treated with heparin, $P = 0.15$.	III	LMWH may be safer and more effective for prophylaxis than mini dose or adjusted dose heparin.
Gündüz et al,[6] *Paraplegia*, 1993	31 SCI patients on low dose heparin therapy underwent venography. Incidence of DVT was 53.3%.	III	Incidence of DVT high in SCI patients despite low dose heparin (therapy started on rehab unit).
Burns et al,[2] *Journal of Trauma*, 1993	Prospective assessment of DVT in high risk trauma patients with US. Found incidence of 21% (12/57) despite low dose heparin or pneumatic boots in 85%.	III	DVT is common despite use of low dose heparin or pneumatic boots.
Lamb et al,[8] *J Am Paraplegia Soc*, 1993	287 chronically injured SCI patients followed. Overall incidence of thromboembolic events was 10%, vast majority of events in first 6 months, 22 of 28 in first 3 months after SCI.	III	Prophylactic therapy not necessary beyond 6 months in SCI population.
Kulkarni et al,[7] *Paraplegia*, 1992	100 SCI patients prospectively treated with low dose heparin. 26% incidence of clinically detected DVT (9% PE) noted.	III	DVT and PE incidence significant despite low dose sq heparin.
Merli et al, *Paraplegia*, 1992[9]	Heparin plus pneumatic stockings equal to historical controls of heparin plus stimulation and better than historical controls of heparin or placebo in SCI patients.	II	Low dose heparin plus pneumatic hose safe effective as DVT prophylaxis in SCI patients.
Waring and Karunas,[14] *Paraplegia*, 1991	Large database (1419) of SCI patients. Incidence of DVT was 14.5%, PE 4.6%. Severity of injury was a predictor of DVT and age was a predictor of PE. No mention made of prophylactic measures.	III	DVT and PE are significant problems in SCI population. Age and injury severity need to be addressed in studies comparing treatment modalities.

(Continues)

TABLE. ***Continued***

Citation	Description of Study	Evidence Class	Conclusions
Yelnik et al,[50] *Paraplegia*, 1991	Prospective study of 127 SCI patients with phlebography. 29/127 had DVT on admission to rehab unit. Of 87 patients with initially negative studies, 12 developed DVT despite prophylaxis for up to 80 days.	III	Incidence of DVT in SCI population is high and high risk period extends to end of third month. Authors recommend periodic screening with phlebography.
Balshi et al,[37] *Journal of Vascular Surgery*, 1989	Case series of 13 quadriplegic patients who had vena caval filters placed for DVT or PE.	III	Filter placement may be associated with significant long-term morbidity in the SCI population, particularly those requiring aggressive pulmonary toilet.
	Abnormalities of the filter were detected in 5/11 patients who had follow-up X-rays. Two patients required laparotomy to remove filters, 4 had distal migration, and 2 had narrowing of diameter associated with caval occlusion. Nine of these 11 patients were treated with the "quad cough" technique.		
DeVivo et al,[42] *Arch Intern Med*, 1989	Epidemiological study of causes of death for SCI patients. Highest ratios of actual to expected causes of death were for pneumonia, PE, and septicemia. The risk ratio for TE dropped significantly from 1-month post injury (SMR 500) to $>$ 6 months post injury (SMR 20).	III	TE is a significant problem for patients who survive SCI. Biggest period of risk is in first few months following injury, but risk continues even after 6 months.
Green et al,[5] *JAMA*, 1988	RCT of Low dose vs adjusted dose heparin in SCI patients. Rate of TE lower in adjusted dose group (7% vs 31%) (intent to treat p = ns), but also had higher rate of bleeding complications (7 of 29).	I	Adjusted dose heparin more effective than low dose heparin, bleeding more common in adjusted dose group.
Merli et al,[21] *Arch Phys Med Rehabil*, 1988	Prospective randomized trial of placebo vs mini dose heparin vs heparin plus electrical stimulation in group of 48 SCI patients.	I	Low dose heparin no better than placebo, heparin plus electrical stimulation much better for DVT prophylaxis in SCI patients.
	Heparin group = placebo group at 50%, stim group significantly fewer DVT		
Weingarden et al,[57] *Paraplegia*, 1988	Retrospective review of 148 SCI patients. Ten had documented DVT or PE. Of 6 patients who had adequate records, all 6 had fever as a presenting sign, 4 had no other clinical signs recorded.	III	Fever may indicate thromboembolic disease in SCI patients.
	All episodes occurred in first 12 weeks.		
Becker et al,[17] *Neurosurgery*, 1987	Randomized trial of rotating vs non-rotating beds in the acute setting following SCI (10 days), N = 15.	I	Rotating beds reduce the incidence of DVT during the first 10 days following SCI.
	Plethysmography and fibrinogen leg scans used.		
Tator et al,[13] *Canadian Journal of Neurological Sciences*, 1987	17% incidence of DVT in series of 208 SCI patients. Incidence was higher in operated patients (23%) compared to non operated (10%). Use of prophylaxis is not mentioned.	III	Patients requiring surgery may have higher incidence of DVT.

(Continues)

TABLE. ***Continued***

Citation	Description of Study	Evidence Class	Conclusions
Chu et al,[52] *Archives of Physical Medicine and Rehabilitation*, 1985	Comparison between doppler US, Venous occlusion plethysmography and clinical exam in SCI patients. All had sensitivity and specificity of 100% in small (n = 21) series. Overall incidence 19%. (Class III because no gold standard used).	III	Doppler US, VOP, and clinical examination all good for diagnosis of DVT.
Myllynen et al,[10] *Journal of Trauma*, 1985	Compared incidence of DVT in immobilized spinal injured patients with and without paralysis. Those with paralysis had a 100% DVT incidence (fibrinogen scan) vs 0% for patients immobilized following spinal fracture without paralysis.	III	Incidence of DVT is very high in SCI patients and is not totally dependent on immobilization.
El Masri and Silver,[3] *Paraplegia*, 1981	Retrospective review of 102 patients with SCI. There were 21 episodes of PE in 19 patients. Twenty of 21 PTE occurred in first 3 months after SCI.	III	Authors cite efficacy of oral anticoagulation. They recommend prolonged treatment (up to 6 months) in patients with obesity or prior history of DVT.
	No patient with PE was adequately anticoagulated at the time of the PE (oral phenindione). Only 8/19 patients had evidence of DVT by exam or VOP.		
Frisbie and Sasahara,[4] *Paraplegia*, 1981	Small prospective controlled study of Low dose (5000 F06D BID) heparin vs Control group. No difference in incidence of DVT noted (only 7% in each group). Authors suggest protective effect of frequent physiotherapy.	II	No difference between low dose heparin and control groups in SCI patients receiving twice daily physiotherapy.
Perkash et al,[48] *Paraplegia*, 1980	Treatment of 8 patients with thromboembolism discussed. Authors used heparin followed by coumadin with reasonable results.	III	Anticoagulation is effective treatment for SCI patients with thromboembolism.
Perkash et al,[11] *Paraplegia*, 1978	Incidence of thromboembolism in 48 SCI patients was 18%.	III	Clinical examination appears to be quite good for detection of DVT in subacute setting. Period of risk may extend beyond 12 weeks.
	Clinical exam sensitivity 89%, specificity 88%, NPV 97%, PPV 62%.		
	One third of thromboembolic events occurred >12 weeks following injury.		
Watson,[49] *Paraplegia*, 1978	Retrospective historical cohort study looking at low dose heparin vs no prophylaxis.	III	Heparin group had fewer TE complications. No TE events after 3 months despite prophylaxis cessation at 3 months.
Casas et al,[18] *Paraplegia*, 1977	Prospective assessment of low dose heparin in 18/21 patients with SCI (mean duration 66 days). No patient treated had symptomatic DVT or PE. No use of US/PG/venography.	III	Low dose heparin may be useful for prevention of symptomatic DVT.
Todd et al,[53] *Paraplegia*, 1976	Used VOP, Fibrinogen scan and venography to study 20 SCI patients for 60 days. Fibrinogen scan was positive in all patients but was confirmed by another test in only half of the cases.	III	DVT is common in SCI population.
Hachen,[19] *Paraplegia*, 1974	Cohort controlled trial of low-dose heparin (5000003F t.i.d.) vs oral warfarin in SCI patients. Heparin group had significantly fewer TE events.	II	Low dose SQ heparin better than oral warfarin for prophylaxis following acute SCI.

(Continues)

TABLE. ***Continued***

Citation	Description of Study	Evidence Class	Conclusions
Naso,[41] *Arch Phys Med Rehab*, 1974	PE occurred in 4/26 patients with acute (<3 months) SCI but none occurred in 17 patients with chronic (>3 months) SCI.	III	SCI patients primarily at risk during first 3 months following injury.
Watson,[20] *Paraplegia*, 1968	Incidence of thromboembolic complications per year ranges from 8 to 40% in same unit (no prophylaxis).	III	Thromboembolic complications are a significant problem and there is variability year to year despite identical treatment strategies.

[a]ASCI, acute spinal cord injury; DVT, deep venous thrombosis; IVC, inferior vena cava; IV, intravenous; LMWH, low molecular weight heparins; NPV, negative predictive value; PE, pulmonary embolism; PG, phlebography; PGF, percutaneous Greenfield filter; PPV, positive predictive value; SCD, sequential compression device; SCI, spinal cord injury; SQ, subcutaneous; TE, thromboembolic; UFH, unfractionated heparin; US, ultrasound; VOP, venous occlusion plethsmography; VTE, venous thromboembolism.

Increased sensitivity is associated with decreased specificity. For example, Roussi et al[25] reported 100% sensitivity and 100% negative predictive value with D-Dimer determinations compared to Doppler ultrasound and the clinical examination. The specificity of D-Dimer was only 34%, and the positive predictive value was only 13%. Similarly, Todd et al[53] found that fibrinogen scanning was positive in all 20 patients studied in a prospective fashion. However, the diagnosis of DVT was confirmed by another test in only half of the cases. Akman and colleagues came to similar conclusions when they studied the D-Dimer assay in 68 patients with stroke, spinal cord injury, and head injury. The specificity and positive predictive value were low, at 55.3% and 48.7%, respectively. However, they reported the test to be 95.2% sensitive, with a 96.2% negative predictive value, suggesting it has value for excluding a diagnosis of VTE.[54]

Overall, no single test is completely applicable, accurate, and sensitive for the detection of DVT in the SCI patient population. Furthermore, a substantial number of patients who suffer from PE are found to have negative lower extremity venograms. The Consortium for Spinal Cord Medicine has recommended the use of ultrasound for the study of patients with suspected DVT, and venography when clinical suspicion is strong and the ultrasound examination is negative.[16] In 2008, the American College of Chest Physicians recommended serial Doppler ultrasonography in spinal cord injury patients. Based upon the reported literature on this subject, Class III medical evidence suggests that each of these diagnostic tests for DVT has merit, each with limitations as noted above.

SUMMARY

Thromboembolic disease is a common occurrence in patients who have sustained a cervical spinal cord injury and is associated with significant morbidity. Class I medical evidence exists demonstrating the efficacy of several means of prophylaxis for the prevention of thromboembolic events. Therefore, patients with SCI should be treated with a regimen aimed at VTE prophylaxis.

Although low dose heparin therapy has been reported to be effective as prophylaxis for thromboembolism in several Class III studies, other Class I, Class II, and Class III medical evidence indicates that better alternatives than low dose heparin therapy exist. These alternatives include the use of low molecular weight heparin, adjusted dose heparin, or anticoagulation in conjunction with rotating beds, pneumatic compression devices or electrical stimulation. Oral anticoagulation alone does not appear to be as effective as these other measures used for prophylaxis.

There appears to be a DVT prophylaxis benefit to early anticoagulation in acute spinal cord injury patients. Class II medical evidence supports beginning mechanical and chemical prophylaxis upon admission after SCI and holding chemical prophylaxis 1 day prior to and 1 day following surgical intervention.

The incidence of thromboembolic events appears to decrease over time and the prolonged use of anticoagulant therapy is associated with a definite incidence of bleeding complications. There are multiple reports of the beneficial effects of the prophylaxis therapy for 6 to 12 weeks following spinal cord injury. Class II medical evidence indicates that the majority of thromboembolic events occur in the first 3 months following acute SCI and very few occur thereafter. For these reasons, it is recommended that prophylactic therapy be discontinued after 3 months unless the patient is at high risk for a future VTE event (previous thromboembolic events, obesity, advanced age). It is reasonable to discontinue therapy earlier in patients with retained lower extremity motor function after spinal cord injury, as the incidence of thromboembolic events in these patients is substantially lower than among those patients with motor complete injuries.

Although the guidelines author group concluded that caval filters appeared to be efficacious for the prevention of PE in SCI patients in the 2002 guideline on this topic, more recent medical evidence suggests that prophylactic filters may be more morbid than initially believed. Caval filters still have a role for SCI patients who have suffered thromboembolic events despite anticoagulation, and for SCI patients with contraindications to anticoagulation and/or the use of pneumatic compression devices.

There are several methods available for the diagnosis of DVT. Venography has long been considered the best test, but is invasive, not applicable to all patients, and is associated with intrinsic morbidity. Duplex Doppler ultrasound, impedence plethysmography, venous occlusion plethysmography and the clinical examination have been

reported to have sensitivities of approximately 90% and are noninvasive. It is recommended that these noninvasive tests be used for the diagnosis of DVT in SCI patients and that venography to diagnose DVT be reserved for the rare situation when clinical suspicion is high and the results of ultrasound or plethysmography testing are negative.

KEY ISSUES FOR FUTURE INVESTIGATION

Although thromboembolic events in the SCI patient are associated with significant morbidity, no study has demonstrated improved outcomes in SCI patients as a result of surveillance testing for them. A prospective study evaluating 6-month outcomes in patients treated with prophylaxis with or without surveillance ultrasound imaging would be a substantial and potentially cost-saving contribution to the literature.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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