

Current Applications of Therapeutic Hemapheresis

Alvaro A. Pineda

Hemapheresis is a therapeutic modality for which many unsubstantiated claims have been made. Initially, hemapheresis was an exciting research tool whose potential applications tempted the practitioner, perhaps somewhat prematurely. Gains in the knowledge of the effect of hemapheresis on the immune system⁽¹⁾ as well as limited basic research and controlled, randomized studies to assess therapeutic efficacy provide, at the present time, a measure of credibility. Hemapheresis evolved from rudimentary attempts to procure blood constituents early at the turn of the century, as in the case of plasma removal by plasmapheresis to procure antibodies from animals.⁽²⁾ With the advent of blood separation technology (automated blood separators) created for the harvesting of leukocytes from donor peripheral blood, the therapeutic removal of large volumes of plasma and cells (hemapheresis) became feasible.⁽³⁾ The blood separators provided for a rapid and efficient separation of blood components on the basis of their differences in density, size, and weight in a gravitation field created by centrifugation.

Historically, the introduction of new and appealing technologies into clinical research and practices creates advocates and adversaries. It has not been different with hemapheresis. Hemapheresis procedures provide the means for the removal of blood components that are abnormal or circulate in excessive amounts and have a defined pathologic role or are thought to have one. Multiple disease processes have been treated with hemapheresis at one time or another. Obviously, diseases characterized by circulating abnormal proteins, antibodies, or excessive number of cells have been inviting targets for therapeutic extraction by hemapheresis. Indeed, the contemporary concept of plasmapheresis as therapy originated from its use in macroglobulinemia and hyperviscosity syndrome.⁽⁴⁾

Although hemapheresis is in widespread use, scientific assessment of its therapeutic effects has lagged behind application of the technology. The high cost of hemapheresis, particularly plasmapheresis, coupled with a paucity of controlled studies to assess therapeutic efficacy or lack thereof, compelled professional groups to promulgate application guidelines for the first time during the mid-1980s. Efforts of the American Medical Association and American Society for Apheresis helped to ensure that the application of therapeutic hemapheresis was based on the best available scientific evidence. Recently, the American Society for Apheresis published revised position papers on the clinical applications of therapeutic hemapheresis.⁽⁵⁾ What follows is a discussion of conditions for which general agreement exists on the beneficial application of hemapheresis in general, with special emphasis on hematologic disease. In addition, the current status of two more advanced forms of hemapheresis - photopheresis and immunoabsorption - will be discussed briefly.

Applications of Therapeutic Plasmapheresis in Non-Hematologic Disease

Plasmapheresis has become the therapeutic mainstay of a number of neurologic conditions. Myasthenia gravis during the acute phase is a reasonable indication for

therapeutic plasmapheresis (TP) or plasma exchange, which removes 1 to 1.5 plasma volumes to be replaced preferentially with normal serum albumin in a 5% solution.⁽⁶⁾ The objective is to reduce the circulating level of anti-acetylcholine receptor antibody. A therapeutic effect characterized by increased muscle strength typically occurs after TP. Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) is a paralytic condition that benefits from TP. In general, the functional deficit has been alleviated substantially, and certain levels of recovery have been observed.⁽⁷⁾

The efficacy of TP was established in controlled, randomized, double-blinded studies in Mayo Clinic patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and polyneuropathy associated with monoclonal gammopathy of undetermined significance. The model for these studies came from two double-blinded studies that previously showed no therapeutic value for TP in the treatment of Raynaud's phenomenon associated to scleroderma and of lymphapheresis for the treatment of rheumatoid arthritis.^(8,9) For CIDP, a paralytic disease of unknown cause, the use of TP has an ameliorating effect on neurologic dysfunction and nerve conduction in approximately 33% of the patients treated.⁽¹⁰⁾ A more recent study from our group confirmed the efficacy of TP in CIDP as well as the efficacy of intravenous gammaglobulin for the same disease.⁽¹¹⁾ In polyneuropathy associated with monoclonal gammopathy of undetermined significance, TP is efficacious in the IgG and IgA types.⁽¹²⁾ The efficient removal of branched, fatty, phytanic acid by plasmapheresis in conjunction with a phytanic acid-poor diet has produced lasting benefit in patients with phytanic acid storage disease (Refsum's disease).⁽¹³⁾

Diseases characterized by circulating antibodies of known or suspected pathologic significance have been a target for plasma extraction as a means of decreasing antibody concentration. The outstanding example is antglomerular basement membrane antibody disease (Goodpasture's syndrome), which was the first condition to be treated effectively with plasmapheresis and immunosuppressive drugs.⁽¹⁴⁾ Surpluses of plasma constituents of known pathologic significance have been effectively reduced by TP, as in familial hypercholesterolemia in which cholesterol levels (low-density lipoproteins) are decreased by periodic treatment.⁽¹⁵⁾ In cases of familial hypercholesterolemia, the plasma constituents can be extracted more specifically and efficiently by affinity chromatography.⁽¹⁶⁾ In the mixed cryoglobulinemias, the effect of cryoglobulin lowering and perhaps modification of immune complexes form the rationale for TP. The beneficial effect of plasmapheresis on the renal, neurologic, and hepatic manifestations of the disease has been reported.⁽¹⁷⁾

Applications of TP in Hematologic Disease

Plasmapheresis is considered established therapy for the hyperviscosity syndrome associated with multiple myeloma and paraproteinemias (Waldenström's macroglobulinemia). The therapeutic aim is to reduce or return the plasma viscosity to normal and to reverse the neurologic symptoms, bleeding diathesis, visual impairment, and cardiovascular effects.⁽¹⁸⁾ Myeloma kidney is a complication of multiple myeloma that is best prevented. However, once present, the most efficient way to remove the nephrotoxic paraprotein is by plasmapheresis. A controlled study showed an efficient

reduction of the paraprotein level and recovery of renal function in patients with mild to moderate histologic evidence of myeloma kidney who were treated with TP and chemotherapy. In patients with advanced histologic evidence of myeloma kidney, TP was ineffective, necessitating hemodialysis support on a long-term basis.⁽¹⁹⁾

Antibody titer reduction is the rationale for the use of TP in ABO-incompatible bone marrow transplantation, in which ABO isoagglutinins are removed in order to prevent hemolysis of the ABO incompatible erythrocytes present in the marrow aspirate.⁽²⁰⁾ In cases of post-transfusion purpura, a platelet-specific alloantibody responsible for peripheral platelet destruction is effectively removed by plasmapheresis, a process that usually results in a prompt increase in platelet counts. Circulating coagulation factor inhibitors have been removed by plasmapheresis to control bleeding and obtain a more effective response to infusion of coagulation factors. In severe cases of coagulation factor deficiency or severe multifactorial deficiency, as seen in patients with advanced hepatic disease awaiting hepatic transplantation, TP permits infusion of very large volumes of fresh frozen plasma that effectively exchange the patient's intravascular compartment correcting the clotting deficiency. Other conditions (in some cases mediated by circulating antibodies) such as immune thrombocytopenias, pure red cell aplasia, aplastic anemia, autoimmune hemolytic anemia, and hemolytic disease of the newborn, have been treated with TP, but the published evidence is insufficient to establish the efficacy of the hemapheresis treatment.

Thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome of adults) is a clinically devastating disorder with overlapping manifestations of microangiopathic hemolytic anemia, thrombocytopenia, renal and neurologic involvement, and fever. The pathogenesis remains uncertain. A variety of treatments have been used, including infusion of fresh frozen plasma, exchange transfusion, and splenectomy.⁽²¹⁾ At the present time the treatment of choice is intensive TP with plasma replacement (fresh frozen plasma or cryoprecipitate-poor in cases of relapsing TTP). A randomized study that compared TP with infusion of plasma demonstrated the therapeutic superiority of TP.⁽²²⁾ Return to normal parameters such as decrease in LDH, increase in platelet count, and improvements of neurologic state and renal function suggest a favorable response and helps to determine when to modify or discontinue treatment.

Applications of Cytapheresis

Removal of abnormal cellular fractions constitute the basis for using cytappheresis or cytareduction in cases of infarcted crisis of sickle cell disease and leukocytosis and thrombocytosis that complicate myeloproliferative disorders. In severe forms of infarctive crisis of sickle cell anemia, automated red blood cell exchange is recommended to remove cells that contain the abnormal hemoglobin and replace them with donor erythrocytes in a more convenient, rapid, and controlled fashion than a manual exchange. Extreme elevations of leukocytes ($> 100 \times 10^9/L$) and platelets ($> 1,000 \times 10^9/L$) complicate myeloproliferative disorders, adding elements of leukostasis, hyperviscosity, and thrombosis or bleeding that require treatment. Cytareduction in acute non-lymphocytic leukemias with counts exceeding $100,000/\mu L$ is effective as a prophylactic measure to prevent CNS complications and to treat pulmonary insufficiency as well as

reducing the tumor burden.⁽²³⁾ A persistent elevation of the platelet count in essential thrombocythemia and polycythemia vera may be associated with either thrombosis or bleeding and benefit from plateletapheresis. Typically, reduction of approximately 50% of the circulating cell count is readily obtained by cytapapheresis.⁽²⁴⁾

Applications of Protein A Immunoabsorption in Hematologic Disease

Selective extraction of plasma constituents is based on principles of affinity chromatography. A substance with a specific binding affinity is linked to an insoluble matrix to bind specifically its complementary substance from a mixture of materials in suspension or solution. The appeal of adsorption resides in its specificity, since in principle it is capable of selectively extracting the material deemed pathogenic. A number of adsorption systems have been described recently.

Some of these systems have had human application. They include protein A to remove IgG and immune complexes, amino acids to remove IgG globulins, DNA to extract the corresponding antibody, synthetic blood group substances to remove the corresponding isoagglutinins, and dextran sulfate and low-density lipoprotein (LDL) antibodies to extract LDL. Protein A is a well-known cell wall protein only found in the Cowan I strain of *Staphylococcus aureus*. It is usually released in the surrounding medium, i.e., culture medium, and possesses IgG-Fc receptor functions, which confers to it the affinity to react strongly with human and mammalian IgG 1, 2, and 4 and more so with antigen-bound IgG, as in circulating immune complexes (CIC). Protein A has been used extensively as an immunological reagent and studied in great detail with regard to specific isolation of immunoglobulins and immune complexes.

Protein A immunoabsorption (PAI) has been used in treatment-resistant adult immune thrombocytopenic purpura. Seventy-two patients with initial platelet counts < 50,000/ μ L who had failed at least two other therapies were treated with PAI an average of six times, adsorbing 0.25 to 2.0 L of plasma per procedure over a 2-3 week period either on-line or off-line. The treatment was followed by an increase in the platelet count to 100,000/L in 15 patients. Clinical responses were associated with significant decreases in levels of specific platelet auto-antibody, platelet-associated Ig, and circulating immune complexes. Thirty percent of treatments were complicated by transient mild to moderate side effects, usually presenting as a hypersensitivity type of reaction.⁽²⁵⁾ The observed therapeutic efficacy of PAI in this group of patients is promising, and controlled studies are warranted to establish the therapeutic efficacy of this new modality.

PAI has been used to treat 54 patients with cancer chemotherapy-associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (CCATTP/HUS). No effective therapy has existed heretofore for this condition, which causes significant mortality (50% within two months and 75% within four months of diagnosis). After an average of six PAIs over a 2.5-week period, improvement in hemolysis, thrombocytopenia, and renal function was achieved in 69% of patients, coupled with greater than eight months survival in 42% of patients. These response rates are impressive when compared to historic controls, receiving no apheresis treatments, or receiving conventional therapy including plasmapheresis. This therapy is particularly effective in patients with no recurrent tumor of whom 96% improved, achieving a survival of ³ eight

months in 80% of cases, in contradistinction to patients with advanced, metastatic disease, in whom the results were poor.⁽²⁶⁾ Thus, PAI fills a critical therapeutic void in CCATTP/HUS patients with complete tumor remission or minimal residual or recurrent malignant disease.

PAI has also been applied to the treatment of 10 patients with immune refractoriness to platelet transfusion who had failed steroids, intravenous Ig, and/or other forms of immunosuppression and who responded to PAI. All patients were receiving multiple platelet transfusions without achieving one-hour corrected count increments; of these, eight had antibodies that reacted with platelets and were directed against HLA class 1 antigens, ABO antigens, and/or platelet-specific alloantigens. The patients received 1 to 14 treatments in which 500 to 2000 ml of plasma was passed over the protein A column (Prosorba[®]) and returned to the patients. Following therapy, six of 10 patients responded with daily platelet counts that averaged $48 \pm 11 \times 10^9$ per L compared with counts of $16 \pm 7 \times 10^9$ per L before treatment ($p = < 0.0005$). Posttransfusion corrected increment counts determined in four patients averaged 2480 ± 810 and $10,060 \pm 3540$ before and after treatment ($p = < 0.0005$).⁽²⁷⁾ These findings suggest that, in certain patients who are alloimmunized and refractory to platelet transfusion, PAI may be an effective means of increasing platelet counts and responsiveness to platelet transfusion.

Another protein A column has been used to exhaustively adsorb IgG antibodies in patients with coagulation factor inhibitors, HLA antibodies, and other specific antibodies. The system consists of two protein A columns (Immunosorba[®], purified staphylococcal protein A linked to agarose) and an elution monitor. A cell separator provides plasma to the columns, which are sequentially eluted and regenerated to maximize IgG removal and expand the capacity of the procedure indefinitely. This system was employed in 10 highly and persistently sensitized patients awaiting renal transplantation to remove anti-HLA antibodies, resulting in significant reduction of circulating IgG levels.⁽²⁸⁾

Application of Extracorporeal Photochemotherapy in Hematologic Disease

Photopheresis or extracorporeal photochemotherapy (ECPCT), originally introduced to treat cutaneous T-cell lymphoma, has been utilized to treat extensive, cutaneous, chronic graft-versus-host disease (GVHD). Eleven patients with cutaneous GVHD resistant to standard immunosuppressive drugs were treated with photopheresis, a therapy that combines the drug 8-methoxypsoralen (incorporated in the DNA of apheresed leukocytes) and ultraviolet-A irradiation by extracorporeal photochemotherapy. Skin lesions showed a complete clearing in 75% of patients with acute GVHD and in 70% of patients with chronic GVHD. No therapeutic effect was observed in three patients.⁽²⁹⁾ This report, along with similar reports on small numbers of patients suggests that photopheresis is a nonaggressive treatment that may benefit patients with conventional therapy-resistant cutaneous GVHD. The reports are promising enough to warrant controlled, randomized studies to establish the efficacy of the therapy.

Therapeutic hemapheresis has ushered in an exciting and novel era in medicine. Presently, clear-cut noncontroversial application of hemapheresis exists for the described conditions. Nonetheless, more study is needed to determine additional reasonable

application and to address issues of dosage, treatment alternatives, and concomitant or adjuvant therapies.

References

1. Pineda AA: How is the immune system affected by therapeutic plasmapheresis? Clin Immunol Newsletter 13: 1, 1993
2. Abel JJ, Rowntree LD, Turner BB: Plasma removal with return of corpuscles (plasmapheresis). J Pharmacol Exp Ther 5: 625, 1914
3. Pineda AA, Brzica SM Jr, Taswell HF: Continuous and semicontinuous flow blood centrifugation systems: therapeutic applications with plasma- platelet- lympho- and eosinapheresis. Transfusion 17: 407, 1977
4. Schwab PJ, Fahey JL: Treatment of Waldenström's macroglobulinemia by plasmapheresis. N Engl J Med 263: 574, 1960
5. Clinical Applications of Therapeutic Hemapheresis (special issue). J Clin Apheresis 8: 189, 1993
6. Seybold ME: Plasmapheresis in myasthenia gravis. Ann NY Acad Sci 505: 584, 1987.
7. The Guillain-Barré Syndrome Study Group: Plasmapheresis and acute Guillain-Barré syndrome. Neurology 35: 1096, 1987
8. McCune MA, Winkelmann RK, Osmundson PH, Pineda AA: Plasma Exchange: A controlled study of the effect in patients with Raynaud's phenomenon and scleroderma. J Clin Aph 1: 206, 1983
9. Bunch TW, O'Duffy JD, Pineda AA, Zinsmeister AR: Lymphapheresis in rheumatoid arthritis. J Clin Apheresis 2: 127, 1984
10. Dyck PJ, Daube J, O'Brien P, Pineda A, Low PA, Windebank AJ, Swanson C: Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. N Eng J Med 314: 461, 1986
11. Dyck PJ, Litchy WJ, Kratz KM, Suarez GA, Low PA, Pineda AA, Windebank AJ, Karnes JL, O'Brien PC: A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy. Ann Neurol 36: 838, 1994
12. Dyck PJ, Low PA, Windebank AJ, Jaradeh SS, Gosselin S, Bourque P, Smith BE, Kratz KM, Karnes JL, Evans BA, Pineda AA, O'Brien PC, Kyle RA: Plasma exchange in polyneuropathy associated with monoclonal gammopathy of undetermined significance. New Eng J of Med 325: 1482, 1991
13. Gibberd FB: Plasma exchange for Refsum's disease. Transfus Sci 14: 23, 1993
14. Pusey CD, Lockwood CM, Peters DK: Plasma exchange and immunosuppressive drugs in the treatment of glomerulonephritis due to antibodies to the glomerular basement membrane. Int J Artif Organs 6: 15, 1983
15. Kamanabroo D, Ulrich K, Grobe H, Assmann G: Plasma exchange in type II hypercholesterolemia. Prog Clin Biol Res 255: 347, 1988.
16. Yokoyama S: Treatment of hypercholesterolemia by chemical adsorption of lipoproteins. J Clin Apheresis 4: 66, 1988

17. Ferri C, Gremignai G, Bombardieri S, Moriconi L, Pontradolfo A, et al: Plasma exchange in mixed cryoglobulinemia. Effects on renal, liver, and neurologic involvement. *La Ricerla Clin Lab* 16: 403, 1986
18. Reinhart WH, Lutolf O, Nydegger U, Mahler F, Straub PW: Plasmapheresis for hyperviscosity syndrome in macroglobulinemia Waldenström and multiple myeloma: influence on blood rheology and the microcirculation. *J Lab Clin Med* 119: 69, 1992
19. Johnson WJ, Kyle, Pineda AA, O'Brien PC, Holley KE: Treatment of renal failure associated with multiple myeloma. Plasmapheresis, hemodialysis, and chemotherapy. *Arch Intern Med* 150: 863, 1990
20. Sniecinski IS, Oien L, Petz LD, Blume KG: Immuno-hematologic consequences of major ABO-mismatched bone marrow transplantation. *Transplantation* 45: 530, 1988
21. Onundarson PT, Rowe JM, Heal JM, Francis CW: Response to plasma exchange and splenectomy in thrombotic thrombocytopenic purpura. *Arch Intern Med* 152: 791, 1992
22. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Keltom JH, Nair RC: Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. *N Engl J Med* 325: 393, 1991
23. Lester TJ, Johnson JW, Cuttner J: Pulmonary leukostasis as the single worst prognostic factor in patients with acute myelocytic leukemia and hyperleukocytosis. *Am J Med* 79: 43, 1985
24. Kessler CM, Klein HG, Havlik RJ: Uncontrolled thrombocythemia in myeloproliferative disorders. *Br J Haematol* 50: 157, 1982
25. Snyder HW, Cochran SK, Balint JP, Bentram JH, Mittelman A, Guthrie TH, Jones FR: Experience with protein-A immunoabsorption in treatment of resistant adult immune thrombocytopenic purpura. *Blood* 79: 2237, 1992
26. Snyder HW, Mittelman A, Oral A, Messerschmidt GL, Henry DH, Korec S, Bertram JH, Guthrie TH, Ciavarella D, Wuest D, Perkins, W, Balint JP, Cochran SK, Peugeot RL, Jones FR: Treatment of cancer chemotherapy associated thrombotic thrombocytopenic purpura/hemolytic uremic syndrome by protein A immunoabsorption of plasma. *Cancer* 71: 1882, 1993
27. Christie DJ, Howe RB, Lennon SS, Sauro SC: Treatment of refractoriness to platelet transfusion by protein A column therapy. *Transfusion* 33: 234, 1993
28. Palmer A, Welsh K, Gjonstrup, P, Taube D, Bewick M, Thick M: Removal of anti-HLA antibodies by extracorporeal immunoabsorption to enable renal transplantation. *Lancet* 1: 102, 1989
29. Aubin F, Brion A, Decominck E, Plouvier E, Herve P, Humbert P, Cahn JY: Phototherapy in the treatment of cutaneous graft-versus-host disease. *Transplantation* 59: 151, 1995.