Orthopaedic Surgery in patients with inhibitors: A Haematologists Perspective

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Inhibitor development is the most serious complication of congenital haemophilia.

Life becomes challenging as bleeding episodes can no longer be treated with FVIII replacement.

Patients become dominated by risk of:
- difficult to control bleeding
- arthropathy
- delays to surgery
- physical disability

Options for treatment are intense and impact on quality of life.
### Inhibitor development in Haemophilia: Risk factors

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of hemophilia</td>
<td>Number of exposure days</td>
</tr>
<tr>
<td>$F8$ gene mutation</td>
<td>Intensity of treatment</td>
</tr>
<tr>
<td>Family history of inhibitor</td>
<td>Age at first exposure</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Type of FVIII concentrates</td>
</tr>
<tr>
<td>Polymorphisms of immune-response genes</td>
<td>Current infection or inflammatory state</td>
</tr>
</tbody>
</table>
Orthopaedic Status of Haemophilia Patients With Inhibitors compared to non-inhibitor patients

<table>
<thead>
<tr>
<th></th>
<th>Group A Inhibitor (14-35y)</th>
<th>Group B Inhibitor (36-65y)</th>
<th>Group C No Inhibitor (14-35y)</th>
<th>A vs C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>n = 38</td>
<td>n = 41</td>
<td>n = 49</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>14-35</td>
<td>36-65</td>
<td>14-35</td>
<td></td>
</tr>
<tr>
<td>Inhibitor Status</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for Orthopaedic Procedures</td>
<td>16%</td>
<td>27%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Use of Wheelchairs</td>
<td>24%</td>
<td>22%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Need for Walking Aid</td>
<td>50%</td>
<td>51%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Pain Evaluation All Joints</td>
<td>3.89 ($\pm$ 3.26)</td>
<td>5.82 ($\pm$ 5.29)</td>
<td>2.27 ($\pm$ 2.67)</td>
<td>(P &lt; .05)</td>
</tr>
<tr>
<td>Clinical Examination</td>
<td>15.4 ($\pm$ 13.6)</td>
<td>23.2 ($\pm$ 11.6)</td>
<td>5.46 ($\pm$ 7.11)</td>
<td>(P &lt; .05)</td>
</tr>
<tr>
<td>Radiological Evaluation</td>
<td>27.8 ($\pm$ 19.6)</td>
<td>35.8 ($\pm$ 26.4)</td>
<td>19.3 ($\pm$ 12.4)</td>
<td>(P &lt; .05)</td>
</tr>
</tbody>
</table>
Joint status in inhibitor patients

**Children**
- Joint ROM in 2378 severe haemophilic children (age 2-19 years)
- n=186 with inhibitors >2-fold greater loss of ROM than non-inhibitor patients

**Adolescents / Young adults**

Joint function (ankles, knees, elbows) in 122 severe hemophiliacs (mean age 22.4 years) and 22 inhibitor patients (mean age 21.2 years)

Leissinger et al, Blood 2001

Soucie et al, Blood 2004
QoL - EQ-5D in Inhibitor Patients Compared With Noninhibitor Patients

Group A: n = 38 severe haemophilia A, aged 14-35 years, with inhibitors >5 years

Group B: n = 41 severe haemophilia A, aged 36-65 years, with inhibitors >5 years

Group C: n = 49 severe haemophilia A, aged 14-35 years, without inhibitors >5 years

Joint Surgery in patients with Haemophilia and inhibitors
Haemostatic control during orthopaedic surgery is one of the most challenging situations of haemophilia care

- For haemostatic control during surgery, two bypassing agents exist in Europe:
  - **FEIBA** (Factor eight inhibitor bypass activity; Baxalta (now part of Shire), Deerfield, IL, USA)
  - **Novo Seven** (Novo Nordisk A/S, Bagsværd, Denmark)

  have been used either separately or in parallel (combined or sequentially)

- A third Haemostatic agent exists in Japan (since Nov 2014)
  - **Byclot** (Kaketsuken, Kumamoto, Japan)
    - a complex concentrate of plasma-derived FVIIa and factor X (FX; pd-FVIIa/FX)
Management of Surgery with bypassing agents

- **Bypassing agents**
  - Recombinant FVIIa (Novoseven) (90-270 ug/kg)
  - Activated prothrombin complex concentrate (FEIBA)
    - 50-100 units/kg
      (max 200 units /24 hours)
  - Both lead to thrombin generation on the platelet surface independent of FVIII
Bypassing agents: laboratory changes with thrombin generation

- Ex-vivo studies of both bypassing agents are unable to generate thrombin to the same level as non-inhibitor patients treated with FVIII.

- Unclear how much improvement in thrombin generation is required to achieve clinical benefit.

- In many even a small improvement may be sufficient.

- May account for significant intra- and inter-individual variability in efficacy.

Limitations of Bypassing Agents

- No laboratory surrogate marker to correlate with haemostatic efficacy
- Haemostasis efficacy determined clinically
- Variability in individual responses to agents
  - limited predictors of efficacy
- Dosage, frequency not well defined
- Duration of therapy not well defined
- Agents infrequently used
  - Needs to be expert-lead
- Requires significant resources
  - Nursing input
  - Multidisciplinary involvement
- Expensive
Efficacy of Bypassing Agents

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Product</th>
<th>No of episodes</th>
<th>Response</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective</td>
<td>FVIII</td>
<td>18</td>
<td>Good 100%</td>
<td>None</td>
</tr>
<tr>
<td>Retrospective</td>
<td>aPCC</td>
<td>32</td>
<td>Good 96.9% (31/32)</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Retrospective</td>
<td>rFVIIa</td>
<td>14</td>
<td>Good 71.4% (10/14)</td>
<td>Bleeding</td>
</tr>
</tbody>
</table>

aPCC efficacy ranges from 64-90%
rFVIIa efficacy ranges from 80-95%

19 Centres
35 surgical procedures
- 37.1% procedures described as ‘high risk’
Haemostasis control
- Good or excellent in 91.2% (31/34)
- Fair in 8.8% (3/34)

“aPCC can be safely and effectively used when performing surgical procedures in Haemophilia A patients with inhibitors”

FEIBA dosing for Major procedures:

- 75-100 U/kg preoperatively
- 75-100 U/Kg 8 hourly for days 1-7
- 75-100 U/kg 12 hourly for days 8-21
- 75-100 U/kg once a day for a week
- 75-100 U/kg alternate day for weeks 5-6
# Dosage recommendations for rFVIIa in surgery

<table>
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<tr>
<th></th>
<th>Pre-OP</th>
<th>Days 1-5</th>
<th>Days 6-14</th>
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<tbody>
<tr>
<td>Minor Orthopedic (eg. arthroscopy)</td>
<td>90-120 ug/kg</td>
<td>90–120 ug/kg q2 h x 4, then q3–6 h for 24 h</td>
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</tr>
<tr>
<td>Minor Non-orthopedic</td>
<td>90-120 ug/kg</td>
<td>90–120 ug/kg q2 h x 4, then q3–6 h for 24 h</td>
<td>90 ug/kg 6hry (until repair) ?</td>
</tr>
<tr>
<td>Major surgery</td>
<td>120 ug/kg</td>
<td>120 ug/kg q 3 h day 2/day 3-5</td>
<td>90-120 ug/kg 6 hrly</td>
</tr>
</tbody>
</table>

rFVIIa in surgery: Using an intermittent pump device
Antifibrinolytic therapy in surgery

Tranexamic acid

- Synthetic Lysine analogue
- Blocks the lysine binding sites on plasminogen and prevent activation to plasmin
- The most favourable anti-fibrinolytic
- Years of experience in bleeding disorders
- Mainly studied in Cardiac and orthopaedic settings
Increasing FVIII levels with porcine FVIII

- Lower chance of cross-reactivity compared to congenital haemophilia A pts
- Good haemostatic efficacy in 78% of bleeds - partial response 11%; no response in 9%.
  (Morrison et al., Blood 1993)

- Adverse events: allergic reactions, thrombocytopenia, development of pFVIII antibodies

- Plasma derived porcine FVIII no longer available;
- Recombinant B-domain deleted porcine FVIII (Obizur) now available
Novel non-replacement therapies in Haemophilia

- Novel non-replacement therapies may be useful as surgical prophylaxis for inhibitor patients
  - **ALN-AT3SC (Fitursiran)**: an RNAi therapeutic targeting the natural anticoagulant antithrombin
  - **ACE910 (Emicizumab)** bispecific monoclonal antibody that mimics FVIII
  - **Anti Tissue factor pathway inhibitor (TFPI)** Concizumab monoclonal antibody

- **Alternative bypassing agents**
  - Factor Xa variants
  - Factor Va variants
Complications of Surgery in Haemophilia patients with inhibitors

Complications include:

- excessive/uncontrolled bleeding
- death
- poor wound healing
- subsequent risk of infection
- anamnestic response
- thromboembolism/disseminated intravascular coagulation
- increased cost of treatment
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Addressing bleeding risk in Haemophilia patients with inhibitors

- Type of surgical procedure
  - minor / major

- Patients inhibitor titre
  - <5BU – FVIII replacement can be considered
  - >5BU – Bypassing agents are treatment of choice

- Patients anamnestic response

- Patients usual response to bypassing agents

- Patients comorbidities
  - May affect response to therapies
Multidisciplinary collaboration is paramount for successful surgery of Haemophilia patients with inhibitors

- A key step for the success of a major elective surgery in inhibitor patients is excellent communication and collaboration:
  - patient
  - expert haematologist
  - experienced surgeon
  - anaesthetist
  - pharmacist
  - Nursing staff
  - laboratory staff
  - Specialist Physiotherapist

Basic principles

Patients with FVIII/IX inhibitors must be registered with, and have their treatment co-ordinated by a Comprehensive Care Haemophilia Centre (CCC) experienced in the management of inhibitors (National Service Specification available at www.ukhnedo.org). Centres must provide 24-h access to senior clinicians with experience in inhibitor management and laboratory services for the measurement of factor levels and inhibitor titres. Patients should be offered inclusion in appropriate clinical trials and reported to registries. UK patients must be registered with the National Haemophilia Database and details of their inhibitor reported as soon as they are confirmed.
Inhibitors are a challenge to all

THANK YOU FOR YOUR ATTENTION!
ANY QUESTIONS?