La gestione peri-operatoria del paziente emofilico

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SISET TRAINING CENTER
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DISCLOSURE INFORMATION

Leonardo Di Gennaro

negli ultimi due anni ho avuto i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario:

- **Supporto per progetti di ricerca:** Bioviiix; Daiichi-Sankjo; Shire (Baxalta).
- **Onorario per relazioni congressuali:** Aspen; Bayer; Bioviiix; Bristol-Myers Squibb; Boehringer-Ingelheim; Pfizer; Sobi.

Agenda del nostro appuntamento

1. Fonti e riferimenti
2. Ingredienti essenziali per la gestione peri/post-operatoria del paziente emofilico
3. Quanto fattore prima dell'intervento/procedura?
4. Tipo di chirurgia e valutazione del rischio
5. Gli obiettivi terapeutici
6. Monitoraggio e gestione post-operatoria

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WFH 50 YEARS OF ADVANCING TREATMENT FOR ALL

WORLD FEDERATION OF HEMOPHILIA
Fédération mondiale de l'hémophilie
Federación Mundial de Hemofilia

GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA 2012

AHCDO

GUIDELINE FOR THE MANAGEMENT OF PATIENTS WITH HAEMOPHILIA UNDERGOING SURGICAL PROCEDURES

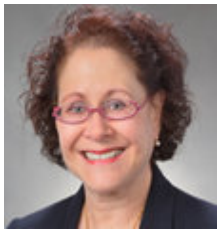
Perioperative management of the bleeding patient

BJA

British Journal of Anaesthesia, 117 (S3): iii18–iii30 (2016)

doi: 10.1093/bja/aew358
Review Article

UpToDate



Amy D. Shapiro

W. K. Hoots

Treatment of bleeding and perioperative management in hemophilia –
Aggiornate ad aprile 2018

UMBERTO I
POLICLINICO DI ROMA

Gemelli

Bambino Gesù
OSPEDALE PEDIATRICO

MALATTIE EMORRAGICHE CONGENITE
PERCORSO DIAGNOSTICO TERAPEUTICO ASSISTENZIALE
(elaborato nel mese di aprile 2013)

Operative model for perioperative laboratory test in hemophilia

EHA EUROPEAN HEMATOLOGY ASSOCIATION

Ferrata Storti Foundation

Haematologica 2016
Volume 101(10):1159-1169

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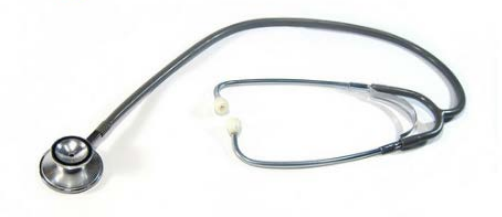
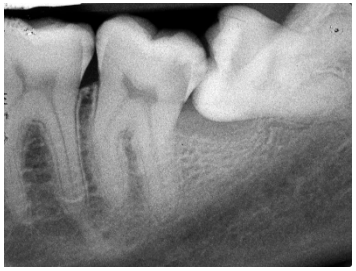
1. Programmazione e per la chirurgia in elezione e consulenza specialistica per la chirurgia d'urgenza
2. Gestione multidisciplinare della procedura chirurgica (Centro Emofilia)
3. Presenza di un anestesista con esperienza in emofilia
4. Laboratorio specialistico
5. Screening dell'inibitore prima e dopo intervento
6. Coinvolgimento della farmacia ospedaliera per approvvigionamento adeguato del concentrato di fattore
7. Coinvolgimento del centro trasfusionale
8. Organizzazione di un follow-up

Caso clínico



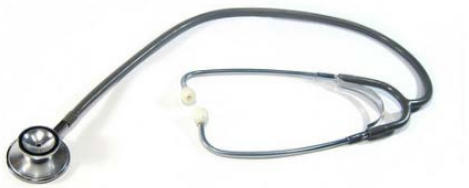
Daniele T., anni 21 emofilia A lieve.
Avulsione del terzo molare (dente del giudizio) incluso



Intervento c/o studio odontoiatrico privato.
Somministrazione profilattica di acido tranexamico per os (una fiala da 500 mg) pre-procedurale.
Centro emofilia non coinvolto.

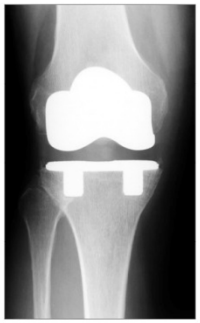
Circa due ore dopo la procedura emorragia importante ed ematoma del massetere facciale.
Ricorso al PS. Somministrazione per 5 giorni di FANHDI al dosaggio di 3000 UI ogni 12 ore.
Inibitore assente.

Caso clínico



Mariu M., anni 71, emofilia A grave, candidato a protesi di ginocchio per grave artropatia emofilica

Rappresentazione di ginocchio protesizzato



Radiografia di ginocchio protesizzato

Intervento c/o ospedale in stato estero con importanti restrizioni sulla disponibilità di fattore e senza un CentroEmofilia di riferimento.

Grave emorragia peri e post-operatoria gestita solo con PFC. Exitus del paziente per ARDS e shock emorragico.

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Dosage Calculations

Generalmente una UI di FVIII per kg di peso corporeo somministrata (sia in caso di ricombinante che di fattore plasma derivato) aumenta la concentrazione del FVIII plasmatico del paziente di 1.8-2 UI/dl (calcolo su un volume di distribuzione pari a 0.5)

Pertanto il dosaggio del FVIII (IU/kg)= FVIII desiderato (in genere 100 IU/dl) x peso del paziente / 2 = 50 UI x peso del paziente

As an example, for a 60 kg patient who requires an increase to 100 percent, the dose would be 60 kg x 100 / 2 = 3000 units of factor VIII.

A typical half-life for standard half-life factor VIII products is approximately **8 to 12 hours.** Approximate half-lives for longer-lasting factor VIII products range from **10 to 20 hours**

Factor VIII Continuous Infusion

Continuous infusions may 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:

Infusion rate (IU/kg/h) = clearance (mL/kg/h) x 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 3.0-5.0 IU/kg/h will produce a FVIII level of approximately 80 IU/dL.

Continuous infusions should not have an attached filter, and the factor product should only be mixed with normal saline.

Emofilia B

This calculation assumes a starting factor IX activity level close to 0 percent, and a desired factor activity level of 100 percent, and a volume of distribution of approximately 1.0.

Il dosaggio da infondere è uguale al peso del paziente (in kg) x il livello di FIX desiderato (100 %) x il volume di distribuzione (circa 1.0 per il FIX).

As an example, for a 60 kg patient who requires an increase to 100 percent, the dose would be 60 kg x 100 x 1 = 6000 units of factor IX.

Some factor IX products require an additional multiplier based on slightly increased or decreased volume of distribution:

- For **AlphaNine, Mononine** no additional calculations are needed
- For **BeneFIX,** multiply by 1.4 for children (ie, weight in kg x desired increase x 1.4) and 1.2 for adults
- For **Alprolix,** multiply by 1.6 for children; no additional calculations are needed for adults
- For **Idelvion,** no additional calculations are needed for children; for adults multiply by 0.77

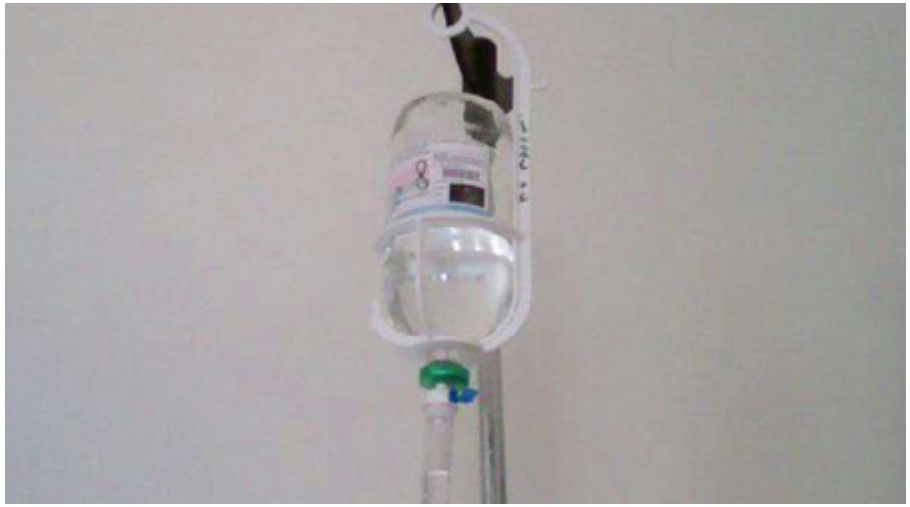
How many times…?

The second and subsequent doses are given at intervals of approximately one half-life of the infused product.

A typical half-life for standard half-life factor IX products is approximately 18 to 24 hours.

Approximate half-lives for longer-lasting factor IX products range from 54 to 104 hours.

Another option is to give the initial factor IX bolus followed by a continuous infusion.
A dose of approximately 6 units/kg/hour of standard half-life factor IX concentrate will often maintain the level initially achieved by bolus infusion.



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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.

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.

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.

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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%

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	3.0-5.0 IU/kg/h
4-6	>50	3.0-5.0 IU/kg/h
7 and beyond	Often change to bolus	

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

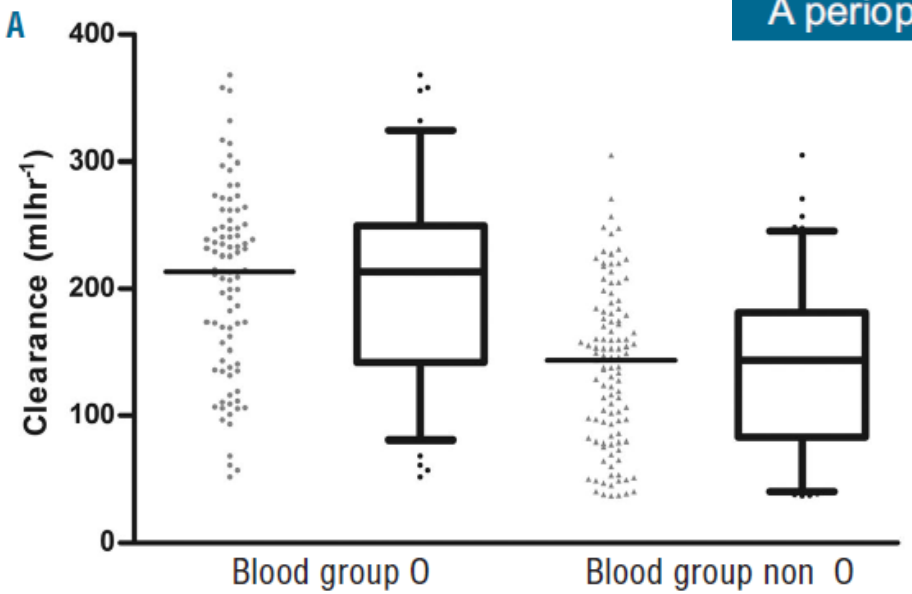
* After pre-op bolus, trough levels can be monitored prior to subsequent doses

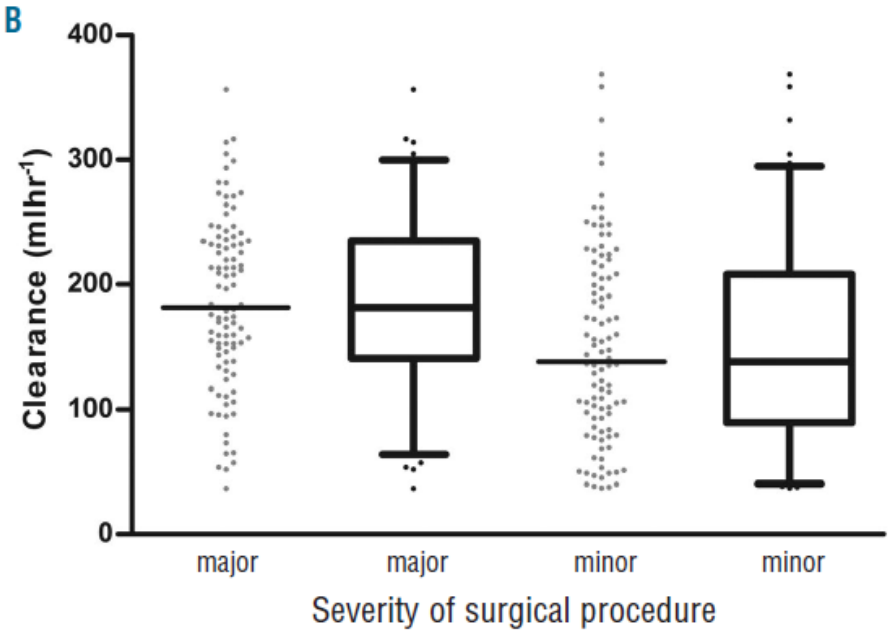
Peak factor aim with pre-op dose is 40-60%

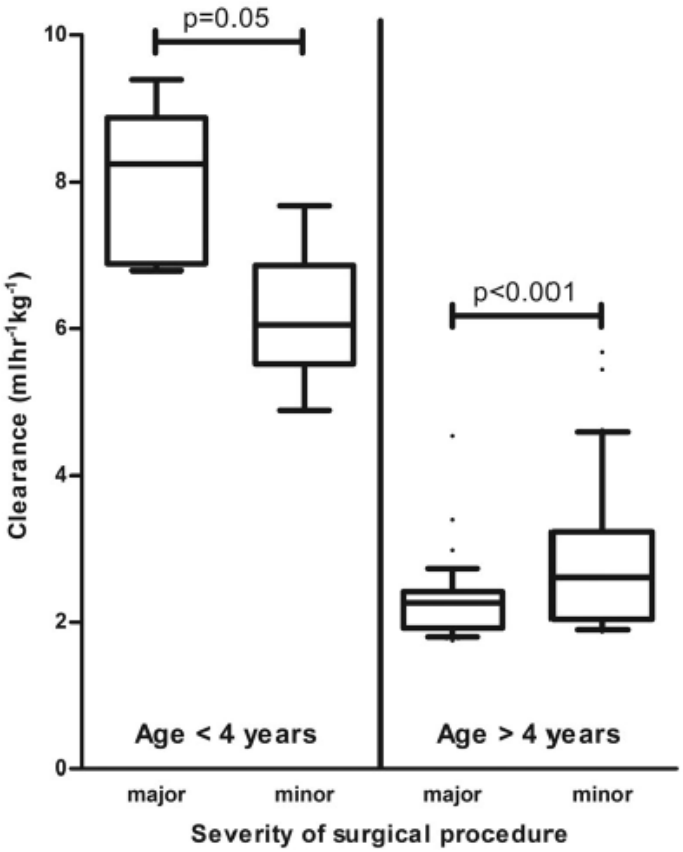
^ Duration for minor surgery may be less than 4 days

DDAVP (desmopressin) is a synthetic analog of vasopressin (antidiuretic hormone) that lacks pressor activity and may be effective for minor bleeding or certain elective procedures in patients with **mild hemophilia A** (typically those with factor VIII activity in the higher range, closer to 40 percent) who have had a documented response to a test dose.
A typical dose is 0.3 µg/kg (maximum dose, 20 µg) administered intravenously or subcutaneously; or as a nasal spray, one puff (150 mcg) in one nostril in patients weighing <50 kg and two puffs (150 mcg in both nostrils) in patients weighing ≥50 kg.

A repeat dose may be given at 12 hours, and subsequent doses are often administered once daily. When using the nasal spray it is important to use the spray intended for hemostasis and not the spray for enuresis, which has a lower concentration.


A
Clearance (mlhr-1)
400
300
200
100
0
Blood group O
Blood group non O


B
Clearance (mlhr-1)
400
300
200
100
0
major
major
minor
minor
Severity of surgical procedure


Clearance (mlhr-1kg-1)
10
8
6
4
2
0
p=0.05
p<0.001
Age < 4 years
Age > 4 years
major
minor
major
minor
Severity of surgical procedure

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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.

Management of bleeding and surgery in patients with hemophilia with an inhibitor (neutralizing antibodies against infused factor)

For a patient with a high titer and high responding inhibitor (eg > 5 BU) who has serious bleeding or requires major surgery, a bypassing product (eg, FEIBA or recombinant factor VIIa) is used. For patients with a low responding inhibitor, options include factor concentrates or other hemostatic agents.

- **rFVIIa** –typically 90 to 120 mcg/kg every two to three hours until hemostasis is achieved and at three- to six-hour intervals after hemostasis has been restored
- **FEIBA** – Dosing of FEIBA is typically 50 to 100 units/kg every 6 to 12 hours, not to exceed 100 units/kg/dose or 200 units/kg/day


Thank You