Therapeutic Plasmapheresis in Patients with Renal Disease

EDWARD E. MORSE, M.D. and PATRICIA T. Pisciotta, M.D.

Department of Hematology/Blood Bank Division,
University of Connecticut Health Center,
Farmington, CT 06032

ABSTRACT

Therapeutic plasmapheresis has been enthusiastically applied in recent years to a number of disease entities associated with renal failure. It seems reasonable to attempt removal of intravascular macroglobulins or immune complexes by this mechanism; however, multiple modalities of therapy are often employed virtually simultaneously, confounding the delineation of successful treatment. Two case reports are presented to illustrate the lack of immediate response to plasmapheresis in patients receiving other modalities of treatment. It is clear that controlled clinical trials are needed to define better the usefulness of plasmapheresis in renal diseases.

Introduction

Plasmapheresis has become popular in the last few years for the treatment of a variety of disorders. The best rationale for its application in patients is the removal of intravascular large molecular species such as macroglobulins, aggregated IgG, cryoglobulins, and immune complexes. The rationale for use of plasmapheresis in the treatment of many other diseases to which it has been applied is sometimes obscure.

The present paper reviews the application of plasmapheresis in two patients whose condition was associated with renal disease and presents some of the controversial applications in other diseases with renal failure.

Methodology

Plasmapheresis is carried out by either continuous flow centrifugation or by intermittent flow centrifugation but newer methods using dialysis equipment are being introduced.

In the present study, plasmapheresis was performed using the Haemonetics Model 30 intermittent flow centrifuge with Acid Citrate Dextrose (ACD) anticoagulant. In a pheresis lasting three to
four hours, it was possible to remove and exchange approximately 3,000 ml of plasma. Replacement was made with either fresh frozen plasma anticoagulated with Citrate Phosphate Dextrose (CPD) or with five percent albumen and saline.

**Case Reports**

**CASE 1**

A 61 year old caucasian male, who had been in good health until three months previously, was admitted to a local community hospital because of increasing fatigue, weakness, frequent epistaxis, and because young plasma cells and rouleaux were noted on a peripheral blood smear. Blood counts revealed a hematocrit of 17 percent with normal indices, a normal white count, and platelet count and the smear previously described. Shortly after admission, the patient was found to be anuric with a urea nitrogen of 126 mg per dl and a creatinine of 9 mg per dl. Peritoneal dialysis was begun the following day and was continued for four days. The patient, however, suffered abdominal and shoulder pains, vomiting, and diarrhea, so dialysis was discontinued. The urea nitrogen had decreased to 88 mg per dl and the creatinine to 7.8 mg per dl (figure 1) but soon increased again. The patient was found to have a total protein of 9.8 g per dl with 6.6 g per dl of IgG, kappa type, and a bone marrow infiltrated with plasma cells. Prednisone, Alkeran and Lasix were given within a few days, the patient's volume of urine had increased to between five and seven liters per day. The patient's BUN remained about 78 mg per dl and the creatinine at 6.7 mg per dl. Hemodialysis was considered, but the patient was found to have coagulation abnormalities, particularly a prolonged thrombin time between 25 and 30 seconds (normal 10 seconds).

In view of the coagulation abnormalities, presumed to be due to the abnormal myeloma protein, it was considered inadvisable to produce surgically an arteriovenous shunt. Instead, plasmapheresis was undertaken in an attempt to reduce the abnormal protein and to improve the chemical condition of the patient's blood. Two plasmaphereses were performed two days apart. The exchange was about 3000 ml of patient plasma each time for 1300 ml of saline and 2200 ml of albumin. The urea nitrogen decreased to 58 mg per dl, the creatinine to 5.8 mg per dl, and the thrombin time to 11 seconds. At this point, although not completely recovered, the patient felt well enough to be discharged from the hospital and refused hemodialysis and further therapy.

**CASE 2**

A 68 year old caucasian female was admitted to the University Hospital because of the sudden onset of aphasia. She could shake her head yes or no in response to questions, but was unable to verbalize...

**Figure 1.** The full hospital course of patient 1 with multiple myeloma is illustrated showing transient responses in BUN and creatinine following peritoneal dialysis, then alkeran, and then plasma exchange pheresis.
responses. She had been treated with ampicillin one week earlier for an E. coli urinary tract infection. Physical examination revealed an expressive aphasia, mild hypertension (BP 180/105) but little else. She showed no petechiae, bruises, fundoscopic changes, localizing neurologic signs nor jaundice. Initial laboratory data were normal except for a urea nitrogen of 29 mg per dl and a slightly reduced platelet count (112,000 per cumm).

The patient was thought to have a cerebrovascular thrombosis and was treated with bed rest. She was given alpha methyl dopa and hydrochlorothiazide for hypertension. Two days later the platelet count was 27,000, and prednisone was prescribed for what was thought to be drug induced thrombocytopenia. On the fifth hospital day, fragmented red cells were noted on the peripheral smear. Her urea nitrogen had increased to 69 mg per dl and her creatinine was 2.4 mg per dl. The combination of neurologic changes, hemolysis, thrombocytopenia, and renal impairment indicated the diagnosis of thrombotic thrombocytopenic purpura. She was treated with aspirin (1200 mg per day), dipyridamole (400 mg per day), and a course of plasmaphereses, each of which exchanged about three liters of the patient's plasma for normal fresh frozen plasma (figure 2). Coincidentally, she had repeated positive urine cultures showing E. coli and was treated successfully with Chloramphenicol for 10 days, then Ancef for a month. No renal abnormalities were evident on ultrasound, IVP, or cystoscopy.

The patient recovered after almost seven weeks of care and five weeks of plasmapheresis. She was discharged on a program of tapering steroids, continuing aspirin, dipyridamole, nitrofurantoin, and haldol for residual mild psychosis. At discharge, the platelet count was 314,000 per cumm, hematocrit 30 percent, urea nitrogen 31 ml per dl, and creatinine 1.6 mg per dl.

Discussion

It is difficult to assess the effect of plasmapheresis in these two patients undergoing treatment with multiple modalities. In the first patient with myeloma, plasmapheresis reduced the concentration of abnormal protein and corrected the coagulation defect, but had relatively slight effect upon the renal disease. In contrast, Misiani et al19 reported three patients with IgG myeloma and severe acute renal failure who were treated with two or three plasmaphereses and in whom complete recovery was observed. The urea nitrogen and creatinine decreased in parallel with the decrease in circulating light chains. However, Misiani's patients were simultaneously treated with peritoneal dialysis and chemotherapy, so attributing

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recovery to plasmapheresis alone is unwarranted.

The authors postulated the light chains interfered with tubule function, causing the renal failure. This is a reasonable conclusion. There is a correlation between renal failure in myeloma and the presence of Bence Jones protein.\textsuperscript{14,20,29} There is experimental evidence that injection of light chains in animals produces typical lesions of myeloma kidney.\textsuperscript{14}

However, circulating light chains have been decreased by chemotherapy and by peritoneal dialysis alone.\textsuperscript{11} Both these modalities were used in parallel with plasmapheresis in the recently reported cases. Unfortunately, there are no good control series comparing one modality of treatment with another. Historical controls show only a 30 percent recovery from renal failure in myeloma,\textsuperscript{6} but these cases were gathered over a remote 10 year period when the conventional therapy was not comparable to that at present. Dialysis was not used as extensively and chemotherapy was not as effective. Hence, it is possible the value of plasmapheresis has been exaggerated.

In thrombotic thrombocytopenic purpura, plasmapheresis is thought to remove immune complexes involved with the damaged blood vessels, red cells and platelets.\textsuperscript{3,9,25} The evidence for immune complexes in this disease is, so far, very scanty.\textsuperscript{25} It is possible that a plasma factor may be missing or used up in the disease process and replaced by plasma-exchange-pheresis. However, plasma infusion by itself has been successful only rarely.\textsuperscript{1,4} Enthusiastic reports of recovery from thrombotic thrombocytopenic purpura after plasmapheresis have encouraged the use of this modality in addition to newer antiplatelet drugs.\textsuperscript{3,21,24,25} No control trials comparing antiplatelet drugs with plasmapheresis have yet been attempted.

Cuttner reported a series of patients with thrombotic thrombocytopenic purpura who responded to splenectomy and dextran infusion.\textsuperscript{5} It may be that splenectomy removes a primary source of antibody production in this disease or the major sequestration organ for removal of immune complex damaged platelets. On the other hand, dextran infusion may interfere with the interaction between platelets and damaged vascular endothelium much as aspirin and dipyridamole are thought to do. Clearly, a controlled trial is required to compare the results of these modalities with plasmapheresis.

Two other disease entities in which plasmapheresis has been used to alter the course of renal disease are Goodpasture's syndrome and glomerulonephritis. Rosenblatt\textsuperscript{23} reported a case of Goodpasture's syndrome with antiglomerular basement membrane antibodies and renal failure treated with hemodialysis, immunosuppression, and plasmapheresis. The patient showed reversal of the crescentic glomerular lesion from 80 percent on the first biopsy to 20 percent on the postpheresis renal biopsy, and a stabilization of the creatinine level at 2.5 mg per dl. Review of historical controls showed 88 percent of patients with Goodpasture's syndrome would either die or require long term hemodialysis.\textsuperscript{23} Sixteen recent reported cases in which plasmapheresis was also used showed nine were still alive and free of hemodialysis.\textsuperscript{23}

McLeish,\textsuperscript{17} on the other hand, reported failure of plasmapheresis to reverse the course of renal failure in a 29 year old female who was treated with enthusiastic plasmapheresis for over a month. Anti-gglomerular basement membrane antibody decreased as did IgG and C\textsubscript{3}, but the renal failure eventually required hemodialysis. McLeish points out that enthusiasm for this new therapy should be tempered by their experience in his case.

The patients that can be expected to benefit from this mode of therapy remain to be identified. The relationship of the
antiglomerular basement membrane antibody activity to the clinical course is still unclear. The ability of renal biopsy to predict response remains to be tested. It is clear that a prospective controlled trial is needed to permit application of plasma exchange to the appropriate group of patients.

Bruns et al² have reported a case of antiglomerular basement membrane glomerulonephritis in which early plasmapheresis was used in conjunction with prednisone and cyclophosphamide. Anti GBM titer decreased and the subsequent biopsies showed a change from acute necrotizing proliferative glomerulonephritis to a more chronic and stable form of sclerosing glomerulonephritis. The authors attribute these changes entirely to plasmapheresis.

However, Mc Phaul and Mullins,¹⁸ in a study of acute glomerulonephritis not involving plasmapheresis, have reported that in half their patients, progressive renal failure did not develop and minimal segmental changes were seen on tissue section. Only 50 percent had detectable anti GBM antibodies. Every patient with diffuse proliferation and epithelial crescents had progressive renal failure and circulating anti GBM antibody. Fifteen percent of their patients with anti GBM nephropathy had sclerosing glomerulonephritis without proliferation of crescents, even without use of plasmapheresis. It is difficult, then, to be certain that plasmapheresis was responsible for the different histologic pictures seen on biopsy in Brun’s patient.

Finally, plasmapheresis has been used to attempt to reverse renal graft rejection by removing humoral factors involved in the rejection reaction.²² Some patients have responded; but, without concurrent controls, it is difficult to separate the effect of plasmapheresis from those of other therapy such as more enthusiastic hemodialysis, transfusions or since 1977, use of cyclophosphamide in place of immuran or 6 azathioprine.

Summary

It seems reasonable to conclude that when renal disease is caused by or contributed to by an intravascular macroglobulin, antibody, or immune complex, plasmapheresis may be helpful, if begun early in the course of the disease, in reducing the damage done by such a molecule. It is difficult, at present, to assess accurately the exact role of plasmapheresis because of the simultaneous use of multiple modalities of therapy in most patients.

Only controlled trials with patients randomly selected to be treated by pheresis plus medication or by medication alone will determine whether or not pheresis plays a significant role in treatment of these various renal diseases.

References