Vitamin K Deficiency

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Risk

- Vitamin K deficiency bleeding (VKDB) from abnormal factors II, VII, IX, and X.
- Controversy exists regarding whether vitamin K deficiency leads to osteoporosis, abnormal cartilage calcification, and possible arterial calcification resulting in CV disease.

Perioperative Risks

- Minor or massive hemorrhage unrecognized as VKDB
- Long-bone fractures during positioning the anesthetized pt (particularly in women)

Worry About

- Underlying risk factors demonstrating unexplained coagulopathy.
- Intracranial hemorrhage in infants (30–60% infants with VKDB) and other occult bleeding sites such as retroperitoneal hemorrhage (more commonly in infants).
- Avoid IM dosing of vitamin K if bleeding is present.
- Anaphylaxis with IV vitamin K replacement (extremely rare).

Overview

- Vitamin K is cofactor for a carboxylase enzyme in the liver, which is essential for normal function of factors II, VII, IV, X and proteins C, S, and Z.
- Coagulopathy manifests as prolonged PT and INR (normal or prolonged aPTT) with normal fibrinogen and factor 5 (both lowered in liver disease and DIC).
- Fat-soluble vitamin K is absorbed in the small bowel and colon and synthesized in gut by bacteria.
- Poor oral intake alone is not sufficient to cause vitamin K deficiency.
- Prevalence is extremely rare in adults with adequate nutrition. Prevalence is as high as 30% in pts with chronic GI disorders. It is more frequent in infancy with classic VKDB occurring in 0–1.5% despite routine prophylaxis.

Etiology

- Inadequate nutrition (often combined with antibiotic therapy)
- Malabsorption diseases (IBD, celiac, short bowel syndrome)
- Total parenteral nutrition
- Parenchymal liver diseases (vitamin K supplementation will not likely correct coagulopathy)
- Biliary diseases
- Drugs (coumadin, salicylates, rifampin, antibiotics, sulfa drugs)
- Hemorrhagic disease of newborn or VKDB
  - Early stage (<24 h): Drugs taken by mother during pregnancy and low placental vitamin K transfer
  - Classic (d 1–7): Inadequate formula intake or breastfeeding only
  - Late (wk to 6 mo): Breastfeeding only or malabsorption disease (most often cholestatic)

Usual Treatment

- Vitamin K can be administered orally, intramuscularly, or through IV, with both route and dosage depending on urgency and degree of coagulopathy.
- Massive bleeding should be treated promptly with FFP, prothrombin complex concentrate (PCC), anti-inhibitor coagulant complex (FEIBA NF), or factor VIIa along with IV administration of vitamin K (most sources recommend an adult dose of 10 mg IV and rarely more than 50 mg in first 6 h).
- Labs for PT, INR, aPTT, fibrinogen, and platelet count should be obtained in urgent situations to determine the etiology of bleeding.
- When vitamin K is administered through an IV, normalization of INR should be noted as soon as 30–120 min and no longer than 12 h. If no correction is noted or there is no improvement in bleeding within 24 h, an alternative etiology other than vitamin K deficiency must be suspected, such as liver dysfunction or DIC.
- In nonurgent settings of prolonged INR without bleeding, other tests available include serum vitamin K level or abnormal prothrombin level (most specific).
- Definitive diagnosis of vitamin K deficiency is made by correction of coagulopathy with vitamin K administration.
- For all routes of administration of vitamin K, sufficient serum vitamin K levels are present within 24 h to reverse coagulopathy in most cases.
- Consider vitamin K therapy in the setting of supratherapeutic warfarin:
  - In the setting of supratherapeutic warfarin therapy and no evidence of bleeding, if INR >9.0 omit next 1–2 warfarin doses and administer 2.5–5 mg oral vitamin K. Oral vitamin K should produce substantial reduction in INR within 24–48 h of administration.
  - For pts with an INR between 5–10 and no evidence of bleeding, provider should hold next warfarin dose and may or may not consider vitamin K administration, oral dose 1–2.5 mg.
  - For pts on warfarin therapy with serious bleeding, administration of 5–10 mg vitamin K IV (over 20–60 min) is appropriate without waiting for lab tests. IV vitamin K should be administered slowly to minimize risk of potential anaphylactic reaction.
  - For life-threatening bleeding in supratherapeutic warfarin pts, at any elevation of INR, or in warfarin-treated pts undergoing emergency surgery, provider should consider PCC, FFP, and/or possibly FEIBA NF. Four-factor prothrombin complex concentrate, or nonactivated PCC (Kcentra), contains the coagulation factors low in warfarin-treated pts including II, VII, IX, and X. PCC, unactivated, rather than FFP, is the recommended therapy by the American College of Chest Physicians. FFP may be considered if PCC is not available or pt is already requiring massive transfusion. Other antifibrinolytic agents may also be considered in this pt population, including tranexamic acid or epsilon-aminocaproic acid or DDAVP for suspected platelet dysfunction. Recombinant activated factor VII is not the recommended therapy for warfarin-associated bleeding, as it does not provide the other affected factors II, IX, and X.

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEME	Insufficient hemostasis, mucosal bleeding, acute or chronic anemia	Bleeding diathesis	Easy bruising, epistaxis, ICH (infants), retroperitoneal bleeding (infants)	Coagulation profile includes PT/INR, aPTT, fibrinogen, Hct, plts
GI/RENAL	Mucosal bleeding, inadequate production of clotting factors, inadequate absorption of vitamins	Inadequate nutrition, parenchymal liver disease, cholestatic disease, malabsorption, bleeding diathesis	Hematuria, GI bleeding, weight loss, jaundice, pale stools, dark urine	Urinalysis, endoscopy
GYN	Mucosal bleeding	Bleeding diathesis	Vaginal bleeding	
METAB/ OTHER		Antibiotic therapy, coumadin, other drugs		

Key Reference: Merli GJ, Fink J: Vitamin K and thrombosis, *Vitam Horm* 78:265–279, 2008; Mansour J, Graf K, Lafferty P: Bleeding disorders in orthopedic surgery, *Orthopedics* 35:1053–1062, 2012.

Perioperative Implications

Preinduction/Induction/Maintenance

- Suspect vitamin K deficiency in pts with underlying risk factors and unexplained anemia, bruising/bleeding, or prolonged PT/INR.
- Providers should have low threshold to correct unexplained prolonged PT/INR with vitamin K supplementation periop. With no signs of bleeding or easy bruising, a 1-mg IV dose of vitamin K is reasonable.
- If VKDB is present, PRBCs and FFP should be available and IV vitamin K should be given concomitantly to promote synthesis of clotting factors. Prothrombin concentrate, though less readily available, is more effective than FFP due to higher concentrations of factors II, VII, IX, and X.
- Large-bore (16 gauge or larger in adults) IV access should be established prior to surgery to allow rapid volume resuscitation in the event of significant hemorrhage.

Monitoring

- Anesthetic monitors recommended depend on degree of coagulopathy and signs of bleeding. Consider Foley catheter and CVP to monitor for volume status, and invasive arterial pressure monitoring to assess beat-to-beat BP during hemorrhage.

General Anesthesia

- Significant coagulopathy can result in easy bleeding with venipuncture, surgical incision, line placement, and airway instrumentation.

Regional Anesthesia

- Prolonged PT and INR precludes neuraxial anesthetic secondary to risk of hematoma and subsequent neurologic injury.
- There is also risk of neuraxial hematoma in the setting of normal preop coagulation parameters in pts who develop vitamin K deficiency in periop period.
- Prolonged PT and INR may result in hematoma formation during plexus anesthesia.

Postoperative Period

- Common setting for unrecognized vitamin K deficient coagulopathy, given inadequate oral intake and aggressive antibiotic therapy.

Anticipated Problems/Concerns

- Oral vitamin K is often ineffective therapy in pts with GI disease or cholestatic disease.
- IV vitamin K should be administered in a diluent such as 0.9% isotonic sodium chloride and administered at a rate no faster than 1 mg/min to reduce the risk of an adverse reaction.
- FFP will only temporize VKDB unless a supplemental source of vitamin K is provided.
- Prolonged PT/INR related to liver disease often will not correct with vitamin K supplementation.

Von Hippel-Lindau Disease

David Hallsworth

Risk

- Rare; approximate incidence is 1:36,000.
- Usually occurs in young adults with complex multiple manifestations.

Perioperative Risks

- Pts with cerebral hemangioblastoma have a 23% incidence of VHLD; assess other systems carefully.

Worry About

- Space-occupying central nervous tumors (retinal and cerebellar hemangioblastomas in 60% of pts).
- Pheochromocytoma (7–20% pts) may be undiagnosed.
- Pregnancy and childbirth may dramatically change disease progression and symptom expression; multidisciplinary involvement essential.

Overview

- VHLD is a complex multisystem disorder, and pts frequently require anesthesia for surgical treatment of tumors and embolizations.
- Most common causes of death are renal cell carcinoma or complications from cerebral hemangioblastomas.

Etiology

- Autosomal dominant with variable expression, due to mutation of a tumor suppressor gene on chromosome 3p25–p26.
- The most common lesions are hemangioblastomas (benign vascular tumors) involving the retina, cerebellum, brainstem, spinal cord, adrenal glands, and kidneys. VHLD is also associated with pheochromocytoma, renal and pancreatic tumors, endolymphatic sac tumors of the middle ear, and papillary tumors of the broad ligament and epididymis.
- Type I pts are less likely to develop pheochromocytoma than type II.

Usual Treatment

- Surveillance and surgical management of tumors with or without radiotherapy.
- Manage active tumors and/or complications of treatment (e.g., pheochromocytoma, diabetes, steroid insufficiency, renal insufficiency).

Assessment Points

System	Effect	Assessment by Hx	PE	Test
HEENT	Retinal hemangioblastomas Glaucoma Hearing loss	Visual loss, blindness	Ocular microscope and pressure testing	Fluorescein angiography
CV	Erythrocytosis	History of venous thromboembolism		Full blood count
RESP	Cystic lung tumor	Chest pain, hemoptysis		CXR, CT
GI	Pancreatic cysts	Abdominal discomfort		US/CT
RENAL	Renal tumors and/or previous nephrectomy			Blood lytes and renal function tests Renal US/CT
ENDO	Pheochromocytoma Adrenal insufficiency due to adrenal resection Diabetes (due to previous pituitary surgery)		Complications of diabetes BP	Urinary catecholamines Plasma metanephrines/normetanephrines, adrenal imaging
CNS	Cerebellar hemangioblastoma Spinal cord hemangioblastoma	Headache, nausea, visual disturbance, motor and sensory deficit	Neurologic examination Ocular signs of raised ICP	CT brain MRI spine
PNS	Nerve root lesions are very rare			
MS	Limb weakness due to CNS tumors		Neurologic examination	

Key References: Plon SE, Jonasch E: Clinical features, diagnosis, and management of von Hippel-Lindau disease. In *UpToDate*, Atkins MB, Firth HV, Perrone RD, et al, editors: *UpToDate*, Waltham, MA (Accessed June 20, 2016); Hallsworth D, Thompson J, Wilkinson D, et al: Intracranial pressure monitoring and caesarean section in a patient with von Hippel-Lindau disease and symptomatic cerebellar hemangioblastomas. *Int J Obstet Anesth* 24(1):73–77, 2015.

Perioperative Implications

Monitoring

- Full invasive monitoring if pheochromocytoma is present or suspected.
- Consider ICP pressure monitoring if pt is symptomatic.

Induction

- Spinal and epidural anesthesia are relatively contraindicated if CNS/spinal tumors are present; discuss with neurosurgeons.

Maintenance

- TIVA has theoretical advantages on cerebral circulation and ICP if cerebral tumors present.

Adjuvants

- Intraop control of blood sugar

Postoperative Period

- May require HDU if complex comorbidity

Anticipated Problems/Concerns

- Surgery for one problem often complicated by other manifestations of the disease