

VASCULAR SPASM AND THROMBOSIS

Thromboembolism (TE) is being increasingly recognised as a significant complication of intravascular catheters in sick newborn infants.

Definitions

- *Vascular spasm* – transient, reversible arterial constriction, triggered by intravascular catheterisation or arterial blood sampling. The clinical effects of vascular spasm usually last < 4 hours from onset, but the condition may be difficult to differentiate from the more serious TE. The diagnosis of vascular spasm may thus only be made retrospectively on documenting the transient nature of the ischaemic changes and complete recovery of the circulation.
- *Thrombosis* – complete or partial occlusion of arteries or veins by blood clot(s)

Assessment

Clinical diagnosis

- peripheral arterial thrombosis/ vasospasm – pallor or cyanosis of the involved extremity with diminished pulses or perfusion.
- central venous line (CVL) associated venous thrombosis – CVL malfunction, superior vena cava (SVC) syndrome, chylothorax, swelling and livid discolouration of extremity
- aortic or renal artery thrombosis – systemic hypertension, haematuria, oliguria.

Diagnostic imaging

- contrast angiography is the “gold standard”, but difficult to perform in critically ill neonates and requires infusion of radiocontrast material that may be hypertonic or cause undesired increase in vascular volume.
- Doppler ultrasonography – portable, non-invasive, useful to monitor progress over time. False positive and false negative results occur, as compared to contrast angiography.

Additional diagnostic tests

- obtain detailed family history in all cases of unusual or extensive TE.
- in the absence of predisposing risk factors for TE, consider investigations for thrombophilic disorders: anticardiolipin, antithrombin III, protein C, protein S deficiency

Management of vascular spasm

- immediate measures to be taken:
 - lie the affected limb in horizontal position
 - if only one limb is affected, warm (using towel) opposite unaffected leg to induce reflex vasodilatation of the affected leg.
 - maintain neutral thermal environment for the affected extremity, i.e. keep heat lamps away from the area.
- inform the paediatrician immediately.
- consider removing the catheter. If mild cyanosis of the fingers or toes is noted after insertion of an arterial catheter, but peripheral pulses are still palpable, a trial of reflex vasodilatation with close observation is reasonable – check continuously to see that the cyanosis is improving within a few minutes. A white or “blanched” appearing extremity is an indication for **immediate** removal of the catheter.
- other risk factors contributing to thrombosis includes dehydration, sepsis, and polycythaemia. These factors may need to be corrected immediately.
- maintain good circulatory volume. If there is no immediate improvement with removal of catheter, try volume expansion 10 mls/kg of normal saline.

- topical nitroglycerine – using patch or topical 2% ointment at a dose of 4mm/kg body weight, applied as a thin film over the affected body area; may be repeated after 8 hours. Monitor for hypotension and be prepared to treat immediately.
- if the limb ischaemia persists for > 1 hour without any improvement, refer urgently to the radiologist if available. A doppler ultrasound needs to be done urgently to ascertain whether the limb ischaemia is caused by vasospasm or thrombosis.

Management of catheter-related thromboembolism

- management of vascular TE may involve one or more of the following: supportive care, anticoagulation, fibrinolytic therapy, surgical intervention
- treatment for neonates is highly individualised and is determined by the extent of thrombosis and the degree to which diminished perfusion to the affected extremity or organ affects function
- consultation with paediatric haematology, orthopaedic or vascular surgeon may be required
- initial management
 - as for vascular spasm for peripheral arterial ischaemia
 - removal of catheter as soon as blanching is seen
 - supportive care – correct volume depletion, electrolyte abnormalities, anaemia and thrombocytopaenia; treat sepsis
- anticoagulant/ thrombolytic therapy
 - the risk of serious bleeding associated with antithrombotic therapy in neonates must be balanced against the possibility of organ or limb loss or death without appropriate treatment. Adequate randomised trials to guide therapy in neonates are not available.
 - contraindications:
 - major surgery within the preceding 10 days
 - major bleeding: intracranial, pulmonary, gastrointestinal
 - pre-existing cerebral ischaemic lesions
 - relative contraindications –
 - platelet count < 100,000 x 10⁹ /L
 - fibrinogen levels < 100mg/dL
 - severe coagulation factor deficiency,
 - hypertension

Note: anticoagulation/thrombolytic therapy can be given after correcting these abnormalities.

- precautions:
 - no arterial punctures
 - no subcutaneous or IM injections
 - no urinary catheterisations
 - avoid aspirin or other antiplatelet drugs
 - monitor serial ultrasound scans for intracranial haemorrhage
- anticoagulants
 - standard or unfractionated heparin (UFH)
 - anticoagulant, antithrombotic effect limited by low plasma levels of antithrombin in neonates. For dosage see Table 1 below.
 - the optimal duration is unknown but therapy is usually continued for 5-14 days
 - monitor thrombus closely during and following treatment.
 - complications: bleeding, heparin-induced thrombocytopaenia
 - antidote: Protamine sulphate – see Table 2 for dosage

Table 1. Recommended dosing of unfractionated heparin

Stage	Description	aPTT(s)	Bolus (U/kg)	Hold (min)	Rate change (%)	Repeat aPTT
I	Loading dose		75 IV over 10 mins			
II	Initial maintenance dose		28/h			
III	Adjustment	<50	50	0	+10	4 hours
		50-59		0	+10	4 hours
		60-85		0	0	next day
		85-95		0	-10	4 hours
		96-120		30	-10	4 hours
		>120		60	-15	4 hours

A loading dose of 75 U/kg over 10 min followed by a maintenance dose of 28 units/kg (infants < 1 year) is recommended. An aPTT should be checked 4h after the heparin loading dose and 4h after every change in infusion rate. Once the aPTT is in the therapeutic range, a complete blood count and aPTT should be checked daily or as clinically indicated. Abbreviations: aPTT, activated partial thromboplastin time

Table 2. Recommended dosing of protamine for reversal of heparin therapy

Heparin: time since last dosing	Protamine dose
< 30 min	1 mg / 100 u heparin received
30-60 min	0.5 - 0.75 mg/ 100 u heparin received
60-120 min	0.375 - 0.5 mg/ 100 u heparin received
>120 min	0.25 - 0.375 mg/ 100 u heparin received
maximum dose	50 mg
infusion rate	10 mg/ml solution; rate < 5 mg/min

- low molecular weight heparin (LMWH)

- advantages: Subcutaneous administration. Heparin induced thrombocytopenia is rarely associated with LMWH.
- antidote: Omit two doses if an invasive procedure is required. Protamine is partially effective, dosage 1mg/100U heparin given within the last 3-4 hours.

Table 3. Low molecular weight heparin dosing

age	initial treatment dose	prophylactic dose
< 2 months	1.5 mg/kg bd	0.75 mg/kg bd
> 2 months	1 mg/kg bd	0.5 mg/kg bd

Therapeutic dose range may vary from 0.95-3.5mg/kg/bd

Note : LMWH have specific anti-factor Xa activity. Therapy is monitored using anti-FXa and not APTT (aim for anti FXa level 0.5-1U/mL), monitoring 4 h after dosage adjustment; weekly once therapeutic level attained. However, monitoring of anti-FXa levels may not presently be available in most laboratories.

• thrombolytic agents

- consider thrombolytic agents (recombinant tissue plasminogen activator, streptokinase) if there is major vessel occlusion causing critical compromise of organs or limbs
- supplementation with plasminogen (from FFP) enhances the thrombolytic effect
- thrombi already present for several days may be resistant to thrombolysis (failure rates ≈ 50%)
- monitoring
 - monitor fibrinogen levels, thrombin time, plasminogen levels before starting, 3-4 hours after starting and 3-4 times daily thereafter. Stop if fibrinogen < 100 mg/dL
 - imaging studies q4-12 hr to allow discontinuing treatment as soon as clot lysis achieved
 - complications: bleeding, embolisation

Table 4 - Thrombolytic regime in neonate

Drug	IV bolus dose	IV maintenance dose
Streptokinase	1000 units / kg	1000 units / kg / hour
Urokinase	4,400 U/kg over 20 mins	4,400 units / kg / hour for 6-12 hrs
Tissue plasminogen activator	0.5 mg / kg over 10 mins	0.015-0.2 mg / kg / hour (dose for direct infusion into thrombus)

Table 5. Recommendations for management of thrombolytic therapy

Before initiating therapy:

- exclude contraindications
- monitor full blood count, including platelets, fibrinogen
- obtain blood type, cross match
- ensure adequate supply of blood products, cryoprecipitate, aminocaproic acid
- obtain cranial ultrasound
- ensure adequate venous access for infusion and monitoring
- have compresses and topical thrombin ready for localised bleeding

During therapy:

- post sign on bed that patient is receiving thrombolytic therapy
- monitor PT, PTT, fibrinogen level every 4 h during infusion and 4h and 12h after infusion
- daily cranial ultrasound
- maintain fibrinogen > 150 mg/dL with cryoprecipitate (1unit/5kg); expect 20-50% decrease
- maintain platelet count > 100,000 / ml
- no IM injections
- no urinary catheterisation, rectal temperatures or arterial puncture
- minimal manipulation of patient
- avoid warfarin, antiplatelet agents