Peri-operative management of patients with haemophilia and inhibitors

Paul Giangrande
Green Templeton College
University of Oxford

paul.giangrande@gtc.ox.ac.uk
Inhibitors and haemophilia:

- Develop in ≈20% of patients with haemophilia A
- Much less common in haemophilia B (≈4%)
- Bleeding episodes not necessarily more frequent but certainly more difficult to control
- Tend to develop early in life (≈ ED 10) in PUPs, but can appear for first time in later life
- Major risk factor is underlying genotype
- Can occasionally develop in patients with mild or moderate haemophilia A (FVIII 1-5%):
  - Incidence of 6% after 50 ED in INSIGHT study
  
Inhibitor testing:

• Appearance of inhibitors in peri-operative period can have serious consequences, particularly if resources are not available to treat patient with bypassing agents

• All patients undergoing surgery should be screened for inhibitors shortly beforehand

• Sensitive screening test required: sample must be drawn after washout period to ensure reliable result is obtained
  • Heat treatment (56°C for 30 mins) improves sensitivity


• Failure to screen patients periodically will result in failure to identify transient and/or low titre inhibitors

• Patients with mild haemophilia can develop inhibitors
  – Intensive treatment with factor VIII (e.g. for surgery) is a recognised risk factor for inhibitor development in such cases
Do not get caught out!

- Negative result can provide false reassurance
- Low titre or fluctuating inhibitory antibodies may not be detected even in very good laboratories
- Important to review previous laboratory test results and clinical records before surgery
- Be alert after surgery! Consider possibility of inhibitor development if patient bleeds despite apparently adequate therapy
- Desirable to have stock of bypassing agents available when operating on any haemophilic patient just in case problems arise unexpectedly
First time development of inhibitors during postoperative period:


- 6/35 (19%) in this series of patients from India developed inhibitors after surgery
- Adverse effect on clinical outcome
- Patients in less affluent countries often have little prior exposure to FVIII before elective surgery
- Failure to screen patients on a periodic basis beforehand can result in transient inhibitor development being missed
  - Poor laboratory technique can also result in false negative screening test immediately prior to surgery
- Bypassing agents very expensive: may simply not be affordable in many countries
“The presence of antibodies to factor VIII or IX remains a contraindication to elective surgery as maintenance of adequate factor levels postoperatively is extremely difficult.”

Prof. R. B. Duthie

In: “Management of musculoskeletal problems in the haemophilias” (1994)
Inhibitors patients often denied surgery:

• “All but essential surgery is generally avoided in haemophilia patients with inhibitor antibodies, because of concern about the reliability with which haemostasis can be achieved and maintained in such patients”
• “Orthopaedic surgical procedures which are not required to preserve life fall under this category.”
• “As a result, patients with inhibitors may be denied operations, which could greatly enhance their quality of life, and which are routinely offered to other haemophilia patients.”
• “We believe that the threshold for offering validated surgical procedures to patients with inhibitors should be re-evaluated in the light of..... the long experience with safe and effective factor VIII inhibitor bypassing agents”
Bypassing agents:

• Both FEIBA and NovoSeven lead to thrombin generation on platelet surface, independently of presence of factor VIII
• These are the only licensed treatments for surgery in haemophilic patients with inhibitors
• Many publications document safe and effective use of two principal agents in setting of surgery
• Antibody titre of no relevance to choice or dose of product
Bypassing agents:

• Efficacy of both agents in controlling bleeds is considered to be similar:
  – “Based on the available randomised evidence, it is not possible to consider one treatment more efficacious or safer than the other.”
  
  Matino D, Iorio A, Makris M. Cochrane Database of Systematic Reviews CD004449 (2015)

• Laboratory monitoring not needed to monitor treatment with either product, even for surgery:
  – Thrombin generation and thromboelastography assays under development but no consensus on application yet
  
FEIBA or NovoSeven? (1):

• Pathogen safety:
  – FEIBA is plasma-derived product
    • Dual viral elimination step (vapour heat and nanofiltration)
    • Long track record of viral safety
  – NovoSeven is a recombinant product

• Half-life/duration of action:
  – Half-life of FEIBA is 6-9 hours as measured by thromboelastography and thrombin generation
  – NovoSeven has short half-life of ≈ 3 hours

• Capacity to boost factor VIII antibody titre:
  – FEIBA contains traces of factor VIII and anamnestic response seen in ≈ 20% of cases
  – This phenomenon is not seen with NovoSeven
  – Only relevant if about to start immune tolerance or hoping to use factor VIII again in near future
FEIBA or NovoSeven? (2):

• Thromboembolism (including DIC, MI, PE):
  – Both bypassing agents associated with risk of venous and arterial thromboembolism
  – Risk arguably lower with NovoSeven
  – Tranexamic acid can be usefully given together with rVIIa but should not be used with FEIBA

• FEIBA contains FIX: should not be used in the rare patients with inhibitors to FIX as this can provoke serious allergic reactions
Factor VIII inhibitor bypassing activity (FEIBA) – addressing safety issues

L. M. ALEDORT
Mount Sinai School of Medicine, New York, NY, USA

Table 2. Incidence of FEIBA-related thrombotic events reported by Aledort [19].

<table>
<thead>
<tr>
<th>Thrombotic events</th>
<th>FEIBA No. of adverse events</th>
<th>Incidence (per $10^5$ infusions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIC</td>
<td>3</td>
<td>1.55</td>
</tr>
<tr>
<td>MI</td>
<td>5</td>
<td>2.58</td>
</tr>
<tr>
<td>PE</td>
<td>2</td>
<td>1.03</td>
</tr>
<tr>
<td>Cerebrovascular thrombosis</td>
<td>2</td>
<td>1.03</td>
</tr>
<tr>
<td>Other thrombotic events</td>
<td>4</td>
<td>2.06</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>8.24</td>
</tr>
</tbody>
</table>

FEIBA, factor VIII inhibitor bypassing activity; DIC, disseminated intravascular coagulation; MI, myocardial infarction; PE, pulmonary embolism.
Thrombogenicity of NovoSeven:

• Review of adverse events report between May 2003-December 2006
• Patients with congenital or acquired haemophilia only (not off-label use)
• Covers administration of ≈ 800,000 doses
• 30 thromboembolic events and 6 fatalities
• 1 case of superficial thrombophlebitis after knee arthroplasty (not requiring anticoagulation)
• Prevalence of thromboembolic events: less than 4/100,000
Planning & practical aspects (1):

- Should only be conducted at a centre with specific surgical experience of inhibitor patients
- Good planning and teamwork required:
  - Ensure availability of key clinical, laboratory and nursing staff throughout scheduled inpatient stay
  - Ensure adequate stock of product available
  - Patient should undergo surgery early in the week and should ideally be scheduled for the morning list
  - Anticipate longer duration of stay than with other patients
  - “No such thing as minor surgery in a patient with haemophilia”
Planning & practical aspects (2):

• History of good response to chosen bypassing agent
• Exclude other haemostatic problems; e.g. check platelet count, prothrombin time:
  – Patient may have chronic liver disease or HIV infection
  – Many drugs (including herbal medications) can interfere with platelet function
• Use of epidural anaesthesia not recommended
• Use of limb tourniquet during surgery advised if possible
• Lignocaine and/or adrenaline for wound infiltration can help to reduce oozing and aid pain relief
• Some form of thromboprophylaxis advisable
Planning & practical aspects (3):

- Fibrin glue may be useful as adjunctive treatment to control capillary oozing.
- Cemented implants associated with less bleeding during surgery.
- Tranexamic acid may be given with NovoSeven:
  - Should not be used together with FEIBA.
- No requirement for laboratory testing to monitor treatment with either bypassing agent:
  - Thrombin generation being evaluated, but
  - No consensus on how to apply results in practice.
- Physiotherapy should be scheduled for shortly after dosing with bypassing agent.
Fibrin sealants:

- Contain human thrombin and fibrinogen: fibrin film forms immediately at site of spray application with double-barrelled syringe
  - Natural human plasma products which are biodegradable
  - Some brands also contain factor XIII and/or tranexamic acid to further enhance clot stability
- Reabsorption of the fibrin clot occurs naturally with normal wound healing
- Application not associated with fibrotic, inflammatory or foreign body reactions
- Particularly useful in patients with associated bleeding problems like thrombocytopenia, prolonged PT etc.
- May reduce need for blood transfusion

Application of fibrin sealant:
Application of fibrin sealant during hepatic surgery to control oozing:
Consensus protocol for the use of recombinant activated factor VII [eptacog alfa (activated); NovoSeven®] in elective orthopaedic surgery in haemophilic patients with inhibitors

Summary. Patients with haemophilia complicated by inhibitors have a significant burden of joint disease, which is associated with a negative impact on their quality of life. Successful elective orthopaedic surgery can result in decreased bleed frequency into a new joint, less time spent in hospital, increased mobility and improved well being. This paper describes a new protocol for use of recombinant activated factor VII (rFVIIa) in elective orthopaedic surgery, based on a review of published data as well as the personal experience of a group of expert physicians. The protocol offers guidance on the planning of the surgery and preoperative testing as well as the bolus schedule for rFVIIa and advice on the concomitant use of antifibrinolytic agents and fibrin sealants. A total of 10 operations involving 13 procedures in eight patients in five comprehensive care centres have been undertaken until now using the protocol, which employs an initial bolus dose of rFVIIa in the range of 120–180 µg kg⁻¹ to cover surgery. The clinical experience reported here encompasses all cases of elective orthopaedic surgery using rFVIIa as initial treatment carried out in the UK and Republic of Ireland over the last 2 years. In all cases, there was good control of haemostasis during surgery and the final outcome was rated as ‘excellent’ or ‘extremely satisfactory’ by the reporting clinicians. Although the initial cost of product to cover surgery such as arthroplasty is high, it needs to be borne in mind that this may be offset in subsequent years by savings resulting from avoidance of bleeding episodes in the affected joint.

Keywords: haemophilia, inhibitors, NovoSeven®, orthopaedic surgery, protocol, recombinant activated factor VII
Use of NovoSeven for surgery:

• Dosing with NovoSeven:
  – pre-op bolus of 120-180µg/kg prior to incision.
  – doses of 90µg/kg 2 hourly throughout surgery
  – final bolus given just prior to final reduction (hips) or tourniquet release (knees)
  – minimise microvessel bleeding using a fibrin sealant
  – take regular samples for clotting screen
  – continue 2 hourly for the next 48 hours

• Then 3 hourly for the next 48 hours (if good haemostasis)

• At day +5, increase interval to 4 hourly for next 3 days

• From day +8, administer doses 6 hourly until discharge (which will typically be around day 10-12)

• Administer a bolus prior to any sutures being removed
UK & Ireland cases:

• Total of 10 operations in 5 Comprehensive Care Centres in UK and Ireland
• Total of 13 procedures in 8 patients:
  – hip arthroplasty (THR): 2
  – knee arthroplasty (TKR): 7
  – shoulder arthroplasty: 1
  – ankle arthrodesis (fusion): 2
  – amputation of leg below knee: 1
• Multiple surgery at same time in 2 cases
• 1 patient had acquired haemophilia
Clinical information:

• Age range: 25-81 years
• Weight range: 50-98 kg
• Preoperative antibody titre range: 0-80 BU
• Initial pre-operative bolus (µg/kg):
  – 120 (1 operation)
  – 150 (1 operation)
  – 160 (2 operations)
  – 180 (6 operations)
Peri-operative course:

- Tranexamic acid given with rVIIa throughout in only 6/10 operations
- No centre used laboratory monitoring such as rVIIa assays, TEG etc
- Intra-operative haemostasis satisfactory in all 10 operations
- Final outcome rated as ‘excellent’ or ‘extremely satisfactory’ in all cases by the reporting clinicians
Recombinant activated factor VII in the treatment of bleeds and for the prevention of surgery-related bleeding in congenital haemophilia with inhibitors

Elena Santagostino\textsuperscript{a,\*}, Miguel Escobar\textsuperscript{b}, Margarethe Ozel\textsuperscript{c}, Luigi Solimeno\textsuperscript{d}, Per Arkhammar\textsuperscript{e}, Hye Youn Lee\textsuperscript{f}, Gabriela Rosu\textsuperscript{f}, Paul Giangrande\textsuperscript{g}

\textsuperscript{a}Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation Maggiore Policlinico Hospital, Milan, Italy
\textsuperscript{b}Gulf States Hemophilia and Thrombosis Center, University of Texas Health Science Center, Houston, TX, USA
\textsuperscript{c}IHTC, Cláudio L.P. Correa, Hemocentro Unicamp, INCT do Sangue, University of Campinas, Campinas, São Paulo, Brazil
\textsuperscript{d}Ortho-trauma Unit, Emergency Department, IRCCS Cà Granda Foundation Maggiore Policlinico Hospital, Milan, Italy
\textsuperscript{e}Novo Nordisk A/S, Søborg, Denmark
\textsuperscript{f}Novo Nordisk Health Care AG, Zürich, Switzerland
\textsuperscript{g}Oxford Haemophilia and Thrombosis Centre, Oxford University Hospitals NHS Trust, Oxford, UK

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\textbf{ABSTRACT}

The availability of recombinant activated factor VII (rFVIIa, eptacog alfa activated) has greatly advanced the care of patients with haemophilia A or B who have developed inhibitors against the infused replacement factor. Recombinant FVIIa is licensed for the on-demand treatment of bleeding episodes and the prevention of bleeding in surgery or invasive procedures in patients with congenital haemophilia with inhibitors. This article attempts to review in detail the extensive evidence of rFVIIa in congenital haemophilia patients with inhibitors. Patients with acute bleeding episodes are best treated on demand at home, to achieve the short- and long-term benefits of rapid bleed control. Key prospective studies have shown that rFVIIa achieves consistently high efficacy rates in the management of acute (including joint) bleeds in inhibitor patients in the home treatment setting. Substantial post-approval data from key registries also support the on-demand efficacy profile of rFVIIa established by the prospective clinical trials. The availability of rFVIIa has allowed major surgery to become a reality for inhibitor patients. Studies in key surgery, including orthopaedic procedures, have found that rFVIIa provides consistently high efficacy rates. Importantly, the wealth of data does not raise any unexpected safety concerns surrounding rFVIIa use; this is likely because rFVIIa is a recombinant product with a localised mechanism of action at the site of vascular injury. In summary, rFVIIa is established as an effective and well-tolerated first-line treatment for on-demand bleeding control and bleed prevention during minor and major (including elective orthopaedic) surgery in inhibitor patients. Use of rFVIIa has been a major step towards narrowing the gap in outcomes between inhibitor patients and non-inhibitor patients.
Recombinant Factor VIIa (Eptacog Alfa)
A Pharmacoeconomic Review of its Use in Haemophilia in Patients with Inhibitors to Clotting Factors VIII or IX

Katherine A. Lyseng-Williamson and Greg L. Plosker

Wolters Kluwer Health  Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

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C.L. Bennett, Department of Health Services, Research and Development, Lakeside Veterans Affairs Hospital, Chicago, Illinois, USA; E. Berntorp, Malmö Centre for Thrombosis and Haemostasis, Malmö University Hospital, Malmö, Sweden; G. Kenet, Israeli National Hemophilia Center, Sheba Medical Center, Tel-Hashomer, Israel; M. Morfini, Agency for Haemophilia, Azienda Ospedaliera Universitaria Careggi, Florence, Italy; M.C. Ozelo, Hematology and Hemotherapy Center, Universidade Estadual de Campinas, Campinas, Brazil; N.I. Zozulya, Haematological Scientific Research Centre, Haemophilia Centre, Moscow, Russian Federation.

Orthopaedic surgery with recombinant factor VIIa to maintain haemostasis in haemophilia patients with inhibitors is generally predicted to be cost saving relative to not having surgery over the medium to long term (table VI).[55-57] In the analyses
Pharmacoeconomic study:

• Independent analysis not linked with NovoNordisk
• Time to break even*: 5-9 years
  *time after surgery when cost is completely offset by savings resulting from avoided bleeding episodes
• Break-even time most sensitive to changes in bleeding rate prior to surgery: cost reduction more evident in patients with high initial bleed rate
• More obvious benefit also seen in arthroplasty as compared to osteotomy, synovectomy etc as number of subsequent joint bleeds is more drastically reduced after more radical surgery
• Combining two procedures in one operative session obviously makes surgery even more cost effective
Consensus recommendations for the use of FEIBA® in haemophilia A patients with inhibitors undergoing elective orthopaedic and non-orthopaedic surgery

S. RANGARAJAN,*† S. AUSTIN,‡ N. J. GODDARD,$ C. NÉGRIER,*¶ E. C. RODRIGUEZ-MERCHAN,*∗†† D. STEPHENSEN‡‡ and T. T. YEE§§

*Centre for Haemostasis & Thrombosis, St Thomas’ Hospital, London, UK; †Haemophilia, Haemostasis & Thrombosis Centre, Basingstoke & North Hampshire NHS Foundation Trust, Basingstoke, UK; ‡St George’s Healthcare NHS Trust Haemophilia Centre, St George’s Hospital, London, UK; ¶Department of Orthopaedic Surgery, Royal Free Hospital NHS Foundation Trust, London, UK; §Haemostasis Division, Hôpital Édouard Herriot, Lyon, France; ∗∗Department of Orthopaedic Surgery, La Paz University Hospital, Madrid, Spain; ††School of Medicine, Autonomous University, Madrid, Spain; ‡‡Kent Haemophilia Centre, Kent & Canterbury Hospital, Canterbury, Kent UK; and §§The Katharine Dormandy Haemophilia Centre and Thrombosis Unit, Royal Free Hospital NHS Foundation Trust, London, UK

Summary. A growing number of publications have described the efficacy and safety of FEIBA as a first-line haemostatic agent for surgical procedures in haemophilia A patients with high-responding FVIII inhibitors. The aim of this study was to provide practical guidance on patient management and selection and also to communicate a standardized approach to the dosing and monitoring of FEIBA during and after surgery. A consensus group was convened with the aims of (i) providing an overview of the efficacy and safety of FEIBA in surgery; (ii) sharing best practice; (iii) developing recommendations based on the outcome of (i) and (ii). To date there have been 17 publications reporting on the use of FEIBA in over 210 major and minor orthopaedic and non-orthopaedic surgical procedures. Haemostatic outcome was rated as ‘excellent’ or ‘good’ in 78–100% of major cases. The reporting of thromboembolic complications or anamnestic response to FEIBA was very rare. Key to the success of FEIBA as haemostatic cover in surgery is to utilize the preplanning phase to prepare the patient both for surgery and also for rehabilitation. Haemostatic control with FEIBA should be continued for an adequate period postoperatively to support wound healing and to cover what can in some patients be an extended period of physiotherapy. Published data have demonstrated that FEIBA can provide adequate, well tolerated, peri and postoperative haemostatic cover for a variety of major and minor surgical procedures in patients with haemophilia A. The consensus recommendations provide a standardized approach to the dosing and monitoring of FEIBA.

Keywords: activated prothrombin complex concentrates, bypassing agents, FEIBA, haemophilia, inhibitors, surgery
Guidelines on use of FEIBA:

- 17 publications reporting on use of FEIBA in over 210 major and minor procedures
- Haemostatic efficacy rated as “excellent” or “good” in 78-100%
- Recommended initial dose of 50-100 U/kg 12-24 hourly for 7 days for minor surgery
- Recommended initial dose of 75-100 U/kg 8 hourly for first 7 days for major surgery
  - reducing to 12 hourly thereafter
Table 2. FEIBA dosing regimen – major & minor surgical procedures.

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Day 1–7</th>
<th>Day 8–21</th>
<th>Weeks 4–6 (Rehabilitation &amp; physiotherapy)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major procedure</td>
<td>75–100 U kg(^{-1}) bw</td>
<td>75–100 U kg(^{-1}) bw at 8 h intervals(^*)</td>
<td>75–100 U kg(^{-1}) bw at 12 h intervals(^†)</td>
<td>75–80 U kg(^{-1}) bw once per day for 1 week, then every other day for weeks 5 &amp; 6</td>
</tr>
<tr>
<td>Minor procedure</td>
<td>50–100 U kg(^{-1}) bw</td>
<td>50–100 U kg(^{-1}) bw at 12–24 h intervals</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^*\)Dosing and frequency should be in accordance with the current local product licence. Carrying out a thrombin generation test may be useful to establish the target dose and monitor patient response.

\(^†\)For up to 21 days if required.

\(^‡\)The rehabilitation phase and requirement for FEIBA prophylaxis may extend beyond 6 weeks for patients undergoing multiple procedures who are at risk of bleeding.
Options if bleeding occurs despite treatment with chosen bypassing agent:

- Consider urgency and site of bleed
- Add in tranexamic acid, if using NovoSeven
- Any other haemostatic disorder?
- Further dose of same product at higher dose
  - Shorten interval between doses
- Review history of response to treatment of previous episodes, if available
- Switch to other bypassing agent
- Sequential or combined therapy, using both bypassing agents:
  - limited case reports; no clinical trials; unlicensed strategy but could be justified in serious cases
A surgeon’s perspective:
Goddard N in: Haemophilia 18 (Suppl. 4): 54-60 (2012)

• “Bypassing agents have made previously impossible surgery possible”
• “Surgeons are more willing to undertake surgery in patients with inhibitors”
• “Follow-up has been relatively short”
• “We are now at a stage when we need to establish the orthopaedic outcomes in these patients rather than merely judging success by achieving haemostasis”
• “A registry should be established”
Principal conclusions:

• Elective surgery of any type now feasible and safe in patients with haemophilia and inhibitors
• Good planning and teamwork is required
• Can use either FEIBA or NovoSeven:
  – FEIBA has longer duration of action
  – NovoSeven is a recombinant product and also has lower risk of thrombogenicity
• Laboratory monitoring not necessary
• Fibrin sealants may be useful intra-operatively
• High initial cost for surgery, but may prove cost-saving in long-term due to reduction in bleeds