Outcomes of low-dose prophylaxis in children

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Egypt
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<tr>
<th>Conflict</th>
<th>Disclosure - if conflict of interest exists</th>
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<tr>
<td>Research Support</td>
<td>Non</td>
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<tr>
<td>Director, Officer, Employee</td>
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<td>Shareholder</td>
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<td>Advisory Committee</td>
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<td>Consultant</td>
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**ADDITIONAL TEXT EXAMPLE**
Progressive nature of haemophilia

Haemorrhage → Synovial inflammation

- Synovial impingement and contracture or function loss
- Recurrent haemarthroses

Synovial hypertrophy

- Direct synovial invasion
- Enzyme degradation

Adapted from: Silva et al. WFH 2004, 33
Prophylaxis

• It is equally well established that if prophylaxis is started early in life, musculoskeletal problems are reduced or prevented (Manco-Johnson et al. NEJM 2007;357:535-544)

• It is recommended therefore that prophylaxis should be
  ✓ the treatment of choice for people with severe haemophilia
  ✓ started at least after the first joint bleed

Prophylaxis

• the main objective of primary prophylaxis is therefore to reduce the number of joint bleeds by maintaining the patient’s plasma FVIII-FIX levels >1 IU/dL

• efficacy of prophylaxis in reducing:
  o the annual number of major bleeds,
  o clinic visits, and hospitalizations,
  o the development of arthropathy

• regular prophylaxis may be an independent negative predictor associated with a 60% lower risk of inhibitor development than on-demand treatment.
MODELS OF PROPHYLAXIS
The Malmö model

Prophylaxis is started around the age of 1 year, when children begin to walk and before the occurrence of the first joint bleed;

*Nilsson et al* reported a large series of 60 patients on prophylaxis who received 25-40 IU/kg
  - three times a week for hemophilia A
  - twice weekly for hemophilia B.

Clinically, no bleeds were observed and the radiologic joint scores were zero, ie, absence of abnormality;

Over the years, the Malmö protocol has been refined and is currently 20-30 IU/kg
  - every other day in hemophilia A and
  - every third day in hemophilia B.

JCD 2010; 2:(2). July 2010
The Dutch intermediate-dose prophylaxis

Prophylaxis is started in children after the occurrence of at least one joint bleed with

- twice weekly infusions for hemophilia A,
- once weekly infusions for hemophilia B and
- the frequency of infusions are intensified over the years according to the patient’s bleeding pattern.

Patients generally receive

- 15-25 IU/kg two or three times a week for hemophilia A and
- 30-50 IU/kg once or twice weekly for hemophilia B.

Bleeding frequency is evaluated by clinical follow-up.
The Canadian-tailored prophylaxis

An individualized approach by dose-escalation is used

**Step 1** - all children with severe hemophilia A begin early prophylaxis with 50 IU/kg of FVIII once weekly.

**Step 2** - 30 IU/kg twice weekly
- three or more hemorrhages into a single joint or
- four clinically determined soft tissue or joint hemorrhages affecting any site within a consecutive 3-month period or
- five or more bleeds into any single joint over any time period,

**Step 3** - 25 IU/kg every other day (three times a week).

JCD 2010; 2:(2). July 2010
The French protocol

• very similar to the Canadian protocol,
• tolerates less breakthrough bleeds.
• as a consequence, patients are escalated quicker in the French protocol compared with the Canadian regimen

JCD 2010; 2:(2). July 2010
Tailored prophylactic regimens

• favored in Canada, the Netherlands and France beginning at a low frequency and escalating with repeated bleeding may prevent
  ✓ arthropathy and
  ✓ life-threatening bleeding at a lower cost than the high dose Malmo® protocol,

• but they carry the risk that certain patients may exhibit some joint bleeds before dose escalation occurs.

JCD 2010; 2:(2). July 2010
Prophylaxis with lower doses of CFCs

Efficacy and feasibility?!
Aim

• Explore feasibility and effectiveness of lower dose prophylaxis in resource limited settings
• Experience from 3 countries in Middle East:
  – Tunisia
  – Algeria
  – Egypt
PROPHYLAXIS IN TUNISIAN PATIENTS WITH HEMOPHILIA

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Medical School of Tunis  
University El Manar
PROTOCOL ADAPTED FOR PROPHYLAXIS HEMOPHILIA A

20 to 30 IU/kg once a week /10 to 15 IU/kg twice a week

Clinical evaluation after one month

No bleeding: OK

Bleeding: 20 IU/kg twice a week

Clinical evaluation after one month

No bleeding: OK

Bleeding: 10 to 15 IU/kg thrice a week
PROTOCOL ADAPTED FOR PROPHYLAXIS HEMOPHILIA B

25 to 35 IU/kg once a week

Clinical evaluation after one month

No bleeding

OK

Bleeding

15 to 25 IU/kg twice a week
WEEKLY MEDIAN
CONSUMPTION IU/kg

- HA: 30 IU/kg week
- HB: 30 IU/kg week
RESULTS AND ASSESSMENT TOOLS

45 CHILDREN

- Number of annual bleeding
- Hemophilia joint score
- Functional independence score in hemophilia
- Absenteeism school
- Quality of life
  - Hemo-QoL
- Some patients underwent an ultrasound exam
AGE OF INITIATION OF PROPHYLAXIS

Mean age 5.06y
Median 4.75y
FOLLOW UP

Mean follow up 3.46 y
Median follow up 3.75y
## TOTAL ANNUAL BLEEDING

<table>
<thead>
<tr>
<th>Total annual bleeding</th>
<th>Before prophylaxis</th>
<th>After prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before prophylaxis</td>
<td>460</td>
<td></td>
</tr>
<tr>
<td>After prophylaxis</td>
<td>42</td>
<td></td>
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</tbody>
</table>
## SCHOOL ABSENTEEISM

<table>
<thead>
<tr>
<th></th>
<th>BEFORE PROPHYLAXIS</th>
<th>AFTER PROPHYLAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDIAN NUMBER DAYS</td>
<td>1-2 week/year</td>
<td>0-1 day/year</td>
</tr>
<tr>
<td>ABSENT FROM SCHOOL/WORK</td>
<td></td>
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</table>
RESULTS

• Reduction of bleeding
• Reduction of absenteeism
• Improvement of quality of life (good compliancy)
Experience in primary Prophylaxis in an emerging country ‘Algeria’ and
The preliminary results of a low dose protocol.

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Hematology Department,
University Hospital Beni Messous
ALGIERS-ALGERIA
Hemophiliacs under low dose IaryP: The *Beni Messous* experience

- Observational, descriptive and prospective study.

- **Purpose of the study:** To compare the group of HA patients under “low dose protocol” (n = 14) with a group of patients under “on demand treatment” DT (n=10).

- **Primary endpoint:** To assess the efficacy of a low-dose protocol vs on demand treatment (DT), in the prevention of bleeding episodes in severe HA.

- **Secondary endpoint:** To compare the factor VIII consumption under low-dose protocol vs DT.
Hemophiliacs under low dose IaryP: The Beni Messous experience

• **Study population:**

  Low dose protocol group: 14
  - Age at baseline: 3 - 4 years
  - **Age at assessment:** 6 – 7 years ➔ average 6.5 years

  On demand treatment: 10
  - Age at baseline: 4 – 5 years
  - **Age at assessment:** 7 – 8 years ➔ average 7.5 years
Hemophiliacs under low dose I\text{ary}P: The Beni Messous experience

• **Study protocols:**
  
  Low dose = 15 IU / kg 2x/week FVIII (Kogenate \textsuperscript{\textregistered} 250 UI)
  
  On demand treatment = 25-30 IU/kg 2 or 3x/day (2 or 3 days)

• **Follow up:**
  
  6 months – 4 years
  
  10/14 patients \(\geq 2\) years \(\Rightarrow\) average 2.5 years

• **Analyze of the results (per protocol):**
  
  10/14 patients low-dose protocol group.
  
  1 Lost (no longer come in consultation)
  
  3 follow up < 2 years
Hemophiliacs under low dose I\textsubscript{aryP} : The *Beni Messous* experience

**Results of the study:**

I\textsubscript{aryP} n=10 vs DT n=10
Bleeding episodes / year:

<table>
<thead>
<tr>
<th>Types of bleeding</th>
<th>DT</th>
<th>IaryP</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>B</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>C</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>E</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4</td>
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A = Haemarthrosis, B = Haematomas, C = mucosal bleeding, D = hemorrhage at the fall of a tooth, E = sutured wound

Number of episodes: DT = 216, IaryP = 43

p = 0.02
Haemarthrosis / year:

Number of episodes

<table>
<thead>
<tr>
<th>Sites of Haemarthrosis</th>
<th>DT</th>
<th>laryP</th>
</tr>
</thead>
<tbody>
<tr>
<td>knees</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>ankles</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>elbows</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>wrists</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>other</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Target joints:

Sites of target joints

- Knees: 8 patients
- Ankle: 4 patients
- Elbow: 2 patients
- Wrist: 0 patients

p < 0.05
Factor VIII Consumption / year:

Average Total consumption / patient / year under:

- Low dose I¹aryP = 21 015 IU / kg
- DT = 16 110 IU / kg
**Target joint?**

- **Under TD**, all patients (100%) had at least one target joint ➔ 14 target joint/10 patients
  ➔ 1 to 3 / patient ➔ knee + + +.
- **Under low dose IaryP**, only 20% of patients had a target joint ➔ 02 target joint/10 patients
  ➔ ankle.

Indeed, regardless of the IaryP protocol, the ankle remains a target joint ➔ which is why, IaryP should start early, before the age of three years.

- Olivieri M, Kurnik K, Pfluger T and Bidlingmaier C. Identification and long-term observation of early joint damage by magnetic resonance imaging in clinically asymptomatic joints in patients with haemophilia A or B despite prophylaxis. Haemophilia (2012), 18, 369–374
Factors VIII Consumption?

- On demand treatment:
  \[ \text{average intake of 1611 IU / kg / patient / year.} \]
- Under low dose I\text{aryP}:
  \[ \text{average intake of 1751 IU / kg / patient / year.} \]

\[ \text{In our study, the consumption of FVIII in the low dose I\text{aryP} group, is substantially, the same as on demand treatment group (p=0.32).} \]
Conclusion: in Algeria

Low Prophylaxis with low dose:

Reduce bleeding episodes, including hemarthrosis.
Keep joints functional in severe hemophilia => avoid motor disability.

with a consumption of FVIII as much as on demand treatment

=> The follow up, in the long term, with regular evaluations (2 years), allow us to judge, the effectiveness of this protocol in the prevention of arthropathy.
Individualized Low-Dose Prophylaxis using S/D-F cryoprecipitate
Egypt
SD-F Cryoprecipitate

**S/D-F cryoprecipitate kit**

**Quality of SD-F Cryoprecipitate (500 batches)**

- Mean FVIII: 9.6 u/ml
- Mean VWF: >10 u RiCof activity/ml
- Mean Fibrinogen: 32mg/ml
- No ABO iso-agglutinins
- No residual blood cells or cell debris
- Suspended in 5% glucose saline and stored frozen at -20°C or colder for 1 year from preparation date

S/D-F: solvent/detergent-filtered
FVIII clotting factor

- Pharmaceutical grade S/D-F cryoprecipitate
- Possibility of FI, FVIII, VWF and FXIII dose labelling
ORIGINAL ARTICLE

Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system

M. El-Ekiaby,1 M. A. Sayed,2 C. Caron,3 S. Burnouf,4,5 N. El-Sharkawy,7 H. Goubran,8 M. Radosevich,6 J. Goudemand,3 D. Blum,4,5 L. de Melo,9 V. Soulié,9 J. Adam9 & T. Burnouf6 1Shabrawishi Hospital Blood Bank, Giza, Egypt, 2Fayoum University, Fayoum, Egypt, 3Laboratoire d’hématologie, Hôpital Régional et Universitaire Lille, 4INSERM, U837, 5Université Lille-Nord de France, IMPRT, Jean-Pierre Aubert Research Centre, 6Human Protein Process Sciences, Lille, France, 7National Cancer Institute, 8Faculty of Medicine, Cairo University, Cairo, Egypt, and 9V.I.P.S. SA Virus Inactivation of Plasma Systems, 2013 Colombier, Switzerland
Original article Clinical haemophilia

Pharmacokinetic study of minipooled solvent/detergent-filtered cryoprecipitate factor VIII

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*Shabrawishi Hospital Blood Bank, Giza, Egypt; †Saskatoon Cancer Centre, University of Saskatoon, Saskatoon, Canada; ‡Faculty of Medicine, Cairo, Egypt; §Human Protein Process Sciences, Lille, France; and ¶College of Oral Medicine, Taipei Medical University, Taipei, Taiwan
Aim

- Explore feasibility and effectiveness of lower dose FVIII prophylaxis in resource limited settings
- Inclusion criteria:
  - Age 2-5 years:
    - Start after second bleed in an index joint
  - No inhibitors
FVIII dose

• Prophylaxis
  - 20 iu of FVIII once/week
  - If breakthrough bleed: increase to 20 iu twice/week
  - If more breakthrough bleed: 20 iu 3 times/week

• Breakthrough bleeding:
  - Minor bleed: 20iu/Kg
  - Major bleed 50iu/Kg

• Resume prophylaxis after control of the bleed
Inhibitors

• Screening for inhibitors
  – Before enrollment
  – Every fourth exposure day for the first 20 exposure days
  – Every 6 months or when signs of poor response to CFC infusion is observed
  – Pre-surgical procedures
Primary outcome measures

- ABR
- Development of inhibitors
- Functional score
- No major CNS or internal bleeds

ABR: annualised bleeding rate; CNS: central nervous system
Follow up

- 12 children with severe hemophilia A are enrolled since January 2011
- 8 children have a mean follow-up period of 33.55 months (12–38 months)
- The mean age at start was 31.11 months (24–38 months)
- The average FVIII consumption/kg/year is 1403 IU (892–2989 IU)
- 6 out of 8 children are on S/D-F cryoprecipitate infusion once weekly, one twice-weekly, and one three-times weekly

HBV: hepatitis B virus; HCV: hepatitis C virus; HJUS: haemophilia joint health score; HIV: human immunodeficiency virus
Follow up

- Mean ABR is 2 (1–6)
- HJHS of the children is 0
- No development of FVIII inhibitors
- No CNS or internal bleeding despite report of head and abdominal trauma in at least 3 kids and in more than one incident
- No adverse events from the infusion of SD cryoprecipitate
- No recorded transfusion transmitted HBV, HCV or HIV

HBV: hepatits B virus; HCV: hepatitis C virus; HJUS: haemophilia joint health score; HIV: human immunodeficiency virus
Conclusion

- Primary data of low dose prophylaxis indicate:
  - low dose prophylaxis reduces ABR
  - Preserves MSK and hence physical, mental and social activities
  - The primary data can be used to model long term needs
General Conclusions

• Experiences from 3 countries demonstrate:
  – Early age of start
  – Annual low dose prophylaxis ranges between 1403 – 1751 IU/Kg
  – Reduced ABR
  – Reduced number of hemarthroses
  – Preservation of functional and social activities

• Algerian study demonstrates that the increase of CFCs in the low dose prophylaxis protocol is significantly not different from on demand treatment protocol