Efficacy of choice of dialysis membrane

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Introduction

Despite the large number of papers on the differences in dialysis membrane biocompatibility and flux, the true effect has long been controversial in the clinical setting. However, some recent studies have suggested that the type of dialysis membrane influences patient morbidity and mortality [1–3]. Several prospective trials have provided some evidence that the membrane choice is important in recovery of acute renal failure [4], preservation of residual renal function [5], improvement of nutritional state [6], and prevention of dialysis-related amyloidosis (DRA) [7]. In particular, DRA is a disabling and occasionally life-threatening problem that appears after very long-term dialysis therapy. We once reported, based on 28 years of experience of maintenance dialysis therapy, that high-flux biocompatible membranes (HF-BCM) compared with low-flux bioincompatible membranes (LF-BICM) reduce the risk of DRA and death [1]. Although the evidence is still not conclusive, we would like to emphasize here the role of the dialysis membrane and dialysate purity in patients on long-term dialysis therapy.

Risk factors of DRA and dialysis membrane

There are several reports indicating that DRA is linked to some clinical factors (Table 1). Age and dialysis duration are the most distinct and well recognized risk factors [1,2]. The correlation between years at carpal tunnel syndrome (CTS) surgery due to DRA and age at initiation of dialysis is shown in Figure 1. It clearly indicates that age is a key risk factor and also suggests that patients > 40 years of age will receive a CTS operation within 15 years of initiation of haemodialysis.

Next comes the dialysis membrane character, i.e. biocompatibility and flux (permeability). LF-BICM, as well as patient age, is suspected to predispose patients to DRA [1,2,7]. We compared the clinical outcome of 819 patients who had received dialysis in a single centre over a 25-year period in relation to the dialysis membrane employed [1]. Adjusted major risk factors were patient age, calendar year at initiation of dialysis, gender, cause of renal failure and type of dialysis membrane (high-flux or low-flux). Membrane type was defined by β2-microglobulin (β2m) removal capacity, and not by nature of the membrane itself. Multivariate analysis of all risk factors indicates that age and membrane type are the only two important statistically significant risk factors for CTS surgery. The relative risk of CTS was reduced to 0.503 by high-flux membranes compared with conventional low-flux membranes (Figure 2). These results are very similar to previous results obtained by Van Ypersele et al. [2] and Kuchle et al. [7].

The major concern of high-flux membranes has been the allowance of significant backfiltration (in-flow) of dialysate contaminated with endotoxins into the blood stream. The dialysate purity has been found to play a role in the development of DRA [8]. Correspondingly, in our study [1,8], dialysate made from reverse osmosis (RO) water has been ultrafiltered by a filter able to remove endotoxin, soon after starting with a high-flux membrane (Figure 3). Mean dialysate endotoxin level remained <20 pg/ml [9] and dialysers were never reused. The results we obtained suggests that the purity of dialysate should be assured if a high-flux membrane is employed. If the membrane is important, dialysate purity must also be important.

What should we expect of a dialysis membrane?

The clinical impact of the membrane has been reported previously as resulting in improvement in dyslipidemia [10], a modification of nutritional state [6], preservation of the residual renal function [5] and less infection [3]. The pathophysiology, linking the membrane to these specific effects, is still incompletely known. The effects might come from better membrane biocompatibility and flux, i.e. less activation of complement or blood cells, and/or from better elimination of large molecular weight uraemic toxins.

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Consequently, a lower mortality rate in patients on HF-BCM therapy has been observed in some recent studies [1,3,11–14]. Survival is in general accepted to be the most paramount end-point in every clinical study. One of the most striking observations in our study is the marked influence of the membrane on patient survival [1]. Our analysis revealed that the relative risk was reduced to 0.613 by HF-BCM. As mortality is a total result of many complicating and confounding factors, the relative risk reduction is highly variable among the studies. The funnel diagram shown in Figure 4 suggests the need for more reports with a large sample size in order to know the real value of this relative risk reduction of mortality.

In contrast to these results, Charra et al. have reported the best long-term survival data in the world [15]. This outstanding survival was attributed to long hours of dialysis and a high $K_d/V$ with excellent blood pressure control. It is interesting to note that a complement-activating membrane and acetate dialysate were used exclusively in that patient cohort. This suggests that the type of membrane is less important than the dose of dialysis. However, a comparison of Charra’s cohort with ours by Kaplan–Meier analysis reveals that the survival rate after 15 years is superior in our cohort after switching to treatment by HF-BCM and

<table>
<thead>
<tr>
<th>Table 1. Risk factors of dialysis-related amyloidosis (DRA)</th>
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<tr>
<td>Association with clinical DRA symptoms</td>
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<tr>
<td>Age &gt;40 years</td>
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<tr>
<td>Dialysis duration &gt;10 years</td>
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<tr>
<td>Bioincompatible membrane (unmodified cellulose)</td>
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<tr>
<td>Low-flux membrane</td>
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<tr>
<td>Contaminated dialysate</td>
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<td>Apolipoprotein e4</td>
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![Graph](image1.png)

Fig. 1. Years up to CTS surgery and age at dialysis initiation.

![Graph](image2.png)

Fig. 2. Significant relative risk reduction for carpal tunnel syndrome.
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Fig. 3. Frequency of patients on high-flux membrane and the use of ultrafiltered dialysate.

Fig. 4. Funnel diagram of relative risk of death in patients treated on high-flux biocompatible membrane compared with on low-flux biocompatible membrane. Each number indicates cited reference. (□: statistically significant; □: n.s.)

ultrapure dialysate [16]. This suggests that HF-BCM has a role in preventing life-threatening complications, occurring specifically after long-term dialysis.

Quality of the proof

A prospective randomized control study is the most reliable method to reach a true conclusion, but will not always be possible from an ethical point of view. A series of experimental evidence on biocompatibility and flux of larger molecules has already suggested that HF-BCM is a preferable means of dialysis treatment to prevent comorbid conditions. Under such circumstances, our policy as dialysis physicians should be based on the following principle: the possibility of dispersing hazardous effects by low quality therapy should be considered serious and a negative conclusion should not be drawn with insufficient evidence.

Choice of dialysis membrane

In the early 1970s, the membrane properties required were mostly better solute diffusion and water removal. However, from the late 1980s to the current time, the emphasis has been on adsorption, biocompatibility, large molecule flux and convective transport. The use of an HF-BCM has steadily increased since the discovery of DRA in 1985, with a subsequent better understanding of the complex nature of the blood–membrane interaction.

Although the mechanisms are still debated, the dialysis membrane is clearly one of the key modifiable components in dialysis practice and is increasingly considered a determinant of clinical outcome. At present, the choice of dialysis membrane should be based on clinical outcome (Figure 5).

Conclusion

The dialysis membrane is no longer seen as a simple semi-permeable barrier for solutes and water, but is considered an important interface with the patients' blood and, subsequently, as an outcome predictor. HF-BCM dialysis with the use of ultrapure dialysate will delay the onset of DRA and prolong patients' survival. Since there is no perfect curative therapy for DRA, this preventive strategy will be of benefit to the patients and should be the first priority, especially for people who have to continue on dialysis for >15 years.
Fig. 5. Considerations in membrane choice.

References