Impact of the type of dialyser on the clinical outcome in chronic haemodialysis patients: does it really matter?

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Introduction

Despite the relative efficiency of modern equipment, haemodialysis (HD) remains inferior to normal kidney function for several reasons. First of all, HD treatment results in a weekly clearance of small molecular weight substances of only 10–15 ml/min, as compared with 90–120 ml/min for normal kidneys. Secondly, so-called ‘middle molecules’ (MMs) as well as some larger peptides, which are normally excreted or metabolized by the healthy kidney, are cleared inadequately and will therefore accumulate in chronic HD (CHD) patients. Thirdly, various undesirable interactions, including both short- and long-term side effects—termed bio(in)-compatibility—may occur between the living organism and the extracorporeal circuit (ECC) [1].

In the last decades, a variety of new dialysers, differing in design, material, membrane surface area and permeability, have been developed. Very recently, one of the world’s largest companies involved in the production and development of dialysers replaced its total set of low-flux (LF) dialysers by a new one with better urea clearances and higher ultrafiltration (UF) coefficients. Actually, these new devices do not fulfil the criteria for LF (UF < 10 ml/mmHg/h), but must be considered medium flux (UF 10–20 ml/mmHg/h). However, today there is no general agreement as to whether the use of dialysers with an increased urea removal and/or a higher UF rate is associated with a better clinical course. In fact, cardiovascular disease (CVD) is already observed in the pre-dialysis phase and is the major cause of death in end-stage renal disease (ESRD) [2]. Dialysis patients suffer from atherosclerotic complications at a relatively young age and die relatively young from ischaemic heart disease [3]. Therefore, it is conceivable that individual patient factors, such as the burden of CVD, greatly surpass the influence of the dialysis equipment in this respect. In this review, we will first discuss various aspects of the dialyser which have been associated with the clinical outcome in CHD patients. Besides the type of membrane, various aspects of bio(in)compatibility and solute mass transport are discussed. Thereafter, we will summarize the influence of the type of dialyser on a number of indirect parameters for CVD, including several biochemical and functional tests. Finally, we will review critically the relevant literature to determine whether the choice of the dialyser contributes to the life expectancy of patients with ESRD.

Dialysers

In the early days of HD, unsubstituted cellulose (UC) membranes with small pore size and large thickness were used. The dialysers were characterized by a relatively inefficient small solute removal and various side effects, including a high degree of complement activation. In the past decades, several improvements in membrane manufacturing have taken place. In the case of cellulose membranes, complement-activating hydroxyl groups have been replaced by other moieties. In addition, a wide variety of synthetic dialysers have been produced, differing in material [polysulfone (PS), polyamide, polyacrylonitrile (PAN) and polymethylmethacrylate (PMMA)], surface area, membrane thickness, pore size, pore distribution, pore number and membrane structure/symmetry. For a recent comment on the different types of membranes, see Bouré and Vanholder [4].

With respect to the influence of the type of dialysers on the clinical outcome of CHD patients, considerable controversy exists on the impact of bio(in)compatibility and solute mass transport, the latter often represented...
by the flux characteristics of the membrane (UF coefficient in ml/mmHg/h), which actually reflects the permeability for water. For convenience, in this overview, we will consider the many different dialysers either biocompatible [modified cellulose (MC) and synthetic membranes (S)] or bioincompatible [UC, and either LF or high flux (HF)].

Bio(in)compatibility

During HD, various undesirable side effects occur between the ECC and the living organism. The sum of these specific interactions has been termed bio(in)compatibility. Depending on the type of dialyser used, blood–membrane contact results in the generation of the complement activation products C3a and C5a, which elicit important physiological reactions, such as changes in the expression of adhesion molecules on peripheral blood mononuclear cells (PBMCs) and polymorphonuclear cells (PMNs) [1]. By virtue of these changes, these cells adhere to the vasculature of the lungs, leading to a transient leukopenia [5]. Another feature of PMN activation is degranulation. Release of intracellular products in response to specific inflammatory stimuli is essential for host defence. Interestingly, during HD with citrate instead of heparin anticoagulation, release of the degranulation product myeloperoxidase, which has been associated with the oxidative stress and catabolic state that is commonly observed in CHD patients, was virtually absent [6]. As mentioned, PBMCs are also stimulated during HD, resulting in the secretion of a variety of proinflammatory cytokines, including interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF-α) [7]. With respect to platelets, both the dialyser and the roller-pump have been implicated in the release of substances that induce a pro-thrombotic state in humans [8] and hypotension in rats [9]. As for blood coagulation, recently we reported on an early decrease in factor XII activity, a steep transient increase in thrombin–antithrombin complexes and a sustained rise of both the prothrombin fragments 1 and 2 and thrombus precursor protein during HD with PAN membranes [10]. In addition, fibrinogen was elevated in the majority of the patients. These findings are in line with other reports [11] suggesting that during a single HD treatment a hypercoagulable state is induced in the efferent line of the ECC. As a consequence, both activated blood cells and reactive protein products enter the systemic circulation of the patients and may harm the endothelial lining of blood vessels.

Solute mass transport

Although urea itself is not very toxic, it serves as a marker for accumulated small molecular weight toxins. The normalized urea clearance per dialysis (Kt/V urea) can be used to compare treatments among patients and to set standards for adequacy. Since its first description some 20 years ago, in various studies it was found that Kt/V urea is an important predictor of both morbidity and mortality in CHD patients [12]. However, not only small molecular weight solutes, but also various large uraemic substances accumulate in ESRD patients. Approximately two decades ago, the ‘middle molecule hypothesis’ was formulated, suggesting that substances with a molecular weight between 0.5 and 2 kDa are important uraemic toxins [13]. More recently, low molecular weight peptides (1–50 kDa) have been recognized as a distinct class of uraemic toxins [14]. As for both MC and synthetic materials, several studies have indicated that HF compares favourably with LF with respect to the removal of higher molecular weight compounds, such as β2-microglobulin (β2M) [15], advanced glycation end-products (AGEs) [16] and leptin [17]. Moreover, after HD with HF devices, promising data were published on lipids [18], plasma homocysteine concentrations [19], quality of life, nutrition [15], inflammation [20], amyloidosis [21], preservation of renal function [22], CVD and mortality [23]. Several of these aspects will be discussed in greater detail in the section on clinical data.

Markers of endothelial dysfunction and cardiovascular disease

Vascular endothelial cell surface markers, such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and E-selectin (E-selectin), and von Willebrand factor (vWF) are thought to be involved in the pathogenesis of atherosclerosis through their actions on leukocyte activation, adhesion, migration and smooth muscle cell proliferation. In ESRD patients, soluble adhesion molecules (SAMs), such as sICAM-1, sVCAM-1 and sE-selectin, and vWF have been linked to inflammation [24], whereas in non-renal patients a correlation was found with atherosclerosis of the carotid artery and future coronary heart disease [25]. With respect to SAMs and vWF, in uncontrolled studies, no change [26], an increase [27] and a decrease [28] have been observed during a single HD session. Recently, we analysed the influence of four types of dialysers (UC, LF PS, HF PS and super-flux polyethersulfon) on these molecules in a crossover, randomized prospective study in 15 stable CHD patients. In line with previous reports, baseline levels of SAMs and vWF appeared to be twice as high as in healthy controls [27]. However, none of the dialysers induced marked changes over a 4 week period, suggesting that the type of dialyser does not substantially contribute to the elevated baseline levels and hence the degree of endothelial activation [29]. Of interest, the inter-individual variability (on average 80%) was far greater than the changes induced by the different dialysers in the same patient (on average 1%). Therefore, from this study, it appears that elevated levels of vascular cell surface molecules in
CHD patients depend on individual patient characteristics rather than the type of dialyser applied. Functionally, endothelial (dys)function can be estimated by measuring flow-mediated dilatation (FMD) of the brachial artery during reactive hyperaemia. In non-renal patients, an impaired FMD response has been related to future cardiovascular events [30]. In ESRD patients, who were compared with a group of age- and sex-matched controls, the FMD response was impaired and correlated with the duration of dialysis and the carotid intima media thickness (cIMT) [31]. With respect to the influence of a single HD treatment on FMD, an impaired response was seen after HD with (UC) devices [32], whereas no effect [33] or an improvement was noted after HD with both vitamin E-coated cellulose [32] and MC [34]. As mentioned, CVD is the most frequent complication and major cause of mortality in ERSD, accounting for more than half of all deaths [2]. Not only in individuals without renal diseases, but also in dialysis patients, various structural and functional markers of vessel wall properties, such as the cIMT, left ventricular mass index (LVMi) and pulse wave velocity (PWV), showed a high predictive power of future cardiovascular events [35–37]. However, as yet it is unknown whether the bio(in)compatibility and/or flux characteristics of the different dialysers influence these parameters.

### Table 1. Overview of clinical studies quoted in the text

<table>
<thead>
<tr>
<th>Author [reference]</th>
<th>Clinical end-point</th>
<th>n</th>
<th>Level of evidence</th>
<th>Membranes studied</th>
<th>Unfavourable outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanholder [44]</td>
<td>Infection</td>
<td>15</td>
<td>B</td>
<td>UC/PS HF/PMMA LF</td>
<td>UC</td>
</tr>
<tr>
<td>Parker [41]</td>
<td>Nutrition</td>
<td>159</td>
<td>A2</td>
<td>UC/PMMA LF</td>
<td>UC</td>
</tr>
<tr>
<td>Rocco [56]</td>
<td>Nutrition</td>
<td>1846</td>
<td>A2</td>
<td>PS LF/CA LF/PS HF/CTA HF</td>
<td>LF = HF (MC and S)</td>
</tr>
<tr>
<td>Caramelo [38]</td>
<td>Residual renal function</td>
<td>22</td>
<td>B</td>
<td>UC vs PS HF/PAN HF</td>
<td>UC=PS HF/PAN HF</td>
</tr>
<tr>
<td>Schiffl [21]</td>
<td>DRA</td>
<td>89</td>
<td>B</td>
<td>UC/LF (PMMA LF/PS LF)/HF (PMMA HF/PS HF/PAN HF)</td>
<td>UC (LF intermediate)</td>
</tr>
<tr>
<td>Schwalbe [42]</td>
<td>DRA (CTS)</td>
<td>239</td>
<td>B</td>
<td>UC/PS HF/PS LF/PAN HF/PA HF</td>
<td>UC</td>
</tr>
<tr>
<td>van Ypersele [43]</td>
<td>DRA (CTS)</td>
<td>221</td>
<td>B</td>
<td>UC/PAN HF</td>
<td>UC</td>
</tr>
<tr>
<td>Kuchle [40]</td>
<td>DRA (CTS)</td>
<td>24</td>
<td>B</td>
<td>UC/PS HF</td>
<td>UC</td>
</tr>
<tr>
<td>Bonominii [49]</td>
<td>Mortality, CTS, infection</td>
<td>128</td>
<td>B</td>
<td>UC/CA/CTA/PAN/PS/PMMA</td>
<td>UC</td>
</tr>
<tr>
<td>Koda [52]</td>
<td>Mortality, CTS</td>
<td>819</td>
<td>B</td>
<td>UC/PMMA HF/PS HF/CTA HF/PAN</td>
<td>UC</td>
</tr>
<tr>
<td>Hakim [50]</td>
<td>Mortality</td>
<td>2410</td>
<td>B</td>
<td>UC/MC/S</td>
<td>UC</td>
</tr>
<tr>
<td>Bloembergen [23]</td>
<td>Mortality</td>
<td>4084</td>
<td>B</td>
<td>UC/MC/S</td>
<td>UC</td>
</tr>
<tr>
<td>Wright [53]</td>
<td>Mortality</td>
<td>521</td>
<td>B</td>
<td>UC/PS HF/PS LF</td>
<td>UC</td>
</tr>
<tr>
<td>Horbenker [51]</td>
<td>Mortality</td>
<td>253</td>
<td>B</td>
<td>UC/PS HF</td>
<td>UC</td>
</tr>
<tr>
<td>Eknoyan [54]</td>
<td>Mortality</td>
<td>1846</td>
<td>A2</td>
<td>PS LF/CA LF/PS HF/CTA HF</td>
<td>LF = HF (MC and S)</td>
</tr>
<tr>
<td>Woods [48]</td>
<td>Mortality</td>
<td>715</td>
<td>B</td>
<td>PS LF/PS HF</td>
<td>LF</td>
</tr>
<tr>
<td>Port [47]</td>
<td>Mortality</td>
<td>12791</td>
<td>B</td>
<td>S HF/LF; MC HF/LF UC</td>
<td>LF (only in bleach reuse group; no-reuse: UC = MC = S)</td>
</tr>
</tbody>
</table>

The level of evidence is indicated according to the following classification: A1, meta-analysis, including at least two A2 investigations; A2, randomized controlled trial of good quality and sufficient size; B, other randomized and non-randomized comparative trials (cohort studies, case-control studies); C, non-comparative investigations; D, expert opinion.

DRA = dialysis-related amyloidosis; CTS = carpal tunnel syndrome; UC = unmodified cellulose; MC = modified cellulose; S = synthetic; PS = polysulfon; PAN = polyacrylonitrile; CA = cellulose acetate; CDA = cellulose diacetate; CTA = cellulose tricetate; PMMA = polymethylmethacrylate; LF = low flux; HF = high flux; MM = middle molecule.

### Clinical data

Based on the aforementioned data, it seems reasonable to assume that the type of dialyser plays an important role in both the morbidity and mortality of ESRD patients. In the last two decades, several investigations have evaluated the influence of the type of dialyser on a number of clinical parameters, such as infections, dialysis-related amyloidosis (DRA), quality of life (QoL) and mortality. However, there are several constraints for most of these studies. First, retrospective or ‘historical prospective’ studies, which constitute the major part of the investigations cited in Table 1, are hampered by the lack of assignment of patients to different dialysers, making it difficult to draw inferences on causal mechanisms. Secondly, conflicting results in the various multicentre studies could also be caused by dissimilar reuse practices at different facilities and inconsistencies in the reuse agents employed. Thirdly, in many publications, data are not readily apparent on critical information, such as the dialysis dose, dialyser specification, quality of dialysate, length of follow-up and co-morbidity, which could explain or contribute to differences in the observed patient morbidity and mortality. Of the various studies cited in Table 1, 14 are retrospective analyses, whereas only six were conducted according
to a prospective design. Of the latter, two were too small to meet the criteria for evidence level A2 (see footnotes of Table 1). Hence, out of 20 publications, 16 are classified evidence level B.

As indicated in Table 1, most of these investigations showed either no difference or an unfavourable outcome in infection rate. DRA, carpal tunnel syndrome, nutritional status, treatment tolerance and QoL in patients treated with UC dialysers, if compared with biocompatible (MC and S) devices (Table 1) [1,45]. None of these publications convincingly showed that HF is beneficial over LF in the case of MC and synthetic membranes. Thus, with respect to the various clinical aspects of the uraemic syndrome analysed, only the use of bioincompatible UC appears to be correlated with an unfavourable outcome. Regarding mortality, three [46–48] out of nine [23,46–53] retrospective analyses suggested superiority of HF over LF. However, in the analysis by Leypoldt et al. [46], mortality was not correlated with the type of dialysers, but with the estimated MM removal based on in vitro data of the devices. From this study, it appeared that use of a dialysers with high calculated MM removal rates was associated with a reduced risk of mortality. However, in this analysis, using data from the 1991 Case Mix Adequacy Study of the United States Renal Data System [50], no differentiation was made between UC, MC or LF. Hence, as low MM removal is a characteristic feature of UC, which was used by approximately two-thirds of the patients, the high mortality rate in this group may also be explained by the use of bioincompatible UC. With respect to the study by Woods et al. [48] comparing HF PS with LF PS, the probability of survival was notably higher in the former modality. However, in a Cox proportional hazard model, flux failed to reach significance as a predictor of mortality after adjustment for patient demographics, comorbidity and Kt/V. According to the authors, the low mortality rate in the HF group was surprising as this group comprised a higher proportion of high risk patients. However, as only 7% of the patients in the HF group received a renal transplant, against 29% in the LF group, and transplantation is generally restricted to persons in good physical shape, the unfavourable outcome in the LF group may also result from the removal of low risk patients by transplantation. In the study by Port et al. [47], the relative risk (RR) for mortality by membrane type (synthetic HF and LF, MC and UC) was calculated in both reuse (bleach vs no bleach) and no reuse facilities. Hence, eight groups were compared. In reuse facilities, the estimated RR was lowest in the group using bleach and synthetic HF dialysers. Comparing the four groups using bleach, synthetic HF was only significantly different from UC. From a separate analysis on synthetic membranes, it appeared that treatment with synthetic HF dialysers, in particular if reused with bleach, was significantly different from LF. In non-reuse facilities, differences were not observed between any of the four modalities. From this rather complicated analysis, it was concluded that reuse with bleach resulted in a superior survival in patients who were treated with synthetic HF devices, possibly due to an increased permeability and clearance of larger molecules. The remaining six [23,49–53] retrospective studies on mortality showed either no difference or superiority of MC and S over UC, which is, in fact, similar to the aforementioned data on morbidity.

So far, the available evidence suggests that at least bioincompatibility and possibly transport characteristics influence the clinical outcome in CHD patients. The only randomized prospective trial sufficiently powered to detect the effect of both Kt/V and flux on clinical end-points, such as mortality and CVD, i.e. the HEMO study [54], failed to document the superiority of HF over LF (MC and S). In fact, it appeared that neither a higher Kt/Varea than recommended by current guidelines, nor the use of HF membranes had any influence on the primary outcome, defined as death from any cause. Moreover, the main secondary outcomes, as defined by hospitalizations and albumin levels, did not differ between treatment groups. However, important shortcomings, such as relatively short treatment times, the inclusion of prevalent patients and frequent reuses, may have influenced the outcome of this study considerably. With respect to other pre-defined end-points of the HEMO study, such as QoL [55], nutrition [56] and infections [57], again no differences could be demonstrated between treatment with HF and LF devices (MC and S).

Finally, apart from biocompatibility and flux characteristics, dialysis time—obtained either by prolonging individual HD sessions or by increasing its frequency—has been associated with an improved clinical outcome. In this respect, long slow dialysis provided outstanding results in terms of morbidity and mortality, whereas survival data are not available for short daily or nocturnal HD [58,59]. However, as the latter investigations are non-comparative follow-up studies (evidence level C, see Table 1), these findings require confirmation in a well designed prospective trial.

Conclusions

Based on theoretical grounds and various experimental data, there seems to be no doubt that biocompatible HF membranes are to be preferred over bioincompatible LF devices. There is general agreement that protein and cellular activation should be avoided as much as possible, since it might contribute to the oxidative stress and CV risk in CHD patients. Activation of PBMCs induces the release of pro-inflammatory cytokines, which might contribute to the micro-inflammatory state in this patient group. Moreover, both in vitro and in vivo studies showed that several larger uraemic toxins, such as β2M and AGEs, are better removed by HF than by LF devices. In line with these considerations, a number of historical and prospective studies, comparing UC with MC and various synthetic materials, showed an increased
incidence in infections, malnutrition, amyloidosis, carpal tunnel syndrome and even death in patients treated with the former. However, none of these studies convincingly showed superiority of HF over LF (MC and S) with respect to any of these clinical parameters, despite a superior removal of uraemic toxins, a better lipid profile, less oxidative stress and less inflammation in HF HD. Even a large prospective randomized study could not detect any difference in the clinical course between these two modalities. Therefore, in our opinion, patient-related factors, such as the presence of CVD, outweigh the effects of the type of dialyzer by far. Whether haemodiafiltration, which is characterized by a superior convective transport, results in a lower morbidity and/or mortality than LF HD is currently under investigation in a multicentre study in The Netherlands (Contrast).

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References