the children's hospital at Westmeac

HEPARIN INFUSION - CHW

DRUG PROTOCOL©

DOCUMENT SUMMARY/KEY POINTS

- Intravenous heparin is indicated for the initial treatment of venous or arterial thrombosis, and anticoagulation of patients with prosthetic heart valves perioperatively.
- Loading dose is 100 units/kg.
- Usual maintenance dose is 20 – 40 units/kg/hour.
- Heparin therapy is monitored using anti-Xa levels. Specify the anticoagulant being used (unfractionated heparin) on the request form. This is ordered as "anti Xa Unfractionated" on PowerChart, and "Unfract Hep" selected in the dropbox for Type of Heparin.
- Monitoring by anti-Xa is available at all times to patients on ECMO.
- For patients **NOT on ECMO,** monitoring by anti-Xa is available between 8am and 10pm on normal working days (sample **must** be received in the laboratory by 10pm), and between 8am and 3pm (sample **must** be received in the laboratory by 3pm) on weekends and public holidays. Samples received in the laboratory at other times will be analysed only during the listed hours.
- If major haemorrhage occurs, heparin may be reversed using protamine sulphate.

CHANGE SUMMARY

- Due for mandatory review. No major changes.

READ ACKNOWLEDGEMENT

- Clinical staff (medical and nursing) who prescribe heparin and/or administer heparin by infusion should read and acknowledge they understand the contents of this document

Approved by:	SCHN Policy, Procedure and Guideline Committee	
Date Effective:	1st August 2020	**Review Period**: 3 years
Team Leader:	Staff Specialist	**Area/Dept**: Haematology CHW

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1 Introduction

The aim of this drug protocol is to guide the administration of heparin by continuous intravenous infusion for anticoagulant therapy.

2 Indications, Uses and Action

2.1 Indications

- Primary or secondary prophylaxis of thrombotic and thromboembolic disorders[1, 2].

2.2 Common Uses

- Primary prophylaxis
    - Anticoagulation of patients with prosthetic heart valves[1].
- Secondary prophylaxis
    - Initial treatment of venous or arterial thrombosis[1].
    - Initial treatment of pulmonary embolus
    - Arterial/venous obstruction after cardiac catheterisation[1].

2.3 Action

While heparin acts at multiple sites in the normal coagulation system[2], its major anticoagulant effect is by potentiating the activity of antithrombin III by over a 1000-fold; leading to inactivation of thrombin and activated factor X (factor Xa). Inactivation of thrombin, in turn, prevents fibrin formation and also inhibits thrombin-induced activation of platelets and factors V and VIII.[3] Heparin does not have fibrinolytic activity; therefore, it will not lyse existing clots[2].

- Onset of action: Effect begins almost immediately.
- The clearance of heparin is dependent on age and dosage; its clearance is more rapid in young children compared to adults. At the usual maintenance dosages, heparin is cleared and coagulation returns to normal within 1 – 2 hours of ceasing the infusion.
- Metabolism is primarily via the reticuloendothelial system; however, at treatment dosages, renal clearance occurs.[4]

3 Contraindications and Precautions

Contraindications

- Severe thrombocytopenia[2]. Heparin can rarely reduce the platelet count. If it is necessary to administer heparin then a reduced loading and maintenance dose should be given[2]. This should be done in consultation with a Haematologist.
- Uncontrolled active bleeding except when the condition is the result of disseminated intravascular coagulation[2].
- Hypersensitivity to heparin[2].

Precautions

- Haemorrhage can occur at any site in patients receiving heparin[2]. An unexplained fall in haematocrit/haemoglobin or a fall in blood pressure may indicate a haemorrhagic event[2].
- Patients with actual (or potential) bleeding sites, including recent surgical sites, cerebral haemorrhage, oesophageal varices and peptic ulceration, should be observed hourly when administering heparin[2].
- Do not commence intravenous heparin infusion in patients who have had lumbar puncture, epidural insertion or removal, or major surgery (especially surgery to the brain, eye and spine) before consultation between the treating physician or surgeon and a haematologist occurs. These patients should be monitored closely, including neurological observations, if they are receiving heparin infusions[2]. Patients with renal impairment receiving heparin infusions require closer monitoring of anti-factor Xa, seek advice from the haematologist for frequency of testing.
- Consult haematologist to discuss patients with a history of coagulation disorders (thrombosis or bleeding) before commencing anticoagulant therapy
- Discontinue intravenous heparin **at least 2 hours but preferably 4 hours**, prior to invasive procedures, such as surgery, insertion or removal of epidural catheters.

3.1 Special Precautions

- The Haematologist on-call should be informed to plan for initial investigation and monitoring of treatment. Prior to administration, check coagulation screening tests which include FBC (Full Blood Count), APTT (Activated Partial Thromboplastin Time), PT (Prothrombin Time) and fibrinogen level (should be greater than 1.5 g/L)[1, 2].
- Intramuscular injections should be avoided in patients on heparin. Place a sign at the patient's bedside stating: **'No intramuscular injections or arterial punctures'**
- A continuous infusion must be maintained to ensure appropriate anticoagulation in view of the short half-life of heparin. The infusion must not be paused or stopped (or infusion line flushed) just prior to blood collection for monitoring.

4 Adverse Drug Reactions

Heparin has several adverse drug reactions. Some are listed below:

- **Haemorrhage with overdose**: This is a major risk of therapy[1]. Haemorrhage ranges from minor local bruising to major haemorrhagic complications. Prolonged bleeding after procedures, or minor bleeding, can usually be controlled by discontinuing heparin[2]. Significant gastrointestinal/genitourinary bleeding may indicate the presence of underlying abnormality. Adrenal haemorrhage has occurred with resulting adrenal insufficiency[2].
- **Osteoporosis** with long term use has been reported[1, 2].
- **Local irritation may occur at the injection site**. If mild, this is not a contraindication to continuing heparin[2]. However, if **skin necrosis** occurs at the injection site, this may be a harbinger of heparin induced thrombocytopenia (HIT, see below) and the haematologist on call MUST be notified.
- **Generalised hypersensitivity**: Chills, fever and urticaria are the most common signs[2]. Asthma, rhinitis, headache, lacrimation, nausea, vomiting, anaphylaxis and shock rarely occur[2].
- **Hyperkalaemia can occur**: Patients at particular risk are those with diabetes mellitus, chronic renal failure, acidosis, raised plasma proteins and those on potassium sparing drugs. The risk increases with the duration of therapy.
- **Heparin - Induced Thrombocytopenia (HIT)** may occur with prolonged therapy and has been reported in 1-5% of adults. The incidence of HIT in children is very low and has not been fully researched[1,2,7,8]. HIT should be suspected if, whilst on heparin therapy, the platelet count drops significantly OR a new thromboembolic event (arterial or venous) occurs OR skin necrosis at the site of injections occurs. **If HIT is suspected, the Haematologist on-call MUST be notified immediately**.

5 Interactions

Interactions with other medicines

- Platelet and coagulation inhibitors (e.g. aspirin, ibuprofen, warfarin, dabigatran) and fibrinolytic agents (e.g. tissue plasminogen activator, streptokinase) increase bleeding risk in patients receiving heparin infusions[2]. Use of these agents with heparin should be discussed with the haematologist before commencement.
- Digitalis, tetracyclines, nicotine or antihistamines may partially counteract the anticoagulant action of heparin[2].

Compatibility

- Many drugs are not compatible with heparin. Do not mix with other drugs. Contact the Medicines Information pharmacist or your ward pharmacist for more information.
- Heparin should be given through in a dedicated line.

6 Dosage

- Prior to commencement of intravenous heparin, all patients should have baseline full blood count (FBC) and coagulation profile ("coags" including PT, APTT and fibrinogen).

Loading dose	**100units/kg** intravenously over 30minutes
Maximum loading dose according to age: • Children less than 1 year: maximum 1500units • Children 1 year to less than 12 years: maximum 5000units • Children 12 years and older: maximum 10,000units	

- **Starting maintenance dose:**
  - **< 1 year old:** start 30 units/kg/hour
  - **1 - 5 years old:** start 25-30 units/kg/hr. (maximum 1000units/hr)
  - **>5 years old:** 20-25units/kg/hr
  - **Post Pubertal:** 20units/kg/hr
- **Maintenance dose:** usual range is 20 – 40 units/kg/hr.
- In obese children, use ideal body weight and consult closely with Haematology since the actual weight is usually **not** appropriate for dosing calculations.

For patients receiving ECMO consult the ECMO Haemostasis protocol.

7 Preparation

To prepare an intravenous heparin infusion, use the 5000units/5mL ampoules and dilute with a compatible solution. Heparin is compatible with NaCl 0.9% and 5% glucose. Heparin is infused via intravenous infusion pump or syringe pump.

7.1 Loading dose

100 units/kg is equivalent to 0.1mL/kg of 5000 units/5mL heparin solution. Draw up the required volume of solution in a syringe and given intravenously over 30 minutes. This does not need to be diluted but may be diluted for ease of administration with up to 10mL NaCl 0.9%. The heparin loading dose should be prescribed on eMM or on a continuous drug infusion chart (MR44a if electronic system not available).

Loading dose of heparin:

- *Dose:* 100 units/kg
- *Volume of heparin required* (mL):

  = Required dose (units) ÷ Strength of Heparin solution (units/mL)

Example of Calculation for 12 kg child:

(using heparin ampoules with 5000 units in 5 mL)

- Required dose = 100 units/kg **x** 12kg = 1200 units
- Volume of heparin required (mL):

  = 1200 units ÷ 5000 units/5mL

  = 1200 units ÷ 1000 units/mL $\left(= \frac{1200 \text{ units}}{1000 \text{ units/mL}} \right)$

  = 1.2mL

Therefore 1.2mL of 5000 units/5mL heparin solution =1200 units (diluted if necessary)

Administer the loading dose over 30 minutes.

7.2 Maintenance dose

- Intravenous Heparin infusion should be re-prescribed oneMM or on a continuous drug infusion chart (MR44a if electronic system not available) every 24 hours.
- A new intravenous heparin infusion should be prepared every 24 hours.

Intravenous Heparin infusion dilution for maintenance treatment:

Note: *The preferred heparin dilution is 500 units/kg in 500mL (1 unit/kg/mL), whenever appropriate. However, in small children (< 15 kg), patients on fluid restriction or those with multiple infusions e.g. a patient in ICU, a more concentrated heparin solution (10 units/kg/mL) may be used*.

- If 500 units/kg (0.5mL/kg of 5000 units/5mL) is made up to 500mL of compatible solution, the concentration of this solution is 1 unit/kg/mL.
- If 500 units/kg (0.5mL/kg of 5000 units/5mL) is made up to 50mL of compatible solution, the concentration of this solution is 10 units/kg/mL.
- Premature infants and neonates in Grace ward: If 1250 units/kg (1.25mL/kg of 5000 units/5mL) is made up to 50mL of compatible solution, the concentration of this solution is 25 units/kg/mL.

Maintenance heparin dose:

- Usual dose range: 20 – 40 units/kg/hr

Children > 15 kg:

- Add 500 units/kg into 500mL of a suitable solution, so

  1 unit/kg/hr = 1mL/hr

  10 units/kg/hr = 10mL/hr

  25 units/kg/hr = 25mL/hr

Children ≤ 15 kg and for patients requiring fluid restriction:

- Add 500 units/kg into 50mL of a suitable solution, so

  10 units/kg/hr = 1mL/hr

  25 units/kg/hr = 2.5 mL/hr

Example of calculation for 12 kg child with a maintenance dose of 25 units/kg/hr

(using heparin ampules with 5000 units in 5mL)

Making infusion solution:

- Units of heparin required = 500 units x weight (kg)

  500 units x 12kg = 6000 units

- Volume of heparin required (mL):

  = Required dose (units) ÷ Strength of Heparin solution (units/mL)

  = 6000 units ÷ 5000 units/5mL

  = 6000 units ÷ 1000 units/mL $\left(= \frac{6000 \text{ units}}{1000 \text{ units/mL}} \right)$

  = 6mL

Therefore 6mL of 5000 units/5mL heparin solution = 6000 units.

Add this volume of heparin to a suitable solution (see below) to make up a total volume of 50mL (e.g. 44mL of normal saline).

Concentration of solution is 10 units/kg/mL, i.e. 1mL/hr = 10 units/kg/hr

1. *Calculating infusion rate:*

Infusing solution is 1mL/hr = 10 units/kg/hr

Therefore, infusion rate for 25 units/kg/hr = 2.5mL/hr

8 Monitoring

8.1 Observations

- 4th hourly observations – pulse, respirations, temperature and blood pressure (more frequent if condition warrants it).
- Hourly infusion observations.
- Hourly intravenous injection site checks as per Intravenous Cannulation and Venepuncture Procedure.
- Daily urinalysis.
- Neurological observations (as per precautions section) as required for specific patients.
- Report to Medical Officer any evidence of bleeding from any site.

8.2 Laboratory Monitoring

- The anti-factor Xa (anti-Xa) assay is used to monitor the anticoagulant effect of heparin.
- Seek advice from the haematologist on-call for the timing and frequency of testing.
- The blood sample for anti-Xa should be collected peripherally or from a heparin-free line.
- The usual therapeutic range for **anti-Xa is 0.3-0.7units/mL** when unfractionated heparin is used for anticoagulation.
- Seek advice from the haematologist on-call if dosage adjustments are required.
- The anti-Xa assay is available between 8am and 10pm on normal working days (sample **must** be received in the laboratory by 10pm), and between 8am and 3pm (sample **must** be received in the laboratory by 3pm) on weekends and public holidays. For patients on ECMO, more frequent anti-Xa monitoring may be performed including outside of these hours. **Patients NOT on ECMO, whether in PICU or on a general ward, should NOT have anti-Xa levels sent to the laboratory outside of the hours detailed above.** Samples received in the laboratory at other times will be analysed only during the listed hours.
- The anticoagulant being used (i.e. unfractionated heparin) must be specified on the Pathology request. This can be ordered as “anti Xa Unfractionated” on PowerChart, and “Unfract Hep” selected in the dropbox for Type of Heparin.
- After 5 days of treatment the platelet count should be monitored twice weekly.

8.3 Overdose

- Slight overdose can be managed by ceasing the heparin infusion[2,6].
- All cases of severe bleeding should be discussed with the Haematologist on-call.
- In severe bleeding, heparin can be reversed with intravenous protamine sulphate after consultation with the Haematologist.
- Protamine sulphate provides an immediate effect with neutralisation of unfractionated heparin within 5 minutes.
- Protamine sulphate should be used with caution, and administered only after coagulation studies and FBC have been collected[2].
- Excessive protamine sulphate can have an anticoagulant effect.
- Resuscitation equipment should be readily available before administration of protamine sulphate [2]. Protamine sulphate can cause severe hypotension and anaphylaxis[2]. Adverse reactions of protamine sulphate are:
  - hypotension,
  - bradycardia,
  - pulmonary and systemic hypertension,
  - dyspnoea,
  - back pain,
  - nausea and vomiting[2].

Protamine Dose[9]

Time Since Last Heparin Dose (minutes)	**Protamine dose (mg) per 100 units heparin** (per 100units heparin received in the previous **2 hours**)
<30	1
30 - 60	0.5 – 0.75
60 - 120	0.375 – 0.5
>120	0.25 – 0.375

- The maximum dose of protamine sulphate is 50mg per dose (except in cardiopulmonary bypass).
- Protamine sulphate is usually administered at a concentration of 10mg/mL.
- The rate should not exceeding 5mg/minute and should be longer than 10minutes (whichever is slower).
- If administered too quickly it may cause cardiovascular collapse.
- Patients with known hypersensitivity to fish, and those who have received protamine containing insulin or previous protamine therapy are at risk of hypersensitivity reactions.

Obtain blood for PT and APTT 15minutes after the administration of protamine sulphate.

9 References

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