Hemostatic Options for Heavy Menstrual Bleeding

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Vision: All women and girls with blood disorders are correctly diagnosed and optimally treated and managed at every life stage
OBJECTIVES

• Review the hemostasis of menstruation

• Identify therapeutic targets

• Therapeutic options for heavy menses in general

• Therapeutic options for inherited bleeding disorders

• Focus on therapeutics in von Willebrand disease
Overview of Hemostasis
Reminder...we do not bleed in a vacuum...
Endothelium

Subendothelial Collagen

Von Willebrand Factor

Fibrinogen

GPIIb/IIIa

GP1b

Subendothelial Collagen

Endothelium
Excessive Fibrinolysis AKA Heavy Menses

Von Willebrand Factor

Subendothelial Collagen

Endothelium

Plasmin
Possible Hemostatic Defects in Menorrhagia (HMB)

INADEQUATE INDUCTION:

- vWF mediated platelet aggregation
- Fibrin formation
- Vasoconstriction
- Tissue regeneration

and/or

OVER-COMPENSATION:

- PG induced platelet inhibition
- Fibrinolysis
- Vasodilatation

Increased menstrual blood flow >80 cc = MENORRHAGIA (HMB)
Where/why a 22 y/o may present with heavy menses (HMB)

Dx - Inherited Platelet Function Disorder (e.g., dense granule deficiency)

Dx - Von Willebrands, Type 1

Dx - Severe FVII deficiency or could also be any severe rare bleeding disorder like Fibrinogen (F1) deficiency or Prothrombin (FII) deficiency or Factor V deficiency or Factor VII deficiency or FVIII or FIX carrier who is lyonized or Factor XI deficiency or FXIII deficiency

Dx - idiopathic HMB- in up to 50% of cases of HMB!
Best Therapy for Heavy Menstrual Bleeding?

- Oral Contraceptive
- Levonorgestrel IUD
- Endometrial Ablation
- Hysterectomy
- Anti-fibrinolytic Therapy
- Intranasal DDAVP (Stimate®)
- VWF/FVIII concentrate
INADEQUATE INDUCTION OF HEMOSTASIS:
- vWF mediated platelet aggregation
- Fibrin formation
- Vasoconstriction
- Tissue regeneration

and/or

OVER-COMPENSATION:
- Vasodilatation
- PG induced platelet inhibition

Fibrinolysis

Increased menstrual blood flow > 80 cc
Heavy Menstrual Bleeding as a Disorder of Increased fibrinolysis

- Reports of increased systemic and localized intrauterine fibrinolysis in heavy menstrual bleeding and in postpartum hemorrhage

- Catheterized samples of increased fibrinolytic activity in HMB patients compared to controls

Winkler UH. Ann NY Acad Sci 1992; 667:289-90
Edlund M, Blomback M, He L.. Blood Coagul Fibrinolysis 2003; 14:593-8
Tranexamic Acid in HMB: Systematic Review

- 12 studies involving 690 women-
  - the reduction in MBL ranged from 34% to 56% in those treated with >3 mg tranexamic acid for 5 days

- Superior reduction in MBL over three cycles compared to mefanamic acid (54% versus 10%, $p < 0.001$)

- Overall, TA significantly reduces MBL in women with HMB. However, it does not reduce the duration of menses or regulate the cycle

A New and Improved Tranexamic Acid? Lysteda – brief history

• Unique formulation that provides a higher per-tablet dose and increases drug absorption

• Designed to maintain efficacy of immediate release TA while minimizing gastrointestinal adverse effects

• Xanodyne Pharmaceuticals program (2003)

• FDA approval in November, 2009
FDA Licensure Trial for Lysteda

Reduction of MBL*

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean MBL (mL)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TA (n=115)</td>
<td>69.6</td>
<td>40.4%</td>
</tr>
<tr>
<td>Placebo (n=67)</td>
<td>12.6</td>
<td>8.2%</td>
</tr>
</tbody>
</table>

*(statistically significant difference, P<.001)

1.3 g tid dosing superior to 650 mg tid dosing


*P < .0001 vs baseline and placebo.

MBL, menstrual blood loss; TA, tranexamic acid (Lysteda; Ferring Pharmaceuticals, Inc, Parsippany, NJ).
Risk Profile of Lysteda

- No statistically significant adverse events compared to placebo
  - No thrombotic events
- Thrombosis has not been observed in men or women receiving tranexamic acid for-
  - bleeding ≥2° to cardiac or oral surgery, acute upper GI bleeding, or ocular trauma
- Use of tranexamic acid not associated with an increased risk or incidence of thromboembolic events compared with the background rate of thrombotic events in women of childbearing age

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tranexamic Acid (n=117)</th>
<th>Placebo (n=72)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menstrual discomfort/ cramps</td>
<td>72 (61.5)</td>
<td>36 (50.0)</td>
<td>.120</td>
</tr>
<tr>
<td>Headache</td>
<td>65 (55.6)</td>
<td>36 (50.0)</td>
<td>.457</td>
</tr>
<tr>
<td>Back pain</td>
<td>28 (23.9)</td>
<td>14 (19.4)</td>
<td>.471</td>
</tr>
<tr>
<td>Nausea</td>
<td>17 (14.5)</td>
<td>11 (15.3)</td>
<td>.888</td>
</tr>
<tr>
<td>Anemia</td>
<td>12 (10.3)</td>
<td>4 (5.6)</td>
<td>.260</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (9.4)</td>
<td>5 (6.9)</td>
<td>.556</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>9 (7.7)</td>
<td>7 (9.7)</td>
<td>.626</td>
</tr>
<tr>
<td>Multiple allergies</td>
<td>10 (8.5)</td>
<td>5 (6.9)</td>
<td>.692</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>8 (6.8)</td>
<td>6 (8.3)</td>
<td>.703</td>
</tr>
<tr>
<td>Cough</td>
<td>7 (6.0)</td>
<td>5 (6.9)</td>
<td>.792</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (5.1)</td>
<td>6 (8.3)</td>
<td>.380</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (6.8)</td>
<td>3 (4.2)</td>
<td>.446</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>8 (6.8)</td>
<td>3 (4.2)</td>
<td>.446</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>3 (2.6)</td>
<td>8 (11.1)</td>
<td>.015</td>
</tr>
<tr>
<td>Migraine</td>
<td>7 (6.0)</td>
<td>4 (5.6)</td>
<td>.903</td>
</tr>
<tr>
<td>Sinus headache</td>
<td>9 (7.7)</td>
<td>2 (2.8)</td>
<td>.161</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified.
* Events that occurred in more than 10 participants irrespective of causality.
* P was determined using a χ² test.

Outstanding Issues With Lysteda

• Concurrent estrogen-containing contraception

--- CONTRAINDICATIONS ---

- Women who are using combination hormonal contraception (4.1)
- Women with active thromboembolic disease or a history or intrinsic risk of thrombosis or thromboembolism, including retinal vein or artery occlusion (4.1)

• Adolescents - as licensure study excluded age < 18 years age
  • However, a pharmacokinetic study in 20 adolescent females aged 12-16 years of age, no dose adjustment was needed

• Recent pilot study (n=17) showed oral TA appeared as efficacious as OC in the management of adolescent HMB by reducing MBL and improving quality of life

DDAVP (1-deamino 8-D-argin vasopressin) binds primarily to antidiuretic type 2 vasopressin receptors compared to type 1 receptors, so reducing undesirable vasoactive side effects and prolongs its half-life when compared to native vasopressin.

DDAVP induces Endothelial cell (EC) via cAMP mediated Weibel-Palade Body secretion increasing membrane-bound and circulating VWF as well as FVIII.

DDAVP also induces platelet release and membrane presentation of P-selectin which Mediates platelet rolling on ECs under high shear conditions through PSGL-1/P-selectin Interaction.

DDAVP increases EC adhesiveness for platelets and platelet adhesion to collagen probably via VWF.

Background, DDAVP responsiveness in VWD

• Type 1 - Usually if FVIII, VWF RCo > 10% will have 2-6 fold response with improved platelet function but-
  • When baseline levels 10-20% beware of Type 1C with its initial excellent response albeit short-lived

• Type 2A - Variable

• Type 2B - Usually contraindicated

Downside of IN DDAVP for VWD-related HMB:

• Quarter of patients experience moderate to severe side effects -
  • Headache
  • Flushing
  • Nausea/Vomiting
  • Fatigue
  • Weight gain
  • Least common but most severe- Hyponatremia>seizure


**CDC Female Data Collection pilot study (n=319): Treatments used for menorrhagia in Inherited Bleeding Disorders**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptive</td>
<td>55%</td>
</tr>
<tr>
<td><strong>DDAVP</strong></td>
<td>34%</td>
</tr>
<tr>
<td>Anti-fibrinolytics</td>
<td>24%</td>
</tr>
<tr>
<td>Blood or plasma products</td>
<td>7%</td>
</tr>
<tr>
<td>Clotting factor products</td>
<td>6%</td>
</tr>
<tr>
<td>Endometrial ablation</td>
<td>4%</td>
</tr>
<tr>
<td>MIRENA</td>
<td>3%</td>
</tr>
<tr>
<td>Uterine artery embolization</td>
<td>2%</td>
</tr>
<tr>
<td>Platelet transfusion</td>
<td>1%</td>
</tr>
</tbody>
</table>

Bleeding Disorder Related Menorrhagia (HMB) Management: TA (Europe, Canada) or DDAVP (U.S.)

Tranexamic acid (TA)
- In non-VWD menorrhagia-randomized study
  ➢ 54% reduction in MBL with TA alone
- In VWD menorrhagia
  ➢ Small studies,
    ➢ Mohri: 3g/dose in 3 patients
    ➢ Ong, et al: 4g/d (1 dose) in 4 patients
    ➢ Onundarson: 4g/d (1 dose) in 1 patient
    ➢ Royal Free London: 15/37 (40%) with PBAC <100

Desmopressin (DDAVP)
- Positive case series experience based on subjective assessment:
  ➢ 80-90% good to excellent
- More recent data:
  Controlled studies using PBAC or spectrophotometry:
  ➢ Royal Free London:
    - Intranasal DDAVP was not better than placebo
  ➢ Karolinska Sweden:
    - Intranasal DDAVP in combination with TA most effective

Bonnar J, Sheppard BL. BMJ. 1996; 313:579-582;
Onundarson PT. Haemophilia. 1999; 5:76.
Women with menorrhagia (HMB)

Diagnostic workup

Offered oral contraceptives, but can refuse for any reason and stay in study

Randomized arm of: tranexamic acid versus intranasal DDAVP

STUDY OUTCOMES

Quality of life

Menstrual flow

Coagulation parameters

PLOT OF MEAN PBAC OVER TIME BY SEQUENCE OF TREATMENT

**IN-DDAVP x 2 cycles then TA x 2 cycle**

**TA x 2 cycles then IN-DDAVP x 2 cycles**

The Center for Disease Control Women With Bleeding Disorder Management Study: Reduction in PBAC - TA vs. DDAVP

The Center for Disease Control Women With Bleeding Disorder Management Study: Improvement in QOL - TA vs. DDAVP

The number of unhealthy days by SF-36 QOL instrument:

The Center for Disease Control Women With Bleeding Disorder Management Study: Improvement in QOL - TA vs. DDAVP, II

- The Center for Epidemiologic Studies Depression Scale (CES-D)
  - summary score decreased from baseline, indicating fewer depressive symptoms in both arms
- Ruta menorrhagia questionnaire-
  - Change in mean score from baseline to after IN-DDAVP, p value=0.008
  - Change in mean score from baseline to after TA, p value=0.003

For DDAVP Failures?

- Combined therapy with TA-

VWF concentrates in DDAVP and/or TA refractory cases in VWD-related HMB

VWF for menorrhagia (HMB): A survey and literature review

• 83 surveys distributed to hemophilia treatment center MDs
  ▪ 20 (24.1%) provided sufficient data for analysis

• Of 1321 women with VWD seen during 2011–2014, 816 (61.8%) had menorrhagia (HMB)
  • Combined oral contraceptives, TA and desmopressin were the most common first-line therapies
  • VWF replacement was a third-line therapy reported in 13 women (1.6%)

• Together with data from 88 women from 6 published studies, VWF replacement therapy safely reduced menorrhagia in 101 women at a dose of 33–100 IU/kg on days 1–6 of menstrual cycle

### FDA Approved VWF products

#### Plasma-derived VWF containing FVIII concentrates

<table>
<thead>
<tr>
<th>Product</th>
<th>Humate</th>
<th>Alphanate</th>
<th>Wilate</th>
<th>Wilfactin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>CSL Behring, USA</td>
<td>Grifols, USA</td>
<td>Octapharma, USA</td>
<td>LFB</td>
</tr>
<tr>
<td>Purification method</td>
<td>Multiple precipitation</td>
<td>Precipitation/heparin ligand CT</td>
<td>Precipitation/ion exchange and size exclusion CT</td>
<td>Ion exchange + affinity chromatography</td>
</tr>
<tr>
<td>Viral Inactivation</td>
<td>Pasteurization</td>
<td>S/D, dry heat</td>
<td>S/D, dry heat</td>
<td>S/D, dry heat/35 nm filtration</td>
</tr>
<tr>
<td>VWF:RCo/VWF:Ag</td>
<td>0.91</td>
<td>0.43</td>
<td>0.9-1.0</td>
<td>0.95</td>
</tr>
<tr>
<td>VWF:RCo/FVIII:C ratio</td>
<td>2.88</td>
<td>0.82</td>
<td>1.0</td>
<td>50</td>
</tr>
<tr>
<td>ULM</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>FDA approved</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Absent</td>
</tr>
</tbody>
</table>

#### Recombinant

- Vorvendi
- Baxalta/Shire
- Chinese hamster ovary cell line
- Not required
- 1.16
- No FVIII
- Present
- Yes

*S/D, solvent detergent; CT, chromatography; FVIII, factor VIII; FVIII:C, factor VIII coagulation activity; VWF:Ag, VWF antigen; VWF:RCo, VWF ristocetin cofactor; ULM, ultra-large multimers.*

*Singal M and Kouides P: Drugs of Today. 2016; 52 (12):653-666*
Thank you!