Therapeutic apheresis (introduction)

Orieji Illoh, MD
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Apheresis

• Removal of blood

• Separation into component parts

• One component is retained and remainder is returned
History

• First tried in animals

• In humans it was first performed in patients with hyperviscosity syndrome (1960)

• Increased use following the arrival of automated cell separators
Goal of Therapeutic Plasma exchange

- remove or reduce levels of pathologic substance
- replace essential substance that is absent
- Modify protein or mediators of inflammation
Frequency of therapeutic procedures by type

- PE with plasma, 33%
- PE no plasma, 37%
- Autologous PBSC, 19%
- RBC exchange, 2%
- Leukopheresis, 2%
- Photopheresis, 2%
- Column depletion, 3%
- Plateletpheresis, 1%
- Other, 1%

*Transfusion* 1999;39:282-288
Instrumentation

cell separation device

- Centrifugation
  Continuous or intermittent flow
- Retrieve one component and return the rest
Centrifugation

- Blood is drawn from patient
- Anticoagulant solution is added
- Pumped to rotator bowl, chamber or tubular rotor
- Layering of components occurs based on density
- Desired fraction is diverted
- Other components are returned to the patient
Membrane filtration

Blood flows across a membrane containing pores of a defined size

http://www.membrana.com/oxygenation/plasma/plasmasep.htm
Separation by adsorption

Can modify centrifugal or membrane devices to absorb specific pathologic materials

http://www.liposorber.com
http://www.freseniushc.com
http://www.adacolumn.com
http://www.liposorber.com
Photopheresis

1) Blood is drawn into XTS

2) Whole blood centrifuged; RBCs and plasma returned to the patient

3) WBCs collected and treated with psoralen (UVADEX®)

4) WBCs photoactivated with UVA light

5) Treated WBCs returned to patient

http://www.apheresis.org/~documents/Marques.pdf
Rheopheresis

For the treatment of age related macular degeneration

www.amdstudy.com
Cobe's body parts

Figure 2-4: Centrifuge chamber

Figure 2-5: Top view of centrifuge
COBE Spectra System

• Uses six parameters to determine flow rates and exchange parameters in TPE
  - Sex
  - Height
  - Weight
  - Hematocrit
  - Type of fluid replacement
  - Fluid balance
Pump flow rates

- **AC infusion rate** – based on TBV and replacement fluid
  - Takes into account citrate content of replacement fluid
  - Initial AC infusion rate:
    0.8 ml/min/Liter TBV (upper limit of 1.2 ml/min/L TBV)
  - Inlet: AC ratio is about 10:1
- **Plasma pump flow rate** : based on patient hematocrit
- **Replace pump flow rate**: based on fluid balance chosen
Types of therapeutic apheresis or exchange procedures

- Plasma exchange
- Red cell exchange
- Plateletpheresis
- Leukopheresis
- Immunoabsorption
- Photopheresis
- LDL extraction
Physiology of apheresis

• Anticoagulation
  – Citrate anticoagulant of choice
    • Chelates calcium and blocks calcium dependent clotting factor reactions
    • Minimizes activation of circulating cellular and plasma components
    • Citrate content varies depending on the anticoagulant used
Calcium homeostasis during apheresis

- A lot of work done on platelet donors
- Citrate levels range between 17mg/dL to over 30mg/dL
  - 23% - 33% reduction in ionized calcium especially in the first 15 minutes
    - Increases renal excretion of calcium, magnesium, potassium, sodium
  - Parathormone rises rapidly in the first 15 minutes then levels off
- Citrate returns to baseline levels 4 hrs after infusion ceases
In TPE...

• Similar effects, more citrate infusion in TPE
  - FFP contains citrate
  - Albumin can bind ionized calcium
    • Usually do not become symptomatic
  - Some citrate is discarded with plasma
  - Poor citrate metabolism in liver failure, alkalosis in renal disease

• Current apheresis equipment limit citrate dose and rate, reactions less with continuous flow instrument
Amount of citrate in replacement fluids

- Plasma: 17.4 mm/L
- Albumin: 4.4 mm/L
- Saline: 0 mm/L
Heparin

- Can theoretically be used
  - Need about the same dose for heparinization of hospitalized patients
- Low toxicity
- However not used
  - Anticoagulant properties neutralized by normal plasma
  - Risk of Heparin induced thrombocytopenia
  - Used for LDL separation
Other changes

• hemodynamic changes
  - Hypo or hypervolemia

• dilutional effects
  - From replacement fluid
  - Requilibration
Effect on proteins

• Depends on whether they are in the intra or extravascular compartment

• Requilibrium

• Rate of protein catabolism

• Synthesis by the liver
### Alterations in blood constituents by a single volume exchange

<table>
<thead>
<tr>
<th>Constituent</th>
<th>% decrease from baseline</th>
<th>% recovery after 48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clotting factors</td>
<td>25-50</td>
<td>80-100</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>63</td>
<td>65</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>30-60</td>
<td>Variable</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>55-60</td>
<td>100</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45</td>
<td>100</td>
</tr>
<tr>
<td>C3</td>
<td>63</td>
<td>60-100</td>
</tr>
<tr>
<td>platelets</td>
<td>25-30</td>
<td>75-100</td>
</tr>
</tbody>
</table>
Fig. 1. Changes in the PT, PTT and concentrations of factors VIII and IX during a single partial plasma exchange with albumin replacement. Individual points represent actual measurements. The Fibrinogen curve is based upon a least squares regression analysis of 13 data points.
Effect on electrolytes

- **Potassium**
  - Observed decrease of 0.25mEq/L after 1.3-2 plasma volume exchanges with albumin and 0.7mEq/L with FFP

- **Bicarbonate**
  - Decreased

- **Chloride**
  - Decreased

- **Sodium**
  - No significant change
Cellular loss

- **Red Blood Cells**
  - Decreased Hb by about 12% when albumin is used, recovery within 24hrs

- **White blood cells**
  - Transient increase in WBC count

- **Platelets**
  - 30% decline, recovery in 48hrs
Drugs

Some drugs especially if protein bound can be removed during plasma exchange
- Antibiotics
- Antiseizure medications
The patient

• Is TPE indicated?
  - History and physical, lab data
  - Co-existing health problems
  - Medications
  - Likelihood of response
  - Published experience
  - AABB and ASFA guidelines
Categories

- **Category I**
  - Primary or standard acceptable therapy

- **Category II**
  - Accepted in a supportive role to other primary therapies

- **Category III**
  - Insufficient data to determine therapy

- **Category IV**
  - No response to apheresis therapy
Current medications

• Can they cause adverse effects?
  - ACE inhibitors

• Will they be removed by apheresis?
  - IV antibiotics

• Needed to treat disease?
Management plan

- **Urgency**
  - TTP
  - Hyperviscosity syndrome
  - Guillain-Barre syndrome
  - *Myasthenia gravis* (crises)
  - Sickle cell disease (acute chest, priapism, stroke)
  - Acute liver failure
Management Plan

Extracorporeal blood volume assessment

- Assess patients ability to tolerate the procedure
- Total extracorporeal volume is the amount of cells and plasma needed to displace the saline used to prime the lines
- RBC Extracorporeal volume is the RBC volume required to fill the bowl or channel or all the tubing
  - Proportional to the hematocrit
Management of Extracorporeal volume

• Total or RBC ECV should not exceed 15%

• If total ECV > 15% but RBC ECV < 15%
  - Give saline bolus or colloid prime

• If total ECV < 15% but RBC ECV > 15%
  - Transfuse RBC
  - Prime with RBC
Management Plan

• Vascular access
  - Peripheral or central? Need to consider risks of central catheters, frequency of procedures
What is the ideal catheter?

- Should allow adequate flow rates
- Double lumen for input and return lines
- Staggered ports
- Minimal length
- Sufficient firmness
- Infection resistance

Courtesy, Beth Hartwell, MD
Peripheral access

Preferred
Fewer side effects
Use medial cubital, cephalic and basilic veins in the antecubital fossa of the arms
Use thin walled steel needles (16 or 18 gauge)
Appropriate skin preparation

http://www.terumomedical.com
Quinton® Mahurkar Dual Lumen Hemodialysis Catheters

**Catheter Advantages**
- Quinton® Mahurkar Dual Lumen Catheters:
  - Preserve peripheral vessels and allow dialysis while chronic access is mature.
  - Provide maximum patient comfort by softening when exposed to body heat.
  - Are made of highly kink-resistant, radiopaque polyurethane and have a special soft tip to reduce trauma to the vein.
  - Can be inserted in the ICU and other bedside situations.
  - Can be used with all standard dialysis machines.
  - Eliminate expensive single-needle equipment and high recirculation values.

**Choice of Sizes and Lengths**
- You have a choice of 10 or 11.5 French sizes (O.D.) and a variety of catheter lengths—each just right for each patient.
- 10 French Mahurkar Catheters:
  - Choice of 14, 15, or 19.5 cm implantable length.
  - ≤ 100 mm Hg venous pressure at 200 cc/min blood flow rate.

**Curved Extensions Option**
- Our 10.5 cm (11.5 Fr) catheter with curved extensions is especially useful for jugular insertions. The catheter extensions bend away from the neck, improving patient comfort. Also, the adapters are positioned caudal, simplifying access for dialysis and catheter care.

**Quinton® Dual Lumen Hemodialysis Catheters—Preliminary Clinical Evaluation**
Management Plan

• **Laboratory data**
  - **CBC, electrolyte panel including ionized calcium**
  - **Related to disease**
    • LDH, ADAMTS13, coagulation profile
    • Antibody assays

• **Hemoglobin should be ~8.0g/dL,**

• **Normal K, Ca^{2+}**
Intensity of exchange

How many plasma or red blood cell volumes?

• Calculation of TBV, PV, RCV
  \[ TBV = 70 \times \text{(weight kg)} \]
  \[ PV = TBV \times (1 - \text{hct}) \]
  \[ RCV = TBV \times \text{hct} \]
  - There are established formula that take into account the weight and BSA

• 1 or 1.5 plasma volumes usually exchanged

• 1 to 2.5X red cell volume
Efficacy of plasma exchange

- Continuous flow exchange (formula 3)
- Discontinuous flow exchange (0.1 plasma volume per cycle)
  Replacement before removal (formula 5)
- Discontinuous flow exchange (0.1 plasma volume per cycle)
  Removal before replacement (formula 4)
## Replacement Fluid

<table>
<thead>
<tr>
<th>Replacement Solution</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloids</td>
<td>Low cost</td>
<td>2-3 volumes required</td>
</tr>
<tr>
<td></td>
<td>Hypoallergenic</td>
<td>Hypooncotic</td>
</tr>
<tr>
<td></td>
<td>No viral risk</td>
<td>No coag factors, immunoglobulins</td>
</tr>
<tr>
<td>Albumin</td>
<td>Iso-oncotic</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td>No viral risk</td>
<td>No coag factors</td>
</tr>
<tr>
<td>Hydroxyethyl starch</td>
<td>Moderate cost</td>
<td>Urticarial and pruritic reactions</td>
</tr>
<tr>
<td></td>
<td>Iso-oncotic</td>
<td>Long term residual levels of HES</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated in renal failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possible coagulopathy</td>
</tr>
<tr>
<td>Plasma</td>
<td>Normal levels of immunoglobulin, coag factors,</td>
<td>Viral transmission risk</td>
</tr>
<tr>
<td></td>
<td>other plasma proteins</td>
<td>Citrate load</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allergic reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>sensitization</td>
</tr>
</tbody>
</table>
Frequency

Depends on the disease you are treating

- Removing something?
  - Characteristics of that something?
    - autoantibody, LDL

- Replacing something?
  - TTP

- Is the patient on something?
  - Need to deal with rebound phenomenon?
## Targets and goals

<table>
<thead>
<tr>
<th>Substance</th>
<th>Treatment volume (mL/kg)</th>
<th>Treatment interval</th>
<th>Treatment endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoantibodies</td>
<td>40-60</td>
<td>24-48</td>
<td>4-6 treatments</td>
</tr>
<tr>
<td>Immune complexes</td>
<td>40-60</td>
<td>24-48</td>
<td>Response</td>
</tr>
<tr>
<td>Paraproteins</td>
<td>40-60</td>
<td>24</td>
<td>Response</td>
</tr>
<tr>
<td>Cryoproteins</td>
<td>40-60</td>
<td>24-48</td>
<td>Response</td>
</tr>
<tr>
<td>Toxins</td>
<td>40-60</td>
<td>24-72</td>
<td>Response</td>
</tr>
<tr>
<td>TTP</td>
<td>40</td>
<td>24</td>
<td>Remission</td>
</tr>
<tr>
<td>Immunologic rebound</td>
<td>40-60</td>
<td>24-48</td>
<td>2-3 followed by immunosuppressives</td>
</tr>
</tbody>
</table>
Other things you need to do

• Obtain Informed consent
• Write a consult note
• Premedication if needed
• Order blood components
Complications of TPE

- Relatively safe procedure
- Adverse events occur in 4 – 17% procedures
- Most adverse reactions are mild
- Rare deaths, most cardiac
## Complications of TPE

<table>
<thead>
<tr>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaso vagal reactions</td>
</tr>
<tr>
<td>Vascular access complications</td>
</tr>
<tr>
<td>Citrate reactions</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>Hypotension (vasovagal, hypovolemia, Bradykinin, neurologic)</td>
</tr>
<tr>
<td>Allergic reaction</td>
</tr>
<tr>
<td>Volume overload</td>
</tr>
<tr>
<td>Coagulopathy</td>
</tr>
<tr>
<td>Arrhythmia</td>
</tr>
<tr>
<td>Infection (blood products, catheter related)</td>
</tr>
</tbody>
</table>
TPE in pediatric patients

Problems
- Extracorporeal fluid volume
- Vascular access
- Lack of universally acceptable indications
- Experienced personnel

- Need to sedate?
- heparin may be preferred
- May need to prime the circuit with RBC
In case you have a few $$ to spare