Therapeutic Plasmapheresis

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- Definitions
- Principles
- Technique
- Replacement
- Anticoagulation
- Complications
- Specific indication

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Plasmapheresis

A procedure in which whole blood is removed from the circulation and the red cells are returned, usually in a saline solution.

- Myasthenia gravis
- Idiopathic thrombocytopenic purpura (ITP)

Plasma exchange

the subject's plasma is replaced by another colloid solution such as purified protein fraction, a mixture of plasma proteins from which immunoglobulins and complement have been depleted, an albumin solution or another plasma.

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$$C_t = C_0 e^{-V_e/V_p}$$

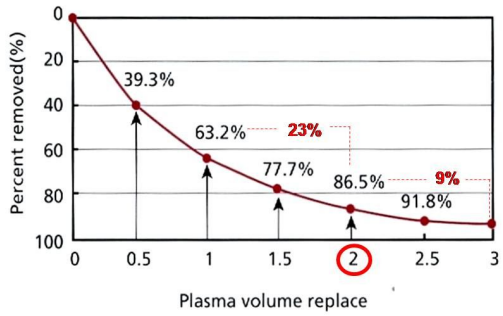
C_0 = initial plasma concentration of macromolecule

C_t = concentration at time t

V_e = volume of plasma exchanged at time t

V_p = estimated plasma volume

Plasma clearance



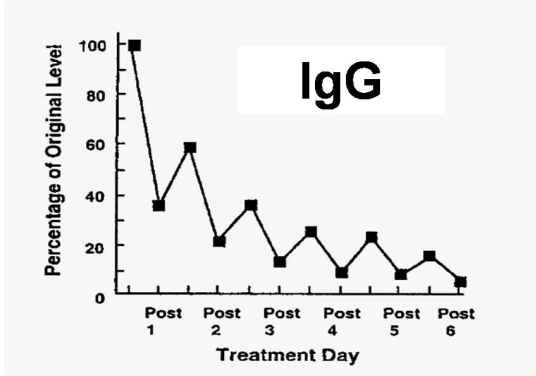
Distribution volumes

of immunoglobulins

substance	Molecular weight	% Intravascular	Half life (Days)	Normal serum conc. (mg/dL)
Albumin	69,000	40	19	3,500-4,500
IgG	180,000	50	21	640-1430
IgA	150,000	50	6	30-300
IgM	900,000	80	5	60-350
LDL	1,300,000	100	3-5	140-200

Reaccumulation

- Lymphatic drainage into vascular space
- Diffusion
- Endogenous synthesis



Concomitant

Immunosuppression

- Corticosteroid
- Cyclophosphamide

Early treatment

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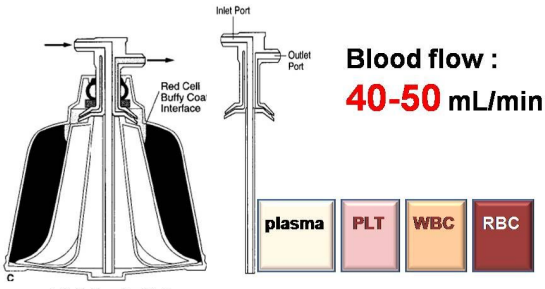
Principles

- **Withdrawal** of venous blood
- **Separation** of plasma from blood cells
- **Reinfusion** of cells plus autologous plasma or another replacement solution

Plasma & cell **Separation**

1) Centrifugation
2) Membrane filtration
3) Selective plasmapheresis

Centrifugal type

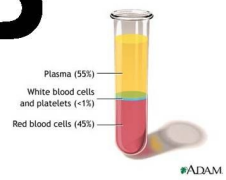


Blood flow : **40-50** mL/min

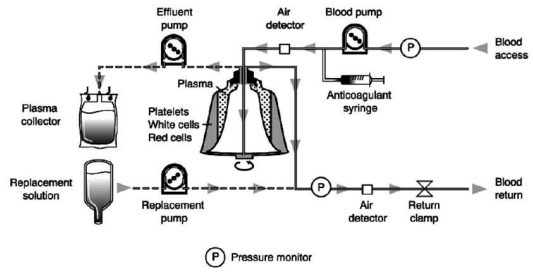
4800 RPM

Postcentrifugal plasmapheresis

PCPP



Centrifugal type



Centrifugal type

- **Intermittent** cell separator
- **Continuous** cell separator

Intermittent

- Drawn in successive batches and separated
- 1–1.5 plasma volumes
- Advantages
  - simplicity
  - portability of the machines
  - a single-needle peripheral venipuncture
- Disadvantages
  - slowness (typically > 4 hr)
  - relatively large extracorporeal blood volume required (>225 ml).

Continuous

- Fed continuously into a rapidly rotating bowl
- Remainder is returned to the patient with replacement fluid
- Advantages
  - Faster
  - Automated
- Disadvantages
  - higher cost
  - Immobility of the equipment
  - Two venipuncture or dual lumen catheter

Intermittent

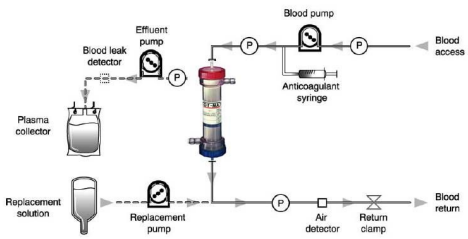
Haemonetics®
MCS 3 P

Continuous

Fenwal CS-3000

COBE Spectra

Membrane type



Plasma separator

Membrane type

selective membrane

Blood cell

Toxic antibody

albumin

plasma

Double filtration plasmapheresis

DFPP

DFPP

Membrane type

- Blood flow rate : 50-200 mL/min
- Membrane pore : 0.2-0.6 μm
- Plasma removal rate : **30-50** mL/min
- **Plasma separators**

  Plasmaflo® (Asahi) Plasmax ® (Toray)
  CPS-10 ® (Baxter) Plasmaflux ® (FMC)
  Prisma TPE 2000® (Hospal)

DFPP Advantages

- **Safe and efficient**
- **using either conventional or continuous hemodialysis equipment.**
- **Average time : less than 3 hours.**

DFPP Disadvantages

- **activation of complement and leukocytes on the artificial membrane,**
- **need for a large vein catheter to obtain adequate blood flow rates.**

Selective plasmapheresis

- **More sophisticated**
- **Disease specific**
- **Examples**

  Cryofiltration : cooling
  Cascade : different pore diameter
  Hemadsorption : toxin, cytokine removal

Application of apheresis techniques for renal diseases

Procedure	Ligands or materials	Removed or adsorbed factors
Plasma exchange	Replacement of plasma	Autoantibodies, CIC, dysproteins
Double filtration	Plasma fractionator	CIC, autoantibodies, dysproteins
Cryofiltration	Plasma fractionator	Cryoproteins
Plasma adsorption	Plasma adsorption Dextran sulfate Protein or Tryptophan Anti-IgG Fc	Anti-DNA, CIC Anti-DNA, CIC, Lupus anticoagulants, LDL IgG, CIC, permeability factors (?) IgG, CIC, permeability factors (?)
Blood adsorption	Polymyxin B (dextran sulfate)	Endotoxin, cytokines
Cytapheresis		
LCAP[b]	Lymphocyte separators	Lymphocytes, activated platelets
GCAP[c]	Granulocyte separators	Granulocytes

CIC, circulating immune complexes; LDL, low-density lipoprotein
a Centrifugal method or plasma separator
b Lymphocytapheresis
c Granulocytapheresis

Yokoyama H, Clin Exp Nephrol (2007) 11:122–127

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Total Plasma Exchange

전체 혈장을 제거한 후, 이를
신선동결혈장(FFP)이나
5% 알부민 용액으로 대치
하는 방법

Plasma Volume

35-40 mL/kg

Normal Hct : 35 mL/kg
Less than normal Hct : 40 mL/kg

Plasma Volume

- Kaplan 1992

  V_p=[0.065 x weight (kg)] x (1-Hct)

- Iodine 131 albumin dilution method

  V_p=(1-Hct)(b+cW)
  W = lean body weight
  b = 1,530 (male), 864 (female)
  c = 41 (male), 47.2 (female)

Plasma Volume

- 70kg with normal Hct (45%)
- Plasma volume
  = 70 x 35 = 2,450 mL

Albumin

Initial replace with colloid : 20-30%
Ringer's lactate solution or
Normal saline 1L

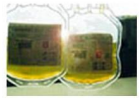
4-5% Albumin replacement
20% albumin (x2) + NS 800 mL

Fresh Frozen Plasma

- 항응고제 (CPDA-1) 처리 백에 400 또는 320ml 전혈을 채혈
- 채혈한지 6시간 이내에 4℃에서 5000 g 로 5분 동안 원심분리
- 혈장을 분리하여 -18℃ 이하에서 냉동 보존하여 제조
- 냉동보존 시 유효기간은 1년
- 반감기가 짧고 불안정한 제 V 및 제 VIII 혈액응고인자를 포함한 모든 혈액응고인자를 함유
- 평균용량 : 160-180 mL

FFP

Risk of hepatitis, HIV
Allergic reaction
Hemolytic reaction
Citrate load
ABO compatible



Replacement

• FFP 3 unit	480 mL
• 5% Albumin	800 mL
• Saline	1,000 mL
	2,480 mL

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Heparin

- Loading : 40-50 units/kg
- Maintenance : 20 units/kg/hour
- Monitoring
  - Activated clotting time
  - 180-220 sec
  - 1.5-2.0 times normal

Citrate

- Chelates calcium : **Hypocalcemia**
- Formula A (ACD-A)
  - Sodium citrate 2.2 g/dL + citric acid 0.73 g/dL
  - Membrane type : Cobe® Asahi®
- Formula B (ACD-B)
  - Sodium citrate 1.32 g/dL + citric acid 0.44 g/dL
  - Centrifugal type : Haemonetics®

Citrate

ACD-A: blood ratio	Maximum blood flow rate (mL/min)
1:10	1.2 x body weight (kg)
1:15	2.0 x body weight (kg)
1:25	3.0 x body weight (kg)

Femoral vein catheter

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Related to **Vascular access**
- Hematoma
- Pneumothorax
- Retroperitoneal bleeding

Related to **Procedure**
- Hypotension from externalization of blood
- Hypotension due to decreased intravascular oncotic pressure
- Bleeding from reduction in the levels of coagulation factors
- Edema formation
- Loss of platelet
- Hypersensitivity reaction

Related to **Anticoagulation**
- Bleeding, especially heparin
- Hypocalcemic symptoms (with citrate)
- Arrhythmia
- Hypotension
- Numbness and tingling of extremity
- Metabolic alkalosis from citrate

Hypocalcemia

- Prophylactic infusion of **10% $CaCl_2$** during treatment

Citrate toxicity

- 원인 : **Hypocalcemia**
- 증상
  얼굴이나 입 주위의 무감각 혹은 얼얼한 느낌, 진동감, 이명 등이 있고 심하면 오심, 구토, 복부경련, 흉부경련, 저혈압, 강축
- 예방
  증상을 조기에 인지하는 것이 중요
  혈액성분 채집술을 받는 환자들에게 구연산 독성에 관한 설명을 미리 해 증상이 나타나면 얘기하도록 한다.

주입 속도를 늦추면 대개 사라진다.

ACE inhibitor

- Risk of anaphylaxis
- Prekallikrein-activating factor in albumin → endogenous bradykinin release

Stop for 24-48 hrs

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Possible **Mechanisms** of apheresis in renal diseases

Removal of circulating pathological factors

Antibodies	**Anti-GBM antibody disease**
Immune complexes	**Lupus nephritis**
Cryoglobulin	**Cryoglobulinemia**
Myeloma protein	**Myeloma cast nephropathy**
Prothrombotic factor	**HUS-TTP**
Bacterial endotoxins	**Sepsis**
Poison or drug overdose	**Methylparathion poisoning**

Replacement of deficient plasma factors

Antithrombotic or fibrinolytic factor	**HUS-TTP**

Effects on the immune system

Removal of cytokines	**Sepsis**
Removal of complement products	**Lupus nephritis**
Effect on immune regulation	**Transplantation**
Improvement in RES function	**Cryoglobulinemia**

TABLE 3. *Evidence of effectiveness of apheresis therapy in renal diseases*

Disease	Method	Study Design (*N*)	Level of evidence	Result
Anti-GBM	PE	RCT (1)	2	Better renal survival with PE
RPGN	PE	RCT (5)	2–3	No benefit for entire group 4/5 trials (80%), Discontinuation of dialysis more on PE 2/5 trials (40%)
	LCAP	RCT (1)	2	More effective than steroid-pulse therapy
Lupus nephritis	PE	RCT (5)	2–3	Early disappearance of autoantibodies No benefit for clinical outcome
FGS				
Primary	PE	UCT (3)	5–6	Remission 11/20 patients (55%)
	LDL-A	UCT (2)	5	Remission 10/21 patients (48%)
	LCAP	UCT (1)	6	Remission 2/3 patients (67%)
Recurrent	PE	UCT/RHT (5)	4–6	Remission 19/29 patients (66%)
	Protein A	UCT (3)	6	Short-term remission 10/11 patients (91%) Long-term remission 2/8 patients (25%)
Dysproteinemia				
Cryoglobulin	PE	UCT (7)	4–5	Clinical improvement in 55–87%
Myeloma	PE	RCT (2)	2	Discontinuation of dialysis more on PE 2/2 trials (100%)
TTP	PE	RCT (2)	2	Remission more on PE (*vs* plasma infusion)
Transplantation	PE	RCT (4)	2–3	No benefit for graft survival 3/4 trials (75%) Better graft survival 1/4 trials (25%)

Anti-GBM, antiglomerular basement membrane disease; RPGN, rapidory progressive glomerulonephritis; FGS, focal glomerular sclerosis; TTP, thrombotic thrombocytopenic purpura; PE, plasma exchange; LCAP, lymphocytapheresis; LDL-A, low-density lipoprotein apheresis; RCT, randomized controlled trial; UCT, uncontrolled trial; RHT, retrospective historical controls.

Yokoyama H, Ther Apher & Dial, Vol. 7, No. 6, 2003

Therapeutic Apheresis Therapy for RENAL TRANSPLANTATIONS

Transplant associated **a**ntibody

- Anti blood type antibody
  Hyperacute rejection
- Anti HLA antibody
  Antibody mediated rejection

Donor (A)→Recipient (B)

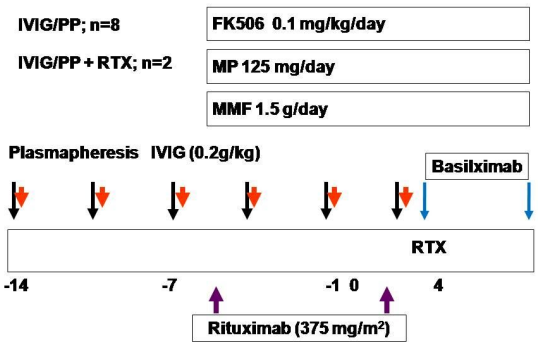
- **Anti-blood type antibodies**
- binding to renal vascular endothelial cells
- Activates complement
  platelet aggregation
  inflammation
- Intravascular thrombosis
  Occlusion of blood flow

Autonephrectomy

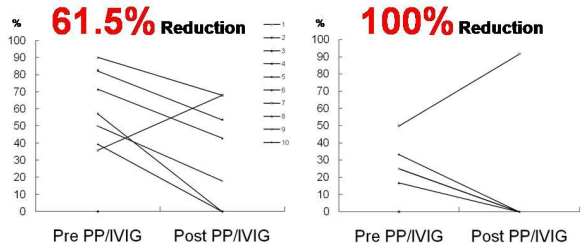
Removal of Anti-blood type antibodies
Removal of Anti-HLA antibodies

- Non-specific depletion
  plasmapheresis vs. plasma exchange
- Selective depletion of antibodies
- Immunoabsorption by affinity column
  (Staphylococcal protein A column)

Desensitization Protocol

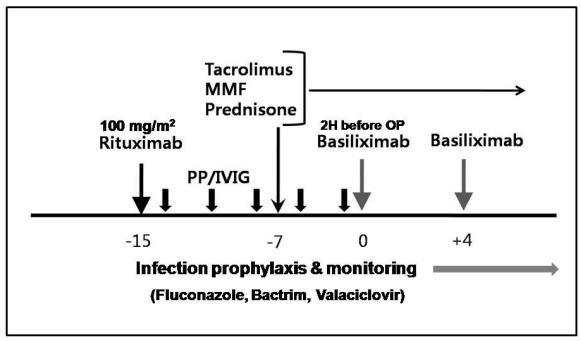


Changes of PRA Levels



CMC PROTOCOL

ABO incompatible KIDNEY TRANSPLANTATION



TPE and IVIG

- pre-transplant **2 weeks** before
- Replacement
  - 5%albumin + saline (+ FFP)
  - B → O : B형 FFP
  - A → B or B → A : AB형 FFP (antibody free)
- IVIG : post TPE 1hr (200 mg/kg)

The number of TPE/IVIG treatments based on initial antibody titer

ABO antibody titer*	Number of treatments	
	Before transplant	After transplant
<16	2	2
16	2	2
32	3	3
64	4	3
128	5-6	3
256	7-8	4
512	9-10	4
1024	10-12	4
>1024	>15	5

* Antibody titer at the AHG phase.

Tobian, AA et al.
TRANSFUSION, 2008

Target Anti-A/B Ab. titer

- Pre op 1:8
- Postop 1st wk 1:8
- Postop 2nd wk 1:16

Monitoring frequency

- PreOP & POD 1st wk
  Check Ab titer before & after each PP/IVIG
- POD 2nd wks — Check Ab titer EOD
- POD 1st month — Check Ab titer weekly, thereafter 2,4,6 12 months

Tolerance and Accommodation

SUMMARY

1. Plasmapheresis vs. plasma exchange
2. clearance rate : 63.2%/plasma volume
3. Technique : PCPP, DFPP, selective PP
4. Replacement : saline + 5% albumin + FFP
   - ✓ 1 plasma volume : 35-40 mL/kg
5. Complications : hypocalcaemia, stop ACEI
6. Application for specific indications
   - ✓ Renal disease
   - ✓ High risk or ABO incompatible KT

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Thank You