Plasma Exchange In Renal Diseases

Essay

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Aim of the work

❖ To present the different techniques, complications and indications of plasmapheresis.

❖ To discuss the different renal diseases which can be treated with plasmapheresis.

❖ To discuss the role of plasmapheresis in different renal diseases.

Abesract

Several renal diseases, especialy those with immunologic bases or those due to putative toxic mediators do not respond well to the usual medical modalitis. These diseases are usually serious and may lead to different morbidities and mortalities. Plasmapheresis may serve as a supplemental therapy in many of these diseases and can lead to better therapeutic response as in focal segmental glomerulosclerosis (post transplant), rapidly progressive glomerulonephritis, IgA nephritis and HSP nephritis.

Key Words:

- Plasmapheresis, Plasma exchange, Therapeutic plasma exchange, Systemic lupus erythematosus, Focal segmental glomerulosclerosis, Rapidly progressive glomerulonephritis, IgA nephritis, Henoch-Schonlein purpura nephritis

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Introduction

Plasmapheresis is a therapeutic model in several renal diseases ***(Kaplan AA, 1996).*** There are several mechanisms by which plasmapheresis exerts its beneficial effects. Its major mode of action is rapid depletion of specific disease-associated factors(eg. Anti glomerular basement membrane antibody (antiGBM), immune complexes, cryoglobins) ***(Ismail et al, 2000)***

Because of the immunologic nature of most diseases treated by plasmapheresis, therapy should almost always include concomitant immunosuppression. These agents would be expected to reduce the rate of resynthesis of pathologic antibodies such as IgG ***(Glockner et al, 1988; Kaplan, 1996)***

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Among renal diseases which can be treated by plasmapheresis are recurrent post transplant FSGS ***(Pradhan et al, 2003)***, hemolytic uremic syndrome ***(Magen et al, 2001)***, crescentic GN ***(Cole et al, 1992),*** anti GBM ***(Kaplan, 1996).***

Plasmapheresis can be done by one of two techniques, centrifugal plasma separation and membrane plasma separation. Different treatment strategies are used according to the disease treated ***(Ismail et al, 2000)***

Plasmapheresis

Definition:

Plasmapheresis is a method by which high molecular weight components or low molecular weight compounds with high degree of plasma protein binding are eliminated from the blood ***(Madore et al, 2002).***

Mechanisms of action of plasmapheresis:

The exact mechanism by which plasmapheresis benefits renal diseases still needs to be clarified. The possible actions of apheresis on renal diseases are summarized in table 1. In addition to the removal of pathological agents such as antibodies, immune complexes and /or immune associated cells, the removal of pro- inflammatory mediators including cytokines, chemokines and complement and a demonstrated improvement of immune system including reticuloendothelial function and the Th1/Th2 balance of helper T cells have been postulated to contribute to the beneficial effects of apheresis ***(Yakoyama et al, 2003).***

In addition, infusion of normal plasma may itself have a beneficial effects in some diseases such as atypical hemolytic uremic syndrome in which the replacement of a deficient plasma may be the principal mechanism of plasma exchange (PE) independent removal of circulating factors defined as anti Von Willebrand cleaving protease antibodies ***(Madore et al, 1996).***

Table 1: Possible mechanisms of apheresis in renal diseases:

1. Removal of pathological circulating factors, abnormal factors or physiologic factors in excess:

   a- Antibodies: anti GBM disease, ANCA associated disease, lupus nephritis (anti DNA), antiphospholipid disease

   b- Immune complexes: lupus nephritis

   c -Toxic factors: Vero toxin (HUS)

   d- Activated lymphocytes: vasculitis, nephrotic syndrome (FSGS).

2. Replacement of deficient plasma factors:

   Hemolytic uremic syndrome

3- Other effects on immune system:

   a-Removal of inflammatory mediators: cytokines, chemokines

   b-Improvement of reticuloendothelial system function

   c-Stimulation of lymphocyte clones to enhance cytotoxic therapy

(Yokoyama, 2003).

Pharmacokinetics of immunoglobulin removal:

The most important rational of therapeutic plasma exchange (TPE) is removal of pathogenic antibodies. Results of experiments in which isotopically labeled immunoglobulins have been infused into humans have demonstrated fundamental concepts: (a) Immunoglobulins have relatively long half-lives *($t_{1/2}$)*, approaching 21 days for IgG and 5 days for IgM. The plasma $t_{1/2}$ will determine how quickly the plasma level of the pathogen will rebound and how often the subsequent plasmapheresis sessions will have to be performed. (b) immunoglobulins have a substantial extravascular distribution . The extent of intravascular versus extravascular distribution will determine how effectively they can be removed in the course of a single plasmapheresis session. Based on these concepts, rational approach to prescribing TPE is one plasma volume exchange daily for 5 consecutive days at intervals of 24 hours ***(Kpalan AA, 1992)*** .

Techniques of plasmapheresis:

The first step in plasmapheresis is to remove plasma from whole blood. There are 2 physical methods of doing this: centrifugation (CF) and membrane plasma filtration (PF). Centrifugation (CF)involves the use of an apheresis machine which separates out different cellular and non cellular components of whole blood depending on the centrifugation speed and the time interval used, thus leukocytes, platelets, stem cells and

plasma can be fractionated from peripheral blood. These machines are usually used in hematology, blood banking and blood transfusion services ***(Kieseier et al, 2002).***

With the development of hemodialysis and continuous replacement renal therapy (CRRT) machines, nephrologists and intensivists have been able to use membrane plasma filtration as an alternative therapeutic plasma exchange (TPE) technique.. The operating principle depends on pumping the blood across a plasma filter, which is part of an extra corporeal blood circuit. Plasma is extruded from the intra-luminal blood compartment of the plasma filter into the plasma effluent pathway and drained into a collection bag. Membranes plasma filters typically have pore size cut-offs that exceed those of haemofilters. Large molecules such as albumin (MW68,000Da), immunoglobulin G (MW 160,000Da), apolipoprotein B (apo B) (MW512,000Da) and immunoglobulin M (MW950,000Da) can be removed from the blood compartment during TPE with this membrane. The sieving coefficient (ratio of concentration in filtrate to blood) of all these proteins have been reported to be ≥0.95 at a blood flow rate of 100ml /min. In addition to the filtration prosperities of membrane plasma filters, their surface area have been also studied ***(Unger et al,2002).***

A porcine experiment showed that larger surface area plasma filters were not more effective than smaller sized ones in cleaning specific measured solutes. Synthetic materials used in membrane plasma filters include polypropylene, polysulphone and polyethylene ***(Hirata et al,2003).***

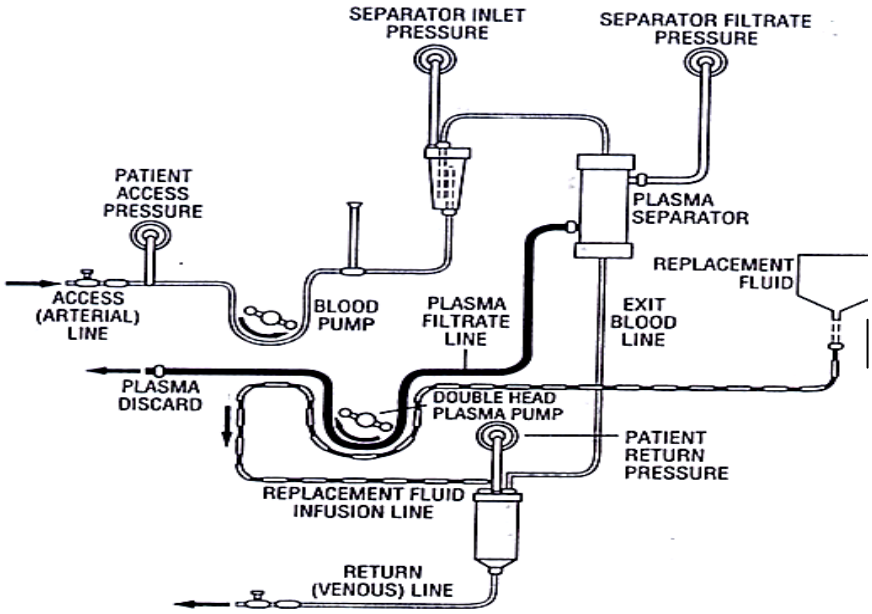

Figure 1: Circuitry for hollow –fiber membrane plasma separator, showing the dual track pump of plasma removal and replacement fluid. (From Asahi Plasma-Flo plasma separator product literature, Apheresis technologies, Palm Harbor, FL,1991.)

Besides plasma filtration another potential mechanism of solute clearance during membrane plasma exchange may be adsorption ***(Rogiers et al, 2003).*** Plasma membrane adsorptive removal of various humoral disease mediators also play a role in the overall elimination of plasma borne disease mediators. Such a role, however, remains to be further elucidated ***(Tan &* Hart, *2005).***

Vascular access:

Therapeutic apheresis is dependent on a functioning access to pump the patient blood through an extracorporeal blood circuit. The type of access is dependent on the need for blood supply as well as whether or not the procedure is done for acute or long-term indications. The access also depends on if the apheresis is done by a sequential (intermittently drawing blood, processing and returning blood) or continuous treatment (drawing blood, processing and returning continuously). A well functioning blood access for therapeutic apheresis facilitates the treatment, although a less well functioning access may still allow completion of the procedure at a slower rate ***(Stegmayr &* Wikdahl, *2003).***

For the centrifuge device systems, a blood flow rate in the range of 40-50 ml/min is required. This can be obtained from a large peripheral vein (antecubital vein). On the contrary, a central venous access is indicated when using membrane apheresis because a blood flow rate between 100-150 ml/min is required for the successful and efficient operation of the filtration system ***(Ismail et al, 2000)*** The vascular access used for acute procedures may be sufficiently supplied by two peripheral veins or catheters placed in the femoral vein or the right internal jugular vein. For chronic treatment it may be necessary to create an arteriovenous fistula or graft ***(Stegmayr &* Wikdahl, *2003).***

Table 2: Suggested size and selection of vascular access for pediatric patients

Patient size	Catheter size and source	Site of insertion
Neonate	Single-lumen 5 Fr (COOK)	Femoral artery or vein
	Dual-lumen 7.0 French (COOK/MEDCOMP)	Internal/external jugular, subclavian or femoral vein
3 - 6 KG	Dual-lumen 7.0 French (COOK/MEDCOMP)	Internal/external jugular, subclavian or femoral vein
	Triple-lumen 7.0 French (MEDCOMP)	Internal/external jugular, subclavian or femoral vein
6 - 15 KG	Dual-lumen 8.0 French (KENDALL,ARROW)	Internal/external jugular, subclavian or femoral vein
>15 KG	Dual-lumen 9.0 French (MEDCOMP)	Internal/external jugular, subclavian or femoral vein
>30 KG	Dual-lumen 10.0 French (KENDALL,ARROW)	Internal/external jugular, subclavian or femoral vein

(*Bunchman *et al, 2002)

Anticoagulation:

Citrate anticoagulation is the anticoagulant of choice when performing CF-TPE, whereas heparin is the conventional anticoagulant used in PF-TPE. A recommended dose of heparin (in the absence of over bleeding diatheses) is 40-60 IU/ kg followed by 20-40 IU/kg/hr every hour for the duration of TPE. Lower dose of anticoagulant should be used or omitted together if there is a very high risk of bleeding . Anticoagulant is administrated pre-plasma filter. Citrate toxicity can occur even if citrate anticoagulant is not used given the relatively high content of citrate (up to 14% by volume) in fresh frozen plasma (FFP), especially if there is significant concomitant renal and / or hepatic dysfunction ***(Tan &* Hart, *2005).***

Comparison of membrane plasma separation(MPS) and centrifugation devices:

Compared with centrifugation devices, MPS has several advantages. For example, equipment requirements are relatively minimal, and only a blood pump and pressure monitors are required. MPS can thus be performed by standard hemodialysis equipment, and patients with acute renal failure who require hemodialysis and plasmapheresis can receive both treatments sequentially using the same machine. On the other hand removal of white cells or platelets is possible only with