Moving beyond small solute clearance; what evidence is there for more permeable dialyzers and haemodiafiltration ?

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Abstract

Dialysers were initially developed for diffusive clearance of uraemic toxins. Diffusion most effectively clears small uncharged solutes from plasma water, such as urea. Sessional urea clearance targets have been shown to be important for short term patient survival, but over the longer term, although low flux dialysis can prolong patient survival, accumulation of middle sized uraemic toxins, such as β2 microglobulin can lead to disabling arthropathy. Although the introduction of high flux dialysers, designed to increase β2 microglobulin clearance, has reduced the prevalence of arthropathy, this has not been translated into a demonstrable significant improvement in patient survival. However, analysis of individual patients recruited into trials of haemo-diafiltration reported that greater convective clearance was associated with better survival, although the individual trials reported mixed outcomes. Most haemodiafiltration trials were not designed to study the effect of convective dose, so although reported patient survival was greater for those receiving greater convective volume exchange, these results could potentially be confounded by patient or centre effects. An alternative approach to increasing middle sized solute clearances would be to use more permeable dialyzers, but as yet there are no trials reporting survival with larger cut-off dialysers. As such, although there is increasing evidence that increasing middle sized molecular uraemic solute clearance is associated with improved patient survival, further prospective trials are required to determine whether as with Kt/Vurea there is

a threshold effect of how much convective or middle sized solute clearance is required to improve patient survival.

Introduction

Haemodialysis is a well-established treatment for patients with chronic kidney disease. Initially all dialyzer membranes were low-flux which allowed solute clearance by diffusion. Urea, a by-product of protein turnover, accumulates in kidney failure patients, and being a relatively small uncharged molecule free in plasma water is readily cleared by diffusion. The National Co-operate Dialysis Study demonstrated that a minimum amount of dialysis sessional urea clearance was required to maintain health over 12 months [1]. This was described as Kt/Vurea to allow for comparison between different sized patients, and subsequently the sessional target was increased from 1.0 to 1.2 by consensus. Later trials, such as the Haemodialysis trial (HEMO study) did not demonstrate any significant overall survival advantage for greater dialyser sessional urea clearance [2]. However, although some dialysis centres, such as Tassin in France, reported impressive patient survival with low-flux dialysis, after 10 years they noted that their patients were at greater risk of developing carpal tunnel compression and arthropathy [3]. These complications were associated with the deposition of β2-micrglobulin (β2M) [4].

High-flux haemodialysis

Loss of kidney function leads to the accumulation of compounds which are normally filtered by the glomerulus and then reabsorbed into the proximal tubular cells and degraded. As such, the serum concentrations of many inflammatory mediators and hormones increase in the dialysis patient. Traditional low flux dialysis does not adequately clear middle sized uraemic toxins, defined as a molecular weight > 500 Daltons, and as such these accumulate in dialysis patients (table 1). Dialyzer flux is currently defined by β2M clearance, with increasing clearance from low to mid to high-flux, with high flux dialysers having a β2M sieving coefficient of > 0.6 [5]. As such dialyser flux is independent of membrane composition [6]. Although synthetic high flux membranes were developed in the 1980s, due to cost differentials, only a small proportion of patients were initially treated with these dialysers. The use of high-flux dialysers was reported to reduce the incidence of carpal tunnel neuropathy and arthropathy associated with β2M deposition in observational reports [7]. Despite the reduction in the long-term complications of β2M deposition, prospective shorter-term studies of high-flux dialysis did not show an overall survival advantage for treatment with high flux dialysers [2,8]. Although sub-analysis of the HEMO study did suggest a survival advantage with high flux haemodialysis for patients who had been previously dialysed for more than 3.5 years, potentially suggesting an advantage for high flux haemodialysis for those patients who had lost residual renal function [2]. In addition, re-analysis of HEMO study did suggest an association between increasing serum β2M and mortality [9]. However residual renal function is a major determinant

of serum β2M, and preservation of residual renal function is associated with survival A later prospective European trial, the Membrane Permeability Outcome (MPO) study reported that high flux dialysis increased survival for some defined patient groups, namely those with diabetes and reduced serum albumin, [8].

In addition to the increased diffusional clearance of middle molecules (>500 Daltons) from the plasma water, there is also increased convective clearance compared to low flux haemodialysers, not only due to ultrafiltration, but also convective clearance. As, depending upon the hydraulic permeability of the high flux dialyser, there will be a varying amount of internal diafiltration due to the relative differences in hydrostatic pressures at the dialyser inflow and out-flow between the blood and dialysate compartments [10].

Haemodiafiltration

On the assumption that middle sized uraemic solutes contribute to the increased risk of mortality for dialysis patients, then there has been a strive to increase larger solute clearance. As the trials of high-flux dialysis did not demonstrate a substantial survival benefit, there has been increased interest in the additional convective clearance obtained with haemodiafiltration. There have been a number of trials of haemodiafiltration, and although haemodiafiltration reduced the risk of intra-dialytic hypotension, most of the trials did not shown any survival benefit [11-13]. However, these trials were not designed to determine whether the amount of convective clearance was important. As there is a variable amount of internal diafiltration with high-flux

dialysis, then re-analysis of these trials showed a survival advantage for those patients who had received the greatest dose of convective clearance. This concept was supported by one prospective trial of high volume on-line haemodiafiltration [14], and the individual patient analyses of these trials [15,16]. As such, this would suggest that there may be a survival advantage for the greater convective clearance achieved with higher volume haemodiafiltration. Only one study included patients who could achieve a prespecified amount of convective volume exchange. As such the amount of convective volume exchange in the other studies could have been confounded, as patients who can achieve higher convective volumes may have been generally healthier with better vascular access than those who cannot [17]. Other studies have reported that centre practices may also influence the convection volumes exchanged [18].

To minimise costs, most centres practice post-dilutional on-line haemodiafiltration [19], but this requires faster blood flows to achieve the higher convective target volumes now proposed (Table 2). Different dialysis machine manufacturers use different algorithms to regulate the amount of convection according to the pre- and post-dialyser pressures, as too high a filtration fraction risks haemoconcentration within the dialyser and clotting within the fibre bundle. Although haemodiafiltration requires a high flux dialyser, high flux dialysers differ in hydraulic permeability and design. To allow for the removal of large volumes of plasma water, hydraulic permeability is important. However, as the hydrostatic pressure in the blood compartment falls

with increasing distance from the blood inlet, there will come a point when the relative pressures in blood and dialysate compartments are similar and no net convection takes place, and distally greater pressure in the dialysate compartment will lead to dialysate entering the blood compartment. Whereas greater surface area is important to increase diffusional losses, the length of the dialyser designed for haemodiafiltration should be shorter compared to that designed for diffusion, so that convective clearance occurs all along the fibre length. Similarly, whereas dialysers designed for diffusion traditionally have very narrow internal fibre diameters to minimise the distance for diffusion, designed to increase diffusive clearance, narrow diameter fibres potentially increase the risk of haemoconcentration and clotting when used for haemodiafiltration. So, high flux dialysers designed for haemodiafiltration have wider internal diameter fibres [20].

In paediatric practice, blood flows are generally much slower than in adult practice, and as such pre-dilutional haemodiafiltration is the more commonly performed. Pre-dilution reduces haemoconcentration, and although in theory would allow greater convective clearances, in clinical practice the removal of larger solutes such as alpha-1 macroglobulin do not differ between pre- and post-dilution modes, due to increased membrane adsorption with the post-dilution mode. Pre-dilution mode requires greater exchange volumes, and as such mid-dilution dialyzers have been developed to try and obtain some of the benefits of pre-dilution, but without using very large volumes of dialysate.

As large volumes of dialysate are directly infused into patients during haemodiafiltration, then ultra-pure dialysis water is required. In theory, ultra-pure water should be used for high flux haemodialysis due to the possibility of internal diafiltration with some dialysate passing into the blood compartment of the dialyser. These large volumes of dialysate passing directly into the patient's blood stream increase cooling during the treatment session, and it has been argued that the benefits reported with haemodiafiltration may be due to the additional cooling and cardiovascular stability, rather than any increased middle sized solute clearance [21]

Increased permeability dialysers

An alternative approach to haemodiafiltration is to use a dialyzer with enhanced permeability to middle sized solutes. This potentially has advantages over haemodiafiltration, in that the dialysis machine does not require an additional pump for the re-infusion fluid, and may not need the strict volumetric control to cope with the large volumes of fluid exchanged during haemodiafiltration, and the additional cost of the re-infusion line [22]. A series of larger pore size superflux diaysers were developed for the intensive care setting, designed to increase the removal of cytokines and other inflammatory mediators [23]. However, these membranes also led to a greater loss of albumin compared to high flux dialysers, and so a new generation of what have been termed medium-cut off dialysers have now been developed, which allow similar or even increased removal of middle sized solutes compared to

haemodiafiltration, but without an increased albumin loss [24]. These dialysers have only been recently introduced into clinical practice, and as yet there are no prospective studies to determine whether these offer a survival advantage.

Solute Adsorption

Although haemodiafiltration and medium-cut off dialysers increase the removal of water soluble middle sized uraemic toxins they do not increase the clearance of protein bound uraemic toxins. Some of the more hydrophobic polymers used to manufacture dialysers, such as polymethylmethacrylate (PMMA) have an affinity to adsorb proteins, and although this may increase the clearance of protein bound solutes, increasing protein deposition along the dialyser membrane may also reduce diffusional solute clearances [25].

Protein bound solutes can be removed by adsorption. So, an alternative approach has been to create mix-matrix membranes, by coating the dialysate side of standard dialyser fibres with activated carbon or other adsorptive particles. Although these mixed membranes have been shown to increase protein bound solutes in the laboratory, they are currently not commercially available [26]. Sorbent cartridges or monoliths can also be used to effectively remove protein-bound solutes in laboratory studies [25], but again are not currently available for clinical usage.

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Summary

Although some centres have reported substantial patient survival with low-flux haemodialysis, in the longer term although surviving these patients developed problems associated with β2M deposition in and around joints and bones, and visceral deposition. Although high flux haemodialysis reduces the prevalence of complications associated with β2M deposition, studies have failed to demonstrate a significant survival advantage. Increasing middle sized solute clearance by high volume haemodialfiltration appears to improve patient survival, however as most studies were not designed to investigate the effect of convection volume, this potential improvement in survival requires further study. Similarly, there is currently no data on whether increased middle molecule clearance using middle-cut off dialysers improves outcomes. None of these dialysis techniques in current clinical practice effectively clear protein bound solutes, and newer approaches are required to remove these putative toxins in the anuric haemodialysis patient .

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Table 1: Middle sized (> 500 Daltons) solutes that potentially increase in the serum of patients with kidney failure

Adrenomedullin
Advanced glycosylation end-products
Angiogenin
Atrial natriuretic peptide
Basic fibroblast growth factor
β endorphin
β2 microglobulin
Brain natriuretic peptide
Calcitonin gene related peptide
cholecystokinin
Clara cell protein
Complement factor D
Cystatin C
Cytokines (interleukin 1β, interleukin 6, interleukin 18, tumour necrosis factor α
Degranulation inhibiting protein 1
δ Sleep inducing peptide
Des acyl-ghrelin
Endothelin
Guanylin
Homocysteine
Hyaluronic acid
κ Light chains
λ Light chains
Leptin
Methionine enkephalin
Motiline
Neuropeptide Y
Oxalic acid
Oxidised low density lipoprotein
Parathyroid hormone
Resistin
Substance P
Uroguanylin
Vasoactive intestinal peptide
Vasopressin

386 Table 2. Ideal Equipment required for high volume on-line haemodiafiltration
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Site	equipment
Dialysis machine	Pump for replacement solution
	Pre and post dialyser pressure monitoring
	Software to regulate filtration fraction
	Volumetric pump
	Re-infusion line
Dialyser	High flux
	High hydraulic permeability
	Wider internal diameter fibres
Dialysis water	Ultra-filter
	Ultrapure quality

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