Deep Venous Thrombosis and Pulmonary Embolism in Neurosurgery:
A Review of the Risks and Benefits of Prophylaxis

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ABSTRACT

Background: In neurosurgery and spine surgery in particular, the unique risks and benefits of utilizing different prophylaxis regimens against deep venous thrombosis (DVT) and pulmonary embolism (PE) must be carefully weighed. Our aim was to comprehensively review the safety and efficacy of different regimens of prophylaxis against DVT and PE in neurosurgical cranial and spinal studies.

Methods: Patients undergoing cranial or spinal procedures may receive one or more types of prophylaxis; elastic stockings (ES), intermittent pneumatic compression stockings (IPC), low dose unfractionated subcutaneous heparin (typically 5000 U q12h), and/or low dose low molecular weight heparin alternatives. The incidence of DVT, PE, and hemorrhage, particularly for those receiving low dose fractionated or low molecular weight heparin, were reviewed.

Results: IPC stockings appeared to be very effective, particularly in spinal surgical series where the frequency of DVT/PE remained lower than in cranial studies. Although the addition of low dose unfractionated subcutaneous or low dose low molecular weight heparin regimens further decreased the frequency of DVT and PE, it carried a 2%-4% risk of major postoperative hemorrhage.

Conclusions: Intermittent compression stocking prophylaxis (IPC) alone provide adequate prophylaxis against DVT and PE in most patients undergoing spinal procedures. The "value added" of low dose unfractionated subcutaneous or low dose low molecular weight heparin regimens regarding further reduction in the incidence of DVT and PE, poses the significant risk of major postoperative hemorrhage.

Key words: deep venous thrombosis, pulmonary embolism, spinal surgery

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INTRODUCTION

The optimal prophylaxis regimen against deep venous thrombosis (DVT) and pulmonary embolism (PE) for spinal surgery remains controversial [10-13, 31] (Tables 1, 2). Although mini-heparin or low-molecular weight heparin/derivatives maximally reduce the incidence of DVT/PE in both cranial and spinal neurosurgical series, they are accompanied by a 2-4% incidence of major postoperative hemorrhage requiring secondary surgical intervention [21, 22, 31] (Table 3). Furthermore, as the overall incidence of DVT/PE is lower in spinal compared with cranial operations, safer mechanical means of prophylaxis, intermittent pneumatic compression stockings (IPC), provide an attractive alternative to mini or low-dose heparin-based therapies.

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Table 1: The Incidence of DVT/PE Utilizing Elastic Stockings and/or Intermittent Pneumatic Compression Stocking Prophylaxis in Neurosurgical Series

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Type of Prophylaxis</th>
<th>Deep Venous Thrombosis (DVT)</th>
<th>Pulmonary Embolism (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Elastic Stockings (ES)</td>
<td>Combined</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intermittent Compression Stockings (IPC)</td>
<td>2.2% DVT (3 ES, 1 IPC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin Regimens</td>
<td>1.1% PE Combined</td>
<td></td>
</tr>
<tr>
<td>August [3]</td>
<td>180 Cranial</td>
<td>ES + IPC</td>
<td>7.7% DVT Cranial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES</td>
<td>1.5% DVT Spinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.19% PE</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.7% (Fatal)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2% DVT (2/111)</td>
<td></td>
</tr>
<tr>
<td>Ferree [10]</td>
<td>185 Spinal</td>
<td>74 ES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>111 IPC</td>
<td></td>
<td></td>
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</tbody>
</table>

REVIEW OF DEEP VENOUS THROMBOSIS AND PULMONARY EMBOLISM

Factors Contributing to DVT

Trauma, vascular surgery, tumor/malignancy, brain or spinal injury/surgery, lower extremity trauma, or infection are associated with an increased incidence of DVT/PE [26]. This frequency is further exacerbated in neurosurgical patients presenting with multiple risk factors; prior DVT, previous surgery, new immobilization, advanced age, heart failure, obesity, and the type and duration of surgery [6, 28]. Where no prophylaxis is utilized, the frequency of DVT in cranial and spinal neurosurgical series employing fibrinogen tagging ranges from 29%-43% [9]. Upper-limb thromboses, most typically associated with central venous (CVP) catheter placement, occur from 0.3%-28.3% of the time [30]. Routine prophylaxis for patients undergoing elective spinal procedures reduces the incidence of DVT to 7.1% [9]. Whereas, postoperative hemorrhages attributed to mini or low dose heparin may prove devastating, mechanical prophylaxis with intermittent pneumatic compression stockings (IPC) poses little to no risk of postoperative bleeds in neurosurgical patients [6] (Table 3). However, select individuals with genetic hypercoagulopathy syndromes including Factor V Leiden mutation, elevated antiphospholipid antibodies, deficiencies of antithrombin, protein C, and protein S will uniquely require early postoperative heparin-related prophylaxis [17].

Recurrent DVT

The susceptibility to post-thrombotic syndromes is also of major concern. DVT has been shown to recur 21.5% of the time within the first 5 years, with comparable 27.9% secondary recurrence rates [18]. Recurrent DVT is most frequently correlated with prior proximal DVT (popliteal, deep femoral, or iliac veins thromboses) [28]. The risk of PE from initial or recurrent calf-vein phlebitis remains low (1.1% risk of clot propagation into the thigh) [16].

Frequency of DVT/PE

Although many regimens of prophylaxis against DVT/PE are available, no one regimen clearly protects against PE in neurosurgical as well as other subspecialty patients (fatal PE 2.6%) [17, 21, 22, 28].
Table 2: Efficacy of Intermittent Compression Stockings Alone or With Low Dose Unfractionated Heparin (Mini-Heparin) or Low Dose Low Molecular Weight Heparin

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Prophylaxis</th>
<th>Deep Venous Thrombosis (DVT)</th>
<th>Pulmonary Embolism (PE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frim [12]</td>
<td>473 IPC</td>
<td>3.2% DVT (15/473)</td>
<td>3.5% PE (16/473)</td>
</tr>
<tr>
<td>611 Cranial/Spinal</td>
<td>138 IPC/Mini-Heparin¹</td>
<td>0% DVT</td>
<td>0% PE</td>
</tr>
<tr>
<td>Macdonald [22]</td>
<td>50 IPC+Mini-Heparin¹</td>
<td>0% DVT (0/50)</td>
<td>0% PE (0/50)</td>
</tr>
<tr>
<td>100 Cranial</td>
<td>50 IPC+Dalteparin²</td>
<td>4% DVT (2/50)</td>
<td>0% PE (0/50)</td>
</tr>
<tr>
<td>Goldhaber [15]</td>
<td>IPC+Mini-Heparin¹ or IPC+Enoxaparin³</td>
<td>Combined</td>
<td>9.3% DVT (14/150)</td>
</tr>
<tr>
<td>150 Cranial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macdonald [21]</td>
<td>106 IPC+Mini-Heparin¹</td>
<td>6.6% DVT (7/106)</td>
<td>0.94% PE (1/106)</td>
</tr>
<tr>
<td>174 Cranial</td>
<td>68 IPC Alone</td>
<td>4.4% DVT (3/68)</td>
<td>2.9% PE (2/68)</td>
</tr>
<tr>
<td>Gerlach [13]</td>
<td>1954 IPC+Nadroparin⁴</td>
<td>Combined</td>
<td>0.7% DVT (13/1954)</td>
</tr>
<tr>
<td>503 Cervical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>152 Thoracic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1299 Lumbar</td>
<td></td>
<td></td>
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</tbody>
</table>

¹ Mini-Heparin (Unfractionated Heparin - 5000U subcutaneous q12h), 2 Dalteparin (2500 U/day), 3 Enoxaparin (40 mg/day), 4 Nadroparin (Fraxiparin 0.3 m./2850 U)

Based on a meta-analysis of patients with PE, DVT is usually suspected in 18% of patients, and proven in 36-45% of individuals [18]. In patients undergoing total hip replacement (THR) and total knee replacement (TKR), DVT was observed in 15-30% upon discharge and increased another 25% within the succeeding 3 weeks [19]. This high incidence of DVT prompted the adoption of prolonged 30-day post-discharge prophylaxis with mini-heparin (unfractionated) (15,000 U/24 hrs), and in one series reduced the incidence of DVT from 21.4% (treated 15 days) to 3% [23]. Few orthopedic patients experienced significant postoperative hemorrhagic complications; utilizing IPC and low molecular weight heparin (enoxaparin 30 mg bid); only one patient developed an upper gastrointestinal bleed following THR (149 patients) and TKR (292 patients) [25].
Table 3: Incidence of Postoperative Hemorrhages Utilizing Mini-Heparin or Low Dose Heparin (Nadroparin, Dalteparin) Prophylaxis Against Deep Venous Thrombosis and Pulmonary Embolism in Neurosurgical Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Prophylaxis</th>
<th>Incidence of Hemorrhages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>152 Cranial 720 Spinal</td>
<td>6 (0.7%) Bleeds 3 Minor 3 Major-2 Spinal, 1 Cranial</td>
</tr>
<tr>
<td>Wen [31]</td>
<td>Mini - Heparin</td>
<td>13 (0.7%) Bleeds 8 Minor 5 Major</td>
</tr>
<tr>
<td>Gerlach [13]</td>
<td>IPC + Nadroparin</td>
<td>4 (2.3%) Bleeds Major</td>
</tr>
<tr>
<td>Macdonald [21]</td>
<td>IPC + Mini Heparin</td>
<td>1 (0.2%) Cranial Bleed Major</td>
</tr>
<tr>
<td>Macdonald [22]</td>
<td>IPC + Mini-Heparin IPC + Dalteparin</td>
<td>2 (4%) Cranial Bleeds Major</td>
</tr>
</tbody>
</table>

Choice of Prophylaxis

Two-thirds of cases of DVT/PE are considered preventable. The most common reasons for failed prophylaxis include the lack of prophylaxis (47.5%), the inadequate duration of prophylaxis (22.7%), or the incorrect type of prophylaxis (20.5%) [2]. In a survey of 58 neurosurgeons in the UK, elastic stockings (ES) and low molecular weight heparin reduced postoperative DVT rates by 79% and 90% and PE by 43% and 67% respectively [14]. However, for those patients receiving low molecular weight heparin begun one day postoperatively, 29% experienced bleeding complications. Among neurosurgeons in the United States, Carman, Kanner, Barnett et. al. found that 81.4% of brain and 78.5% of spine surgeons utilized DVT prophylaxis; of interest, 76.2% of brain procedures employed mechanical prophylaxis alone because of the risk of mini or low dose heparin induced postoperative hemorrhages [8].

Elastic Stockings (ES) and Intermittent Compression Stocking (IPC) Prophylaxis

Elastic stockings are less effective than intermittent pneumatic compression stockings when utilized as prophylaxis against DVT/PE in general/orthopedic and neurosurgical patients (Table 1). Elastic stockings (ES) alone reduced the incidence of DVT by 64% in general surgical and by 57% in orthopedic patients undergoing total hip replacements [1]. In 523 neurological and neurosurgical patients utilizing intermittent pneumatic compression stocking (IPC) prophylaxis alone, a 2.3% incidence of DVT and 1.1% frequency of PE were documented on lung scans/angiograms (Table 1) [5]. Combining ES and IPC in 2643 neurosurgical patients treated over a 5-year period, a 7.7% incidence of DVT for cranial and 1.5% frequency of DVT for spinal procedures was documented (Table 1) [11]. The early detection and management of proximal clots amongst patients...
undergoing cranial surgery accounted for the low frequency of PE (0.19%). A 1% incidence of DVT and 1% frequency of PE were encountered utilizing IPC alone in 100 of the author’s patients undergoing single level anterior corpectomy/fusion (ACF); this patient was homozygous for Factor V Leiden mutation (submitted). IPC alone in a separate series of 100 of the author’s patients undergoing multilevel anterior corpectomy/ fusion with simultaneous posterior fusion (requiring an average of 9.5 hours), resulted in a 7% incidence of DVT; only 2 instances of DVT localized to the iliac veins resulted in PE (2%).

**Elastic Stockings (ES) and Intermittent Pneumatic Compression Stockings (IPC) Prophylaxis**

Evaluating duplex studies following the adoption of ES (74 patients) and IPC (111 patients) prophylaxis in patients undergoing spinal procedures, 5.4% of ES versus 2% of IPC patients developed DVT (Table 1) [10]. For 180 patients undergoing craniotomy with brain-mapping procedures, ES were used bilaterally, but IPC only unilaterally; DVT occurred in 2.2% of patients (3/ES, 1/IPC) and 2 (1.1%) developed PE (1.1%) (Table 1) [3].

**IPC vs. IPC + Subcutaneous Unfractionated Heparin/Low Molecular Weight Heparin**

Comparing IPC and IPC plus mini-heparin regimens, the incidence of DVT was variable, but the frequency of PE was lower for the IPC/heparin group. IPC alone (473 patients) versus IPC plus mini-heparin (unfractionated-5000 U q12 h) begun the first postoperative day (138 patients) were utilized for patients undergoing both cranial and spinal procedures (Table 2) [21]. DVT occurred in 3.2% and PE in 3.5% of those managed with IPC alone, while 0% developed DVT and 0% had PE for those receiving IPC and mini-heparin combined. In a separate cranial series, IPC alone (68 patients) was compared with IPC and mini-heparin prophylaxis (unfractionated 5000 U q12 h) (106 patients) (Table 2) [6]. Those treated with IPC alone showed a 4.4% (3 patients) incidence of DVT and 2.9% frequency of PE (1 fatal), while the IPC-mini-heparin patients showed a 6.6% (7 patients) incidence of DVT and 0.94% (1 patient) of PE.

**Mini and Different Low-Dose Heparin Regimes with or without IPC**

Although mini or low dose heparin regimens combined with IPC reduced the incidence of DVT/PE; patients also developed major postoperative hemorrhages 0.7%-4% of the time. In Macdonald, Amidei, Baron et al. randomized cranial series, 50 patients received mini-heparin (unfractionated, 5000 U subcutaneous q12 h) with IPC, and the other 50, low molecular weight heparin (Dalteparin 2500 Units/day) with IPC; heparin prophylaxis was begun on induction and continued for 7 postoperative days (Table 2) [22]. DVT occurred in 0 (0%) treated with mini-heparin, and in 2 (4%) receiving Dalteparin; none developed PE. Nevertheless, 1 (2%) patient on mini-heparin developed a postoperative hemorrhage requiring surgical evacuation, and 2 (4%) patients on Dalteparin developing significant postoperative bleeds. Gerlach, Raabe, Beck et al. studied the risk of postoperative hemorrhage in 1954 spinal procedures (503 cervical, 152 thoracic, and 1299 lumbar) performed utilizing Nadroparin (Fraxiparin 0.3 ml 2850 U), begun on the first postoperative day with IPC (Table 2) [13]. The overall incidence of DVT was 0.7%. Postoperative hemorrhages were observed in 13 patients; 8 (0.4%) bleeds were minor but 5 (0.25%) were major (Tables 2, 3). Additionally, 10 of 13 patients demonstrating bleeds developed significant neurological deficits; 4 were permanent. When mini-dose heparin (5000 U q 12h) (begun preoperatively) without IPC was utilized for 152 cranial and 720 spinal procedures, 3 patients experienced minor and 3, major postoperative hemorrhages [31]. The minor bleeds, including 2 superficial lumbar wound hematomas and 1 gastrointestinal bleed, did not warrant further surgery. However, all 3 major postoperative hemorrhages, consisting of 2 spinal epidural hematomas and one intracranial bleed, required secondary surgical excision. In a prospective randomized double blind trial involving 150 patients undergoing craniotomy for brain tumors, 75 were treated with Enoxaparin (40 mg/day) with IPC, and 75 with mini-heparin (5000U subcutaneous q12h) and IPC; patients exhibited a
combined 9.3% incidence of DVT, and 10 of 14 clots were limited to the calves (Table 2) [15]. In another series where patients with intracerebral hemorrhages developed DVT or PE, the initial 5-10 day course of full anticoagulation was followed by 3 months of low-dose low molecular weight heparin rather than Warfarin as this resulted in fewer bleeding complications [19].

**Ultrasound (Doppler) Surveillance**

Routine Doppler studies screening for DVT, performed 3 days, 7 days, and once a week for several postoperative months, proved more useful following 2643 cranial rather than spinal procedures (Table 1) [11]. The higher yield for cranial as compared with spinal patients prompted the recommendation that Doppler studies be largely reserved for spinal patients with history of malignancy or paralysis.

**Inferior Vena Cava Filters (IVC)**

Prophylactic preoperative IVC filter placement may be considered in patients with a history of DVT or PE who are about to undergo lengthy neurosurgical procedures. Britt, Zolfaghari, Kennedy et. al. found a high frequency of DVT/PE in patients who sustained brain/spinal cord injuries or lower extremity trauma; they utilized prophylactic IVC filters in 7 of 50 patients [7]. In 2 of the author’s 100 patients undergoing circumferential cervical procedures, both with prior histories of DVT, IVC filters were presumptively placed; one developed postoperative calf-vein DVT that required no further treatment.

**Animal Models**

When is it safe to administer full anticoagulation to a neurosurgical patient? To address this issue, Schaible, Smith, Fessler et. al. performed intracranial surgery in a Holtzman rat model and instituted full heparinization (PTT 1.5x to 3x above control) postoperative days 2, 4, 7, 10, and 14; it was continued for 3 days. [24]. The risk of intracranial bleeding was high (14.7%) if anticoagulation was started within 7 days of surgery; the risk of delayed hemorrhage, however, dropped to 0% when full-dose heparin was administered 10 and 14 days later.

**Practical Application of Prophylaxis Regimens**

Clinical data indicate that full anticoagulation therapy is contraindicated in neurosurgical patients who have had surgery within the last 10 days [4]. Mini-heparin, low dose heparin, and full-dose heparin treatment within this early period all carry an increased risk of postoperative hemorrhage. Early ilioc vein DVT (< 10 days postoperative) should largely be treated with IVC filter placement. Early calf vein DVT, although less likely to result in PE, should be considered for IVC filter placement, especially if patients are non-ambulatory or exhibit other significant risk factors for embolization. For some patients with early postoperative PE where full anticoagulation is contraindicated due to the risk of postoperative hemorrhage, IVC filter placement alone may reduce the potential for further PE [27]. For those developing later postoperative DVT/PE, full dose heparinization with or without IVC filters may be considered. Where full heparinization is instituted, prospective screening utilizing MR or CT studies may warn of initial and clinically silent postoperative hemorrhages, which could be addressed prior to the evolution of a devastating, permanent neurological deficit.

**CONCLUSION**

Appropriate prophylaxis and treatment for DVT/PE for patients undergoing spinal surgery may be divided into two major time periods. Less than 10 days postoperatively (early period), low dose heparin increases the risk of postoperative hemorrhage. Therefore, mechanical prophylaxis with intermittent pneumatic compression stockings is preferred with some notable exceptions; hypercoagulable syndromes, histories of DVT/PE and others. Patients with DVT may require IVC filter placement, avoiding full dose heparinization in many instances. PE, however, requires full heparinization. Alternatively, more than 10 days postoperatively, low dose heparin regimens for prophylaxis and full dose heparinization for DVT/PE are better tolerated with a reduced risk of postoperative hematomas.
ACKNOWLEDGEMENT

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REFERENCES

20. Kelly J, Hunt BJ, Lewis RR, Rudd A: Anticoagulation or inferior vena cava filter placement for patients with primary intracerebral


Reviewer's comment : Yoichi Katayama, M.D., Ph.D.
Department of Neurological Surgery, Nihon University School of Medicine,
Tokyo, Japan

The prophylaxis of deep venous thrombosis (DVT) and pulmonary embolism (PE) has recently received much attention in the perioperative management of patients undergoing neurological surgery. The Japanese guidelines for the prevention of venous thromboembolism (http://www.jsth.org/12indices/gaido.php) recommend the prophylactic usage of an intermittent pneumatic compression stocking and/or low dose heparin following craniotomy for brain tumor. The present paper by Dr. Epstein provides a very useful review for understanding such prophylactic management procedures, especially on how to employ heparin following neurosurgery. Dr. Epstein also mentions the significance of inferior vena cava (IVC) filter placement in the early period after surgery in order to avoid heparin-induced bleeding. Further experience and studies are needed to determine the indications for IVC filter placement in patients undergoing neurosurgery.

Reviewer's comment : Akira Matumura, M.D., Ph.D.
Department of Neurosurgery, University of Tsukuba, Institute of Clinical Medicine
Ibaraki, Japan

This review article by Prof. Epstein, regarding the prophylaxis against deep venous thrombosis (DVT) and pulmonary embolism (PE) for spinal surgery, highlights the necessity of the prophylactic procedure during and after surgery. The article also mentions that mini-heparin or low-molecular-weight heparin/derivatives reduced the incidence of DVT/PE while these drugs may increase the incidence of major postoperative hemorrhage (2-4%).

This article is informative and important, and it will raise awareness of DVT/PE in neurosurgical procedures, a subject that has received scant attention in Japan. Although it has been reported that the occurrence of DVT/PE is lower in Asian than Caucasian races (Klatksy AL et al. Am J Cardiol 85, 2000; 1334-7), recently the tendency toward DVT/PE has increased in the Japanese population. Thus, tight stocking and external pneumatic compression should be routinely applied during the neurosurgical operative procedure. The use of heparin should be carefully considered according to the risk factors of patients.

I appreciate Prof. Epstein's timely and thoughtful review regarding DVT/PE, which may help Japanese neurosurgeons prevent and treat DVT/PE in their daily clinical activities.