Objectives:
Upon completion, the participant will be able to:

- Name at least 3 things have been identified as risk factors for developing a thrombus & thus requiring anticoagulant therapy
- List 2 adverse reactions that you will monitor the patient for when administering heparin as an anticoagulant to resolve a thrombosis
- List at least 2 lab tests that will be monitored to assure safe & effective anticoagulant therapy
- List at least one other use for the infusion of heparin in the NICU
- Describe at least 2 safety measures that have been implemented in our hospital to enhance the safety of heparin administration
Anticoagulant Therapy in Neonates

Thrombus formation is uncommon in the pediatric population. The most common sites of thrombus formation are the renal vein, the central nervous system, the superior & inferior vena cava and the aorta. Since the formation of a thrombus is rare, it naturally follows that anticoagulant therapy in neonates is uncommon. The use of anticoagulant therapy in neonates is not well studied due to a lack of trails in this vulnerable population and the nature of the therapy. The risk involved and lack of good, sound evidence to support this practice basically adds to the rarity of this therapy. The determination to treat or not to treat is not taken lightly.

The formation of a thrombus is most commonly associated with the following:

- **Risk factors:**
  - umbilical catheters
  - asphyxia
  - sepsis
  - polycythemia
  - hyperviscosity (associated with Infants of Diabetic Mothers (IDM), dehydration, & Congenital Heart Disease (CHD))
  - shock
  - deficiencies in protein C,S,ATIII, factor V Leiden

- **Clinical conditions:**
  - Renal Vein Thrombosis
    - This is associated with IDM, toxemia, maternal thiazide therapy, polycythemia, placental insufficiency, birth asphyxia, prematurity, RDS, & sepsis. The classic presentation includes hematuria, enlarged kidney, thrombocytopenia and hypertension.
  - Renal Artery Thrombosis
    - This is most commonly associated with umbilical artery catheters. The symptoms can include hematuria, hypertension, thrombocytopenia and oliguria.
  - Aortic Thrombosis
    - They present with cool, pale extremities, decreased pulses and capillary refill and upper extremity hypertension.
Once the decision has been made to initiate anticoagulation therapy in neonates, the goals will include:

- Prevention of organ damage related to the formation of a thrombus.
- Preventing the extension of a clot once it has formed.
- Preventing loss of limb related to formation of thrombus and subsequent impaired circulation to the area.

Once a thrombus or clot has formed, consultation with a pediatric hematologist is recommended. Options that can be implemented to treat such a patient include supportive care while the body absorbs the clot, non-specific therapies (such as warming the contra lateral limb), anticoagulants, thrombolytic therapy and surgical removal. Treatment is determined by:

- Assessment prior to determine if the benefits outweigh risks, burden, and costs.
- Evaluating for presence of hemorrhage, particularly in the CNS.
- It is not recommended in infants with platelet counts < 50,000/mm³.
- Anticoagulation therapy is reserved for massive or life-threatening thrombosis with limb or organ compromise.
- Heparin IV or SQ low-molecular-weight form is normally the initial drug chosen.
- Fibrinolytic agents such as recombinant tissue plasminogen activator (r-TPA) can be added to help break up the clot. This is of concern due to potential bleeding complications (15%), & attempts are made to instill the medication locally if the area is accessible.
- Surgical removal is an option for those areas that can be accessed, but often times the patient has been tried on anticoagulants & is at risk to bleed, so the surgical procedure will be delayed until the baby’s bleeding times are stabilized.

Systemic anticoagulation is accomplished by administering heparin. It is difficult to apply adult principles of therapy in neonates because the heparin clearance is accelerated in newborns & the values that are normal for adults are not transferable to the neonatal population.

**Heparin Therapy:**
Heparin is prepared from beef lung or porcine intestinal mucosa. It inhibits the sequence of events that leads to blood clotting by potentiating the action of antithrombin-III, inactivating thrombin,
factors IX, X, XI, XII and plasmin. It also prevents fibrinogen from converting to fibrin. It will prevent clots from forming but cannot lyse clots.

Dosage and administration:
(Neofax)

- 75 units/kg bolus over 10 minutes, followed by 28 units/kg per hour continuous infusion. Four hours after initiating therapy, measure aPTT, then adjust dose to achieve an aPTT that corresponds to an anti-factor Xa level of 0.35 to 0.7 (this is usually equivalent to an aPTT of 60 to 85 seconds). Treatment should be limited to 10 to 14 days. Some experts recommend switching to low molecular weight heparin after 3 to 5 days. For renal vein thrombosis requiring treatment, 6 weeks to 3 months of heparin/low molecular weight heparin therapy is recommended
  - Increase or decrease dose by 5 units/kg/hour depending on the clotting study results
  - Dose requirements decrease as clot dissolves
- Intermittent dosing: 100 units/kg Q 4 hours IV

(Manco-Johnson, M., Rodden D. & Hays)

- Loading dose:
  - Term: 100 units per kilogram IV bolus over 1 minute. No dilution is required.
  - Preterm: 50 units per kilogram IV bolus over 1 minute. No dilution is required
- Continuous infusion:
  - Term: 25 to 50 units per kilogram per hour
  - Preterm: 15-35 units per kilogram per hour

Low-Molecular-Weight Heparin (Enoxaparin)

- 1.7 mg/kg Sub-Q every 12 hour; adjusted to maintain anti-Xa activity
- Level of 0.5 to 1 unit/mL 4 hour after injection

- Duration of therapy: Treatment should be limited to 10-14 days/ continue for 48 hours after clot resolves
- Adjunct therapy with a thrombolytic (TPA) may be more effective

Adverse effects:
- Bleeding events such as pulmonary, GI, CNS hemorrhage and
- Allergic reactions.

Precautions:

- Monitor for adverse effects:
  - Bleeding:
    - Suction cautiously.
      - Be certain that the depth of insertion of the suction catheter does not exceed the length of the ET tube.
      - PEEP can serve as a deterrent to pulmonary hemorrhage if the baby is intubated. The pressure acts to stop the bleeding, similar to maintaining pressure on a bleeding wound externally. It is therefore important not to interrupt the delivery of this pressure exerted on the pulmonary bed by the medical gas unless absolutely necessary.
    - Monitor neurologic status.
    - Monitor for petechiae, bleeding heelsticks or IV sites, & blood in urine, stools or gastric contents.
  - Allergic reaction
    - Monitor for fever, urticaria, and increased liver enzymes.

- Double check all doses/ pump rates with a Pharmacist or another RN
- Antidote: Protamine

Monitor lab results:

- It is recommended that the following be monitored every 4-8 hours after initiating or altering dosage infusing:
  - Platelet count
    - normal values (vary depending on gestational age, chronological age & the reference you cite):
      - VLBW (< 1.5 kg) .... 275,000 +/- 60,000
      - Preterm (< 2.5 kg) .. 290,000 +/- 70,000
      - Term .................. 310,000 +/- 68,000
    - In the presence of infection the platelet count may be low
  - aPTT (activated Partial Thromboplastin Time which uses commercial activating material) or PTT (Partial Thromboplastin Time which uses partial thromboplastin)
    - Evaluates how well the coagulation sequence is functioning by timing clot formation after activating material is added
- Is abnormal in 90% of coagulation defects
- Screens for deficiencies of all factors except VII & XIII
- Times measured to assess therapeutic heparin levels are 60-85 sec for newborns.

- Activated Clotting Time (ACT)
  - Normal values vary according to the system used
  - Measures the ability of the blood to clot once an activator has been added
  - It is more sensitive to the effects of factor VIII deficiency & heparin
  - Used widely during invasive procedures & high-level anticoagulation
  - Can be performed at bedside
  - Titrate drip to maintain ACT at 1.5-2.5 times the baseline values (target 180-250 seconds)

- Periodic assessment of the hematocrit is recommended.

**Reversal with Protamine:**
- Administer 1 mg/ 100 units of heparin given in the last 4 hours (Max 50 mg)
- If it has been some time since heparin administration use smaller dose as heparin has a short half life
  - Give half the dose if it has been 30 minutes
  - Give ¼ the dose if it has been >2 hours
- May need to be repeated
- Give slow IV over 3 minutes to avoid hypotension & anaphylaxis
- Neutralizes heparin within 5 minutes

**Other uses of heparin in NICU:**
Other instances where we use heparin in NICU include the addition of minimal amounts of heparin to promote long life & prevent complications from central lines. This is not anticoagulation therapy.
- We add small amounts of heparin to central lines such as umbilical artery catheters (UAC), umbilical venous catheters (UVC), peripherally inserted central lines (PICCs) & surgically placed central lines such as Broviac catheters.
- The heparin is intended to prevent the formation of fibrin sheaths that can form due to the presence of this foreign object within the body.
- This small amount of heparin added to the IV fluid has demonstrated that it can prolong the usability of peripherally inserted central venous catheters in neonates (Cochrane reviews)
Heparin infusion rate recommended by evidence related to PICC line maintenance: 0.5 units/kg per hour.

**Enhanced Safety**

In a review of medication errors in a large general hospital, pediatric medication errors occurred at a higher rate (5.89 errors per 1000 patients) than in the emergency department and medicine, surgery, and obstetric and gynecology (OB-GYN) units, with dosage calculation errors being the most common problem.

Investigators estimate that 8% of drug doses calculated and administered in NICU are at least 10 times greater or less than the ordered dose.

Another error risk arises from the practice of diluting medications when the desired dose is too small to measure accurately in concentrations that are commercially available.

Safety measures implemented in NICU:

- Ideally all IVF will be prepared in the Pharmacy
- Whenever preparing heparin for administration, the process is verified/double checked by another licensed professional
- Whenever feasible, medications will be prepared in a quiet, undisturbed area such as the medication room
- Heparin flush (1 unit per ml) syringes have been provided pre-made
- We have eliminated access to other strengths of heparin in NICU & the Pharmacy is responsible to prepare anything requiring the addition of heparin
- We have annual competency assessment to assure that the RN has maintained her ability to calculate & prepare medications
References:

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