Anticoagulation, Preoperative

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Risk

- Pts with mechanical heart valves, atrial fibrillation, pulm embolism, or recent venous thrombosis.
- Oral anticoagulant therapy (warfarin, oral Xa inhibitor-rivaroxaban, apixaban, and edoxaban) and direct thrombin inhibitor (dabigatran) and use of low-molecular-weight heparin, fondaparinux may increase potential risks in elective or emergency surgery.
- Other populations include pts who receive heparin IV before vascular or cardiac surgery and pts undergoing cardiac surgery with extracorporeal circulation.

Perioperative Risks

- Balance between risk of bleeding versus thromboembolic complication is a major periop risk.
- Risk is greater with major and emergency versus elective surgery.

Worry About

- Excessive allogeneic transfusions, either to correct effects of anticoagulation or for risk of excessive bleeding.
- In pts with valvular heart disease, concomitant hepatic dysfunction due to HF may produce abnormal PT and/or thrombocytopenia.
- Heparin-induced thrombocytopenia can be associated with heparin therapy due to acute administration or prolonged use (~5 d).

Overview

Heparin (Standard Unfractionated)

- For preventive therapy and acute management, cofactor antithrombin III binds to thrombin and factor X to inhibit their effects.
- Variability in response to heparin depends on:
  - Prep of heparin administered.
  - Individual characteristics of pts.
  - Duration of therapy (due to decreased antithrombin III levels).
- Duration of action depends on dose and method of administration.
  - 100 U/kg: $T_{½}$ 56 min.
  - IV: 60 min.
  - 400 U/kg: $T_{½}$ tripled.
  - SQ: 3 h.
- Depolymerized in endothelial cells.
- Eliminated in urine.
- Heparin resistance (many proteins neutralize anticoagulant therapy; prolonged therapy can lower antithrombin III levels).
- Monitoring of the anticoagulant effect: PTT or ACT.

Heparin (LMWH)

- $T_{½}$ 4 to 7 h
- Higher and more predictable bioavailability: 100%
- Removed by renal filtration; accumulates with renal failure
- Not reversed with protamine; no current reversal therapy except time

Heparin Reversal Treatment

- Protamine reversal according to the ratio heparin:protamine 1:1.3 (or start with 50 to 100 mg and check the ACT)
- Monitoring: ACT in cardiac surgery

Warfarin

- Oral anticoagulant.
- Member of the coumarin family.
- Vitamin K antagonist causing inactivation of factors II, VII, IX, and X and anticoagulants C/S.
- Used for thromboembolic complication prevention.
- Peak plasma concentration reached 1-4 h after ingestion.
- $T_{½}$: 36 to 42 h.
- INR required: 2-3.
- Stop for surgery: bridge with heparin, but new data questions this.

Warfarin Reversal Treatment

- Vitamin K: 10-20 mg PO, lower doses IM, or IV, but takes several days for normalization of INR
- Fresh frozen plasma starting with 2 U but higher doses required, Tx reactions common or circulatory overload, and lowest INR ~1.5
- Purified protein concentrates of II, VII, IX, and X with protein C/S (KCENTRA in US); Beriplex and Octaplex outside of US

Novel Agents Approved in Other Countries Not Yet Available in the United States

- Rivaroxaban, apixaban and edoxaban are oral Xa inhibitors.
- Dabigatran is an oral thrombin inhibitor.
- These agents studied in periop DVT prophylaxis and AF treatment.
- For dabigatran reversal, idarucizumab, a monoclonal antibody Rx, at 5 g, completely reverses its effects (Praxbind).
- For Xa reversal, andexanet is under investigation, but growing data about use of PCCs in this setting.

Assessment Points

System	Effect	Assessment by Hx
ENDO	Risk of protamine reactions is 10- to 30-fold higher in diabetics receiving protamine-containing insulin	Hx of insulin use

Key References: Levy JH, Spyropoulos AC, Samama CM, et al: Direct oral anticoagulants: new drugs and new concepts, *JACC Cardiovasc Interv* 7(12):1333–1351, 2014; Douketis JD, Spyropoulos AC, Kaatz S, et al: Perioperative bridging anticoagulation in patients with atrial fibrillation, *N Engl J Med* 373(9):823–833, 2015.

Perioperative Implications

Preoperative Preparation

- Elective surgery/warfarin therapy.
  - Stop warfarin 5 d before surgery.
  - Depending on situation, potentially replace with heparin in checking INR, PTT, and platelet count.
  - Stop heparin a minimum of 2-3 h before surgery.
  - Recent evidence (BRIDGE Trial) suggests that bridge therapy may result in increased bleeding without reduction in thromboembolic benefits in patients on anticoagulant therapy for AFIB.
- Reversal for emergency surgery.
  - Warfarin therapy can be acutely reversed with PCC, and heparin therapy can be reversed with protamine; dabigatran can be reversed with idarucizumab.
- Consider avoiding regional anesthesia.
- Approach anticoagulation reversal cautiously in the anticoagulated patient.

Postoperative Period

- Restart heparin therapy immediately after surgery (PTT, plt count, blood cell count, and bleeding).

Anticipated Problems/Concerns

- Introduction of epidural or spinal anesthesia requires minimum 60-120 min between stopping and restarting heparinization; consider removing cath at least 120 min after stopping heparinization and complete restoration of normal clotting time. Longer times are required with other longer-acting anticoagulation agents.

Antithrombin III Deficiency

Ellise Delphin | Vasanti Tilak

Risk

- Incidence in USA: 1:2000-5000 (may be higher)
- Men and women equally affected and no racial or ethnic difference

Perioperative Risks

- Risk of postop thromboembolic phenomena; 40% to 70%, most common (in descending order): DVT, pulm embolus, mesenteric thrombosis, cerebral venous, and retinal thrombosis; highest risk in those with antithrombin III (AT III) levels <50% of normal
- Risk of pregnancy-related venous thromboembolism may be >50% in untreated pts
- Heparin resistance is common

Worry About

- Hypercoagulable state periop
- Thrombus formation on indwelling cath
- Pulm emboli or DVT with immobility
- Mesenteric, inferior vena cava, or CNS thrombosis
- Withdrawal of warfarin sodium preop, as pts may be heparin resistant
- Timing of neuraxial anesthesia in anticoagulated pts

Overview

- AT III is an α_2-globulin and a serine protease inhibitor, capable of inactivation of thrombin and factor Xa in blood.
  - It has antiinflammatory properties via interactions with the endothelium.
  - AT III deficiency results in an unusual susceptibility to thromboembolic disease.
- Heparin resistance may be problematic during surgery.
- Massive thromboembolism can occur periop with AT III levels <50.

Etiology

- Genetic: Reduced AT III synthesis inherited as an autosomal dominant trait, manifests as thromboembolism in late teens to early 30s
- Acquired: Secondary to consumption of AT III due to massive thromboembolic disease, DIC, renal disease with proteinuria (especially nephrotic

syndrome), chronic liver disease, prolonged heparin therapy, and increased protein catabolism
- Conflicting data about role of oral contraceptive use, pregnancy, and CAD

Usual Treatment

- Medical therapy: LMWH, unfractionated heparin, sodium warfarin, or combination of oral anticoagulants
- Periop: FFP, cryo-precipitate, AT III concentrate (plasma derived or recombinant), and heparin (heparin resistance can be treated with FFP).

Assessment Points

System	Effect	Assessment by Hx	PE	Test
CV	CAD		Angina, dyspnea	ECG, CXR, angiography
PVS	DVT Arterial occlusion		Gangrene, absent pulses	
RESP	Pulm embolus	Dyspnea Exercise tolerance decreased	SOB	CXR V/Q scan
GI	Mesenteric artery/vein occlusion Decreased AT III	Abdominal pain Chronic liver disease symptoms	Rectal bleeding, jaundice, hepatomegaly	Serum albumin, AT III level
HEME	Bleeding and thrombosis	DIC	Petechiae, purpura, thrombosis	FDP, PT, PTT, plt count, AT III level Anti-Xa assay
GU	Decreased albumin and AT III levels	Nephrotic syndrome, proteinuria	Edema	Urinalysis, serum albumin
CNS	CVA	Sudden onset; Hx of other embolic disease	Seizure, loss of vision/motor function	CT scan, angiogram

Key References: Maclean PS, Tait RC: Hereditary and acquired antithrombin deficiency: epidemiology, pathogenesis and treatment options, *Drugs* 67(10):1429–1440, 2007; Paidas MJ, Forsyth C, Quere I, et al: Perioperative and peripartum prevention of venous thromboembolism in patients with hereditary antithrombin deficiency using recombinant antithrombin therapy, *Blood Coagul Fibrinolysis* 25(5):444–450, 2014.

Perioperative Implications

Preinduction/Induction/Maintenance

- Assess whether congenital or acquired; if acquired, treat primary disease if possible.
- Weigh risks of thromboembolic phenomenon versus excessive bleeding.
- Stop oral anticoagulation and substitute FFP or AT III concentrate to bring AT III level to 80% to 120% normal.
- Heparin to provide PTT of >1.5 times control.
- Provide mechanical and pharmacologic thromboprophylaxis.

Monitoring

- Careful attention to temp
- Volume status and resp variables
- PTT, AT III levels, and anti-Xa activity assay

General Anesthesia

- No special concerns with airway, induction, or adjuvant drugs.
- Maintain normothermia to avoid hyperviscosity.
- Maintain intravascular volume.
- IV heparin effect should be monitored.
- Careful evaluations of hypotension or change in $ETCO_2$.

Regional Anesthesia

- Neuraxial techniques require meticulous attention to the timing of
  - Neuraxial anesthesia in relation to the last dose of anticoagulant.
  - First postop dose of anticoagulant in relation to the placement of neuraxial block and/or removal of indwelling cath.
- For plexus and peripheral blocks, follow ASRA guidelines for anticoagulated pts.

Postoperative Period

- Consider ICU for monitoring.
- Continue anticoagulation.
- Early mobilization.
- Remove indwelling cath ASAP.
- Oral anticoagulation might be reintroduced ASAP.

Anticipated Problems/Concerns

- Embolic phenomena can occur intraoperatively
- Monitoring lines may be foci for thrombus formation
- Perioperative thromboembolic events' major concern; continuous anticoagulation is required, as is operative prophylaxis with AT III concentrate (plasma derived or recombinant), FFP, and heparin

Anxiety Disorders

Misako Sakamaki

Risk

- Lifetime prevalence approximately 30% in USA
- Gender: Female (2× more likely compared with male)
- Environmental: Traumatic or stressful events
- Age: Often develop in childhood and early adulthood; however, may occur any time after a stressful event
- Medical conditions: Chronic mental or physical illness
- Genetics: Family psychiatric history

Perioperative Risks

- Generalized anxiety disorder leads to chronic autonomic hyperactivity with increased risks for CAD and Htn.
- Uncontrolled anxiety and fear may predispose pts to greater risk for acute postop pain and postop N/V.
- Increased risk of periop complications due to impaired response to stress.

Worry About

- Inadequately treated anxiety disorders affecting pt's decision-making and communication capacities, which may complicate medical courses
- Altered drug anesthetic requirements and drug metabolisms associated with psychiatric medications
- Systemic side effects from psychiatric medications
- Potential medication interactions with anesthetics
- Signs/symptoms may overlap with other medical conditions (e.g., hyperparathyroidism) and drug-induced causes (e.g., alcohol, caffeine, nicotine, withdrawal), which could be life-threatening.

Overview

- Types
  - Generalized anxiety disorder
  - Panic disorder
  - Social anxiety disorder
  - Specific phobias
  - PTSD
  - OCD
- Characterized by excessive apprehension, physical tension, physiologic symptoms, dissociative anxiety, and fear leading to significant distress or impairment
- Comorbidity with major depression (60%), other mental disorders, and substance abuse
- Associated with a variety of chronic medical conditions

Etiology

- Genetics: ↑ norepinephrine metabolites, ↓ GABA level, ↓ postsynaptic alpha-2 adrenergic receptor sensitivity, and ↓ benzodiazepine binding sites on platelets and lymphocytes; altered central processing involving amygdala and nuclei of basolateral complex that play central roles in fear and anxiety responses
- Stress
- Drugs: Caffeine, alcohol, nicotine, and withdrawals

Usual Treatment

- Lifestyle changes (e.g., regular exercise, reduce caffeine/alcohol/nicotine intake)
- Psychotherapy
- Pharmacotherapy
  - SSRI/SNRI
  - Benzodiazepines
  - Beta-blockers (for phobias)
  - Adjuvants therapy: TCAs, MAOIs, antipsychotics, buspirone, and pregabalin
- Alternative remedies: Kava-kava, valerian root, and passion flower
- Deep brain stimulation (OCD)
- Surgery: Cingulotomy (OCD)