Plasma exchange in systemic lupus erythematosus

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SUMMARY Eight out of 10 patients studied longitudinally received benefit from plasmapheresis. The patients were used as their own controls, being treated in a steady state as far as was possible. Levels of circulating complexes did not bear a close relationship with clinical results. On this evidence plasma exchange alone does not appear to represent an important part of the long-term management of patients with systemic lupus erythematosus but may well be of value in combination with other therapy.

Since the first reported attempts¹ to perform therapeutic plasma exchanges on patients with hyperviscosity the technique has grown steadily, both in sophistication through the advent of double plastic blood-collecting bags, and more recently through cell-separators, and in the range of disorders treated.^{2–8}

It is now widely accepted that the clinical manifestations of systemic lupus erythematosus (SLE) are mediated through immune complexes,⁹ and it has been shown that intensive plasma exchange can be an effective method of reducing circulating immune complexes^{6,8} and other plasma components.^{5,10} Previous studies have suggested that plasmapheresis can be useful therapeutically in patients with high levels of immune complexes.^{6,8} However, changes in disease activity might be accounted for by changes in drug therapy and the natural fluctuations of the disease itself.

SLE is a disease remarkable for its varied clinical presentation and for apparently spontaneous remissions and relapses. A controlled study of treatment with plasma exchange would obviously be ideal. We did not consider this feasible, however, in view of the probable need to match patients for organ involvement, with a relatively small number of patients available for study. Consequently the aims of this study were to stabilise other forms of therapy

as far as possible and to follow up the patients longitudinally in order to use them as their own controls, thus establishing as nearly as possible that any change in disease activity was due to plasmapheresis alone. It was also hoped to establish whether plasmapheresis has a role in the treatment of acute exacerbations or is likely to be of benefit in the long-term treatment of SLE, and to assess whether the materials used in exchange for the plasma differ in their therapeutic effects.

Patients and methods

Clinical features of the patients are summarised in Table 1.

All patients complied with the American Rheumatism Association's preliminary criteria for the diagnosis of SLE.¹¹ A heterogeneous group of 10 female patients with SLE received a total of 13 courses of plasmapheresis. Patient 1 had received 2 short courses of plasmapheresis 12 months previously resulting in transient clinical benefit, since when she had fully relapsed to her preplasmapheresis state. Two patients were treated acutely, being too ill to be followed up over a long period, and 8 patients were studied according to the following protocol.

Before plasmapheresis each patient's treatment was progressively stabilised, corticosteroids in particular being reduced to an acceptable minimum. During a final run-in period of at least 6 weeks the drugs were maintained at a constant dosage. When possible, the patient was admitted to hospital for a 5-day period of bedrest, discharged, then readmitted

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Table 1 Patients: clinical features and previous treatment

Patient No.	Age	Major clinical features	Base-line treatment
1*	56	Polyarthrits, skin rash, cerebral symptoms (abnormal EEG and oxygen scan)	Prednisolone 7 mg daily. Salicylates
2	32	Polyarthralgia, skin rash, alopecia, Raynaud's phenomenon	Salicylates
3	54	Polyarthrits, thrombocytopenia	Prednisolone 10 mg daily. Salicylates
4	26	Polyarthralgia, skin rash, (C2 deficiency)	Prednisolone 5 mg daily
5	39	Skin rash, nephritis, (proteinuria 8 g/24 hours)	Prednisolone 10 mg daily
6	33	Skin rash, nephritis, (proteinuria 12 g/24 hours)	Prednisolone 10 mg and azathioprine 150 mg daily
7	38	Skin rash, cerebral symptoms (abnormal EEG and oxygen scan)	Prednisolone 10 mg daily
8	25	Raynaud's phenomenon, cutaneous vasculitis, gangrenous toes	Prednisolone 10 mg daily
9	26	Polyarthralgia and skin rash. Admitted with acute fulminating SLE involving cerebral, cardiac and respiratory disease, alopecia, cutaneous vasculitis and renal failure	(Previously Prednisolone 10-20 mg daily). Initially to 40 mg then 1 g daily $\times$ 3
10	48	Polyarthralgia, cerebral symptoms, hemiparesis, thrombocytopenia	Initially, methylprednisolone 1 g daily $\times$ 3

*See text for previous treatment.

when it had become apparent that no appreciable change in the clinical status of the patient had occurred on bedrest alone. At each clinic visit the following observations were made: (1) the patient's feeling of well-being on a 10 cm horizontal visual analogue scale; (2) duration of morning stiffness in hours; (3) the existence and severity of hair loss, skin rash, and cutaneous vasculitis (grades 0 to +++); (4) existence and severity of signs and symptoms of central nervous system involvement (graded, as far as feasible, 0 to +++); (5) the time taken to walk 100ft (30 m); (6) grip strength using a bag inflated to 30 mmHg attached to a sphygmomanometer; (7) articular index for tender joints.¹²

The following laboratory assessments were made as far as possible at each visit: full blood count, platelets and ESR, immunoglobulins, urine analysis for protein and casts; serum immune complexes, serum double stranded DNA binding capacity,¹³ and complement activity.¹⁴ At intervals, where relevant, creatinine clearance and urinary protein excretion were measured. Electroencephalograms (EEG), electrocardiograms (ECG), and pulmonary function testing were performed when appropriate. Oxygen brain scans¹⁵ were also arranged with the kind co-operation of Dr T. Jones of the Cyclotron Unit, Hammersmith Hospital.

PLASMAPHERESIS

Ten exchanges of approximately 3 l each were performed over a period of 12 days. The plasma was exchanged with an equivalent volume of either fresh frozen plasma or plasma protein fraction. Plasmapheresis was performed with a Haemonetics Model 30 blood processor used with a flow rate of 30-50 ml/min, citrate being used as an anticoagulant. Care was taken to limit hypovolaemia to a minimum. Exchange was performed either through a venous peripheral line or a centrally placed subclavian catheter when peripheral veins were inadequate.

CIRCULATING IMMUNE COMPLEXES (CIC)

The C1q solid phase radioassay was performed as described previously.¹⁶⁻¹⁸ C1q was coated on to the surface of polystyrene tubes. Immune complexes were bound to the solid phase C1q and then detected by the addition of radiolabelled, immunoabsorbent purified anti-IgG, confirming the immunoglobulin nature of the material bound to the C1q.

CIC were also determined by precipitation with polyethylene glycol by a modification¹⁹ of the method of Creighton *et al.*²⁰ After washing, precipitates were redissolved and the IgG and IgM were quantitated by single radial immunodiffusion.

STATISTICAL ANALYSIS

Patients were used as their own controls. Change in their clinical state was assessed by the Mann-Whitney U test comparing the mean of preplasmapheresis data with postplasmapheresis data in each individual. Immune complex data were assessed for the group as a whole by the paired *t* test.

Results

There was no change in the clinical status of patients during the bed rest period (6 patients). However, in some patients there was a reduction in levels of circulating immune complexes, which returned to pretreatment levels after the patient became mobile once more.

The clinical benefits of plasmapheresis are summarised in Table 2. Appreciable changes in many parameters could be seen for several days after plasmapheresis, but data in the table are confined to those observed at intervals of more than 1 week. Of 11 plasmaphereses on patients Nos. 1-8 performed according to our protocol 9 resulted in statistically significant ($P < 0.05$) improvement in at least 1 of the clinical parameters measured. The duration of some degree of statistically significant benefit lasted from 1 week to over a year, with a mean of 11 weeks. In patient No. 8 no improvement occurred, and patient No. 4 actually deteriorated but returned to her

Table 2 Results of plasmapheresis in 10 patients, clinical data: duration of improvement following treatment (in weeks)

Patient Treatment	Visual analogue index	Articular index	Raynaud's phenomenon	Skin rash	Hair loss	Walking time	Grip strength	CNS features	ESR	Immune complexes		Platelets	Renal function
										C1q	PEG		
1 Bed	—	—	—	—	—	—	—	—	—	—	—	—	—
PPF	2(2)	—(7)	—	—(4)	—	—(5)	—2	—	2	2	—	—	—
FFP	12(12)	7(12)	—	6(10)	—	—(4)	12(12)	—	1(†5)	ns(†5)	—	—	—
2 Bed	—	—	—	—	—	—	—	—	—	n/a	n/a	—	—
PPF	3(4)	4(4)	—(4)	—(4)	—(4)	—(3)	—	—	1	1	—	—	—
FFP	12(16)	8(16)	—(1)	2(6)	—	2(12)	—	—	4	1	†2	—	—
3 Bed	—	—	—	—	—	—	—	—	—	—	—	—	—
PPF	—	—(3)	—	—	—	—(10)	—(2)	—	—	1	—	—	—
FFP	2(6)	—(4)	—	—	—	8(8)	3(3)	—	—	—	—	—	10
4 Bed	—	—	—	—	—	—	—	—	—	—	—	—	—
PPF	—	—	—	1†	—	—	—	—	—	—	—	—	—
5 Bed	—	—	—	—	—	—	—	—	3	1	—	—	24 hour proteinuria > 52 weeks
PPF	—	—	—	—	—	—	—	—	3	1	—	—	Creatinine clearance > 52 weeks
6 FFP	—	—	—	—	—	> 1yr	—	—	—	—	—	—	—
7 Bed	—	—	—	—	—	—	—	—	—	—	—	—	—
PPF	10	—	—	12	—	—	—	12	—	—	—	—	—
8 PPF	—	—	—	—	—	—	—	—	—	—	—	—	—
9 3G	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	Gradual recovery following plasmapheresis. See text								Gradual recovery following plasmapheresis. See text				
PPF	—								—				
10 3G	—	—	—	—	—	—	—	—	—	—	—	—	—
Steroids	No effect on clinical parameters over 14 days								No effect on clinical parameters over 14 days				
PPF	CNS features unchanged. See text								Platelets returned to normal. See text				

Key: 1 = Number of weeks up to which there was a statistically significant difference from base-line. (1) = Number of weeks to return to pretreatment baseline value. — = No significant difference from baseline. Blank = Not applicable. n/a = Not available.

pretreatment state within 3 days of ending plasmapheresis. This latter patient had homozygous C2 deficiency. Subjectively all but patients Nos. 4 and 8 claimed substantial benefit. A further 2 patients, Nos. 9 and 10, were admitted with fulminant SLE, and thus were of necessity treated in a nonsteady state. Of these 2, patient No. 9 recovered fully after plasmapheresis while the other, patient No. 10, obtained little benefit, although she had only 5 exchanges because of difficulties of vascular access. She had severe cerebral involvement with an established hemiparesis.

Three patients (Nos. 1, 2, 3) were treated initially with plasma protein fraction (PPF) and subsequently with fresh frozen plasma (FFP) after they had fully returned to their pretreatment level of disease activity. Benefits from plasmapheresis with FFP lasted longer in all 3 patients.

Apart from the patient (No. 4) with homozygous C2 deficiency none of the patients suffered any worsening of the disease as a result of plasmapheresis, and the procedure itself was well tolerated. Occasional feelings of faintness and mild citrate toxicity, which was rectified easily, were the only problems apart from 1 patient (No. 7) whose central venous catheter became infected and had to be resited.

The clinical pattern of organ involvement (renal, arthralgia, etc.) appeared to have little relation to the outcome following plasmapheresis.

Patient No. 6 was the only patient who was also

being treated with azathioprine. Her benefit was considerably longer in duration than the other patients' (52 weeks).

The reduction in levels of circulating immune complexes for the whole group of patients was highly significant immediately after plasmapheresis ($P < 0.001$) and was still significant 1 week after finishing treatment ($P < 0.05$). The difference had ceased to be significant after 2 weeks ($0.975 < P > 0.96$). The mean percentage drop in levels of circulating immune complexes immediately after plasmapheresis was 52.2% and after 1 week was 18.2%.

Discussion

From the above data it is clear that a temporary beneficial response to plasmapheresis can usually be obtained. It is not clear whether longer lasting remissions may be attributed to the treatment or to natural fluctuations in the disease itself. Our data (to be published elsewhere) also confirm that plasmapheresis can be an effective means of reducing circulating immune complexes, complement, antibodies, and other plasma components at least temporarily, although it appears to be more effective in some patients than others. We did not find that initial levels of circulating immune complexes were related to the success of the procedure, contrary to the findings of Verrier-Jones and co-workers.⁶ Indeed, good improvement was observed in patient

No. 5 who had normal levels of complexes, suggesting that other factors such as alteration in the qualitative properties of circulating immune complexes and removal of inflammatory mediators may be important. Although bed rest was not shown to affect the course of the disease, the change in levels of circulating immune complexes accompanying it is interesting. The reasons for this are not clear but may represent a change in vascular permeability as much as an alteration in production of immune complexes. This phenomenon also suggests that mechanisms other than mechanical removal of plasma components may be involved. It has been suggested that exposure of blood to plastic surfaces during dialysis may result in lowering of circulating immune complexes, and this mechanism may also have some importance during plasmapheresis.

Three patients were subjected to plasmapheresis, on different occasions, with PPF and FFP. It has been shown that complement is involved in the clearance and solubility of immune complexes,²¹ suggesting that exchange with FFP may be more beneficial than with PPF. Against this, complement also acts as a mediator of inflammation, and its addition may exacerbate the disease. Our evidence is insufficient to make a case for either replacement fluid, but length of remission was slightly longer after the FFP exchanges.

We found that DNA binding was considerably reduced. In view of the possibility that complexes observed in tissues may be formed locally rather than deposited from the circulation, a lowering of antibody levels may influence this complex formation.

The mechanism of benefit of plasmapheresis is probably complex. The physical removal of immune complexes and other inflammatory mediators^{6,8} presumably has an effect. It is also possible that plasmapheresis may improve the ability of the reticuloendothelial system to remove circulating immune complexes. Antibody affinity may affect the pathogenicity of immune complexes,²² and removal of antibody might influence this. It has also been suggested that plasmapheresis may exacerbate the illness through stimulating antibody production,^{5,23} though we have no evidence for this or for a sustained influence on the factors contributing to immune complex formation and deposition.

The major role of plasmapheresis would seem to be in the control of the acute exacerbation, and it is less likely to be of practical value in chronic disease, though it may be useful when other forms of therapy have failed. It may be relevant that feedback control may be stimulated by reduction in antibody, at which phase the use of cytotoxic drugs could be especially relevant. There may be a place for combining plasma exchange with other treatment such as

cytotoxic drugs, high dose pulses of steroids, antilymphocyte globulin, or levamisole in the initial control of the disease. Such forms of treatment might best be tested with multicentre controlled trials.

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