Prophylaxis for deep venous thrombosis in neurosurgery: a review of the literature

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The incidence of deep venous thrombosis (DVT) and subsequent pulmonary embolism (PE) in patients undergoing neurosurgery has been reported to be as high as 25%, with a mortality rate from PE between 9 and 50%. Even with the use of pneumatic compression devices, the incidence of DVT has been reported to be 32% in these patients, making prophylactic heparin therapy desirable. Both unfractionated and low-molecular-weight heparin have been shown to reduce the incidence of DVT consistently by 40 to 50% in neurosurgical patients. The baseline rate for major intracranial hemorrhage (ICH) following craniotomy has been reported to be between 1 and 3.9%, but after initiation of heparin therapy this rate has been found to be as high as 10.9%. Therefore, neurosurgeons must balance the risk of PE against the increased risk of postoperative ICH from prophylactic heparin for DVT. The authors review the literature on the incidence of DVT and PE in neurosurgical patients, focusing on the incidence of ICH related to the use of unfractionated and low-molecular-weight heparin in this patient population.

Key Words • deep venous thrombosis • pulmonary embolism • low-molecular-weight heparin • unfractionated heparin

Definition and Incidence of DVT and PE in Neurosurgical Patients

Deep venous thrombosis occurs in the deep draining veins of the extremities, with a propensity to appear in the large veins of the lower extremities. More recently, the term VTE has been used to refer to both DVT and PE. A variety of factors place the neurosurgery population at increased risk for DVT; these include intracranial surgery, malignant tumors, duration of surgery, decreased mobilization postoperatively, postoperative paralysis, and older age. The classic presenting symptom for DVT is a painful, swollen, erythematous limb. Propagation of the clot within deep draining veins can result in dislodgment of an embolus to downstream organs, usually the lungs.

Symptoms of PE include shortness of breath, pleuritic chest pain, and tachycardia. In the US, fatal PE occurs in an estimated 50,000 to 200,000 people per year. In fact, 90% of patients in whom PE develops outside the hospital setting die within 1 hour. Although the actual incidence of a clinically significant PE is relatively rare in the general population, its occurrence increases dramatically in hospitalized neurosurgical patients.

In a review of the incidence of DVT and PE in neurosurgical patients treated in the early 1990s who were diagnosed using various techniques (for example, compression ultrasonography, venography, and ventilation/perfusion lung imaging) investigators demonstrated an incidence of 18 to 50% for DVT and 0 to 25% for PE. In one large prospective study of neurosurgical patients, the rate of VTE was 25% (33 of 130); of these 7% (nine of 130) were symptomatic, with two deaths occurring from PE. The highest risk for DVT is in patients with brain tumors (28–43%), followed by patients undergoing craniotomy (25%), and those with head injury (20%). Hamilton, et al., noted that the risk of a PE in the general neurosurgical population was 5%, with a mortality rate ranging from 9 to 50%. Altschuler, et al., reported an 8.4% rate of PE in patients with brain tumors and a mortality rate of 2% from PE in patients with spinal cord injury.

The 2001 ACCP consensus on DVT prophylaxis acknowledged a high incidence of this disorder in neurosurgical patients, noting that in 22% of patients fibrinogen uptake test results were consistent with evidence of DVT, and that the rate of proximal DVT found on duplex studies was 5%. Wen and Hall stated that “in neurosurgical patients if one assumes a conservative rate of clinically apparent PE at 0.5% with a 50% mortality rate, and that 700,000 neurosurgical cases (3500 surgeons, 200 cases/year) are performed annually in the United States, a halving of the rate of pulmonary embolism could save 875 lives each year.” The primary prevention method for fatal PE is averting the formation of a DVT.

Abbreviations used in this paper: ACCP = American College of Chest Physicians; DVT = deep venous thrombosis; ICH = intracranial hemorrhage; PE = pulmonary embolism; VTE = venous thromboembolism.
**Suggested DVT Prevention Guidelines**

The timing and methods of providing DVT prophylaxis to patients undergoing neurosurgery is controversial. Neurosurgeons must weigh the benefits of DVT prophylaxis against the risk of bleeding complications. In recent years, a number of researchers have looked at the incidence of DVT formation in neurosurgical patients treated with various prophylactic regimens. Unfortunately, no consensus has been reached regarding a DVT prophylaxis regimen.

Apart from the neurosurgical literature, the most commonly referenced guidelines for DVT prophylaxis come from the consensus statement published by the ACCP as a supplement to the journal *Chest.* The most recent guidelines from 2001 provide recommendations regarding the prevention and treatment of VTE in neurosurgical patients. After extensive review of the then-current state of knowledge regarding DVT prophylaxis in 2001, the authors of the consensus statement concluded that mechanical methods (intermittent pneumatic compression with or without elastic stockings) should be the standard of care. Nevertheless, the use of low-dose unfractionated heparin was left to the discretion of the practitioner, and the use of low-molecular-weight heparin was generally regarded as unsuitable in the setting of the perioperative period.

Although the ACCP consensus statement of 2001 offered some guidelines regarding DVT prophylaxis, no clear protocols for the use of unfractionated or low-molecular-weight heparin were agreed upon. Over the last 5 years, numerous articles have appeared in which the use of pneumatic compression devices, unfractionated heparin, and low-molecular-weight heparin (for example, enoxaparin) have been discussed. Overall, studies conducted in patients who have undergone neurosurgery, in whom the use of pneumatic compression devices alone has been compared with the use of heparin alone, show a clear reduction of the incidence of DVT and PE (by 40–50%) when heparin is used. The rate of major postoperative ICH, however, may rise from its baseline of 1 to 3.9% to as high as 10.9% when heparin is introduced.

In this article we review the literature on unfractionated and low-molecular-weight heparin for prevention of VTE, with an emphasis on the incidence of ICH.

**Pneumatic Compression Devices**

The use of intermittent pneumatic compression boots with or without elastic stockings has been accepted as standard of care for DVT prophylaxis in the neurosurgical population. Sequential-gradient intermittent pneumatic compression induces prompt and specific increases in both hemodynamic and fibrinolytic function, and its antithrombotic activity is likely related to both of these mechanisms. The increase in fibrinolytic activity, which seems best reflected in fibrin degradation products, subsides rapidly once compression has been stopped. The optimal antithrombotic efficacy of sequential-gradient intermittent pneumatic compression devices is achieved when they are worn continuously.

Complications from pneumatic compression devices include nerve compression leading to neuropathy and rare incidences of allergies to the component materials. Overall, intermittent pneumatic compression boots with or without elastic stockings provide a safe and partially effective prophylactic regimen for neurosurgical patients postoperatively. The major benefit of this treatment is that there is no increased risk of postoperative ICH.

**Unfractionated Heparin: Mechanism of Action**

Unfractionated heparin is a heterogeneous mixture of glycosaminoglycans with a molecular weight range of 4 to 30 kD. Its anticoagulation effect is mediated by the activation of antithrombin III, which then inactivates with relatively equal potency the coagulation enzymes thrombin (factor IIa) and factor Xa (Table 1). Other antithrombotic effects include inhibition of platelet aggregation and additional antithrombin III–independent mechanisms. The partial thromboplastin time may be elevated because of inactivation of thrombin. Heparin has a short halflife in plasma (t½ = 1.5 hours) and has variable and extensive binding to plasma proteins and cells. At our institution, the dosage regimen of unfractionated heparin is typically 5000 U given subcutaneously twice daily for patients who weigh less than 90 kg and three times daily for patients who weigh more than 90 kg, starting 24 hours after the conclusion of surgery. Cost comparisons for various isoforms of unfractionated and low-molecular-weight heparin are provided in Table 2.

**Subcutaneous Unfractionated Heparin and Incidence of DVT**

Studies have consistently shown a reduction in DVT risk after administration of subcutaneous heparin. Wen and Hall state that “it is generally accepted in general surgery and many other surgical specialties that the use of low-dose heparin, started before surgery, will reduce the risk of DVT by two-thirds and pulmonary embolism by one-half.” Historically, in 1977 Barnett, et al., were among the first to note the safety and efficacy of minidose heparin administered in neurosurgical patients. Iorio and Agnelli, in a metaanalysis published in 2000, suggested that the use of heparin (unfractionated and low-molecular-weight heparin were combined in their analysis) resulted in a 45% relative risk reduction for the development of DVT.
Prophylaxis for DVT in neurosurgery: review of the literature

VTE in neurological patients. Frim, et al., reported in 1992 that prophylaxis with pneumatic compression devices plus heparin significantly reduced the incidence of thromboembolic complications (p = 0.02). In their study none of the 138 patients treated with a pneumatic compression device plus heparin exhibited clinical evidence of PE or DVT (Table 3).

**Risk of ICH With Unfractionated Heparin**

In 2001 Raabe, et al., reviewed several studies in which unfractionated heparin was used for DVT prophylaxis (Table 3), and several important findings were demonstrated. In studies in which patients were given 5000 U unfractionated heparin either two or three times a day in the immediate preoperative period, the hemorrhage rate was 1.3 to 5.2%, compared with 2 to 4.3% for patients in the control groups who did not receive preoperative prophylaxis. For unfractionated heparin administered in the postoperative period, Raabe, et al., referenced a prospective study from 1992 by Frim, et al., in which no postoperative hematomas were demonstrated in 138 patients. Individuals in this protocol received 5000 U unfractionated heparin twice daily, starting within 24 hours after surgery.

Wen and Hall reviewed the complication rate of low-dose unfractionated heparin delivered at doses of 5000 U twice daily, commencing the night before surgery. Of 152 cranial procedures, only one patient experienced a postoperative complication following a needle biopsy procedure, yielding a complication rate of 0.66%. In their review of the literature, Wen and Hall found an overall incidence of postoperative hematoma in 19 (1.2%) of 1612 patients given subcutaneous heparin, whereas the control groups in these studies demonstrated a postoperative hemorrhage risk of approximately 1.7% (13 of 785). Overall, the relative risk from the prophylactic use of subcutaneous heparin is quite low and most institutions have mandated the use of low-dose unfractionated heparin for postoperative thromboembolism prophylaxis.

The use of subcutaneous heparin in the setting of acute traumatic brain injuries remains more controversial. Kim, et al., demonstrated no increased risk of hemorrhage in patients admitted for traumatic head injury when subcutaneous heparin was initiated for prophylaxis within 72 hours of admission compared with patients in whom heparin therapy was started after 72 hours. Importantly, no studies have been performed in which unfractionated heparin was administered within 24 hours of presentation to the hospital in patients suffering neurotrauma.

### TABLE 3

**Literature review of postoperative ICH and VTE rates after intracranial procedures followed by perioperative administration of unfractionated or low-molecular-weight heparin**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Study Design</th>
<th>Medication</th>
<th>ICH Rate (%)</th>
<th>VTE Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic treatment started preop</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>1/50 (2)</td>
<td>17/50 (34)</td>
</tr>
<tr>
<td>Barnett, et al., 1977</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>2/46 (4.3)</td>
<td>5/40 (12.5)</td>
</tr>
<tr>
<td>Cerrato, et al., 1978</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>3/58 (5.2)</td>
<td>5/40 (12.5)</td>
</tr>
<tr>
<td>Bostrom, et al., 1986</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>0/22 (0)</td>
<td>3/22 (13.6)</td>
</tr>
<tr>
<td>Dickinson, et al., 1998</td>
<td>P</td>
<td>enoxaparin 30 mg BID</td>
<td>4/106 (3.8)</td>
<td>5/46 (10.9)</td>
</tr>
<tr>
<td>Macdonald, et al., 1999</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>5/68 (7.4)</td>
<td>4/106 (3.8)</td>
</tr>
<tr>
<td>Macdonald, et al., 2003</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>1/49 (2)</td>
<td>5/40 (12.5)</td>
</tr>
<tr>
<td>treatment started &lt;24 hrs postop</td>
<td>P</td>
<td>dalteparin 2500 U QD</td>
<td>2/51 (3.9)</td>
<td>5/40 (12.5)</td>
</tr>
<tr>
<td>Frim, et al., 1992</td>
<td>P</td>
<td>UFH 5000 U BID</td>
<td>15/473 (3.2)</td>
<td>0/138 (0)</td>
</tr>
<tr>
<td>Nurmohamed, et al., 1996</td>
<td>P &amp; R</td>
<td>fraxiparin 7500 U BID</td>
<td>47/179 (26.3)</td>
<td>3/166 (18.7)</td>
</tr>
<tr>
<td>Agnelli, et al., 1998</td>
<td>P &amp; R</td>
<td>enoxaparin 40 mg QD</td>
<td>43/130 (33.1)</td>
<td>22/130 (16.9)</td>
</tr>
<tr>
<td>Raabe, et al., 2001</td>
<td>R</td>
<td>UFH 5000 U TID</td>
<td>13/1564 (0.8)</td>
<td>5/75 (6.7)</td>
</tr>
<tr>
<td>Goldhaber, et al., 2002</td>
<td>P &amp; R</td>
<td>UFH 5000 U BID</td>
<td>9/75 (12)</td>
<td>5/75 (6.7)</td>
</tr>
<tr>
<td>Gerlach, et al., 2003</td>
<td>P</td>
<td>nadroparin 0.3 ml QD</td>
<td>7/255 (2.7)</td>
<td>5/75 (6.7)</td>
</tr>
</tbody>
</table>

* NA = not applicable; P = prospective; P & R = prospective, randomized; R = retrospective; UFH = unfractionated heparin.
**Low-Molecular-Weight Heparin: Mechanism of Action**

Low-molecular-weight heparin is formed by the fractionation of heparin molecules. This form has greater bioavailability at lower doses, more predictable anticoagulant responses than unfractionated heparin, and a lower risk of heparin-induced thrombocytopenia. The currently available low-molecular-weight heparins in the US are dalteparin, enoxaparin, and tinzaparin; nadroparin is available only in Europe. These forms of the drug all have different indications and have been studied for a variety of uses.

Compared with the unfractionated form, low-molecular-weight heparin has a greater ratio of anti–factor Xa/anti–factor IIa activity, greater bioavailability, and longer duration of action, allowing for once-daily doses for prophylaxis. Various isoforms of low-molecular-weight heparin are on the market and each exhibits different pharmacokinetic and overall disposition patterns (Table 1). In reviewing the literature on neurosurgical VTE prophylaxis, it is important to understand that various isoforms have different potencies. When normalized to the same injected dose (1000 IU anti–factor Xa), the relative actual amount of plasma anti-Xa activity generated by enoxaparin is 1.48 times greater than that of nadroparin and 2.28 times greater than that of dalteparin, and the anti-Xa activity of nadroparin is 1.54 times greater than that of dalteparin. At our institution, enoxaparin is on formulary and is delivered subcutaneously for VTE prophylaxis either once daily at a dose of 40 mg or twice daily at a dose of 30 mg.

**Risk of ICH With Low-Molecular-Weight Heparin and Incidence of DVT**

The use of low-molecular-weight heparin has been suggested to be a more efficacious method for thromboembolic prophylaxis. Surgical specialties other than neurosurgery have adopted the routine use of low-molecular-weight heparin in the perioperative period. The routine use of unfractionated or low-molecular-weight heparin in neurosurgery has raised concern regarding the increased risk of postoperative hemorrhage. Numerous studies have been published during the past 10 years in which the efficacy and safety of low-molecular-weight heparin in neurosurgical patients has been discussed.

A study by Dickinson, et al., in 1998 compared enoxaparin with sequential compression devices for DVT prophylaxis. In this study, enoxaparin was started preoperatively at a dose of 30 mg every 12 hours and continued until patients were discharged from the neurosurgery service. This study was terminated early because of the increased incidence of ICH in the enoxaparin group (Table 3). It is important to reiterate that in this study enoxaparin was given preoperatively.

In 2000, Iorio and Agnelli published a metaanalysis of previous studies in which low-molecular-weight heparin was used for thromboembolism prophylaxis. Three placebo-controlled, double-blinded clinical trials were assessed for treatment efficacy and the presence of bleeding complications. Treatment with low-molecular-weight heparin resulted in a 38% relative risk reduction for VTE. It was necessary to treat 9.2 patients with low-molecular-weight heparin to prevent a single case of VTE (39 events were prevented by treatment of 360 patients). The overall bleeding risk ranged from 4.1 to 11.8% for the low-molecular-weight heparin cohort, with control patients demonstrating an overall bleeding risk of between 1.2 and 7.1%. The risk of a major ICH was between 2.2 and 2.6% for the low-molecular-weight heparin cohort and between 0.8 and 2.6% for the control group, coinciding with a risk of one major bleeding event per every 115 treated patients. Iorio and Agnelli concluded that “one may expect to have one major nonfatal bleeding event in excess of every 11 thrombotic events prevented or one major nonfatal bleeding event for every 7 proximal DVTs prevented.”

Goldhaber, et al., reviewed their experience after completing a randomized, prospective, double-blinded study comparing the efficacy of unfractionated with low-molecular-weight heparin in 150 patients with brain tumors. They demonstrated an overall asymptomatic VTE rate of 9.3%, with no episodes of symptomatic DVT or PE. No statistical significance was found between the use of unfractionated and low-molecular-weight heparin. Two patients who were receiving enoxaparin had major bleeding episodes, one of which was intracranial. Goldhaber, et al., noted that the way their study was designed, it was underpowered for detection of a difference between unfractionated and low-molecular-weight heparin.

Two studies published in 2003 addressed the use of low-molecular-weight heparin for thromboembolic prophylaxis in patients who underwent craniotomy procedures. MacDonald, et al., performed a randomized prospective study comparing unfractionated heparin (5000 U delivered subcutaneously twice daily) with dalteparin (2500 U delivered once daily), with treatment initiated at the time of anesthesia induction. Overall, DVT developed in none of 49 patients who received unfractionated heparin and in two of 51 in whom dalteparin was administered (one of whom was symptomatic). Two patients who received dalteparin experienced hemorrhages postoperatively that were treated nonsurgically, whereas in one patient in the unfractionated heparin group a postoperative hemorrhage developed that required surgical reexploration. Again, this study was underpowered for detection of a statistically significant difference between low-molecular-weight and unfractionated heparin.

Gerlach, et al., conducted a 3-year prospective study of the risk of postoperative hemorrhage in patients receiving low-molecular-weight heparin (nadroparin) within 24 hours of the conclusion of a neurosurgical procedure. An overall incidence of postoperative hemorrhage requiring repeated operation occurred in 43 (1.5%) of 2823 intracranial procedures, with no resultant deaths in the cohort. Clinically overt VTE occurred in seven (0.25%) of 2823 patients, with one fatal PE.

Although the use of low-molecular-weight heparin remains controversial in the setting of elective neurosurgical procedures, few investigators have assessed the efficacy and safety of this therapy in the setting of traumatic closed head injury. Norwood, et al., reported on the safety of administering enoxaparin for VTE prevention in patients with injuries resulting in ICH. Enoxaparin was given 24 hours after the time of admission or after the conclusion of surgery. The results of the study demonstrated progression of ICH in six (4%) of 150 patients after initiation of enoxaparin therapy. Two patients experienced postsurgical bleeding that required repeated operation; however,
these two received heparin within 24 hours of the postoperative period. The other four patients in whom ICH progressed were in the nonsurgically treated group. In two of these patients the protocol was violated; they received enoxaparin within 12 hours of admission, and the second patient received a double dose of enoxaparin within 30 hours of admission. Two patients suffered DVT while adhering to the protocol and none had a clinically recognized PE. The authors compared their outcome with a retrospective review by Patel, et al., who demonstrated a 12% incidence of computerized tomography–confirmed ICH progression after admission for blunt closed head injuries. Based on these reports, Norwood, et al., concluded that enoxaparin could safely be administered 24 hours after an injury leading to ICH without an increased risk of hemorrhage progression or new bleeding.

CONCLUSIONS

Prophylaxis for VTE in neurosurgical patients remains controversial. Patients are at risk for postoperative hemorrhagic complications resulting from low-dose heparin therapy or administration of low-molecular-weight heparin. Nevertheless, without appropriate prophylaxis neurosurgical patients are at increased risk of suffering a VTE (on the order of 32% even with sequential compression devices). Although many scientific articles in the last 5 years have contributed to our understanding of the use of unfractionated and low-molecular-weight heparin in neurosurgical patients, no studies have yet been able to define what should be the standard of care in the postoperative period. Based on the current literature, the use of both unfractionated and low-molecular-weight heparin appears to be safe when given at least 24 hours after the conclusion of surgery or admission for traumatic closed head injury. Double-blinded prospective studies are needed to address definitively the safety and efficacy of unfractionated and low-molecular-weight heparin for VTE prophylaxis in neurosurgical patients.

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References


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Note Added in Proofs

After this article was accepted for publication, new guidelines for antithrombotic therapy were recommended by the Seventh American College of Chest Physicians Conference (Geerts WH, Pineo GF, Heit JA, et al: Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 126 (Suppl 3):338S–400S, 2004). According to these guidelines, thromboprophylaxis is strongly recommended in patients undergoing major neurosurgery involving intermittent pneumatic compression with or without graduated compression stockings. The use of low-dose unfractionated heparin or postoperative low-molecular-weight heparin was deemed an acceptable alternative, and combined therapy (that is, mechanical prophylaxis and pharmacological prophylaxis) should be considered in high-risk neurosurgical patients.