Current Recommendations for Detecting and Preventing Coagulation Disorders, Deep Venous Thrombosis, and Pulmonary Embolism in Neurosurgical Patients, and Future Treatments

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Presenter Disclosure Information

John D. Heiss, M.D.
Title: Current Recommendations for Detecting and Preventing Coagulation Disorders, Deep Venous Thrombosis, and Pulmonary Embolism in Neurosurgical Patients, and Future Treatments
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No Unlabeled/Unapproved Uses are Disclosed.

Objectives

Upon completion of my presentation, participants should be better able to
1. Describe standard pre- and intraoperative prophylactic measures that are employed to reduce the incidence of postoperative deep venous thrombosis and pulmonary embolism
2. Name a few inherited and acquired conditions that increase the risk of postoperative deep venous thrombosis
3. Describe management of coagulation disorders in neurosurgery patients
4. Describe the management of dural sinus thrombosis in postoperative patients
Complications of Glioma Surgery

<table>
<thead>
<tr>
<th>Neurologic</th>
<th>Regional</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor or sensory deficit</td>
<td>Seizure</td>
<td>Pulmonary infection</td>
</tr>
<tr>
<td>Aphasia/dysphasia</td>
<td>Hydrocephalus</td>
<td>Deep-vein thrombosis</td>
</tr>
<tr>
<td>Visual field deficit</td>
<td>Pneumocephalus</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td>Cerebrospinal fluid leak</td>
<td>Gastritis</td>
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<tr>
<td></td>
<td>Wound infection</td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Central line infection</td>
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</table>


Venous Thromboembolism (VTE) Includes Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE)

Virchow’s Triad for Thrombus Formation

[Diagram]


Rates of VTE After Glioma Surgery

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Number of Patients with VTE</th>
<th>Intracranial Major Bleeds 1st 6 months</th>
<th>Major Bleeds 1st 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight heparin (Dalteparin 5000 U subQ once daily)</td>
<td>99*</td>
<td>9 (9%)†</td>
<td>3 (3%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>87*</td>
<td>13 (15%)††</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
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<tr>
<td>Total for Study</td>
<td>186</td>
<td>22 (12%)</td>
<td>3 (2%)</td>
<td>6 (3%)</td>
</tr>
</tbody>
</table>

*Randomized study failed to enroll enough (217) subjects in the treatment and placebo groups to provide statistical power for efficacy and bleeding comparisons.
†LMWH dosing began within 4 weeks of surgery
†† Note 15% rate of VTE in glioma patients without prophylactic anticoagulation

VTE Prophylaxis in Brain Tumor Surgery
Prospective clinical trial
746 consecutive patients undergoing intracranial surgery
418 major intracranial procedures
59 (7.9%) high-grade glioma, 67 (8.9%) metastasis,
328 minor procedures
Managed by our deep vein thrombosis prophylaxis protocol.
Elastic stockings
Perioperative mechanical pneumatic sequential compression leg device
Sodium Tinzaparin (LMWH) 3500 U daily starting 24 h after surgery
Patients considered to be at higher risk to develop deep vein thrombosis,
Sodium Tinzaparin 7000 U started 5-7 d before surgery, but held for 24 h
before surgery
Results
8 (1.07%) significant postoperative hemorrhages were recorded
6 (0.8%) among patients undergoing major procedures
1 of these was a high-grade glioma patient
3 patients (0.4%) with clinical evidence of deep vein thrombosis
1 patient (0.13%) died of fatal PE 2 months after surgery

VTE Risk in Cancer Patients is Increasing
• Frequent, high resolution imaging
  – Staging and re-staging lung CT scans pick up PE
• More effective cancer treatments
  – Cancer patients are living longer, increasing their lifetime
  risk of developing VTE
• Thrombogenic new cancer treatments
  – Anti-angiogenesis drugs
    • Bevacizumab

Presentation of Venous Thromboembolism (VTE)
DVT: Only one-half of people have signs and symptoms
  History and Exam
  Lower extremities
    Swelling; may be along a vein
    Pain or tenderness, worse with standing or walking
    Warm, red skin
  Homans’s sign insensitive and non-specific
  Lab: D-dimer (conjugated D domains of 2 fibrin monomers) immunoassay
    Highly sensitive: 95% exclusion of DVT or PE
  Diagnostic study: Lower extremity Doppler ultrasonography

PE: May be 1st indication of DVT
  History and Exam
  Unexplained shortness of breath, hemoptysis
  Pain with deep breathing (pleuritic chest pain)
  Crepitus on chest auscultation
  Tachycardia/Tachypnea
  Diagnostic study: CT Pulmonary Angiography (CTPA)
Modified Caprini risk assessment for VTE in general surgical patients

Caprini score ≥5 is “high risk” for VTE

<table>
<thead>
<tr>
<th>Risk score</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
<th>5 points</th>
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<tbody>
<tr>
<td>Age 41 to 60 years</td>
<td>Age 61 to 74 years</td>
<td>Age ≥75 years</td>
<td>Stroke (&lt;1 month)</td>
<td>Minor surgery</td>
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<tr>
<td></td>
<td>Arthroscopic surgery</td>
<td>History of VTE</td>
<td>Elective arthroplasty</td>
<td>BMI &gt;25 kg/m²</td>
</tr>
<tr>
<td></td>
<td>Major open surgery (&gt;45 minutes)</td>
<td>Family history of VTE</td>
<td>Hip, pelvis, or leg fracture</td>
<td>Swollen legs</td>
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<tr>
<td></td>
<td>Laparoscopic surgery (&gt;45 minutes)</td>
<td>Factor V Leiden mutation</td>
<td>Acute spinal cord injury (&lt;1 month)</td>
<td>Varicose veins</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignancy</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Prothrombin 20210A mutation</td>
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<td></td>
<td>Pregnancy or postpartum</td>
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<td>Confined to bed (&gt;72 hours)</td>
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<td>Lupus anticoagulant</td>
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<td></td>
<td>History of unexplained or recurrent spontaneous abortion</td>
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<td>Immobilizing plaster cast</td>
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<td></td>
<td>Anticardiolipin antibodies</td>
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<td></td>
<td></td>
<td>Oral contraceptives or hormone replacement</td>
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<td></td>
<td>Central venous access</td>
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<td></td>
<td></td>
<td>Elevated serum homocysteine</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Sepsis (&lt;1 month)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>Heparin-induced thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Serious lung disease, including pneumonia</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Other congenital or acquired thrombophilia</td>
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<td></td>
<td>Abnormal pulmonary function</td>
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<td></td>
<td>Acute myocardial infarction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Congestive heart failure (&lt;1 month)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>History of inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medical patient at bed rest</td>
</tr>
</tbody>
</table>

**Interpretation**

<table>
<thead>
<tr>
<th>Surgical risk category*</th>
<th>Score</th>
<th>Estimated VTE risk in the absence of pharmacologic or mechanical prophylaxis (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low (see text for definition)</td>
<td>0</td>
<td>&lt;0.5</td>
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<tr>
<td>Low</td>
<td>1 to 2</td>
<td>1.5</td>
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<tr>
<td>Moderate</td>
<td>3 to 4</td>
<td>3.0</td>
</tr>
<tr>
<td>High</td>
<td>≥5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; BMI: body mass index.

* This table is applicable only to general, abdominal-pelvic, bariatric, vascular, and plastic and reconstructive surgery.


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**Clotting: Primary Platelet Plug**

- Endothelial Surface injury
- von Willebrand factor (vWF) release from EC
- vWF binds to collagen
- Platelet Adhesion
- Platelet Activation
- Platelets release signaling molecules ADP & thromboxane A2
- Activated platelet express fibrinogen receptor (GpIIb/IIIa)
- Fibrinogen
- Platelet Aggregation-fibrinogen linkage
- Primary Platelet Plug (primary hemostasis)

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**Clotting: Secondary Hemostasis**

- Endothelial Surface injury
- von Willebrand factor (vWF) release from EC
- vWF binds to collagen
- Platelet Adhesion
- Platelet Activation
- Platelets release signaling molecules ADP & thromboxane A2
- Activated platelet express fibrinogen receptor (GpIIb/IIIa)
- Fibrinogen
- Platelet Aggregation-fibrinogen linkage
- Fibrinogen-platelet clot
Venous vs. Arterial Thrombi

- Venous thrombi
  - More dependent on stasis & hypercoagulability than endothelial injury
  - Composed mainly of fibrin and RBC
    - Relatively few platelets
  - Rx & prevention focuses on fibrin clot development
- Arterial thrombi
  - Result more from endothelial injury, primary platelet plug, and endothelial repair response
  - Platelets, fibrin, and RBC
  - Rx & prevention focuses on prevention of platelet activation and aggregation that initiates the primary platelet plug

Thrombosis Prevention
Virchow’s Triad for Thrombus Formation

Pre-Operative VTE Prophylaxis

- All patients should have sequential compression devices (SCD’s) placed prior to incision\(^1\)
- SCD’s should be used for at least 18 h/day except when ambulatory\(^1\)
- Compression stockings do not add benefit to patients already using SCD’s
- Pharmacologic prophylaxis except in craniotomy and spinal surgery patients

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Post-Operative VTE Prophylaxis

- **Length of therapy**
  - All patients until discharge
  - Post discharge (Outpatient enoxaparin through POD28)
    - Patients with:
      - Cancer undergoing abdominal or pelvic surgery
      - Other cancer procedures
      - Hypercoagulable states (i.e. Cushing's disease)

- **Circumstances for monitoring of LMWH prophylaxis**
  - Check "Anti-Xa, Low Molecular Weight Heparin" level for all patients with obesity and/or renal insufficiency receiving LMWH for prophylaxis.
  - Draw 4 hours post injection after 3rd or 4th dose with target level of 0.2-0.4 for prophylaxis.

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### NIH Clinical Center Peri-Operative Anti-coagulation Guidelines for Adult High Risk Patients

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>LMWH</th>
<th>Prophylaxis</th>
<th>LMWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op Prophylaxis</td>
<td>Enoxaparin 40mg SQ daily; begin POD1</td>
<td>Post-op Prophylaxis</td>
<td>Enoxaparin 40mg SQ daily; begin POD1</td>
</tr>
<tr>
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<tr>
<td>Pre-op Prophylaxis</td>
<td>Enoxaparin 40mg SQ daily; begin POD1</td>
<td>Post-op Prophylaxis</td>
<td>Enoxaparin 40mg SQ daily; begin POD1</td>
</tr>
</tbody>
</table>

**Abbreviations**: SCD = Serial Compression Devices; LDUH = Low-Dose Unfractionated heparin; LMWH = Low molecular weight heparin (enoxaparin is recommended), POD = Post-Operative Day; HIT = Heparin-induced thrombocytopenia

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### Heparin-Induced Thrombocytopenia (HIT)

- **Type 1 HIT** (1-5% of surgical patients), 20-30 times greater risk with fractionated heparins compared to LMWH
  - Mechanism
    - Antibodies against heparin/platelet factor 4 (PF4) conjugates
  - Antibody/heparin-PF4 complexes activate platelets, which release serotonin
  - Diagnosis
    - Immunoassay (ELISA) detects heparin-dependent antibodies
    - Serotonin release when donor platelets are exposed to patient serum
    - Platelet count decrease
    - Mild platelet count falls >50% after heparin but usually remains >150K
    - Begins 4-14 days after exposure to heparin
    - Large vessel thrombosis: Precedes thrombocytopenia in up to 25% of patients
    - Venous thrombosis (VTE) more often than MI
    - Ultrasound, CT angiogram
  - Treatment
    - Discontinue heparin immediately
    - Avoid platelet transfusion because it can increase thrombosis
    - Direct thrombin inhibitor: argatrobin or bivalirudin for 3 months

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**References**

Venous Thromboembolism (VTE) in Brain Tumor Patients Undergoing Craniotomy


Study Population: Patients in the National Surgical Quality Improvement Program (NSQIP) who underwent craniotomy for brain tumor from 2006 and 2014 were analyzed to identify risk factors for postoperative VTE.

Results There were 629 instances of VTE among 19,409 craniotomies for brain tumor (3.2%) recorded in NSQIP. Occurrence of VTE was associated with other postoperative complications on univariate analysis, including pneumonia, respiratory failure, stroke, and sepsis (all p < 0.001).

Conclusions VTE occurs in approximately 3% of patients undergoing craniotomy for brain tumor resection. Independent predictors for developing VTE include older age, higher BMI, recent steroid use, and total operative time.

Considerations in Treatment of VTE

1) Efficacy in preventing recurrent VTE
2) Bleeding risk
   Should wait at least 3 days after craniotomy--Kawamata T. Surg Neurol 44:438-43, 1995
3) Patient compliance in continuing and monitoring the therapy
4) Cost

Anti-VTE Agents

http://www.eclinpath.com/hemostasis/physiology/primary-hemostasis/
Efficacy & Bleeding Risk: Daily LMWH Rx is More Effective than Coumadin in Preventing Recurrent VTE in Cancer Patients

Prevention of recurrent PE

CLOT Trial: 676 Patients with cancer with acute DVT &/or PE
Dalteparin vs. Warfarin (starting after 5 days of Dalteparin)
Lee AV, et al. NEJM 2003;349:146-153
6 month trial with recurrent VTE as primary endpoint
Greater recurrent VTE risk with warfarin (17% vs. 9%; p=0.002)
Major bleeding with warfarin 4%, Dalteparin 6%
Mortality with warfarin 41%, Dalteparin 39%

CATCH Trial: 900 Patients with cancer with acute DVT &/or PE
Tinzaparin vs. Warfarin (starting after 5-10 days of Tinzaparin)
6 month trial with recurrent VTE as primary endpoint
Greater recurrent VTE risk with warfarin (10.5% vs. 7.2%; p=0.07)
Major bleeding with warfarin 2.4%, Tinzaparin 2.7%
Mortality with warfarin 30.6%, Tinzaparin 33.4%

Patient Compliance: Long-Term Anticoagulation in Cancer Patients after VTE

Subcutaneous LMWH vs. warfarin (Coumadin)
LMWH is more effective than warfarin in preventing recurrent VTE in clinical trials
Difference in efficacy linked to irregular warfarin blood levels
Therapeutic INR (2-3) only 45% of the time in clinical trials
Interruption of warfarin therapy to perform procedures
Interaction of chemotherapeutic agents with warfarin
Dietary and nutritional issues
Warfarin advantages vs. LMWH in cancer patients
Delivered orally rather than via daily subcutaneous self-injection with LMWH
Much less expensive than LMWH (although generic forms of LMWH are available)

Warfarin disadvantages vs. LMWH
Requires frequent INR (International Normalized Ratio) testing; ratio of patient’s PT to normal PT
Must avoid high Vitamin K foods and interacting drugs
NOACs (Non-Vitamin K antagonist Oral Anti-Coagulants)
No randomized trials of NOACs vs. warfarin or LMWH to prevent recurrent VTE in cancer patients
Subgroup analysis in trials suggest similar efficacy of NOACs and warfarin in cancer patients
NOACs in clinical trials for cancer-associated VTE

The Role of NOACs in Cancer-Associated Thrombosis CME / ABIM MOC
Alok A. Khorana, MD Medscape Education Cardiology: http://www.medscape.org

Costs of VTE Treatment

<table>
<thead>
<tr>
<th>Medication</th>
<th>Cost of medication</th>
<th>Cost of lab monitoring</th>
<th>Cost of bleeding complications</th>
<th>Costs to treat complications of ineffective therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumadin</td>
<td>$ (Low)</td>
<td>$5 INR</td>
<td>$5 in studies (↑ real world)</td>
<td>$5 (30-45% less effective than LMWH)</td>
</tr>
<tr>
<td>LMWH</td>
<td>$ (Generic forms available)</td>
<td>$ (None except in renal failure &amp; obesity, Rx)</td>
<td>$</td>
<td>$</td>
</tr>
<tr>
<td>NOACs</td>
<td>$5</td>
<td>$</td>
<td>$ (None)</td>
<td>$</td>
</tr>
</tbody>
</table>

The Role of NOACs in Cancer-Associated Thrombosis CME / ABIM MOC
Alok A. Khorana, MD Medscape Education Cardiology: http://www.medscape.org
### Drugs to Prevent & Treat Venous Thromboembolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade name</th>
<th>Targeted molecule/system</th>
<th>Clinical use</th>
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<tbody>
<tr>
<td>warfarin</td>
<td>Coumadin</td>
<td>vitamin K antagonist</td>
<td>venous thrombosis, long-term prophylaxis</td>
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<tr>
<td>unfractionated heparin</td>
<td>Heparin</td>
<td>thrombin, factor Xa</td>
<td>blocks coagulation, venous thrombosis</td>
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<tr>
<td>low molecular weight heparin</td>
<td>Enoxaparin</td>
<td>Factor Xa</td>
<td>blocks coagulation, venous thrombosis</td>
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<td>fondaparinux</td>
<td>Aritheta</td>
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<td>Xarelto</td>
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<td>dabigatran</td>
<td>Pradaxa</td>
<td>thrombin</td>
<td>prevent thrombosis during/after joint surgery</td>
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<tr>
<td>desirudin</td>
<td>Iprivask</td>
<td>thrombin</td>
<td>venous thrombosis during/after joint surgery</td>
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<tr>
<td>lepirudin</td>
<td>Refludan</td>
<td>thrombin</td>
<td>prevent thrombosis in patients with heparin-induced thrombocytopenia</td>
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</table>


### Drugs Used to Treat Congenital Coagulopathies

<table>
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<th>Drug</th>
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<th>Clinical use</th>
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<tr>
<td>factor VIII</td>
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<td>hemophilia A</td>
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<tr>
<td>factor IX</td>
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<td>hemophilia B</td>
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<td>desmopressin</td>
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<td>tranexamic acid</td>
<td>Lysteda</td>
<td>fibrinolysis</td>
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<td>Humate-P</td>
<td>von Willebrand factor</td>
<td>von Willebrand disease</td>
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### Coagulopathy Management in Neurosurgery

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Minimum Diagnosis</th>
<th>Treatment of Abnormality</th>
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</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>Thrombocytopenia</td>
<td>Platelet infusion; 1 U per 5-10K deficit in adults</td>
</tr>
<tr>
<td>PT (pro-thrombin time)</td>
<td>Anti-platelet drug (aspirin; Plavix)</td>
<td>Platelet infusion; Factor VII</td>
</tr>
<tr>
<td>PTT (partial thromboplastin time)</td>
<td>Coumadin effects</td>
<td>VIT K (Aquamephyton) 10 mg IM; in emergency 2-6 U FFP or prothrombin complex concentrate (factors II, IX, &amp; X)</td>
</tr>
<tr>
<td></td>
<td>Undiagnosed coagulopathy</td>
<td>2-3 U FFP (contains all coagulation factors); hematology consultation</td>
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<tr>
<td></td>
<td>Heparin effects</td>
<td>Protamine 1 mg per 100U heparin</td>
</tr>
<tr>
<td></td>
<td>Factor deficiency</td>
<td>Factor replacement (Heme consult)</td>
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<tr>
<td></td>
<td>Lupus anticoagulant</td>
<td>Increased VTE surveillance</td>
</tr>
</tbody>
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Ref: Greenberg MS: Handbook of Neurosurgery, Thieme, 2010
Management of dural sinus thrombosis in post-operative patients

Apri et al. Presentation and management of lateral sinus thrombosis following posterior fossa surgery. JNS 2016
180 patients who underwent surgical removal of posterior fossa mass
12 (6.7%) developed postoperative lateral sinus thrombosis
T2* hypointensity within the venous sinus and/or a filling defect on postcontrast MRI or CT scan

Risk factors:
- Hx of DVT (p = 0.016)
- Oral contraceptives (p = 0.004)
- Midline surgical approach (p = 0.035)
- Surgical exposure of the sinus (p < 0.001)

12/12 (all) asymptomatic
7 treated with anticoagulation
6/7 lateral sinus recanalized, at mean 272 days
No anticoagulation-related complications
5 untreated
1/5 lateral sinus recanalized at mean 272 days
Conclusion: Surgical occlusion of lateral sinus in generally well-tolerated

Management of symptomatic dural sinus thrombosis in post-operative patients

Rare occurrence
Treatment is empirical and anecdotal, to preserve brain and life
- Hydrocephalus
  - Shunt
- Cerebellar swelling or infarction
  - Extensive posterior fossa decompression
  - Resection of infarcted cerebellum
- Increased intracranial pressure
  - Consider intravascular stent, urokinase, TPA; sinus shunting
- Begin anticoagulation at least 3 days after surgery
- Systemic anticoagulation takes months to resolve the thrombosis


Review of Lecture Objectives

Upon completion of my presentation, participants should be better able to

1. Describe standard pre- and intraoperative prophylactic measures that are employed to reduce the incidence of postoperative deep venous thrombosis and pulmonary embolism
   - A. Sequential compression devices
   - B. Post-operative subcutaneous heparin, unfractionated heparin or LMWH
2. Name a few inherited and acquired conditions that increase the risk of postoperative deep venous thrombosis
   - Inherited—Leiden factor V and prothrombin 20210A mutation
   - Acquired—Cancer, immobilization/inactivity, hx of DVT, anti-angiogenic drugs, HIT (heparin-induced thrombophilia), lupus anticoagulant
3. Describe management of coagulation disorders in neurosurgery patients
   - A. Replace deficient clotting factors
4. Describe the management of dural sinus thrombosis in post-operative patients
   - A. Most patients with transverse sinus thrombosis will be asymptomatic
     1. Treat secondary events such as hydrocephalus and brain swelling first
     2. Anticoagulation usually restores sinus patency over months but no apparent difference in outcomes compared to untreated patients
   - B. Management of non-surgical sinus thrombosis requires anticoagulation
References


