CLINICAL GUIDELINE

Guideline for Prophylactic Anticoagulation

Southern African Society of Thrombosis and Haemostasis

Introduction. Prophylactic anticoagulation in South Africa is unfortunately under-prescribed. This has led to unacceptable mortality and morbidity in numerous patients.

Method. The Southern African Society of Thrombosis and Haemostasis held two meetings at which all the available literature as well as guidelines from other societies were reviewed. The specialties represented on the committees included Anaesthetics, Cardiology, Clinical Haematology, Critical Care, Gynaecology, Haematopathology, Internal Medicine, Neurology, Orthopaedic Surgery, Pulmonology and Vascular Surgery. A draft document was presented at both meetings, which was altered by consensus agreement. The guidelines were adjudicated by a recognised external international expert to avoid local bias.

Results and conclusion. A guideline for prophylaxis in medical and surgical patients has been produced for the South African situation. It is hoped that this will lead to improved anticoagulation practice in this country, which we believe will directly benefit patient outcome.

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1. Medically ill patients

1.1 Background

In the absence of anticoagulation, the risk of deep-vein thrombosis (DVT) in medically ill patients is comparable to that observed in surgical patients (10 - 20%). While the clinical significance of asymptomatic distal DVT is debatable, pulmonary embolus (PE) is the commonest preventable cause of death in hospital patients, contributing 10% of all hospital deaths. Three-quarters of these deaths occur in medically ill patients. The efficacy of heparins in preventing venous thrombo-embolism (VTE) in medically ill patients is now well established. However, their use is associated with an increased risk of major bleeding episodes and this should be balanced against the thrombotic risk.

1.2 Definitions

1.2.1 High-risk conditions

- Severe cardiopulmonary disease (particularly cardiac/respiratory failure)
- Nephrotic syndrome
- Diabetic keto-acidosis
- Stroke, acute myocardial infarction (in these conditions prophylactic anticoagulation may be altered by concomitant therapy and should be assessed individually — separate guidelines will be developed for these)
- ICU patients
- Certain thrombophilic states (antithrombin/protein C/protein S deficiency, antiphospholipid syndrome)
- Inflammatory bowel disease
- Pregnancy.

1.2.2 Associated risk factors

- Age > 60 years
- Past history of VTE
- Underlying malignancy
- Obesity
- Prolonged immobility
- Oestrogen replacement therapy
- Any underlying thrombophilic states.

1.3 Recommendations for prophylaxis

The recommended prophylactic doses for low-molecular-weight heparins (LMWHs) are as follows:

- Enoxaparin 40 mg (4 000 U) subcutaneosly (s.c.) daily
  OR
- Nadroparin 0.3 ml (2 850 U) s.c. daily
  OR
- Dalteparin 0.2 ml (5 000 U) s.c. daily.

LMWH should be given to all bedridden medically ill patients with:

- Conditions associated with a high risk of thrombosis (see above)
  OR
- Other medical conditions (such as acute infections or acute rheumatic disease) with at least one associated risk factor.
  Note: Prophylaxis is not required for patients who are mobile.
- In patients at high risk of bleeding, the use of mechanical

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prophylaxis such as graduated compression stockings or intermittent pneumatic compression (IPC) should be considered as an alternative if the thrombotic risk is high (grade 3 recommendation).
- These guidelines do not supercede registered Medicines Control Council indications. It is the responsibility of the pharmaceutical companies to obtain registration for specific indications.

1.4 Monitoring (see 'General considerations in use of LMWH')

2. Surgical patients

2.1 Background

VTE is an important cause of morbidity and mortality in surgical patients. However, the relative risk of developing VTE varies between patients and some measure of risk assessment is required for appropriate selection of patients for prophylaxis. These guidelines attempt to simplify risk assessment models that are often too complicated for routine use.

Both patient-related and procedure-related risk factors should be considered.

2.1.1 Patient-related risk factors for VTE

- Age > 60 years
- Previous history of VTE
- Immobility
- Underlying malignancies
- Pregnancy
- Oestrogen replacement therapy
- Obesity
- Underlying hereditary thrombophilic state
- Underlying inflammatory bowel disease.

2.1.2 Procedure-related risk factors

- Duration of procedure
- Degree of tissue damage (orthopaedic/trauma surgery carry the greatest risk)
- Degree of immobility following surgery
- Nature of surgical procedure (e.g. lower limb orthopaedic surgery, neurosurgery, etc.)

2.2 Recommendations for prophylaxis

2.2.1 Patients undergoing low-risk procedures (minor surgery) with no patient-related risk factors

- No specific prophylaxis is required
- Early mobilisation is recommended.

2.2.2. Patients undergoing higher risk procedures (major surgery) with no patient-related risk factors OR patients undergoing low-risk procedures with additional patient-related risk factors

- Enoxaparin 40 mg (4 000 U) s.c. once daily (o.d.)
  OR
- Nadroparin 0.3 ml (2 850 U) s.c. o.d.
  OR
- Dalteparin 0.2 ml (5 000 U) s.c. o.d.

This prophylaxis should be given 2 hours before surgery and once daily postoperatively (see notes on 'Timing of prophylaxis').

IPC may be an acceptable alternative, particularly if minor bleeding is likely to be harmful or other factors suggest an increased bleeding risk.

2.2.3 Patients undergoing higher-risk procedures (major surgery) with additional patient-related risk factors OR patients undergoing very high-risk procedures (orthopaedic or trauma surgery)

- Enoxaparin 40 mg (4 000 U) s.c.
  OR
- Dalteparin 5 000 U s.c.
  OR
- Nadroparin, dose adjusted according to the manufacturer's guidelines (weight-adjusted prophylaxis is definitely indicated in very high-risk patients).

Prophylaxis should be given 12 hours before surgery and daily after surgery (see notes on 'Duration of prophylaxis').

Consideration should be given in these patients to additional use of mechanical measures (graduated compression stockings or IPC).

2.3 Timing of prophylaxis

This is extremely controversial.
- Data are available confirming the benefits of prophylactic anticoagulation initiated pre-operatively.
- European guidelines advise that a dose be given 2 hours pre-operatively in most cases. If procedure-related intra-operative bleeding is expected to be a problem, a 50% reduced dose given 12 hours pre-operatively or within 6 hours post-operatively is acceptable.
- In patients at high risk of bleeding or undergoing regional anaesthesia (see section 3 below) anticoagulation should be avoided for 12 hours prior to surgery.
- Not all experts agree that pre-operative dosing is essential and it seems that 6 hours postoperative will become the preferred method.

2.4 Duration of prophylaxis

- LMWH prophylaxis should be continued until the patient is *fully* mobile.
- For major surgery in patients with additional risk factors or very high-risk procedures (major orthopaedic surgery) at least 7 - 10 days of prophylaxis is indicated.

- Extended out-of-hospital prophylaxis (up to 1 month) with LMWH or warfarin started immediately postoperatively and adjusted to maintain INR 2 - 3 has been shown to provide additional benefit.

2.5 Monitoring of LMWH (see 'General considerations in use of LMWH')

3. Recommendations with reference to centroneuraxial blockade (spinal and epidural anaesthesia)

- A catheter should not be placed or removed within 10 - 12 hours following a dose of LMWH.
- LMWH should not be commenced within 2 hours of insertion or removal of a neuraxial catheter.
- LMWH should be delayed at least 24 hours if there is blood in the needle or neuraxial catheter during needle insertion.
- Neurological monitoring is mandatory for a minimum of 12 hours after neuraxial blockade in association with anticoagulation.
- Extreme caution should be exercised in patients on other agents such as aspirin and non-steroidal anti-inflammatory agents that interfere with normal haemostasis.

4. Recommendations with reference to prophylaxis in pregnancy

- In healthy pregnant women undergoing a procedure (e.g. caesarean section) under centroneuraxial blockade with no specific risk factors, it is recommended that non-pharmacological methods and early mobilisation be practised.
- In pregnant women with risk factors for thrombosis (e.g. obesity), LMWH prophylaxis is safe for the mother and fetus and can be used as described above.

5. General considerations in use of LMWH

5.1 Management of bleeding patients

- Do not use prophylaxis if there is severe bleeding.
- Discontinue LMWH as well as any other haemostatically active agents that may contribute to haemorrhage.
- Supportive care includes transfusion of blood products.
- Measurement of anti-Xa levels may be indicated.
- Protamine sulfate is effective in neutralising the antithrombin activity of LMWH but has limited effect on the anti-Xa activity. Protamine sulfate should be considered if bleeding is severe.
- A dose of 1 mg protamine sulfate should be given for every 100 anti-Xa units of LMWH (1 mg enoxaparin is equivalent to 100 anti-Xa units, hence 40 mg protamine sulfate should be administered to 'reverse' the effect of 40 mg enoxaparin.
- If required, a repeat dose of 0.5 mg protamine sulfate per 100 anti-Xa units of enoxaparin can be given for a maximum of two additional doses.

5.2 Monitoring of patients on LMWH

- The patient's platelet count should be checked on initiation of LMWH, after 5 days, and thereafter not less than once every 3 months, while on therapy.
- Anticoagulant activity is measured using an anti-Xa activity assay.
- Anti-Xa measurement is only indicated in pregnancy, in renal failure or in excessively obese patients in whom large doses are required.
- The anti-Xa assay must be calibrated for each LMWH tested.
- The anti-Xa assay is currently available for enoxaparin and nadroparin at the Johannesburg Hospital Haematology Laboratory ((011) 488-3068 or (011) 489-8552).
- 5 ml citrated blood taken 3 hours after a LMWH dose is required for the assay.

5.2.3 Target levels

- Prophylaxis target is 0.3 - 0.5 anti-Xa U/ml of blood.
- Therapeutic target is 0.6 - 1.0 anti-Xa U/ml of blood.

6. Treatment of venous thrombo-embolism (VTE)

6.1 Initiation of anticoagulation

LMWH offers definite advantages over unfractionated heparin in terms of convenient dosing, no need for monitoring and the possibility of outpatient management. It may also result in a reduced risk of recurrence. The guidelines below pertain to the use of LMWH.

- Enoxaparin 1 mg/kg s.c. twice daily (b.d.)
  OR
- Nadroparin weight adjusted 0.1 ml/10 kg s.c. b.d. (according to manufacturer's guidelines)
  OR
- Dalteparin 100 U/kg s.c. b.d.
  should be given for at least 7 days.
- Warfarin should be started at a dose of 5 mg p.o. daily from day 2 of anticoagulation. The practice of giving a 'loading dose' has been discontinued.
- The INR should be measured 2 - 3 days after starting warfarin and then daily with dose adjustments to achieve a therapeutic range of 2 - 3 (for most indications).
- LMWH must be given for at least 7 days even if the INR has reached therapeutic level.
- LMWH can be discontinued once the INR has been in the

therapeutic range for 2 consecutive days.
- For massive thrombosis or pulmonary embolism LMWH should be given for at least 10 days.
- For massive pulmonary embolism, thrombolytic therapy should be initiated.

6.2 Duration of oral anticoagulation

This needs to be individualised according to the patient's thrombo-embolic risk level and only basic recommendations are given.
- Patients with reversible or time-limited risk factors should be treated for at least 3 months.
- Patients with idiopathic DVT and all patients with PE should be treated for at least 6 months.
- Patients with recurrent idiopathic VTE, continuing risk factors, life-threatening event or thrombosis in an unusual site will probably benefit from longer duration anticoagulation, probably lifelong in some patients. However, this needs to be individualised and consideration should be given to the ability of both the prescribing physician and the patient to maintain a stable INR.
- Underlying antithrombin deficiency, antiphospholipid syndrome or malignancy carry the highest risk of relapse, and lifelong anticoagulation as secondary prophylaxis should be considered in these settings. The presence of multiple concurrent risk factors also significantly increases the risk of recurrence. (*Note*: The presence of heterozygous factor V Leiden or the prothrombin 20210A mutation is not an independent risk factor for recurrence and is not an indication for long-term anticoagulation following a first event.)

6.3 Thrombophilia screening

- The presence of an underlying hereditary thrombophilic state does not alter initial management and thrombophilia screening should be delayed until 2 weeks after discontinuation of therapy as the results are altered by the acute event and by anticoagulant therapy.

6.4 Outpatient management

Management of VTE in the outpatient setting is safe and cost-effective provided that:
- The patient is able to understand and administer therapy himself/herself
- The patient is able to attend regular follow-up
- There are no complicating factors (for example an increased bleeding risk)
- There is adequate compression treatment (with surgical stockings).

6.5 Management of non-therapeutic INRs

This should be individualised according to bleeding risk. The following are general guidelines.

6.5.1 INR > 3 < 5, no significant bleeding

- Omit warfarin
- Re-start lower dose once the INR is in the therapeutic range.

6.5.2 INR > 5 < 10, no significant bleeding

- Omit warfarin
- Monitor INR daily until back in the therapeutic range
- Restart warfarin at a lower dose
- Consider low-dose oral vitamin K if INR remains prolonged.

6.5.3 INR >10, no significant bleeding

- Stop warfarin
- Give vitamin K 2 mg orally
- Monitor INR daily until in the therapeutic range (repeat vitamin K as required)
- Restart warfarin at a lower dose.

6.5.4 Patients with significant bleeding

- Stop warfarin
- Give fresh-frozen plasma (FFP) at a dose of 15 ml/kg or prothrombin complex concentrate (if the bleeding is life threatening)
- Give vitamin K 1 mg slowly intravenously.

Special caution should be exercised when reversing anticoagulation in patients with prosthetic heart valves.

7. Bibliography

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8. Southern African Society of Thrombosis and Haemostasis

The Southern African Society of Thrombosis and Haemostasis (SASTH) is a scientific and educational organisation aiming to bring together clinicians and scientists in a broad array of disciplines dealing with thrombosis, haemostasis and vascular biology. The objectives of the Society are:

- To promote the acquisition, dissemination, exchange and application of knowledge in thrombosis, haemostasis and vascular biology.
- To identify thrombosis and haemostasis problems affecting populations in southern Africa, the African continent and the rest of the world.
- To provide a forum for the discussion of these problems through scientific meetings and publications.
- To promote and enhance multidisciplinary research and scientific enquiry into these problems.
- To develop, standardise and critically evaluate new and existing diagnostic tests, instrumentation and reagents used in thrombosis, haemostasis and vascular biology.
- To synthesise and evaluate evidence-based and consensus guidelines for the management of thrombotic and bleeding disorders.
- To encourage and promote collaborative activities among Society members as well as with other national and international organisations.
- To provide a translational environment that supports and fosters outstanding clinical care for South Africans with thrombotic and haemostatic disorders.

This guideline was written by a multidisciplinary committee comprising specialists throughout South Africa who have an interest and expertise in their particular specialties pertaining to prevention of VTE. The purpose of the guideline is to provide a practical approach for all relevant practitioners and thereby decrease the incidence of VTE in South Africa.

8.1 Executive Guidelines Committee

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