



GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH HAEMOPHILIA UNDERGOING SURGICAL PROCEDURES

Australian Haemophilia Centre Directors'
Organisation

July 2005

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's expert judgement and the patient's preference in each individual case. The guidelines are designed to provide information to assist decision-making and are based on consensus opinion at the time of compilation (July 2005).

These guidelines will be reviewed in 2008.

Users of these guidelines are encouraged to contact the Australian Haemophilia Centre Directors' Organisation if they have comments to make. These comments will inform the revision process.

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Introduction

The Guideline for the Management of Patients with Haemophilia Undergoing Surgical Procedures has been developed by the Australian Haemophilia Centre Directors' Organisation (AHCDO). The guidelines have drawn on past Australian guidelines [1], recent NBA sponsored evidence based guidelines [2] and local and international evidence [3, 4, 5] and practice [6].

1 General principles

There are several important considerations regarding therapy for the haemostatic management of patients with haemophilia undergoing surgical procedures:

1.1 General Considerations

- Episodes of bleeding in people with haemophilia require replacement therapy or treatment with desmopressin (DDAVP) if applicable.
- An accurate diagnosis of the type of bleeding disorder and knowledge of the baseline levels of factor VIII and factor IX are essential.
- Factor therapy must be administered promptly in doses adequate to control bleeding and continued for sufficient duration to ensure that haemostasis or wound healing is complete.
- Adequate levels of clotting factor must be achieved in the patients plasma for the duration of any interventional surgical procedure or invasive dental treatment
- The presence of an inhibitor must be excluded before undertaking any surgery or dentistry in people with haemophilia.
- Surgery should only be undertaken if adequate supplies of factor replacement are available for a full course of prophylactic treatment.
- Surgery should be undertaken in a hospital associated with a Haemophilia Treatment Centre whenever possible, or else in close consultation with a haematologist in a Haemophilia Treatment Centre.

1.2 Coagulation Factor Replacement Products Available in Australia as at July 2005

Table 1 Main Coagulation Factor Products for Haemophilia in Australia

Product	Trade Name	Manufacturer	Available under NBA contract
FVIII Recombinant	Recombinate	Baxter	Yes
FVIII Recombinant	Kogenate	Bayer	No
FVIII Recombinant	Refacto	Wyeth	No
FVIII Recombinant	Advate	Baxter	No
FVIII Plasma	Biostate	CSL	Yes
FIX Recombinant	BeneFix	Wyeth	Yes
FIX Plasma	MonoFIX	CSL	Yes
FIX Plasma (PCC)	Prothrombinex HT	CSL	Yes
FVIIa	NovoSeven	Novo Nordisk	Yes

For a full list of coagulation factor replacement products refer to 'Guidelines on therapeutic products to treat haemophilia and other hereditary coagulation disorders in Australia' [7].

Haemostasis in patients with haemophilia undergoing surgical interventions can often be supplemented with tranexamic acid. Desmopressin (DDAVP) may have a role in patients with mild haemophilia and some symptomatic carriers.

1.3 Pharmacological Principles

The in vivo recovery and half life of factor VIII and factor IX need to be considered in dosage calculations of these products. Table 2 gives indicative ranges.

Table 2 Recovery and Half-life for Factor VIII and IX products [8-11]

	Adjusted Recovery*	Half-life Adult (hr)	Half-life Paediatric (hr)
Recombinant FVIII	0.9-1.0	14.6	8-12
Plasma-derived FVIII	1.0	11-15	8-12
Recombinant FIX	0.35-0.4	16-18	14-18
Plasma-derived FIX	0.45-0.5	16-18	14-18

* Adjusted Recovery – Factor rise (IU/dL) per infusion (IU/kg)

1.4 Dosage Calculations

Factor VIII

Based on recovery data it is expected that one International Unit (IU) of FVIII per kilogram body weight (IU/kg) will result in an increase of recombinant factor VIII concentration in the recipient's plasma of 1.8-2.0 IU/dL (sometimes referred to as 1.8-2%). The rise when using plasma-derived FVIII is expected to be 2 IU/dL. This can be represented by the formula:

$$\text{FVIII dose (IU/kg)} = (\text{desired rise in FVIII IU/dL}) \div 2$$

Example. To increase the factor VIII from 0 to 80 IU/dL, as might be required for a surgical procedure in a patient with severe haemophilia A, the factor VIII dose will be $80 \div 2 = 40$ IU/kg

Factor VIII Continuous Infusion

Continuous infusions provide improved coagulation factor cover, are associated with improved bleeding outcomes and may use less coagulation factor than bolus regimes. After an initial bolus injection of FVIII, an infusion is started to maintain coagulation factor levels at 70-100%, according to the following formula:

$$\text{Infusion rate (IU/kg/h)} = \text{clearance (mL/kg/h)} \times \text{steady state concentration (IU/mL)}$$

Clearance can be calculated from pre-operative pharmacokinetic studies which can be used to guide initial infusion rates over several days.

Alternatively, an infusion rate of 4.0-5.0 IU/kg/h will produce a FVIII level of approximately 80 IU/dL.

Factor IX

Based on recovery data it is expected that one IU of FIX per kilogram body weight (IU/kg) will result in an increase of recombinant factor IX concentration in the recipient's plasma of 0.85 IU/dL (sometimes referred to as 0.85%). The rise when using plasma-derived FIX is expected to be 1 IU/dL. For recombinant FIX, this can be represented by the formula:

$$\text{FIX dose (IU/kg)} = (\text{desired rise in FIX IU/dL}) \div 0.85$$

Example. To increase the factor IX from 0 to 50 IU/dL, as may be required for a patient with severe haemophilia B undergoing dental extraction, the factor IX dose is $50 \div 0.85 = 59$ IU/ kg.

2. Surgical Management

Surgical intervention in the person with haemophilia may be elective or occasionally of an emergency nature. By its nature, emergency intervention may need to be undertaken when conditions and coagulation factor availability are less than optimal. In these circumstances, if great care is taken with haemostasis and minimal haemostatic levels are achieved by coagulation factor replacement, then the patient's chances are better than if a non-intervention policy is pursued in surgical emergencies. Whenever possible, the patient should be transferred to a Haemophilia Treatment Centre.

2.1 Planning for Surgery

Planning is important and adequate amounts of coagulation factor replacement should be available. If the bleeding risk is very high, elective surgery should be postponed. Anti-platelet agents should be avoided peri-operatively. Major surgery in an adult with an average weight of 70kg, with severe haemophilia A when intermittent therapy is employed will generally require between 50,000 and 80,000 units of factor VIII.

It is imperative when surgery is undertaken that there is co-operation and communication between the treating haematologist, surgeon, anaesthetist, and the suppliers of factor VIII or factor IX concentrates. Planning should also involve assessment for presence of inhibitors and dose calculations which may include pre-operative pharmacokinetic studies. Although these pharmacokinetic studies are not mandatory they may be helpful in selected cases.

2.2 Classification of Surgery

Surgery is commonly classified as 'major' and 'minor' according to perceived or proven bleeding risk. Major surgery often refers to major abdominal, intracranial, cardiovascular, spinal, major orthopaedic (eg joint replacement) and any other surgery which has a significant risk of large volume blood loss or blood loss into a confined anatomical space. In children this may include adeno-tonsillectomy. Minor surgery refers to removal of skin lesions, arthroscopy, minor dental procedures and dental extractions etc.

2.3 Therapeutic Aims

Coagulation factor replacement therapy for surgery is based on target coagulation factor levels. The trough factor level is the minimum factor level measured immediately before the next bolus injection. The peak factor level is the maximum factor level measured within 1 hour of a bolus injection. The trough factor level should be raised to at least 50% for the first five days. Tables 3a and 3b outline coagulation factor level guidelines for major surgery and Table 4 for minor surgery.

Continuous infusion can be considered for an in-patient undergoing minor surgery using doses which would achieve the same factor levels as described in Table 3.

Table 3a Guidelines for coagulation factor target levels in adults undergoing major surgery using continuous infusion

Day	Continuous Infusion	
	FVIII steady state level (%)	Dose (IU/kg)
Pre-op		80-100 IU/kg load
1-3	>50	2.5-3.0 IU/kg/h
4-6	>50	2.5-3.0 IU/kg/h
7 and beyond	Often change to bolus	

Table 3b Guidelines for coagulation factor target levels in adults undergoing major surgery using bolus dosing

Day	Bolus Dosing					
	Trough Factor Level *		Dosage (IU/Kg)		Interval frequency (h)	
	FVIII	FIX	FVIII	FIX	FVIII	FIX
Pre-op #			40-50	80-120	Pre-op	Pre-op
1-3	80-100	80-100	20-25	60-80	8-12	12
4-6	60-80	60-80	15-20	50-60	8-12	12
7 and beyond	40-60	40-60	10-20	70-80	12	24

*After pre-op bolus, trough levels can be monitored prior to subsequent doses

Peak Factor aim with pre-op dose is 80-100%

Table 4 Guidelines for coagulation factor target levels in adults undergoing minor surgery

Day	Bolus dosing					
	Trough Factor Level *		Dosage (IU/kg)		Interval	Frequency (h)
	FVIII	FIX	FVIII	FIX	FVIII	FIX
Pre-op #			20-30	40-70	Pre-op	Pre-op
1-3	40-50	40-50	20-25	40-60	12	24
4 and beyond	20-30	20-30	20-30	30-50	24	24

* After pre-op bolus, trough levels can be monitored prior to subsequent doses

Peak factor aim with pre-op dose is 40-60%

2.4 Monitoring

During surgery, when prolonged courses of therapy are administered, it is imperative that factor VIII or factor IX levels are monitored frequently. It is useful to check pre-operative factor levels and perform an inhibitor screen.

It is advisable to check post-operative coagulation factor levels after major surgery. During the post-operative period it is wise to obtain assays of plasma levels following FVIII or FIX replacement (peak levels) and also trough levels just prior to subsequent therapy. This may be performed a minimum of once a day during the first 2-3 days and less frequently thereafter. Removal of sutures, drains and physiotherapy manoeuvres are best carried out at the time of peak levels.

For patients receiving continuous infusion therapy, a level performed within 6-12 hours of the start of infusion and then daily for the duration of the infusion is recommended. Following completion of the continuous infusion, bolus dosing, either as an inpatient or outpatient, following the schedule shown in Table 3 is required.

3 Specific Surgical Interventions

3.1 Liver biopsy

In the person with haemophilia the performance of a transjugular [12] liver biopsy may be necessary for total assessment of hepatic status. With respect to coagulation factor replacement, the protocol published in the literature should be followed [12] and the patient should remain hospitalized for 48 hours.

3.2 Dental Procedures [13]

The values suggested for factor VIII replacement for the person with haemophilia undergoing invasive dental procedures are outlined in Table 5. Due to mucosal alterations with dental procedures, the use of an antifibrinolytic agent in support of factor replacement is strongly recommended. This may be administered orally from the immediate post extraction period and continued for 5 days. Premature termination of antifibrinolytic may precipitate delayed mucosal bleeding. The antifibrinolytic may be taken in tablet form or as a mouth rinse.

Tranexamic acid (Cyclokapron) is currently the antifibrinolytic of choice. The dose is 15-20 mg/kg orally, three times a day. For dental extraction complicated by infection or abscess formation, or when the patient is HIV positive, the use of prophylactic antibiotic therapy is recommended.

The patient may remain in hospital at least overnight after dental extraction so that therapy can be supervised and the patient carefully monitored, however this may not always be possible. Major or multiple extractions may require a hospital stay of two or three nights, although it is more likely that the patient would return to the Haemophilia Treatment Centre as an outpatient.

Generally, recombinant Factor IX will be used in patients with haemophilia B and tranexamic acid may be prescribed.

Table 5 Coagulation factor dosing for dental procedures

Day	Bolus dosing					
	Peak Factor level (%)		Dosage (IU/kg)		Frequency Interval (h)	
	FVIII	FIX	FVIII	FIX	FVIII	FIX
Pre-op	70-80	50-60	35-40	60-70	Pre-op	Pre-op
1*	50-60	30-40	25-30	35-50	12	12-18

*and to cessation of therapy as clinically determined.

4 Mild Haemophilia and Carriers

Occasionally it is necessary for surgery to be undertaken in a person who is a carrier of haemophilia. Most carriers have factor VIII or IX levels within normal range and replacement therapy is not indicated. For carriers with low levels of FVIII or FIX replacement therapy should be instituted according to the guidelines for patients with haemophilia.

4.1 Desmopressin (Deamino-D-arginine vasopressin (DDAVP))

In people with mild haemophilia A and carriers with low FVIII levels, whose baseline factor levels are not extremely low, it may be possible to manage minor surgery or dental procedures by the use of desmopressin (DDAVP) [14]. A pre-operative desmopressin (DDAVP) test dose with FVIII level assessment may be considered. An intravenous or subcutaneous [15] dose of 0.3µg/kg usually increases factor FVIII levels by 3-5 times baseline levels. Repeated doses may be given, however the response may decrease and coagulation factor replacement may be required. The desired coagulation factor level (peak levels) for patients with mild haemophilia A or carriers is the same as for patients with severe disease. Desmopressin (DDAVP) should be avoided in children under 2 years of age and women during puerperium, and fluid balance and electrolytes monitored in all other patients because of the risk of hyponatraemia. Fluid restriction during desmopressin (DDAVP) therapy should be considered. It should be used with caution in the elderly because of the risk of coronary artery disease and spasm.

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