

Antithrombotics and DVT prevention/management

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Introduction

- In Neurosurgery, antithrombosis is a critical and controversial issue.
- Deep Vein Thrombosis (DVT) is a serious concern for Neurosurgical patients
- Many neurosurgery patients are prone to clotting:
 - Long operative times
 - Paralysis/prolonged bed rest
 - Hypercoaguability
 - Trauma/SAH
 - Stroke

Introduction

- The coagulation cascade
- Hypercoaguability
- Classes of Antithrombotics - a review of the drugs
- DVT and Surgical prophylaxis

Inherited Hypercoaguability (HC)

- There are many causes of inherited HC:
 - Factor V Leiden
 - Hyperhomocysteinemia
 - Prothrombin G20210A
 - AT, or Protein C and/or S deficiency
 - Antiphospholipid antibody syndrome
 - Factor deficiency (VII, IX)
 - Dysfibrinogenemia
 - Plasminogen deficiency

Acquired Hypercoaguability

- There are many causes of acquired HC as well:
 - Lupus anticoagulant
 - Malignancy/myeloproliferative disorders
 - TP
 - Estrogen
 - Hyperlipidemia
 - DM
 - Hyperviscosity
 - CHF
 - Pregnancy
 - Obesity
 - Old age

Hemostasis

- VIRCHOW'S TRIAD
- Primary Hemostasis
 - Platelet adhesion
- Secondary Hemostasis
 - Contact activation pathway (intrinsic)
 - Tissue factor pathway (extrinsic)
 - Final common pathway

Hemostasis: Virchow's Triad

- Endothelial injury/dysfunction
- Hypercoaguability
- Hemodynamic changes
 - Stasis
 - Turbulence

Primary Hemostasis

- Activated when subendothelial connective tissue is exposed
- Starts with rapid platelet aggregation
 - Within seconds
- Platelets will then aggregate at the site of injury
 - von Willenbrand Factor (vWF)
- Platelets will bind to each other using fibrinogen and glyoprotein IIB/IIIa complexes

Contact activation pathway (intrinsic)

- Hageman factor (Factor XII), High-Molecular-weight Kininogen (HMWK), and prekallikrein (PK) form a complex on subendothelial collagen
- Factor XII \rightarrow XIa \rightarrow Xa \rightarrow final common path
- Monitored by PTT
- *Probable minor role in coagulation as patients with deficiencies have normal hemostasis*

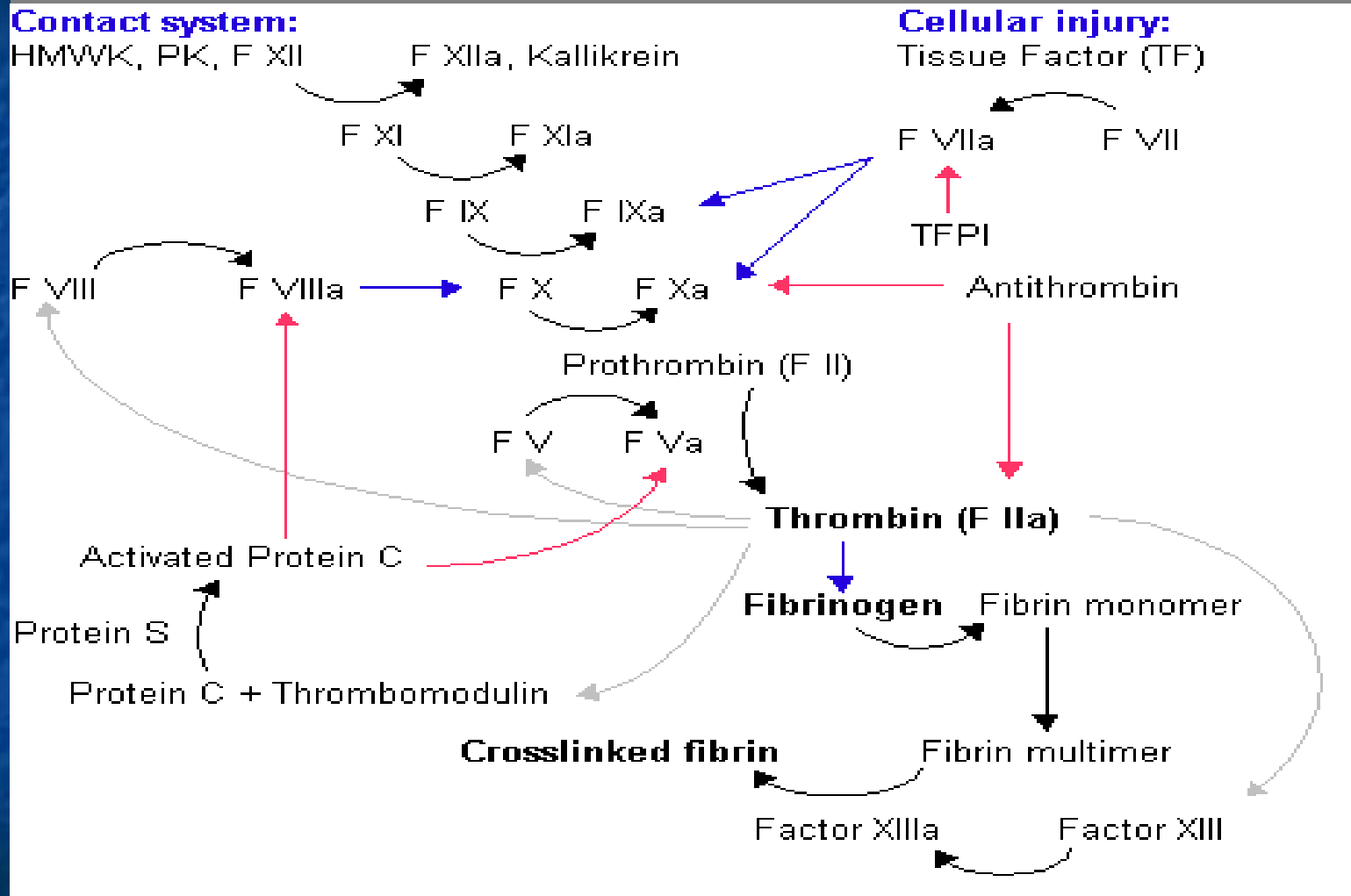
Tissue factor pathway (extrinsic)

- Factor VII is activated into a protease, forming a complex with Tissue Factor which is then converted to factor Xa
- Vitamin K dependent
- Monitored by PT
- Major role in coagulation

Final common pathway

- Factor X is activated (Xa) by Factor VIII by activated factor IX (IXa)
- Xa and factor V then convert prothrombin into thrombin using several other factors
 - Calcium, phospholipid
- Thrombin then bind fibrinogen and form fibrin
- Fibrin then uses factor XIII to cross-link

The Coagulation Cascade



Antithrombotics - Two major classes

■ Antiplatelet

- Glycoprotein IIB/IIIa inhibitors
- ADP receptor/P2Y inhibitors
- Cox inhibitors

■ Anticoagulants

- Vit K antagonists (inhibits II, VII, IX, X)
- Factor Xa inhibitors (some II inhibition)
- Direct thrombin (II) inhibitors
- Other: Antithrombin III

Classes of Antithrombotics - Antiplatelet

- Glycoprotein IIB/IIIa inhibitors
 - **Abciximab (ReoPro)**, tirofiban
- ADP receptor/P2Y inhibitors
 - **Plavix**, ticlopidine
- Cox inhibitors
 - **Aspirin**
- Other
 - Dipyridamole

Acetylsalicylic Acid (Aspirin)

- Irreversibly inhibits cyclooxygenase and prevents synthesis of thromboxane A₂, which prevents platelet aggregation
- Peak concentration in 1 hour, lasts up to a week (duration of platelet life-span)
- Platelets for reversal

Clopidogrel (Plavix)

- Irreversibly inhibits P2Y2 subset of the ADP receptor
 - The ADP receptor is important in platelet aggregation and the cross-linking of platelets by fibrin
- Inhibition detectable 2 hrs after 400mg dose
- Platelet function returns 7 days after last dose
- Alternative for aspirin

Abciximab (ReoPro)

- GIIb/IIIa inhibitor - prevents fibrinogen adhesion
- Binds to platelets with half-life of 10 minutes, but effects can last up to 48 hours
- Indicated for use in individuals undergoing percutaneous coronary intervention (angioplasty with or without stent placement)
 - The use of abciximab in this setting is associated with a decreased incidence of ischemic complications due to the procedure

Reversal of Antiplatelets in Spontaneous ICH

Author	Number (n)	Agent	Design	Intervention	AP Effects	Author	Number (n)	Agent	Design
Roquer, 05	194 total 47 Antiplatelet	43 ASA, 2 T, 1 C, 1 D	Prospective, Observational	n/a	Independent predictor of 30 day mortality p=0.004 OR 2.77 (1.38–5.59)	Roquer, 05	194 total 47 Antiplatelet	43 ASA, 2 T, 1 C, 1 D	Prospective, Observational
Toyoda, 05	251 total 57 Antiplatelet	33 ASA, 12 T, 3 CI, 7 ASA+T	Retrospective, Observational	n/a	Independent predictor of hematoma enlargement p=0.01 OR 7.67, (1.62 to 36.4) Predictor of need for emergent surgical evacuation OR 3.10 (1.18–8.15)	Toyoda, 05	251 total 57 Antiplatelet	33 ASA, 12 T, 3 CI, 7 ASA+T	Retrospective, Observational
Cantalapiedra, 06	500 total 49 Antiplatelet	37 ASA, 3 C, 4Tri, 3D	Retrospective, Observational	n/a	30 day mortality for AP group 44.9% vs controls 29.9%	Cantalapiedra, 06	500 total 49 Antiplatelet	37 ASA, 3 C, 4Tri, 3D	Retrospective, Observational

Reversal of Antiplatelet Agents in Traumatic ICH

Author	Number (n)	Age	Agent	Type of ICH	Design	Intervention	AP Effects
Reymond, 92	198 Total	All	All ASA	Severe ICH	Retrospective	N/A	ASA is a risk factor for ICH after head injury (13%) Of all ASA patients, none had insignificant bleeding compared to 6 controls
Rozzelle, 95	157 Total 31 Antiplatelet	>65	Not Specified	Subdural Hematoma	Retrospective	N/A	Similar in-hospital mortality (34.5% in AP group vs 30.0% in controls), but AP group required more craniotomies (79.3% vs. 76.4%)
Mina, 02	71 Total 34 Anticoagulation	All	12 W, 19 ASA, 1 E, 1 C, 1 P	Any traumatic head injury*	Retrospective	N/A	Increased in-hospital mortality (38% of AP vs 8% of controls, p=0.006)
Spektor, 03	231 Total 110 Antiplatelet	>60	100mg ASA	Mainly Mild Head Injury*	Prospective, observational 2 centers	N/A	Similar rates of ICH in both groups (24.5% vs. 25.6%) Similar rates of surgical intervention in both groups (4.5% vs 4.1%)
Ohm, 05	179 Total 90 Antiplatelet	>50	50 ASA, 12C, 20 combination	Any traumatic ICH	Retrospective	24 patients received transfusion	Increased in-hospital mortality (23% of AP vs 8.9% of controls, p=0.016)
Jones, 06	1020 All Trauma 43 Antiplatelet	>50	43 C	25 Head Injury*	Retrospective	29 patients received platelet transfusion	No statistics provided, but higher numbers of cranial surgery, rebleeds, and transfusions in Clopidogrel group Comparable lengths of stay

Classes of Antithrombotics - Anticoagulants

- Vit K antagonists (inhibits II, VII, IX, X)
 - Warfarin
- Factor Xa inhibitors (some II inhibition)
 - Heparins, lovenox
 - Direct Xa inhibitors
 - Rivaroxaban
- Direct thrombin (II) inhibitors
 - Lepirudin
 - Argatroban
- Other: Antithrombin III

Heparin

- Heparin is produced by bovine lung and porcine mucosa
- Heparin binds to, and activates, the inhibitor anti-thrombin III (AT)
- The activated AT then inactivates thrombin and factor Xa

Heparin

- Heparin does not break down clots that have already formed
- It allows the body's natural clot lysis mechanisms to work normally to break down clots that have formed
- Use protamine for reversal

Heparin - HIT

- H.I.T. - Heparin induced thrombocytopenia
- IgG antibodies to PF4 in patients previously exposed to heparin
- IgG, PF4, and heparin form complex which activates platelets and clots > decreased platelet number

Enoxaparin

- Enoxaparin decreases thrombin formation and ultimately prevents fibrin clot formation.
 - It binds to Antithrombin III which then inhibits factor Xa.
 - Factor Xa catalyzes the conversion of prothrombin into thrombin which then is used for fibrin clot formation
- Enoxaparin does not affect the INR, PT, or PTT.
- The only monitoring is to measure anti-Factor Xa levels
- Protamine can be used for reversal

Fondaparinux (Arixtra)

- Mediates effect indirectly through AT
- It is selective for factor Xa
 - Unlike Heparin
- Lower incidence of H.I.T
- Half-life is 130 hours
 - May be longer in pt's >75yrs or <50kg

Argatroban

- A small molecule direct thrombin inhibitor.
- Indicated for prophylaxis or treatment of thrombosis in patients with HIT
- Liver metabolized; monitored by PTT
- May falsely elevate INR
 - The combination of argatroban and warfarin may raise the INR to greater than 5.0 without a significant increased risk of bleeding complications.

Coumadin (Warfarin)

- Inhibits Vitamin K-dependent synthesis of clotting factors II, VII, IX, and X as well as Protein C and Protein S
- Is monitored by the PT or INR
- May be reversed with vitamin K, factor IX (prothrombin), or fresh frozen plasma

Tissue Plasminogen Activator (tPA)

- Obtained from β -hemolytic strep
 - Pt's with prior exposure to tPA or previous strep infections may be resistant to tPA
- Binds to serine protease found on endothelial cells of vessels
 - Catalyzes plasminogen to plasmin conversion
 - Cleaves the single chained plasminogen into two chains
- Must be used within 3 hours of onset of CVA symptoms
- aminocaproic acid works as an antidote

DVT Morbidity and Mortality



DVT Morbidity and Mortality

- Mark et al. reported a 24.8% prevalence rate of PE in a consecutive autopsy series of 101 patients with neurological disease. Pulmonary embolism was the primary cause of death in almost half of these patient

DVT Morbidity and Mortality

- Dalen and Alpert estimated the incidence of PE in the United States to range as high as 630,000 cases per year, resulting in 200,000 (32%) deaths.
- Risk Factors: older age, obesity, varicose veins, immobility, pregnancy, puerperium, estrogen therapy, previous DVT or PE, deficiency of antithrombin III, protein C or protein S, trauma, surgery, malignancy, heart failure, and infection

DVT Morbidity and Mortality

- DVT can lead to pulmonary embolism with subsequent cardiopulmonary arrest
 - Stroke from paradoxical emboli
- In Neurosurgery patients PE formation rates range between 0 and 5%, with a significant mortality rate varying from 9 to 50%

DVT Morbidity and Mortality

Series (Ref. No.)	Patient No.	Assessment	DVT (%)	PE (%)	PE Mort (%)
General neurosurgical population					
Wetzel et al., 1960 (174)	599	Autopsy		3	
Joffe, 1975 (93)	23	¹²⁵ I	43	0	0
Turpie et al., 1977 (162)	63	¹²⁵ I	19.1	0	0
Cerrato et al., 1978 (25)	50	¹²⁵ I	34		
Skillman et al., 1978 (152)	48	¹²⁵ I	25	4.2	50
Turpie et al., 1979 (161)	96	¹²⁵ I	20.8	0	0
Valladares et al., 1980 (167)	100	¹²⁵ I	29	1	0
Zelikovski et al., 1981 (181)	20	¹²⁵ I	50	5	100
Mark et al., 1986 (110)	101	Autopsy		24.8	
Head injury					
Kaufman et al., 1983 (98)	23	¹²⁵ I	20		
Subarachnoid hemorrhage					
Black et al., 1986 (10)	56	Doppler	18		
Brain tumors					
Brisman and Mendell, 1973 (20)	238	Autopsy		8.4	
Kayser-Gatchalian and Kayser, 1975 (99)	334	Autopsy	27.5		
Sawaya et al., 1989 (145)	46	¹²⁵ I	45		
Lumbar discectomy					
Ramirez and Thisted, 1989 (135)	28,395	Clinical		0.1	9

* DVT, deep vein thrombosis; PE, pulmonary embolism; Mort, mortality; ¹²⁵I, ¹²⁵I-fibrinogen; PE was diagnosed clinically except when screened for at autopsy.

Table 1. Thromboembolism and Neurological Disease (Neurosurgical Patient Population)^a

DVT Morbidity and Mortality

Series (Ref. No.)	Patient No.	Assessment	DVT (%)	PE (%)	PE Mort (%)
Spinal cord injury					
Bors et al., 1954 (14)	99	Venogram	58.6		
Phillipps, 1963 (131)	25	Venogram	12		
Tribe, 1963 (160)	28	Autopsy		21.4	
Todd et al., 1976 (158)	20	¹²⁵ I	100		
Brach et al., 1977 (18)	10	¹²⁵ I	70	10	0
Perkash et al., 1978 (128)	50	¹²⁵ I	16	8	50
Rossi et al., 1980 (137)	18	¹²⁵ I	72		
Frisbie and Sasahara, 1981 (44)	17	IPG	5.9		
Myllynen et al., 1985 (120)	23	¹²⁵ I	100	9	0
Mark et al., 1986 (110)	101	Autopsy		24.8	
Merli et al., 1988 (116)	17	¹²⁵ I	47		
DeVivo et al., 1989 (39)	459	Clinical		9	
Myllynen et al., 1989 (121)	54	Clinical		13	42.8
Petaja et al., 1989 (129)	9	¹²⁵ I	67		
Yelnik et al., 1991 (180)	127	Venogram	22.8	0.8 ^b	0
Spinal fracture without cord injury					
Myllynen et al., 1985 (120)	14	¹²⁵ I	0	0	0
Petaja et al., 1989 (129)	12	¹²⁵ I	8.3		

^a DVT, deep vein thrombosis; PE, pulmonary embolism; Mort, mortality; ¹²⁵I, ¹²⁵I-fibrinogen; IPG, impedance plethysmography; PE was diagnosed clinically except when screened for at autopsy.

^b In this portion of the study, all patients with evidence of DVT underwent anticoagulation to prevent PE.

Table 3. Thromboembolism and Spinal Injury^a

In the Beginning...

- In 1993, Laohaprasit and Mayberg looked at the optimal postoperative interval after which heparin therapy can be safely initiated...
- They used fifty rats weighing 450 to 500 g that were assigned to 10 groups
- Nine groups of five rats each had heparin started 1, 2, 3, 5, or 7 days after standardized bilateral frontal corticectomy and was continued for 7 days.
- The last group was the control - saline

In the Beginning...

- There were two ranges, 1.5x therapeutic, and 3x therapeutic
- After 7 days the rats were sacrificed and the brains were stained for amount of blood
- Intracerebral hematomas were classified according to three categories: minimal (0-10 mm³), small (10-50 mm³), or large (>50 mm³)

In the Beginning...

Hematoma Size (mm ²)	Postoperative Day of Heparin Therapy Initiation					
	Control	1	2	3	5	7
None (<10)	10	7	9	10	10	9
Small (10-50)	0	1	1	0	0	1
Large (>50)	0	2	0	0	0	0
Total	10	10	10	10	10	10

Table 1. Intracerebral Hemorrhage after Experimental Corticectomy and Therapeutic Heparin Administration

In the Beginning...

Hematoma Size (mm ³)	Postoperative Day of Heparin Therapy Initiation				
	Control	1 ^a	3 ^a	5	7
None (<10)	10	2	4	8	9
Small (10-50)	0	4	0	0	1
Large (>50)	0	4	6	2	0
Total	10	10	10	10	10

^a $P < 0.01$.

Table 2. Intracerebral Hemorrhage after Experimental Corticectomy and Supratherapeutic Heparin Therapy

In the Beginning...

- Conclusion: heparin therapy can be safely initiated at 48 hours after craniectomy and corticectomy in the rat,
- supratherapeutic anticoagulation is associated with intracerebral hemorrhage from 3 to 5 days after surgery.

DVT prophylaxis

- Non-pharmacologic:
 - TED's/SCD's have class I evidence for efficacy
 - Early ambulation
- TEDs/SCD's should not be used in confirmed DVT

DVT Prophylaxis - Heparin

- Levin et. al did a retrospective analysis of 10 studies looking at VTE rates in patients who were H.I.T. positive
- They compared UFH to LMWH hypothesizing that development of H.I.T. is associated with higher VTE rates
- The frequency of HIT-associated VTE among UFH and LMWH (12.8% [31 of 242 patients] vs 0.7% [1 of 144 patients];
 - odds ratio, 21.0; 95% confidence interval, 2.8 to 156; $p < 0.001$.

DVT at TJU

- The frequency of DVT and PE in untreated patients with SCI is around 67-100%
- PE is the third leading cause of death in the SCI population

DVT at TJU

- Literature review looking at 23 studies comparing different modalities of DVT prophylaxis in patients with spinal cord trauma with and without injury

DVT at TJU

- Looked at several variables:
 - Mechanical vs. combined prophylaxis in acute SCI
 - vitamin K antagonist vs. non-vitamin K antagonist prophylaxis in acute SCI
 - UFH vs. LMWH in acute SCI
 - Start and duration of prophylaxis in acute SCI

DVT at TJU: Inclusion Criteria

- Randomized studies
- Adequate compliance
- Adequate duration of treatment
- Objective tests for DVT, PE and bleeding (LEUS, VQ, CTA, positive guiac etc)

DVT at TJU

- The prevalence of deep-vein thrombosis was significantly lower in patients without spinal cord injury (odds ratio = 6.0; 95% confidence interval = 2.9 to 12.7; $p < 0.00001$, fixed effects)
- however, the prevalence of pulmonary embolism did not differ significantly between the two groups (odds ratio = 1.5; 95% confidence interval = 0.2 to 15.4; $p = 0.73$, fixed effects).

DVT at TJU: Results

- LMWH is more effective than UFH for the prevention of DVT in patients with acute SCI
- Both are equivalent for PE prevention
- LMWH has had fewer bleeding complications than UFH in patients with acute SCI

DVT Prophylaxis - LMWH (Lovenox)

- Tetri et. did a retrospective analysis of 407 patients who were admitted for ICH of 3 month mortality.
- 232 received lovenox, 175 did not
- There was a higher incidence of increased hemorrhage in the treated group that was statistically significant.
- However, there was an increase in PE in the non-treated group
- Overall, there was a decrease in mortality in the treated group, but it wasn't statistically significant
- Also, there was a significant worsening of GOS in the treated group...

DVT Prophylaxis - LMWH (Lovenox)

- Spyropoulos et. al looked retrospectively at venous thromboembolism prevention in cancer patients
- 922 neurosurgery patients were split into LMWH and no treatment groups.
- There was a statistically significant decrease in VTE in treated patients ($p < 0.001$)
- However there was also an increase in major bleeding events and for every 7 VTE's prevented there was 1 major bleeding event.

DVT Prophylaxis - LMWH (Lovenox)

- Dickinson LD et. al looked prospectively at DVT prophylaxis in 68 patients undergoing craniotomy
- Three Groups were compared over a month using ANOVA
 - SCD 22 patients
 - Lovenox 23 patients
 - Both 23 patients

DVT Prophylaxis - LMWH (Lovenox)

- Inclusion criteria
 - Age \geq 18 with diagnosis of intracranial neoplasm
 - Undergoing surgery
- Exclusion criteria
 - History of DVT or pulmonary embolism
 - Allergy to heparin or other anticoagulant agents
 - History of surgery or major trauma to the lower extremities
 - Concurrent condition requiring anticoagulation therapy
 - cranial base neoplasms and pituitary adenomas

DVT Prophylaxis - LMWH (Lovenox)

- DVT was observed for 8 of the 66 study patients, yielding an overall DVT incidence of 12%
- All patients with DVT had undergone craniotomy procedures

DVT Prophylaxis - LMWH (Lovenox)

- DVT incidence in treatment group was
 - 3 of 22 (13.6%) in the SCD-treated group
 - 1 of 21 (4.76%) in the enoxaparin-treated group
 - The difference was not statistically significant ($P = 0.53$).
- DVT incidence in the combined group was 4 of 23 (17.4%)
 - also not significantly different from that for the SCD-treated group ($P = 0.90$).

DVT Prophylaxis - LMWH (Lovenox)

- Post-op ICH did not occur in the SCD-treated group
- 5 of 46 patients receiving low-molecular weight heparin suffered clinically significant intracranial hemorrhage
- The study was terminated because of the increased incidence of adverse events in the enoxaparin-treated groups.

DVT Prophylaxis - LMWH (Lovenox)

- Lovenox groups received 30mg SQ *in the anesthesia holding room.*
- Lovenox was continued from holding at 30q12 until discharge

DVT Prophylaxis - LMWH (Lovenox)

- Four of the five patients with intracranial hemorrhaging demonstrated gliomas in histological examinations.
- Three developed a new neurological deficit within 6 hours of recovery from anesthesia,
 - two required an emergency return to the operating room for evacuation to prevent herniation

DVT and PE treatment

- The only current absolute contraindications for anticoagulation are patients with an unsecured aneurysm after a subarachnoid hemorrhage or patients with an acute intracerebral hemorrhage or hematomyelia
- Although the possible outcome of an intracranial hemorrhage might include increased neurological disability or death, there is no doubt about the very high mortality associated with PE

DVT and PE treatment

- Level I evidence has substantiated the efficacy and safety for starting warfarin on the same day as the heparin therapy is started.
- Warfarin should always be overlapped with heparin for 4 to 5 days, with discontinuation around 5 to 7 days

DVT and PE treatment

- What about Inferior vena cava filters (IVCF)?
- IVCF are an alternative to full anticoagulation in those patients at highest risk for catastrophic hemorrhagic complications
- IVCF has a limited role after a patient has passed out of the high-risk period for bleeding complications
 - beyond securing the aneurysm or beyond 1 to 2 weeks after intracranial surgery
- Therefore, full anticoagulation should be reconsidered, because the patient remains at risk for continued venous thrombosis and postphlebotic syndrome.

DVT and PE treatment

- Unfortunately there is no information to define the the risk for hemorrhage after the first week after intracranial surgery.
- There is weaker evidence to suggest the safety of therapeutic anticoagulation between postoperative Week 1 and Week 6

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