Therapeutic Plasma Exchange in nephrology. Where it applies?

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ABSTRACT

Plasma exchange had been proposed to treat many kidney diseases. A few controlled studies, observational studies, and mechanistic evidence have specified the better indications, which are thrombotic microangiopathies, kidney transplantation and ANCA-associated vasculitides.

Plasma removal can be realized by filtration, centrifugation, or immunoadsorption, with differences in efficacy, but these also impact on volume load and anticoagulation in patients with renal failure.

Plasmapheresis was used in nephrology to treat Goodpasture syndrome in 1975, systemic lupus erythematosus in 1976, and thrombotic thrombocytopenic purpura in 1977. Since then, Plasma exchange has been used in many kidney diseases although evidence-based medicine remains relatively poor. National registries have been established to compensate for this lack of evidence-based medicine. While treatment of thrombotic thrombocytopenic purpura is supported by evidence-based medicine, the use of Plasma exchange to treat other renal diseases is mainly based on observational studies. Plasma exchange cannot be properly provided by untrained teams and remains at a high cost, considerations which are to be taken into account before implementation.

Technical considerations

Technics for Plasma exchange have known spectacular improvements. Physicians must know the advantages and drawbacks of each of these techniques for the best bedside choice. Plasmapheresis is a general word for any kind of apheresis which removes plasma. Plasma exchange involves the replacement of the removed plasma making large volume procedures possible. Plasma removal is realized either by centrifugation or filtration. Centrifugation requires a trained team and an expensive device but can be done via a peripheral vein. Plasmafiltration is easier to realize with a polyvalent generator which is often present in ICUs but needs a central vein catheterization. Conventional plasma exchange is no longer the unique procedure. Double filtration cascade and immunoadsorption have risen as alternatives. The double filtration cascade adds to a second step to a first plasma separation with a selective filtration of different sieving coefficients. It allows reduction of volume compensation. Immunoadsorption is also a two-step procedure. After centrifugation or filtration, plasma is directed to a column in which ligands catch immunoglobulins. Manufactured columns are semi-selective protein-A-sepharose columns, semi-selective GAM peptide columns, or selective anti-A or anti-B columns. The very high cost of these columns is counterbalanced by a large reutilization in the same patient.

The first goal of plasma exchange is to remove an unwanted substance of high molecular weight which is not possible with hemodialysis. In this case, the removed plasma is replaced

by 5% human serum albumin, which has the inconvenience of an increased risk of bleeding. Removal of unwanted substances mainly concerns immunoglobulins: autoantibodies (ANCA in case of vascularitides), alloantibodies (anti-HLA antibodies in allograft patients), immune complexes, cryoglobulins, and immunoglobulin light chains. Unfortunately, a rebound is frequently observed after the end of plasma exchange, the level of immunoglobulins could rise up to 50%. The use of high dose intravenous immunoglobulins is therefore proposed to prevent this rebound effect. In all cases, one might consider the addition of immunosuppressive agents to treat the underlying disease. Another goal of Plasma exchange is to replace a deficient substance. Then, the exchange fluid is a plasma product such as fresh frozen plasma, which might expose the patient to plasma antigens and viruses. Replacement of deficient substances includes the ADAMTS13 protein and complement regulatory proteins. To be exhaustive, the final effect of Plasma exchange is to obtain hemodilution in hyperviscosity syndromes.

Many renal diseases which need Plasma exchange require a kidney biopsy. Anticoagulation is achieved with heparin or with citrate. Heparin favors bleeding; citrate induces hypocalcemia and requires a high volume injection. Plasma removal by centrifugation leads to a more pronounced low platelet count. A very low platelet count (such as in microangiopathies) is a contra-indication to heparin, a citrate anticoagulation being better in these cases. Therefore, it is important to take into consideration the risk of bleeding to schedule the time of the biopsy, and to choose an appropriate techniques for plasma exchange.

When the disorder is accompanied by acute renal failure, either with sustained diuresis or with anuria, the patients also need to be treated by hemodialysis. To receive both therapies is exhausting for them. A common solution is to give plasma exchange and dialysis on alternate days. It is now possible to give both during the same session in a cascade process.

Treatment of kidney diseases

Recommendations for the use of Plasma exchange have arisen recently [1] but well-designed trials are needed to clarify the potential role of plasma exchange in renal disease [2].

Thrombotic microangiopathies are the most common renal indications for plasmapheresis. Thrombotic thrombocytopenic purpura (TTP) was definitively distinguished from hemolytic uremic syndrome (HUS) when their different pathophysiological mechanisms were discovered although clinical symptoms could be misleading. TTP presents with thrombocytopenia and hemolytic anemia, and a classical predominant neurologic picture. TPP is due to a deficient enzyme that normally cleaves von Willebrand factor multimers, namely ADAMTS13, which prevents extended capillary thrombosis. A low ADAMTS13 level is generally due to the presence of a specific inhibitor. Before this discovery, it had long been proven that plasma exchange was superior to plasma infusion to treat TPP [3]. Although highly advisable, demonstration of a low ADAMTS13 level is rarely available before initiation of treatment. Plasma exchange is compulsory and the recommendation is to start within 24 hours of presentation, with daily exchanges of 1.5 plasma volumes per session, until normalization of the platelet count and hemolysis parameters [4]. Rituximab has been proposed in refractory TTP. A constitutive ADAMTS13 deficiency is a very uncommon cause of TPP. Plasma infusion could be sufficient in this case but the genetic documentation of ADAMTS13 mutation is rarely available in time. On the other hand, plasma exchange seems of poor efficacy in treating certain secondary forms of TTP, such as in cancer or after mitomycin C therapy.

Renal involvement is typical of HUS. The microangiopathic hemolytic anemia and thrombocytopenia are accompanied by severe renal failure. The classic diarrheic HUS is secondary to intoxication with Shiga toxin-producing bacteria, such as *E.Coli* O157:H7. Atypical HUS (aHUS) refers to non-diarrheic HUS. The distinction between secondary HUS and pure aHUS is progressively evanishing [5]. A genetic predisposition in the complement system is latent in up to 70% of patients. Mutations in complement factor H, complement factor I, complement C3, membrane cofactor protein MCP, thrombomodulin, are the most frequently identified. Anti-complement factor H antibodies are another cause of aHUS. Many triggers, such as pregnancy, organ transplantation, infection, and auto-immune diseases are known to unveil the latent mutation and provoke clinical onset of HUS. Plasma infusion is the easiest treatment of diarrheic HUS, unless anuria prevents sufficient volumes to be administered. With plasma exchange, the plasma load can reach 40-60 ml/kg. Plasma exchange was the initial treatment of HUS but this challenge was with the availability of

Eculizumab. Eculizumab is an anti-C5 antibody which blocks the activation of the complement cascade. It has initially proved to be an effective therapy for HUS resistant to plasma exchange and is now the first-line treatment to be initiated within 24 hours after presentation [6]. A 2-year analysis of the original studies established the maintenance of early clinical benefits [7]. Nevertheless, plasma exchange remains the initial therapy in patients with a microangiopathy, while waiting for ADAMTS13 and complement levels, and sufficient evidence to start Eculizumab. The use of Eculizumab in typical diarrheic HUS needs to be clarified. Beyond the sole endothelial aggression by verotoxins, diarrheic HUS could induce an alteration in the alternative pathway of complement, making Eculizumab a logical treatment.

Plasma exchange is widely used in **kidney transplantation**. The first reason is to give highly sensitized patients access to transplantation ie, patients who remain on the waiting list for years and who are at risk for a hyper acute rejection. Also, patients who could get a kidney from a living donor but who have donor-specific antibodies (DSA) benefit from the removal of these antibodies. Plasma exchange is used prior to transplantation in desensitization protocols. Three different situations are encountered: 1/ the presence of DSA and a positive lymphocytotoxic crossmatch, 2/ the presence of DSA with a positive flow cytometry crossmatch and 3/ the presence of DSA with a negative crossmatch, by decreasing rank of risk for rejection. Plasma exchange is conducted until DSA disappear and crossmatch becomes negative. Anti-CD20 antibodies or IVIg are sometimes added to avoid rebound of antibodies production. Usually, recipients are treated with anti-thymocytes globulins to ensure a sufficient post-transplant immunosuppression. Once grafted, these desensitized patients will find a survival benefit when compared to those who stay on the waiting list [8,9]. Immunoabsorption seems to have a higher efficiency to remove anti-HLA antibodies [10].

The second situation is to prepare patients to receive an ABO-incompatible transplant, a historical contra-indication to kidney transplantation. In fact, Plasma exchange has been used since the 70's, especially in Japan, but with the need for a splenectomy. The availability of anti-CD20 antibodies has allowed to avoid splenectomy and excellent survival rates have been achieved [11,12]. The keys points are the level of antibodies, which remains uneasy to

assess due to poor titration methods, and the A1 or A2 blood groups which give strong or weak immunologic reactions respectively. The current protocols include sufficient Plasma exchange sessions to reduce the antibody titer to a low threshold, and a single anti-CD20 administration. Usually, the accommodation phenomenon avoids continuing plasma exchange after transplantation. Specific anti-A or anti-B immunoadsorption columns are marketed and may have a better efficacy [13] provided the antibodies are of the IgG isotype.

Plasma exchange is often proposed to treat antibody-mediated rejection episodes. AMR episodes have become far more frequent than cellular rejection episodes. They have pathological lesions of vascular aggression and the presence of DSA. When such rejection occurs, it is tempting and seems logical to remove antibodies and especially DSA.

Nevertheless, evidence of clinical usefulness is weak, and no efficient treatment for antibody-mediated rejection is presently available.

Focal segmental glomerulosclerosis [FSGS] is a nephrotic glomerulopathy of many etiologies. The so-called primary FGSG seems related to a T and B lymphocyte dysfunction with production of a putative nephritic soluble factor. Recurrence after kidney transplantation is frequent and may occur within minutes. Plasma exchange in addition to high-doses of intravenous cyclosporin A are started as soon as possible, until proteinuria is reduced to the lowest level. Success is not always achieved and the procedures may last for weeks [14].

Anti-neutrophil cytoplasmic (ANCA) vasculitides refer to granulomatosis with polyangiitis, usually with the presence of anti-proteinase 3 antibodies, and to microscopic polyangiitis, usually with the presence of anti-myeloperoxidase antibodies. These ANCAs are pathogenic albeit not sufficient *per se* to provoke the vasculitis. For decades, cyclophosphamide and glucocorticoids have been the standard therapy for ANCA-associated vasculitides. Rituximab recently arose as an alternative for both induction and maintenance. The benefit of plasma exchange for ANCA-associated vasculitides is debated [15]. A meta-analysis of randomized studies was in favor [16] but not the large MEPEX European study [17]. Usually, plasma exchange is advocated in case of severe renal dysfunction (creatinine >500 $\mu\text{mol/L}$) or diffuse alveolar hemorrhage [18]. Observational studies only support this last indication but this life threatening condition advocates the use of plasma exchange [2]. All in all, non-

randomized studies and case series have indicated a renal recovery rate of 75% in ANCA-associated vasculitides patients treated with plasma exchange when presenting with renal failure and creatinine >500 umol/L. **Goodpasture syndrome** is a disease with the same presentation of a rapidly progressive glomerulonephritis and diffuse alveolar hemorrhage. Anti- glomerular basement membrane antibodies, which recognize the non collagenic domain of the alpha-3 chain of type 4 collagen, are specific for Goodpasture syndrome. The antibodies are not always found in the plasma, but renal biopsy samples exhibit a specific pattern of linear glomerular IgG deposits. The disease is so rare that no good randomized trial is available [19]. Whatever the treatment, it is unlikely to reverse renal dysfunction once dialysis is needed [20,21]. Alveolar hemorrhage might represent the better indication for plasma exchange [22].

Plasma exchange has been proposed in many other renal diseases, with very poor evidence, unfortunately.

In the case of **cryoglobulinemia**, treatment of the underlying cause (hepatitis C virus, lymphoproliferative disorder, connective tissue diseases) is the priority [23]. Plasma exchange is often used as an adjunctive treatment, given its ability to remove cryoglobulins from plasma. Due to the IgM nature of the antibody, plasma exchange should be preferred to immunoadsorption. The role of plasma exchange to treat cryoglobulinemia has been evaluated in a unique trial [24].

Plasma exchange has been shown to be useless to treat **systemic lupus erythematosus** [25,26]. Nevertheless, it is seldom proposed in the case of catastrophic anti-phospholipid syndrome or thrombotic microangiopathy associated with systemic lupus erythematosus. Old reports favored the use of plasma exchange for **polyarteritis nodosa** when associated to the hepatitis B virus [27].

Myeloma and Waldenstrom disease might lead to a **hyperviscosity syndrome**. The clinical presentation is a neurological disorder. Plasma exchange is very powerful in normalizing blood viscosity [28] and allows a rapid correction of the hyperviscosity syndrome. While plasma exchange had been proposed to treat the myeloma cast nephropathy [29,30], a most recent study did not confirm any benefice [31]. Modern chemotherapy and maybe, high cut-off dialysis membranes [32], have outshone plasma exchange.

Conclusion

The rarity of renal diseases is the main obstacle to conducting randomized studies. Plasma exchange, often an adjunctive therapy, is less likely to be evaluated than common immunosuppressive regimens. Observational studies, as well as mechanistic evidence, underlie the use of plasma exchange. Albeit this low level of evidence, indications for plasma exchange to treat renal diseases remain numerous, especially to treat microangiopathies, ANCA-associated vasculitides and in the context of renal transplantation.

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FIGURES

Figure 1: Therapeutic plasma exchange

Modified from: Walter Linz. Principles of apheresis technology 6th ed. ASFA. April 2017 53-63