



Cirugía y hemofilia



Dra. Carme Altisent
Unitat d'Hemofília.
Barcelona

Primera descripción



□ Talmud, Yebanot 64 b

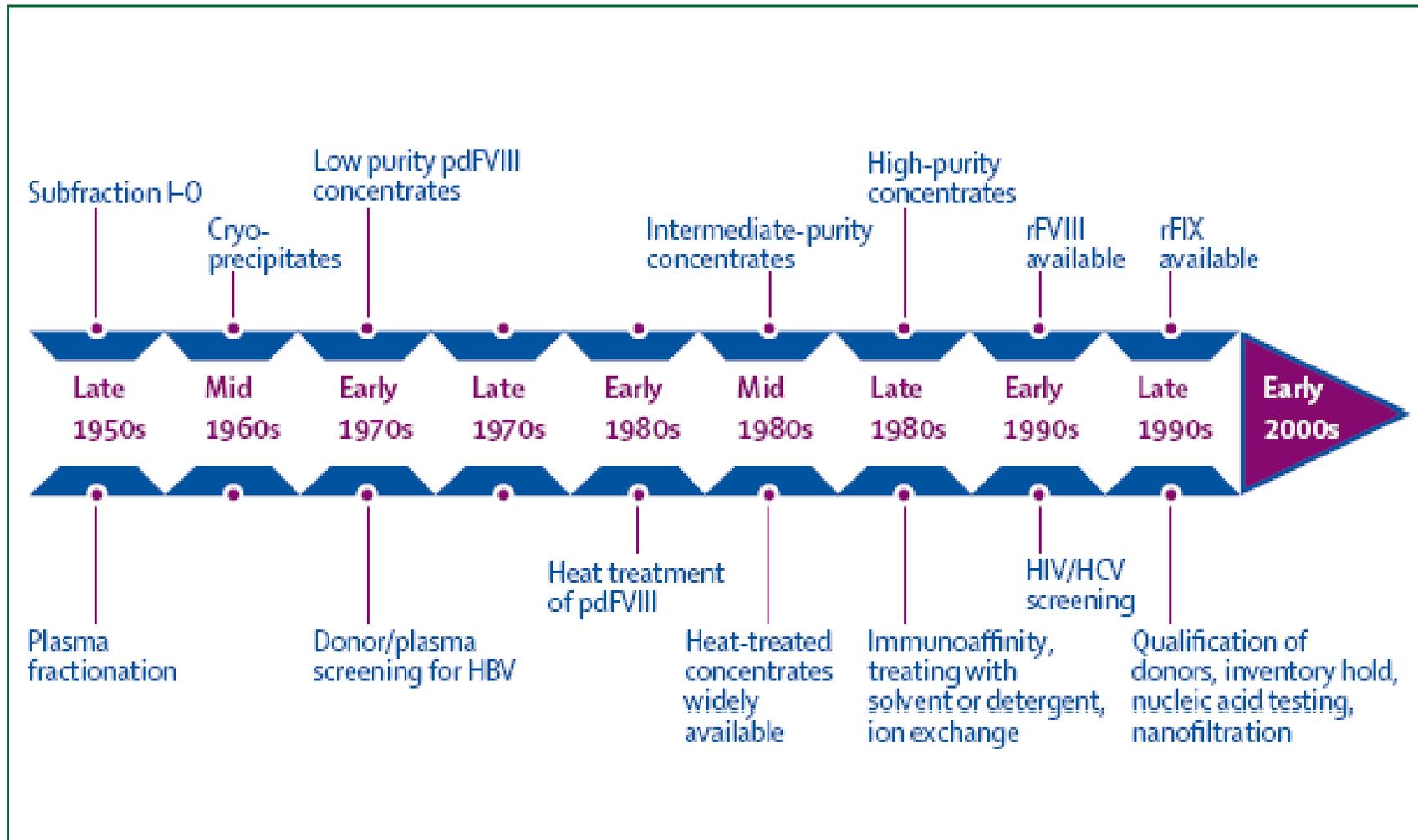
- *...si el primer hijo de una mujer es circuncidado y muere y el segundo hijo es circuncidado y muere, no debería circuncidarse al tercero...*

Rabi Judah



Cronología del tratamiento

Key N S, Negrier C. *The Lancet* 2007

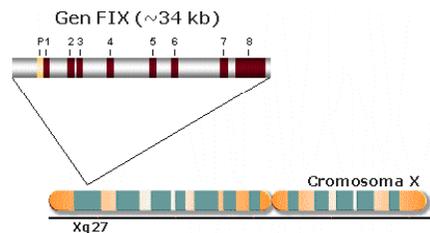
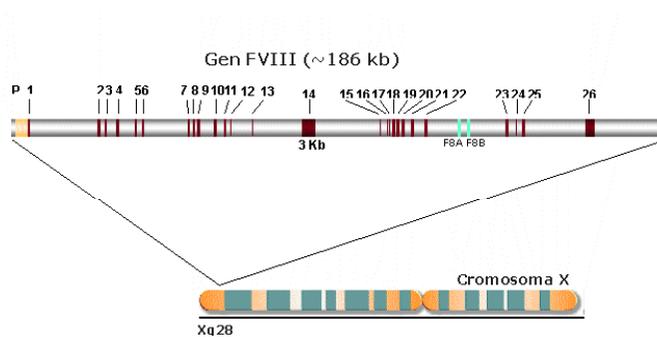


Puntos clave



- Tipo y grado de hemofilia
- Descartar la presencia de inhibidor
- Valorar el estudio de trombofilia
 - Factores de riesgo tromboembólico
 - Tipo de intervención quirúrgica
- Administración de tratamiento
 - En bolos
 - En infusión continua
- Niveles de factor en el pre y postoperatorio
- Días de tratamiento postintervención
- Indicación de la profilaxis tromboembólica

Tipos y grados de hemofilia



A: Factor VIII

B: Factor IX

Grave <1%

Moderada 1-5%

Leve 5-30%

Hemorragias



Grave

- espontáneas
- mínimos traumatismos

Moderada

- traumatismos leves o moderados

Leve

- asintomática
- estudio familiar
- estudio de hemostasia
- sangrado postquirúrgico

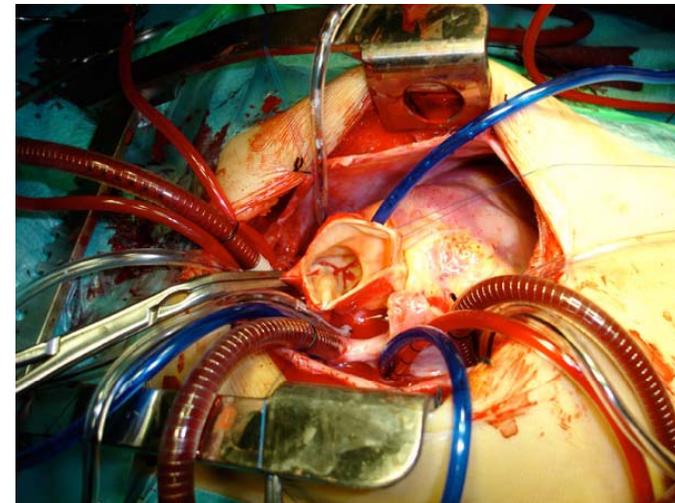
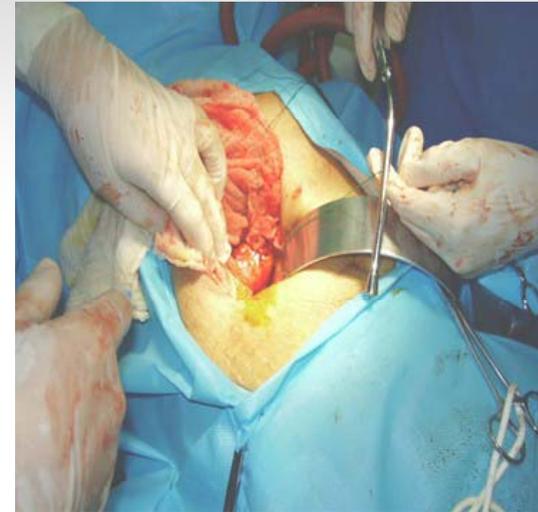
Riesgo quirúrgico

- ❑ Grave
 - ❑ de alto riesgo
- ❑ Moderada
 - ❑ de alto riesgo
- ❑ Leve
 - ❑ sangrado postquirúrgico



Hemorragia

- Intraoperatoria
 - Hemostasia insuficiente
- Postoperatoria inmediata (<48 h)
 - Causa local
 - Hemostasia insuficiente
- Postoperatoria tardía (>48 h)
 - ¿Hemostasia insuficiente?



Hemorragia postquirúrgica: 1,4-6,5%

Valoración de la hemostasia



Table 1-6. Definition of adequacy of hemostasis for surgical procedures [64].

	Excellent	Intra-operative and postoperative blood loss similar (within 10%) to the non-hemophilic patient. <ul style="list-style-type: none">• No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND• Blood component transfusions required are similar to non-hemophilic patient
	Good	Intra-operative and/or postoperative blood loss slightly increased over expectation for the non-hemophilic patient (between 10 and 25% of expected), but the difference is judged by the involved surgeon/anaesthetist to be clinically insignificant <ul style="list-style-type: none">• No extra (unplanned) doses of FVIII/FIX/bypassing agents needed AND• Blood component transfusions required are similar to non-hemophilic patient

Valoración de la hemostasia



Fair

Intra-operative and/or postoperative blood loss increased over expectation (25–50%) for the non-hemophilic patient and additional treatment is needed

- Extra (unplanned) dose of FVIII/FIX/bypassing agents factor needed OR
- Increased blood component (within 2 fold) of the anticipated transfusion requirement



Poor/none

Significant intra-operative and/or postoperative blood loss that is substantially increased over expectation (>50%) for the non-hemophilic patient, requires intervention, and is not explained by a surgical/medical issue other than hemophilia

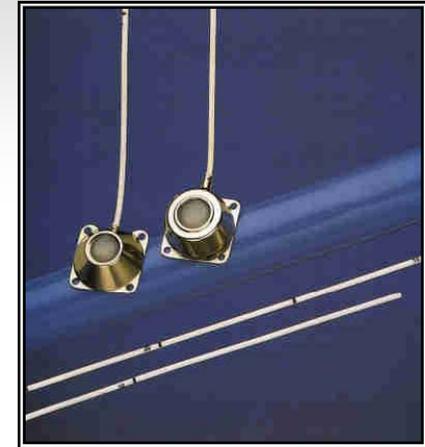
- Unexpected hypotension or unexpected transfer to ICU due to bleeding OR
- Substantially increased blood component (>2 fold) of the anticipated transfusion requirement

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Cirugía menor



- Adenoidectomía
- Implantación de catéter central**
- Circuncisión
- Cirugía dental
- Cataratas
- Biopsia hepática



Operative management and outcomes in children with congenital bleeding disorders: a retrospective review at a single haemophilia treatment centre

1999-2010

Table 2. Surgical procedures.

Type of procedure	Number of procedure	% of Total procedures
CVL placement/removal	69	41
Dental	19	11
Myringotomy/tympanoplasty	16	10
Tonsillectomy/adenoidectomy	15	9
Musculoskeletal (non-synovectomy)	13	8
Synovectomy	8	5
Circumcision	8	5
Nasal cautery/septoplasty	7	4
Excision of subcutaneous cyst	4	2
Miscellaneous	9	5
Total	168	100

N=7%

R. G. WATTS and R. P. COOK

Division of Pediatric Hematology-Oncology, University of Alabama at Birmingham, Birmingham, USA



2000-2007

ORIGINAL ARTICLE *Paediatrics*

To circumcise or not to circumcise? Circumcision in patients with bleeding disorders

V. RODRIGUEZ,* R. TITAPIWATANAKUN,* C. MOIR,† K. A. SCHMIDT* and R. K. PRUTHI*

**Division of Pediatric Hematology and Oncology; and †Division of Pediatric Surgery, Mayo Clinic, Rochester, MN, USA*

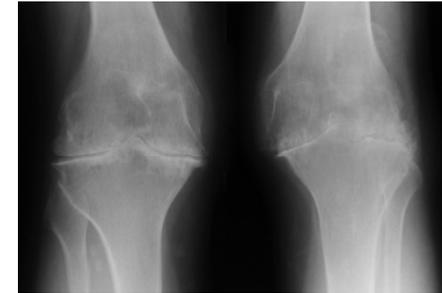
We live in an era different from the times described in the Talmud, in which medical advances in the care of patients with bleeding disorders have made surgical interventions possible, minimizing the risk of bleeding if factor replacement is adequately provided. Although we discuss openly with our patients and parents the risks and benefits of circumcision, we always stress that bleeding complications can still occur despite appropriate coagulation factor replacement.

N=48

23%

Total knee replacement in patients with end-stage haemophilic arthropathy

25-YEAR RESULTS



Conclusions

→ In our study infection has not been a common problem. The results appear to be comparable to those of TKR in the non-haemophilic population²⁵⁻³⁰ with a prevalence of infection of under 2% and long-term survival of 95.0% at 20 years.

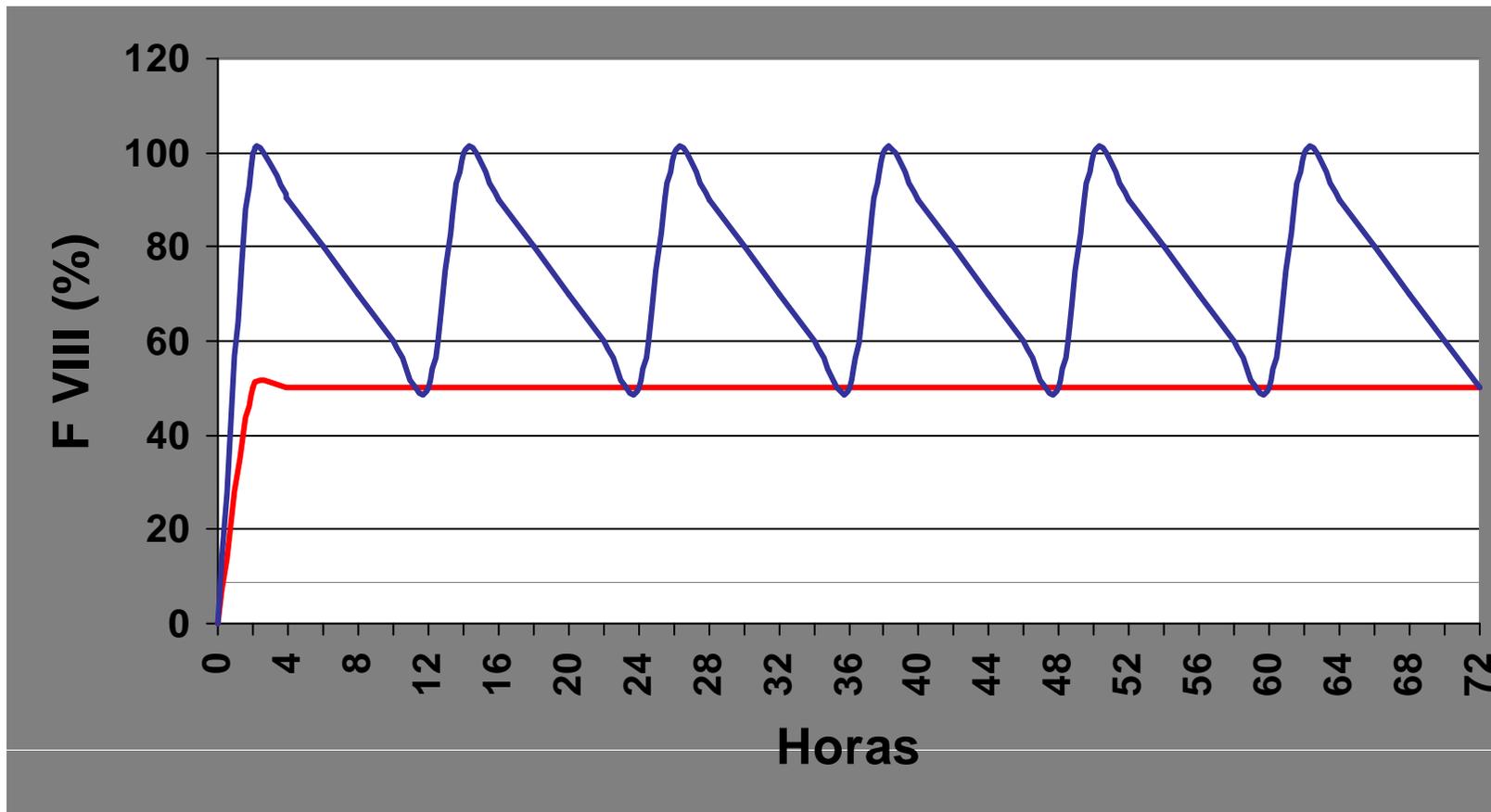
The use of continuous infusion Factor replacement during the pre-, peri- and early post-operative phases may account for the improved results. ←

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Administración del tratamiento



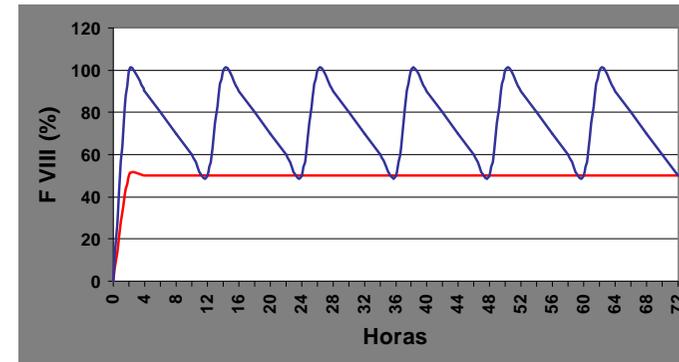
Tratamiento sustitutivo

- ❑ Debe administrarse el factor antes de la intervención y con control analítico postdosis
- ❑ Dosis
 - ❑ FVIII: 1 UI/ Kg ↑ 2 UI/dl
 - ❑ FIX: 1UI/Kg ↑ 1UI/dl

Infusión continua

❑ Inicio en bolos

❑ Velocidad de infusión en bomba



❑ $U/kg/h \text{ de FVIII} = 3,52 \text{ (ml/kg/h)} \times \text{concentración deseada (U/ml)}$

❑ $U/kg/h \text{ de FIX} = 4,99 \text{ (ml/kg/h)} \times \text{concentración deseada (U/ml)}$

Infusión continua

□ Ventajas

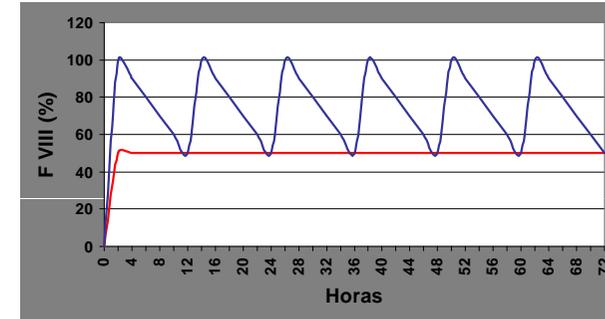
- Mantiene niveles terapéuticos constantes
- Fácil monitorización

□ Inconvenientes

- Disponer de bomba de infusión
- Complicaciones locales

□ Dudas

- Profilaxis de flebitis local





ORIGINAL ARTICLE *Clinical haemophilia*

Continuous infusion during total joint arthroplasty in Japanese haemophilia A patients: comparison study among two recombinants and one plasma-derived factor VIII

H. TAKEDANI

Department of Joint Surgery, Research Hospital of The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

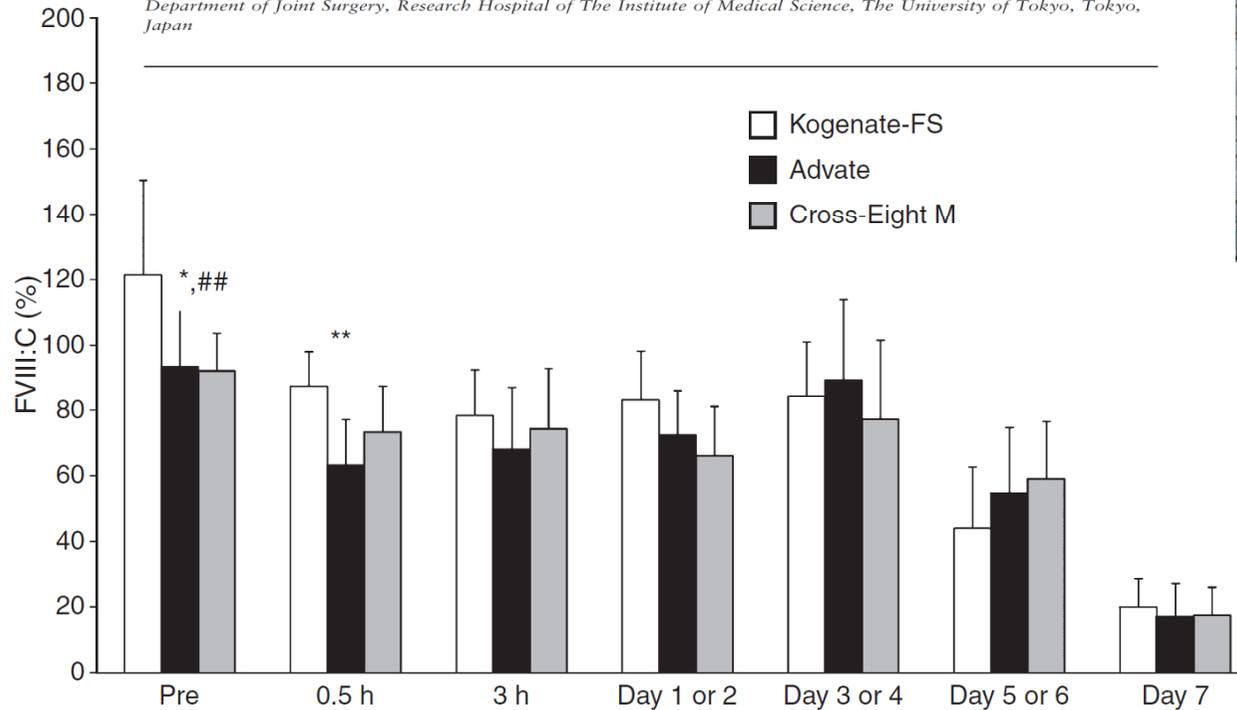


Table 2. Pharmacokinetic analysis and product factor activity.

	Unit	Kogenate-FS	Advate	Cross-Eight M	Total	Statistic
Sample	Counts	11	6	11	28	
IVR	(IU dL ⁻¹) per (IU kg ⁻¹)	1.91 ± 0.4	1.86 ± 0.5	1.83 ± 0.2	1.86 ± 0.4	<i>ns</i>
Half-life	h	13.7 ± 3.2	11.7 ± 4.0	13.2 ± 3.5	13.1 ± 3.5	<i>ns</i>
Batches	Counts	15	14	21		
Activity	IU per vial	1147 ± 47.4	1041 ± 34.7	1135.2 ± 39.1	1112 ± 60.3	<i>*,†</i>

No inhibitor development after continuous infusion of factor concentrates in subjects with bleeding disorders undergoing surgery: a prospective study

G. AUERSWALD, A BADE, K. HAUBOLD, D. OVERBERG, S. MASURAT and C. MOORTHY

Table 2. Continuous infusion treatments.

Treatments (N = 46)	No. of subjects (%)
VWD (n = 11)	
Haemate [®] HS/Humate-P ^{®*}	11 (100)
Haemophilia A (n = 29)	
Full-chain recombinant FVIII [†]	13 (45)
High-purity plasma-derived concentrate [‡]	10 (34)
Haemate [®] HS/Humate-P ^{®*}	3 (10)
B-domain-deleted FVIII concentrate [§]	3 (10)
Haemophilia B (n = 6)	
Plasma-derived FIX concentrate [¶]	6 (100)



Surgery type, n (%)	
Otolaryngology	12 (26)
Orthopaedic	10 (22)
Abdominal	9 (20)
Neurosurgery	3 (7)
Central-line insertion	2 (4)
Other (e.g. obstetric and severe dental)	10 (22)

Puntos clave

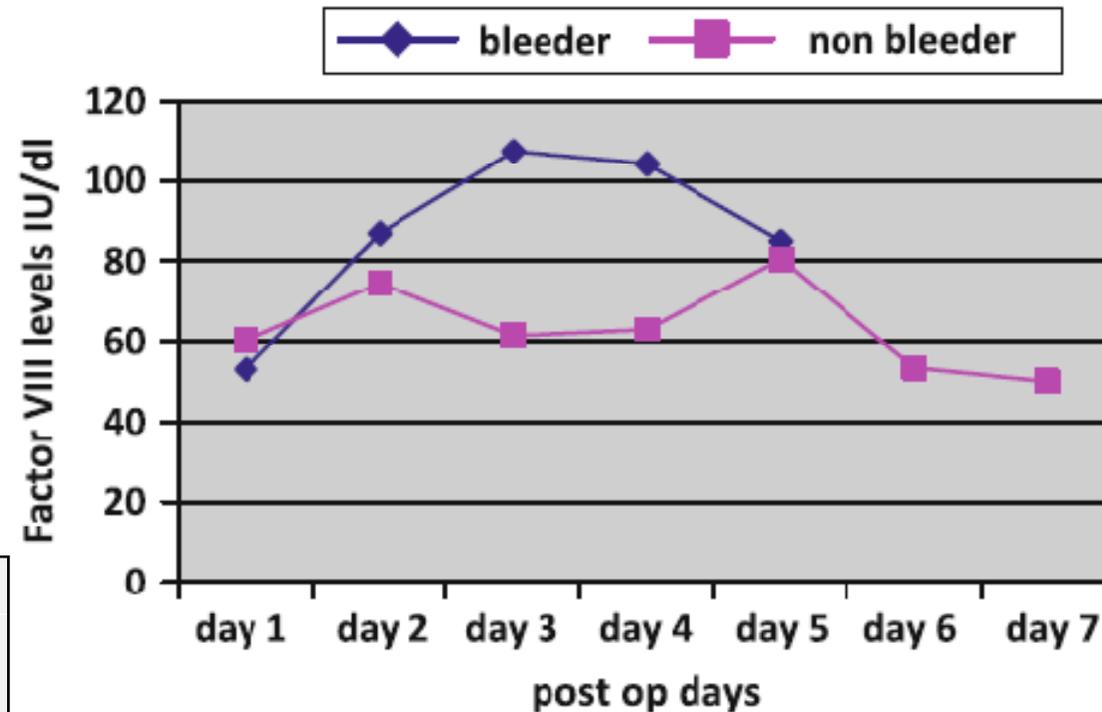


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General Surgery in Patients With a Bleeding Diathesis: How We Do It

Kamal R. Aryal · D. Wiseman · Ajith K. Siriwardena ·
Paula H. B. Bolton-Maggs · Charles R. M. Hay ·
James Hill

1998-2008



N=144/113

Fig. 5 Postoperative mean trough levels in hemophilia patients

Hemorrhagia: 4%/10%



REVIEW ARTICLE

Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations

C. HERMANS,* C. ALTISENT,† A. BATOROVA,‡ H. CHAMBOST,§ P. DE MOERLOOSE,¶
A. KARAFOLIDOU,** R. KLAMROTH,†† M. RICHARDS,‡‡ B. WHITE§§ and G. DOLAN¶¶ on
behalf of THE EUROPEAN HAEMOPHILIA THERAPY STANDARDISATION BOARD

Haemophilia 2009; 15: 639-658.

Encuesta europea

European Haemophilia Therapy Standardisation Board

Ámbito

- Países 15
- Centros 26
- Pacientes 3.633 (hemofilia A grave)

Objetivos

- Conocer pautas terapéuticas
- Identificar
 - Puntos de controversia
 - Problemas por resolver
 - Futuras investigaciones
- Elaborar recomendaciones



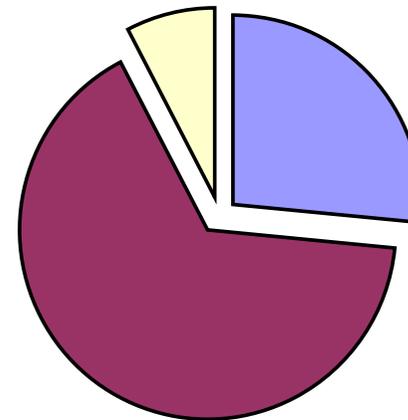
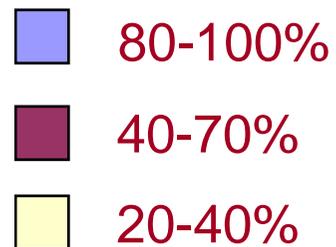
Haemophilia 2009; 15: 639-658.

Extracción dentaria



European Haemophilia Therapy Standardisation Board

Niveles preoperatorio



Haemophilia 2009; 15: 639-658.

Implantación de catéter central

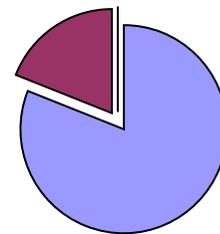
European Haemophilia Therapy Standardisation Board



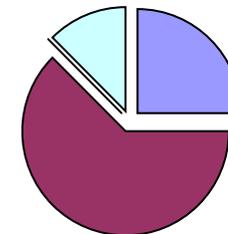
Niveles pre y postoperatorio



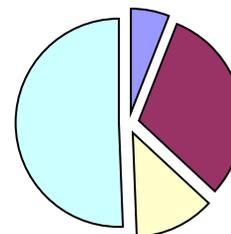
Preoperatorio



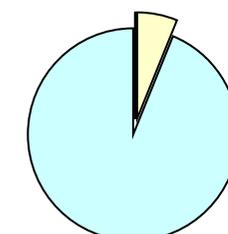
1-3 días



4-7 días



>7 días



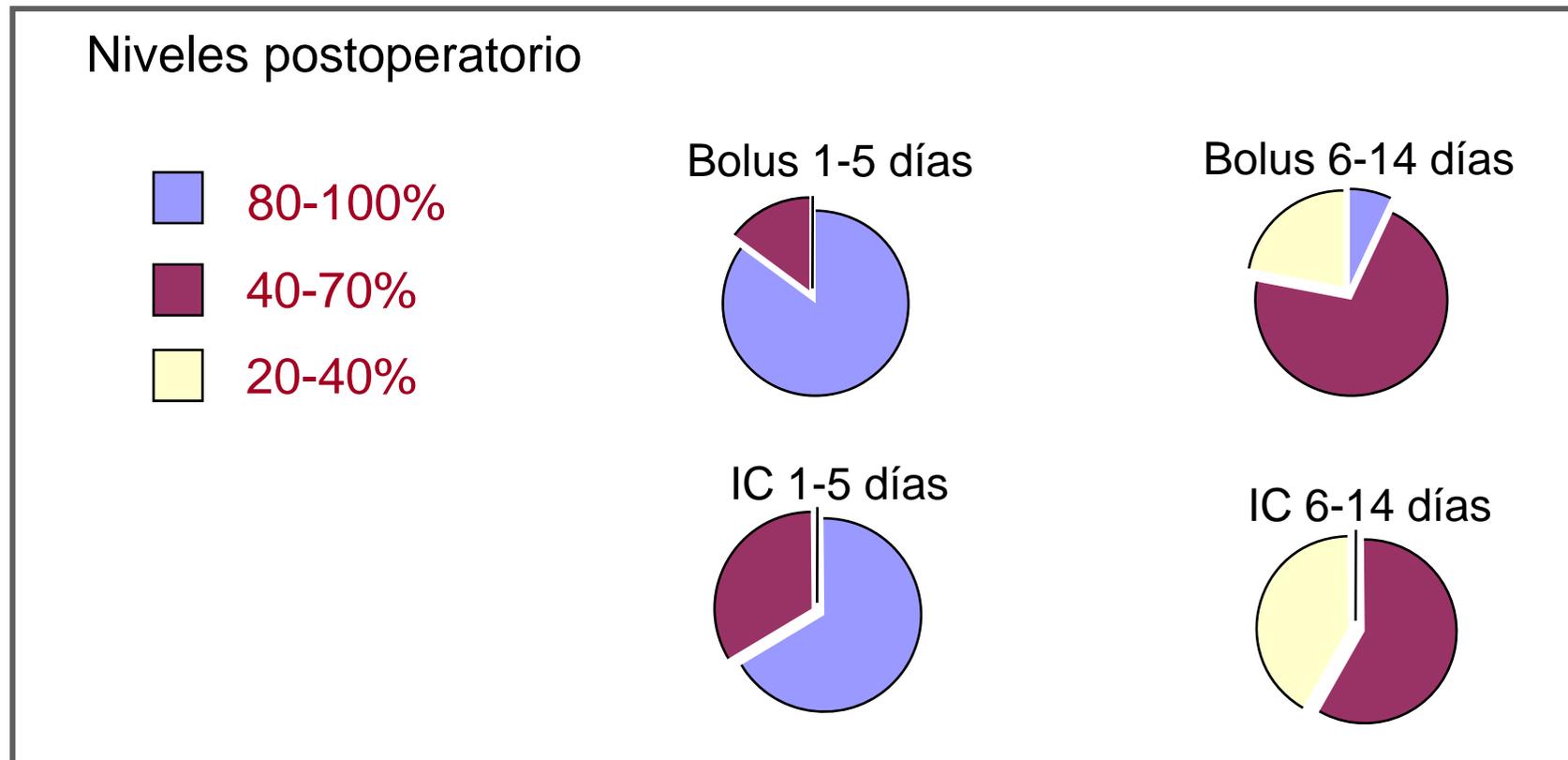
Haemophilia 2009; 15: 639-658.

Artroplastia de rodilla

European Haemophilia Therapy Standardisation Board



Nivel preoperatorio 80-100%



Revisión bibliográfica cirugía mayor



<input type="checkbox"/> Estudios clínicos	35
<input type="checkbox"/> Analizables	31
<input type="checkbox"/> Pacientes	1.114
<input type="checkbox"/> Hemofilia A	862
<input type="checkbox"/> Hemofilia B	241
<input type="checkbox"/> Intervenciones	1.328
<input type="checkbox"/> Ortopédicas	707
<input type="checkbox"/> Tipo de tratamiento	
<input type="checkbox"/> En bolos	23
<input type="checkbox"/> Infusión continua	16
<input type="checkbox"/> Ambos	5

Haemophilia 2009; 15: 639-658.

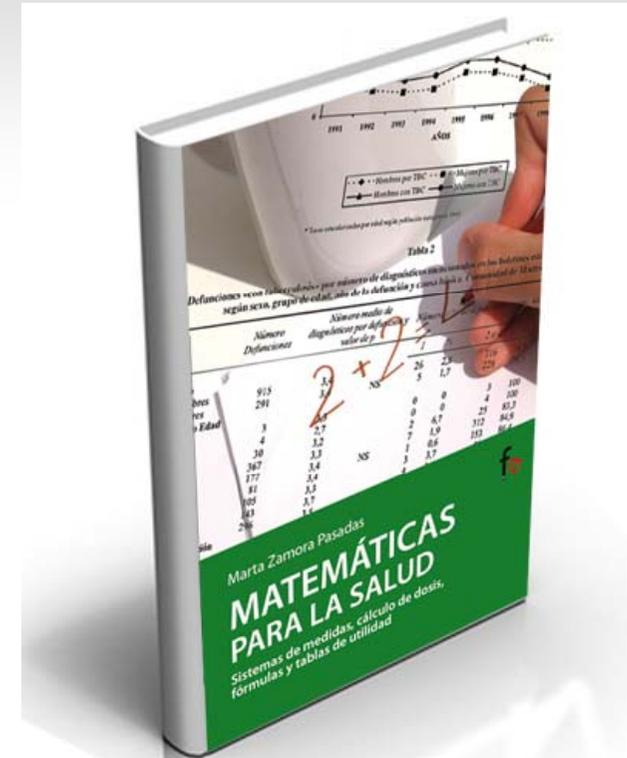
Table 1. Major surgery in patients with haemophilia: literature review of replacement therapy.

First author	Year	References	Level of evidence	All (n)	Major surgery			Orthopaedic surgery (n)	Bolus infusion (n)	Continuous infusion (n)	Factor operative level, pre-operative (%)	Factor level, 1st week postoperative (%)	Factor level, 2nd week postoperative (%)	Duration of treatment (days)	Antifibrinolytics (yes/no)	Outcome bleeds (n)	Phlebitis (n)
					A (n)	B (n)	all (n)										
Nilson IM	1977	10	3 (sc, uc)	77	61	16	108	53	108	0	>90	>30-40	>10-20	14-28	Yes	4	0
Krieger JN	1977	11	3 (sc, uc)	31	25	6	58	18	58	0	100	60	40	5-12	No	3	0
Rudowski WJ	1981	12	3 (sc, uc)	101	85	16	121	33	121	0	>50	>50	NA	NA	NA	11	NA
Willert HG	1983	13	3 (sc, uc)	18	16	2	18	18	18	0	>60	50	50	NA	No	0	0
Kasper CK	1985	14	3 (sc, uc)	163	163	0	350	194	350	0	>80	50	50	14	NA	72	0
Brown B	1986	15	3 (sc, uc)	22	18	4	23	0	23	0	100	50	25	7-14	NA	4	0
Kitchens CS	1986	16	3 (sc, uc)	36	30	6	36	NA	36	0	>80	NA	NA	5-18	NA	2	1
Martinowitz U	1992	17	3 (sc, hc)	25	25	0	25	NA	11	14	>80	>50	>30	7-14	Yes	0	0
Schulman S	1994	18	3 (sc, hc)	12	12	0	12	10	0	12	>80	>50	>30	4-18	Yes	0	5
Bushan V	1994	19	3 (sc, uc)	37	32	5	26	14	26	0	80/ 50-80	20-40/ 15-30	20-40/ 15-30	10	No	7	NA
Lofqvist T	1996	20	3 (sc, uc)	66	53	13	98	98	98	0	100	>30-40	>10-20	14-28	Yes	1	0
Hay CR	1996	21	3 (sc, uc)	24	24	0	21	20	0	21	100	80	NA	5 (CI)	No	0	0
Shapiro AD	1997	22	2 (mc, uc)	74	0	74	34	24	34	0	>60	>30	NA	10	No	0	0
White GC	1997	23	2 (mc, uc)	13	13	0	9	5	NA	NA	NA	NA	NA	NA	NA	0	NA
Srivastava A	1998	24	3 (sc, uc)	18	11	7	20	14	20	0	>80/ >60	>20-40/ >15-30	>15-30/ >10-20	11	No	1	0
Heeg M	1998	25	3 (sc, uc)	9	8	1	12	12	12	0	>100	>50	>25	14	No	1	0
Campbell PJ	1998	26	3 (sc, hc)	21	18	0	18	18	8	10	100	>80	NA	13-17	No	8	1
Gosh J	1998	27	3 (sc, uc)	16	12	4	7	2	7	0	>60	>30	NA	10	Yes	2	0
Negrier C	1998	28	3 (sc, uc)	13	9	4	13	10	0	13	>80	>80	>50	9-22	No	0	0
Tagariello G	1999	29	3 (sc, hc)	15	14	1	11	9	0	11	>80	>70/>40	>40/>20	10	Yes	0	2
Rochat C	1999	30	3 (sc, hc)	5	5	0	5	5	0	5	>80	>50	NA	5 (CI)	No	0	5
Scharrer I	2000	31	2 (mc, uc)	15	15	0	8	4	8	0	NA	NA	NA	12	No	0	0
Batorova A	2000	32	2 (sc, c)	40	40	0	43	31	18	25	>80	>50	>30	12	Yes	3	4
Bastounis E	2000	33	3 (sc, uc)	65	43	15	58	6	58	0	>80	>30	>30	14	No	2	0
Chowdary P	2001	34	3 (sc, uc)	6	0	6	5	3	0	5	>80	>80	NA	3-10	No	0	2
Scharrer I	2002	35	2 (mc, uc)	22	22	0	13	7	13	0	NA	NA	NA	12-26	No	0	0
Mishra V	2002	36	3 (sc, uc)	9	6	2	8	8	0	8	>90	>50-70	>30	9	Yes	0	0
Ragni MV	2002	37	2 (mc, uc)	26	0	26	23	11	14	9	>80	NA	NA	10-20	No	0	1
Dingli D	2002	38	3 (sc, uc)	28	28	0	35	25	0	35	>80	>80	>50	6 (CI)	No	5	0
Hoots WK	2003	39	2 (mc, uc)	28	0	28	25	21	0	25	>90	>70	NA	6 (CI)	No	0	3
Evans G	2003	40	3 (sc, uc)	4	0	4	5	5	0	5	>90	>70	NA	3-54	No	1	0
Lusher JM	2003	41	2 (mc, uc)	42	42	0	48	NA	48	0	>70	NA	NA	NA	NA	0	0
Wolf DM	2004	42	3 (mc, uc)	8	8	0	5	5	5	0	>90	NA	NA	9-21	NA	0	0
Stieltjes N	2004	43	3 (mc, uc)	16	16	0	18	15	0	18	NA	NA	NA	5-21	Yes	4	1
Lee V	2004	44	3 (sc, uc)	9	8	1	9	9	7	2	>80	>30	>10-20	5-44	No	0	0
				1114	862	241	1328	707	1101	218						131	25

CI, continuous infusion; hc, historical controls; mc, multi-centre; NA, not available; sc, single centre; uc, uncontrolled.

Resultados niveles hemostáticos

- Preoperatorio inmediato 26/31
 - >80% en 26 de 31
- Postoperatorio 1ª semana 27/31
 - > 70% en 8
 - > 50% en 11
 - > 20-30% en 8
- Postoperatorio 2ª semana 18/35
 - > 50% en 7
 - > 30% en 4
 - > 10-20% en 7
- Duración
 - 5-14 días en 19
 - 15-21 días en 6
 - >28 días en 6



Haemophilia 2009; 15: 639-658.

Resultados

niveles hemostáticos

Indicación	Variación	Días	Hemorragia
Biopsia hepática	70-100%	1-7	0,5%
Amigdalectomía	90-100%	5-11	5%
Catéter	100%	3-10	10%
Circuncisión	50-60%	2-4	50%
Cirugía dental	30-50%	1	ND

Revisión bibliográfica



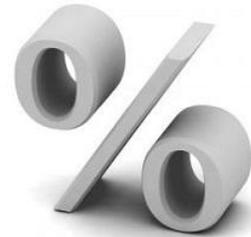
- No existe una clara correlación entre el sangrado postoperatorio y los niveles de factor
- Flebitis local de 25 de 218 infusiones continuas
- No se recomienda tratamiento profiláctico tromboembólico con anticoagulantes

C. HERMANS,* C. ALTISENT,† A. BATOROVA,‡ H. CHAMBOST,§ P. DE MOERLOOSE,¶
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Limitaciones de la bibliografía

- Escaso número de pacientes
- Información insuficiente
 - niveles terapéuticos
 - días de tratamiento
 - complicaciones hemorrágicas



C. HERMANS,* C. ALTISENT,† A. BATOROVA,‡ H. CHAMBOST,§ P. DE MOERLOOSE,¶
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Extracción dentaria



- ❑ Nivel mínimo: 50% (B-III)
- ❑ Antifibrinolíticos durante 7 días (A-I)
- ❑ Considerar la aplicación de hemostático local

Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations

Port-A-Cath

- ❑ Preoperatorio: 80%
- ❑ Postoperatorio 3 días (B-III)

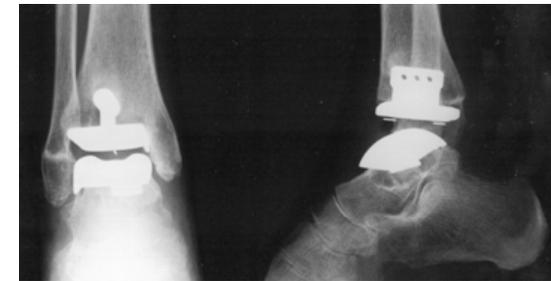
- ❑ ¿Cuándo puede utilizarse?



Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations

Cirugía ortopédica

- ❑ Preoperatorio: 80-100% (B-III)
- ❑ Postoperatorio (C-IV)
 - ❑ >50% → primera semana
 - ❑ >30% → segunda semana
- ❑ Infusión continua segura
- ❑ Valorar antifibrinolíticos y tromboprofilaxis



Replacement therapy for invasive procedures in patients with haemophilia: literature review, European survey and recommendations

Guidelines for the management of hemophilia

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 FEDERATION OF HEMOPHILIA

	Hemophilia A		Hemophilia B	
	Desired level (IU dL ⁻¹)	Duration (days)	Desired level (IU dL ⁻¹)	Duration (days)
Surgery (major)				
Pre-op	80–100		60–80	
Post-op	60–80	1–3	40–60	1–3
	40–60	4–6	30–50	4–6
	30–50	7–14	20–40	7–14
Surgery (minor)				
Pre-op	50–80		50–80	
Post-op	30–80	1–5, depending on type of procedure	30–80	1–5, depending on type of procedure

Haemophilia (2013), 19, e1–e47

How to manage invasive procedures in children with haemophilia

Rolf C. R. Ljung and Karin Knobe

- Circuncisión
- Cirugía dental
- Cateter
- Amigdalectomia



In summary, there is no established consensus of how to treat a child with haemophilia during different surgical procedures. However, the literature suggests rather uniform agreement on some guiding principles:

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How to manage invasive procedures in children with haemophilia

- 1 FVIII/IX concentration at 80–100% before a surgical procedure.
- 2 Approximately 3 d postoperative treatment after minor surgery, 7–10 d after major surgery and even longer after intracranial procedures.
- 3 The youngest children have a shorter half-life of FVIII/IX and are in need of more frequent dosing and monitoring of factor concentrations.
- 4 Surgery is possible in patients with inhibitors by use of bypassing agents but at a higher risk of bleeding complications.



How to manage invasive procedures in children with haemophilia

- 5 Children with mild haemophilia A should, if possible, be treated with DDAVP and antifibrinolytics.
- 6 Surgical procedures should be avoided during the first 20 exposure days due to a potential risk of inhibitor development.
- 7 In the neonate, and in particular in the preterm neonate, special considerations may be necessary due to different concentration of various coagulation factors compared to after the neonatal period.

Puntos clave

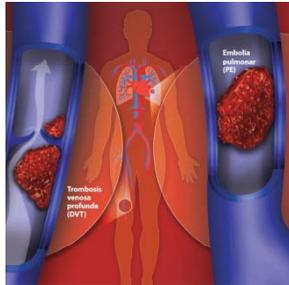


- Tipo y grado de hemofilia
- Descartar la presencia de inhibidor
- Valorar estudio de trombofilia
 - Factores de riesgo tromboembólico
 - Tipo de intervención quirúrgica
- Administración de tratamiento
 - En bolos
 - En infusión continua
- Niveles de factor en el pre y postoperatorio
- Días de tratamiento postintervención
- Indicación de la profilaxis tromboembólica**

Venous thromboembolic disease in patients with haemophilia

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Thrombosis Research 130 (2012) S50–S52

□ Hermans et al.

- Según un cuestionario multicéntrico europeo, el 50% de los centros utilizan profilaxis anticoagulante en cirugía ortopédica

□ Zakarija et Aledort

- En 19 centros de adultos de Estados Unidos, el 47% usa profilaxis postquirúrgica

□ Pradham et al.

- En 60 centros de Estados Unidos, el 67% utiliza profilaxis en cirugía de rodilla y de cadera

Venous thromboembolic disease in patients with haemophilia

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- Falta de consenso
- Ausencia de guías
- Necesidad de mayor investigación, especialmente en cirugía ortopédica
- Incremento del riesgo debido a la mayor edad de los pacientes



Surgery in patients with hemophilia: Is thromboprophylaxis mandatory?

Margareth C. Ozelo *



Nevertheless, although the occurrence of DVT is uncommon in patients with hemophilia patients and those with other inherited bleeding disorders, a careful risk assessment for thrombosis should be evaluated to help the decision regarding thromboprophylaxis for patients undergoing surgical procedures. Some thrombotic risk factors that should be considered are age over 60 years, obesity (body mass index [BMI] over 30 Kg.m⁻²), confirmed thrombophilia, and personal or family history of VTE [26].

Estudio de trombofilia

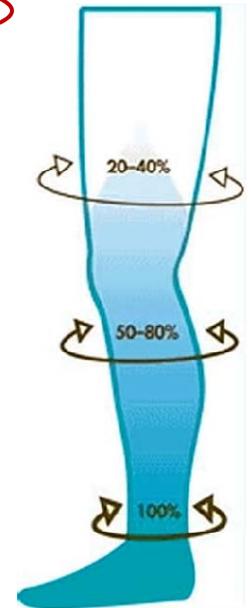
Thrombosis Research 130 (2012) S23–S26



Surgery in patients with hemophilia: Is thromboprophylaxis mandatory?

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Regarding the thrombotic risk in hemophilia patients who undergo orthopedic surgeries, the use of graduated **compression stockings** and early mobilization can be sufficient to prevent VTE for the majority of these patients [27]. In fact, this is the recommendation of the current American College of Chest Physicians (ACCP) guideline for patients with a high risk of bleeding following major orthopedic surgeries [2].



The use of pharmacologic thromboprophylaxis, such as LMWH or fondaparinux, should be considered just for patients with relevant **additional risk factor for thrombosis**. In this case, a careful control of the coagulation factor replacement and the administration of reduced doses of anticoagulants are recommended. In addition, for hemophilia patients with inhibitors, according to the Canadian consensus for orthopedic surgery in inhibitor patients, pharmacologic thrombosis prophylaxis should not be routinely used for those patients [28].

Conclusiones



- ❑ Pueden efectuarse intervenciones quirúrgicas si se dispone de
 - ❑ un equipo experimentado
 - ❑ tratamiento sustitutivo apropiado

- ❑ Son necesarios estudios que permitan optimizar el elevado coste del tratamiento sustitutivo

- ❑ No existe consenso en la profilaxis tromboembólica y debiera individualizarse

EQUIPO MULTIDISCIPLINAR

