Perspective Management of Hemophilia: Past, Present & Future

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New Globulin Gives Hope to Hemophiliacs


Philadelphia, Sunday, November 10, 1963
Management of Hemophilia in Thailand

Past: The former success
Present: The ongoing service
Future: The brilliant future
MEDICAL AWARD
INTERNATIONAL PRIZE “HENRI CHAIGNEAU”
JUNE 1996
## Replacement Therapy for Thai Hemophilia

<table>
<thead>
<tr>
<th></th>
<th>Western Countries</th>
<th>Thailand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole blood</td>
<td>1930</td>
<td>1939-1964</td>
</tr>
<tr>
<td>Plasma</td>
<td>1943-1965</td>
<td>1964-1978</td>
</tr>
<tr>
<td>Cryoprecipitate &amp; FFP</td>
<td>1965-1970</td>
<td>1965</td>
</tr>
<tr>
<td>Intermediate purity factor concentrate</td>
<td>1970-1980</td>
<td>–</td>
</tr>
<tr>
<td>Virus inactivated high purity factor concentrate</td>
<td>1990</td>
<td>1995</td>
</tr>
<tr>
<td>First generation recombinant factor concentrate</td>
<td>1990</td>
<td>2003</td>
</tr>
<tr>
<td>Second to third generation recombinant factor concentrate</td>
<td>2000+</td>
<td>–</td>
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</tbody>
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Success in the Past

• Control of acute bleeding episode
• Home care treatment
• Prophylactic treatment
• Management of complicated hemophiliacs
• Prevention of hemophilia
• Prevention of transfusion-HIV infection
• Technology transfer of fibrin glue
• Diagnostic kit to determine hemophilia A and B at bedside
• National advocacy for the high cost treatment of hemophilia
• International Hemophilia Training Center-Bangkok
Between 1977-1979

Questionnaire covered 12,769,937 population

Prevalence of hereditary bleeding disorder was 1:20,000. If the relatives were included, the prevalence would be 1:13,000

Clustered sampling with complete blood tests covered 1,704,696 populations in 7 provinces, the prevalence rate was 1:25,000

5th National Health Development Plan 1982-1986

- University hospital
  - Super specialized care → Complicated cases
    - Regional hospital
      - 3\textsuperscript{o} medical care → 3\textsuperscript{o} hemophilia care
        - Provincial hospital
          - 2\textsuperscript{o} medical care → 2\textsuperscript{o} hemophilia care
            - District hospital
              - 1\textsuperscript{o} medical care → 1\textsuperscript{o} hemophilia care
                - Health station
                  - 1\textsuperscript{o} health care → home care treatment

- Total: 8,765
Organization of Laboratory Investigation

- Medical personnel
- Equipment
- Reagents
Equipment
Hemophilia in Thailand

- Report 24 cases of hemophiliacs at Siriraj Hospital Medical Conference
- Reported 164 cases of hemophilia (A 137, B 19, C 8) in Thailand from 1964-1977 Siriraj Hospital and Ramathibodi Hospital
- Replacement therapy: cryoprecipitate, FFP
- Intracranial hemorrhage 19 cases (12%)
- Surgeries 7 episodes
- Mortality rate 2.4% (4/164)

Care of Thai Hemophilia Patients from 1969 to 1991

- 140 hemophilia (A 121, B 19 cases)
- Replacement therapy: single-unit preparation of cryoppt, FFP
- Episodic treatment started 1965
- Home treatment of early bleeding started 1979
- Anti HIV screening in blood donor started 1987-1989

Sites of Bleeding

- Hemarthrosis: 54.0%
- Muscles: 17.9%
- Gum & teeth: 15.2%
- Others: 12.9%
Locally-Produced Blood Products

Fresh Dry Plasma

Lyophilized Cryoprecipitate
Continuous Infusion

Comparison of FVIII:C Levels between Bolus Injection and Continuous Infusion

การรักษาโรคฮีโมฟิเลียที่บ้านในประเทศไทย

 criesoprecipitate

.factor concentrate

heat-treated lyophilized cryoprecipitate

fresh dry plasma

2522 2525 2540-2542 2545
Home Care Treatment Initiated in 1979

- A patient with severe hemophilia A from Phitsanulok Province, received cryoppt at home
- Father kept cryoppt at -20°C refrigerator, dissolved and performed venepuncture
Role of Patients and Family Members

- Transportation, storage and dissolving blood component
- Venepuncture procedure
Early Treatment

• At the first sign of tingling sensation associated with early bleeding into muscles or joints

• Immediate after trauma

• When treatment is given early, less blood product was used and less further bleeding occurs compared to delayed treatment
HOME THERAPY FOR HEMOPHILIA IN THAILAND

Parttraporn Isarangkura, Ampaiwan Chuansumrit, Wanpen Panthangkura, Phongjan Hathirat and Sawong Pandhawong*

Department of Pediatrics, Ramathibodi Hospital, Mahidol University and *The National Blood Center, Thai Red Cross, Bangkok, Thailand.

- 10 hemophilia A (severe 9, moderate 1) aged 7-15 year
- 252 bleeding episodes: joint 70%, muscle 19%, gum and teeth 6.5%, other 4.5%
- Annual hospitalization from 6-8 to 1-2 episodes

Case Study from Ramathibodi Hospital

• Parents provide proper care to prevent bleeding episodes

• Provide early bleeding treatment at home, nearby health stations or hospitals
  - 1-10 years  250 units every 7 days
  - 11-15 years  500 units every 10 days
  - 16-20 years  500 units every 15 days

• Hospitalization
  - 1-15 years  3 hospitalizations per year
  - 16-20 years  2 hospitalizations per year
Dose of Factor VIII / Factor IX

• Children less than 10 years of age received 250 units of factor VIII concentrate weekly
  - Age 1 yr, BW 10 kg, 25 units/kg
  - Age 3 yr, BW 14 kg, 18 units/kg
  - Age 5 yr, BW 18 kg, 14 units/kg
  - Age 7 yr, BW 22 kg, 11 units/kg
  - Age 9 yr, BW 26 kg, 10 units/kg
24-Hour Hotline Consultation

- 089-4413100 International Hemophilia Training Center - Bangkok
## Benefit of Early Treatment among Thai Hemophilia

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>47</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>15 (31.9%)</td>
<td>30 (51.7%)</td>
<td>40 (67.8%)</td>
</tr>
<tr>
<td>receiving home treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of patients</strong></td>
<td>27 (62.8%)</td>
<td>43 (75.4%)</td>
<td>49 (84.5%)</td>
</tr>
<tr>
<td>with unaided proper walking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of deaths</strong></td>
<td>14 (29.8%)</td>
<td>8 (13.8%)</td>
<td>3 (5.1%)</td>
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</tbody>
</table>

National Health Advocacy
April 24, 2005
Nationwide Coverage of Hemophilia Starting 2006

- Set up a hemophilia / hematology clinic
- A limited budget to purchase factor concentrate for treating early bleeding episode
- A limited budget to treat life-threatening bleeding episodes or emergency surgery
- Patient has to conduct self-care to avoid bleeding
Laboratory Diagnosis of Hemophilia A & B

- Prolonged APTT
- Low level of FVIII:C or FIX:C
- Bedside diagnostic kit
Short Course Training for Medical Personnel

- 28-29 Jul, 2006
  Chiang Mai University Hospital

- 17-18 Jan, 2008
  Ratchaburi Regional Hospital

- 25-26 Aug, 2011
  Sawanpracharak Regional Hospital

- 22-23 May, 2008
  Nakhon Si Thammarat Regional Hospital

- 26-27 Apr, 2007
  Khon Kaen University Hospital

- 24-25 Nov, 2011
  Sappasitprasong Regional Hospital

- 12-13 Nov, 2009
  Chiang Rai Regional Hospital

- 25-26 Feb, 2010
  - Saraburi Regional Hospital
  - Thammasat University Hospital
  - Srinakarinviroj University Hospital

- 24-25 Nov, 2011
  Sappasitprasong Regional Hospital
Hemophilia Day Started  30 April, 1995
Comparison between Before and After Receiving Factor Concentrate for Treating Early Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total episodes of hospitalization</td>
<td>681</td>
<td>445*</td>
</tr>
<tr>
<td>Episodes of hospitalization/case</td>
<td>2.7 ± 3.1</td>
<td>1.8* ± 2.4</td>
</tr>
<tr>
<td>Total days of hospitalization</td>
<td>3,230</td>
<td>1,724*</td>
</tr>
<tr>
<td>Days of hospitalization/case</td>
<td>12.8 ± 14.3</td>
<td>6.8* ± 10.7</td>
</tr>
<tr>
<td>Days of hospitalization/bleed</td>
<td>4.7</td>
<td>3.9*</td>
</tr>
</tbody>
</table>

*P < 0.001

## Comparison between Two Policies

<table>
<thead>
<tr>
<th>Severity</th>
<th>Policy</th>
<th>Life time cost of treatment (THB)</th>
<th>QALY</th>
<th>Cost per QALY</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>No home base care</td>
<td>4,998,017</td>
<td>23.29</td>
<td>214,595</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Home base care</td>
<td>5,225,394</td>
<td>26.11</td>
<td>200,103</td>
<td>80,542</td>
</tr>
<tr>
<td>Moderate</td>
<td>No home base care</td>
<td>13,659,490</td>
<td>16.47</td>
<td>829,504</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Home base care</td>
<td>11,198,618</td>
<td>22.44</td>
<td>499,157</td>
<td>Cost saving</td>
</tr>
<tr>
<td>Severe</td>
<td>No home base care</td>
<td>25,908,099</td>
<td>12.21</td>
<td>2,122,085</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Home base care</td>
<td>20,189,367</td>
<td>20.61</td>
<td>979,557</td>
<td>Cost saving</td>
</tr>
</tbody>
</table>

*Pattanaprateep O et al. VIHRI 2014;3C:37-8.*
Prophylaxis in Hemophilia

- **Primary prophylaxis:**
  - Maintain factor level >1% at all time with the dose of 25-40 U/Kg, 3 times weekly for hemophilia A and 2 times weekly for hemophilia B
  - Start before 2 years or after first joint bleeding

- **Canadian escalated regimen**
  - 50 units/kg once weekly
  - 30 units/kg twice weekly
  - 25 units/kg three times/week
6 hemophilia boys with FVIII:C ranged from 1-3.5%

Age 11-16 years

Received 8-10 units/kg twice weekly for one year

Bleeding episodes seldom occurred, absence from school was reduced and not need for hospitalization
Teaching Material for Genetic Counseling
### Molecular Analysis

#### Cumulative Informative Markers in Thai

<table>
<thead>
<tr>
<th>Marker</th>
<th>% Heterozygosity</th>
<th>% Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bcl I</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>Intron 13</td>
<td>58.5</td>
<td>72.8</td>
</tr>
<tr>
<td>Intron 22</td>
<td>47.3</td>
<td>85.7</td>
</tr>
<tr>
<td>Xba I</td>
<td>48</td>
<td>92.6</td>
</tr>
<tr>
<td>ST 14</td>
<td>70</td>
<td>97.8</td>
</tr>
<tr>
<td>DX 13</td>
<td>32</td>
<td>98.5</td>
</tr>
</tbody>
</table>

#### Cumulative Informative Markers in Thai

<table>
<thead>
<tr>
<th>Marker</th>
<th>% Heterozygosity</th>
<th>% Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mse I or Sal I</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Nru I</td>
<td>36</td>
<td>64.2</td>
</tr>
<tr>
<td>Dde I</td>
<td>13.7</td>
<td>69.1</td>
</tr>
<tr>
<td>Hha I</td>
<td>13.7</td>
<td>73.3</td>
</tr>
</tbody>
</table>

*Hemophilia 2000; 6:715-6.*

#### The Mean Amount of Obtained DNA

![DNA amounts over time](image)

Carrier Detection & Prenatal Diagnosis

- 1988  Carrier detection by assaying FVIII:C, FIX:C, vWF:Ag
- 1991  Addition of DNA analysis
- 1994  Prenatal diagnosis for females at risk of having a hemophiliac son with severe and moderate degrees
  - Chorionic villus sampling at 11-14 weeks of gestation
  - Amniocentesis at 16-20 weeks of gestation
  - Cordocentesis at 20-24 weeks of gestation

## Surgery in Hemophiliac Patients

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<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Orthopedic</td>
<td>9</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Explore hip</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Appendectomy</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Open heart*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eye</td>
<td>3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>22</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

*Combining factor V and factor VIII deficiency

Cryoppt, cryoprecipitate; FFP, fresh frozen plasma; LC, lyophilized cryoprecipitate
Prevention of HIV Infection

• Anti-HIV negative donated blood with positive HIV-antigen in 1991 was 1:3,400

• HIV transmission by seronegative blood in 2 hemophilias occurred in June and July 1991 (Vox Sang 1993;63:114-6)

• HIV antigen test was routinely performed in donated blood in Thailand since September 1991

• HIV seropositive among hemophiliacs receiving blood component therapy between 1973 to 1988 was 1.9% (1/54)

Fibrin Glue

- Fibrinogen + Thrombin
  - to treat superficial wound
  - to prevent bleeding in
  - dental extraction, surgery
Dental Splint

Recombinant Factor VIIa in Bleeding Control for Hemophilia with Inhibitor


Joint WHO / WFH Meeting

• Prevention and control of hemophilia
  - 26-28 March 1990 in Geneva, Switzerland
  - 16 June 1997 in Geneva, Switzerland
  - 11-13 February 2002 in London, UK
Ongoing at Present

- โครงการโรคเรื้อรังที่มีค่าใช้จ่ายสูง: โรคฮีโมฟิลี
- Nationwide prophylaxis
- Prevention of new case of hemophilia in the family
- Treatment of hemophilia with inhibitor exhibiting bleeding
- Immune tolerance therapy
โครงการโรคเรื้อรังที่มีค่าใช้จ่ายสูง: โรคฮีโมฟีเลีย

<table>
<thead>
<tr>
<th>ประเภทผู้ป่วย</th>
<th>ฮีโมฟีเลีย เอ</th>
<th>ฮีโมฟีเลีย ปี</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(บาท/คน/เดือน)</td>
<td>(บาท/คน/ปี)</td>
</tr>
</tbody>
</table>

### 1. อายุน้อยกว่า 10 ปี

- รุนแรงมาก
  - 24,000  | 288,000 |
  - 18,900  | 226,800 |
- รุนแรงปานกลาง
  - 12,000  | 144,000 |
  - 12,600  | 151,200 |
- รุนแรงน้อย
  - 3,000   | 36,000  |
  - 6,300   | 75,600  |

### 2. อายุน้อยกว่า 10 ปี

- รุนแรงมาก
  - 24,000  | 288,000 |
  - 25,200  | 302,400 |
- รุนแรงปานกลาง
  - 12,000  | 144,000 |
  - 12,600  | 151,200 |
- รุนแรงน้อย
  - 6,000   | 72,000  |
  - 6,300   | 75,600  |
Nationwide Prophylaxis

- **Children <10 yr**
  - 250 units weekly or twice weekly
  - Dose/kg depends on weight: 10-25 units/kg

- **Children ≥10 yr**
  - 250 units twice weekly
  - Dose/kg depends on weight: 7-8 units/kg

- **Adults**
  - 500 units once weekly: 5-7 units/kg at present
  - 500 units twice weekly: 5-7 units/kg (2017-2018)
  - 250 units three time weekly
Hemophilia with Inhibitor

- The most problematic complication
- Difficulty in effective bleeding control
- Higher treatment costs
- Increased morbidity and mortality
- Prevalence of factor VIII inhibitor
  - 25-30% of patients with severe hemophilia A
- Prevalence of factor IX inhibitor
  - 2-3% of patients with hemophilia B
An 8-year-old Boy with High Inhibitor

- Cyclophosphamide
- Cyclosporine
- Intravenous immunoglobulin
- Methylprednisolone
- Plasma exchange 2 time plasma volume x 8 cycles
- Factor VIII concentrate loading 100 unit/kg of factor VIII followed by continuous infusion of 16 unit/kg/h of factor concentrate and cryoprecipitate

Control Bleeding in Hemophilia with Inhibitor

• Bypassing agents of APCC & rFVIIa are on the process of submitting into the essential drug lists (ง2)

• Allowance for complicated hemophiliacs
  - 150,000 baht per episode (max 2 episodes/month)
  - 300,000 baht per episode

• Insufficient budget for adult hemophiliacs
Immune Tolerance Induction

- Lyophilized cryoprecipitate 13 units/kg 3 times/week

**Inhibitor (BU/mL)**

![Heat treated lyophilized cryoprecipitate](image)

Dose of Factor VIII

Plasma-derived factor VIII concentrate

- 100 units/kg 3 times/week for 6 months
- 50 units/kg 3 times/week for 6 months
- 50 units/kg 1-2 times/week for 1 year
Immune Tolerance Induction

Factor VIII conc 50 u/kg x 2/wk  100 u/kg x 3/wk  50 u/kg x 3/wk  70 u/kg x 2/wk
PCC 50 u/kg x 2/wk

<table>
<thead>
<tr>
<th>Week</th>
<th>FVIII:C (BU)</th>
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<tbody>
<tr>
<td></td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>87</td>
<td>0</td>
</tr>
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<td>0</td>
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Plasma Fractionation Centre
National Blood Centre, Thai Red Cross Society
Expectation in the Future

- Gene therapy
- Alternative treatment for subcutaneous administration
  - Emicimab (ACE 910)
  - AntiTFPI (concizumab)
  - Fitusiran (anti-antithrombin)
Novel Alternate Hemostatic Agents for INHIBITORS

- Coagulation factor mutants or mimics
- Natural anticoagulant knockdown or disruption

Management of Hemophilia in Thailand

Proud with success in the past
Busy with ongoing treatment at present
Dream for effective management in the future
Thank you for your attention