Coagulopathy and Blood Component Therapy

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Outline

- Concept – appropriate blood transfusion, indication
- Blood transfusion is not without risk
- Knowledge about blood product
- Massive transfusion
- Useful references
Definition: coagulopathy

A pathological condition that reduces the ability of the blood to coagulate, resulting in uncontrolled bleeding.

a clotting defect in which bleeding does not stop in the usual time period.
When our patient is bleeding...

- We want to stop bleeding ....and support bleeding patient.

- We may need to transfuse them....

- But transfusion may not have benefit or even harmful if we do not know about it.
Concern about blood transfusion

- One unit of whole blood
  - Rbc
  - White cells $1-3 \times 10^9$/unit ($1,000,000,000$)
  - Platelets at least $7-8 \times 10^{10}$
  - Plasma protein
  - Organism – viruses ?? CMV, HIV (1000- 1 million cpm )/HBV, malaria, Zika, Dengue …..

- Came from human donors

Question 1

History: 58 years old patients with CA colon receive red cells blood transfusion donated by his son. 10 days later, he developed fever, rash and dyspnea. Clinical course – rash progress to all over body and he developed diarrhoea, hepatitis and pancytopenia not response to any treatment and finally died of severe infection.

What is the most likely diagnosis in this case?

a. CA colon advanced stage
b. Transfusion-transmitted hepatitis
c. Transfusion-associated graft versus host disease
d. Hypersensitivity to medication that may present in blood product
Adverse effect of blood transfusion

- Foreign antigen – antibody to red cells - hemolysis
  - acute /delayed/alloimmunization
  - white cells – alloimmunization – FNHTR, TRALI
  - platelet refractoriness
  - plasma protein – allergy (rash –mild --- anaphylaxis )

- Hemolysis : non-immune
- Volume overload
- Iron overload
- Hypothermia
- Citrate toxicity
- Hyperkalemia
- Dilution-coagulopathy

- Immunomodulation

- Infectious complication: HIV, HBV, HCV, Dengue, malaria, bacteria etc...........

- Transfusion associated
  - Graft-versus host disease

- Blood product

- Foreign antigen – antibody to red cells - hemolysis
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Blood donation

Whole blood donation

Apheresis donation

http://www.fivepointsoflife.com/teach-learn/what-are-the-five-points/apheresis-donation

https://library.med.utah.edu/WebPath/TUTORIAL/BLDBANK/BBAPHER.html
How do we produce blood products

- Centrifugation forces – separate whole blood into components on the basis of differences in density
  - Rbc 1.100
  - Wbc
    - monocyte 1.062
    - lymphocyte 1.072
    - neutrophil 1.082
  - Platelets 1.058
  - Plasma 1.026

- Equipment – refrigerated centrifuge
A 67 y-o Chronic liver disease male need bilateral total knee replacement which is schedule for tomorrow at 2 pm.
His coagulogram showed – PT 25 sec , aPTT 70 sec.

When will you transfuse FFP to him ?

a. Today
b. Tonight
c. Tomorrow at 6 am
d. Tomorrow just to finish before operation
e. Give free flow FFP in OR
Patient with deep vein thrombosis who receive heparin IV drip has lung hemorrhage.

The laboratory result showed that aPTT > 180 sec.

What is the appropriate treatment?

a. FFP
b. cryoprecipitate
c. wait for heparin to metabolite
d. reverse heparin with protamine sulfate
e. recombinant factor VIIa
Fresh frozen Plasma

FFP contain all coagulation factors (> 0.7 IU/ml) and plasma proteins and is free of red cells, platelets and leukocytes.

Indication

Patient with

multiple factor deficiencies (liver disease, DIC, dilutional coagulopathy)

bleeding

will undergo an invasive procedure

congenital factor deficiencies - no factor concentrate available

reversal of Warfarin effect in patient who are bleeding or need surgery.

replacement solution for plasma exchange in TTP

Do not use for reversal of Heparin
# Blood product: plasma and platelets

<table>
<thead>
<tr>
<th>Product</th>
<th>Content</th>
<th>Volume</th>
<th>Adult dose</th>
<th>Number of bag</th>
</tr>
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<tbody>
<tr>
<td>Jumbo plasma</td>
<td>Plasma contain all coagulation factors and F VIII &gt; 0.7 IU/ml</td>
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<tr>
<td>Cryo-remove plasma</td>
<td>Plasma after removal of cryoprecipitate</td>
<td>200 ml</td>
<td>NA</td>
<td>Use for TTP Plasma exchange</td>
</tr>
</tbody>
</table>
Dosage

- 10-20 ml of FFP/kg body weight
- Each unit should be infused completely within 4 hours (recommend 2 hours) or 10-20 ml/kg/hr
- Transfuse via blood filter

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Donor group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st choice</td>
</tr>
<tr>
<td>O</td>
<td>O</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
</tr>
</tbody>
</table>

Coagulation factor 25-50%

Do not transfuse overnight.
There is some short half-life coagulation factor!!
Maximum effect immediate after transfusion.
## Half-life of coagulation factors

<table>
<thead>
<tr>
<th>factor</th>
<th>level</th>
<th>% recovery</th>
<th>half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100-150</td>
<td>50</td>
<td>3-6 days(S)</td>
</tr>
<tr>
<td>II</td>
<td>40 %</td>
<td>40-80</td>
<td>2-5 days(S)</td>
</tr>
<tr>
<td>V</td>
<td>15-25%</td>
<td>80</td>
<td>15-36 hours(U)</td>
</tr>
<tr>
<td>VII</td>
<td>5-10%</td>
<td>70-80</td>
<td>2-7 hours(S)</td>
</tr>
<tr>
<td>VIII:c</td>
<td>10-40%</td>
<td>60-80</td>
<td>8-12 hours(U)</td>
</tr>
<tr>
<td>IX</td>
<td>10-40%</td>
<td>40-50</td>
<td>18-24 hours(S)</td>
</tr>
<tr>
<td>X</td>
<td>10-20%</td>
<td>50</td>
<td>1.5-2 days(S)</td>
</tr>
<tr>
<td>XI</td>
<td>15-30%</td>
<td>90-100</td>
<td>3-4 days(S)</td>
</tr>
<tr>
<td>protein C</td>
<td></td>
<td></td>
<td>2-8 hours</td>
</tr>
<tr>
<td>protein S</td>
<td></td>
<td></td>
<td>7-72 hours</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td></td>
<td></td>
<td>24 hours</td>
</tr>
</tbody>
</table>

Dynamic condition !!
Monitor clinical outcome, PT, PTT, Platelet count fibrinogen

Splenomegaly, low platelet, DIC
Precaution

- Maximum therapeutic effect – immediate after transfusion
- Be careful about volume overload!
- Side effect – allergy, volume overload
- Outcome
  - may vary, bleeding always – dynamic
  - Monitoring of outcome – adjust transfusion need
What is cryoprecipitate?

FFP ---- cold thaw at 4 C
There is precipitation of
factor VIII
vWF
fibrinogen
fibronectin
factor XIII

Remove majority of plasma
Cryoprecipitate

- Volume ~ 20 ml
- Fibrinogen ~ 200 mg
- Factor VIII:C ~ 100 IU
- von Willebrand’s factor
- Factor XIII

- Storage at -20°C for 1 year

Indication

- Source of factor VIII:C replacement when factor VIII:C concentrate is not available
- Fibrinogen defect (qualitative and quantitative)
- Other complexes deficiency states like DIC
- Factor XIII deficiency
- Source of von Willebrand factor
- Source of fibrinogen for fibrin glue
Cryoprecipitate dose

Factor VIII replacement
(not treatment of choice)

Factor VIII 1 IU/kg
raise factor VIII 2 %

1 bag of cryo – 100 IU F VIII
e.g. BW 50 kg need FVIII 40 %

Give Factor VIII 1000 IU =
10 bag Cryo

Raise fibrinogen

Cryo 2 unit / BW 10 kg
raise fibrinogen 100 mg/dl
กระบวนการเตรียม Cryoprecipitate

Use within 6 hours after thaw and should be infuse as soon as possible
Do not refrigerate again after pooling.

Take time for pooling
Question 4

- Nurse ask you where she should keep the pool of 20 units cryoprecipitate. Your answer is..

  a. transfuse to patient immediately
  b. keep in refrigerator at Ward
  c. return to blood bank to be stored in shaker
  d. return to blood bank to store in monitor refrigerator
  e. keep frozen to preserve fibrinogen and thaw later
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</tr>
<tr>
<td>Cryoprecipitate</td>
<td>Very few plasma, FVIII 100 IU/bag, F XIII, vWF, fibrinogen 200 mg</td>
<td>20 ml</td>
<td>BW 10 kg/2 bag</td>
<td>8 -10 bags</td>
</tr>
</tbody>
</table>
20 years old Hemophilia A patient come to ER because he has muscle pain after play football. His weight is 50 kilogram. His right thigh was painful and 20 cm bigger than left thigh

What will you give him to treat muscle pain?

a. Analgesic
b. Observe and conservative treatment
c. Give cryoprecipitate 13 units
d. Give Factor VIII concentrate 25 IU/kg
From: Thierry Burnouf, P, Plasma fractionation: Technical and organisational points to consider IPFA workshop Indonesia 2017
## Treatment of coagulopathy

### Hereditary coagulation defect:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Product</th>
<th>Calculate dose</th>
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</thead>
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<tr>
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<td>Factor VIII concentrate or r FVIII</td>
<td>F VIII 1IU/kg raise factor VIII 2 % , $T_{1/2}$ 8-12 hours</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Factor IX concentrate or r FIX</td>
<td>F IX 1IU/kg raise F IX 1 % , $T_{1/2}$ 12-24 hours</td>
</tr>
<tr>
<td>Von Willebrand Disease type II,III</td>
<td>DDAVP Factor VIII concentrate with high vWF vWF concentrate</td>
<td></td>
</tr>
<tr>
<td>Other Factor deficiency II,V,VII,IX,X,XIII</td>
<td>Plasma –prefer pathogen inactivation /PCC (not for F V deficiency)</td>
<td></td>
</tr>
</tbody>
</table>
Massive transfusion

Definition:
Transfusion > total blood volume within 24 hours
Transfusion > 4 units RBC within one hour
Transfusion > 50% total blood volume within 3 hours

Definition – amount of blood transfuse over a period of time – indicate of uncontrolled major hemorrhage

Breaking vicious cycle

- Control hemorrhage
- Use possible resuscitation products
- Prevent hypothermia
- Prevent hemodilution
- Treat coagulopathy

Massive transfusion – may associated with hemostatic and metabolic complications
Management of massive transfusion

From Erber WN Massive blood transfusion elective surgical setting, Transfusion apheresis Science 2002;27
Massive transfusion

Previous approach / practice

Crystalloid/RBC tx

Lab evidenced of coagulopathy
plt< 50 K, PT,aPTT > 1.5
fibrinogen < 100 mg/dL

Transfuse platelet/ FFP/CRYO

Poor Outcome
Dilutional coagulopathy !!
Abdominal compartment syndrome
Increase fibrinolysis
New pathophysicsiology

Rationale Treatment in Massive Transfusion

- Damage control concepts: stop bleed
- Early transfusion – give blood product for "hemostasis resuscitation"

Ratio of blood product:

- RBC: platelet: FFP – 1:1:1
- cryoprecipitate 10 units/6 RBC

(Raise fibrinogen to 150-200 mg/dL)
Proposed Protocol

Activation of MTP: when??

“hemorrhage expected to be massive”

anticipated need to replace > 50% TBV within 2 hours

bleeding continue despite transfuse 4 RBCs (within 1-2 hours)

systolic BP <90 mmHg, HR > 120/min – uncontrolled bleeding

Blood bank – fast tract for MTP

Blood is rapidly issue for transfusion

Fast blood issue for massive transfusion

Compatibility testing
May omit in massive transfusion
Switch to type specific
Or use of group O red cells

Test for anti-A, anti-B in patient’s blood before resume
Transfusion with patient’s type

Platelets
Pre-pooled platelet
LPPC
Apheresis platelet

Plasma
Pre-thawed plasma every ABO group

We have pooled cryoprecipitate
-5 unit cryo for massive transfusion.
Take shorter time before issue
Our MTP for trauma

Trauma activate MTP

Send EDTA blood 6 ml
Issue set 1 - PRC O 2 u/FFP AB 3 U

BB receive call prepare set 1

Send porter to BB

BB prepare set 2 and 3

Trauma decide for set 2 and call BB

BB prepare set 3 include CRYO

Trauma decide for set 3 and call BB

Issue set 2: PRC O 3 u/FFP group specific 3 u PLT 1 dose

Issue set 3: PRC O 3 u/FFP group specific 3 u PLT 1 dose CRYO 10 u

4 RBC Gr O available at Trauma refrigerator
PCC and rVIIa

PCC: prothrombin complex concentrate
Profinine – II, IX, X
FEIBA- II, VIIa, IX, X
May be used in life threatening hemorrhage
(concerning thrombosis risk)

Recombinant VIIa (rVIIa)
May increase risk of arterial thrombosis
Use when platelet count > 50k,
Fibrinogen > 50-100 mg/dL,
Temperature > 32 °C
normal ionized calcium

http://www.baxter.com,
pr/images/patients_and _caregivers/products/feiba_vh.jpg

www.novosevenrt.com
Precaution in Massive Transfusion Protocol

- We used group O red cell (Rh positive) – avoid incompatible transfusion
- Transfusion – record every unit that was transfused
- Check patient at bedside as standard procedure

Avoid lethal triad

- acidosis
- Hypothermia
- coagulopathy
Precaution in Massive Transfusion

- **Hypothermia**: 6U RBC transfusion will reduce body temperature by 1°C

- **Hypocalcemia**: citrate in blood product bind ionized calcium – fall of Calcium ion

- **Hyperkalemia**: K leak from store red cells (use RBC age < 10 days)

- **Metabolic alkalosis**: citrate metabolism – create bicarbonate

**Bedside monitoring of coagulation**: TEG/ROTEM is useful to guide transfusion

**Fast Flow Fluid Warmers** allow rapid infusion of warm fluids/blood while providing the extra level of protection of an integrated Air Detector Clamp.

Hess JR. UpToDate 2016
Bedside evaluation: TEG, ROTEM

To identify the problem and fix it immediately

Qualitative interpretation (InTEG)

- Normal
- Thrombocytopenia or low fibrinogen
- Lysis
- Heparin or factor deficiency

Low platelet
Inadequate coagulation factor
Low fibrinogen
Increase fibrinolysis

http://crashingpatient.com/medical-surgical/hematology/hemostatic-disorders.htm/
What we should emphasized ..

- Bleeding patient – need **correct specimen collection** for blood request
- Transfusion – **check at bedside by 2 persons** --- we must make sure that right blood is given to the right patient.
The end

Doctors order blood products

Blood product

Patient’s condition

Order appropriate product, dose
Transfuse properly
Monitor for expected outcome
Thank you for your attention