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Acute Pharmacological DVT Prophylaxis after Spinal Cord Injury

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Abstract

A systematic review of the literature was performed to address pertinent clinical questions regarding deep vein thrombosis (DVT) prophylaxis in the setting of acute spinal cord injury (SCI). Deep vein thromboses are a common occurrence following SCI. Administration of low-molecular-weight heparin (LMWH) within 72 h of injury is recommended to minimize the occurrence of DVT. Furthermore, when surgical intervention is required, LMWH should be held the morning of surgery, and resumed within 24 h post-operatively.

Key words: deep vein thrombosis; spinal cord injury

Introduction

A common complication following spinal cord injury (SCI) is deep vein thrombosis (DVT). The incidence of DVT that has been reported in the literature varies widely depending on the screening tool, with rates ranging from 9–100% (Teasell et al., 2008). Venous thromboses are a significant cause of morbidity and mortality, and are responsible for 9.7% of all deaths in the first year following SCI (DeVivo et al., 1999). In fact, within the first month post-injury, SCI patients have a 500-fold increased risk of PE-related death relative to age- and gender-matched noninjured controls (DeVivo et al., 1989). This vulnerability to DVT may be due in part to the presence of Virchow's triad of stasis, hypercoagulability, and vessel intimal injury (Furlan and Fehlings, 2008). Additional pathophysiological mechanisms have also been implicated, including impaired circadian variations of hemostatic and fibrinolytic parameters, as well as changes in platelet function and fibrinolytic activity (Iversen et al., 2002; Winther et al., 1992).

Strategies used for the prevention of DVT have included oral anticoagulants, heparin (both unfractionated and low-molecular-weight heparin), antithromoboembolic stockings, external compression devices, and vena cava filters. Among the pharmacological approaches, a previous systematic review has suggested that low-molecular-weight heparin (LMWH) is more effective than standard or unfractionated heparin in preventing DVT in the SCI population (Teasell et al., 2008); however, the optimal timing of initiation of LMWH administration has not yet been established. The following clinically relevant question regarding DVT prophylaxis following acute SCI was used to guide this systematic review: What is the ideal time for initiation of DVT prophylaxis with LMWH: after SCI or after surgery?

Methods

Search strategy

A primary literature search was performed using PubMed. The search was conducted for the following terms: "thromboembolism," "VT," "DVT," "venous thrombosis," and "deep vein thrombosis." These key words were then paired with "SCI," "spinal cord injuries," and "spinal cord injury," as well as the MeSH term "Spinal Cord Injuries." The search was limited to English language articles and research involving human subjects. Given the advantage of LMWH over unfractionated heparin (Teasell et al., 2008), this review focused on studies utilizing only LMWH.

Articles included were those that addressed the timing of LMWH thromboprophylaxis initiation, or those that described LMWH administration in the perioperative period (i.e., whether the dose was held preoperatively, and the timeline of resumption of LMWH). Articles excluded were those that did not address either efficacy or complication rates; those that focused on unfractionated heparin rather than LMWH; any articles not related significantly to SCI (i.e., mixed trauma patients in whom the majority of patients did not have an SCI); any articles specific for chronic SCI; any single-case reports; any commentaries, opinions, or reviews; and mainly pediatric reports. Key reviewed articles were examined for more papers.

Article review process

Relevant articles from the search were rated by two independent reviewers according to Downs and Black scoring scheme (Downs and Black, 1998). Any variance in the scoring between the two reviewers was addressed by a third reviewer. Data were presented to the Spinal Cord Injury

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Solutions Network (Acute Practice Network), and subjected to a modified Delphi review process to establish an expert consensus to address the guiding question.

Results

In all 312 articles were returned by the search. Abstracts were screened, and five met inclusion/exclusion criteria. The relevant articles were then subjected to scoring according to the Downs and Black criteria (Table 1)

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Only one of the studies reviewed was specifically designed to determine the effects of the timing of prophylaxis post-SCI. However, four other studies that met the inclusion/exclusion criteria did specify when DVT prophylaxis was administered relative to the time of injury, and addressed efficacy and/or complications.

Aito and colleagues compared an early group (DVT prophylaxis within 72 h, including LMWH) to a late group (prophylaxis started after 72 h). DVT incidence was based upon color Doppler ultrasonography, which was performed on admission, at 45–60 days, and whenever clinically indicated. The incidence of DVT in the early group was 2%, whereas the late group had an incidence of 26% (Aito et al., 2002).

Green and associates conducted a study designed to compare LMWH to unfractionated heparin. They initiated LMWH DVT prophylaxis within 72 h of injury. Prophylaxis was held on the day of surgery and resumed the next morning. They found a 3.3% rate of pulmonary embolism (PE) and a 10% rate of DVT, as measured by ultrasound at 8 weeks (upon completion of LMWH), and every week thereafter for 4 weeks, as well as daily clinical exams for signs and symptoms of thromboembolism. Only one complication was reported, consisting of bleeding in a patient with pre-existing hematuria secondary to a gunshot wound (Green et al., 1994).

An earlier study by Green and associates was also designed to compare LMWH to unfractionated heparin (Green et al., 1990). Patients were enrolled within 72 h of injury; LMWH was not initiated until at least 24 h after injury. Thromboprophylaxis was held the morning of surgery, and resumed the day following surgery. Daily clinical assessments as well as serial venous flow studies were used to detect thromboembolism. Among the 20 patients in this study receiving LWMH, none had PE or DVT, nor did any have significant bleeding. (Conversely, the cumulative event rate for bleeding or DVT was 34.7% among the standard heparin group.)

A randomized controlled trial (comparing unfractioned heparin and intermittant compression stockings vs. enoxaparin) followed the same timeline of LMWH administration, instituting prophylaxis within 72 h, holding the drug on the day of surgery, and resuming treatment the first postoperative morning. Patients were assessed for DVT using Doppler ultrasound at 14 days post-injury, and for PE via ventilation-perfusion scan, spiral CT, or pulmonary angiography. The rates of PE and DVT among those on LMWH were 5.2% and 60.3%, respectively; however, the rate of symptomatic DVT was just 1.7%. Minor bleeding occurred in 14.8% of patients receiving enoxaparin, with a rate of major bleeding of 2.6% (Spinal Cord Injury Thromboprophylaxis Investigators, 2003).

Harris and co-workers completed a retrospective chart review of 105 patients who received LMWH post-SCI beginning at the time of admission. The drug was held the morning of surgery, and resumed 24 h later (Harris et al., 1996). There was no clinical evidence of DVT in any of the patients reviewed; among the 60 patients who underwent ultrasonography, there was no evidence of DVT, although 11/105 patients had some bleeding as evidenced by a decline in hemoglobin of 2 g/dL or greater. Enoxaparin was found to be contributory in three of these cases. The drug continued to be administered in all but two of the patients (one with bleeding cause unknown, the other with a hematoma secondary to a gunshot wound), yet there was no evidence that continued administration led to exacerbation of the bleeding. Although there were five deaths, none were attributable to DVT prophylaxis.

Discussion

In the absence of thromboprophylaxis, SCI patients have a higher incidence of DVT than any other hospitalized group (Geerts, 2008). This patient population also presents a diagnostic challenge, since thromboembolism can often be clinically silent or difficult to distinguish from other common SCI complications (Chen, 2003). Nonpharmacological treatment modalities such as early mobilization can be hampered by associated injuries, respiratory insufficiency, or spinal instability (Chen, 2003).

Regarding pharmacological management, it has been previously established that LMWH is preferable to unfractionated heparin in the SCI population due to its longer half-life, lower risk of bleeding complications, and more predictable dose effect relative to unfractionated heparin (Teasell et al., 2008). Thus in this review we focused our attention on the optimal timing of prophylaxis administration. Although only one study has examined this directly (Aito et al., 2002), the difference between early administration and administration later than 72 h was large (2% and 26% incidence of DVT, respectively). Complication rates associated with LMWH were relatively low (1.6–10%), including when thromboprophylaxis was resumed within 24 h post-operatively (Green et al., 1990, 1994; Harris et al., 1996; Spinal Cord Injury Thromboprophylaxis Investigators, 2003). This parallels recommendations for the major trauma population, in whom thromboprophylaxis should be initiated as soon as it considered safe to do so (in the absence of contraindications) (Geerts, 2008).

Systematic review recommended answers to the clinical question: What is the ideal time for initiation of DVT prophylaxis with LMWH: After SCI or after surgery?

- DVT prophylaxis should be instituted within 72 h post-injury. (*Single study but large difference; therefore suggest strong recommendation with weak data*.)
- LMWH should be held on the morning of surgery and resumed within 24 h following surgery. (*Balance of risks and benefits; strong recommendation, weak data*.)

Table 1. Results of the Literature Search

Authors	Title	Study Type	Downs and Black score	PEDro	Methods	Outcome
Aito et al., 2002	Primary prevention of DVT and PE in acute SCI	Experimental prospective non-randomized controlled trial	26		Permanently-dressed gradient elastic stockings (PGES); SC LMWH 0.4 cc once a day; external sequential pneumatic compression of the legs (ESPC) 3 h/d in 2 applications; early mobilization of the lower limbs. Complete prophylactic treatment for at least 30 days; LMWH and ESPC were continued 2 more months (depending on the patient's progress). Protocol was initiated within 72 h to early-admitted patients (EAP), while another group (late-admitted patients, LAP) did not receive the same treatment at the early stage, but started it from the date of admission (range 7–28 days post-injury; mean 12 days).	*DVT:* incidence in EAP was 2%, and in LAP was 26%. Of those, 60% were detected on admission, while the remaining 40% developed it over a period not exceeding 6 weeks of hospitalization; 65% of detected DVT did not show any evident clinical signs. Those with ASIA grade A were more likely to develop DVT (36%), while only 7% of those with ASIA grade D on admission did so. No PE was recorded. *Complications:* Not listed.
Green et al., 1994	Prevention of thromboembolism in SCI: Role of LMWH	Experimental non-randomized controlled trial	34	7	Tinzaparin 3500 U SC once a day within 72 h of injury; continued for 8 weeks. Held on the day of surgery, resumed the next morning. Ultrasound (US) was done after 8 weeks; if negative LMWH was discontinued. Repeat US weekly for 4 weeks, then discontinue from study if negative. Bleeding was considered an event if obvious fresh hemorrhage present, or if the ward team decided bleeding warranted discontinuation of LMWH.	*PE:* 2/60 (3.3%). *DVT:* 6/60 (10%): 4 proximal DVT + 2 calf-vein thromboses. *Complications:* Bleeding in 1/60 (1.6%, in patients with multiple gunshot wounds of bowel and bladder plus hematuria prior to LMWH initiation).

(*continued*)

Table 1. Continued

Authors	Title	Study Type	Downs and Black score	PEDro	Methods	Outcome
Green et al., 1990	Prevention of thromboembolism after SCI using LMWH	Randomized controlled trial	30	7	Logiparin 3500 U SC once a day. Clinical exam daily for DVT, PE, and bleeding. Impedence plethysmography, Doppler flow measurements and DUS used. Not started until at least 24 h after injury. Morning dose held on the day of surgery, and resumed the next morning, Clinical finding of DVT confirmed by contrast venography. Bleeding event defined as necessary to discontinue drug (decision made by physicians not participating in the trial).	*PE/DVT:* 0/20 patients. *Complications:* 0/20 patients.
Spinal Cord Injury Thromboprophylaxis Investigators	Prevention of thromboembolism in the acute treatment phase after SCI: A randomized, multicenter trial comparing low-dose heparin plus intermittent pneumatic compression with enoxaparin	Randomized controlled trial	40	7	30 mg enoxaparin SC every 12 h begun within 72 h of injury. Held on the day of surgery, resumed within 24 h after surgery. Complete blood cell count on days 3, 7, and 14; partial throm boplastin time and serum creatinine on days 7 and 14. DUS and bilateral contrast venography at day 14 or within 2 days of last dose; assessment of PE via ventilation-perfusion scan, spiral CT, or pulmonary angiography. Major bleeding defined as overt bleeding occurring within 48 h of a dose of study medication, or resulting in any of the following: death or threat to survival; decrease in hemoglobin of at least 2 g/dL; transfusion of two or more units of blood; perispinal, intracranial, intraocular, or retroperitoneal bleeding. Minor bleeding defined as overt bleeding that did not meet criteria of major bleeding.	*PE:* 3/58 (5.2%). *DVT:* 35/58 (60.3%). *Symptomatic DVT:*1/58 (1.7%). *Complications:* Major bleeding in 6/230 (2.6%), 1 with chest injury found to have hemothorax on day 5, and 1 with retroperitoneal hematoma on day 11. Minor bleeding in 34/230 (14.8%) of enoxaparin patients. Transfusion required during study period in 25.7% of enoxaparin patients (median 2.0 units); 2 deaths: one from pneumonia and overwhelming sepsis, the other from respiratory failure. Factors that predict major bleeding: age >50; low baseline hemoglobin; shorter duration of anticoagulant therapy. Odds ratio of surgery before or during acute phase of study for major bleeding events = 1.85 (95% confidence interval 0.71,4.8; $p = 0.20$); 53% had surgery before or during the acute treatment phase.

Harris et al., 1996	Enoxaparin for thromboembolism prophylaxis in spinal injury	Retrospective chart review	24	Enoxaparin 30 mg every 12 h. Held on the morning of surgery, resumed 24 h later.	*DVT:* No clinical evidence of DVT (all 105 patients reviewed); no ultrasound evidence of DVT (60 patients). *Complications:* 11/105 (10.5%) cases of hemoglobin decline of 2 g/dL or more, 6 due to gastrointestinal bleed, and enoxaparin deemed contributory in 3. Decline in hemoglobin in other patients associated with surgery in 1, sepsis in 1, expanding liver hematoma secondary to gunshot wound in 1, and unknown cause in 2 other patients. Drug held in one patient with low hemoglobin due to unknown cause, and the patient with the gunshot wound, but others continued to receive the drug without evidence of bleeding exacerbation. 5 deaths: 1 due to sepsis with acute respiratory distress syndrome; 1 with ventilator dependency with multiple medical problems; 1 with cardiomyopathy; 1 with complications from femoral artery bypass surgery; 1 with anoxic brain damage. None of the deaths had bleeding attributable to enoxaparin prophylaxis.

DVT, deep venous thrombosis; LMWH, low-molecular-weight heparin; SCI, spinal cord injury; PE, pulmonary embolism; SC, subcutaneous; ASIA, American Spinal Injury Association grade; DUS, duplex ultrasound; PEDro, physiotherapy evidence database (de Morton, 2009).

Author Disclosure Statement

No competing financial interests exist.

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