REVIEW ARTICLE (META-ANALYSIS)

Venous Thromboembolism After Spinal Cord Injury

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Objective: To review systematically the published literature on the treatment of deep venous thromboembolism after 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 patients with SCI. 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 complications were more common. Nonpharmacologic treatments were also reviewed, but again limited evidence was found to support these treatments.

Key Words: Rehabilitation; Spinal cord injuries; Venous thrombosis.

DEEP VENOUS THROMBOSIS and subsequent PE remain significant causes of morbidity and mortality in patients with SCI. The incidence of DVT in patients with acute SCI was reported to be greater than 50% in early prospective studies,[1-5] with the incidence of fatal PE estimated as high as 5%.[1,6-8] The prevalence of DVT in acute SCI has been found to range from 14% to 100%[9] and from 9% to 90%.[10] Various test methods exist for diagnosing DVTs in patients; however, venography has been considered the criterion standard.[11]

The clinical diagnosis of DVT and PE are often unreliable, 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, and it 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[12] and measures a fibrin degradation product, D-dimers, because fibrin is the main component of thrombosis formation. The D-dimer test is highly sensitive, but it lacks specificity because D-dimers are found in other disease states, reducing the specificity of the test.[13]A positive diagnosis of DVT can be made only if the venogram is positive or if the venous ultrasound is positive for 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 patients with acute SCI is a consequence of the simultaneous presence of all 3 components

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
IVC	inferior vena cava
LMWH	low-molecular-weight heparin
PE	pulmonary embolism
PEDro	Physiotherapy Evidence Database Scale
RCT	randomized controlled trial
s/c	subcutaneous
SCI	spinal cord injury
SCIRE	Spinal Cord Injury Rehabilitation Evidence Review
UFH	unfractionated heparin
VT	venous thrombosis

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of the Virchow triad: hypercoagulability, stasis, and intimal (venous inner wall) injury,[10] with stasis being the greatest concern. VT most commonly begins with a calf DVT.[14-16] Although only 20% of DVTs extend into the proximal veins,[17-19] these result in over 80% of symptomatic DVTs.[20] Distal calf DVTs that do not extend proximally rarely are a source of PEs, so they are much less worrisome.[17] Nonetheless, even those who caution against overtreatment of distal DVTs concede that there is a need for randomized trials to assess the usefulness of diagnosing and treating distal DVTs.[21]

Proximal (ie, at the level of the knee or above) DVTs continue to be the primary source of concern.[17] PE is reported in 8% to 14% of patients with an acute SCI,[8,9] with most asymptomatic or unrecognized. Symptomatic PEs tend to be relatively large, with reported mortality rates of up to 5%.[8-10]

This article reviews various interventions used when treating venous thromboemboli in patients with SCI and is part of the SCIRE, the details of which are available at *http://www.icord.org/scire*.

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.[22] This search involved reviewing over 17,000 titles and 8400 abstracts, and the final analysis of approximately 700 articles. Studies were included for analysis only if at least 50% of subjects had an 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 the Downs and Black methodology for randomized and nonrandomized studies, respectively.[23,24] 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), and 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). Because of 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.[24] Tables provided in this article 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.[25] 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 came 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.[22,25]

RESULTS

Pharmacologic Agents for Deep Venous Thrombosis 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 is often 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, although its occurrence is relatively infrequent. Thrombocytopenia is another uncommon but serious side effect of treatment[26] (table 1).

Historically, UFH has been the standard treatment for the prevention of venous thromboembolism acutely post-SCI. Merli et al[6] evaluated 53 patients with acute SCI 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[27] conducted a non-RCT of 32 patients with SCI 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[28] studied 75 patients with SCI randomized to receive 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 had 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 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[6] found that heparin plus electrical muscle stimulation significantly reduced the incidence of venous thrombosis relative to heparin alone.

Unfractionated heparin for prophylaxis: 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.

Low-molecular-weight heparin for prophylaxis. LMWH is derived from standard heparin. Standard heparin has a molecular weight of 5000 to 30,000 d, whereas the molecular weight of LMWH ranges from 1000 to 10,000 d. 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

Table 1: Efficacy of Unfractionated Heparin Versus Placebo as Prophylaxis Against Venous Thromboembolism in Spinal Cord Injuries

Author/Year/Country/PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Merli et al,[6] 1988 USA PEDro=4	Inclusion: greater than 15y; SCI less than 2wk before the initial evaluation. Exclusion: underlying bleeding disorder; recent myocardial infarction; long bone fractures; arterial trauma; renal function values twice normal; pregnancy; receiving anticoagulant drugs.	RCT: 53 patients with SCI 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 with the heparin plus electric stimulation group, the level of significance was much greater ($P<.008$).
Green et al,[28] 1988 USA PEDro=7	Inclusion: complete motor SCI and sustained their injury within the previous 72h. Exclusion: severe head injury; bleeding disorders; uncontrolled hypertension; severe hepatic or renal disease; severe trauma to lower extremities.	RCT: 75 patients with SCI were randomized to 1 of 2 treatment groups: fixed vs adjusted-dose heparin.	Incidence of DVT and bleeding.	Patients on an adjusted-dose regimen received a mean of 13,200±2200U heparin per dose and had APTT 1.5 times higher than those on the fixed-dose regimen. Thromboembolism was detected in 9 of 29 patients (3%) randomized to the fixed-dose regimen vs 2 of 29 (7%) on adjusted-dose regimen. While no patient receiving the adjusted-dose regimen and whose APTT reached the target level experienced thrombosis, bleeding occurred in 7 patients. No patient on the fixed-dose regimen bled.
Frisbie and Sasahara,[27] 1981 USA D&B=10	Inclusion: significant neurologic deficit admitted within 1wk of injury. Exclusion: no contraindications to anticoagulation; no evidence of DVT by impedance plethysmography.	Prospective controlled trial: 32 patients with SCI were included in the study. 17 patients served as controls while 15 were treated with 5000 IU heparin subcutaneously every 12h until the 60th day postinjury.	Incidence of DVT.	VT was uncommon in both control (1 of 17) and heparin (1 of 15) group.

Abbreviations: D&B Score, Downs and Black quality assessment scale score[22]; ES, electrical stimulation.

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.[29]

Heparin analogs 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.

Low-molecular-weight heparin versus unfractionated heparin 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.[30] Four trials have compared UFH and LMWH (table 2).

The SCI thromboprophylaxis investigators[31] conducted a non-RCT comparing low dose UFH (5000 IU s/c every 8 hours) and enoxaparin (40mg once daily) during a 6-week rehabilitation phase in patients with SCI. Venous thromboembolism was detected in 21.7% of UFH and 8.5% of enoxaparin patients, a difference that approached statistical significance ($P=.052$).

The SCI thromboprophylaxis investigators[32] also conducted an RCT involving 476 patients with SCI assigned to receive thromboprophylaxis with either a combination of low-dose

Table 2: Low-Molecular-Weight Heparin Versus Unfractionated Heparin as Prophylaxis Against Venous Thromboembolism in Spinal Cord Injury

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Spinal Cord Injury Thromboprophylaxis Investigators,[32] 2003 USA PEDro=9	Inclusion: SCI (C2–T12) within previous 72h, ASIA impairment classification of grade A, B, or C. Exclusion: objective evidence of bleeding around the spinal cord related to various causes.	RCT: 476 subjects with SCI were enrolled and assigned to receive thromboprophylaxis 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 vs 65.5% with enoxaparin (P=.81). The incidence of pulmonary embolism was 18.4% with UFH-IPC vs 5.2% with enoxaparin (P=.03). Among all randomized patients, the incidence of major bleeding was 5.3% with UFH-IPC vs 2.6% with enoxaparin (P=.14).
Spinal Cord Injury Thromboprophylaxis Investigators,[31] 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 patients with SCI 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 vs 5 of 59 enoxaparin patients (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,[33] 2002 United Kingdom D&B=18	Inclusion: not specified; however, 173 were assessed for a VT. Exclusion: patients on anticoagulation more than 1y before injury; nontraumatic acute admissions and nonacute admissions.	Case series: 101 patients with SCI 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 20–30d after injury and the second 90–100d postinjury.
Winemiller et al,[38] 1999 USA D&B=13	Inclusion: not specified. Exclusion: not specified.	Case series: of 285 patients with SCI selected, only 84 developed a DVT or PE. A daily log was kept on the use of antithrombotic prophylaxis for 42d after injury.	Venous thromboembolism risk factors; methods of surveillance and prophylaxis; thromboembolic events within first 6wk after 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 14d or anytime within 42d. Although the estimated risk reduction for heparin was about twice that for SCD/GES, this difference was not statistically significant.

Table 2 (Cont'd): Low-Molecular-Weight Heparin Versus Unfractionated Heparin as Prophylaxis Against Venous Thromboembolism in Spinal Cord Injury

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Green et al,[35] 1994 USA D&B=13	Inclusion: not specified. Exclusion: head trauma; hemothorax; long bone fractures; cardiovascular instability; pregnancy; refusal by patient or next of kin to give informed consent.	Pre-post: LMWH 3500 anti-Xa IU given subcutaneously once daily to 48 patients with SCI for 8wk. If venous color flow ultrasonography was negative, medications were discontinued.	Incidence of DVT, pulmonary embolism, and bleeding.	The differences in bleeding between the 2 forms of heparin were significant (P=.04) favoring LMWH. There was a trend toward fewer thrombotic events with LMWH.
Green et al,[34] 1990 USA PEDro=8	Inclusion: patients referred to a regional SCI Care System with complete motor SCI sustained within the preceding 72h. Exclusion: bleeding injuries not accessible to hemostatic control; severe trauma to head or lower extremities as well as spinal column; evidence of thrombosis at baseline examination; cardiovascular instability.	RCT: 41 patients with SCI received either UFH LMWH (5000 units q 8h or 3500 anti-Xa units/d).	Documentation of thromboembolism.	The cumulative event rate was 34.7% (95% CI, 13.7–55.3). None of those treated with LMWH had thrombosis or bleeding (95% CI, 0–14). Difference between 2 groups was significant (P=.006, log-rank test).

Abbreviations: CI, confidence interval; D&B Scores, Downs and Black quality assessment scale scores[22]; GES, gradient elastic stockings; SCD, sequential pneumatic compression device.

UFH (5000 IU s/c every 8 hours) plus IPC at least 22 hours each day, or enoxaparin 30mg given subcutaneously every 12 hours. Three hundred sixty-nine patients were excluded from the study because of 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 common in the LMWH group, but the difference did not achieve significance.

Thumbikat et al[33] retrospectively compared 1 group of patients with SCI (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[34] 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[35] also studied 60 patients with acute SCI with complete motor paraplegia, all of whom received a daily dose of 3500 IU of LMWH subcutaneously. Forty-eight of those recruited were able to complete the study; however, 12 were unable to complete the study because of 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 had 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 toward 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[33] (see table 2).

Low-molecular-weight heparin versus unfractionated heparin for prophylaxis: 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.

Low-molecular-weight heparin for prophylaxis after spinal cord injury. Three studies were found that 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[36] retrospectively examined 105 subjects (66 had had an 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[37] reported a nonrandomized trial involving 129 patients with acute SCI 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[9] randomized 95 patients with acute SCI 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 enoxaparin was noted to be greater than that of dalteparin.

Low-molecular-weight heparin for prophylaxis after spinal cord injury: 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 was no difference in the rate of bleeding complications.

Prevention of Deep Venous Thrombosis 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[38] retrospectively examined the hospital records of 285 patients with an 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 greater decreased risk of venous thromboembolism in patients with SCI treated with heparin within the first 14 days, with lesser effect from 14-42 days. 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[5] studied whether rotating treatment tables prevent the development and progression of DVT in patients with acute SCI. The authors noted that, up to that time, rotating treatment tables had been used with patients with acute SCI to maintain spinal alignment while facilitating nursing care, al-

Table 3: Low-Molecular-Weight Heparin Alone in Prophylaxis Against Venous Thromboembolism After Spinal Cord Injury

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Hebbeler et al,[37] 2004 USA D&B=15	Inclusion: 129 patients with acute SCI admitted to inpatient rehabilitation unit. Exclusion: patients with nonacute injuries (defined as those occurring greater than 2mo before admission to rehabilitation).	Case-control: enoxaparin was administered subcutaneously (40mg once daily [n=80], or 30mg twice daily [n=48]) to patients with acute SCI.	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 (χ^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 (χ^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 (χ^2=.228, NS).
Chiou-Tan et al,[9] 2003 USA PEDro=6	Inclusion: patients from district level 1 trauma centers, Veterans' Affairs, private rehabilitation hospitals. Exclusion: contraindications for anticoagulation; history or presence of DVT; hypersensitivity to drugs or porcine products; active bleeding; thrombocytopenia; regional anesthesia; and so forth.	RCT: 96 patients with SCI were randomized into 1 of 2 groups: 1 group received 30mg enoxaparin subcutaneously every 12h; 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 (χ^2=.44, P=.51). Four percent developed bleeding while receiving dalteparin and 2% while receiving enoxaparin (χ^2=.13, P=.72). There were no DVTs or hemorrhages reported after discharge home. There was 99% compliance (χ^2=.88, P=.50) with taking medication while in the hospital.
Harris et al,[36] 1996 USA Case series	Inclusion: all patients admitted to SCI program. Exclusion: not specified.	Case series: 105 patients with SCI received 30mg enoxaparin subcutaneously every 12h, beginning at the time of admission. If patient was scheduled for surgery, drug was withheld on the morning of operation, resumed 24h 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 Scores, Downs and Black quality assessment scale scores[22]; NS, not significant.

Table 4: Evaluating Physical Methods for the Prevention of Deep Venous Thrombosis

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Spinal Cord Injury Thromboprophylaxis Investigators,[32] 2000 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 subjects with SCI 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% vs enoxaparin 65.5% (P=.81). Incidence of PE: UFH-IPC 18.4% vs enoxaparin 5.2% (P=.03). Incidence of major bleeding: UFH-IPC 5.3% vs enoxaparin 2.6% (P=.14).
Becker et al,[5] 1987 USA PEDro=6	Inclusion: greater than 15y; injured less than 2wk before initial evaluation; classified as either complete motor or incomplete-preserved motor, nonfunctional (C2–T11) lesions. Exclusion: not specified.	RCT: 15 patients with SCI 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,[38] 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. A daily log was kept on the use of antithrombotic prophylaxis for 42d after injury.	Venous thromboembolism risk factors; methods of surveillance and prophylaxis; thromboembolic events within first 6wk after 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 14d or anytime within 42d. Although estimated risk reduction for heparin was about twice that for SCD/GES, the difference was not statistically significant.

Abbreviations: D&B Scores, Downs and Black quality assessment scale scores[22]; GES, gradient elastic stockings; IPG, impedance blood plethysmography; SCD, sequential pneumatic compression device.

lowing for the even distribution of ventilation and preventing pressure ulcers. 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) patients with SCI 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 patients with acute SCI.

Prevention of Deep Venous Thrombosis with Combined Measures

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

Merli et al[39] studied 36 patients with SCI, of these 17 patients served as controls and received no treatment while 19 received 2 weeks of prophylaxis with external sequential pneumatic compression devices plus gradient elastic stockings and low-dose heparin 5000 IU 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}

Table 5: Combined Pharmacologic and Physical Measures for the Prophylaxis of Venous Thromboembolism After Spinal Cord Injury

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Green et al,[40] 1982 USA PEDro=7	Inclusion: consecutive patients with acute SCI. Exclusion: not specified.	RCT: 28 patients with SCI randomized to 1 of 2 regimens: (1) EPCC alone (n=15); (2) EPCC combined with aspirin, 300mg twice daily and dipyridamole 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/dipyridamole as well as EPCC ($P<0.1$). No differences were observed in the PAR of patients treated with EPCC alone vs EPCC combined with ASA and dipyridamole. Factor VIII levels generally lower in patients treated with EPCC alone vs those also receiving ASA and dipyridamole.
Merli et al,[39] 1992 USA D&B=12	Inclusion: age greater than 15y; C2 through T12 complete motor or motor nonfunctional acute SCI within the past 72h. Exclusion: underlying bleeding disorder; recent (<6mo) myocardial infarction.	Case series: 38 patients with SCI were included in the study. 17 patients served as controls (no treatment) and 19 received prophylaxis with external pneumatic compression plus gradient elastic stocking and low-dose heparin for 2wk.	Incidence of DVT; Marder score.	Of 19 patients, 17 had negative fibrinogen scan on 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,[10] 2002 Italy D&B=12	Inclusion: all patients with acute traumatic SCI consecutively admitted with complete or incomplete motor lesions (ASIA grade A to D). Exclusion: formerly known abnormalities of any coagulation factor; contraindications to heparin or to lower limb mechanical compression.	Case series: 275 patients with SCI 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 6wk 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; D&B Scores, Downs and Black quality assessment scale scores[22]; EPCC, external pneumatic calf compression; PAR, platelet aggregation ratio.

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[10] studied 275 patients with SCI, 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 a day, given in 2 applications. There was also 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 (8–28d 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[40] randomized 28 patients with a complete SCI to either external pneumatic calf compression alone or external pneumatic calf compression combined with acetylsalicylic acid

300mg twice daily and dipyridamole 7mg twice daily. 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 with 3 (25%) of 12 receiving acetylsalicylic acid/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 compared with mechanical treatments alone, even though study numbers were small and most intergroup differences did not achieve statistical significance.

The quality of evidence is not strong for combined DVT prophylaxis measures. Given the additive effects of the Virchow triad, different measures designed to treat different risk factors should have an additive effect and be more effective than individual treatments.[10]

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 antiplatelet agents (acetylsalicylic acid and dipyridamole) is more effective than pneumatic compression alone.

Vena Cava Filtration

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

Jarrell et al[41] studied 21 patients with acute SCI in whom a Kim-Ray Greenfield filter[a] was inserted in the IVC. Although 1 patient died of a PE perioperatively, on follow-up, no additional PEs were noted. Two patients did develop thrombosis within the IVC, a presumed complication of the IVC filter.

In a retrospective chart audit, Wilson et al[42] studied 22 patients with acute traumatic SCI who were treated with IVC filter insertion. No complications were associated with IVC insertion. No patient developed venous thrombosis during the acute hospitalization (median, 22d), and no patient developed a PE after filter insertion.

Khansarinia et al[43] in a case-control study compared 108 patients who had sustained multiple trauma, were at high risk for PE (including patients with SCI), 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 had a pulmonary embolism, compared with 13 patients (4.2%) in the control group ($P<.009$), 9 of whom died ($P<.03$). 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[44] 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. Fifteen 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 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 an SCI.

Performing a retrospective chart audit, Maxwell et al[45] studied 111 patients with SCI to determine whether 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."[45(p902)]

Conclusions. There is level 3 evidence that IVC filters reduce the risk of PE in high-risk patients with SCI.

Treatment of Acute Venous Thromboembolism in Spinal Cord Injury

Research has focused on the prevention of venous thromboemboli. Little research has examined the treatment of newly diagnosed venous thromboembolism in patients with SCI. 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 warfarin, which generally is maintained for 3 to 6 months. Increasingly, unfractionated heparin is being replaced by LMWH. In this regard, we found only 1 small study comparing UFH with LMWH (table 7).

Tomaio et al[30] studied 6 patients with SCI 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 performed 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 patients with SCI.

Conclusions. 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 after 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.[45] There is evidence in the literature that 5000 IU 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; 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

Table 6: Prophylactic Vena Cava Insertion in Patients With Traumatic Spinal Cord Injury

Author/Year/Country/ PEDro/ D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Maxwell et al,[45] 2002 USA D&B=19	Inclusion: patients with SCI. Exclusion: not specified.	Case series: 111 patients with SCI underwent DVT prophylaxis with sequential compression devices and unfractionated heparin 5000 units subcutaneously every 12h (changed to 30mg s/c every 12h).	Injury severity score; incidence of DVT and PE.	111 of 8269 patients with SCI, with incidences of DVT and PE of 9% and 1.8%, respectively. Around 41% had paraplegia and 58.6% tetraplegia; 17.1% of patients had severe closed-head injury. Hospital stay: 23±20d for patients with SCI. 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 patients with SCI with long bone fractures was 37.5%, significantly greater than for total SCI population ($P<.02$).
Wilson et al,[42] 1994 USA D&B=18	Inclusion: all patients with SCI admitted to medical center. Exclusion: not specified.	Case-control: 15 patients with SCI 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-d patency of 100% and 1-y patency of 81.8%. The lower rate at 1 year follow-up felt to represent the trapping of thrombus.
Khansarinia et al,[43] 1995 Mexico 1995	Inclusion: injury severity score of greater than 9; expected to survive longer than 24h; 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 vs controls 47 (22%) of 216; *P* is not significant.

Table 6 (Cont'd): Prophylactic Vena Cava Insertion in Patients With Traumatic Spinal Cord Injury

Author/Year/Country/ PEDro/ D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Rogers et al,[44] 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±3.9d. 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,[41] 1983 USA D&B=11	Inclusion: patients with SCI. Exclusion: not specified.	Case series: 21 patients with SCI had Kim-Ray Greenfield filter inserted into IVC below renal veins to interrupt the IVC. Patients remained on full anticoagulation throughout performance of procedure. A repeat IVC gram was performed if there was any doubt about position of filter or patency of IVC.	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 caused by PE in patient with a filter. 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 Score, Downs and Black quality assessment scale score[22]; PGF, prophylactic Greenfield filter.

Table 7: Unfractionated Heparin Versus Low-Molecular-Weight Heparin as Treatment of Acute Venous Thromboembolism in Spinal Cord Injury

Author/Year/Country/ PEDro/D&B Scores	Eligibility Criteria	Study Design and Methods	Outcome Measures	Results
Tomaio et al,[30] 1998 USA D&B=11	Inclusion: not specified. Exclusion: not specified.	Case series: 3 patients with SCI 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 Scores, Downs and Black quality assessment scale score[22]; IV, intravenous; PTT, partial thromboplastin time.

limited evidence supporting this has emerged; however, the current evidence suggests that pharmacologic measures are the more important of the two.

CONCLUSIONS

A systematic review of the treatment of venous thromboembolism in patients with SCI has provided reasonably good evidence supporting pharmacologic prophylaxis, while research into nonpharmacologic prophylaxis or treatment of venous thromboembolism specifically in patients with SCI is lacking.

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Supplier

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