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Membranes, technologies and long-term results in chronic haemodialysis

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Introduction

The ability to keep patients alive by artificial replacement of lost internal organ function is one of the outstanding achievements of modern medicine. In the case of chronic haemodialysis, however, this highly beneficial result is obtained by a set of procedures that are substantially negative in their effect [1].

If this basic assumption that an excellent clinical result is obtained by a clinical repetition of unbiological events is correct, it should be no less true that a large number of factors may jointly affect the long-term results of haemodialysis therapy (Figure 1). Some factors concern the patient, others the biomaterials used in blood purification, the techniques applied and the so-called 'ancillary' therapy (e.g. erythropoietin); yet others are non-medical factors, but are of tangible, constant importance, such as the cost of treatment.

Among technological factors, in recent years a great deal of attention has been paid to the role of membrane composition (cellulose, modified cellulose or synthetic) and to the techniques used in chronic dialysis, based on diffusion, convection or diffusion plus convection (Figure 2). In addition, the strict link and reciprocal interaction between efficiency and biocompatibility of the haemopurification procedure cannot be overlooked. The patient cannot be separated from the device and its components [2].

Role of membranes and technologies

Much work has been aimed at highlighting the different results achieved with cellulose-based or synthetic membranes and, likewise, different dialysis methodologies. The conclusions reached by the various studies are far from unanimous and are often markedly discordant. Many parameters have been taken into account for

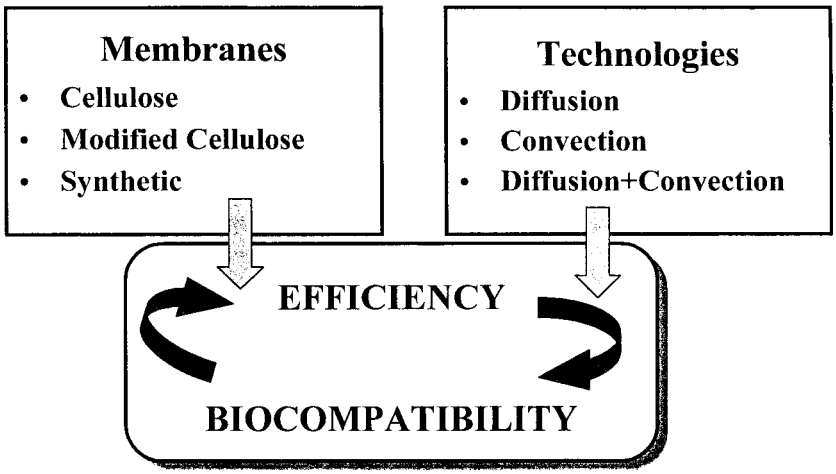

Fig. 1. Long-term results in renal dialysis therapy: relationship between membranes, technologies, efficiency and biocompatibility.

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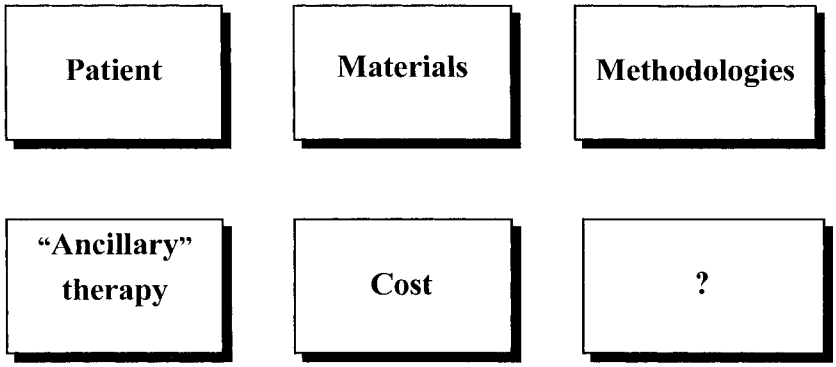

Fig. 2. Factors affecting renal dialysis therapy results.

comparative evaluation: firstly survival, then various forms of morbidity, nutritional status, metabolic alterations, hospitalization time, etc. Some authors have shown evidence in favour of better results being obtained by the use of synthetic rather than cellulose-based membranes; others have demonstrated that there are no major or even significant differences.

Bonomini *et al.* [3], in a study involving 122 highly selected and homogeneous patients (64 treated with cellulose and 58 with synthetic membranes), found no difference in mortality, general morbidity or biological–nutritional factors.

Locatelli *et al.* [4] reported on a multicentre study involving 380 patients, treated with cellulosic and synthetic membranes, and divided into four subgroups according to purification technique: 132 on haemodialysis with cellulosic membranes, 147 on low-flux synthetic membranes, 51 on high-flux synthetic membranes and 50 on haemodiafiltration. No difference was found in mortality, morbidity, dialysis adequacy, tolerance of treatment, nutritional status and incidence of carpal tunnel syndrome (CTS). The only difference found was that the β_2-microglobulin blood levels were lowest among those on haemodiafiltration and those on high-flux synthetic membranes dialysis.

Hakim *et al.* [5] conducted a prospective study including 2410 patients, chosen from a total caseload of >6536 patients, the treatments being with either cellulosic, modified cellulosic or synthetic membranes. The results showed a $>25\%$ lower relative risk of mortality among patients on synthetic or modified cellulosic membranes than those on cellulosic membranes. Koda *et al.* [6] switched patients from conventional (with cellulosic membranes) to high-flux membrane treatment. From this monocentric study, the switch proved to have lowered the mortality risk by $\sim 40\%$ and the incidence of CTS by $\sim 50\%$.

In more recent studies on a large number of patients (6444), Locatelli *et al.* [7] showed an $\sim 40\%$ lower relative risk of CTS among patients on high-flux (synthetic) membranes, while the mortality risk was virtually the same in patient population treated with either cellulosic or synthetic membranes.

In clinical terms, there is thus a great disparity in results, while no pattern of substantial differences distinguishes the results with the various membranes and methods employed.

Opinions and results continue to differ widely when considering less clinical but more biological parameters [8]. Carracedo *et al.* [9] found that cuprophan, but not AN69 membranes, increase the percentage of mononuclear cell death due to apoptosis. The opposite conclusion is reached by Heidenreich *et al.* [10] who found no demonstrable differences in apoptosis of monocytes between patients dialysed with cuprophan and those on a high-flux polysulfone membrane. While studies by our group ascertained feasible platelet-derived growth factor (PDGF) release during and after haemodialysis with cuprophan membrane [11], at the same time no differences emerged in the patterns of PDGF serum levels, whether the dialysis used modified cellulose or polysulfone (Figure 3). Similar findings for DNA synthesis and number of interleukin receptors were obtained [12].

Furthermore, whether on cellulosic or synthetic membranes, the same blood values of homocysteine

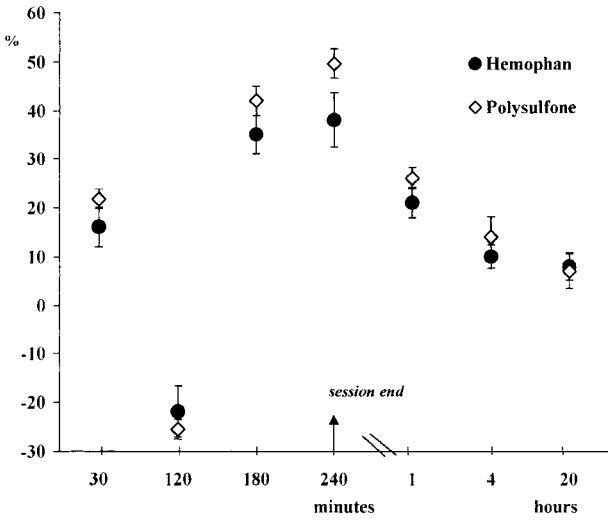

Fig. 3. Platelet-derived growth factor (PDGF) intra-and post-dialytic serum levels with hemophan and polysulfone membranes (from Cianciolo G *et al.*, Intra- and post-dialytic platelet activation and PDGF-AB release: hemophan vs polysulfone membranes submitted for publication).

are found in long-term dialysis patients. Increased homocysteine levels are a concrete risk factor for cardiovascular disease [13], the major cause of death in dialysis patients.

$A\beta_2M$-Amyloidosis

One concrete yardstick for comparing the possible long-term effects of the two categories of membranes is the incidence of β_2-microglobulin amyloidosis ($A\beta_2M$-amyloidosis) in differently treated patients. Once again, the results are conflicting: some authors have found a greater incidence of $A\beta_2M$-amyloidosis in patients treated with cellulosic membranes than in those with synthetic membranes [7,14,15]; others found no significant differences [16–18].

In a previous study [19], our group reported no differences between patients dialysed long-term with cellulosic *vs* synthetic membranes in terms of incidence of CTS. That study took the need for surgery as the only parameter for comparing the presence of $A\beta_2M$-amyloidosis between the two groups of patients. Though the parameter is a valid one, it is a rather late index of $A\beta_2M$-amyloidosis because the damage is already done. This led us to a more detailed analysis of our case material. A limited group of patients was identified in whom the presence of $A\beta_2M$-amyloidosis could be detected not only by the need for CTS surgery but also through serial, systematic clinical evaluations, as well as by imaging techniques such as X-ray, computerized tomography (CT) and nuclear magnetic resonance (NMR). The number of patients included in the study was 51; 24 patients had always been on treatment with cellulosic membranes (95.4 ± 13.0 months), and 27 patients with synthetic membranes (96.3 ± 11 months).

The results of this study [20] show no difference in amyloidosis incidence, progression or clinical course between patients on cellulose or synthetic membranes. No differences in the number of patients with CTS requiring surgery or an amyloidosis diagnosed by CT or NMR investigations could be demonstrated (Table 1).

It would therefore seem reasonable to think that in the emergence of certain typical long-term renal dialysis therapy pathologies (and amyloid is a 'king' among these), the membrane type does not play a decisive role in the onset or non-onset of the process. Probably the membrane effect is masked by other factors such as, for example, the duration of dialysis treatment and the patient's age at the time of starting dialysis.

Table 1. Signs of the presence of Aβ2M-amyloidosis in long-term renal dialysis therapy patients treated with cellulosic or synthetic membranes

	Cellulosic $n=24$	Synthetic $n=27$
Osteoarticular pathology score	1.5 ± 1.2	1.4 ± 1.1
Imaging (% positivity)		
Rx	12.5	11.1
CT	20.8	22.2
NMR	28.6	31.8
CTS surgery	12.5%	14.8%

The study by van Ypersele and co-workers [21] shows that amyloid may appear right from the early months of dialysis treatment (the sterno-clavicular articulation being the prime site), while the incidence increases in patients as the years of dialysis go by, reaching 100% after 13–15 years, regardless of the mode of treatment or membrane used.

Further doubts as to the existence of any casual connection between the nature of the membrane used and the incidence of amyloidosis stem from two painstaking, well-documented papers. Chary-Valckenaere *et al.* [22] performed a prospective study, monitoring for amyloid by histological staining on portions of tissue removed from chronic dialysis patients who had undergone CTS surgery (41 samples from 30 patients). Biocompatible synthetic membranes were used in most patients included in the study. The authors conclude that all subjects who had been receiving dialysis treatment for $\geqslant 15$ years had amyloid deposits, whereas no deposits were observed in patients who had been dialysed for $\leqslant 5$ years.

Schwalbe *et al.* [23] claim that in their centre the prevalence and severity of $A\beta_2M$-amyloidosis unexpectedly decreased by $\sim 80\%$ between 1988 and 1996. They conclude that given the relatively short time spent by patients on high-flux haemodialysis, increased β_2-microglobulin removal is unlikely to account for the decrease. According to these authors, other factors, for example dialysate composition and purity, may be involved.

The importance of dialysate purity was raised long ago by Baz *et al.* [24], and recently has been taken up again by Ledebo *et al.* [25]. According to the latter, the effect of using contaminated dialysis fluid is similar to that of using complement-activating cellulosic membranes.

Conclusion

There is no doubt that in the search for improvement of the general results of chronic dialysis (higher survival, lower morbidity, better quality of life), further studies are called for on the relationships between 'technologies' (including membrane type and purification methodologies) and the patient's biological and clinical profile. However, one should not underestimate the role played by clinical patient aspects in the overall treatment: basic factors such as control of blood pressure, achievement of osmotic stability, proper nutritional status, appropriate correction of anaemia and a timely start to chronic dialysis treatment all need our attention [26].

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