A View of Coagulation from Transfusion Medicine Perspective

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Haemostasis and Transfusion Medicine
General concepts of Haemostasis
Defects in haemostasis resulting in bleeding
Bleeding disorders
Role of Conventional tests
Massive transfusion
Near Patient testing / POCT
Knowledge of hemostasis is important to transfusion medicine specialists.

- Understand the test used to assess hemostasis
- Role of conventional coagulation tests in diagnosis and management
- Clinical utility of near patient testing/POCT
- Role of blood components and other hemostatic agents in the management
Figure 24-1  Coagulation is a sine wave of activity at the site of tissue injury. It goes through four stages: initiation, acceleration, control, and lysis/recanalization. (Redrawn with permission from Spiess BD: Coagulation function and monitoring. In Lichtor JL [ed]: Atlas of Clinical Anesthesia. Philadelphia, Current Medicine, 1996.)
Blood Coagulation

- Initiation, acceleration, propagation

Coagulation is a wave of biological activity occurring at the site of tissue injury.

- Thrombin is the most important modulator, interacts with clotting factors, platelets, plasminogen activator, prostacyclin, nitric oxide and WBCs.

- Serine proteases vs inhibitors eg antithrombin.

- The protein reactions in coagulation have important roles in signalling inflammation.
Vascular Injury

1. Vasoconstriction (First)
2. Platelet Adhesion, Aggregation, and Activation (Primary Hemostasis, Second)
3. Release of Tissue Factor
4. Coagulation Cascade (Secondary Hemostasis, Third)
5. Stable Fibrin/Platelet Clot
6. Fibrinolysis [as needed]
Factor VII – Tissue Factor “two-unit enzyme”

- Factor VIIa – catalytic component
- Tissue factor – regulatory component (not on EC or circulating blood cells)
- TF-VIIa (extrinsic Xase) complex catalyzes X to Xa
- Extrinsic Xase activates IX
- Factor VIIa + IXa form the intrinsic factor Xase
  - Intrinsic Xase 50x more effective at catalyzing factor X activation than extrinsic Xase
The Many Roles of Thrombin

Coagulation System
- Clot formation:
  - Fibrinogen → Fibrin
  - F XIII → F XIIIa
- Amplification/Activation:
  - F V → F Va
  - F VIII → F VIIIa

Platelets
- Aggregation
- Release reaction
- TxA2-synthesis

Leukocytes
- Chemotaxis
- Cytokine production

Macrophages
- Chemotaxis

Tumor cells
- Adhesion
- Metastasis
- Cell growth

Neurons
- Neurite growth regulation

Endothelial Cells
- Synthesis and release:
  - Prostacyclin
  - EDRF, t-PA
  - Endothelin
  - Tissue factor
- Activation:
  - Protein C → PCa
  - Thrombomodulin

Fibroblasts
- Proliferation

Smooth Muscle
- Contraction
- Mitogenesis

Heart
- Positive inotrope
Physiologic Anticoagulant Mechanisms

- Tissue Factor + VII
  - PL
  - TF-VIIa
  - IX
  - IXa
  - Proteins C & S (+ thrombomodulin)
  - PL
  - VIIIa
  - TFPI
  - Antithrombin III
  - Prothrombin (II)
  - Xa
  - PL
  - Va
  - Xa
  - Thrombin
  - Fibrinogen
  - Fibrin (weak)
  - Fibrinolysis
  - XIIIa
  - Fibrin (strong)
Bleeding disorders

• Inherited
  • Clotting factor deficiencies
  • Platelet disorders

• Acquired
  • DIC
  • Liver disease
  • Massive transfusion
Platelet Defect or Factor Deficiency?

- Platelet defect or von Willebrand disease
  - Mucocutaneous bleeding
  - Excessive bruising, gingival bleeding, frequent nose bleeds
- Coagulation factor defects
  - Muscle and joint bleeds
- Both groups will bleed excessively from injuries and at the time of surgery!
Inherited Defects of Platelet Function

- **Platelet function disorders with normal platelet numbers**
  - Collagen aggregation defects (variable inheritance)
  - Glanzmann thrombasthenia (AR)
  - Dense body deficiency (AR)
  - Secretion defect (varies)

- **Thrombocytopenia (large platelets)**
  - Alport’s syndrome (AD)
  - Autosomal dominant thrombocytopenia (AD)
  - Bernard-Soulier (AR)
  - Gray platelet syndrome (AD)
  - May Hegglin anomaly (AD)
  - Fechnter syndrome (AD)
  - Montreal giant platelet syndrome (AD)

- **Thrombocytopenia (normal sized platelets)**
  - Chédiak-Higashi syndrome (AR)
  - Thrombocytopenia with absent radius (TAR, AR)
  - Factor V Quebec (AD)

- **Thrombocytopenia (small platelets)**
  - Wiskott-Aldrich syndrome (X-linked)
**Laboratory Monitoring of Coagulation**

- Four causes of elevated aPTT and response to 50:50 mix
  - Factor XI, IX, or VIII deficiency
    - Corrects with 50:50 mix (normal pool plasma)
  - Factor XI, IX, or VIII specific factor inhibitor
    - May correct at time zero but then prolongs
  - Heparin contamination
    - Does not correct at all with normal pool plasma
  - Antiphospholipid antibodies
    - Does not fully correct at time zero or any time point
Laboratory Monitoring of Coagulation

- Thrombin Clotting Time (TCT)
  - Add thrombin to patient’s plasma
    - This should directly clot fibrinogen
  - Elevated in
    - Heparin use
    - DIC
    - Dysfibrinogenemia
    - Low fibrinogen levels
    - High fibrinogen levels
    - Uremia
Contact activation

Intrinsic

XII, PK, XI, HK, PF3, VIII

Partial thromboplastin time

Coagulation time

Extrinsic

Tissue thromboplastin

Common

PF3, X, V

Prothrombin, fibrinogen

Screening tests of coagulation

Fibrin
When to evaluate bleeding tendency?

- H/O abnormal bleeding tendency
- Bleeding tendency in one or more family members
- Abnormal coagulation test result as a part of routine investigation
- Abnormal coagulation test result as a part of pre operative screening
- Unexplained diffuse bleeding after surgery
Screening tests
(simple and rapid)

Tests for primary haemostasis:
- Platelet count
- Bleeding time

Tests for secondary haemostasis:
- Prothrombin time
- Activated partial thromboplastin time
When to do?

- When one or more screening tests are abnormal
- High clinical index of suspicion for an unusual systemic coagulopathy

What tests?

- Correction tests using PT and APTT – mixing studies
- Factor assays
- Inhibitor study
Prolonged PT with normal APTT

Defect in the extrinsic pathway

- Factor VII deficiency
- Oral anticoagulant therapy
Defect in the intrinsic pathway
- Factor VIII or IX deficiency
- Factor XI or XII deficiency
- Von Willebrand disease
- Circulating anticoagulant inhibitors

Prolonged APTT with normal PT
Prolonged PT and APTT – Common pathway

- Deficiency of Factor V, X, prothrombin and fibrinogen
- DIC
- Liver disease
- Vitamin K deficiency
- Rare congenital defect in V, X or prothrombin
- Combined V and VIII deficiency
Transfusion Medicine specialist

- Consultative role
- Guide transfusion of blood components
- What, when and how much and how often to transfuse
- How to monitor the response to treatment
- When to stop transfusion
Massive transfusion
• Bleeding patient is subjected to haemostatic derangement.

• Urgent need to maintain intravascular blood volume before identification of the cause of bleeding
  • Successful resuscitation includes:
    • Arrest blood loss
    • Restore blood volume
    • Adequate ventilation
    • Haemostatic management

• Monitoring of haemostasis should confirm and specify the clinical diagnosis of bleeding diathesis, goal directed therapy and predict transfusion requirements
Massive blood transfusion

- Replacement of one blood volume in 24 hour period
- >10 units within 24 hours
- Transfusion >4 units in 1 hour
- Replacement of 50% of blood volume in 3-4 hours
- A rate of loss >150ml/hour
• Mortality is high in massive transfusion
• Aetiology is multifactorial
• The lethal triad of Hypotension, acidosis, coagulopathy has the highest mortality rate
• Underlying cause and the consequences of major haemorrhage result in complications
• Administration of large volumes of blood and fluids add to the complications
Parameters to be monitored

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Values for which to aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>&gt;35°C</td>
</tr>
<tr>
<td>Acid-base status</td>
<td>pH &gt;7.2, base excess &lt; -6, lactate &lt; 4 mmol/L</td>
</tr>
<tr>
<td>Ionised calcium (Ca)</td>
<td>&gt;1.1 mmol/L</td>
</tr>
<tr>
<td>Haemoglobin (Hb)</td>
<td>This should not be used alone as a transfusion trigger; and, should be interpreted in context with haemodynamic status, organ and tissue perfusion</td>
</tr>
<tr>
<td>Platelets (Plt)</td>
<td>≥50 x 10⁹ /L</td>
</tr>
<tr>
<td>PT/APTT (activated partial thromboplastin time)</td>
<td>≥1.5 x of normal</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>≥1.0 g/L</td>
</tr>
</tbody>
</table>
Transfusion associated complications.....

- **Citrate toxicity** causing hypocalcemia in combination with hypothermia and acidosis causes reduction in cardiac output, bradycardia and other dysrhythmias.

- Citrate is usually rapidly metabolised to bicarbonate. It is therefore unnecessary to attempt to neutralise the acid load of transfusion.

- There is very little citrate in red cell concentrates.

- **Acidosis** in patients with massive transfusion is more likely to be the result of inadequate treatment of hypovolemia than due to effects of transfusion.

- **Hyperkalemia**, due to transfusion of stored blood is rarely clinically significant.
Transfusion associated complications

• The increased acid load from RBC units may also contribute to coagulopathy.

• The pH of an RBC unit is low, and decreases progressively during storage, due to the production of lactic acid by RBCs, from around 7.0 initially to around 6.3 at the end of its shelf-life.

• Because of the high buffering capacity of plasma in the circulation, transfusion of RBCs with such low pH does not usually cause acid–base disturbance.

• Massive transfusion of RBCs further increases the acid load, which may in turn exacerbate the ongoing coagulopathy.
PT/APTT vs TEG

• Conventional tests-PT and APTT – kinetic tests used to detect delayed coagulation

• Are Capacity coagulation measurements that detect integrated amount of thrombin or fibrin clot formation better suited to detect defect in haemostasis?

• Biochemical understanding of the changes in the coagulation process in the blood from coagulopathic patients is necessary for strategic development of evidence based transfusion regimens
Although blood transfusion can be life-saving, its numerous negative effects have been well documented.

Our transfusion behavior should aim at minimizing the occurrence of indiscriminate transfusion and empiric hemostatic intervention.
Massive transfusion-Specific situations

- Obstetric- pregnancy, PPH
- Cardiac surgery
- Liver transplantation
- Trauma
• Pregnancy is associated with marked changes in haemostasis
• Elevated procoagulants, normal/decreased antagonists of coagulation
• Platelet counts decrease
• Anemia and preeclampsia can increase transfusion requirement, the latter is associated with thrombocytopenia and DIC
• Fibrinolytic activity is diminished in pregnancy but increased in post partum period leading to consumption and depletion of clotting factors esp fibrinogen
• Conventional tests – D-dimer and FDP levels reflect past rather than current events and have long TAT
• TEG or ROTEM based tests detect ongoing fibrinolysis
Coagulopathy in cardiac surgery

- Hyperfibrinolysis
- Platelet dysfunction
- Reduced clotting factors
- Haemodilution
- Hypothermia
- trauma
Liver Transplantation

• Quantitative and qualitative deficiencies of pro and anticoagulant plasma proteins
• Reduced clearance of activated factors
• Enhanced fibrinolysis
• Thrombocytopenia
• Abnormal platelet function
• Replacement of blood loss with fluids and blood products, function of engrafted liver, myriad of unexpected intraop events challenge the coagulation system
Intraoperative Bleeding

“Surgical”
Discrete bleeding points
Obvious source
Typical scenario

Find it: Look at potential sites

(Get help, if needed)

Venous
Pack
Get more help!
Direct suture
Ligate
Pack and close

Arterial
Proximal and Distal control

Transfusion reaction
Medications

“Coagulopathic”
Diffuse oozing

Late in case?
Early in case?
Pre-existing problem?

Suspect congenital or pre-existing problem

Progressive?

Hypothermia
Acidosis
DIC
Dilution
Primary fibrinolysis

Treat as indicated
Hematology assistance?
Trauma associated Coagulopathy

- Coagulation factor substrates are consumed in clotting
- In high energy transfer injury, in which millions of endothelial microtears occur, each of the factors is continuously activated and consumed.
- Tissue injury releases tissue factor, histones and RNA, which either bind or activate coagulation factors.
- Once activated, factor VIIa and Xa are inactivated by tissue factor pathway inhibitor.
- IIa, IXa, Xa, XIa and XIIa are irreversibly bound and cleared by antithrombin and Va and VIIIa are inactivated by protein C.
- The more severe the injury, the greater is the degree of both activation and consumption.
- With severe injury, the balance between extent of injury and capacity of coagulation system to modulate fibrinolysis can be exceeded.
Limitations of routine coagulation tests

- Time lapse for reporting routine coagulation tests
- Insufficient identification of haemostatic defect
- Routine lab tests are recommended as a guide to massive transfusion because lab based transfusion algorithm is superior to transfusion based on clinician’s experience alone

- TEG/ROTEM- Viscoelastic point of care haemostatic tests
  - Timely detection of underlying pathophysiology
  - Goal directed therapy
• PT, APTT, platelet count and fibrinogen assays are well validated and accepted. Variations in reagent sensitivity, operator influence, method variations, insufficient standardisation contribute to their limitation

• Clauss method of fibrinogen assay may be falsely high in the presence of synthetic colloidal solutions administered in fluid resuscitation of perioperative cases

• Standard coagulation panel are poor predictors of mortality and bleeding

• Severely abnormal coagulation parameters are predictors of major bleeding and increased mortality

• Poor correlation between severity of coagulation defects and amount of blood products received
Replacement of one blood volume will lead to fibrinogen deficiency.

Fibrinogen substitution reverses dilutional coagulopathy induced by crystalloids and colloids.

Addition of fibrinogen increases clot strength even in the presence of reduced platelet count and function.

Simple reduction of PT and APTT are not useful to identify responders, however, lack of reduction of prolonged PT and APTT may identify non responders.
Trauma blood management strategies

- Rationale for judicious use of blood
- Other components of an evidence based resuscitation strategy, e.g. temperature control
- Blood conservation strategies – cell salvage
- Goal directed therapy for massive transfusion
- Transfusion in an attempt to correct anamolous lab tests is not justified and potentially harmful
- Numerical improvement in FFP requires 4-6 units of FFP transfusion
Transfusion related adverse events in trauma

- A multitude of studies have demonstrated that transfusions are an independent risk factor for the following:
  - Renal injury
  - Lung injury (TRALI/TACO/ARDS)
  - Multi-organ Dysfunction/ Multi-organ system failure
  - Infections/Sepsis
  - Mortality

Dunne, JTrauma 2009;66
Dose response for post injury multiple organ failure

MOF(%) vs Units Transfused

OR 7.4- 13.2
n = 513

Moore et al, Arch Surg 1997;132
• Stored Blood is an Imperfect Substitute
  - Sticky and inflexible (storage lesion)
  - Nitric oxide scavenger (plasma free Hb)
  - Pro-inflammatory and Pro-thrombotic (cytokines)
  - Biological response modifiers (BRMs)
Trauma management principles

- Rapid control of bleeding
- Prevention and treatment of hypothermia and metabolic acidosis
- Minimising dilutional coagulopathy
- Early transfusion of blood components and clotting factors
- Damage control surgery
- Independent risk of mortality was high in those who received low FFP:PRBC ratio <1:2
- Antifibrinolytics – EACA, TXA reduce bleeding in cardiac and orthopaedic surgeries
Recombinant Factor VIIa

- In haemophilia patients with inhibitors against FVIII or IX
- Dose: 90 microgram/kg i.v. every 2-3 hours, or continuous infusion
- Half-life 2-3 hours
- Excellent efficacy in haemophilia patients with inhibitors
- Rarely thrombo-embolic events in these patients
- Tissue factor dependent mechanism of action
- Activates FX on activated platelets
- Inhibits fibrinolysis by upregulating TAFI by generation of thrombin
Indications for Factor Recombinant VIIa

• Without pre-existing coagulopathy
  • Excessive, uncontrollable bleeding post-surgery, trauma
  • Major surgery (prostatectomy, cardiac surgery)
  • Acute intracerebral hemorrhage

• With coagulopathy
  • Liver surgery, transplantation
  • Thrombocytopenia
  • Gastro-intestinal bleeding
  • Bleeding associated with anticoagulant treatment
1. Initiation phase

2. Amplification phase

3. Propagation phase
Near patient testing/POCT – TEG/ROTEM

- Incorporation of POCT into integrated transfusion algorithms has been shown to reduce transfusion requirement and adverse outcomes
- Viscoelastic tests measure the unique properties of the clot as it is forming, organising, strengthening and lysing
- It requires longer than one hour to detect the initiation of fibrinolysis. If fibrinolysis is enhanced, the result may be obtained in 30 minutes
- Use of simple stepwise decision tree for standardised component therapy
Recommended time points for hemostasis monitoring

- At admission to trauma unit or at baseline of surgery with high risk of bleeding
- When bleeding is overt or not surgically correctable
- After each blood volume exchange
- After procoagulant therapeutic intervention
- Postoperatively to detect hypercoagulability
Thromboelastography (TEG) (Haemoscope)

ThromboelastoMeter (Autometer) (TEM-A) (Framer)
Thromboelastogram

Rotating axis (+/- 4.75°)

Spring

Light source

Detector

Ball bearing

Plastic sensor

Cuvette with blood

Fibrin strands and platelet aggregates between surfaces

Heated cuvette holder
Monitoring of coagulation system: TEG

- **Reaction time (R)**
  - Time until initial fibrin formation
- **Coagulation time (K)**
  - From ‘R’ until the amplitude of TEG reaches 20 mm
- **Alpha angle**
  - Represents the acceleration of fibrin build-up and cross-linking
- **MA**
  - Maximum strength of clot
- **A60**
  - Amplitude 60 min after MA
TEG

- kinetics of clot formation
  - Strength and stability of clot

- Parameters
  - Reaction time $r$: 5 - 15 min, reflects coagulation factor levels
  - Coagulation time: $k$ 3-6 min
  - Clot formation rate $\alpha > 45^\circ$ reflects fibrinogen activity
  - Maximum amplitude 50-60 reflects platelet function and fibrinogen activity
  - Lysis time $> 180$ min

- Measures whole blood coagulability

- Guides component transfusion and pharmacological interventions
Conclusion

Transfusion medicine specialist plays a multidisciplinary role in patient care.

Proper understanding of the coagulation mechanisms, role of diagnostic tests and the factors that influence their variability are essential to guide transfusion.
Thank you