Neurosurgical Perspectives on VTE Prophylaxis in Trauma Patients

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Overview

- Historic Neurosurgical perspectives
- When to start VTE px
- What agent and dose is safe and effective
- Neurosurgical trauma patients as specific entity
## Historical Approach to VTE prevention in Neurosurgical Patients

| Scanning Protocol | • Routine weekly LE duplex  
| | • No routine scan on admission from outside hospital |
| Mechanical prophylaxis | • IPC device in OR  
| | • Poor compliance on floors |
| Chemical prophylaxis | • Unfractioned heparin 5000 units BID, start POD1-2  
| | • BMI >40: Heparin 7500 units BID |
| IVC filters | • Consult to Vascular or Interventional Radiology  
| | • Permanent v. retrievable filter determined by the consulting service  
| | • Filter related complications underappreciated |
| Documentation & Coding | • Reviewed by HIM  
| | • No physician review process |
VTE Rates: Neurosurgery
QI Goals

1. Identify high risk neurosurgical patient populations

2. Reduce unnecessary screening for DVT in low risk, asymptomatic patients and develop a unified protocol for screening of neurosurgical patients

3. Develop a unified protocol to pharmacological VTE prophylaxis in neurosurgical patients

4. Develop a unified protocol for the treatment of VTE in neurosurgical patients
# Risk Factors for VTE in Neurosurgical Patients

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>1.</strong></td>
<td>SIRS, sepsis, or septic shock</td>
</tr>
<tr>
<td><strong>9.</strong></td>
<td>Age &gt; 60</td>
</tr>
<tr>
<td><strong>2.</strong></td>
<td>Pneumonia</td>
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<tr>
<td><strong>10.</strong></td>
<td>Chemotherapy (actively or within the past 3 months)</td>
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<td><strong>3.</strong></td>
<td>UTI</td>
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<tr>
<td><strong>11.</strong></td>
<td>OR time &gt; 4 hours</td>
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<td><strong>4.</strong></td>
<td>Quadriparesis/dependant functional status</td>
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<td><strong>12.</strong></td>
<td>Cushing’s Disease</td>
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<tr>
<td><strong>5.</strong></td>
<td>Hemiparesis/paraparesis</td>
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<tr>
<td><strong>13.</strong></td>
<td>Spinal Cord Injury</td>
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<td><strong>6.</strong></td>
<td>Ventilator dependance within 48 hours or surgery or &gt; 48 hours postoperatively</td>
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<tr>
<td><strong>14.</strong></td>
<td>History of VTE</td>
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<tr>
<td><strong>7.</strong></td>
<td>Return to OR</td>
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<tr>
<td><strong>15.</strong></td>
<td>High grade glioma</td>
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<tr>
<td><strong>8.</strong></td>
<td>CNS tumor</td>
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Risk Factors for VTE in Neurosurgical Patients

- 67% had OR time >4 hours

- Mean LOS 20 days

- Mean ICU LOS 16 days

- Notable cases included:
  - 16-hour OR time, ICU LOS 20 days
  - Fatal PE in a septic patient
  - 10 hour OR time, postop infection, ICU LOS 42 days
  - Trauma
QI Goals

1. Identify high risk neurosurgical patient populations

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Screening:
Lower Extremity Duplex On Admission:
✓ Transfer from outside facility
✓ Admitted from home and not ambulatory for 48 hours
✓ History of VTE
✓ Cushing’s Disease

Notes:
- Cushing’s Disease duplex on: admission, POD #3, then weekly
- No routine screenings on asymptomatic ambulatory patients

High Risk Patients:
LE Duplex on admission or at any time during the hospital course if 4 or more of the following risk factors are present:
- SIRS, Sepsis, or septic shock
- Pneumonia
- UTI
- Quadriplegia/dependent functional status
- Hemiparesis/paraparesis
- Vent dependence within 48hrs of surgery, or >48hrs postop
- Return to OR
- CNS tumor
- Age >60
- Chemotherapy, actively or within past 3 months
- OR time >4hrs

Prophylaxis:
Standard Heparin Protocol:
- <50 kg: 150u/kg/day, given in two divided doses, every 12 hours
- 51-79 kg: 5000 units, every 12 hours
- >80 kg: 5000 units, every 8 hours

Standard Enoxaparin Protocol:
- BMI >50: 40 mg daily
- BMI <50: 30 mg daily

Spine:
Standard Extradural Spine:
Enoxaparin - PACU
Intradural vascular or intramedullary:
Enoxaparin – morning POD #1

Trauma Spine:
Enoxaparin – within 24hrs, if stable

Cranial:
Standard Cranial Surgery:
Heparin – morning POD #1

Tumor resection specific:
Heparin – morning POD #1
Enoxaparin – transition to POD 2

Transsphenoidal for Cushing’s:
Heparin – morning POD #1
Enoxaparin – transition to POD 2, and continue 1 month postop
**Trauma Brain:**
Heparin - Consider rescanning, if hemorrhage stable at 24 hours consider starting. For injuries consistent with:
- Subdural hemorrhage < 8 mm
- Epidural hemorrhage < 8 mm
- Largest single contusion < 2 cm
- No more than one contusion per lobe
- Isolated subarachnoid hemorrhage
- Isolated intraventricular hemorrhage

**Subarachnoid hemorrhage:**
Heparin – within 24 hrs of securing

**Intracranial hemorrhage:**
Heparin – within 48 hrs of admission with stable clot

**Re-hemorrhage or high risk of in setting of trauma, tumor, other:**
Heparin – attending discretion when to restart

**Assay proven HIT:**
Fondaparinux 2.5 mg SC

**Drains:**

**External Ventricular and Lumbar:**
- Enoxaparin - hold
- Heparin - change to 8hrs post d/c, then follow protocol, hold 1 dose prior to insertion or removal

**Special notes on drains:**
If considering EVD or LD, follow standard Heparin protocol, hold 1 dose prior to insertion.

Other drains (i.e. JP): follow diagnosis based pathway, no need to hold anticoagulation

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**Treatment:**

**Distal DVT:**

**Asymptomatic:** Repeat LE duplex weekly x2, if no progression, stop weekly scan.

**Distal DVT, Symptomatic:**
- Treat all symptomatic DVTs, if risk factors for bleeding are low
- If increased risk factors for bleeding, repeat duplex weekly x2
  - Apixiban (Eliquis) 10 mg BID x 7 days, then 5 mg BID (easier to dose in renal patients)
  - OR Rivaroxaban (Xarelto) 15mg PO/PT BID x 21 days, then 20 mg QD

**Proximal DVT:**

**Asymptomatic and Symptomatic:**
- If increased risk for bleeding, IVC filter
- Start anticoagulation as soon as possible once safe.

Use option A or B:

a. Enoxaparin (Lovenox) 1mg/kg subq every 12 hours OR 1mg/kg subq every 24 hours for CrCl<30 and convert to oral therapy with Apixiban (Eliquis) or Rivaroxaban (Xarelto) when appropriate
b. Apixiban (Eliquis) 10mg BID x 7 days then 5mg BID OR Rivaroxaban (Xarelto) 15mg PO/PT BID x 21 days then 20mg QD

**VTE:**

**Mild symptoms, hemodynamically stable:**
- If no contraindication start therapy as soon as safe. Use option A or B.
- Lower extremity duplex if VTE present, then consider placement of IVC filter

**Severe symptoms:**
- Consider tPA and intervention if hemodynamically unstable
- Heparin infusion OR Bivalirudin (Angiomax) infusion for HIT possible etiology
- If high risk for bleeding, consider lower extremity duplex to screen for LE VTE, if positive consider retrievable IVC filter. Transition to Apixiban or Rivaroxaban once stable

**Notes:**
- If there is any deviation from protocol based on individual patient need, please document in chart, and notify QI officer
- See full protocol for duration of treatment recommendations
- See full protocol for clinical considerations for VTE with Cancer diagnosis
- Patients with BMI >40 on therapeutic Enoxaparin need anti-Xa levels 4 hours after the 3rd dose in order to ensure dose is therapeutic
Historical Studies in Neurosurgery
Unfractionated Heparin

• Frim DM et al. Neurosurgery 1991
  – Prospective, non-randomized case-control
  – 138 adults, major neurosurgical procedures
  – 473 historical controls
  – Intraoperative SCDs, unfractionated heparin
    • 5000 U BID started morning POD #1
  – Thromboembolic events: 3.2 % control v. 0% treatment group (p=0.02)
    • 8 DVT; 7 PE
  – No major hemorrhagic complications
    • Control – 1 wound hematoma

Frimm DM et al Neurosurg. 1991 30(6): 830-832
Fractionated heparin: Enoxaparin

- Agnelli et al. NEJM 1998
  - Multicenter, randomized, blinded
  - N=307 (80% cranial): 154 placebo; 153 Enoxaparin
  - Thigh-length TED hose until discharge
  - **Enoxaparin 40mg QD, starting 24hrs post op** for 8 ± 1 days
  - Dopplers + confirmatory venogram; all patients venogram at study end

<table>
<thead>
<tr>
<th></th>
<th>Placebo # (%)</th>
<th>Enoxaparin # (%)</th>
<th>RR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE or DVT</td>
<td>43 (33)</td>
<td>22 (17)</td>
<td>0.51</td>
<td>0.004</td>
</tr>
<tr>
<td>PE</td>
<td>1 (1)</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>17 (13)</td>
<td>7 (5)</td>
<td>0.41</td>
<td>0.04</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4 (3)</td>
<td>4 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>7 (5)</td>
<td>14 (9)</td>
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Enoxaparin: negative precedent

- Gupta SK et al. NEJM 1998
  - Prospective, randomized
  - Patients >18 yrs old, with intracranial tumors
  - N=68: 22 SCD; 23 enoxaparin; 23 enoxaparin +SCD
  - **Enoxaparin 30mg Q12, started in preop holding**, continued until discharge
  - Screening dopplers day 1, 3, 5-7, 10-14, 1 month

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<th>SCD # (%)</th>
<th>Enoxaparin # (%)</th>
<th>Enoxaparin + SCD # (%)</th>
<th>p value</th>
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<tbody>
<tr>
<td>DVT</td>
<td>3 (14)</td>
<td>1 (5)</td>
<td>4 (17.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0</td>
<td></td>
<td>5 (24)†</td>
<td></td>
</tr>
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</table>

Study halted due to high rate postoperative bleeding: 1 EDH, 4 ICH.
Fractionated heparin: Nadroparin

- Gerlach R et al. Neurosurgery 2003
  - Prospective, single center
  - N=2823 cranial patients, assigned to 2 groups
    - 1319 ‘major’ (47%) and 1504 ‘minor’ (53%) neurosurgical procedures
  - Nadroparin 2850 Units within 24 hrs of OR
  - Post op neuroimaging 24-48 hrs (major), 48 hrs (minor)
  - DVTs evaluated by LE duplex or venography
  - Primary endpoints: VTE and hemorrhage rate

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<tr>
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<th>Major # (%)</th>
<th>Minor # (%)</th>
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<tr>
<td>Hemorrhage</td>
<td>42 (3.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>VTE</td>
<td>6 (0.53)</td>
<td>0</td>
</tr>
</tbody>
</table>

Low molecular weight heparin is standard of care in Germany

Fractionated heparin: Enoxaparin

- Cage TA et al. J. Neurooncol 2009
  - Single center, single surgeon, case control
  - 24 patients with meningioma treated with enoxaparin
    - 40 mg daily x 7 days, started 24 - 48 hrs post op
    - Exclusion criteria: hx ICH, HIT or thrombocytopenia, LD in place
  - 62 patients with meningiomas treated with unfractionated heparin
  - DVT evaluated by LE doppler

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<thead>
<tr>
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<th>Heparin # (%)</th>
<th>Enoxaparin # (%)</th>
<th>p value</th>
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<tbody>
<tr>
<td>PE or DVT</td>
<td>3 (5)</td>
<td>0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>PE</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>2 (3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5 (8)</td>
<td>1 (4)</td>
<td></td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>8 (12.9)</td>
<td>3 (12.5)</td>
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Institutional standard: enoxaparin started the morning of POD2

Risk Factors for VTE in Neurosurgical Patients

- 67% had OR time >4 hours
- Mean LOS 20 days
- Mean ICU LOS 16 days
- Notable cases included:
  - 16-hour OR time, ICU LOS 20 days
  - Fatal PE in a septic patient
  - 10 hour OR time, postop infection, ICU LOS 42 days
  - Trauma
Parkland Protocol: Precedent for Change

- Big step forward for collaboration
- Neurosurgical trauma “high-risk”
  - Essentially excluded
  - 40% w/o px 7 days post injury
  - Considered for prophylactic IVCF
- Enoxaparin 30mg q12
- TQIP, national guidelines
- Nuanced literature, retrospective data

LMWH: Collision of Subspecialty Bias

- Neurosurgeons with historical bias toward unfractioned heparin
- Minimal evidence in neurosurgical literature
- No evidence that BID dosing enoxaparin safe
- No anti-Xa based guidance
Safety of Enoxaparin in Neurosurgical Trauma Patients at UCSD

Beaumont & Costantini

- Retrospective cohort from TQIP, 5 years
- 183 “high risk” patients - craniotomy/craniectomy
  - Enoxaparin 30mg BID, occasionally UFH
- 11 patients with return to OR for neurosurgical procedure(s)
  - 2 patients (1.1%) returned to OR based on immediate postop CT
    - Neither had received chemoprophylaxis
- 0 patients returned to OR for reaccumulation of ICH beyond immediate perioperative period
- Wound washout, shunts, cranioplasties
Safety of Enoxaparin in Neurosurgical Trauma Patients at UCSD

Beaumont & Costantini

• Plan for prospective cohort
  • Currently using enoxaparin 40 mg daily, start 48 hrs postop with stable CT
  • Compare to 30mg BID?
• Primary endpoints:
  – Return to OR for reaccumulation or new SDH, expansion ICH
  – VTE rate
  – Death
• Assess anti-Xa
Safety of Enoxaparin in Neurosurgical Trauma Patients

Byrne JP et al. JAMA Surgery, March 2022

- TQIP Retrospective cohort
- 4951 “high risk” patients
  - craniotomy/craniectomy, ICP monitor or EVD within 24 hours admission
  - Enoxaparin 30mg BID or UH
- Earlier initiation of px associated with:
  - Repeated neurosurgery
  - Death
- Adjusted for injury baseline
Conclusions

- All agree lovenox is a superior to unfractionated heparin regarding general efficacy, and so does the literature.

- Paucity of data about the safety, dosing and timing of lovenox in neurosurgical trauma patients.

- Prospective data is needed to objectively address the above questions.

- In the interim, additional discretion regarding drug selection, timing and dose is warranted for neurosurgical trauma patients.
Thank you