Practical Issues in Plasmapheresis: Set-up and Troubleshooting, Combined CRRT and Apheresis

1. David M. Ward, MD, FRCP
   Use of Hybrid Apheresis/CRRT circuits

2. Isagani (‘Jhun’) Marquez, RN, BSN
   and Noel Oabel, RN, BSN, CNN
   Hands-on demonstration of simultaneous Plasma Exchange and CRRT
Practical Issues in Plasmapheresis:
Set-up and Troubleshooting, Combined
CRRT and Apheresis

1. Use of Hybrid Apheresis / CRRT circuits

David M. Ward, MD, FRCP, HP(ASCP).
Professor of Clinical Medicine, Division of Nephrology, UCSD.
Medical Director, Therapeutic Apheresis Program.
Associate Medical Director, Kidney/Pancreas Transplantation.
DISCLOSURES:

The speaker has the following potential conflicts

- TerumoBCT, Inc. – Honoraria, Consulting
- Therakos, Inc. – Honoraria
- Alexion Pharmaceuticals – Advisory Board
- Aethlon Medical Inc. – Consulting

WARNING:

Some uses are discussed that are not FDA-approved
OUTLINE:

- Case reports: patients requiring simultaneous TPE (therapeutic plasma exchange) + CRRT (continuous hemodiafiltration)
- Citrate-anticoagulated CRRT
- In parallel circuit design: TPE + CRRT
- In series circuit design: TPE + CRRT
- TPE + secondary plasma purification + CRRT
- Other methods of secondary plasma processing
Case reports

- The first 3 patients at UCSD (2001 - 2005)
  - who received liver transplants that were ABO incompatible ("A" liver into "O" recipient)
  - and developed post-operative acute renal failure.

- All required continuous renal replacement therapy (CRRT)
  - we used the UCSD citrate-a/c system to avoid bleeding*.

- All required therapeutic plasma exchange (TPE) for removal of anti-A antibodies to overcome antibody-mediated rejection
  - we used centrifugal plasma separation.

- All recovered renal function and survived with good function of the liver transplant.

Case reports

- Citrate-CRRT was originally Arterio-Venous (1989-1992)

CITRATE-ANTICOAGULATED C.A.V.H.D.

CITRATE

"4% Na₂Citrate"

(volume as per usual calculation)

170 ml/hr

(range 170-200)

REPLACEMENT

NS (0.9%)

DIALYSATE

999 ml/hr

\[ \frac{1}{2} \text{NS (0.45%) } \]

\[ + 50 \text{ml } 50\% \text{ dextrose }/l \]

\[ + 4.5 \text{mEq } \text{KCl }/l \]

\[ + 1 \text{mEq } \text{MgSO₄ }/l \]

add 23.4\% NaCl as needed (4mEq/ml), usually 10ml (40mEq/l).

this results in dialysate:

Na⁺ 117
Cl⁻ 121.5
K⁺ 4.5
Mg²⁺ 1.0 (mEq)
Dextrose 2.5%

ZERO Ca²⁺ (because extra Ca²⁺ increases citrate need)

ZERO Alkali (because citrate supplies enough → too much, anyway)

CALCUM

20ml 10% CaCl₂ in 250ml NS

= 1mEq Ca²⁺/10l

40ml/hr = 4mEq (range 30-40)

DMW 27 Feb 89
“Firsts” in citrate a/c of external blood circuits

1961: Apheresis (leukapheresis).

1961: Intermittent hemodialysis (IHD) – acute (with zero Ca^{++} dialysate).

1983: IHD – acute and chronic (with zero Ca^{++} dialysate).

1989: Continuous arterio-venous hemodiafiltration (CAVHDF).

1992: Continuous veno-venous hemodiafiltration (CVVHDF).


2011: Review Article:
   “Citrate Anticoagulation for Continuous Renal Replacement Therapy in Critically Ill Patients: Success and Limits”
Since 1992 at UCSD, CRRT has been veno-venous (CVVHDF)

Case reports

- Our 3 liver transplant patients received TPE plus CRRT

![Diagram of plasmapheresis and hemodiafiltration process](image-url)
Case reports

- Our 3 liver transplant patients received TPE plus CRRT
Case reports

- We used a TPE circuit in parallel with the CRRT circuit

**CENTRIFUGAL PLASMAFHERESIS**

- Citrate
- Effluent Plasma
- Replacement: Albumin/FFP
- Blood return
- Ca++

**CONTINUOUS HEMODIAFILTRATION**

- Prefilter
- Dilution
- Hemofilter
- Ultra-filtrate + Effluent Dialysate
- Ca++- free Dialysate
- Postfilter Replacement

**Case reports**
IN PARALLEL: Centrifugal Plasmapheresis and CVVHDF

Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

Citrate

CENTRIFUGAL PLASMAPHERESIS

Replacement: Albumin/FFP

Effluent Plasma

CONTINUOUS HEMODIAFILTRATION

Prefilter
Dilution

Hemofilter

Ca++- free Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

In addition:
- Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

- Citrate

- Ca++

- Blood return

- Pre- filtrate + Effluent Dialysate

- Ultra-filtrate + Effluent Dialysate

- Prefilter Dilution

- Hemofilter

- Ca++- free Dialysate

- Postfilter Replacement

- Ultra-filtrate + Effluent Dialysate

- Prefilter Dilution

- Hemofilter

- Ca++- free Dialysate

- Postfilter Replacement

- Ultra-filtrate + Effluent Dialysate

- Prefilter Dilution

- Hemofilter

- Ca++- free Dialysate

- Postfilter Replacement

- Ultra-filtrate + Effluent Dialysate
IN PARALLEL: Centrifugal Plasmapheresis and CVVHDF

Blood flow splits here
- Need higher total blood flow
- Need higher anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

Centrifugal Plasmapheresis

- Blood flow: 200 ml/min
- Citrate
- 100 ml/min
- Effluent
- Plasma
- Replacement: Albumin/FFP

Continuous Hemodiafiltration

- Prefilter
- Dilution
- 100 ml/min
- Hemofilter
- Ca++-free Dialysate
- Postfilter Replacement
- Ultra-filtrate + Effluent Dialysate

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running.
IN SERIES: Centrifugal Plasmapheresis and CVVHDF

Lower total blood flow - lower anticoagulant dose

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

100 ml/min

CENTRIFUGAL PLASMAPHERESIS

Blood return

CA++

replacement: Albumin/FFP

100 ml/min

Effluent Plasma

CONTINUOUS HEMODIAFILTRATION

Prefilter Dilution

Hemofilter

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

Citrate

Ultra-filtration

Ca++- free Dialysate

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

Blood pump (roller pump of CRRT machine) can run whether or not apheresis machine is running

100 ml/min

100 ml/min

100 ml/min

Lower total blood flow - lower anticoagulant dose
Use the apheresis machine’s citrate pump. (Switch to CRRT citrate pump when apheresis is stopped and bypass line is in use.)
IN SERIES: Centrifugal Plasmapheresis and CVVHDF

Centrifugal Plasmapheresis:
- Effluent Plasma
- Replacement: Albumin/FFP
- Citrate

Continuous Hemodiafiltration:
- Prefilter Dilution
- Hemofilter
- Ultra-filtrate + Effluent Dialysate
- Postfilter Replacement
- Ca++-free Dialysate

Blood Return from Patient:
- Ca++

Citrate
IN SERIES: Membrane Plasmapheresis and CVVHDF

- FROM PATIENT
  - Citrate

- REPLACEMENT:
  - Albumin/FFP

- EFFLUENT PLASMA
  - Prefilter
    - Dilution
    - Ca++-
      - free

- DIALYSATE
  - Ultra-filtrate + Effluent Dialysate

- BLOOD RETURN
  - Ca++

- CONTINUOUS HEMODIAFILTRATION
  - Hemofilter
  - Postfilter Replacement

UC San Diego
Health Sciences
dmward@ucsd.edu
IN SERIES: Membrane Plasmaseparator and CVVHDF

- FROM PATIENT: Heparin
- REPLACEMENT: Albumin/FFP
- EFFLUENT PLASMA
- PREFILTER REPLACEMENT: Dialysate
- POSTFILTER REPLACEMENT: Ultra-filtrate + Effluent Dialysate
- CONTINUOUS HEMODIAFILTRATION
- BLOOD RETURN

UC San Diego
Health Sciences
dmward@ucsd.edu
### DFPP and CRRT

**DOUBLE FILTRATION PLASMAPHERESIS**
- Heparin
- Blood return from patient
- Heparin
- Whole plasma
- Albumin fraction
- Effluent globulin fraction

**CONTINUOUS HEMODIAFILTRATION**
- Prefilter
- Dilution
- Hemofilter
- Ultrafiltrate + Effluent Dialysate
- Dialysate
- Postfilter Replacement

**Additional colloid (optional)**

**Specifications**

**#1: Plasma-filter**
- Pore size: ~0.3 microns
- Cut-off: >2000 kDa

**#2: Plasma-fractionator**
- Pore: 0.01-0.03 microns
- Cut-off: ~ 100 kDa
- (Albumin ~ 67 kDa)
- (IgG ~ 140 kDa)

Specifications are those of Asahi products

dmward@ucsd.edu
Coupled Plasmafiltration Adsorption (CPFA)

Continuous Plasmafiltration with Adsorption Column + Continuous High-volume Hemodiafiltration

- Prefilter dilution
- Ultra-filtrate + effluent dialysate
- Resin column
- Whole plasma
- Purified plasma
- Hemofilter
- Dialysate
- Blood return
- Plasmafilter
- Heparin
- From patient
- Blood return

Secondary plasma processing

(a) 

Albumin fraction

#1

#2

Whole plasma

blood return

from patient

(b) 

Albumin fraction from patient blood return

Whole plasma

Effluent

Purified plasma

Purified plasma (a) (b)

Plasma regeneration (on-line purification)

**Centrifugal TPE**

- Blood return
- Centrifugal apheresis machine
- Whole plasma
- From patient

**Membrane TPE**

- Blood return
- Plasma separator (hollow fiber membrane with large pore size)
- Whole plasma
- From patient

Purified plasma

Email: dmward@ucsd.edu
Plasma regeneration (on-line purification)

- DFPP (cascade plasmafiltration)
- adsorption columns containing
  - Staphylococcal Protein A
  - immobilized antibodies (Ab)
  - adsorption resins
  - immobilized antigen (Ag)
  - covalently-bound peptide ligands
Cascade Plasmafiltration (Double-Filtration)

from patient blood

Whole plasma

#1: Plasma-filter
Pore size: large
Cut-off: >1000 kD

#2: Plasma-fractionator
Pore size: medium
Cut-off: ~ 100 kD
(Albumin ~ 67 kD)
(IgG ~ 140 kD)
(IgM ~ 970 kD)

Additional colloid (optional)

Effluent

Membrane specifications are those of Asahi products (Asahi Kasei Kuraray Medical Co., Tokyo 101-8,101, Japan)
Protein-A Immunoabsorption (PA-IA)

- Staph Protein A has high avidity for Fc portion of IgG (IgG\textsubscript{1}, IgG\textsubscript{2}, IgG\textsubscript{4})
- Removal of antibody or antigen-antibody complexes

Staphylococcal Protein A immuno-adsorption column (Prosorba\textregistered) (Immunosorba\textregistered)

- ITP: FDA-approved.
- RA: Double-blind sham-controlled trial positive (Felson, 1999).
- Refractory TTP (Mitomycin): anecdotal successes.

- But columns no longer available.
- Also controversy: super-antigen (pharmacological) mechanism?
Antibody Immunoabsorption with Anti-IgG

- Removes IgG (all subclasses)
- Used in Europe and Japan for
  - autoimmune diseases
  - transplant alloimmunization
- Brands:
  - TheraSorb™ (Miltenyi Biotec)
  - others
Dextran adsorption (Kaneka Liposorber®)

- Removes LDL, Lp(a), and VLDL.
- Minimal effect on HDL or albumin.
- Effective LDL apheresis
- LDL-Apheresis

Kaneka® system is FDA-approved

Blood from patient returns Purified plasma through Perfusion columns containing Dextran sulfate.

Whole plasma flows through 5% Saline and 0.9% Saline with Waste collection.
Braun “HELP”® System
(Heparin-induced Extracorporeal Lipoprotein Precipitation)

Acidity (pH 5.12) plus heparin causes precipitation of lipoprotein complexes

Bicarbonate dialysis and ultrafiltration to correct pH and volume

Precipitate filter captures lipoprotein complexes

Ultrafilter

Heparin adsorber

Purified plasma

Whole plasma

From patient

Blood return

dmward@ucsd.edu
Perfusion columns containing immobilized antigen can extract specific autoantibodies from patient blood.

Purified plasma

For anti-GBM nephritis:

For SLE:

Clinically unsuccessful due to Ag leaching.
Covalently-bound peptide ligands for Immunoadsorption (IA)

Peptide ligands covalently linked to sepharose mimic the epitope and specifically immuno-adsorb pathogenic autoantibodies. effective in

**Autoimmune type Idiopathic Dilated Cardiomyopathy**

which is due to autoantibodies with

1. agonist-like effect on the Beta-1 adrenergic receptor
2. now known to cross-react with and damage cardiac myosin.

But Ab’s against different epitopes may cause similar disease

Covalently-bound ligands for Immunoadsorption (IA)

Column containing synthetic terminal trisaccharide A or B blood group antigen linked to a Sepharose matrix

Purified plasma

Blood return

Whole plasma

From patient

Glycosorb ABO column (Glycorex Transplantation AB),

Not FDA-approved

Secondary plasma purification + CRRT

from patient

PLASMA FILTER

Glycosorb ABO column

PLASMA PURIFIER

Hemofilter

CONTINUOUS HEMODIAFILTRATION

Prefilter Dilution

Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

blood return

Not FDA-approved
Secondary plasma purification + CRRT

from patient

Glycosorb ABO column

blood return

CENTRIFUGAL SEPARATION

PLASMA PURIFIER

CONTINUOUS HEMODIAFILTRATION

Prefilter Dilution

Hemofilter

Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

Not FDA-approved
IN SERIES: Centrifugal Plasma separator and CVVHDF

CENTRIFUGAL PLASMA EXCHANGE

from patient

blood return

Replacement: Albumin/FFP

Effluent Plasma

CONTINUOUS HEMODIAFILTRATION

Prefilter Dilution

Hemofilter

Ca^{++}- free Dialysate

Postfilter Replacement

Ultra-filtrate + Effluent Dialysate

blood return from patient
**IN PARALLEL:** Centrifugal Plasmaseparator and CVVHDF

**CENTRIFUGAL PLASMA EXCHANGE**

- Effluent Plasma
- Replacement: Albumin/FFP

**CONTINUOUS HEMODIAFILTRATION**

- Prefilter Dilution
- Hemofilter
- Ca++- free Dialysate
- Postfilter Replacement
- Ultra-filtrate + Effluent Dialysate

Blood return: from patient to blood return
SUMMARY:

- Case reports: patients requiring simultaneous TPE (therapeutic plasma exchange) + CRRT (continuous hemodiafiltration)
- Citrate-anticoagulated CRRT
- In parallel circuit design: TPE + CRRT
- In series circuit design: TPE + CRRT
- TPE + secondary plasma purification + CRRT
- Other methods of secondary plasma processing
Thank you for your attention
SAVE THE DATE
March 12 - 14, 2015

VISIT THE WEBSITE
cme.ucsd.edu/apheresis

• A 2½-day conference for MDs and RNs, from established practitioners to those starting a new program.
• Nationally prominent faculty.
• Didactic sessions on the basics.
• Symposia on plasma exchange, cell apheresis, disease applications, special patient populations, new science, program management, etc.
• Hands-on workshops.
• Breakfasts with the experts, etc.

Conference Organizing Committee:
David M. Ward, MD
Amber P. Sanchez, MD
Eileen Lischer, BSN, RN, CNN
Isagani Marquez, Jr., BSN, RN
Odette Ada, BSN, RN
Majella Vaughan, MPH