A GUIDE TO USE OF HEPARIN IN

CLINICAL PRACTICE

Authors

Dr Nishadya Ranasinghe
MBBS, Diploma in Pathology, MD (Haematology), FRCPA (Haematology)

Dr Buddhika Badugama
MBBS, Diploma in Pathology, MD (Haematology), FRCPath (Haematology)

Heparin is the most widely used parenteral anticoagulant. It prevents the formation of clots and extension of existing clots within the blood.
Either low molecular weight heparin or standard unfractionated heparin can be used to prevent or treat deep vein thrombosis, pulmonary embolism and arterial thromboembolism.

Unfractionated Heparin (UFH)

Effects of Anticoagulation.
Intravenous (IV) - in 30 min.
Subcutaneous (SC) - in 2 hrs.
Bioavailability – 50% (SC)

Effects wean off in
IV - 45-60 min.
SC - 10 hours.
Clearance – Endothelial cells, platelets (platelet factor 4) & Macrophages

- The anticoagulant response to IV unfractionated heparin varies widely among patients with thromboembolic disease, possibly because of variations in the plasma concentration of heparin-binding proteins.
- UFH treatment required monitoring to maintain the ratio of patient's Activated Partial Thromboplastin Time (APTT) to the mean control APTT within a defined target range of approximately 2.0–3.0.
- Dose adjustment is complicated because unfractionated heparin displays saturation kinetics.

Before treatment, all patients requiring unfractionated heparin should have:

- No allergy or previous history of heparin-induced thrombocytopenia.
- FBC (specially to check baseline platelets)
- Full clotting profile including APTT & PT
- Urea & Electrolytes before starting heparin and then twice weekly if IV unfractionated heparin likely to continue for >7 days or patient has raised baseline serum potassium, diabetes mellitus, chronic kidney disease or acidosis, or is taking a potassium-sparing agent

Low molecular weight Heparin (LWMH)

After SC administration the bio-availability of
LMWH - 90%- 100%
Half-life – IV – 2 hrs.
SC – 4 hrs.
Clearance - renal

Can successfully use once / twice daily without monitoring its action. But Monitoring of anticoagulation action can be done with anti Xa assay.

Monitoring with anti – Xa is required when,

- End stage kidney disease.
- Extremes of body weight.
- Having therapeutic doses during pregnancy.
- Infants & Neonates.
- Those with unexpected bleeding or thrombosis on LMWH.

Sampling

- Fresh citrated blood (sample MUST reach the laboratory within 1 hour of collection)
- Three to four hours post morning dose of LMWH
- Therapeutic level: 0.35 - 0.7 anti-Xa units/mL

Which Heparin to Select

Consider 1) Patient risk (thrombosis or bleeding)
2) Disorder risk.
3) Relative efficacy and bleeding risk.

Indications for parenteral anticoagulation with Heparin

Low dose (Prophylactic) UFH

1) As thromboprophylaxis in major non orthopaedic surgeries.
2) Prevention of clot formation in indwelling arterial and central venous cannulas.
3) DIC and critically ill.

Low dose (Prophylactic) LMWH

1) Major elective orthopaedic surgeries.

2) Hip fractures.

3) Major trauma when not contraindicated by bleeding risk.

4) Immobilization in lower limb plaster casts.

5) Medical patients.
With a hospital stay ≥6 days having Congestive Cardiac Failure (CCF), Acute respiratory failure or having a medical condition prone to VenousThrombo Embolosm (VTE).

6) To prevent Cancer related thrombosis.

7) Sickle cell crisis until recovery.

8) Prevention of pregnancy associated VTE.

9) All acute MI patients.

10) Prevention of clot formation in indwelling arterial and central Venous cannulas.

Therapeutic dose UFH/LMWH

1) DVT and pulmonary embolism.
2) Central venous thrombosis.
3) Mesenteric/ hepatic/portal (not splenic) vein thrombosis.
4) Superficial vein thrombosis.
5) Peripheral vascular reconstructive surgery (Intra op and early post op)
6) Acute critical limb ischemia.
7) Acute coronary syndromes.
8) After thrombolysis (once APTR <2 & Clauss fibrinogen >1.5 after 24 hrs.)
9) Coronary angioplasty (IV UFH before, during and continue up to 24 hrs.)
10) Hemodialysis (UFH 250-1000u/h) until the procedure is Completed.
11) DIC with thrombosis (UFH 5-10/Kg/hr.)

Cautions & Contraindications to Heparin

Relative contraindications:

- Untreated Hemophilia and other hemorrhagic disorders.
- Thrombocytopenia with platelets < 50 $x10^{2.}$
- History of HITT.
- Peptic ulcers, varices, aneurysm, recent organ biopsy,
- Proliferative retinopathy
- Recent cerebral haemorrhage.
- Uncontrolled severe hypertension (SBP >200 mmHg. DBP >120 mm Hg)
- Severe liver disease
- Major trauma, recent brain or eye surgery

- Not in conjunction with spinal or epidural analgesia.

If eGFR is <30 ml/min the anticoagulation of choice would be warfarin or UFH
If LMWH is used suggest 50% of prophylactic dose up to eGFR of 15ml/min with anti FXa monitoring.

<u>Complications of Heparin use</u>:

1) **Bleeding** - Increased age. renal failure, concomitant Thrombolytic therapy, anticoagulants and antiplatelets.

   Reversal - 1mg Protamine Sulphate neutralizes 80-100 U UFH
   Slow administration 1-3 min within 15min of Heparin dose.
   But be aware that protamine carries significant risk of serious adverse drug reactions.
   50mg Protamine Sulphate is enough for most bleeds.

2) **HITT** - Platelet count before starting heparin and then on alternate days from day 5 (day 2 if unfractionated heparin, dalteparin or any other low-molecular-weight heparin given within last 100 days).
   - Suspicious if platelet counts drop 50% of pre-therapeutic count. (Refer to HITT pretest probability scores)
   - Act on suspicion
   - Stop all Heparins including flushes.
   - Send for HITT immunoassay & Optical Density (OD) if the pretest probability score is intermediate or high.
   - Potentially thrombotic situation, platelets are contraindicated unless in the presence of life threatening bleeding.
   - Further anticoagulation – argatroban/danaparoid till the platelets coming up. (monitoring with APTT/Anti Xa against danaparoid curve)
   - Fondaparinux can be used out of license, more convenient SC, Once Daily (OD) weight-based dosing.
   - Once platelets > 150, can use Warfarin.
   - Duration: If associated thrombosis 3 – 6 months. If not 4 weeks.

3) **Osteoporosis** – 2-3% on therapeutic doses >01 month.
(LMWH lower risk than UFH), hence preferred
In pregnancy.

4) **Heparin resistance**
Patients require > 35 000 IU/24 hrs UFH
Dose adjusted to maintain anti Xa 0.35 – 0.70 IU/ml

Management of Thromboembolic Episode with UFH

Collect pretreatment blood for PT/APTT, FBC & U &E s.

Drug Administration

i) IV bolus injection of UFH 5000 IU or 80 IU/Kg over 5 minutes.
ii) Followed by IV infusion 1000 IU/hr or 18 IU/Kg/hr.
iii) APTT should be maintained 1.5 –2.5 times the base line level.

Monitoring frequency:
- Before starting (base line)
- 6hrs after any dose change.
- When steady state is achieved, monitor daily.

02 ways of continuing and monitoring

Once steady state is reached
Can convert to 12 hrly SC
(Amount needed to reach
Steady state in divided doses)
(250 U/Kg/ bd SC)

APTT 4-6 hrs after sc injection
Same time each day.

continue IV infusion
with monitoring of APTT
daily.

Initiation of Treatment – Loading Dose

- Weigh patient.
- give bolus dose of unfractionated heparin (1000 units/mL) 80 units/kg IV Over 5 min (**Table 1**)
- If patient unfit to be weighed, give bolus dose of unfractionated heparin 5000 units (5 mL 1000 units/mL) IV over 5 min.

Table 1

Volume of 1000 units/mL solution required to give loading dose of 80 units/kg												
Weight (kg)	45	50	55	60	65	70	75	80	85	90	95	100
Draw up required mL of heparin and administer IV over 5 min	3.6	4.0	4.4	4.8	5.2	5.6	6.0	6.4	6.8	7.2	7.6	8.0

UFH can be administered in 2 ways:

1) Infusion pump:
   It is the best method to administer UFH infusion and to adjust the dose Accurately.

2) Burette set:
   In restricted resource setting.
   Only to be used in instances where infusion pumps are not available.

Infusion Pump:

The following steps are recommended to make uniform rate adjustments and make it more standardize.

One 5ml vial - 25000IU
Dissolve the amount to be taken to make it up to 20ml.

If the rate is 1000 IU/hr

Take 20 000 IU (4 ml) in to 16 ml Normal Saline.

- (1000 units/ml).
- Take 20 mL unfractionated heparin 1000 units/mL (which therefore contains 20,000 units)
- Add the same volume of sodium chloride 0.9% injection to produce a total volume of 40 mL
- 40 ml - 20000 IU – 20hr.
- 01ml - 500IU - 1 hr
- 02ml - 1000 IU - 1 hr.

- Start infusion dose at 18 units/kg/hr which is equivalent to 0.036 mL/kg/hr (see **Table 2**)
- Check APTT ratio 4 hr (6 hr if no loading dose) after starting infusion and then 4 hr after any dose change
- Adjust rate as dictated by APTT ratio (**Table 3**)
- Patients with renal impairment may have delayed clearance of heparin
- Once APTT ratio lies within target range of 1.5- 2.5, check APTT once daily

Table 2:

Infusion rate of IV heparin 500 units/mL required for a range of body weights to give 18 units/kg/hr												
Weight (kg)	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**
Rate in mL/hr	1.6	1.8	2.0	2.2	2.3	2.5	2.7	2.9	3.1	3.2	3.4	3.6

Table 3: APTT ratio and corresponding change in infusion rate

APTT ratio	Change in infusion rate
>5.00	Stop infusion for 1 hr, then reduce by 1 mL/hr. If infusion rate is ≤1 mL/hr, stop infusion for 1 hr then restart after reducing rate by one-third
4.01–5.00	Reduce by 0.6 mL/hr
3.51–4.00	Reduce by 0.2 mL/hr
3.01–3.50	Reduce by 0.1 mL/hr
2.00–3.00	No change
1.50–1.99	Increase by 0.2 mL/hr
1.20–1.49	Increase by 0.4 mL/hr
<1.20	Increase by 0.8 mL/hr

Burette Set - Volume 150 ml

455ml normal Saline + 25 000 IU (01 vial=5ml) UFH
01ml contains - 50 IU
100ml contains – 5000 IU
20 ml contains – 1000 IU

It is necessary to give,
20 ml in 60 min.

1/3 ml in 1 min.
In burette set 1ml –60 drops.
Therefore should adjust the drip rate to **20 drops/ min to give 1000 IU/hr.**

Algorithm for adjustment of UFH infusion using burette set.

Table 4: APTT ratio and corresponding change in infusion rate

Patient's weight taken around **50 Kg -** 1000 IU/hr.

Burette Set			
APTR	Dose change drops/min	Additional action	Next APTT in (hrs)
<1.2	24 drops/min	Re bolus 80U/Kg 4000 IV	06hrs.
1.2 – 1.5	22 drops/min	Re bolus 40U/Kg 2000 IV	06 hrs.
1.5 – 2.5	No change 20 drops/min		
2.5 –3.0	18drops/min		06 hrs
>3	17 drops/min	Stop infusion for 1hr.	06hrs

Body weights outside this range, the drip rates must be modified, and a weight adjusted dose of 18 IU/Kg/hr should be used.

Table 5: APTT ratio and corresponding change in infusion rate

Calculations for **70Kg** adult. 1250 IU/hr

Burette Set			
APTR	Dose change drops/min	Additional action	Next APTT in hrs
<1.2	31 drops/min	Re bolus 5500IU	6hrs
1.2-1.5	28drops/min	Re bolus 2800IU	6hrs
1.5-2.5	No change 25drops/min		
2.5 -3	22drops/min		6hrs
>3	21drops/min	Stop infusion for 1hr	6hrs

*Take normal Saline 500cc and 1 vial 5ml.(25000IU) UFH

Table 6: APTT ratio and corresponding change in infusion rate

Calculations for **40Kg** person 750 IU/hr

Burette set			
APTR	Dose change drops/min	Additional action	Next APTT in hrs
<1.2	18 drops/min	Re bolus 3000IU	6HRS.
1.2 –2.5	17 drops/min	Re bolus 2500IU	6HRS.
1.5- 2.5	*15drops/min		
2.5-3	13drops/min		6hrs
>3	12drops/min	Stop infusion for 1hr.	6hrs.

*Take normal Saline 500 cc and 1 vial 5ml (25000IU) UFH.

MONITORING

- Platelet count before starting heparin and then on alternate days from day 5 (day 2 if unfractionated heparin, or low-molecular-weight heparin given within last 100 days). If platelet count falls by >50% during heparin therapy, **suspect heparin-induced thrombocytopenia.**
- Monitor for hyperkalaemia U&E before starting heparin and then twice weekly if IV unfractionated heparin likely to continue for >7 days or patient has raised baseline serum potassium, diabetes mellitus, chronic kidney disease or acidosis, or is taking a potassium-sparing agent
- If starting a pregnant woman on IV unfractionated heparin, **contact consultant haematologist to arrange anti-Xa monitoring**

HEPARIN REVERSAL

- In the event of bleeding associated with unfractionated heparin therapy, protamine can be given to reverse the anticoagulant effect but be aware that protamine carries significant risk of serious adverse drug reaction.

- **Contact Consultant Haematologist for advice if necessary.**

IV unfractionated heparin is supplied in various concentrations. Check concentration carefully to avoid risk of overdose and death due to over anticoagulation.
IV heparin therapy without strict monitoring as stated above carries high risk of bleeding. Warn all staff members involved when patient on IV heparin infusion

Management of Thromboembolic Episodes with LMWH

Table 7

	Prophylactic Dose<50Kg	Prophylactic dose >50Kg	High Prophylactic dose	Therapeutic dose
Daltaparin (Fragmin)	5000IU/d	5000IU/d	5000 IU/bd	100 IU/Kg/bd Or 200IU/Kg OD ***
Enoxaparin (Clexane)	20mg/d	40mg/d	40mgbd	1mg/kgbd 1.5mg/kgdaily
Tinzaparin (Innohep)	3500u/d	4500u/d	4500u bd	90u/kg/bd 175u/kg/daily

*** Total dose can be used once daily (OD) if it does not exceed 18 500 IU.

Use of Heparin in thrombocytopenia with recent VTE

>50 - Therapeutic dose
50 - 30 - Prophylactic dose
< 30 - Do not use /Under cover of platelet transfusions

Obese patients,
The dose of LMWH is based on their actual body weight (and not capped at 18,000 U/day)

Renal impairment

- Different low molecular weight heparins have different pharmacologic characteristics and are not equal
- Patients with renal impairment given LMWH require careful assessment for potential bleeding risks and observation for signs and symptoms of bleeding

- Data on the use of LMWH in patients with CrCl less than 20 mL/min and hemodialysis are very limited
- CrCl should be estimated using the Cockcroft-Gault equation in all patients who are prescribed LMWH. The use of estimated GFR for dosing calculations should be avoided
- Extended use (>7 days) of enoxaparin in patients with moderately impaired renal function (CrCl 30–60 mL/ min) requires anti-Xa measurement, close vigilance and adjustment of dose if accumulation is noted

Prophylaxis Doses

- For patients with mild-to-moderate renal impairment (CrCl 30–90 mL/min), adjustment of prophylaxis doses of LMWH is generally not needed
- In severe renal impairment (CrCl <30 mL/min)

When using enoxaparin for prophylaxis, consider a lower dose of 30 mg subcutaneously once daily

When using dalteparin dose adjustment is not be needed with short-term use (<7 days)

For longer-term use, consider monitoring of anti-Xa activity and adjust dose if accumulation is noted

Treatment Doses

- Mild-Moderate renal impairment (CrCl >30ml/min)

Treatment dose of LMWH does not require dose adjustment in patients with mild-moderate renal impairment. Careful clinical monitoring is recommended. Monitor renal function and adjust dose if worsening renal function. Consider alternative if high risk of bleeding

- Severe Renal Impairment (Cr Cl <30ml/min)

Clinical data on adjusted doses of LMWH is limited in patients with severe renal impairment. If no alternative preferably use enoxaparin

Enoxaparin VTE treatment dose in patients with severe renal impairment: 1mg/kg SC OD

No specific dose adjustment recommendation can be made for dalteparin or tinzaparin. Some hospital protocols give 60% of licensed dose in two divided doses. If used > 7 days, monitor anti-Xa levels

References:

1. T. Baglin, T. W. Barrowcliffe, A. Cohen and M Greaves for the British Committee for Standards in Haematology Department of Haematology, Addenbrookes NHS Trust, Cambridge, UK 'Guidelines on the use and monitoring of heparin' JAN 2006 British Society for Haematology, Volume 133, Issue 1, pp. 19–34.

2. Hirsh J1, Guyatt G2, Albers GW3, Harrington R4, Schünemann HJ5, ' Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)', Chest. 2008 Aug; 134(2):473.

3. Kearon C1, Akl EA2, Comerota AJ3, Prandoni P4, Bounameaux H5, Goldhaber SZ6, Nelson ME7, Wells PS8, Gould MK9, Dentali F10, Crowther M11, Kahn SR12.' Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines.' Chest. 2012 Dec; 142(6):1698-1704.

4. FACP Rodger L. Bick, Departments of Medicine and Pathology, University of Texas South-western Medical Centre, Dallas Thrombosis Haemostasis Clinical Centre, 10455 North Central Expressway, Suite 109, PMB 320, Dallas, TX 75231, USA 'Antithrombotic Therapy: Current Practice and Future Trends' February 2005Volume 19, Issue 1, Pages xi–xvi.

5. M. Valgimigli, E. Frigoli, S. Leonardi, M. Rothenbühler, A. Gagnor, P. Calabrò, S. Garducci, P. Rubartelli, C. Briguori, G. Andò, A. Repetto, U. Limbruno, R. Garbo, P. Sganzerla, F. Russo, A. Lupi, B. Cortese, A. Ausiello, S. Ierna, G. Esposito, P. Presbitero, A. Santarelli, G. Sardella, F. Varbella, S. Tresoldi, N. de Cesare, S. Rigattieri, A. Zingarelli, P. Tosi, A. van 't Hof, G. Boccuzzi, E. Omerovic, M. Sabaté, D. Heg, P. Jüni, and P. Vranckx, for the MATRIX Investigators*' Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes', , New England Journal of Medicine, vol. 373, no. 11, pp. 435-439.

6. Marotti, Sally B. MClinPharm, FSHP, CGP; Barras, Michael GDipClinPharm, PhD; Kirkpatrick, Carl BPharm(Hons), PhD,' Comparison of 2 Weight-Based Heparin Dosing Nomograms in Neurology and Vascular Surgical Patients' Therapeutic Drug Monitoring: February 2015 - Volume 37 - Issue 1 - p 33–39

7. Blood coagulation & fibrinolysis: an international journal in haemostasis and thrombosis, Dec 2014, vol. 25, no. 8, p. 838-844

8. NICE guidance CG 144, CG 92