New Dialysis Technology, & Biocompatible Materials

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Abstract
        Although haemodialysis is an established treatment for patients with end stage kidney disease sustaining life for more than 2 million patients world-wide, the mortality of dialysis patients remains high, greater than that for some of the more common solid organ cancers. As such the question arises as to whether more efficient clearance of the waste products of metabolism which accumulate would improve outcomes. Recent reports of an association between improved patient survivals with higher volume on-line haemodiafiltration exchanges would support this hypothesis. This has led to both the development of newer dialyser designs based on micro-fluidics using convective clearances to increase middle molecule clearances and also a generation of superflux dialysers designed to remove larger molecular weight azotaemic toxins which have yet to be studied in large randomised prospective clinical trials. However haemodiafiltration and superflux dialysers do not affectively clear protein bound azotaemic toxins, and there is accumulating evidence that some of these toxins increase cardiovascular morbidity and mortality. This has led to resurgence in the interest of developing adsorption devices, using activated carbon technology, and the development of composite dialyser membranes by either adding carbons or other biomaterials to increase adsorption capacity to the standard dialyser.
        Once anaphylactoid reactions were a recognised complication of haemodialysis, however improvements in dialyser membrane bio-incompatibility,

and changing sterilisation techniques have markedly reduced these reactions. Organic chemicals can leach out from the plastics in the blood lines and dialyser and attention is required to adequately rinse the extracorporeal circuit to reduce patient exposure.

Introduction

Advances in dialysis technology have allowed the development of haemodialysis services from a treatment limited to a few patients with acute kidney injury in one or two centres in highly industrialised countries in the 1940s and 1950s, to now a life sustaining treatment for more than two million patients with chronic kidney disease worldwide.

Compared to the original collodion blood tubing and rotating drum dialyzer, the current generation of dialysis machines delivering very effective small solute clearance represent major technological advances in the delivery of dialysis treatments [1]. However despite these technological advances the mortality of haemodialysis patients remains high, greater than that for some of the more common solid organ cancers. On the positive side, there have been advances which have demonstrated benefit to patients, including the introduction of modified and synthetic dialyzers for the treatment of patients with acute kidney injury [2], and high volume on-line haemodiafiltration increasing middle molecule clearances [3].

As such there is a pressing clinical need to improve the delivery of haemodialysis treatments, to reduce reactions to the extracorporeal circuit and improve clearance of azotaemic toxins, to potentially improve patient outcomes.

Improving the design of the extracorporeal circuit

As blood passes through the extracorporeal circuit leukocytes, monocytes and platelets become activated leading to the release of lipid rich microparticles which then accelerate thrombin generation and clotting within the extracorporeal circuit. Activation of inflammatory cells can occur both due to mechanical stress and also bio-incompatibility of the extracorporeal biomaterials. Mechanical stress occurs as blood passes through the vascular access, particularly narrow diameter fistula needles, and dialysis catheters, the blood pump segment which changes shape with greater pre-pump pressures and the dialyzer.

Over time the standard blood pump for dialysis circuits changed from a small three headed peristaltic rotary positive displacement pump to the current two headed rotary pump. Clinical studies using blood flows < 350 ml/min were unable to demonstrate red cell fragmentation, but laboratory studies reported increased haemolysis with blood flows increasing above 300 ml/min with increasing pre-pump pressures of –150 mmHg [4,5]. This mechanical trauma to cells is reduced by using lower pump speeds, but also by redesigning the blood pump. Alternative designs include shuttle pumps which combine rotary and piston design techniques, with two channels allowing fluids of different physical characteristics to be pumped simultaneously, at a half-cycle phase difference,

by alternatively compressing the two chambers [6]. The advantage of this design is that alternating pressure waves across the capillary dialyzer reduces protein deposition on the membrane surface, so improving transfer of larger solutes and middle molecules [7]. Alternative designs to develop smaller more ergonomically efficient blood pumps for dialysis include ripple pump technology, in which a series of fingers are aligned on both sides of the blood tubing, and controlled by a cam mounted on a shaft and oriented at different angles so that they sequentially activate the fingers to propel blood forward [8].

Most fibrin clot is deposited within the dialyzer, as this represents the greatest surface area of the extracorporeal circuit. The choice of anticoagulant plays a key role in preventing clot formation with fibrin and platelet deposition reduced by changing anticoagulation from unfractionated heparin to low molecular weight heparins and then to citrate, however the latter adds complexity and costs to standard haemodialysis treatments. Changes in dialyzer design to improve blood flow velocity in the outer capillary fibre bundle [9], and changing the internal capillary fibre diameter to allow for higher convective clearances with haemodiafiltration reduce thrombin generation and micro-particle generation [10]. Other adaptions have included bonding unfractionated heparin to the dialyzer surface, however although initial studies were very promising when tested in a randomised prospective multicentre trial was shown not to be inferior, rather than superior to intermittent pre-dialyzer saline flushes in preventing extracorporeal clot formation to in patients at risk of bleeding [11].

Clotting within the extracorporeal circuit also occurs at points of turbulence in the circuit and also where there is an air-blood interface. As such the internal diameter of the blood tubing should be single diameter and "T" insertions to the circuit minimised. Similarly the internal surface of the blood tubing should be smooth and redundant loops of extracorporeal circuit minimised. Fibrin clot is often noted in the venous air detector chamber, and alternative designs are now available, dispensing with this section of the extracorporeal circuit, replacing this with a section of biocompatible gas permeable plastic tubing segment [12]. Some circuit designs have an arterial reservoir chamber in which blood is forced upwards and sprays out mixing with air. Redesigning the arterial reservoir to make it narrower and so that blood does not spray up and mix with air reduces clot formation. Simply introducing heparin bonded plastic tubing for the extracorporeal circuit was not shown to substantially reduce clot formation and anticoagulant requirements. Newer developments to try and reduce clotting have included adding thrombomodulin and complement inhibitors to the dialyser surface, but these have not as yet been adopted into clinical practice. Vitamin E coating of dialysers have been available for some time, but trials of cellulosic dialysers coated with vitamin E have not been convincing in demonstrating beneficial effects, although the current trials have generally been under powered, and trials of the newer polysulfone dialysers coated with vitamin E are awaited.

Clot formation within the extracorporeal circuit is dependent upon both patient characteristics, in terms of pro-coagulant tendency [13] and then activation of inflammatory cells and platelets within the circuit. Cooling reduces platelet and leukocyte activation, but until circuits are redesigned to reduce leukocyte and platelet activation and minimising blood-air interfaces regional or systemic anticoagulation will be required for the majority of patients.

Improving uraemic solute clearances

Haemodialysis predominantly removes solutes by diffusion, depending upon maintaining a concentration gradient, membrane pore size, membrane resistance to solute passage, surface area, surface charge, the distance required to diffuse and temperature. Diffusion is more efficient for smaller and uncharged solutes with high concentrations in plasma water compared to larger and charged solutes, and those bound to plasma proteins and other moieties. Convection allows a greater clearance of larger sized solutes, depending on relative size compared to membrane pores and plasma water concentration.

Although diffusive clearance increases with increasing blood and dialysate flows, there comes a point when further increase in velocity no longer improves clearances. However simply having high flows does not guarantee effective clearances, as blood flow may not be equally distributed between central and outer capillary fibres, and similarly dialysate flow may not be equally distributed between the capillary fibres. As such manufacturers have adopted different designs to improve blood flow and counter-current dialysate flow distribution within the dialyzer, by using an inverted pyramid or spiral designs to distribute blood flow entering the dialyzer, or introducing an additional vortex flow with an "O" ring or external compression using the dialyzer casing, and changing dialysate flow patterns by altering the internal baffle angle, depth and internal surface length [14] (Figure 1).

During dialysis and haemodiafiltration proteins are adsorbed onto the dialyzer surface, so limiting the effective pore size and restricting the passage of larger sized solutes. Although this may reduce some clearances by protein "caking" the dialyser membrane surface, the removal of middle molecules in clinical practice is similar for both pre and post-dilution haemodiafiltration, due to increased membrane protein adsorption in post-dilution mode, whereas in theory clearances should be greater for pre-dilution mode. Some manufacturers have deliberately altered dialyser surface membrane charges, or membrane composition to increase protein adsorption. Protein deposition can be reduced by manufacturing fibres with a wave formation rather than straight fibres, adding external mechanical vibration, or by generating cycling pressure waves across the dialyzer [7].

An alternative approach is to change the dialyzer design from the current paradigm of a hollow fibre capillary dialyzer. One such approach is to develop membranes designed for high convective transport, similar to a storm drain in the street made from a silica nanostructure membrane [12]. Another design is to mimic the arterial tree branching into arterioles into capillary

micro-channels (figure 2). This design has been possible due to the technical advances in microfluidics. Applying a pressure across the channels results in a controlled convective transport, and haemoconcentration is prevented by re-infusion of a replacement fluid. The flow pattern within these structures minimises activation of leukocytes and platelets so reducing the risk of thrombin generation and clot formation. Compared to standard capillary dialyser design at which some point along the length of the dialyser capillary the hydrostatic pressure gradient across the dialyzer falls so that zero or back filtration occurs, these newer designs have constant effective convective clearance along the length of the channel. These microfluidic devices need to be stacked to have the clearance of current hollow capillary dialyzers. However the convective flow from one layer to the one beneath reduces protein deposition on the membranes, so preventing protein fouling and reducing the clearance of larger solutes. As these channels are very narrow, they become inefficient if microbubbles form. Bicarbonate can dissociate to carbon dioxide depending upon pressure and temperature. As such these novel designs require pressure monitoring. Different research groups have used different membranes ranging from polysulphone with polyvinylpyrrolidone (PVP) to polycarbonate. Coating polycarbonate micro-channels with polyethylene oxide (PEO)-polybutadiene (PB)-polyethylene oxide reduces microbubble formation [15].

Improving azotaemic toxin clearances

As studies failed to demonstrate an improvement in patient survival with greater urea clearance, there has been interest in removing larger solute clearances. More recently higher volume on-line haemodiafiltration has been suggested to be associated with greater patient survival [3]. The introduction of nanotechnology into manufacturing has led to an improvement in the standardisation of pore width size and smoothness of the walls of the pores. Increasing pore size increases the size of solutes cleared. However there is a trade off as larger pores will remove albumin and other larger plasma proteins, as with plasma exchange membranes. As such a generation of "super" flux hollow fibre capillary dialysers have been produced, which remove free plasma light chains, cytokines and other larger solutes (Figure 3). These membranes will allow the loss of some albumin, as to achieve a standard pore size of 25-30 kD, some pores will be larger. Preliminary trials of these dialyzers have not shown an improvement in patient outcomes and trials in patients with acute kidney injury due to plasma chain deposition similarly have both shown a benefit.

However increasing pore size dies not significantly remove protein bound azotaemic toxins. There will be some increase, but only in proportion to albumin losses. Similarly haemodiafiltration does not increase p-cresyl sulfate (PCS) or indoxyl sulfate (IS) clearance [16]. These protein bound toxins have been shown in experimental setting to be toxic to the endothelium and heart in animal models, and reported in observational studies in haemodialysis patients to be associated with increased cardiovascular mortality. However these protein bound toxins can be removed by adsorption using activate carbon. Traditional

activated carbons are microporous which have limited internal penetration by proteins, so reducing efficiency of adsorption and also are typically bio-incompatible. A newer generation of meso-porous carbons allow greater protein penetration through channels in the carbons monoliths improving efficiency, and also offer improved bio-compatibility characteristics [17]. Microporous carbons have little or no absorption for urea, but newer mesorporous are being developed which can absorb urea (Figure 4).

Due to the biocompatibility of carbons an alternative approach has been to develop composite dialyser membranes coating the outer surface of the standard synthetic hollow fibre membrane with a carbon, which has been shown to improve protein bound toxin clearances [18]. However these membranes are difficult to manufacture, so others are developing novel biocompatible composite membranes comprising a heparin-mimicking polymer brush functionalised carbon nanotubes and polyethersulfone (PES), using atom transfer polymerization. In-vitro testing of these composite membranes showed decreased protein adsorption, prolonged clotting times, and suppressed platelet adhesion compared to PES membranes, but with greater clearance of uraemic toxins [19]. Other options under development include a zeolite–polymer composite nanofiber mesh using poly(ethylene-co-vinyl alcohol) (EVOH) as the primary matrix polymer to which zeolite nanotubes are incorporated which are capable of selectively adsorbing uraemic toxins such as creatinine [20].

Environmental considerations

Single haemodialysis treatments require a large amount of water, as the water prepared by reverse osmosis only represents less than 1% of the original water intake. Expansion of dialysis services to countries where water is a scare resource, and even in highly developed countries saving water is now a priority. As such water systems are being developed to recycle rejected water and use this as non-drinking domestic water supply and for agricultural usage.

Portable and wearable haemodialysis devices require sorbent technology to recycle dialysate [6]. However there have been few advances in the development of sorbents for dialysis until recently, with most devices using a combination of activated carbon with a series of ion exchangers. As conventional carbons do not readily adsorb urea, then urea has to be additionally cleared by enzymatic or hydrolytic methods. Improvements in adsorption, particularly the development of carbons capable of adsorbing urea would potentially allow a new generation of adsorbent dialysis devices and reduce the environmental impact of current haemodialysis water requirements.

There have been advances in polymer technology in terms of reducing the use of polyvinyl chloride in the production of the plastics used to manufacture the extracorporeal blood tubing, bicarbonate cartridges, containers for acid concentrate and general packaging, to provide a newer generation of more biodegradable plastics. Similarly testing the integrity of hollow fibre capillary dialyzers no longer uses Freon™ which damaged the ozone layer. However if the extracorporeal circuit is not adequately rinsed, then organic chemicals can be

leached from plastics and the dialyser header into the patient, with reports of increased nonane, chloroethane, l-butane and dichlormethane in particular, in the exhaled breath of dialysis patients shortly after starting the haemodialysis session, and bisphenol-A released into the patient. Dialysers are no longer sterilsed with ethylene oxide, but some manufacturers continue to use this process to sterilise blood lines. So although anaphlyactoid reactions to dialysis are now rare, it is not uncommon for haemodialysis patients to demonstrate a mild eosinophilia due to constant exposure to organic chemicals leached from the extracorporeal circuit. Alternative methods of sterilisation including electron beam have been reported to produce thrombocytopaenia.

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Figure 1 : Schematic diagram of the hollow fibre capillary dialyser

Figure 2 : reduction in plasma free lambda light chains using a superflux dialyser (high cut off dialyser HCO) and standard high flux dialyser (Polyflux)

Figure 3 : Microfluidics capillary channel dialyser

Figure 4 : urea clearance with a mesoporous activated carbon monolith

Blood

Header

Baffle

Dialysate

"O" ring

Dialysate

Pyramid

Blood

% reduction lambda free light chains

60

40

20

0

All   < 10   10-99   100-999   1000-9999

HCO
Polyflux

Blood flow →

Blood flow →

serum urea mmol/l

pre   60 min   240 min

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