Medical Management Of Deep Vein Thrombosis

Dr Devender Singh
Venous Thrombosis

Thrombus formation in deep veins of legs or thighs

Approximately 600,000 new cases are diagnosed in the U.S. each year
Venous Thrombosis

Thrombus formation in deep veins of legs or thighs

Approximately one-third develop pulmonary embolism (PE)

Source: sirweb.org
Morbidity/Mortality of Pulmonary Embolism
Progression of Chronic Venous Insufficiency

**Stasis dermatitis** Advanced pigment changes of stasis dermatitis are characterized by red oozing skin (worse on the left anterior leg) with some scaling on the ankle. Courtesy of Patrick C Alguire, MD.

**Skin changes of chronic edema** Longstanding edema in this patient with chronic venous insufficiency led to moderately advanced pigment changes on the medial and lateral ankles, which extend onto the dorsum of the foot. The left medial ankle displays a healed venous ulcer below the malleolus; the right lateral ankle has a small, active, venous ulcer (arrow). Courtesy of Patrick C Alguire, MD.

**Venous stasis ulcer** Large venous ulcer on the medial ankle in a patient with chronic venous stasis. The ulcer is shallow and red-based with irregular borders. Courtesy of Patrick C Alguire, MD.
Management : Virchow’s Triad
BRIEF CLINICAL DETAILS
Recurrent DVT.

SITE
F N A C from right supraclavicular region.

GROSS
Prepared 7 fixed smears and stained with H & E, PAP
2 Air dried smear stained with MGG.

MICROSCOPIC EXAMINATION
- Smears are cellular and show neoplastic cells arranged in three dimensional clusters and singles.
- These cells have high N:C ratio with irregular nuclei with coarse chromatin and moderate amount of vacuolated cytoplasm.
- Tumor giant cells noted.

DIAGNOSIS / COMMENTS
- Features are suggestive of Metastatic Adenocarcinoma deposits in right supraclavicular lymph node.
- Suggested primary in the upper aerodigestive tract / breast.
- Clinico-Radiological correlation is suggested.

*********** END OF THE REPORT **********
Goals of Pharmacologic Intervention

• Prevent clot formation
• Stop clot from getting bigger
• Prevent clot from breaking loose and resulting in an embolus
• Prevent DVT from re-occurring.
From the first case of DVT to the pre-anticoagulant era (1271–1920s)

- 1271, Raoul, a 20-year-old Norman cobbler suffered unilateral pain and swelling of the right calf that subsequently extended up to the thigh.
Pre-anticoagulant era (1271–1920s)

- Pregnancy-related DVT, which was the leading, or even only, cause of reported DVT at that time
- It was also thought that postpartum DVT was caused by retention of unconsumed milk in the legs (‘milk leg’)
- In 1700s, breast-feeding was encouraged to prevent DVT
- Bloodletting technique was used to treat DVT until the end of the 19th century
First pathologic evidence-based treatment of DVT (1784 to early 1920s)

- Hunter (1793) hypothesized that it was an occlusion of the vein by blood clots
- He performed venous ligations above thromboses, to prevent extension of clots
- This surgical treatment was widely used until the mid-20th century
- High morbidity and mortality
For fear of thrombus migration, strict bed rest was prescribed, and constituted, at least from the end of the 19th century, the cornerstone of DVT treatment.

(i) Bed rest to fix the thrombus in place
(ii) Elevation of the extremity involved to favor venous return;
(iii) Application of heat with warm compresses to reduce vasospasm and to increase collateral circulation
From the discovery to the development of anticoagulants (1920s–1950)

• The first anticoagulant that could be effectively used for the treatment of DVT was heparin. It was discovered in 1916 by McLean,
• In 1933, Charles and Scott succeeded in producing pure crystalline heparin, allowing its use in humans, which began in 1935
• Mortality from PE among inpatients with symptomatic DVT dropped from 18% to 0.4%
From the discovery to the development of anticoagulants (1920s–1950)

- Warfarin, discovered by Link, was initially launched in 1948 as the ideal rodenticide, and was considered to be too toxic for human use.

*Wisconsin Alumni Research Foundation*
Abandoned treatments

Numerous other therapeutic options, sometimes surprising, were tried during this period and later abandoned because of insufficient efficacy:

- Antibiotics (sulfanilamide, sulfapyradine, and sulfathiazole),
- Application of leeches,
- X-ray therapy,
- Mecholyl iontophoresis,
- Anesthesia of the paravertebral lumbar sympathetic system
The modern era: Ambulatory management of DVT and the development of complementary treatments (since 1950)

• The last 60 years have been characterized by major progress in the field of diagnostics rather than therapeutic management

• Venography, was developed by Berberich and Hirsch

• Physicians no longer treat clinically suspected DVT but objectively confirmed DVT
• The most significant step in the simplification of anticoagulant treatment was the development of LMWH, which, in most cases, does not require monitoring.
• In 1996, Levine demonstrated that LMWH given at home was as safe and effective as unfractionated heparin administered in the hospital to treat proximal DVT
• Thus, DVT became an ambulatory disease.
The development of complementary treatments

• Medical treatments: compression therapy

• Compression bandages started to be more widely used when anticoagulants became available.

• A demonstration of their usefulness in preventing post-thrombotic syndrome (PTS) was provided by Brandjes in 1997
Surgical and endovascular treatments

• Heparin was the treatment of choice for DVT in the 1950s, but surgery was still used, notably in cases of severe VTE

• The surgical procedure was mainly bilateral, femoral or IVC ligation

• IVC ligation was associated with a high fatality rate (14%)
Mid-1950s onwards

• Temporary or partial interruption of the IVC: temporary exclusion of the IVC with removable metal or plastic clips;
• Temporary ligation of the IVC with absorbable catgut;
• Plication or compartmentalization of the IVC with a mechanical stapler, dividing it into multiple small channels
Mid-1950s onwards

A Plication of Vena Cava (Spencer)
B De Weese harpgrip filter
C Adams-DeWeese Clip
D Mobbin-Uddin Filter
E Greenfield filter
• In 1958, De Weese constructed the first intraluminal ‘harpgrip’ filter, which could block the transit of emboli without significantly disturbing the function or dynamics of the venous system.

• It showed promising results in preventing PE, but its placement still required major surgery and general anesthesia.

• This problem was solved with the Mobin–Uddin umbrella (1967), which could be installed with a simple catheter under local anesthesia.

• Potential migration, and obstruction of IVC was the major concern.

• In 1981, Greenfield developed the first true percutaneous filter, which did not necessitate any venotomy; this was followed by a rapid increase in the indications for and number of implantations of IVC filters.
From thrombectomy to thrombolysis to decrease the PTS burden

This patient underwent a thrombectomy. The thrombus has been laid over the approximate location in the leg veins where it developed.
From thrombectomy to thrombolysis to decrease the PTS burden
Management of VTE

• Heparin and warfarin are the two traditional anticoagulants
• Anticoagulant drugs help prevent the development of harmful clots in the blood vessels by lessening the blood's ability to cluster together
• The function of these drugs is often misunderstood because they are sometimes referred to as blood thinners; they do not in fact thin the blood
• These drugs will not dissolve clots that already have formed, but it will stop an existing clot from becoming worse and prevent future clots
Heparin

• Heparin is given by injection or drip into a vein (intravenously) or by injection under the skin (subcutaneously) for treatment and prevention
• It is derived from porcine intestinal mucosa, standardized for anticoagulant activity
• Heparin works by inhibiting the three major clotting factors (thrombin, thromboplastin, and prothrombin)
• It slows the process of thromboplastin synthesis, decelerates the conversion of prothrombin to thrombin, and inhibits the effects of thrombin on fibrinogen, blocking its conversion to fibrin
• The agent also causes an increase in the number of negatively charged ions in the vascular wall, which helps prevent the formation of intravascular clots.
Figure 1. Sites of action of unfractionated heparin.
# Heparin Protocol for systemic anticoagulation

<table>
<thead>
<tr>
<th>Weight based Nomogram</th>
<th>Action</th>
</tr>
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<tbody>
<tr>
<td><strong>Initial dose</strong></td>
<td>80 u/kg bolus, then 18 u/kg per hour</td>
</tr>
<tr>
<td>APTT &lt; 35 seconds (&lt;1.2 × control)</td>
<td>80 u/kg bolus, then 4 u/kg per hour</td>
</tr>
<tr>
<td>APTT 35 to 45 seconds (&lt;1.2 to 1.5 × control)</td>
<td>40 u/kg bolus, then 2 u/kg per hour</td>
</tr>
<tr>
<td>APTT 46 to 70 seconds (&lt;1.5 to 2.3 × control)</td>
<td>No change</td>
</tr>
<tr>
<td>APTT 71 to 90 seconds (&lt;2.3 to 3 × control)</td>
<td>decrease infusion rate by 2 u/kg per hour</td>
</tr>
<tr>
<td>APTT &gt;90 seconds (&gt;3 × control)</td>
<td>hold infusion 1 hour, then decrease infusion rate by 3u/kg per hour</td>
</tr>
</tbody>
</table>
Low molecular weight heparin (LMWH)

Pros
- More predictable anticoagulant response
- Do not require lab monitoring
- Long half-life (4-6 hours) – once daily or BID admin
- Lower affinity for platelet factor 4, so less HIT
- Less bleeding complications
- Can be done at home

Cons
- More expensive
- Patients may not like injections
- Pharmacokinetics unclear is not known in certain patients (i.e. pregnancy, obesity, renal impairment)
- Can’t reverse it with antidote (protamine)
Pregnancy, Cancers..... Favours LMWH

Mechanism of Heparins

Unfractionated heparin inactivates both Factor IIa and Xa

LMWH has increased affinity for Factor Xa

Fondiparinux is only a pentasaccharide sequence

Weitz. NEJM, 1997; 337:688
<table>
<thead>
<tr>
<th></th>
<th>Low molecular weight heparin (%)</th>
<th>Unfractionated heparin (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deep vein thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>86/1998 (4.3)</td>
<td>113/2021 (5.6)</td>
<td>0.75 (0.55–1.01)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>30/2353 (1.3)</td>
<td>51/2401 (2.1)</td>
<td>0.60 (0.39–0.93)</td>
</tr>
<tr>
<td>Mortality</td>
<td>135/2108 (6.4)</td>
<td>172/2137 (8.0)</td>
<td>0.78 (0.62–0.99)</td>
</tr>
<tr>
<td><strong>Pulmonary embolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrent VTE</td>
<td>30/988 (3.0)</td>
<td>39/895 (4.4)</td>
<td>0.68 (0.42–1.09)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14/1023 (1.4)</td>
<td>21/928 (2.3)</td>
<td>0.67 (0.36–1.27)</td>
</tr>
<tr>
<td>Mortality</td>
<td>46/988 (4.7)</td>
<td>55/895 (6.1)</td>
<td>0.77 (0.52–1.15)</td>
</tr>
</tbody>
</table>
Fondaparinux

- Fondaparinux is given via injection once daily
- It is licensed for initial treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and for venous thromboembolism prevention in patients undergoing surgery for hip fracture or hip/knee replacement
Exclusion Criteria for Outpatient DVT Management

- Suspected or proven concomitant PE
- Significant cardiovascular or pulmonary comorbidity
- Ileofemoral DVT
- Contraindications to anticoagulation
- Familial or inherited disorder of coagulation – ATIII deficiency, prothrombin 20210A, protein C or protein S deficiency, or factor V Leiden
- Familial bleeding disorder
- Pregnancy
- Morbid obesity >150 kg
- Renal failure (creatinine >2 mg%)
NEW DELHI: BJP leader and former cricketer Navjot Singh Sidhu was on Tuesday admitted to a private hospital here and is undergoing treatment for acute deep vein thrombosis (DVT).
Warfarin

• Warfarin is an oral medication
• It is a synthetic derivative of coumarin, a chemical found naturally in many plants -- it decreases blood coagulation by interfering with vitamin K metabolism
• Warfarin inhibits the effective synthesis of biologically active forms of the vitamin K-dependent clotting factors: II, VII, IX and X, as well as the regulatory factors protein C, protein S and protein Z
Vitamin K Antagonists – Limitations

• Unpredictable pharmacokinetics and pharmacodynamics, which are affected by:
  – Genetic factors (CYP 2C9 mutation)
  – Drug–drug interactions
  – Consumption of alcohol and foods containing vitamin K

• Monitoring and frequent dose adjustment required to maintain INR within therapeutic window
  – Monitoring is costly, and a burden on patients and society

• Slow onset and offset of action (e.g. if patient requires surgery), requiring bridging with heparin or LMWH

Ansell et al., Chest 2004
Drug Interactions with VKAs

Increased Effect

- Acetylsalicylic acid
- Allopurinol
- Alufibrat
- Amiodarone
- Amloidone
- Amoxapine
- Anabolika
- Androsteron
- Anthranilic acid derivatives
- Azapropazone
- Bezafibrate
- Benziodarone
- Broad spectrum antibiotics
- Cefalosporins
- Chinidinpräparate
- Chloralhydrate
- Chloramphenicol
- Cimetidine
- Clofibrate
- Clopramine
- Cloxacillin
- Desipramin
- Dextrans
- Disulfiram
- Doxepins
- Enthromyic acid
- Ethacrynic acid
- Fenoprofene
- Fluconazole
- Glucagone
- Immunsuppressants
- Indomethacin
- Itraconozol
- Lofepramine
- Lokalanästhetika
- Mefenaminsäure
- Metylandrostenol
- Metronidazol
- Monoaminoxidasehemmer
- Muttermolkalkaloide
- Nalidixinsäure
- Naproxene
- Nicotinsäurederivate
- Nortriptyline
- Oxyphenbutazone
- Paraaminosalicylsäure
- Phenothiazinepräparate
- Phenytoin
- Piroxicame
- Pufuroxene
- Rauwolfiaaparate
- Salicylat
- Steroide, anabole
- Sulfonylurea
- Sulfinpyrazon
- Sulfonylurea
- Thiourear
- Thyroxine

Decreased Effect

- Gluthetimide
- Griseofulvin
- Haloperidol
- Laxanzien
- Mercaptogurine
- Neuroleptika
- Ovulationshemmer
- Phenytoin
- Purinderivate
- Pyrithyldon
- Rifampicine
- Strophantine
- Thioracil
- Thyroestatics
- Vitamin K Preparations
- Vitamin supplements

Close INR monitoring is required with EVERY change in medication!
<table>
<thead>
<tr>
<th>Event Description</th>
<th>Duration</th>
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<tbody>
<tr>
<td>1st event, reversible risk factor</td>
<td>3-6 months</td>
</tr>
<tr>
<td>1st event, spontaneous</td>
<td>&gt;= 6 months</td>
</tr>
<tr>
<td>2nd event</td>
<td>&gt;=12 months or lifelong</td>
</tr>
<tr>
<td>2nd spontaneous event, or 1st spontaneous and life threatening</td>
<td>Lifelong</td>
</tr>
<tr>
<td>3rd event or Ongoing risk factors</td>
<td>Lifelong</td>
</tr>
</tbody>
</table>
Indefinite anticoagulation recommended

- Two or more spontaneous thromboses
- One spontaneous thrombosis in case of AT deficiency or the APS
- One life-threatening thrombosis
- One spontaneous thrombosis at an unusual site
- One spontaneous thrombosis in the presence of multiple genetic thrombophilia defects
Venous Thromboembolism

Deep vein thrombosis

Pulmonary embolism

PROPHYLAXIS
Prevention/Interventions

- Mobility-foot pumps, exercise
- Compression stockings
- Early ambulation following surgery
- Close management of CHF, HTN and/or Diabetes
- Smoking cessation
- Weight management
- Prevent dehydration
- Pharmacologic interventions (see below)

- Elastic compression stockings
- Foot pumps when immobilized in bed or chair
- Monitor anticoagulant therapy
- Monitor Vit K intake (green leafy vegetables, soybean oil, and canola oil)
- Increase fluids and avoid alcohol
Patient/Family Education

- Basic disease instruction including S/S of DVT extension & pulmonary embolism; complications
- Lifestyle modification related to smoking and weight management
- Indications & actions of medications/herbals; dose & schedule; target INR & lab work; missed dose strategy
- Medication interactions (that increase or decrease INR); diet (foods to avoid, limit, & eat)
- Self-care (i.e., leg elevation, avoid crossing legs & standing for long periods); anticoagulant safety issues (avoid sharp objects & injury; monitor common bleeding sites – gums, nose, GI, GU, skin; actions to take if bleeding)
- Dental considerations (soft bristle toothbrush; notifying dentist)
- Cultural considerations of animal derived products (heparin) and alternative synthetic options for whom animal derived products are objectionable
Patient/Family Education

Deep Vein Thrombosis Information for Patients Taking Acitrom

HELP US TO HELP YOUR CLOT GO

Dos

✓ Take your Acitrom exactly as your healthcare provider tells you.
✓ Get your blood tested when you are supposed to.
✓ Use a calendar to record all of your Acitrom doses and each INR result.
✓ Tell your healthcare provider about all other medications you are taking. Also, talk to your healthcare provider BEFORE you change, start, or stop any medicines (prescription or over-the-counter), supplements or herbal products.
✓ Keep your eating habit and activities somewhat similar every day. Sudden changes can affect your INR.
✓ Eat foods that contain vitamin K such as green vegetables.
✓ Tell your healthcare provider when you get sick or injured, or have bleeding that is more severe than you expect.
✓ Keep Acitrom (and all other medications) out of reach of children.
✓ Tell your doctor if you are pregnant or are planning to get pregnant.
✓ Tell all healthcare providers (e.g., doctors, dentists and pharmacists) that you are taking Acitrom.
✓ Refill your prescription BEFORE running out of Acitrom.
✓ Remember to take your Acitrom (and other medications) when you travel.
✓ Consider wearing a Medic Alert bracelet or carrying a wallet card that states that you are taking an oral anticoagulant.

DON’ts

✗ Take Acitrom if you are pregnant or plan to get pregnant without contacting your doctor.
✗ Change the dose of Acitrom on your own.
✗ Stop Acitrom on your own even if you feel well.
✗ Start or stop any other medicines without checking with your healthcare provider first.
✗ Make big changes in your diet, lifestyle, or activities without first telling your healthcare provider.
✗ Participate in contact sports that may result in bleeding or bruising injuries.
✗ Drink too much alcohol. 1 or 2 drinks per day is generally OK unless you have been told not to drink alcohol. NEVER BINGE DRINK.

Mr. Dileep (9966885000) Vascular access coordinator
Dr. Devender Singh (9866396657) Vascular Surgeon

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Medical Management Of Deep Vein Thrombosis

To be continued........

Thank you