Current Practice in Therapeutic Plasmapheresis

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CURRENT PRACTICE IN THERAPEUTIC PLASMAPHERESIS

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PREFACE

In Asian traditional medicine, bloodletting played an important role. The methods, which are still in use in Japan, are to suck the blood out with glass cups, or with leeches attached to the patient's neck. This principle of removing blood which contains toxic substances has developed into the modern technique of plasmapheresis.

The 17th International Congress of Internal medicine was held in Kyoto, Japan, on Oct. 7 to 12, 1984. The symposium at this meeting entitled Therapeutic Plasmapheresis, chaired by Dr. Horst Klinkmann (FRG) and Dr. Yuichi Shiokawa (Japan), was held on Oct. 11. It was felt that this was an important opportunity for much-needed discussion and exchanges of views on plasmapheresis to take place between Japanese and foreign participants. Therefore, a satellite symposium, sponsored by the Japanese Society for Plasmapheresis, was held at the same place, on Oct. 12. At these meetings, there was vigorous discussion on issues ranging from technology to the clinical application of plasmapheresis. This book contains the product of both meetings.

Previously, one of us (YS) examined all the medical papers on plasmapheresis which appeared during the years 1974 to 1981, using the MEDLARS and JICST reference systems. From Jan. 1974 to Dec. 1980, the number of medical papers published in the world amounted to 1,740,741, of which 390, or 224 per million, were on plasmapheresis. In contrast, during the period January to December 1981, 254 of 274,888 papers, or 920 per million, were devoted to the problems of plasmapheresis. This increase in the number of papers demonstrates how rapidly interest in plasmapheresis was growing at that time.

Furthermore, the papers on plasmapheresis covered more than 180 kinds of diseases, almost all the diseases included in the medical textbooks. This study was performed five years ago, but we believe that plasmapheresis still remains one of the major topics in medicine worldwide, and the number of papers on it are still increasing.

In addition, despite recent rapid progress in the development of the membranes and machines used in plasmapheresis, the mechanisms of action of apheresis are not fully understood. There is still controversy as regards the clinical efficacy of the procedure; there are very few studies based on well-controlled clinical studies; and there is debate on the ethics of use of sham pheresis as a control procedure.

This book has the title *Current Practice in Therapeutic Plasmapheresis.* We do not think that plasmapheresis is yet an established medical procedure, but wish and hope that this very old, but very new, medical technique will be studied further, and will contribute to the treatment of disease in future.

Finally, we wish to thank the members of the Japanese Society for Plasmapheresis for their assistance and participation in the organization of the meetings, and of the publication of this book.

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PROGRESS IN THERAPEUTIC PLASMA EXCHANGE: A FIVE-YEAR RETROSPECTIVE

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Key words: membrane plasma separation, plasma fractionation, plasmapheretic immune modulation, controlled studies

INTRODUCTION

Membrane plasma separators first became commercially available in Germany in May 1979.[1] While centrifugal systems were used for plasmapheresis in the 1960s,[2] the literature indicates that significant interest appeared only in the late 1970s, after membrane devices were introduced.[1,3] This report addresses the state of the art as it was five years ago and our hopes at that time, and examines the progress made since then.

MEMBRANE PLASMA SEPARATION

It is not surprising that the first plasma filter to appear on the market, the Asahi Plasmaflo 01®, was somewhat deficient when applied to separation of plasma from whole blood as it was designed and originally used for reinfusion of cell-free ascitic fluid. Used for plasma separation, it rejected certain proteins, particularly in the high molecular weight range.[1] Better transport properties have been achieved by designing membranes specifically for plasma exchange, and all membranes introduced in the past four years have been characterized by a sieving coefficient of nearly 1.0. Each of the 14 plasma separators available today has equivalent sieving characteristics,[4] and the plasma removed with these is similar in its composition to that obtained by centrifugation.

An interesting recent development is a system which uses a flat membrane device plus a fluid cycler (TPE, Cobe). A microprocessor responds to a range of patient parameters by adjusting pressure on the filter stack via a hydraulic clamp in order to optimize channel height.[5]

Rotating tube geometry is another recent innovation that has proved highly efficient. A central cigar-shaped element is rotated at up to 3,600

RPM to produce the necessary shear forces. While containing less than 50 cm^2 of membrane, the performance of these cartridges corresponds to those of previous devices 50 to 500 times larger.

Performance of membrane devices is affected both by membrane properties and by geometry. Filtration rate has been found to be independent of surface area above an area of about 600 cm^2.[6] This phenomenon, which can be explained mathematically, accounts for the fact that the maximum plasma filtration rate at a blood flow of 100 ml/min is 30 to 40 ml/min for all the devices currently available despite the reduced surface areas of many of the filters.[6] The smallest of them has a surface area of 1,200 cm^2 and a filtration rate of 28 ml/min.

In technical terms, therefore, plasma separation with flat sheet membranes or hollow fibers can be seen to have made adequate progress: priming volumes are smaller as a result of the reduced surface areas of today's plasma separators and sieving coefficients are entirely satisfactory. Emphasis should now shift to therapeutic investigation.

PLASMA FRACTIONATION

Plasma exchange in the 1970s consisted of separating the patient's plasma, discarding it, and replacing it with albumin or fresh-frozen plasma (FFP). There are several problems with this approach:

1. allergic or quasi-anaphylactic reactions to the infusion fluid in up to 20% of treatments;[7]
2. a risk of infection, especially with FFP; and
3. logistical and economic factors.

This practice of discarding over 100 g of useful plasma proteins in order to remove the minute quantities of pathogen that are involved in many diseases seems wasteful; in Goodpasture's syndrome, myasthenia, and lupus, as well as some immune complex-mediated diseases, the proteins which are the target of treatment are present only in milligram quantities. Clearly it would be preferable to extract only the pathogens and to return the plasma thus purified to the patient. Since it was first described,[8] this method, known as plasma fractionation or selective plasmapheresis, has been the subject of intense research, and two approaches have been developed. These are filtration by selectively permeable membranes or processes and selective adsorption of pathogenic proteins by binding to a solid matrix.

Plasma filtration: The first use of this technique was in 1978, when Agishi et al.[9] used a secondary filter which retained high molecular proteins while allowing albumin to pass through to process plasma filtrate before returning the albumin-containing fraction to the patient. Of the membranes which have been developed since then, all of which have been tested by the authors or their colleagues,[4] only a few have been placed in clinical use.

The membranes which are available at present do not provide good enough separation of IgG from albumin, an important objective in the treatment of most autoimmune diseases. At present, it is possible only to separate molecules the size of IgM from proteins of less than 500,000 daltons in molecular weight. Separation which makes use of the fact that albumin is positively charged while most other plasma proteins carry a negative charge by means of a modified membrane may prove more effective in this area than molecular sieving alone, i.e., fractionation on the basis of electrochemical charged density.

Adsorption: This method, which uses column perfusion, is more selective than filtration. There are three broad approaches in use:

1. The pathogen is bound by chemical interaction with a substance contained in the solid matrix. An example of this is the removal of β-lipoprotein by a heparin-agarose column. This has the disadvantage of also removing antithrombin III.[8,10]
2. The pathogen is bound by an antigen-antibody reaction to its natural target fixed on the surface of the matrix. An example of this method is the binding of anti-DNA antibodies to DNA fixed in the column.[11]
3. The pathogen is again bound by an antigen-antibody reaction, but in this case the antibody, which is directed against the target protein, is fixed in the matrix. An example here is the removal of low-density lipoproteins (LDL) by binding to fixed anti-LDL antibodies.[12]

Details of about 50 such systems have been published.[13] Table I outlines the systems which have been used in vivo. The first clinical application, in a case of familial hypercholesterolemia, was described in 1976.[8] The 1 MRÉ cartridge for removing IgG and the Asahi I-02 system for removing the anti-acetylcholine receptor antibodies of myasthenia gravis, which were the first

Table I. Adsorption systems in clinical use.

Adsorbent	Substance removed
Heparin	Low- and high-density lipoproteins
Protein A	IgG, IgG-containing immune complexes, C3
Anti-LDL	Low- and very low-density lipoproteins
DNA	DNA antibodies
A and B blood group antigen	ABO blood group antibodies
Synthetic blood group B antigen	Blood group B antibodies
Factor IX	Factor IX antibodies
Insulin	Insulin antibodies
I-02®	Rheumatoid factor, circulating immune complexes, anti-DNA antibodies, ribonucleoprotein antibodies, smooth muscle antibodies
"IMP"	Rheumatoid factor, immune complexes

adsorption systems to be put on the market, appeared in 1983. Few of the systems which have been described are specific for a single pathogen.

Adsorption has to overcome several difficulties before its clinical application can become wider: most of the systems await thorough investigation; and a number of large intrinsic problems must be resolved, namely, cost of treatment, specificity of pathogen removal, biocompatibility, sterilization, reusability, and biological stability.

PLASMAPHERETIC IMMUNE MODULATION

In the early 1970s, severe cases of Goodpasture's syndrome were treated by nephrectomy, but this did not always prevent death from massive pulmonary hemorrhage, while in other cases the disease developed in the transplanted kidney. Goodpasture's syndrome is now known to involve self-limited production of autoantibodies[14]; when patients are treated with a combination of cytotoxic drugs and plasmapheresis, autoantibodies disappear in less than eight weeks.[14] Where therapy is less aggressive, disappearance time is longer, usually four to six months; permanent tissue damage caused by circulating antibodies can be prevented by using plasmapheresis during the active stages of the disease. In many autoimmune diseases, e.g., myasthenia gravis and lupus, plasmapheresis stimulates antibody synthesis unless immunosuppressive agents are administered simultaneously[15]; Goodpasture's syndrome is therefore unusual in that autoantibody manufacture stops.

It can be seen from this example that apheresis has proved a useful tool in researching immunopathogenic mechanisms.

Our knowledge of severe immune complex-mediated disorders has also been increased by plasmapheresis: impairment or blockade of endogenous breakdown of antigen-antibody complexes has been found. In 1974, Mannik et al.[16] gave animals an excess load of artificial immune complexes and demonstrated prolonged circulation of these complexes and, by inference, saturation of the reticuloendothelial system (RES). Lockwood,[17] studying patients with severe vasculitis or nephritis, demonstrated blocked clearance of immune complexes by the RES.

Repeated plasmapheresis treatment reverses the blockade of the RES and normal breakdown of immune complex ensues (Figure 1). In contrast to the response to immunosuppressive treatment alone (Figure 2), the effect of combined plasmapheresis and immunosuppression is to induce an initial elevation of circulating levels of immune complexes followed by sudden disappearance of the complexes, reflecting the re-establishment of their catabolism by the RES.

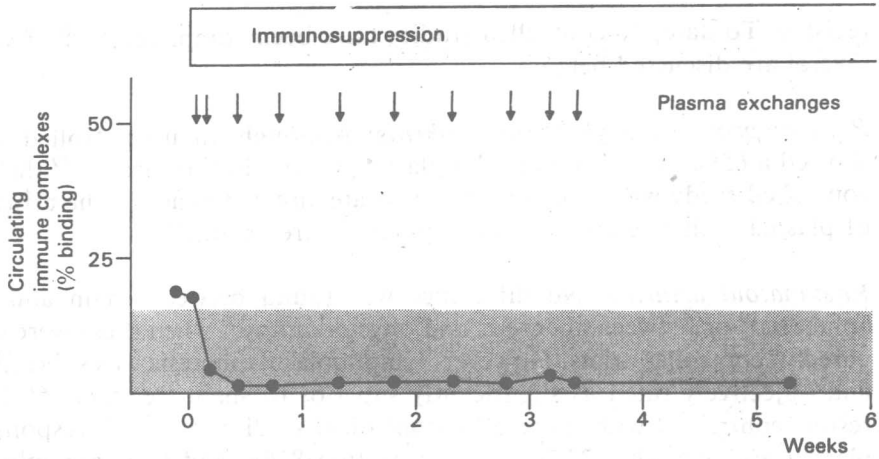

Figure 1. Changes in levels of circulating immune complexes (Clq fluid phase RIA) during combined immunosuppressive and plasma exchange therapy in a 19-year-old male patient with rapidly progressive glomerulonephritis.

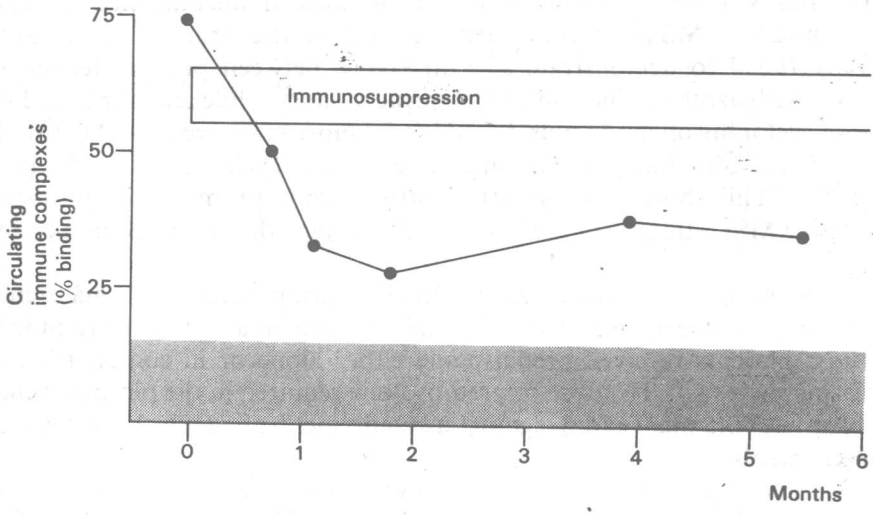

Figure 2. Incomplete reduction of levels of circulating immune complexes (Clq fluid RIA) during azathioprine and steroid therapy in a 25-year-old female patient with vasculitis.

CONTROLLED STUDIES OF PLASMAPHERESIS

In order to evaluate plasma exchange therapy systematically in the current environment of some 150 diseases now suggested as indications for this methodology, attempts are underway to establish an international apheresis

registry. To date, 11 controlled studies have been completed,[18-28] of which several are discussed below.

Rapidly progressive glomerulonephritis: Although an uncontrolled study showed a 65% rate of response to plasmapheresis in this disease,[29] the only controlled study was unable to demonstrate any difference in the efficacies of plasma exchange and immunosuppressive treatment.[18]

Rheumatoid arthritis: No difference was found between sham and true apheresis[19] or between apheresis and physiotherapy[20] when these were compared in controlled trials. However, lymphoplasmapheresis was subjectively and objectively rated as significantly superior to sham treatment.[21] These results contrasted with those of uncontrolled studies, in which response to plasma exchange was 75%, to cryofiltration 81%, and to lymphoplasmapheresis 100%. These discrepancies may be the result of differences in the definition of response used. Benefits of plasma exchange treatment in advanced rheumatoid arthritis rarely last more than a few months.

Multiple sclerosis: In contrast to the findings of uncontrolled studies, in which 72% of MS patients benefitted from plasma exchange,[7] one controlled study failed to demonstrate any difference between plasmapheresis combined with azothioprine and azothioprine alone,[22] while another found high-dose cyclophosphamide plus ACTH to be more effective than ACTH alone or in combination with plasmapheresis and cyclophosphamide in low doses.[23] This short a course offers little, if any, promise for chronic progressive MS; a treatment time of months or years has been recommended.[30]

Bullous pemphigoid: A significant steroid-sparing effect of plasma exchange treatment has been demonstrated in this disease. In a controlled randomized study, patients received prednisolone either alone or in combination with plasmapheresis.[24] The dose of prednisolone required in the plasma exchange group was 0.5 mg/kg/day against a requirement of nearly 1 mg/kg/day in the controls.

Methodological problems limit the value of many of the studies to date and no definitive answers have been obtained. The implementation of controlled studies at this stage itself remains a subject of controversy.

SUMMARY

In technical terms, the performance of primary filters that has been achieved is very satisfactory. While plasma fractionation remains a promising technique for future application, neither filtration nor adsorption systems are yet adequately advanced.

Plasmapheresis has extended our understanding of immunomodulation

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