PROTOCOL FOR
TRANSFUSION SUPPORT
IN
BLEEDING DISORDERS

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INTRODUCTION

• Patients who have an abnormality of platelets or the coagulation/fibrinolytic system may suffer from severe bleeding due to childbirth, surgery or trauma.

• Recognition that a patient may have a bleeding disorder and the correct diagnosis and treatment can influence the timing and type of elective surgery, reduce the need for transfusion and avoid risks to the patient due to bleeding.
Coagulation and platelet disorders can be classified as follows:

- **Acquired coagulation disorders**, arising as a result of disease or drug therapy
  - Liver disease,
  - Aspirin-induced platelet dysfunction or
  - Disseminated intravascular coagulation

- **Congenital coagulation disorders**
  - Haemophilia A or B
  - von Willebrand disease
DONOR SCREENING - PROTOCOL

- Age 18-55yrs
- Donor weight: Minimum 50 Kgs
- Hb: >12.5 g/dl

Donated blood and blood components are screened for
- HIV
- HbsAg
- HCV
- Syphilis
- Malaria
DEFINITIONS

BLOOD PRODUCT:
Any therapeutic substance prepared from human blood.

WHOLE BLOOD:
Unseparated blood collected into an approved container containing an anticoagulant preservative solution.

BLOOD COMPONENT
1. A constituent of blood, separated from whole blood by differential centrifugation
   • Red cell concentrate
   • Plasma
   • Platelet concentrates
2. Plasma or platelets collected by apheresis
3. Cryoprecipitate prepared from fresh frozen plasma
BLOOD COMPONENTS USED IN BLEEDING DISORDERS

- Whole blood
- PRP (Platelet rich plasma)
- Platelet concentrate
- FFP (Fresh frozen plasma)
- Cryoprecipitate
COMPONENT PREPARATION

**Principle - Differential centrifugation**

- Red cells
  - Packed cells
- Plasma
  - Fresh frozen plasma
- Platelets
  - Platelet rich concentrate
  - Platelet rich plasma
- Cryoprecipitate

Whole blood

RBC

Buffy

Plasma + Platelets
WHOLE BLOOD

- Whole blood contains 350+49 ml of blood plus anticoagulant solution (CPDA-1)

- Stored at 2-6 deg C for 35 days

- Stored blood has no functional platelets and no labile coagulation factors V and VIII after few hours.

- Complications:
  1. Dilutional thrombocytopenia
  2. Congestive cardiac failure
PLATELETS

• Platelet units can be either
  • Random donor units
  • Apheresis units

• 1 random donor unit contains $55 \times 10^9$ platelets.

• 1 apheresis unit contains $240 \times 10^9$ platelets.

• Stored at 20-24 deg C in continuous agitation for 5 days in platelet agitator.
PLATELET RICH PLASMA & PLATELET RICH CONCENTRATE

Preparation:

• 450 ml of fresh blood by centrifugation or by Apheresis.

• A unit of platelet concentrate prepared from 450 ml of fresh blood contains:

  – Plasma vol. 40-70ml.
  – Platelet yield $5.5 \times 10^{10}$
  – RBC traces to 0.5ml.
  – pH 6.0 or more
PLATELET CONCENTRATE

COMPLICATIONS:
1. Chill, Fever, Allergic reaction
2. Alloimmunisation
3. Platelet refractory state
4. Graft vs. host disease

CONTRA INDICATIONS:
1. TTP
2. Heparin induced thrombocytopenia
Fresh Frozen Plasma (FFP)

- Quantity: 200 - 250 ml
- Also collected by apheresis
- All coagulation factors and other proteins

**Storage**
- At less than -20 deg C for 1 yr
- Dose
  - 10-15 mL/kg
- Contains both F VIII and F IX (1 IU/ml)
- Expect 20-30% increase in all factor levels
FRESH FROZEN PLASMA

• Contains labile & non labile clotting factors, albumin and immunoglobulin.

• Factor VIII level at least 70 % of normal fresh plasma level

• Dosage - Initial dose of 15 - 20 ml / kg
FRESH FROZEN PLASMA

Before use thawed at 37 °C

Precaution
- Acute allergic reaction are common
- Anaphylactic reaction may occur

Administration
- Must be ABO compatible, Rh not required
- Infuse as soon as possible after thawing
- using standard blood administration set
FRESH FROZEN PLASMA

Contra-indications

1. Should not be used as blood volume expander
2. Hypo-proteinemia
3. Source of immunoglobulin
4. Nutritional support
5. Wound healing
CRYOPRECIPITATE

- Made from 1 unit partially thawed FFP
- Quantity: 15 - 30 mL
- Fibrinogen, factor VIII, VWF, factor XIII
- Stored 1 year frozen, 6 hours thawed
- If pooled must be given in 4 hours
- Dose
  - 1 unit/10 kg
  - 10-20 units required in adult of 70 kg.
Deficiencies of Factor VIII and IX

• Haemophilia A and haemophilia B are caused by inherited deficiencies of Factors VIII and IX respectively.
• These two factors interact to activate Factor X, which is needed for the production of thrombin and hence coagulation.
• Both are X-linked recessive disorders affecting males mostly.
# SEVERITY OF HEMOPHILIA

<table>
<thead>
<tr>
<th>Severity</th>
<th>F VIII/IX level (IU/dl)</th>
<th>Clinical picture</th>
<th>Hemophilia A incidence</th>
<th>Hemophilia B incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;1</td>
<td>Spontaneous bleeding</td>
<td>70</td>
<td>50</td>
</tr>
<tr>
<td>Moderate</td>
<td>1-5</td>
<td>Bleeding with minimal trauma/Surgery</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Mild</td>
<td>6-30</td>
<td>Bleeding with major trauma or Surgery</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

*World Hemophilia federation/WHO*
TRANSFUSION PROTOCOL IN HAEMOPHILIA

Management of a case of acute bleeding
1. Avoid anti-platelet agents such as aspirin and non-steroidal anti-inflammatory drugs.
2. Do not give intramuscular injections.
3. Administer coagulation factor concentrates to treat bleeding episodes as quickly as possible.
4. Do not incise swellings in haemophiliacs.
5. Start physiotherapy early to minimize loss of joint function.
**Desmopressin (DDAVP)**

- Desmopressin releases stored endogenous Factor VIII and von Willebrand factor, so may be useful in mild or moderate haemophilia A. It is not indicated in Factor IX deficiency.

**Replacement with factor concentrates**

- It is imperative to use factor concentrates that are licensed and certified to be virus-inactivated.
- If coagulation factor concentrates are not available, use:
  - Cryoprecipitate in Haemophilia A
  - Fresh frozen plasma in Haemophilia B.
# DOSAGE OF FACTOR VIII IN HAEMOPHILIA A

<table>
<thead>
<tr>
<th>Severity of bleed</th>
<th>Required Factor VIII dose</th>
<th>Factor VIII concentrate (500 iu/bottle)</th>
<th>Cryoprecipitate* (80–100 iu/pack)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild bleed: nose, gums, etc.</td>
<td>14 iu/kg</td>
<td>1–2 bottles (adult)</td>
<td>1 pack/6 kg</td>
</tr>
<tr>
<td>2. Moderate bleed: joint, muscle, gastrointestinal tract, surgery</td>
<td>20 iu/kg</td>
<td>2–4 bottles (adult)</td>
<td>1 pack/4 kg</td>
</tr>
<tr>
<td>3. Major bleed: Cerebral bleed</td>
<td>40 iu/kg</td>
<td>4–6 bottles (adult)</td>
<td>1 pack/2 kg</td>
</tr>
<tr>
<td>4. Prophylaxis for major surgery</td>
<td>60 iu/kg</td>
<td>6–10 bottles (adult)</td>
<td>1 pack/1 kg</td>
</tr>
</tbody>
</table>
CALCULATION OF DOSE

Cryoprecipitate requirement (No of bags)

• No of bags = 
  (desired F VIII level-initial FVIII level )X Plasma Vol /FVIII content of each bag (IU)

• 1 IU /kg of F VIII increases plasma level by 2 %
• 1 IU /kg of F IX increases plasma level by 1 %
CALCULATION OF DOSE OF FVIII

- Blood volume in adults = wt (in kgs) \times 70\text{ml/kg}
- Plasma volume = blood volume \times (1 - pcv)
- units of FVIII required = plasma volume \times (\text{desired F VIII level-initial FVIII level})
• As adjunct to factor replacement in mucosal or gastrointestinal bleeding and surgery, give fibrinolytic inhibitor:
  
  Tranexamic acid (oral): 500–1000 mg 3 times/day. Do not use for haematuria.

• In an emergency, use fresh frozen plasma to treat bleeding in haemophiliacs (give 3 bags initially) if none of the above are available.

• If FFP is also not available, transfuse fresh whole blood (1 IU of F VIII/IX present in about 2 ml of fresh whole blood)
MANAGEMENT OF PATIENTS WITH FVIII INHIBITORS
Residual FVIII activity > 5%, bleeding minor

- Yes DDAVP Trial
- FVIII inhibitor Titer <5BU

- NO Ab titer (BU) against human/porcine VIII
- FVIII inhibitor titer >5BU
CLASSIFICATION OF PATIENTS WITH FVIII INHIBITORS

**Low responders**
- Inhibitors < 5 BU
- Inhibitors not ↑ on exposure to F VIII
- Respond to factor replacement therapy
- Sometimes inhibitors disappear

**High responders**
- Inhibitors > 5 BU
- 60-70 % high responders
- Inhibitors ↓ in absence of replacement therapy
- Even become undetectable
- Re-exposure inhibitors ↑ over 4-7 days.
MANAGEMENT OF HIGH RESPONDERS

• Removal & suppression of inhibitors
  – Plasmapheresis + chemotherapy (cyclophosphamide or steroids or Rituximab)
  – Slow response, time consuming

• IVIG therapy
  – For both autoantibodies and alloantibodies to FVIII in some cases of hemophilia A
  – Effect is due to anti-idiotype antibodies

• Porcine FVIII
  – Mostly used in high titer FVIII inhibitors when titer <50 BU
  – 100 U/Kg every 24 hourly.
• **Prothrombin complex concentrate (PCC)**
  - Contain varying amounts of vit K dependent factor (II, VII, IX, X), manipulated to get partial activation of factors VII, IX and X.
  - 65-95% effective
  - Used only in mild hemophilia A with FVIII inhibitors and hemophilia B
  - Dose 50-100 U/kg. Max 200 U/kg/day

• **rFVIIa**
  - Dose 90µg/kg
  - Allows FVIIa to attach to activated platelet surface mediating conversion of FX to FXa on platelet surface.
## DOSAGE OF FACTOR IX IN HAEMOPHILIA B

<table>
<thead>
<tr>
<th>Severity of bleed</th>
<th>Required Factor IX dose</th>
<th>Factor IX concentrate (500 iu/bottle)</th>
<th>Fresh frozen plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mild bleed</td>
<td>15 iu/kg</td>
<td>2 bottles (adult)</td>
<td>1 pack/15 kg</td>
</tr>
<tr>
<td>2 Major bleed</td>
<td>20–30 iu/kg</td>
<td>3–6 bottles (adult)</td>
<td>1 pack/7.5 kg</td>
</tr>
</tbody>
</table>
Note:
1. Repeat in 24 hours if bleeding continues.

2. Factor VIII concentrate and cryoprecipitate are not useful for haemophilia B so accurate diagnosis is essential.

3. As adjunct to replacement therapy:
Tranexamic acid (oral): 500–1000 mg 3 times/day, as for haemophilia A.
VON WILLEBRAND DISEASE (VWD)

- Von Willebrand factor (vWF) is a protein which is involved in platelet adhesion, both to other platelets and to the subendothelium.

- It also acts as a carrier protein for Factor VIII.

- Deficiency of von Willebrand factor is inherited as an autosomal dominant condition affecting both males and females.
MANAGEMENT OF VWD

The aim of treatment is to normalize bleeding time by
• Increasing endogenous vWF levels with desmopressin (DDAVP)
  or
• Replacing vWF using an intermediate-purity Factor VIII product that is known to contain some vWF
  or
  with Cryoprecipitate.
Dose regime
• Treat as for mild or moderate bleed of haemophilia A, except that the haemostatic dose may be repeated not 12-hourly, but after 24–48 hours, as von Willebrand factor has a longer half-life than Factor VIII.

1. Desmopressin (DDAVP)
0.3–0.4 μg/kg IV lasts 4–8 hours and avoids the need to use plasma products.
The dose can be repeated every 24 hours, but the effect is reduced after some days of treatment.

2. Factor VIII concentrates
Reserve for patients unresponsive to desmopressin.

3. Cryoprecipitate
Dosage: 4-6 packs/adult
ACQUIRED BLEEDING AND CLOTTING DISORDERS

• Disseminated intravascular coagulation (DIC)
• Deficiency Vitamin K dependent coagulation factors
• Gastrointestinal bleeding
• Bleeding problems associated with surgery
TRANSFUSION PROTOCOL IN DIC

1. If the PT or APTT is prolonged and the patient is bleeding:
   - Replace red blood cell loss with the freshest whole blood available as it contains fibrinogen and most other coagulation factors
   
   *and*

   - Give fresh frozen plasma as this contains labile coagulation factors: 1 pack/15 kg body weight (4–5 packs in adults)
   - Repeat FFP according to the clinical response.
2. If fibrinogen is low or the APTT or thrombin time is prolonged, also give cryoprecipitate (to supply fibrinogen and Factor VIII): 1 pack/6 kg (8–10 packs in adults).

3. If the platelet count is less than $50 \times 10^9$/L and the patient is bleeding, also give platelet concentrates: 4–6 packs (adult).

4. The use of heparin is controversial.
MANAGEMENT OF DEFICIENCY OF VITAMIN K-DEPENDENT COAGULATION FACTORS

• 1 Remove the underlying cause of vitamin K deficiency:
  ■ Stop anticoagulants (warfarin)
  ■ Treat malabsorption or dietary deficiency.

• 2 Replace coagulation factors with fresh frozen plasma, as necessary.

• 3 Reverse warfarin with intravenous vitamin K if the patient is bleeding and the INR is prolonged. Doses of vitamin K exceeding 1 mg may make the patient refractory to further warfarin for up to 2 weeks.
## GUIDELINES ON TRANSFUSION IN GASTROINTESTINAL BLEEDING

<table>
<thead>
<tr>
<th>Severity of bleed</th>
<th>Clinical features</th>
<th>Iv infusion/ Transfusion</th>
<th>END POINT</th>
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<tbody>
<tr>
<td>Mild Bleed</td>
<td>Pulse full, Haemoglobin normal</td>
<td>Maintain IV access until diagnosis is clear</td>
<td>Ensure blood is available</td>
</tr>
<tr>
<td>Moderate Bleed</td>
<td>Resting pulse &gt;100/min and/or Haemoglobin &lt;10 g/dl</td>
<td>Replace fluid</td>
<td>Maintain Hb &gt;9 g/dl*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Order compatible red cells (4 units)</td>
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| Severe Bleed      | History of collapse and/or Shock  
■ Systolic BP <100 mmHg  
■ Pulse >100/min | Replace fluid rapidly  
■ Ensure blood is available  
■ Transfuse red cells according to clinical assessment and Hb/Hct | Maintain urine output >0.5 ml/kg/hr  
■ Maintain SBP >100 mm Hg  
■ Maintain Hb >9 g/dl* |
PATIENTS FULLY ANTICOAGULATED WITH WARFARIN

• Emergency surgery
  1. Give vitamin K, 0.5–2.0 mg by slow IV infusion.
  2. Give fresh frozen plasma, 15 ml/kg. This dose may need to be repeated to bring coagulation factors to an acceptable range.
  3. Check INR immediately prior to surgery.
  4. Commence surgery if INR and APTT ratio are <2.0.
PATIENTS FULLY ANTICOAGULATED WITH HEPARIN

Elective surgery
1 Stop heparin 6 hours preoperatively.
2 Check APTT ratio immediately prior to surgery.
3 Commence surgery if APTT ratio is <2.0.
4 Restart heparin as soon as appropriate postoperatively.

Emergency surgery
• Consider reversal with IV protamine sulphate.
  1 mg of protamine
THANK YOU