Superficial Vein Thrombosis: The “Rodney Dangerfield” of Venous Thromboembolism

Keith E. Swanson MD
North Dakota Academy of Family Physicians
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Disclosures

• None!

What is SVT?

• Inflammation + thrombosis in a superficial vein
  • Result: pain, tenderness, erythema and induration along course of superficial vein, surrounding edema, often a palpable cord
  • Possible venous distention proximal to the thrombosis
  • Look for the company it is keeping
    • CVD, VV, skin pigmentation etc.
  • Great Saphenous Vein – small saphenous – upper extremity veins
    • 60-80% GSV; 10-20% LSV
  • Recent "shift" in nomenclature….SVT vs. phlebitis
    • Emphasis on the thrombotic potential more so than the associated inflammation

"Doc, my vein is hard and painful"

What SVT is not...

• Superficial femoral vein thrombosis ➔ Superficial vein thrombosis
  • The "fatal misnomer"
  • SFV is a deep vein (and a large one at that)
  • All professional societies have banned this term!
• Infusional thrombosis
  • Localized Inflammation of a small peripheral IV related to INT or chemical irritation
  • Usually resolves with removal of the IV and conservative care (warm compresses, compression)
• AC not needed
• Suppurative superficial thrombophlebitis
  • Remove the line, "source control" (if abscess present) and start prompt IV abx
  • Again, really no role for AC.
  • Septic = systemic s/s ➔ fever, Leukocytosis, hemodynamic compromise

Why this “lack of Respect”

• We are just more comfortable when we can see it!
• A step back in time...
  • 125 years ago...no understanding of hypercoagulability; no US.
  • Thus, because SVT was so easily identifiable, it was held separate and apart from the more subtle and occult DVT
• 1885 leading medical treatise:
  • "Except in the cases of superficial veins, in which the vessel may be felt as a hard cord, the affection cannot be recognised in life."
• Bottom-line:
  • The ease of clinical diagnosis somehow was translated into its being safer than its more occult and dangerous cousin DVT
**Epidemiology**

- Generally, poorly understood
  - 123-125K cases per year in USA
  - 10-20% of those with varicose veins will suffer SVT at some point in their life.
  - Generally, thought to be more common than DVT (1:1000)
- Typical pt: 65 y/o obese female with a h/o of varicose veins.
- Seasonal variation?
  - More common during summer
  - DVT more prevalent in winter
- Less mortal than DVT/PE
  - 1% vs ~5%
  - Likely d/t differences in the frequency of comorbid disease

**What contributes to SVT?**

- Trauma
- IVDU
- IV catheters
- Direct blow
- Thick blood
- Acute illness
- Malignancy
- Inflammatory states
- Hormones
- Pregnancy
- Obesity
- Post op
- Varicose veins

**DVT in SVT**

- OPTIMEV
  - N=788 with SVT, mostly outpatients
  - 28.8% with DVT/PE (39.4% if no varicose veins)
- Key findings:
  - even with varicose vein SVT, rate of concomitant DVT far from negligible i.e. 23.3%!
  - localized signs and symptoms of SVT helpful but not good enough
    - 14% with local signs still had concomitant DVT!
  - Bottom line, all patients with SVT need an ultrasound

**DVT in SVT**

- Sobreiria et al
  - N=60
  - 21% with concomitant DVT
  - Non-contiguous DVT quite common
    - 53% contiguous vs. 43% non-contiguous
  - Physical exam frequently underestimates true extent
    - 82% of the time (Others: 77%)
  - 9x greater likelihood in the absence of VV

**DVT in SVT**

- POST trial
  - N=855; all with symptomatic SVT > 5 cm
  - 24.9% with DVT/PE!
  - 8% rate of symptomatic thromboembolic complication at 3 months!
  - 0.5% pulmonary embolism
  - 2.8% deep vein thrombosis
  - 3.3% SVT extension
  - 1.9% SVT recurrence
  - Predictors for thromboembolic complications at three months:
    - Male sex
    - H/o DVT/PE
    - Cancer
    - Absence of VV
  - This is despite the fact that 90.5% received some form of anticoagulation!

**DVT in SVT**

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DVT in SVT

Summary

- Concomitant DVT surprisingly common in SVT
- Several large prospective trials providing convincing evidence
- About ¼ of SVT have DVT
- Isolated SVT needs close f/u
- 8% thromboembolic complication at 3 months
- Features of SVT should “raise your antenna”
  - h/o of DVT, absence of varicose veins, males, cancer
- We’re not good enough to rule out DVT by clinical exam alone
  - About ½ of the time, underestimated!
- DVT often non-contiguous

• Which statement is correct regarding DVT in the setting of known SVT?
  - A. Overall incidence is ~25%
  - B. When present, it is almost always contiguous with the SVT
  - C. Incidence is variable depending on pt characteristics
  - D. Approximately 25% Not uncommonly non-continuous

Incidence of almost 40% if SVT occurring in the absence of VV

SVT and Cancer

- DVT/PE clearly associated with subsequent development of cancer
  - 2-4 fold increased risk of cancer within 1 year of diagnosis
  - About 1 in 10 will eventually present with occult malignancy
    - Over 2 years
  - So...was Trousseau right?

- Van Doormaal FF, et al. 2010
  - N= 250; all with unprovoked first SVT
  - After analyzing 38K record b/t 1995-2004
  - Age and Gender matched controls 2:1 and followed for 2 years
  - 2% incidence new malignancy both groups
  - Take-home:
    - No increased risk of cancer among a group with first episode of unprovoked SVT

Unprovoked SVT, like VTE, is clearly associated with cancer.

So great, in my opinion, is the semiotic value of phlegmasia in the cancerous cachexia, that I regard this phlegmasia as a sign of the cancerous diathesis as certain as sanguinolent effusion into the peritoneal cavities.
SVT and cancer

- Prandoni et al. *Blood* 2011
- 737 with isolated SVT not involving the SFJ. Retrospective
- 2:1 control/case followed for 2 years
- Cancer rate: 3.5% case vs. 3.9% controls
- Conclusion: no increased risk

Cancer and SVT

Summary

- SVT, unlike DVT and PE, may not be a strong predictor of future cancer development.
- With SVT, exhaustive cancer search not recommended
  - Even if unprovoked
- May not apply to migratory SVT in unusual places (i.e. Trousseau's)

SVT and Thrombophilia

- Many studies showing similar prevalence when compared with DVT.
  - Especially in the setting of non VV SVT
- Think about a thrombophilia:
  - Lack of trauma (external or internal)
  - absence of VV
  - Concomitant DVT especially in the setting on non VV SVT
- Ask yourself: Will it change management?
  - Hint: often, it will not

In terms of prevention of thromboembolic sequelae, which Rx is considered most efficacious for “isolated” SVT:

- A. Take 2 ASA and call me in the morning
- B. Rivaroxiban 15 mg po BID x 3 wks followed by 20 mg po qd x 9 additional weeks
- C. "prophylactic" dose LMWH SQ daily for 30 days
- D. "prophylactic" dose fondaparinux SQ daily for 45 days

Management

- Two principles of SVT treatment:
  - 1. symptom relief
  - 2. prevention of thromboembolic complications
- Symptom relief: NSAIDs, relative rest, avoidance of trauma, anticoagulants
  - Once symptoms controlled: graduated compression garments (e.g. varicose veins)
- Generally, a trend toward more aggressive Rx with anticoagulants
  - dt/1 clearer understanding of the potential morbidity of untreated disease
  - Unfortunately, (still) no solid trials on which to base therapy
  - To date: only one RCT demonstrating clear superiority for a prophylactic dose of Fondaparinux
  - All other studies had serious flaws
    - Dose too small
    - Duration woefully too short
    - Only short term (30"

Management

- The “Curbside Barometer”

- Rx all over the map:
  - POST: dose from "prophylactic" to “therapeutic”. Rx duration: 1-262 days
  - Netherlands: only 20% with Rx and most with NSAIDs only.
The typical study...

- Arch of Int Med 2003
- Double blind trial 427 pts with acute symptomatic SVT of the legs
- 3 groups:
  - 1. SQ intermediate dose enoxaparin daily
  - 2. SQ enoxaparin 1.5 mg/kg daily
  - 3. oral Tenoxicam (a British NSAID) once daily
  - 4. oral placebo once daily
- Each given once daily for 8-12 days!
- Of the 30 randomized trials of SVT Rx, 27 are about the same as above!
- Cochrane Collaboration 2013

**STEFLUX (LMWH trial)**

- RDBCT LMWH for SVT
  - Inclusion:
    - out-patient with acute, symptomatic SVT of LE; age >18; b/w 50-130 kg; at least 4 cm long
  - Exclusion: several but not as restrictive as CALISTO
  - Allowed those with h/o of previous SVT or DVT/PE
- The players:
  - “intermediate dose” LMWH for 10 days
  - “intermediate dose” LMWH for 30 days
  - “Prophylactic dose” LMWH for 30 days

**STEFLUX Trial Design**

- All instructed to wear ECS
- All re-evaluated at 0,10, and 30 days
- All told to contact clinical center immediately in case of symptoms
- At 90 days, either clinical exam or telephone call
- Blood samples done at 0,10, and 30 days
- Hb, leucocytes, platelets, ALT and AST. Cr measured only at day 0
- Ultrasound 0 and 30 days and any time clinical signs and symptoms of suspected recurrence or extension of SVT, DVT, PE.
- US at 90 days left to the discretion of the attending MD

**STEFLUX outcomes assessed**

- Primary outcome (at 30 days):
  - Composite of symptomatic and asymptomatic DVT
  - Symptomatic PE
- Secondary outcome:
  - Reduction in local symptoms during Rx
  - Combined efficacy endpoint (see above) at 90 days
- Primary safety outcome:
  - Major bleeding
- Secondary safety outcome:
  - Minor bleeding, thrombocytopenia, or any other allergic reactions

**STEFLUX Efficacy Results**

- Stopped early d/t large difference in the rate of primary outcome among the three groups.
  - Short course (30 days) of “intermediate” dose: 11.3%
  - 30 d course of “prophylactic” dose: 5.7%
  - 30 d course of “intermediate” dose: 1.5%
- Absolute Risk Reduction:
  - 30 d “Intermediate” dose vs. 30 d “intermediate” dose: 13.7% (p < 0.001)
  - NNT 7 (5-12)
  - RR(67% (64-95%)
  - 30 d “Intermediate” dose vs. 30 d “prophylactic” dose: 5.5% (p = 0.011)
  - NNT 30 (13-61)
  - RR(58% (76-91%)
  - 10 d “Intermediate” dose vs. 30 d “prophylactic” dose: 8.8% (p=0.012)
  - NNT 20 (16-72)
  - RR(88% (73-98%)}
STEFLUX Safety Results

- No major bleeding events or Death in any group
  - During the active Rx phase (first 30 days) OR f/u phase (90 days after randomization)
- Liver enzyme increases in 2 pts
  - 1 in 30 d “intermediate” dose group
  - 1 in 30 d “prophylactic” dose group
  - LFTs returned to normal after Rx stopped
- NO thrombocytopenia in any of the Rx arms
- Injection site hematoma in ~ 2.5%
  - Similar rates regardless of dose/duration

STEFLUX Take home points

- Prophylactic dose LMWH is inferior to intermediate dose.
  - Don’t use Lovenox 40 mg SQ daily!!
- Rx duration is important
  - 10d Rx came in last!!
  - Once active Rx stopped (no matter the Rx) event rates immediately increased across the three groups
  - ? Need for even longer Rx duration

Subject criteria

- Inclusion criteria: Acute, symptomatic lower limb superficial vein thrombosis at least 5 cm long (on standard duplex)
  - Age > 18
  - Hospitalized or non-hospitalized
- Exclusion criteria: Several.
- Key differences b/t CALISTO and STEFLUX
  - Hospitalized pt allowed in CALISTO (not in STEFLUX)
  - Generally CALISTO more restrictive
    - Any previous DVT/PE within last 6 months excluded
    - Major surgery in the past 3 months (CALISTO) vs. 1 month (STEFLUX)
CALISTO
Outcomes assessed...

• Primary efficacy outcome:
  • Composite of death from any cause, symptomatic PE (confirmed), symptomatic DVT (confirmed by various methods) or symptomatic extension of SVT up to day 47
• Secondary efficacy outcome:
  • as above, only now out to 77 days, each component of the primary outcome and surgery for SVT
• Primary safety outcome:
  • major bleeding
• Other Safety outcomes:
  • clinically relevant non-major, minor and any bleeding

CALISTO
Results

• Primary efficacy outcome:
  • 13 of 1502 (0.9%) fonda group vs. 88/1500 (5.9%) placebo group
  • RR 0.15 (95CI 0.08-0.26) P <0.001
  • NNT 20
  • Each component with significantly less occurrence in fonda group; including PE
    • Except: incidence of death similar in each group
    • NNT to prevent 1 PE = 300 (similar to NNT for chemical prophylaxis in acutely ill medical patients)
    • Risk of DVT or PE reduced by 85% in fonda group
• All efficacy results maintained at day 77
• Surgery for SVT much more common in placebo group than fonda group
  • 52 (3.5%) vs. 8 (0.5%) or 81% RRR

CALISTO
Safety results

• Major, Clinically relevant non-major, minor, and any bleeding no difference b/t groups
• Similar at both 45 days (active treatment phase) and 77 days
• No clinically relevant between group differences in the incidence of any other adverse events.
• No episodes of thrombocytopenia in fonda group.
CALISTO
Take home points

• Fonda is clearly better than a placebo
• Efficacy seems to hold after Rx discontinuation
  • No “catch-up” after Rx drug stopped
• Fonda 2.5 mg daily is safe and well tolerated
• Fonda Rx may prevent many surgical procedures for SVT
• Fonda Rx = lower % requiring “Step up” therapy to full dose systemic anticoagulation

Where the rubber meets the road...

• Price seems to be as important (often more) than management/prognosis
• Out-of-pocket price of Fondaparinux (2.5 mg SQ x 45d)
  • A. $123.48
  • B. $269.58
  • C. $485.69
  • D. $585.79
  • E. $749.50
  • F. Son, forget about college this year...

Expense

• Fonda x 45 days $749.50
• LMWH (intermediate dose) x 45 days $723.51
• LMWH x 10 days $168.11
  • VKA mild additional expense

Cost effectiveness results

• Fonda: ICER of $500,000 per QALY (10x higher than a “cost effective” ICER per QALY)
  • Strikingly different compared to other indications for anticoagulants
    • Cost per VTE avoided $141,000
  • Prevents 123 VTE’s and 2 deaths per 10,000 pts!!
• Take home:
  • HIGH cost/MODEST benefit
  • Specific subgroups should be targeted. (h/o VTE, cancer, lack of VV)
• Caveat:
  • Fondaparinux 5 times cheaper in Europe

Simple MATH: $750/SVT x 300 SVT = $225,000 to PREVENT 1 PE

The “Rub”:
Even though the relative effectiveness (of fonda) is substantial, the absolute difference b/t drug and placebo was quite modest
Let's make it simple

• SVT is not benign
  • Incidence of VTE is at least 25%
  • With therapeutic anticoagulation, the risk of bleeding is relatively low
• Why are we making the distinction then b/t the Rx of SVT and DVT?
  • Theoretically, wouldn't even need an US!!

Take Home Points

• Despite its prevalence, SVT remains poorly understood.
• SVT's underlying pathophysiology and causes are very similar to DVT
• It appears that SVT carries a real risk of concomitant DVT/PE
  • Think about the "big 4" risk factors...
  • I/e prior VTE; absence of varicose veins; cancer; male gender
• Venous Duplex now recommended in most SVT
• Rule out DVT/determine extent of SVT
• Malignancy does not seem to be as closely a/w SVT when compared to DVT
  • Especially with a single unprovoked event

Take Home Points

• Anticoagulants favored over conservative cares or surgery
• If within 3 cm of the SIJ, Rx exactly the SAME as DVT
• 25% rate of extension in several studies.
• Fondaparinux is the preferred anticoagulant in the Rx of SVT
  • Grade Bb (chest guidelines)
  • Effective... but at what cost to (American) Society?
• IF treating with LMWH...
  • 1. Treat for a minimum of 30 days
  • 2. Intermediate dose superior to prophylactic dose
• As SVT seems to gain an equal footing with DVT, perhaps the treatment should be the same
  • More treatment options, less resource utilization, more cost effective.

Suggested Reading

• General Review

• Association of DVT

• Association of Malignancy

• Treatment

Thank You!