Plasma exchange and plasmapheresis

Plasma exchange and plasmapheresis are unsophisticated methods of treating a variety of diseases of frequently uncertain etiology and poorly understood pathogenesis for which there is no adequate therapy. Although plasma exchange was first used therapeutically in man in about 1968, the number of diseases treated with it has increased rapidly. Plasmapheresis has been in use since the turn of the century. The two procedures differ in concept; plasma exchange involves removal of plasma and replacement of it with various fluids, whereas plasmapheresis involves only the removal of plasma (plasma + Gr. *aphairesis,* or removal). Unfortunately the two terms are often used synonymously in the medical literature.

Various replacement solutions have been used but there is still no ideal substitute for plasma. Saline is relatively safe for small-volume exchanges, for the first 1000 mL or so of a large-volume exchange and in even larger quantities for treating the hyperviscosity syndrome due to paraproteinemia.

In Great Britain plasma protein fraction (PPF) has been found to be superior to fresh frozen plasma (FFP). As with albumin, PPF is free of the risk of transmitting hepatitis, but because of its low content of calcium and potassium, supplementation with these ions is necessary.[1] In contrast to albumin, it contains vasoactive substances, such as bradykinin, that may cause severe adverse reactions.[2] Although PPF lacks procoagulant factors it is rarely necessary to replace them after plasma exchange.

Other solutions, such as dextran 110 and 150, have been used for volume replacement. Up to 1000 mL of these solutions is usually well tolerated, and they may reduce clot formation within the extracorporeal circuit by reducing platelet aggregation. They are, however, antigenic, so that subsequent exposure to them may result in hypersensitivity reactions. Albumin, diluted with saline or Ringer's lactate or given as a bolus, is also satisfactory.

There is no uniformity with respect to the choice of anticoagulant. Many centres employ heparin only, while others continue to use citrate. Because of the complications that may arise with the use of protamine sulfate it is customary not to reverse the action of heparin at the end of a plasma exchange. Routine observation of the patient for about 1 hour after the exchange to exclude hemorrhage is safer and therefore recommended.[3]

Short- and long-term benefits of plasma exchange in the hyperviscosity syndrome associated with malignant paraproteinemia have been well demonstrated.[4] The longest-lasting results have been in patients with Waldenström's macroglobulinemia, in which most of the abnormal protein is in the intravascular space: more than 80% of it can be removed by a 5-L plasma exchange.[5] In some patients plasma exchange has been used as the sole form of therapy on a long-term basis without evidence of accelerated protein synthesis.[6] Although impressive results may also be seen in the hyperviscosity syndrome associated with IgA and IgG multiple myeloma, they are of short duration because the paraprotein tends to be distributed between the intra- and extravascular spaces and its synthesis is frequently rapid. Immediate cessation of bleeding is often seen in patients with a coagulation defect caused by a paraprotein.[7] Patients with cryoglobulinemia also have definite but short-lived relief of their symptoms with plasma exchange. Treatment by plasma exchange of cold hemagglutinin disease that is resistant to chemotherapy has been disappointing; the response is brief and the reduction of hemolysis is minimal.

Dramatic improvement and sometimes permanent cure may result from the use of plasma exchange combined with immunosuppressive therapy in some patients with Goodpasture's syndrome and rapidly progressive nephritis.[8] For optimal results plasma exchange should be started as early as possible, since it is of little benefit when irreparable kidney damage has occurred and renal failure is well established. The total volume exchanged may be as large as 35 L per patient, but is justified because some patients eventually recover normal renal function and the high cost of long-term hemodialysis with or without renal transplantation is eliminated. Despite the administration of large amounts of anticoagulants during plasma exchange, hemoptysis in Goodpasture's syndrome is rapidly controlled.

Less encouraging results have been obtained in the treatment of acute systemic lupus erythematosus; some authors have suggested that there is a difference in the therapeutic response between PPF and FFP.[9] The poor results may be explained by the considerable immunologic rebound phenomenon after plasma exchange in systemic lupus erythematosus compared with Goodpasture's syndrome (D.S. Terman: unpublished data, 1978). Plasma exchange may be useful in the management of the nephritis associated with Henoch-Schönlein purpura, which may be caused by increased concentrations of cryoglobulins.[10] Preliminary results suggest that plasma exchange also may be useful in the management of the rejection of renal transplants.[11]

Intensive antenatal plasma exchange now offers the possibility of a normal infant being born to a woman with high titres of antibody to the Rhesus antigens, and it may eventually eliminate the need for intrauterine transfusions.[12]

Preliminary evidence suggests that plasma exchange may be beneficial in patients with homozygous familial hypercholesterolemia, a disease with a poor prognosis and a high mortality due to coronary artery disease. A few patients who have been managed with this form of therapy have had a reduction in angina, improvement in their coronary angiograms and a decrease in the size of their xanthomas associated with continued reduction of serum lipid concentrations. Plasma exchange must be an adjunct to dietary and drug therapy in this condition.[13]

The management of patients with hemophilia who have high titres of factor VIII inhibitor is difficult, particularly when surgery is required. Plasma exchange will markedly reduce the titre of the inhibitor for several days and allow a surgical procedure to be performed under the cover of factor VIII concentrates given immediately after completion

of the initial plasma exchange. More prolonged reduction of the titre of factor VIII inhibitor may be achieved by combining plasma exchange with immunosuppression. Bleeding is not a problem and good hemostasis can be obtained.[14] Thrombotic thrombocytopenic purpura is another lethal hematologic disease in which the use of plasma exchange looks promising,[15] but the simple infusion of plasma may be just as beneficial.[16] Postperfusion or post-transfusion purpura and idiopathic thrombocytopenic purpura may benefit from plasma exchange.[17]

Preliminary results have been reported on the treatment of severe myasthenia gravis by plasma exchange in a small number of patients, but the results are inconclusive.[18] More impressive results have been obtained by the use of plasma exchange in combination with immunosuppression.[19] Plasma exchange may have a considerable placebo effect, but a prospective randomized trial would be difficult for this disease.[20]

Concern has been expressed with respect to the use of succinylcholine and other paralyzing agents in patients who have undergone a recent large-volume plasma exchange because of a prolongation of their effect due to lowered plasma cholinesterase concentrations.[21]

Despite encouraging preliminary results, plasma exchange has not been thoroughly evaluated in the treatment of endotoxic shock or fulminant liver failure,[22] and few communities are willing to devote much of their blood product resources to long-term support of persons with liver failure. Plasma exchange has also been used to a limited extent in children with subacute sclerosing panencephalitis, the best result being that it halted the progression of the disease. Plasma exchange has been used in the treatment of melanoma and other solid tumours to reduce concentrations of blocking antibody, which increase cell-mediated cytotoxicity, and may be adjunctive to other forms of therapy.[23] In desperate situations it may be useful in the treatment of thyroid storm, but this is unproven.[24] Endocrinologists are also evaluating plasma exchange in patients who are resistant to insulin because of antibodies to the insulin receptor. A randomized prospective trial is under way to evaluate plasma exchange in the treatment of Raynaud's disease and other small-vessel diseases.[25]

Plasma exchange prior to bone marrow transplantation can lower the titre of certain substances in the plasma of the recipient that may inhibit the growth of stem cells from the donor; the nature of these substances is poorly understood. Even ABO-incompatible donors can be used if plasma exchange is performed in the recipient immediately before transplantation.[26] Furthermore, responsiveness to platelet transfusions in patients who have undergone bone marrow transplantation or intensive chemotherapy may be restored by plasma exchange.

We are just beginning to appreciate the usefulness of plasmapheresis for procuring large volumes of plasma that contain substances of value for therapeutic and research purposes — anti-D, antitetanus, antihepatitis B and antiherpes virus antibodies, for example.

At present there are no established international guidelines for the screening of healthy donors before plasmapheresis. However, the Canadian Red Cross blood transfusion service follows strict guidelines developed by Health and Welfare Canada for plasmapheresis, which are currently under revision. In healthy donors who undergo long-term plasmapheresis the immunoglobulin concentrations may fall below normal; therefore, they should be measured every 4 months;[27] the function of thymus-derived lymphocytes appears to be unaffected, however.[28]

Although the number of diseases for which plasma exchange and plasmapheresis are being used is increasing rapidly, the mode of action of these procedures is seldom clearly understood. The response obtained in patients with myasthenia gravis correlates incompletely with reduction of cholinesterase activity or titres of antibody to the acetylcholine receptor. Why do patients with Goodpasture's syndrome benefit from plasma exchange? Is it the result of lowering the concentration of serum complement or of plasma fibrinogen, the effect of anticoagulation or the clearing of immune complexes or basement membrane antibody? These and similar questions are as yet unanswered.

New methods are being developed for the specific removal of unwanted blood components such as immune complexes or antibodies by passing plasma over antigens immobilized on membranes or columns.[29] Until such procedures are perfected and the requirement for replacement plasma is eliminated, indiscriminant resort to plasma exchange for the treatment of a wide variety of disorders for which no satisfactory therapy exists is to be condemned. Plasma exchange should only be employed as a treatment of diseases for which it is not established therapy in specialized centres with the proper research facilities to investigate and evaluate its efficacy. Blood products are too valuable to be used irresponsibly for unproven therapeutic endeavours when all else has failed.

NOEL A. BUSKARD, MD, FRCP[C]
World Health Organization fellow
Bone marrow transplantation unit
University of Washington
Seattle, Washington

References

1. BUSKARD NA, VARGHESE Z, WILLS MR: Correction of hypocalcaemic symptoms during plasma exchange. *Lancet* 2: 344, 1976
2. Adverse reactions to plasma protein. *Fed Drug Adm Bull* 7: 20, 1977
3. BUSKARD NA, GOLDMAN JM: Reversal of heparin action after cell separation. *N Engl J Med* 295: 677, 1976
4. RUSSEL JA, TOY JL, POWLES RL: Plasma exchange in malignant paraproteinemias. *Exp Hematol* 5 (suppl 1): 100, 1977
5. BUSKARD NA, GALTON DAG, GOLDMAN JM, et al: Plasma exchange in the long-term management of Waldenström's macroglobulinemia. *Can Med Assoc J* 117: 135, 1977
6. SWAIN CP, BUSKARD NA: A method of measuring the effect of plasma exchange on plasma protein synthesis in man, in *Abstracts of the Second International Symposium on Leucocyte Separation and Transfusion,* London, 1976
7. PILLER G, DRUML W, HOECKER P, et al: *Plasmapheresis Treatment of Paraproteinemia with Thrombopathy and Inhibitor Haemophilia,* vol 6, Haemonetics Research Institute, Natick, Mass, 1978 (in press)
8. LOCKWOOD CM, REES AJ, PUSSELL B, et al: Experience of the use of plasma exchange in the management of potentially fulminating glomerulonephritis and SLE. *Exp Hematol* 5 (suppl 1): 117, 1977
9. MORAN CJ, PARRY HF, MOWBRAY J: Plasmapheresis in systemic lupus erythematosus. *Br Med J* 1: 1573, 1977
10. GARCIA-FUENTES M, CHANTLER C, WILLIAMS DG: Cryoglobulinaemia in Henoch-Schönlein purpura. *Br Med J* 2: 163, 1977
11. CARDELLA CJ, SUTTON D, ULDALL PR, et al: Intensive plasma exchange and renal-transplant rejection. *Lancet* 1: 264, 1977

12. GRAHAM-POLE J, BARR W, WILLOUGHBY MLN: Continuous-flow plasmapheresis in the management of severe rhesus disease. *Br Med J* 1: 1185, 1977
13. THOMPSON GR, LOWENTHAL R, MYANT NB: Plasma exchange in the management of homozygous familial hypercholesterolaemia. *Lancet* 1: 1208, 1975
14. MCCULLOUGH J, EDSON JR, FORTUNY IE, et al: Rapid plasma exchange with continuous flow centrifuge. *Transfusion* 13: 94, 1973
15. BUKOWSKI RM, KING JW, HEWLETT JS: Plasmapheresis in treatment of thrombotic thrombocytopenic purpura. *Blood* 50: 413, 1977
16. BYRNES JJ, KHURANA M: Treatment of thrombotic thrombocytopenic purpura with plasma. *N Engl J Med* 297: 1386, 1977
17. BRANDA RF, TATE DY, MCCULLOUGH JJ, et al: Plasma exchange in the treatment of fulminant idiopathic (autoimmune) thrombocytopenic purpura. *Lancet* 1: 688, 1978
18. PINCHING AJ, PETERS DK, DAVIS JN: Remission of myasthenia gravis following plasma exchange. *Lancet* 2: 1373, 1976
19. DAU PC, LINDSTROM JM, CASSEL CK, et al: Plasmapheresis and immunosuppressive drug therapy in myasthenia gravis. *N Engl J Med* 297: 1134, 1977
20. FINN R, COATES PM: Plasma exchange in myasthenia gravis. *Lancet* 1: 190, 1977
21. WOOD GJ: Plasmapheresis and plasma-cholinesterase. Ibid, p 1305
22. BUCKNER CD, CLIFT RA, VOLWILER W, et al: Plasma exchange in patients with fulminant hepatic failure. *Arch Intern Med* 132: 487, 1973
23. HOBBS JR, BYROM N, ELLIOTT P, et al: Cell separators in cancer immunotherapy. *Exp Hematol* 5 (suppl 1): 95, 1977
24. ASHKAR FS, KATIMS RB, SMOAK WM, et al: Thyroid storm treatment with blood exchange and plasmapheresis. *JAMA* 214: 1275, 1970
25. TALPOS G, HORROCKS M, WHITE JM, et al: Plasmapheresis in Raynaud's disease. *Lancet* 1: 416, 1978
26. BUCKNER CD, CLIFT RA, SANDERS JE, et al: ABO incompatible marrow transplants (submitted for publication)
27. FRIEDMAN BA, SCHORK MA, MOCNIAK JL, et al: Short-term and long-term effects of plasmapheresis on serum proteins and immunoglobulins. *Transfusion* 15: 467, 1975
28. SALVAGGIO JE, ARQUEMBOURG PC, BICKERS J, et al: The effect of prolonged plasmapheresis on immunoglobulins, other serum proteins, delayed hypersensitivity and phytohemagglutinin-induced lymphocyte transformation. *Int Arch Allergy Appl Immunol* 41: 883, 1971
29. TERMAN DS, TAVEL T, PETTY D, et al: Specific removal of antibody by extracorporeal circulation over antigen immobilized in collodion-charcoal. *Clin Exp Immunol* 28: 180, 1977