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Venous Thromboembolism Following Spinal Cord Injury

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Abstract

Objective—To systematically review the published literature on the treatment of deep venous thromboembolism post-spinal cord injury (SCI).

Data Sources—MEDLINE/Pubmed, CINAHL, EMBASE, and PsycINFO databases were searched for articles addressing the treatment of deep venous thromboembolism post-SCI. Randomized controlled trials (RCTs) were assessed for methodologic quality using the Physiotherapy Evidence Database Scale, while non-RCTs were assessed using the Downs and Black evaluation tool.

Study Selection—Studies included RCTs, non-RCTS, cohort, case-control, case series, pre-post, and postinterventional studies. Case studies were included only when no other studies were available.

Data Extraction—Data extracted included demographics, the nature of the study intervention, and study results.

Data Synthesis—Levels of evidence were assigned to the interventions using a modified Sackett scale.

Conclusions—Twenty-three studies met inclusion criteria. Thirteen studies examined various pharmacologic interventions for the treatment or prevention of deep venous thrombosis in SCI patients. There was strong evidence to support the use of low molecular weight heparin in reducing venous thrombosis events, and a higher adjusted dose of unfractionated heparin was found to be more effective than 5000 units administered every 12 hours, although bleeding complication was more common. Nonpharmacologic treatments were also reviewed, but again limited evidence was found to support these treatments.

Keywords

Rehabilitation; Spinal cord injuries; Venous thrombosis

Deep venous thrombosis and subsequent PE remain significant causes of morbidity and mortality in spinal cord injured patients. The incidence of DVT in patients with acute SCI was reported to be greater than 50% in early prospective studies– with the incidence of fatal PE estimated as high as 5%.,– The prevalence of DVT in acute SCI has been found to range from 14% to 100% and from 9% to 90%. Various test methods exist for diagnosing DVTs in individuals; however, venography has been considered the criterion standard.

The clinical diagnosis of DVT and PE are often unrealiable and diagnostic testing is necessary to confirm the diagnosis. Diagnostic testing varies from center to center, but 3

tests for DVT have become important; venous ultrasound, venography, and the D-dimer assay; for PE 2 commonly used tests are the ventilation/perfusion scan and the spiral CT scan. Venography is considered the definitive test for DVT but is an invasive study. Venous ultrasound is cheap and noninvasive, can be done as a screen or serially to monitor the patient. Sensitivity is only 73% for distal clots, but 95% for the more dangerous proximal clots. The D-dimer assay is a rapid, noninvasive, and inexpensive test and measures a fibrin degradation product, D-dimers, as fibrin is in the main component of thrombosis formation. D-dimer test is highly sensitive, but lacks specificity because D-dimers are found in other disease states, reducing the specificity of the test. A positive diagnosis of DVT can only be made if venogram is positive or if venous ultrasound is positive of 2 or more sites of proximal vein. Nuclear ventilation/perfusion scans are often used to diagnose a PE and the likelihood of a positive diagnosis increases with the size, shape, and number of deflects on perfusion scanning with a normal ventilation scan. A spiral CT scan is a quick CT scan of the entire thorax in 1 breath-hold and is most accurate when the PE is large.

The high risk of DVT in acute SCI patients is a consequence of the simultaneous presence of all 3 components of Virchow's triad: hypercoagulability, stasis, and intimal (venous inner wall) injury, with stasis being the greatest concern. VT most commonly begins with a calf DVT.– Although only 20% of DVTs extend into the proximal veins,– these result in over 80% of symptomatic DVTs. Distal calf DVTs which do not extend proximally rarely are a sources of PEs, so that they are much less worrisome. Nonetheless, even those who caution against over-treatment of distal DVTs concede that there is a need for randomized trials to assess the usefulness of diagnosing and treating distal DVTs.

Proximal (ie, at the level of knee or above) DVTs continue to be the primary source of concern. PE is reported in 8% to 14% of patients with an acute SCI,, with the majority being asymptomatic or unrecognized. Symptomatic PEs tend to be relatively large, with reported mortality rates of up to 5%.–

The following article reviews various interventions used when treating venous thromboemboli in individuals with SCI and is part of the Spinal Cord Injury Rehabilitation Evidence Review (SCIRE), the details of which are available at http://www.scireproject.com.

Methods

A systematic review was conducted of all relevant literature published from 1980 to 2007 using multiple databases (MEDLINE/PubMed, CINAHL, EMBASE, and PsycINFO) and SCIRE methodology. This search involved reviewing over 17,000 titles and 8400 abstracts, and the final analysis of approximately 700 articles. Studies only were included for analysis if at least 50% of subjects had a SCI, there were at least 3 subjects, and there was a definable intervention being studied. A quality assessment was conducted for each article using either the PEDro scoring system or Downs and Black methodology for randomized and nonrandomized studies, respectively., The PEDro tool consists of 11 questions, but uses only questions 2 through 11 to assess study quality. The maximum score yielded by any RCT was 10, with higher scores indicating better study quality. The following cut-points were used to

categorize studies by quality: excellent (9–10); good (6–8); fair (4–5); poor (<4). The Downs and Black tool consists of 27 questions that evaluate the quality of data reporting, external validity, and internal validity (both bias and confounding). Due to ambiguity in the last question, a slight modification was made; thus, the total score any reviewed article could receive was 28 (1 question was scored out of 2), with a higher score indicating higher methodologic quality.

Tables provided in this paper include the PEDro or Downs and Black scores, inclusion and exclusion criteria, the type of study, a brief summary of the interventions and outcome measures, and study results. Levels of evidence were assigned to the studies for each intervention, using a modified Sackett approach. Sackett's levels of evidence were modified and collapsed into the following: level 1 evidence came from RCTs with a PEDro score of higher than 6; level 2 evidence was applied to RCTs with PEDro scores of 5 or less or nonrandomized prospective controlled or cohort studies; level 3 evidence from case control studies; level 4 evidence was assigned to pre-post/posttest/case-series; and level 5 evidence included those studies that were observational or case reports.,

RESULTS

Pharmacologic Agents for DVT Prophylaxis

Unfractionated heparin for prophylaxis—Heparin acts as an anticoagulant by forming a complex with antithrombin, catalyzing the inhibition of several activated blood coagulation factors: XIIa, XIa, IXa, Xa, and thrombin. Heparin's onset of action is immediate and, for that reason, it often is used for acute conditions. Bleeding is the most common adverse effect of heparin. Osteoporosis has been associated with the prolonged use of high doses of heparin, though its occurrence is relatively infrequent. Thrombocytopenia is another uncommon but serious side-effect of treatment (table 1).

Historically, UFH has been the standard treatment for the prevention of venous thromboembolism acutely post-SCI. Merli et al evaluated 53 acute SCI patients who were randomly assigned to 1 of 3 treatment arms: (1) placebo saline (n=17); (2) 5000 IU heparin (n=16); and (3) heparin 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, but there was a significant improvement in the heparin and electrical stimulation group. The study was prematurely discontinued because of the apparent benefit of the heparin plus electrical stimulation. Frisbie and Sasahara conducted a non-RCT of 32 SCI patients comparing 5000 IU heparin given subcutaneously every 12 hours until day 60 post-SCI versus no heparin. VT was uncommon in both the control (1 of 17) and heparin groups (1 of 15).

Green et al studied 75 SCI patients randomized to receive either 5000 IU subcutaneously every 12 hours of either fixed-dose or adjusted-dose heparin. The dose was adjusted based on the APTT, to a maximum of 15,000 IU subcutaneously every 12 hours. Patients on the adjusted-dose regimen received a mean of 13,200 IU subcutaneously every 12 hours. Thromboembolism was detected in 9 (31%) of 29 on the fixed-dose regimen but only 2 (7%) of 29 on the adjusted-dose regimen. No bleeding complications were noted with the fixed

dose regimen; however, 7 suffered bleeding complications with adjusted dosing. In this study, higher doses decreased the risk of venous thromboemboli, but increased the risk of bleeding complications.

Typically, prophylactic treatment involves 5000 IU of heparin given subcutaneously every 12 hours. One RCT and 1 controlled study examining the efficacy of this dose versus placebo identified no difference in the incidence of venous thrombosis. Interestingly, Merli et al found that heparin plus electrical muscle stimulation significantly reduced the incidence of venous thrombosis relative to heparin alone.

Conclusions

There is level 2 evidence (based on 1 low-quality RCT and 1 non-RCT) that 5000 IU of unfractionated heparin given subcutaneously every 12 hours is no more effective than placebo as prophylaxis against venous thrombosis post-SCI. There is level 1 evidence (based on 1 RCT) that an adjusted (higher) dose of subcutaneous heparin is more effective as prophylaxis against venous thromboembolism than the administration of 5000 IU subcutaneous heparin every 12 hours; however, the adjusted dose appears to be associated with a higher incidence of bleeding complications.

LMWH for Prophylaxis

LMWH is derived from standard heparin. Standard heparin has a molecular weight of 5000 to 30,000 daltons, whereas the molecular weight of 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 its predictability, dose-dependent plasma levels, long half-life, and reduced bleeding for a given antithrombotic effect. Thrombocytopenia has not been associated with the short-term use of LMWH. LMWH is administered once or twice daily and is used both during the high-risk period when prophylaxis for DVT is recommended, and while waiting for oral anticoagulation to take effect in the treatment of DVT. It is not necessary to monitor the APTT, or adjust the dose of the drug.

Heparin Analogues for Prophylaxis

Danaparoid sodium (Orgaran) is an alternative anticoagulant for patients who have developed heparin-induced thrombocytopenia. Danaparoid is a low molecular weight heparinoid. Its active components consist of heparin sulfate, dermatan sulfate, and chondroitin sulfate; however, it exerts effects similar to other LMWHs and acts by deactivating thrombin.

LMWH versus UFH for Prophylaxis

The most commonly studied LMWH for the prophylaxis of venous thromboembolism post-SCI is enoxaparin. Enoxaparin has a plasma half-life of 4.4 hours, versus 0.35 hours for UFH, and its subcutaneous bioavailability is 50% versus 20% for UFH. Four trials have compared UFH and LMWH (table 2).

The SCI thromboprophylaxis investigators conducted a non-RCT comparing low dose UFH (5000 IU subcutaneously every 8 hours (q8h)) and enoxaparin (40mg once daily) during a 6-week rehabilitation phase in SCI patients. Venous thromboembolism was detected in 21.7% of UFH and 8.5% of enoxaprin patients, a difference that approached statistical significance (*P*=.052).

The SCI thromboprophylaxis investigators also conducted a RCT involving 476 SCI patients assigned to receive thromboprophylaxis with either a combination of low-dose UFH (5000 IU s/c q8h) plus IPC at least 22 hours each day, or enoxaparin 30mg given subcutaneously every 12 hours. Three hundred and sixty nine patients were excluded from the study due to protocol deviations, bleeding or other clinical events, withdrawal of consent, intercurrent illness, thrombocytopenia, or other adverse laboratory findings. Among 107 assessable patients, the incidence of VT was 63.3% with UFH/IPC versus 65.5% with enoxaparin (*P*=.81). The incidence of PE was 18.4% in the UFH/IPC group versus 5.2% with enoxaparin (*P*=.03). The incidence of major bleeding was 5.3% with UFH/IPC versus 2.6% with enoxaparin (*P*=.14). This was the only study in which the incidence of venous thromboemboli was not significantly less with LMWH relative to UFH, an effect likely attributable to the addition of the pneumatic compression. Pulmonary emboli still were less in the LMWH group, but the difference did not achieve significance.

Thumbikat et al retrospectively compared 1 group of SCI patients (n=101) who received a combination of UFH followed by warfarin and another group (n=72) who received enoxaparin (LMWH). Four patients in the UFH/warfarin group (4%) and 13 patients in the LMWH group (18.1%) developed venous thromboembolic episodes. Of the 72 patients on enoxaparin, 2 (15%) of 13 on 40mg daily and 10 (17%) of 59 on 20mg once daily developed DVT/PE. One patient on UFH and 6 on LMWH developed DVT postmobilization with discontinuation of anticoagulation.

Green et al randomized 41 patients with SCI to either standard heparin or LMWH. Five patients in the standard heparin group (n=21) had thrombotic events, including 2 patients with fatal pulmonary emboli. Two other patients had bleeding severe enough to necessitate withdrawal of the heparin. The cumulative event rate in the standard heparin group was 34%, while the LMWH group had neither thrombotic events nor bleeding episodes. The difference between the 2 groups was significant (*P*=.006). Green et al also studied 60 acute SCI patients with complete motor paraplegia, all of whom received a daily dose of 3500 IU of LMWH given subcutaneously. Forty-eight of those recruited were able to complete the study; however, 12 were unable to complete the study due to discharge from care, transfer to other facilities or death. Treatment began within 72 hours of injury and continued for 8 weeks. Forty patients completed the 8 weeks of prophylaxis uneventfully, while 8 suffered a thrombotic event (17%). Of the thrombotic events, 2 were pulmonary emboli, 4 were proximal DVTs, and 2 were distal calf DVTs. The differences in bleeding between standard heparin and LMWH, when combined with data from a previous study (68 LMWH [20 from previous study] and 79 UFH), significantly favored LMWH (*P*=.04), with a trend towards fewer thrombotic events with LMWH (*P*=.15). There is convincing evidence that LMWH, in particular enoxaparin, is more effective than standard UFH at preventing venous

thromboembolism. The evidence provided by RCTs in favor of LMWH outweighs the conflicting conclusions of the nonrandomized study by Thumbikat et al. (see table 2).

Conclusions

There is level 1 evidence (based on 2 RCTs) that LMWH, in particular enoxaparin, is more effective than standard subcutaneous heparin at reducing venous thromboembolic events. Moreover, the incidence of bleeding complications appears to be less with LMWH.

LMWH for Prophylaxis Post-SCI

Three studies were found which examined the effects of LMWH. The studies looked at the effects of LMWH given independently, given in different doses, or given as a combination of different LMWH medications. From the previous discussion, it is clear that LMWH is superior to UFH, both as prophylaxis against venous thromboembolism and at reducing the risk of bleeding complications (table 3).

Harris et al retrospectively examined 105 subjects (66 had had a SCI) given 30mg of enoxaparin subcutaneously every 12 hours, beginning at the time of hospital admission. If a patient was scheduled for surgery, the drug was withheld on the morning of the operation, resumed 24 hours later, and continued until the patient's discharge. No patient developed clinical evidence of venous thromboemboli and none of the 60 venous ultrasound examinations demonstrated a DVT.

The optimal dose of enoxaparin has not yet been established. Hebbeler et al reported on a nonrandomized trial involving 129 acute SCI patients who received prophylactic enoxaparin either 40mg once daily or 30mg twice daily. The incidence of symptomatic thromboemboli did not differ between the 2 groups, with DVT occurring in only 1 patient in each group. There also was no difference in the incidence of bleeding complications between the 2 groups.

Many new LMWHs are becoming available and studies comparing their efficacy are starting to appear in the literature. Chiou-Tan et al randomized 95 acute SCI patients into 1 of 2 groups: 1 received enoxaparin (30mg s/c q12h) while the other received 5000 IU of dalteparin daily. There were no significant differences between the 2 groups, in terms of DVTs or bleeding complications. The cost of enoxaporin was noted to be greater than that of dalteparin.

Conclusions

There is level 4 evidence that 40mg daily enoxaparin, used prophylactically, is no more effective than 30mg daily at reducing the incidence of deep venous thrombosis; the 2 doses also appear similar with respect to bleeding complications. There is level 1 evidence (based on 1 RCT) that enoxaparin is no more effective than dalteparin at reducing the risk of DVT; and, again, there is no difference in the rate of bleeding complications.

Prevention of DVT through Mechanical Methods

Although pharmacologic measures generally have been the preferred mode of venous thromboembolism prophylaxis post-SCI, mechanical means of limiting venous stasis also can reduce the incidence of DVT post-SCI. Mechanical treatments are designed to limit stasis in the paralyzed lower extremities; however, the use of these devices should be accompanied by twice-daily inspection for skin discolorations or breakdown. Furthermore, pneumatic compression devices are not suitable for patients with severe arterial insufficiency (table 4).

Winemiller et al retrospectively examined the hospital records of 285 patients with a SCI. Of these, 84 were diagnosed with a DVT or PE, while the remaining 201 were used as a comparison group. Multivariate analysis demonstrated that the use of sequential pneumatic compression devices or gradient elastic stockings was associated with a reduced risk of a diagnosed venous thromboembolism. Multivariate analysis also revealed a decreased risk of venous thromboembolism in patients with SCI treated with heparin within the first 14 days, or anytime within 42 days of the SCI. Although the risk reduction with heparin was approximately twice that of sequential pneumatic compression devices/gradient elastic stockings, the difference was not statistically significant.

Becker et al studied whether or not rotating treatment tables prevents the development and progression of DVT in acute SCI patients. The authors noted that, up to that time, rotating treatment tables had been used with acute SCI patients to maintain spinal alignment while facilitating nursing care, allowing for the even distribution of ventilation and preventing pressure sores. It was hypothesized that, because these appliances rotate continuously, they may serve to inhibit thrombosis formation by reducing venous stasis. This RCT involved 15 patients with acute SCIs. Four of the 5 control (nonrotated) patients developed distal and/or proximal thrombi, as assessed by I^{125} fibrinogen scanning and impedance plethysmography, while only 1 of the 10 treated (rotated) SCI patients developed either distal and proximal venous thrombi (P=.007).

Conclusions

There is level 4 (limited) evidence that the use of sequential pneumatic compression devices or gradient elastic stockings reduces the risk of venous thromboemboli post-SCI. There is level 1 evidence (based on 1 small RCT) that rotating treatment tables reduces the incidence of venous thrombi in acute SCI patients.

Prevention of DVT with Combined Measures

Pharmacologic approaches have been examined in combination with several mechanical methods (table 5).

Merli studied 36 SCI patients (19 in the present study [treatment group] and 17 from a previous study [control group]) receiving 2 weeks of prophylaxis with external sequential pneumatic compression devices plus gradient elastic stockings and low dose heparin 5000 subcutaneously every 12 hours. Results from the current study indicated that 17 of the 19 patients treated had negative fibrinogen scans on completion of the study, while the 2

remaining patients developed a positive fibrinogen scan on days 6 and 8 of the study. In comparison, 6 of 17 patients, in the control group, developed positive I^{125} fibrinogen scans, all of which were confirmed by venography. The incidence of thrombosis was significantly higher in the control group than in the treatment group (P=.04).

Aito et al studied 275 SCI patients, 99 of whom were treated within 72 hours of injury, while 176 were treated more than 8 days post-SCI. Treatment involved continuous gradient elastic stockings, subcutaneous LMWH 0.4ml once daily, and external sequential pneumatic compression of the lower limbs 3 hours per day, given in 2 applications. There also was early mobilization of the lower limbs. The complete prophylactic treatment lasted at least 30 days post-SCI; LMWH and external sequential pneumatic compression were continued for 2 more months, depending on the patient's progress. In those treated earlier, DVT incidence was 2%, while the incidence in those treated later was 26%. Of the DVTs that occurred, 60% were detected at time of later admission (8–28 days posttrauma), while the remaining 40% developed within 6 weeks of hospitalization. Sixty-five percent of detected DVTs did not exhibit any obvious clinical signs. ASIA grade A patients were more likely to develop a DVT (36%), while only 7% of ASIA grade D patients did so on admission.

Green et al randomized 28 SCI patients with complete injuries, to either external pneumatic calf compression alone, or external pneumatic calf compression combined with acetylsalicylic acid (ASA) 300mg twice daily (bid) and dipyridamole 7mg bid. Twenty-seven subjects completed the study – DVT was detected in only 9 (33%) of 27 patients, an incidence significantly less than the 78% recorded in 37 patients (from a previous study) who had not received any prophylactic treatment (P<.001). Thrombi developed in 6 (40%) of 15 patients treated solely with external pneumatic calf compression compared to 3 (25%) of 12 receiving ASA/dipyridamole in combination with external pneumatic calf compression (P<.10). The authors concluded that the early application of pharmacologic plus mechanical treatment reduces the risk of DVT complications when compared to mechanical treatments alone, even though study numbers were small and most inter-group differences did not achieve statistical significance.

The quality of evidence is not strong for combined DVT prophylaxis measures. Given the additive effects of Virchow's triad, different measures designed to treat different risk factors should have an additive effect and be more effective than individual treatments.

Conclusions

There is level 4 evidence that comprehensive prophylactic treatment combining external pneumatic compression, gradient pressure stockings and low-dose heparin reduces venous thrombosis risk post-SCI. There is level 4 evidence that a comprehensive prophylactic regimen of pharmacologic and physical measures is more effective at preventing venous thrombosis post-SCI when instituted earlier rather than later. In a single, small RCT, a trend is noted (P<.10) suggesting that pneumatic compression plus anti-platelet agents (ASA and dipyridamole) are more effective than pneumatic compression alone.

Vena Cava Filtration

Vena cava filtration involves inserting a mechanical filter in the inferior vena cava to prevent emboli, initially formed in the lower extremities, from traveling to the lungs. This is a highly invasive procedure, associated with significant morbidity. Routine use of inferior vena cava filters in the prophylaxis of PE post-SCI has been the subject of observational trials and case series (table 6).

Jarrell et al studied 21 acute SCI patients in whom a Kim-Ray Greenfield filter was inserted in the IVC. Although 1 patient died of a PE peri-operatively, on follow-up, no additional PEs were noted. Two patients did develop thrombosis within the inferior vena cava, a presumed complication of the inferior vena cava filter.

In a retrospective chart audit, Wilson et al, studied 22 acute traumatic SCI patients who were treated with inferior vena cava filter insertion. No complications were associated with inferior vena cava insertion. No patient developed venous thrombosis during the acute hospitalization (median, 22d), and no patient developed a PE after filter insertion.

Khansarinia et al in a case-control study, compared 108 patients who had sustained multiple trauma, were at high risk for PE (including SCI patients), and had received a prospectively-placed prophylactic Greenfield filter, versus 216 historically-matched control patients. No patient in the prospectively-placed prophylactic Greenfield Filter group suffered a pulmonary embolism, compared to 13 patients (4.2%) in the control group ($P<.009$), 9 of which were fatal ($P<.03$). The overall mortality rate was less in the prospectively-placed prophylactic Greenfield Filter group (18 of 108, 16%) than in controls (47 of 216, 22%), but this difference was not statistically significant.

Rogers et al in a chart audit, pre-post and in comparison with historical controls, studied 63 of the 3151 patients admitted to the trauma service who had received a prophylactic vena cava filter – 15 of these patients had head injuries, 25 had SCIs, and 23 had pelvic fractures. The mean time to insertion of the vena cava filter was 4.3 days postadmission. Overall, 19 patients (30%) with prophylactic vena cava filters developed a DVT. When the incidence of pulmonary embolism in high-risk patients was compared from before and after the prophylactic vena cava filter policy was instituted, there was a significant reduction ($P<.001$) in the incidence of PE in the group receiving filters. It was unclear how many of these 19 patients who had developed a DVT had suffered a SCI.

Performing a retrospective chart audit, Maxwell et al studied 111 SCI patients to determine if they differed from other trauma patients in DVT and PE incidence, and concluded that they did not differ. Maxwell noted: “there are high risk patients with SCI …that probably deserve prophylactic IVC filter placement. They include patients that have failed DVT prophylaxis or have contraindications to anticoagulation. SCI patients with long bone fractures also appear to be at extreme risk for DVT and may also benefit from IVC filter placement.”(p902)

Conclusion

There is level 3 evidence that inferior vena cava filters reduce the risk of PE in high-risk SCI patients.

Treatment of Acute Venous Thromboembolism in SCI

Research has focused on the prevention of venous thromboemboli. Little research has examined the treatment of newly-diagnosed venous thromboembolism in SCI patients. The standard treatment of newly-diagnosed venous thromboembolism post-SCI has been anticoagulation, generally beginning with intravenous unfractionated heparin, followed by the gradual transition to Coumadin, which generally is maintained for 3 to 6 months. Increasingly, unfractionated heparin is being replaced by LMWH. In this regard, we found only one small study comparing UFH to LMWH (table 7).

Tomaio et al studied 6 SCI patients with acute DVT, half of whom were treated with intravenous heparin followed by warfarin, with the remainder treated with subcutaneous enoxaparin followed by warfarin. Although the study was small, the authors did a careful cost analysis. Even though more research is needed, subcutaneous enoxaparin was regarded to be a safe, cost-effective and less labor-intensive treatment of DVT in SCI patients.

Conclusion

There is level 4 evidence that enoxaparin, administered subcutaneously, is safe, cost-effective and less labor-intensive than intravenous heparin for acute DVTs post-SCI.

DISCUSSION

Venous thromboembolism following SCI is a source of significant morbidity and mortality. Virtually all of the research into treatment has focused on prophylaxis to prevent venous thromboembolism in this high-risk population. Guidelines based on best evidence for DVT prophylaxis in SCI include the use of sequential compression devices for 2 weeks and anticoagulants for 8 to 12 weeks after injury. There is evidence in the literature that 5000 IU of UFH delivered subcutaneously every 12 hours may not be sufficient in this population to provide adequate protection. The research suggests that LMWH is more effective and should be considered the standard of treatment, particularly given the lower risk of bleeding complications. Physical measures, in particular gradient pressure stockings and intermittent pneumatic compression, are designed to reduce the impact of stasis that results from the SCI patient’s lower extremities being immobilized for a prolonged period of time; to date, such devices have been shown to have a positive, but limited, impact. There is an intuitive benefit to combining treatments (ie, pharmacologic with mechanical treatment) and limited evidence supporting this has emerged; however, the current evidence suggests that pharmacologic measures are the more important of the 2.

CONCLUSIONS

A systematic review of the treatment of venous thromboembolism in SCI patients has provided reasonably good evidence supporting pharmacological prophylaxis, while research

into non-pharmacological prophylaxis or treatment of venous thromboembolism specifically in SCI patients is lacking.

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List of Abbreviations

APTT	activated partial thromboplastin time
ASIA	American Spinal Injury Association
CT	computed tomography
DVT	deep venous thrombosis
IPC	intermittent pneumatic compression
IU	international units
LMWH	low molecular weight heparin
PE	pulmonary embolisml
PEDro	Physiotherapy Evidence Database Scale
RCT	randomized controlled trial
s/c	subcutaneous
UFH	unfractionated heparin
VT	venous thrombosis

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Table 1

Efficacy of Unfractionated Heparin Versus Placebo as Prophylaxis Against Venous Thromboembolism in 90 SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Merli, 1988 USA PEDro=4	Inclusion: greater than 15 years; SCI less than 2 weeks before the initial evaluation. Exclusion: underlying bleeding disorder; recent MI; long bone fractures; arterial trauma; renal function values twice normal; pregnancy; receiving anticoagulant drugs.	RCT - 53 SCI patients were divided into 3 treatment groups (placebo; heparin; heparin with ES).	Incidence of DVT.	ES plus heparin significantly (P<.05) reduced the incidence of DVT relative to the 2 other treatments. No differences were noted between the heparin and placebo groups. Pooling data from the heparin and placebo groups and comparing them to the heparin plus electric stimulation group, the level of significance was much greater (P<.008).
Green et al, 1988 USA PEDro=7	Inclusion: complete motor SCI and sustained their injury within the previous 72 hours. Exclusion: severe head injury; bleeding disorders; uncontrolled hypertension; severe hepatic or renal disease; severe trauma to lower extremities.	RCT - 75 SCI patients were randomized to 1 of 2 treatment groups: fixed versus adjusted-dose heparin.	Incidence of DVT and bleeding.	Patients on an adjusted-dose regimen received a mean of 13,200±2200U of heparin per dose, and had APTT 1.5 times higher than those on fixed-dose regimen. Thromboembolism was detected in 9 of 29 patients (3%) randomized to fixed- dose regimen versus 2 (7%) of 29 on adjusted-dose regimen. While no patient receiving the adjusted- dose and whose APTT reached the target level experienced thrombosis, bleeding occurred in 7 patients. No patient on fixed-dose regimen bled.
Frisbie and Sasahara, 1981 USA N=32 D&B=10	Inclusion: significant neurologic deficit admitted within 1 week of injury. Exclusion: no contraindications to anticoagulation; no evidence of DVT by impedance plethysmography.	Prospective controlled trial - 32 SCI patients were treated with 5000 IU heparin subcutaneously every 12 hours until the sixtieth day postinjury.	Incidence of DVT.	VT was uncommon in both control (1 of 17) and heparin (1 of 15) group.

Abbreviations: D&B, Downs and Black quality assessment scale score; ES, electrical stimulation.

Table 2

Low Molecular Weight Heparin Versus Unfractionated Heparin as Prophylaxis Against Venous Thromboembolism in SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Spinal Cord Injury Thromboprophylaxis Investigators, 2003 USA PEDro=9	Inclusion: SCI (C2–T12) within previous 72 hours, ASIA impairment classification of grade A, B, or C. Exclusion: objective evidence of bleeding around the spinal cord related to various causes.	RCT - 476 SCI subjects were enrolled and assigned to receive thrombo-prophylaxis with either (1) a combination of low-dose UFH (5000 IU subcutaneously every 8h) plus IPC (to be used at least 22h/d); or (2) enoxaparin (30mg subcutaneously every 12h).	DVT, PE, major bleeding.	Among 107 assessable patients, the incidence of venous thromboembolism was 63.3% with UFH-IPC versus 65.5% with enoxaparin (*P*=.81). The incidence of pulmonary embolism was 18.4% with UFH-IPC versus 5.2% with enoxaparin (*P*=.03). Among all randomized patients, the incidence of major bleeding was 5.3% with UFH-IPC versus 2.6% with enoxaparin (*P*=0.14).
Spinal Cord Injury Thromboprophylaxis Investigators, 2003 USA D&B=17	Inclusion: completion of acute phase without objective evidence of DVT on contrast venography or bilateral duplex ultrasound. Exclusion: not specified.	Pre/Post - 119 SCI patients were administered either low- dose UFH 5000 IU or enoxaparin 40mg once daily. For those previously receiving IPC, the medication was discontinued during this phase of the study.	Thromboprophylactic efficacy and safety.	New venous thromboembolism was demonstrated in 13 of 60 UFH versus 5 of 59 enoxaparin patiets (21.7% vs 8.5%; *P*=.052). Enoxaparin appeared more effective than heparin in the prevention of thromboembolic complications during rehabilitation after SCI. Both interventions were deemed safe.
Thumbikat et al, 2002 UK D&B=18	Inclusion: not specified; however, 173 were assessed for a VT. Exclusion: patients on anticoagulation more than 1 year before injury; nontraumatic acute admissions and nonacute admissions.	Case Series - 101 SCI patients received a combination of heparin followed by warfarin and mechanical treatments for thromboprophylaxis; while 72 received enoxaparin as a thromboprophylactic agent started on the day of admission.	Documentation of DVT or PE; complications and duration of anticoagulation; results of Doppler studies; ventilation/perfusion scans; unexplained decreases in hemoglobin and/or platelet levels.	Four patients on UFH and 13 patients on LMWH developed venous thromboembolic episodes. Three of 13 were on enoxaparin 40mg once daily and 10 of 59 were on 20mg once daily. In UFH group, 1 thrombotic event occurred postmobilization. Six of 13 thrombotic events on LMWH occurred after patients had been mobilized and anticoagulation stopped. Two periods of peak incidence of venous thromboembolism were noticed in both groups- the first 20 to 30 days following injury and the second 90 to 100 days postinjury.
Winemiller et al, 1999 USA D&B=13	Inclusion: not specified. Exclusion: not specified.	Case series - of 285 SCI patients selected, only 84 developed a DVT or PE and were put on antithrombotic prophylaxis for 42 days after injury.	Venous thromboembolism risk factors; methods of surveillance and prophylaxis; thromboembolic events within first 6 weeks following injury.	Multivariate analysis suggested that the use of SCD or GES is associated with reduced risk of venous thromboembolism. Multivariate analysis also suggested a decreased risk of thromboembolism in SCI patients treated with heparin within the first 14 days or anytime within 42 days. Although the estimated risk reduction for heparin was about twice that for SCD/GES, this difference was not statistically significant.
Green et al, 1994 USA D&B=13	Inclusion: not specified. Exclusion: head trauma; haemothorax; long bone fractures; cardiovascular	Pre/post - LMWH 3500anti-Xa IU given subcutaneously once daily to 48 SCI patients for 8 weeks. If venous color flow ultrasonography	Incidence of DVT, pulmonary embolism, and bleeding.	The differences in bleeding between the 2 forms of heparin were significant (*P*=.04) favoring LMWH;

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
	instability; pregnancy; refusal by patient or next of kin to give informed consent.	was negative, meds were discontinued.		There was a trend toward fewer thrombotic events with LMWH.
Green et al, 1990 USA PEDro=8	Inclusion: patients referred to a regional SCI Care System with complete motor SCI sustained within the preceding 72 hours. Exclusion: bleeding injuries not accessible to haemostatic control; severe trauma to head or lower extremities as well as spinal column; evidence of thrombosis at baseline examination; cardiovascular instability.	RCT- 41 SCI patients received either UFH LMWH (5000 units q 8h or 3500 anti-Xa units/daily.	Documentation of thromboembolism.	The cumulative event rate was 34.7% (95%CI, 13.7–55.3). None of those treated with low-molecular weight heparin had thrombosis or bleeding (95% CI, 0–14). Difference between 2 groups was significant (*P*=.006, log-rank test)

Abbreviations: ASIA, American Spinal Injury Association; CI, confidence interval; D&B, Downs and Black quality assessment scale score; GES, gradient elastic stockings; SCD, sequential pneumatic compression devices.

Table 3

LMW Heparin Alone in Prophylaxis Against Venous Thromboembolism Post-SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Hebbeler et al, 2004 USA D&B=15	Inclusion: 129 acute SCI patients admitted to inpatient rehabilitation unit. Exclusion: patients with nonacute injuries (defined as those occurring greater than 2 months prior to admission to rehabilitation).	Case-Control – enoxaparin was administered subcutaneous (40mg once daily (n=80), or 30mg twice daily (n=48)) to acute SCI patients.	Safety and efficacy of enoxaparin.	Equivalent prophylaxis efficacy was seen in both enoxaparin groups. Symptomatic venous thromboembolism did not differ, with DVT occurring in 1 (2%) of 49 patients receiving twice-daily enoxaparin, and 1–1.3%) of 80 (patients receiving once-daily enoxaparin (X^2 =.125, NS). PE was seen in 1 (2%) of 49 patients treated with twice-daily enoxaparin and in none of the patients in the once-daily group (X^2 =1.64, NS). Bleeding complications also did not differ between the 2 treatment groups; these were observed in 2 (4.1%) of 49 patients receiving twice-daily enoxaparin and in 5 (6.3%) of 80 patients receiving once daily enoxaparin (X^2 =.228, NS).
Chiou-Tan et al, 2003 USA PEDro=6	Inclusion: patients from district level 1 trauma centers, Veterans' Affairs, private rehab hospitals. Exclusion: contraindications for anticoagulation; history or presence of DVT; hypersensitivity to drugs or porcine products; active bleeding; thrombocytopenia; regional anesthesia; etc.	RCT- 96 SCI patients were randomized into 1 of 2 groups: 1 group received 30mg of enoxaparin subcutaneously every 12 hours; the other received 5000 IU of dalteparin s/c once daily. Patients received a duplex ultrasound to screen for DVT at admission. Those suspected of having DVT during hospitalization also received a duplex ultrasound to confirm diagnosis. Those suspected of bleeding episode by physical examination, tilt test, or guaiac stool test had blood drawn for measurement of hemoglobin concentration. Patients who were started on LMWH before entry into the study usually were continued on the drug.	Daily log book; short form health status survey; follow-up questionnaire.	Six percent of patients developed DVT on enoxaparin and 4% on dalteparin (X^2=.44, *P*=.51). Four percent developed bleeding while receiving dalteparin and 2% while receiving enoxaparin (X^2=.13, *P*=.72). There were no DVTs or hemorrhages reported after discharge home. There was 99% compliance (X^2=.88, *P*=.50) with taking medication while in hospital.
Harris et al, 1996 USA Case series	Inclusion: all patients admitted to SCI program. Exclusion: not specified.	Case series - 105 SCI patients received 30mg of enoxaparin subcutaneously every 12 hours, beginning at the time of admission. If patient was scheduled for surgery, drug was withheld on the morning of operation, resumed 24 hours later, and continued until discharge.	Not specified.	No patient developed clinical evidence of thromboembolism and none of the 60 venous ultrasound examinations revealed a DVT.

Abbreviations: D&B, Downs and Black quality assessment scale score; NS, not significant.

Table 4

Evaluating Physical Methods for the Prevention of DVT

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Spinal Cord Injury Thromboprophylaxis Investigators, 2003 USA PEDro=9	Inclusion: SCI from C2 to T12 within previous 72 hrs, ASIA grade A, B, or C. Exclusion: objective evidence of bleeding around the spinal cord related to various causes.	RCT- 476 SCI subjects assigned to receive thromboprophylaxis with either (1) a combination of low- dose UFH (5000U subcutaneously every 8h) plus IPC (to be used at least 22h/d); or (2) enoxaparin (30mg subcutaneously every 12h).	DVT, PE, major bleeding	Incidence of VT (n=107): UFH-IPC 63.3% versus enoxaparin 65.5% (*P*=.81). Incidence of PE: UFH-IPC 18.4% versus enoxaparin 5.2% (*P*=.03). Incidence of major bleeding: UFH-IPC 5.3% with versus enoxaparin 2.6% (*P*=.14).
Becker et al, 1987 USA PEDro=6	Inclusion: greater than 15 years; injured less than 2 weeks before initial evaluation; classified as either complete motor or incomplete-preserved motor, nonfunctional (C2–T11) lesions. Exclusion: not specified.	RCT- 15 SCI patients placed on rotating treatment tables.	IPG.	Four of 5 control patients developed positive fibrinogen leg scans. All 4 became positive by IPG. Four of 10 in the treatment group had positive fibrinogen leg scans, but only 1 had a positive IPG.
Winemiller et al, 1999 USA D&B=13	Inclusion: patients admitted to hospital with SCI. Exclusion: those excluded from the study were admitted 6 or more weeks after their injury.	Case series - of 285 patients selected for inclusion, 84 developed a DVT or PE and were put on antithrombotic prophylaxis for 42 days after injury.	Venous thromboembolism risk factors; methods of surveillance and prophylaxis; thromboembolic events within first 6 wks following injury.	Multivariate analysis suggested that the use of SCD or GES is associated with reduced risk of venous thromboembolism. Multivariate analysis suggested a decreased risk of thromboembolism in patients with SCI treated with heparin within the first 14 days or anytime within 42 days. Although estimated risk reduction for heparin was about twice that for SCD/GES, the difference was not statistically significant.

Abbreviations: ASIA, American Spinal Injury Association; D&B, Downs and Black quality assessment scale score; GES, gradient elastic stockings; IPG, impedance blood plethysmography; SCD, sequential pneumatic compression devices.

Table 5

Combined Pharmacologic and Physical Measures for the Prophylaxis of Venous Thromboembolism Post-SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Green et al, 1982 USA PEDro=7	Inclusion: consecutive patients with acute SCI. Exclusion: not specified.	RCT- 28 SCI patients randomized to 1 of 2 regimens: (1) EPCC alone (n=15); (2) EPCC combined with aspirin, 300mg twice daily and dip 75mg twice daily (n=13).	Incidence of DVT; PAR; factor VII coagulant activity.	Of 27 patients who completed the study, DVT was detected in 9 of 27 patients, an incidence significantly less than the 78% previously recorded in 37 patients not receiving prophylaxis (P<.001). Thrombi developed in 6 of 15 patients treated solely with EPCC, and in 3 of 12 receiving ASA/dip as well as EPCC (P<0.1). No differences were observed in the PAR of patients treated with EPCC alone versus EPCC combined with ASA and dip. Factor VIII levels generally lower in patients treated with EPCC alone versus those also receiving ASA and dip.
Merli et al, 1992 USA D&B=12	Inclusion: age greater than 15; C2 through T12 complete motor or motor nonfunctional acute SCI within the past 72 hour. Exclusion: underlying bleeding disorder; recent (<6mo) myocardial infarction.	Case series-38 SCI patients received prophylaxis with external pneumatic compression plus gradient elastic stocking and low-dose heparin for 2 weeks.	Incidence of DVT; Marder score.	Of 19 patients, 17 had negative fibrinogen scan upon completion of study. The 2 remaining patients developed positive fibrinogen scan on days 6 and 8 of study. In comparison, 6 of 17 controls developed positive 125 I fibrinogen scans, all confirmed by venography. Incidence of thrombosis was significantly lower in the treated group (P=.04).
Aito et al, 2002 Italy D&B=12	Inclusion: all acute traumatic SCI patients consecutively admitted with complete or incomplete motor lesions (ASIA grade A to D). Exclusion: Formerly known abnormalities of any coagulation factor; contra- indications to heparin or to lower limb mechanical compression.	Case series-275 SCI patients admitted to 1 facility were given nadroparine, plus early mobilization, permanently dressed gradient elastic stockings and external sequential pneumatic compression of lower limbs.	Diagnosis of DVT.	DVT incidence: early admitted patients equals 2%; later admitted patients equals 26%. DVTs: 60% detected on admission; 40% developed within 6 weeks of hospitalization; 65% were clinically silent. ASIA grade A patients more likely to develop a DVT (36%) than those who were ASIA grade D on admission (7%).

Abbreviations: ASA, acetylsalicylic acid; ASIA, American Spinal Injury Association; D&B, Downs and Black quality assessment scale score; dip, dipyridamole; EPCC, external pneumatic calf compression; PAR, platelet aggregation ratios

Table 6

Prophylactic Vena Cava Insertion in Patients With Traumatic SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Maxwell et al, 2002 USA D&B=19	Inclusion: patients with SCI. Exclusion: not specified.	Case series-111 SCI patients underwent DVT prophylaxis with sequential compression devices and unfractionated heparin 5000 units subcutaneously every 12h (changed to 30mg s/c q12h).	Injury severity score; incidence of DVT and PE.	One hundred and eleven of 8269 SCI patients, with incidences of DVT and PE of 9% and 1.8%, respectively. Around 41% were paraplegics and 58.6% tetraplegics: 17.1% of patients had severe closed-head injury. Hospital stay: 23±20 days for SCI patients. Incidences of DVT and PE in those patients with SCDs alone were 7.1% and 2.3%; for SCDs plus s/c heparin, the incidences were 11.1% and 2.8%; and for SCDs plus LMWH, incidences were 7.4% and 0%, respectively. Incidence of DVT in SCI patients with long bone fractures was 37.5%, significantly greater than for total SCI population (P<.02).
Wilson et al,1994 USA D&B=18	Inclusion: all SCI patients admitted to medical center of Vermont. Exclusion: not specified.	Case-control-15 SCI patients had prophylactic vena cava filter inserted.	Injury severity score; impedance plethysmography; lower extremity duplex ultrasound.	No complications were associated with vena cava filter insertion. No patients developed venous thrombosis during acute hospitalization (median, 22d); no patients developed PE after filter insertion. At follow-up, deep abdominal duplex scan of the vena cava was performed, with a 30-day patency of 100% and 1-year patency of 81.8%. The lower rate at 1 year follow-up felt to represent the trapping of thrombus.
Khansarinia et al, Mexico 1995	Inclusion: injury severity score of greater than 9; expected to survive longer than 24 hours; met 1 of the following criteria: (1) severe head injury with prolonged ventilator dependence; (2) severe head injury with multiple lower-extremity fractures; (3) SCI with or without paralysis; (4) major abdominal or pelvic penetrating venous injury; (5) pelvic fracture with lower extremity fractures. Exclusion: not specified.	Case-control: 324 individuals with SCI admitted over a 2- year period to a trauma center. Those in treatment group (n=108) underwent PGF placement. The remaining subjects (n=216) were a historical control group.	Injury Severity Score; Glasgow Coma Scale; fluoroscopy; B- mode ultrasonography; ventilation/perfusion scan; pulmonary arteriography.	There were no statistical differences between the 2 groups. PGF group no patients had a PE; control group, 13 patients had PE, 9 of which were fatal. Differences significant for PE (P<.009) and PE-related death (P<.03). Mortality rate: PGF group 18 (16%) of 108 versus controls 47 (22%) of 216; P is not significant.
Rogers et al 1995 USA D&B=13	Inclusion: not specified. Exclusion: not specified.	Case-control-63 patients were selected but only 55 were inserted with prophylactic vena cava filters.	Incidence of PE.	Time from admission to prophylactic insertion of vena cava filter was 4.3±3.9 days. Three cases of DVT occurred after discharge from hospital. Overall 19 patients (30%) with prophylactic vena cava filters developed a DVT. When incidence of PE was compared in a high- risk trauma population before and after inserting a prophylactic vena cava filter, there was a significant PE reduction (P<.001).
Jarrell et al, 1983 USA D&B=11	Inclusion: SCI patients. Exclusion: not specified.	Case Series-21 SCI patients had Kim-Ray Greenfield filter inserted into IVC below renal veins to	Documentation of DVT or PE.	All patients with an indication for Kim-Ray Greenfield filter were technically capable of having device inserted. There was 1 death due to PE in patient with a filter.

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
		interrupt the IVC. Patients remained on full anti-coagulation throughout performance of procedure. A repeat IVC gram was performed, if there was any doubt about position of filter or patency of IVC.		No other suspected or proven PE after insertion of a filter since institution of policy requiring preoperative IVC gram and postoperative studies to prove proper location. Follow-up of 23 remaining patients revealed 2 instances of IVC thrombosis.

Abbreviations: D&B, Downs and Black quality assessment scale score; IVC, inferior vena cava; PGF, prophylactic Greenfield filter.

Table 7

Unfractionated Heparin Versus LMW Heparin as Treatment of Acute Venous Thromboemblolism in SCI

Author/ Year/ Country/ PEDro/ D&B scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Tomaio et al, 1998 USA D&B=11	Inclusion: not specified. Exclusion: not specified.	Case series-3 SCI patients were given intravenous heparin followed by warfarin, while 3 were treated with s/c enoxaparin followed by warfarin.	Cost analysis.	The average cost of initial anticoagulation of group 1 (intravenous heparin) patients was $413.33 (range, $331.20–$502.80), which included the costs of heparin, IV pump and tubing, and laboratory monitoring of the PTT. The average cost in group 2 (enoxaparin) patients was $362.27 (range, $197.60–$617.50), which included just the cost of medication. Enoxaparin was slightly less expensive (mean cost of enoxaparin = $362.27, intravenous heparin = $413.33) when peripheral costs taken into account. Subcutaneous enoxaparin was safe, cost-effective, and less labor- intensive, in the treatment of DVT post-SCI.

Abbreviation: D&B, Downs and Black quality assessment scale score.