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Present Status of Hemoperfusion/ Hemodialysis in Italy

V. BONOMINI,[1,*] S. STEFONI,[1] G. FELICIANGELI,[1] L. COLÌ,[1] M. P. SCOLARI,[1] R. PRANDINI,[1] C. U. CASCIANI,[2] M. TACCONE GALLUCCI,[2] A. ALBERTAZZI,[3] V. MIOLI,[4] AND F. MASTRANGELO[5]

[1]Institute of Nephrology and Dialysis, St. Orsola University Hospital, University of Bologna, Bologna, Italy; [2]Institute of Surgical Pathology, University of Rome, Italy; [3]Department of Nephrology and Dialysis, University of Chieti, Italy; [4]Department of Nephrology and Dialysis, University of Ancona, Italy; [5]Department of Nephrology and Dialysis, Lecce, Italy

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ABSTRACT

The use of charcoal hemoperfusion in the treatment of chronic renal failure has been proposed and applied by several authors. The availability of coating membranes of increased biocompatibility currently allows a safer and wider use of this purifying technique. It has been recently demonstrated that long-term treatment with combined hemodialysis/hemoperfusion yields an improvement of certain dialysis-resistant uremic signs in patients on regular dialysis treatment, while in selected patients it affords a marked reduction (up to one-third) in the overall time of treatment per week. The tolerance of long-term treatment is good. In line with these findings, a multicenter study has been carried out in Italy with two main aims: (1) to see whether long-term treatment with charcoal hemoperfusion is really safe and substantially free from side effects; (2) to verify in a larger and more varied population of patients whether such long-term treatment actually improves certain uremic signs persisting despite adequate dialysis

*Author to whom all correspondence and reprint requests should be addressed.

treatment. A third phase of the multicentric study (reducing the weekly time of treatment) is currently being worked on. Five nephrology and dialysis departments took part in the study: in Bologna, Rome, Chieti, Ancona, and Lecce.

Index Entries: Hemoperfusion; charcoal in hemodialysis; hemodialysis; artificial organs; uremia, and hemodialysis.

INTRODUCTION

Twenty years ago all chronic uremics were doomed to die. Since then, there has been a steady and spectacular improvement in both medical knowledge and technology, and today the loss of renal function does not necessarily mean the death of the individual. Of the various means of renal substitutive therapy, some are of proven worth, others need further clinical evaluation. Table 1 gives our experience up to December 1982 with the various substitutive therapies available for chronic uremia.

Both renal transplantation and regular dialysis treatment (RDT) afford spectacular survival (70–80% average, after 5 yr). Although rehabilitation *for work* shows similarities between the two programs, a marked difference exists when one comes to consider the real rehabilitation of the patient *from uremia.*

It is also confirmed by our experience that only renal transplantation succeeds in rehabilitating the patients from uremia. On chronic dialysis, on the contrary, most uremic problems persist, or even worsen with time until a high risk clinical state may be reached. These high risk conditions may explain the persistence of far too high a morbidity in dialysis, sometimes to the point of debarring dialysis patients from renal transplant programs. These views have been amply stated in previous papers of ours (*1–3*). There we have drawn attention to the usefulness of "early dialysis" (ED) (*4–7*) in preventing the appearance and subsequent progression of many uremic problems and its greater viability over standard late dialysis in terms of survival, hospitalization, allowing full-time work and candidacy for transplantation (12 yr followup). Standard late dialysis be-

TABLE 1
Institute of Nephrology and Dialysis, St. Orsola University Hospital. Replacement Program for Chronic Uremia (Dec. 31, 1982)

Program	Patients
Transplantation	237
Hemodialysis	480
Hemoperfusion	61
Hemofiltration	13
CAPD	9

gins after years of low protein diet with a residual creatinine clearance (Ccr) of 0–4 mL/min; ED begins when clinically necessary, after brief low protein diet, with residual Ccr at 10–12 mL/min.

True though this is, it is no less true that: (1) renal transplantation (the ideal solution for *reversing* uremia) is possible in no more than 30% of the cases, our data confirming a general trend in the literature; (2) early dialysis to *prevent* uremia is unfortunately mainly confined to the experience of Bologna, at least officially. For a wide range of reasons, ranging from prejudice to force of circumstance, over 90% of the 250,000 RDT patients in the world actually continue to be treated by "late dialysis," an approach suggested more than 15 yr ago when dialysis was in its infancy.

With its emergence from infancy to maturity, artificial substitutive therapy has revealed its well-nigh miraculous potential, but also undoubted limitations. The miracles are rather hard to explain. Not so the limitations (*8*).

It remains for speculation to decide whether the majority of uremic problems persist on dialysis because uremia is caused by the loss of the endocrine as well as the excretory function (and the former clearly cannot be made up for by any artificial means), or whether uremia persists through a failure to remove all the uremic toxins.

Two facts are, however, clear:

1. The dearth of cadaver donors restricts renal transplantation to some 30% of the patients in the "waiting-list".
2. Artificial substitutive therapy, as usually employed, yields unsatisfactory results in terms of real rehabilitation from uremia.

A new line is needed to boost renal transplantation; and new technological areas are needed for exploring how to enhance the results of artificial substitutive therapy. Previous papers have set out these problems in some detail (*1,2*).

The present report focuses on the use of charcoal hemoperfusion (HP) in chronic uremia as a potential technique to improve the results of artificial therapy owing to the wide absorptive capacity of charcoal itself. The first results on this topic have been published elsewhere (*9,10*). Here we report the long-term results both of our experience and of a multicenter trial involving five cities: Bologna, Rome, Ancona, Chieti, and Lecce.

HEMOPERFUSION IN CHRONIC UREMIA

Basic Assumptions

In the treatment of chronic renal failure, a condition in which a wide range of "toxic" molecules are retained in the body, activated charcoal

has been used orally, inserted in the dialysate circuit, or by direct blood hemoperfusion.

Several studies from different centers (*11*) have clearly demonstrated that charcoal hemoperfusion removes creatinine, uric acid, guanidines, phenols, middle molecules, and other "toxins." However, the step from the first theoretical and experimental studies to the current clinical application in uremic patients has been a long one and certain problems still remain to be overcome. The major drawbacks have been the poor biocompatibility of charcoal and its incapacity to absorb urea, electrolytes, and water.

In the first applications, the poor compatibility of the absorbent caused a severe depletion of blood components (platelets, red and white cells, fibrinogen, etc.) and serious effects on patients because of the release of charcoal microemboli (*12,13*). Chang's research (*14,15*) into the miocroencapsulation of charcoal within a polymer coating (the principle of artificial cells) led to a decisive improvement in the biocompatibility and tolerance of charcoal hemoperfusion. Subsequently, ever more reliable coating membranes and hemoperfusion devices (*11*) have been developed. Coated charcoal has been found to have a high sorption capacity as good as uncoated.

Extensive recent reviews have centered on the studies and results with hemoperfusion in uremia, for both short and long-terms (*16*). All these studies confirm two facts: (1) that hemoperfusion with coated activated charcoal can at present be regarded as a safe and reliable procedure, and (2) that in uremia a combination of hemoperfusion with dialysis or ultrafiltration is indispensable, because charcoal is incapable of absorbing urea, electrolytes, and water, whose cyclical removal is indispensable in chronic uremic patients.

Hemoperfusion Device

Since 1978 we have used a cartridge (Biotec Hemoperfusion System, Tecnologie Biomediche, Bologna, Italy) containing activated charcoal coated with a methacrylate-based membrane of high biocompatibility. The characteristics of the device have previously been described (*9,17*). The charcoal content of the cartridge was initially 300 g; later on in the program, the quantity was reduced to 150 g. This device was used in Bologna and all the other cities concerned in the multicentric trial. Since 1982 we have also used cartridges containing charcoal coated with cellulose (Gambro Adsorba 150 C).

Coating Membrane

The coating membrane of the Biotec Hemoperfusion System is 1.5 μm thick and utilizes hydroxyethyl methacrylate as a basic element. When suitably crosslinked, this forms a block copolymer in which the hydrophilic block has the property of swelling, whereas the hydrophobic

block contributes mechanical strength to the moist membrane. Methacrylate membranes have already been used for coating charcoal (*18*), but the results were not satisfactory (platelet depletion and aggregation). This is very likely caused by the scanty uniformity of the coating and the rather low hydrophilic action of the hydrogel (40% water absorption). The coating membrane of the device we used afforded 60% water absorption. Increased hydrophilic effects were made possible by copolymerization of hydroxy-methacrylate with an unsaturated heterocyclical compound that is highly hydrophilic in the presence of appropriate crosslinks. The expected deterioration of the mechanical properties was minimized by introducing into the tridimensional polymeric network a fourth monomer with hydrophobic and elastomeric properties (*19*).

Biocompatibility

The biocompatibility of hemoperfusion devices is of primary importance where long-term treatment is concerned. The procedure must be absolutely safe for patients. The biocompatibility of the methacrylate-coated charcoal has been assessed both for short and long terms (*9,10*).

The platelet depletion in each single hemoperfusion procedure proved to be less than 5%, while white blood cells, red blood cells, and fibrinogen were practically unaffected (Table 2). The effects of hemoperfusion on lymphocytes structure (monoclonal antibodies) and function (mitogen stimulation) have also been evaluated (*20*).

The patients' subjective tolerance to the hemoperfusion procedure is of primary importance: poor tolerance greatly limits the compliance with any new therapeutic approach. In our experience, the charcoal-related side effects (mainly chills, fever, and hypotension) have been considerably restricted (*9,10*).

Efficiency

The efficiency of methacrylate-coated charcoal has been evaluated (*9*) in vivo and in vitro by measuring the sorption capacity for substances of increasing molecular weight. The smaller quantity of charcoal contained in the cartridge (150 g) affords a fairly low clearance of small molecules (less than 200 daltons) compared with standard dialyzer and other

TABLE 2
Effects of the Combined HD/HP Treatment on Platelets, White Cells, and Fibrinogen[a]

	Months		
Platelets, $n/mm^3 \times 1000$	181 ± 22	195 ± 15	183 ± 22
White cells, n/mm^3	6800 ± 600	6400 ± 900	6900 ± 700
Fibrinogen, mg/dL	302 ± 56	293 ± 61	296 ± 50

[a]Data refer to 7 patients treated up to 12 months without interruption.

300 g charcoal cartridge. However, for substances of greater molecular size (up to 3000 daltons) the reduced quantity of charcoal seems to ensure an equally satisfactory removal. Methacrylate-coated charcoal shows a capacity, albeit limited, for removing substances of molecular weight up to 14,000 daltons.

Clinical Applications

The two main clinical questions we asked ourselves (*9*) when we approached the combined hemodialysis–hemoperfusion treatment were:

1. Can this combined approach be of benefit to patients with technically adequate but clinically inadequate dialysis?
2. Can the combined program afford a reduction in time of treatment in patients with technically and clinically adequate dialysis?

The first problem was studied in 64 cases (Table 3). Despite the apparent adequacy of dialysis from a technical viewpoint, many subjective and objective clinical signs of uremia persisted in these patients, mainly severe peripheral neuropathy, recurring fibrinous pericarditis, pruritus, anemia, nausea, and lack of well-being.

The pattern was not one of underdialysis, but of *resistance to dialysis* although correctly performed (*9*). In these patients one of the weekly dialysis sessions was replaced by one combined hemodialysis/hemoperfusion (HD/HP) procedure. The remaining two sessions remained unchanged. Each patient, therefore, continued to undergo three procedures per week, one of combined HD/HP and two of conventional hemodialysis (HD). Diet and drug regimen were maintained unchanged. Technically speaking, in the combined session, a cartridge containing 150 g of activated charcoal was inserted in the circuit in series with the dialyzer (flat plate or hollow fiber). The cartridge is left *in situ* throughout the whole session. As a rule the circuit is rinsed with 1500 mL of normal saline, containing 30,000 IU heparin. The patient is connected to the circuit without wasting the priming volume. The further amount of heparin needed for the HD/HP procedure is generally the same as that used in hemodialysis alone. The care required by the staff for the HD/HP procedure is similar to that for dialysis alone. All patients were thoroughly

TABLE 3
Patients and Procedures in the Multicenter Trial

	Patients	Procedures
Bologna	28	1853
Rome	11	264
Chieti	9	320
Ancona	8	208
Lecce	8	256

TABLE 4
Effects of Combined HD/HP Treatment on Dialysis-Resistant Clinical Signs

	Bologna	Rome	Chieti	Ancona	Lecce
Pericarditis	+++				
General status	++++	+++	++++	+++	+++
Anemia	No effect		No effect	No effect	No effect
Nausea	++	++	+++	++	++
Anorexia	+++	+++	+++	++++	++++
Peripheral neuropathy	++++	+++	++		
Asthenia	+++		+++	++++	+++
Pruritus	++++	++++	No effect		

briefed on the pros and cons before treatment. They volunteered to take part in the program.

Both the Bologna experience and the multicenter trial as a whole show that HP as an adjunct to HD can clear up various clinical problems that resist HD alone (Table 4), mainly pruritus, severe neuropathy, recurring fibrinous pericarditis, and a decline in general status. The improvement we found may take place within a month, or even weeks, of starting the combined treatment. An objective improvement was also found (Fig. 1) in motor nerve conduction velocity (MNCV). Why this should be is not fully understood. Of the various biochemical-clinical correlations so far studied, the most regular finding was the parallel running between MNCV changes and phenilalanine–tyrosine serum changes.

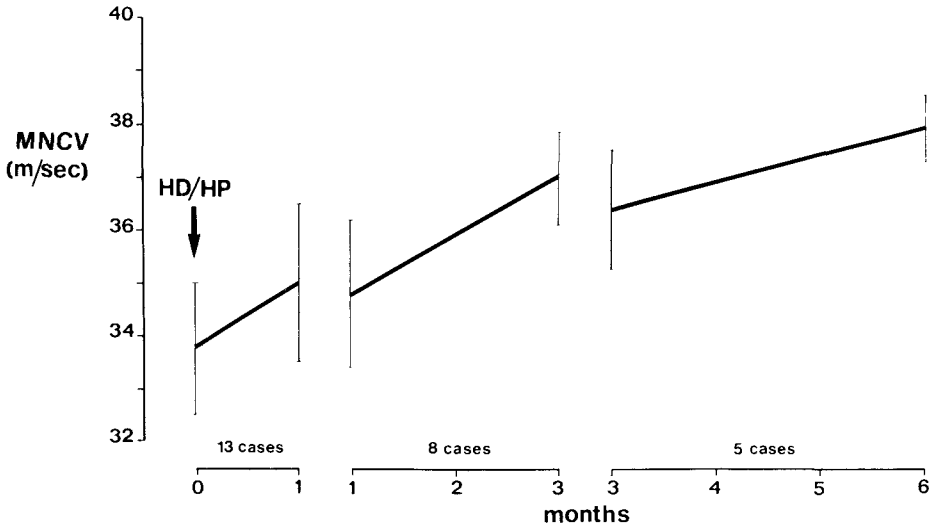

Fig. 1. Effects of combined HD/HP treatment on motor nerve conduction velocity (*Int. J. Artif. Organs*, Wichtig Editore, with permission).

The "true" connection between these findings, however, is still to be proven.

As for the hematochemical values, the multicenter trial confirms (Table 5) that HD/HP treatment leads after 3–4 wk to a reduction in plasma levels of uric acid, creatinine, and urea. Since charcoal has no capacity to absorb urea, the last finding has been subjected to more detailed metabolic research. They will be published elsewhere (*21*). Of certainty is that the reduction in urea in HD/HP was asssociated with a reduction in protein catabolic rate.

An exact assessment of the cost–benefit and cost–effectiveness ratios in combined HD/HP is hard to achieve in this first patient population, since the number of combined sessions required for a clinical steady state to be reached varies widely from case to case. Such short-term combined HD/HP, however, would itself argue that hemoperfusion poses no real cost problems in those countries where HD is already institutionally accepted and routinely applied.

The cost problem becomes more important and requires more careful assessment when the combination of HD and HP is employed in an attempt to reduce the weekly dialysis time. This possibility was studied in 33 patients.

The clinical and metabolic conditions in all patients were good. The residual Ccr ranged from 0.2 to 1.6 mL/min. In these patients the weekly time of treatment was reduced by 20–35%, until one entire weekly session was eliminated. Despite this reduction in hours of treatment, patients' clinical and metabolic conditions remained unchanged. Table 6 shows the behavior of plasma urea, creatinine, and uric acid, which remained stable during the reduced-time program. In all patients the tolerance to treatment was good. Personal, family, and social rehabilitation improved. In this reduced-time program a careful choice of patients and their compliance with treatment is indispensable.

In this second schedule of regular combining HD/HP the yearly increase in cost is 30% higher than HD alone. The increase, however, is associated with better social and family rehabilitation of the patient owing to the lower machine-dependency time per week, and the enhancing of facilities for the dialysis Centers. The two facts are still hard to quantify in terms of money, which explains why further study for a correct assessment of cost–benefit and cost–effectiveness is needed.

TABLE 5
Percentage Decrease of Plasma Values of Creatinine, Uric Acid, and Urea after 3 Months of Combined HD/HP Treatment

	Bologna	Rome	Chieti	Ancona	Lecce
Creatinine	−15	−27	−10	+5	−3
Uric acid	−26	−24	−17	−17	−15
Urea	−19	−22	−11	−20	−10

TABLE 6
Course of Urea, Creatinine, and Uric Acid in Seven Patients Treated up to 12 Months with the Reduced-Time HD/HP Program

	Months			
	0	4	8	12
Urea, mg/dL	181 ± 35	184 ± 30	195 ± 40	193 ± 33
Creatinine, mg/dL	12.0 ± 1.8	12.6 ± 2.1	12.6 ± 2.9	12.8 ± 2.8
Urate, mg/dL	7.0 ± 0.6	7.2 ± 0.7	7.3 ± 0.5	7.1 ± 0.5

CONCLUSIONS

From the long-term results of this multicenter trial, certain conclusions on the role that HP may play in the treatment of chronic uremic patients can reasonably be drawn.

The safety of repeated use of HP is now established, in view of the established improved biocompatibility of the coating membranes. Owing to its intrinsic limits, HP may act as an adjunct rather than an alternative to HD, and its use can be envisaged in chronic uremic patients on artificial substitutive therapy carried out according to standard programs. Rehabilitation in patients on combined HD/HP may benefit from a double point of view: clinical and logistic.

Clinical Rehabilitation

In the presence of residual clinical signs of uremia despite technically adequate dialysis, HP therapy may be of real value. If one of the 3 weekly HD sessions is replaced by 1 of combined HD/HP, better clinical results are very likely to take place thanks to the enhanced removal of toxins and generally require no more than 1–3 months. The cycle may be repeated whenever clinically required. In this patient population the cost–benefit and cost–effectiveness ratios are difficult to establish, owing to the unpredictable length of the combined program.

Logistic Rehabilitation

In clinically and technically adequate dialysis, a combined HD/HP program is logistically promising for both the patient (social and family environment) and the Dialysis Centre (enhanced capacity). It affords an actual 30% saving in time of weekly treatment without modifying the patient's clinical and metabolic conditions.

Whether these last results are to be explained solely in terms of enhanced removal of toxins, or also in terms of other mechanisms (like a lower protein catabolic rate) still requires clearer definition. Compared to HD alone, the overall yearly increase in cost of combined HD/HP is 30%.

But the true cost–benefit and cost–effectiveness values still need further study, above all with regard to the modified logistic realities.

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