Venous Thromboembolism in Spinal Cord Injury Patients*

Russell D. Hull, M.B.B.S., M.Sc., F.C.C.P.

Pulmonary embolism remains the most common preventable cause of death in the hospital. It is estimated that 100,000 patients or more die from massive pulmonary embolism in the hospital each year. Many of these deaths occur in terminally ill patients, but a significant proportion occur in patients who would otherwise have led a normal life.1-3

Clinical risk factors for venous thrombosis have been identified and include advanced age, previous venous thromboembolism, the presence of malignant disease, cardiac failure, prolonged immobility or paralysis, obesity, and varicose veins.14-6 Certain surgical procedures and spinal cord injury are associated with an exceptionally high risk of postoperative venous thromboembolism (either venous thrombosis or pulmonary embolism, or both). The frequency of fatal pulmonary embolism ranges from 0.1% to 0.8% in patients undergoing elective general surgery7,8 and from 1% to 7% in high risk patients (for example, hip surgery and spinal cord injury patients).9-12 Deep vein thrombosis (DVT), the precursor of pulmonary embolism, occurs at a very high frequency in patients with spinal cord injury, with reported incidences of up to 70% or more in the absence of prophylaxis (Table 1).13-19

Two approaches can be taken to prevent fatal pulmonary embolism. First, early detection of subclinical venous thrombosis by screening high risk patients (for instance, screening high risk patients with B-mode imaging of the lower extremities or impedance plethysmography [IPG]). Second, primary prophylaxis can be instituted using either drugs or physical methods that are effective for preventing DVT and pulmonary embolism. Primary prophylaxis is likely to be the more effective approach and is less expensive.5,11,20-22 A number of prophylactic measures have been suggested for antithrombotic prophylaxis in patients with spinal cord injury, including low-dose subcutaneous heparin,23-26 adjusted-dose heparin subcutaneously,27-30 intermittent pneumatic compression of the leg,31-35 low molecular weight heparin,36 and combined modalities (such as intermittent pneumatic compression plus low-dose heparin) (Table 2).36-43

The use of primary prophylaxis in patients with spinal cord injury remains controversial because of doubts about both the effectiveness and the safety of the individual prophylactic measures.5,14 In recent years, however, an improved understanding of the requirements for adequately designed and appropriately executed clinical trials evaluating alternative prophylactic approaches has occurred.42-44 In making specific recommendations for approaches to this important clinical problem, the strength of the evidence supporting each individual recommendation should be considered. A firm recommendation is possible when the following criteria have been met:

1. The clinical trial should be prospective, with a concurrent control group.
2. Ideally, the study should be double blind; if double-blinding is not possible, the end points should be interpreted by an independent observer without knowledge of the patient's treatment category.
3. The patients should be randomly allocated to the alternative prophylactic approaches in order to avoid the potential for conscious or unconscious bias in selection of patients.
4. Comparability of the treatment groups with respect to important prognostic variables should be demonstrated.
5. A sufficient number of patients should be studied to allow valid conclusions.
6. Properly defined end points should be used for the evaluation of effectiveness and safety.
7. Appropriate statistical methods should be used to analyze the data.

Because of the inaccuracy of clinical diagnosis of both venous thrombosis and pulmonary embolism, it is essential that reliable objective diagnostic methods be used to measure the end points. These techniques include ultrasonographic B-mode imaging of the lower limb,44-45 impedance plethysmography,46-48 and ascending venography49 for the diagnosis of venous thrombosis and ventilation-perfusion lung scanning50-53 and pulmonary angiography for pulmonary embolism54-56 (or pulmonary embolism demonstrated at autopsy).

The use of noninvasive screening tests, such as IPG, and venography at a fixed interval postoperatively, provides an effective method for the early detection of subclinical DVT, and thus, an effective method for preventing death due to

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of Patients</th>
<th>Objective Documentation</th>
<th>DVT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yelnik et al, 1991</td>
<td>127</td>
<td>Venography</td>
<td>23</td>
</tr>
<tr>
<td>Petjä et al, 1989</td>
<td>9</td>
<td>120-fibrinogen*</td>
<td>67</td>
</tr>
<tr>
<td>Merli et al, 1988</td>
<td>17</td>
<td>120-fibrinogen*</td>
<td>47</td>
</tr>
<tr>
<td>Myllnen et al, 1989</td>
<td>33</td>
<td>120-fibrinogen*</td>
<td>100</td>
</tr>
<tr>
<td>Frisbie and Sasahara, 1981</td>
<td>17</td>
<td>IPG*</td>
<td>6</td>
</tr>
<tr>
<td>Rossi et al, 1960</td>
<td>18</td>
<td>120-fibrinogen*</td>
<td>72</td>
</tr>
<tr>
<td>Perkash et al, 1975</td>
<td>50</td>
<td>IPG*</td>
<td>16</td>
</tr>
<tr>
<td>Brach et al, 1977*</td>
<td>40</td>
<td>120-fibrinogen/IPG*</td>
<td>70</td>
</tr>
<tr>
<td>Todd et al, 1976</td>
<td>20</td>
<td>120-fibrinogen</td>
<td>100</td>
</tr>
<tr>
<td>Philipp, 1969</td>
<td>25</td>
<td>Venography</td>
<td>24</td>
</tr>
<tr>
<td>Bors et al, 1964</td>
<td>99</td>
<td>Venography</td>
<td>59</td>
</tr>
</tbody>
</table>

*Confirmed by venography.

---

*From the Division of General Internal Medicine, University of Calgary, Health Sciences Center, Calgary, Alberta, Canada.
Reprint requests: Dr. Hull, c/o B. Doucette, Rm 1431, Department of Medicine, University of Calgary, 3330 Hospital Drive, Calgary, Alta, Canada T2N 4N1

---

658S

Venous Thromboembolism in Spinal Cord Injury Patients (Russell D. Hull)
Table 2—Thromboembolism Prophylaxis in Patients with Spinal Injury

<table>
<thead>
<tr>
<th>Author</th>
<th>Level of Evidence</th>
<th>No. of Patients</th>
<th>Objective Documentation</th>
<th>Method</th>
<th>DVT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al, 1990 ⁴⁸</td>
<td>I</td>
<td>21</td>
<td>IPG/Doppler*</td>
<td>Heparin†</td>
<td>24</td>
</tr>
<tr>
<td>Green et al, 1988 ⁴⁸</td>
<td>I</td>
<td>20</td>
<td>IPG/Doppler*</td>
<td>LMWH</td>
<td>0</td>
</tr>
<tr>
<td>Merli et al, 1986 ⁴⁸</td>
<td>I</td>
<td>17</td>
<td>Fibrinogen*</td>
<td>Heparin†</td>
<td>31</td>
</tr>
<tr>
<td>Becker et al, 1987 ⁴⁸</td>
<td>II</td>
<td>5</td>
<td>Fibrinogen/IPG</td>
<td>Control</td>
<td>47</td>
</tr>
<tr>
<td>Jarrell et al, 1983 ⁴⁸</td>
<td>V</td>
<td>209</td>
<td>Fibrinogen/IPG*</td>
<td>Heparin†</td>
<td>7</td>
</tr>
<tr>
<td>Green et al, 1982 ⁴⁸</td>
<td>II</td>
<td>15</td>
<td>Fibrinogen/IPG*</td>
<td>Leg compression</td>
<td>40</td>
</tr>
<tr>
<td>Frisbie and Sasahara, 1981 ⁴⁸</td>
<td>III</td>
<td>17</td>
<td>IPG*</td>
<td>Control</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td></td>
<td>Heparin†</td>
<td>7</td>
</tr>
</tbody>
</table>

*Confirmed by venography.
†Fixed dose of heparin 5,000 IU 2 to 3 times per day.

Pulmonary embolism. The effectiveness of these tests for detecting subclinical DVT (and thus preventing pulmonary embolism) has made it possible to perform randomized trials that include a control group of patients who are not receiving active prophylaxis. ⁴⁴

Unfortunately, the strength of evidence for the use of the various prophylactic measures in spinal cord injury patients is limited. Thus, current clinical practice is dictated by the best evidence available. Because many of the articles dealing with prophylaxis in patients with spinal cord injury do not incorporate the above criteria, it is clear that there is a pressing need for multicenter trials of prophylaxis using the rigorous criteria described above.

Pathophysiologic Basis for Alternative Prophylactic Measures

Venous thrombi usually develop at sites of slow or disturbed flow and begin as small deposits of platelets, fibrin, and red cells in valve-cusp pockets or in the intramuscular sinuses of the veins of the lower limb. ⁷⁶ As the thrombus grows, it occludes the lumen of the vein, producing venous stasis, and then extends both proximally and distally as a coagulation thrombus composed of red blood cells with interspersed fibrin. The mechanisms that are recognized to be important in the pathogenesis of venous thromboembolism are venous stasis, activation of blood coagulation, and endothelial damage. ⁷⁷ A relatively high proportion (up to 30% or more) of thrombi in patients with spinal cord injury involve the popliteal or femoral venous segments. ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷

The prophylactic methods that have been evaluated clinically have been directed at 1 or more of these pathogenic factors and include anticoagulants that counteract the activation of blood coagulation, ⁴⁴ ⁴⁵ ⁴⁶ ⁴⁷ drugs that suppress platelet function and the interaction of platelets with the damaged vessel wall, ⁴⁴ ⁴⁷ and mechanical devices that prevent venous stasis. ⁴⁴ ⁴⁵ ⁴⁷ ⁴⁸

Oral Anticoagulant Prophylaxis

Oral anticoagulant prophylaxis using warfarin sodium is effective for preventing venous thromboembolism in patients undergoing high risk surgery. ¹ ³ ¹ ⁴ ¹ ⁶ ¹ ⁷ ¹ ⁸ However, the risk of bleeding complications has contraindicated the use of oral anticoagulant prophylaxis in spinal cord injury patients in the immediate postinjury phase. ¹ ³ ¹ ⁸

Heparin

Although effective in general surgical patients, ⁶⁰ prophylaxis with low-dose subcutaneous heparin (5,000 U every 8 or 12 h) is relatively ineffective for preventing venous thromboembolism in high risk patients. ⁴⁴ ⁴⁵ ⁴⁶ It is likely that any protection provided by low-dose heparin is incomplete in spinal cord injury patients. ⁴⁴ ⁴⁵ ⁴⁶ Low-dose heparin prophylaxis after surgery appears to be associated with an increased risk of development of a wound hematoma; otherwise, the risk of bleeding is low. ⁴⁶ ⁴⁷

Leyvraz et al reported a randomized trial in patients undergoing elective hip surgery. They used a prophylactic approach that overcame the thrombotic tendency by increasing the dose of subcutaneous heparin to a level that restored to normal the disturbed hemostatic equilibrium that occurred as a pathophysiologic response to the operation, without producing therapeutic anticoagulation. These investigators demonstrated that the shortening of the activated partial-thromboplastin time that occurs during the first postoperative week can be restored to normal, and venous thrombosis can be prevented by using adjusted doses of subcutaneous heparin.

There is evidence in the spinal cord injury literature to support the effectiveness of adjusted-dose heparin. Green et al ⁴⁴ reported a randomized trial comparing low-dose heparin and adjusted-dose heparin with 9 thrombotic events in the 29 patients (31.0%) receiving low-dose heparin while only 2 of the 29 patients (6.9%) receiving adjusted-dose heparin had thrombotic events. In addition, there were no bleeding events in the 29 patients receiving low-dose heparin while in the 29 patients receiving adjusted-dose heparin, there were 7 (24.1%) with bleeding episodes. In patients with high risk disorders such as spinal cord injury, the efficacy of low-dose heparin appears to be less than desired.

Based on the findings of Green et al, ⁴⁴ it appears that prophylaxis with adjusted-dose heparin is an effective method for preventing venous thrombosis in patients with
spinal cord injury but with an increased risk of bleeding.

**Aspirin**

It was originally hoped that the antiplatelet action of aspirin would provide protection against DVT, but the results have been generally disappointingly negative in high risk patients.2,4,38

**Intermittent Pneumatic Compression**

Intermittent pneumatic compression of the legs is an attractive form of prophylaxis that is effective in patients with spinal cord injury. External pneumatic compression overcomes venous stasis by intermittently squeezing the leg, and this also enhances fibrinolysis. Thus, intermittent compression has both a physical and a pharmacologic effect.2,4,38

Prophylaxis with intermittent pneumatic compression of the leg provides incomplete protection in spinal cord injury patients but is virtually free of side-effects and without risk of bleeding.4 For these latter reasons, pneumatic compression may well prove to be the preferred method of prophylaxis in the immediate days following spinal injury when patients are at high risk for bleeding.

**Combined Modalities**

On theoretic grounds, combined prophylactic approaches that interact to work against two or more of the pathogenic factors promoting postoperative venous thrombosis are attractive. Such approaches include intermittent pneumatic compression of the lower limb combined with low-dose heparin.

Some physicians have argued that they feel more comfortable using intermittent pneumatic leg compression for the first 10 to 14 days after an event such as spinal cord or head injury, then switching to low-dose or adjusted-dose heparin when the major risk period for any heparin-associated hemorrhage has passed. The main disadvantage of intermittent pneumatic leg compression, however, lies in its less dramatic efficacy for high risk patients, such as in spinal cord injury.2,4

**Low-Molecular-Weight Heparin**

In recent years, low-molecular-weight fractions of heparin have been prepared with a mean low-molecular weight of 4,000 to 5,000 d as compared to conventional heparin, which has a mean molecular weight of 12,000 to 16,000 d.8,9,28 Pharmacokinetic studies indicate that the bioavailability of low-molecular-weight heparin after subcutaneous injection is very high26-27 and that the half-life of low-molecular-weight fractions of heparin is longer than that of unfractionated heparin.9,4,32-34

Studies of models of venous thrombosis in laboratory animals have shown that some low-molecular-weight fractions of heparin have antithrombotic efficacy equal to or greater than that of heparin, with fewer hemorrhagic effects.28,32-34,38 These properties have not been consistently demonstrated in humans.32-35,4,38 A meta-analysis35 of randomized clinical trials evaluating low-molecular-weight heparin as prophylaxis against DVT suggested that it is more effective than low-dose heparin, but with an increased risk of bleeding. In contrast, a large randomized trial36 comparing the prophylactic use of low-molecular-weight heparin with moderate doses of subcutaneous heparin in hip surgery patients showed that low-molecular-weight heparin produced significantly fewer hemorrhagic complications for an apparently equivalent antithrombotic effect. Whether this reflects an intrinsic property of low-molecular-weight heparin or an effect related to the dose is uncertain.36

Green et al37 reported on the experience with thrombo-prophylaxis in 41 spinal cord-injured patients comparing low-dose unfractionated heparin with the low-molecular-weight heparin (Loptaparin). The incidence of DVT evaluated by IPC and Doppler and confirmed by venography, was 5 of 21 patients (23.9%) with 2 of 21 patients (9.5%) experiencing fatal pulmonary embolism in the low-dose heparin group, while in the 20 patients in the low-molecular-weight heparin group, there were no episodes of DVT or pulmonary embolism. Again, there were no episodes of significant bleeding in the low-molecular-weight heparin group, while in the low-dose heparin group, the drug was stopped in 10% of the patients because of severe bleeding. This interesting clinical trial demonstrated efficacy that appears superior to low-dose heparin while offering significantly greater safety than observed with adjusted-dose heparin.

**Practical Recommendations**

Venous thromboembolic complications occur frequently after spinal cord injury. However, the individual physician may be reluctant to use prophylaxis for multiple reasons. First, death from pulmonary embolism is relatively infrequent. Second, there are doubts about the safety of antithrombotic drugs and the effectiveness of certain prophylactic approaches. Finally, at the institutional level, there has been reluctance to add interventions whose cost-effectiveness has not been adequately evaluated.

Screening with combined IPC and B-mode imaging of the lower limb in addition to routine venography at a fixed interval postoperatively will provide early detection of venous thrombosis, but this approach is expensive and logistically demanding. Primary prophylaxis with antithrombotic drugs or intermittent pneumatic compression, or the use of combined modalities (such as intermittent compression and low-dose heparin) is more effective and less expensive and is the preferred approach. The ideal primary prophylactic method should be effective, safe, well accepted by patients, nurses, and medical staff, and easily administered. It should also be inexpensive and require minimum monitoring. Secondary prevention by screening with B-mode imaging and IPC is reserved for patients in whom primary prophylaxis is thought to be relatively ineffective.

At present, based on the data reported in the literature, 3 approaches to primary prophylaxis have been shown to be effective and should be considered in patients with spinal cord injury. These prophylactic approaches entail the use of (1) low-dose heparin; (2) adjusted-dose subcutaneous heparin; or (3) intermittent pneumatic compression. The choice of prophylactic regimen depends on the potential risk of bleeding in the individual patient. The results of trials with low-molecular-weight heparin plus further clinical trials will no doubt modify these recommendations, but given the potentially serious nature of venous thromboembolic disease and the demonstrated effectiveness of these approaches, it is clearly imprudent to withhold primary prophylaxis while...
ACKNOWLEDGMENT: The assistance of B. L. Doucette, BFE, Operations Analyst, is appreciated.

REFERENCES

1 Dallen JE, Alpert JS. Natural history of pulmonary embolism. Prog Cardiovasc Dis 1975; 17:259-79
66 Biello DR, Mattar AG, McKnight RC, et al. Ventilation-perfusion studies in suspected pulmonary embolism. AJR 1979; 133:1033-37
76 Silver JB. The prophylactic use of anticoagulant therapy in the prevention of pulmonary embolism in one hundred consecutive spinal injury patients. Paraplegia 1974; 12:188-96

Venous Thromboembolism in Spinal Cord Injury Patients (Russell D. Hull)
83 Verstraete M. Pharmacotherapeutic aspects of unfractionated and low molecular weight heparin. Drugs 1990; 40:498-530