Pitfalls in Management of Bleeding Disorders

Ponlapat Rojnuckarin
Chulalongkorn University
Primary platelet plug

Adhesion and aggregation

Collagen and von Willebrand Factor (vWF)
**Intrinsic Pathway**

- PK, HMWK
- Surface
- XII → XIIa
- XI → Xla
- Ca²⁺
- IX → IXa
- Phospholipid
- X → Xa
- VIIIa → VIIa
- Xa

**Extrinsic Pathway**

- TF
- Ca²⁺
- VIIa
- Vlla
- TF
- VII

**Common Pathway**

- Prothrombin
- Phospholipid
- Ca²⁺
- Thrombin
- Va
- Fibrinogen
- Fibrin
- IIa
- Fibrin

**In Vitro Coagulation Pathway**

- VCT
- APTT
**In Vitro vs. in vivo coagulation**

**Intrinsic Pathway**
- PK, HMWK
- Surface

**Extrinsic Pathway**
- TF
- Ca\(^{2+}\)

**Common Pathway**
- Fibrinogen
- Thrombin
- Fibrin

**In Vitro**
- FXa
- FXIIa

**In vivo**
- FXa
- FXIIa

**Coagulation**
- Fibrin Crosslinked
Cell-based coagulation
Localization of fibrinolysis
Screening Coagulogram

Platelet count
Peripheral blood smear
Bleeding time
APTT
PT
TT
Blood smear: Pseudothrombocytopenia

Platelet clumping
EDTA-dependent pseudothrombocytopenia

- Presence of autoantibody that agglutinates platelet in EDTA at RT
  - 20% IgM that also agglutinates at 37 C and in citrate
- In vitro artifact, No clinical significance
- Avoid unnecessary investigations, transfusion or delaying procedure
- May repeat count in heparin

Blood smear: Causes of thrombocytopenia
Blood smear: Platelet granularity

Storage pool disease: Hypogranular platelets
**Blood smear: Platelet size**

**May-Hegglin Anomaly:**
No bleeding, Thrombocytopenia, Giant platelets and Döhle body
Blood smear: Platelet size

Bernard-Soulier syndrome:
Severe bleeding, Thrombocytopenia, Giant platelets
Thrombocytopenia

- Hematological diseases
  - Impaired production (Pancytopenia)
  - Peripheral destruction

- Systemic diseases
  - Any critical illnesses
  - Special situations
ผู้ป่วยหญิงอายุ 24 ปี

5 วัน จุดแดงออกไปตามตัว มีอาเจียนเป็นเลือด

PE: Afebrile, extensive petechiae at her body and legs, others: WNL

CBC: Hb 12.0 g/dl, MCV 82 fl, WBC 4.7 x 10⁹/L, N 75%, L 20%, M 4%, Eo 1%, PBS: no abnormal cells, platelet 4.0 x10⁹/L. Anti HIV is negative.
ITP: Diagnosis by exclusion

- Blood smear
- Liver diseases: Asymptomatic
- Anti HIV
- Anti HCV
- Bone marrow: Abnormal RBC/WBC, old age, refractory
**ITP with Major bleeding**

- High dose steroid
  
  Ex. Dexamethasone 40 mg/d

- Intravenous immunoglobulin

- Avoid invasive procedures, e.g. surgery, endoscopy, NG larvage

- Still bleeding after improving platelet counts: look for local lesion
ผู้ป่วยหญิงอายุ 40 ปี underlying ITP on prednisolone และ cyclophosphamide

มาด้วยพูดจาสับสน 1 วัน ตรวจร่างกาย T 39 C, PR 120, BP 90/60 mmHg, Petechiae both legs, No focal sign

CBC: Hb 11 g/dL, WBC 20 x 10^9/L, N 80%, L 20%, Platelet 5.0 x10^9/L

CT brain: No CNS bleeding

A. IVIg

B. Antibiotic

C. Platelet transfusion

D. Pulse dexamethasone
Thrombocytopenia in critically ill patients

- Sepsis
- DIC
- Spleen
- Drug-induced
- Dilutional: Massive Transfusion
- Indwelling Catheter
- Cardiopulmonary bypass

- TTP/HUS
- HIT
- Post transfusion purpura
- Catastrophic APA syndrome
Thrombocytopenia in critically ill patients

Combinations or Unknown*

Platelet transfusion:
keep $\geq 10-20 \times 10^9$/L, if no bleeding
keep $\geq 50-100 \times 10^9$/L, if bleeding

*Chest. 1999;115:1363
A 70-yr-old woman with easy bruising, normal CBC, PT, PTT

The most appropriate test

1. Bleeding time
2. Thrombin time
3. Skin biopsy
4. Fibrinolytic test
5. No further test
Bleeding Time

- Platelet Dysfunction

- Some vascular diseases
Bleeding time
Bleeding time

- Variable, affected by anemia and platelet count
- Cannot be used as a screening test for asymptomatic patients (e.g. pre-operation) due to low positive predictive value.
- May cause scar
- Can cause large hematoma in senile purpura

Blood 1991; 77: 2457-62
Low Sensitivity of bleeding time

- Prolonged bleeding time (N=148)
  - von Willebrand disease type 1: 42%
  - Platelet secretion defect: 42%

- Prolonged bleeding time (N=128)
  - von Willebrand disease type 1: 29%
  - Platelet secretion defect: 33%

Is there any use of bleeding time before special tests?

- Clinically suggestive: Special tests
  Clinically unlikely: No test

- Emergency setting: active bleeding from suspected platelet dysfunction or vWD
  (Anemia: prolonged bleeding time)

- If BT > 20 min: Likely to be true positive
Coagulation tests
Specimen Collection

1. Avoid stasis, probing
2. Double syringe, plastic syringe
3. Plastic tube, exact ratio of anticoagulant
4. Immediate centrifugation
5. Immediate testing and freezing
6. Correction for high hematocrit
Mixture of plasma from 20-30 healthy individuals

The factor activity should be about 100% activity (or 1U/ml).

Report as control values. They are performed daily.

Control values from the same lab should be within the acceptable range.
Normal range

- Normal range should be defined locally by each laboratory
- Tests are performed in at least 30 healthy individuals giving the normal distribution of the results.
- Normal range = mean $\pm$ 2 SD
Mixing study

Prolonged coagulation assay
1:1 mixing of patient v.s. normal plasma

Correctable : Factor deficiency
Uncorrectable : Factor inhibitor
Isolated prolonged APTT

Without Bleeding
Mix Correctable: Contact factor def.
Mix not Correctable: lupus anticoagulant
Pre-analytical error: Heparin, too long storage

With Bleeding
Mix Correctable: Hemophilia A, B, C, vWD
Mix not Correctable: F VIII inhibitor
Isolated prolonged PT

Early vitamin K deficiency or antagonist

Mild liver disease

Factor VII deficiency (rare)
Prolonged APTT & PT, Normal TT

Vitamin K deficiency or antagonist*
Moderate to severe liver diseases*
Massive transfusion
Common pathway deficiency: congenital or acquired

* PT prolonged > APTT
Prolonged TT

Without bleeding
  Heparin contamination
  Hyperfibrinogenemia

Bleeding
  Hypofibrinogenemia
  Dysfibrinogenemia
  Impaired fibrin polymerization
  Heparin, Paraprotein, FDP, anti IIa
Bleeding with normal screening coagulogram

1. Mild bleeding disorders  
2. Factor XIII deficiency  
3. Hyperfibrinolysis: antiplasmin deficiency, tPA excess, PAI deficiency  
4. Vascular diseases
Male 53 yr
Left Chest wall mass for 1 week

PH: No previous history of bleeding
PE: Huge mass with massive pleural effusion
CBC: Hb 7.5 g/dL, MCV 83 fl, WBC 8.5 x10⁹/L, N 69%, L 21%, M 10% Platelet 305 x10⁹/L
  APTT 105.2 sec (25-42 sec)
  PT   15.4 sec  (11-15 sec)
  TT   11.0 sec  (10-15 sec)
Ecchymosis
Chest X ray

The most helpful investigation?

A. Liver function test
B. Lupus anticoagulant
C. Mixing study
D. Factor XII assay
E. Pleural tapping
Clinical Approach

? Bleeding tendency
- Spontaneous Bleeding, multiple sites

? Congenital vs Acquired
- Acquired

? Primary vs Secondary defect
- Secondary
- Ecchymosis, deep tissue bleeding
**Isolated prolonged APTT**

- Improper specimen collection
- Mixing study (with bleeding)
  - Correctable: Hemophilia A, B, C, vWD
  - Uncorrectable: Inhibitor
Male 53 yr
Left Chest wall mass for 1 week

Large Hematoma with pleural effusion
Lab: Anemia and Normal platelet count
  APTT  105.2 sec (25-42 sec)
  Mixing study:  uncorrectable
  Factor VIII  1%
  Factor VIII inhibitor 12 Bethesda unit

Appropriate treatment?
A. Cryoprecipitate  B. Tranexamic acid
C. Corticosteroid  D. Surgical removal of clot
Acquired Hemophilia

Secondary causes (40-50%)
- Post-partum (1-4m, recovery in 30 m)
- Autoimmune disease
- Malignancies
- Drug e.g. penicillins, sulphonamides, phenyltoin

Br J Haematol 2003; 121:21
Treatment of bleeding

- Low Titer < 5 BU
  High dose factor VIII concentrate
- High titer > 5 BU
  Bypassing agents: Recombinant factor VIIa, FEIBA
Immunosuppressive

- 36% spontaneous resolution
- Prednisone (1 mg/kg/d) abolishes the inhibitor in 30% of patients (Green & Lechner, 1981; Spero et al, 1981; Green et al, 1993)
- Addition of cyclophosphamide (1-2 mg/kg/d) response rate: 60-100% (Green et al, 1993; Shaffer & Phillips, 1997; Bayer et al, 1999)
Female 24 yr
Major bleeding after dental extraction 2 times

Lab: Platelet 325x10⁹/L
APTT 39.0 sec. (26.7-38.3)
PT 12.5 sec. (10.3-13.2)

Which is a possible diagnosis?
A. Lupus anticoagulant
B. Von Willebrand disease
C. Vitamin K deficiency
D. Liver disease
Clinical Approach

- ? Bleeding tendency
  - ▲ Bleeding after surgery (repeatedly)

- ? Congenital vs Acquired
  - ▲ Congenital vs acquired?

- ? Primary vs Secondary defect
  - ▲ ? undefined
Detailed bleeding history

- Bruise (> 4 cm, >4 sites, hematoma)
  Normal: Shin (1 ft over the ground), forearm
- Epistaxis (> 15 min)
- Bleeding after dental extraction or surgery requiring medical attention and/or transfusion
Menorrhagia

- นานเกิน 7 วัน
- ใช้ผ้าอนามัยมากกว่า 30 ผืนต่อ 1 cycle
- เปลี่ยนผ้าอนามัยทุกชั่วโมง (0.5-2 hr)
- ต้องใช้ผ้าอนามัยที่ซึมซับดีเป็นพิเศษ
- ประจำเดือนเป็นผ้าบ่อยครั้ง
- เกยมีเลือดจากเนื้องจากขาดเหล็ก
- ต้องหยุดงานหรือหยุดเรียนเพราะมีประจำเดือน

*Haemophilia 2002; 8: 330–338*
Isolated prolonged APTT

*zWith bleeding
  ▶ Von Willebrand Disease
  ▶ Carrier of Hemophilia (lyonization)
  ▶ Inhibitor (usually transient)
Isolated prolonged APTT

- With bleeding
  - Von Willebrand Disease
  - Carrier of Hemophilia (lyonization)
  - Inhibitor (usually transient)

- Bleeding time 16 min. (<9 min.)
- Blood group O
**von Willebrand disease**

- **Type 1** (partial quantitative defect)
- **Type 2** (qualitative defect)
  - 2A, 2B loss high MW multimer
  - 2N (Normandy): loss factor VIII binding (low F VIII, normal plt function)
  - 2M Normal multimer, normal factor VIII binding
- **Type 3** (complete deficiency)
vWF multimer assay

Normal       Type 3       Type 1       Type 2 A or 2B
von Willebrand factor

- **Antigen**: ELISA
- **Activity**
  - Ristocetin cofactor activity (RiCof)
  - Collagen binding assay (CBA)
- **Factor VIII activity**
Female 24 yr
Major bleeding after dental extraction 2 times

1. Factor VIII assay 45% (60-150)
2. vWF antigen (ELISA) 40% (50-150)
3. vWF function
   - Ristocetin cofactor activity 14% (50-150)
   - Collagen binding assay 12% (50-150)

Dx von Willebrand disease type 2
Disproportion of vWF function: Ag (activity: antigen < 0.6)

- Suggests type 2 vWD
- Run vWF multimer
- Type 2B will be hyper-aggregable to low dose ristocetin. DDAVP causes thrombocytopenia
Von Willebrand’s disease

Before surgery
- DDAVP IV (Not in type 2B)
- Cryoprecipitate
- Factor VIII concentrate
- Tranexamic acid during menstruation for hypermenorrhea
Female 22 yr
Admitted to ICU for sepsis
Now, clinically improved, no bleeding

Lab: Platelet count 330 x 10^9/L
APTT 64.3 sec (25-35 sec)
PT 15.7 sec (10-13 sec)

Which is a possible diagnosis?
A. Lupus anticoagulant
B. Hemophilia carrier
C. Liver disease
D. Pre analytical error
Female 22 yr
Admitted to ICU for sepsis
Now, clinically improved, no bleeding

Lab: Platelet count 330 x 10⁹/L
APTT 64.3 sec (25-35 sec)
PT 15.7 sec (10-13 sec)
TT > 120 sec (10-13 sec)
Fibrinogen 4.5 g/L (1.7-4.0)
Repeat venepuncture from peripheral line: normal TT
Heparin contamination
Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication

PH: no peripartum bleeding

PE: ecchymosis and hematoma

Lab: APTT 266.3 sec (25-35)

PT 300.0 sec (10-13)

TT 11.5 sec (10-13)
Prolonged APTT & PT, Normal TT

Vitamin K deficiency or antagonist*
Moderate to severe liver diseases*
Massive transfusion
Common pathway deficiency: congenital or acquired (inhibitor)

* PT prolonged > APTT
Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication
PH: no peripartum bleeding
PE: ecchymosis and hematoma
Lab: PT 300 sec
   PT (mix with normal plasma 1:1) 13.4 sec
   LFT normal
Female 75 yr
Spontaneous bruising 3 days

2 wk History of Rt leg pain went to another hospital, unknown medication
PH: no peripartum bleeding
PE: ecchymosis and hematoma
Rx: Vitamin K 10 mg IV PT became normal within 24 hrs
Medication is warfarin (prescribed 3/wk, but she took t.i.d.)
Male 55 yr with diagnosis of cirrhosis, stable condition
Bleeding per gum

PE: poor oral hygiene
Platelet count 90 \times 10^9/L
APTT 38.2 sec (25-35)
PT 17.0 sec (10-13)
Bleeding tendency in liver diseases I

Thrombocytopenia
  Splenic pooling
  Alcohol & Folate def.
  Thrombopoietin def.
  DIC (with acute complication)
Bleeding tendency in liver diseases II

Coagulation defects

Synthetic failure: VIII and I preserved

Hyperfibrinolysis: $\downarrow$ t-PA clearance

DIC: $\downarrow$ Antithrombin, protein C, S

$\downarrow$ activated clotting factors clearance

Dysfibrinogenemia: Hepatoma
Bleeding tendency in liver diseases

Most common: combination of all
Treatment according to the predominant mechanisms
DIC is often found in cirrhosis with acute complications.

Hyperfibrinolysis
  Bleeding unresponsive to transfusion
  Bleeding per gum (Fibrinolytic activity in saliva)
Differential Diagnosis

- Thrombocytopenia and coagulopathy
- Cirrhosis with hyperfibrinolysis
- DIC in acute complications
Euglobulin lysis time (ELT)

- Plasma clot: takes 24 hr to lyse
- Euglobulin fraction of plasma: high fibrinolytic activity
- Euglobulin clot: observe lysis time (Hyperfibrinolysis: lysis within 4 h)
Euglobulin lysis time

Plasma

Euglobulin Fraction

Clot

Lysis time
Coagulogram

- Fibrinogen: 3.3 g/L (1.7-4.0)
- Euglobulin lysis time: 85 min (> 240)
- D dimer: 800 ng/ml
Tranexamic acid

- Hyperfibrinolysis: Liver, cardiac bypass surgery
- Low thrombin burst: susceptible to fibrinolysis
  - Friable fibrin
  - Low thrombin activatable fibrinolysis inhibitor
Tranexamic acid and oral surgery

- High fibrinolytic activity in saliva
- Systemic tranexamic acid: undetectable in saliva
- Mouthwash 5% w/v (1 cap/H₂O 1 ml) 2 minutes q.i.d. for 7 days after surgery
## RCT: Tranexamic acid in trauma

Tranexamic acid 1 g q 8h

<table>
<thead>
<tr>
<th>Condition</th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause of death</td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85-0.97)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76-0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion*</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44-1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75-1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87-1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other causes</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74-1.20)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

CRASH-2 trial. Lancet 2010; 376: 23
ผู้ป่วยหญิง อายุ 35 ปี

G2P0A1, GA 38 wk

- แข็งแรงดีมาก่อน ไม่มีเลือดออกง่ายมาก่อน
- มาคลอดบุตรตามปกติ แต่หลังคลอดประมาณ 2 ชั่วโมง มีเลือดออกประมาณ 2 ลิตร จากทางช่องคลอด
- PE: BP 90/60 mmHg, HR 120/min
  Multiple skin ecchymoses and bleeding from IV site
Massive post-partum hemorrhage

- Systemic bleeding disorder?
  - Local and systemic
- Congenital or Acquired?
  - Acquired
- Platelet or Coagulation?
  - Coagulation by clinical
Causes

- Retained product of conception:
  - Check the placenta
- Uterine atony:
  - Check uterine contraction
- Genital tract trauma:
  - PV exam
- Coagulation abnormalities: DIC
  - Coagulogram if available, VCT
Diagnosis of DIC

- **Clinical features**
  - Cause of DIC
  - Bleeding and/or thrombosis

- **Laboratory features**
  - Thrombocytopenia
  - Prolonged coagulation time
  - FDP or D-dimer
Treatment of DIC

1. Correction of the underlying diseases

2. Replacement therapy (If bleeding)
   Cryoprecipitate, Platelet, FFP

3. Heparin (if thrombosis)
Conclusions

Diagnosis of bleeding disorders

- History and physical examinations
- Screening coagulogram
- Special laboratory tests
Patient: Female, age 35 years, G2P0A1, GA 38 wk

Massive post-partum hemorrhage

 CBC: Hb 7.0 g/dL, WBC 20.6 x 10⁹/L, Platelet 12.0 x 10⁹/L
 PT 70.6/12.8 sec, APTT 60.5/27.4 sec

Disseminated Intravascular Coagulation