Review Article

Novel Trends in Haemodialysis: Where Are We Heading?

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Abstract

The mortality and morbidity of end-stage renal failure patients undergoing conventional thrice weekly in-centre haemodialysis remain alarmingly high despite continuing advances in haemodialysis technologies and improvements in clinical care. Home haemodialysis continues to be under-utilised in many parts of the world despite the reported benefits. Alternative haemodialysis regimens including longer and/or more frequent dialysis (e.g. nocturnal haemodialysis and short daily haemodialysis), haemodiafiltration and the use of high flux dialysers have become more widespread in recent years as nephrologists struggle to improve the dismal survival figures. Whilst most of the encouraging data have come from observational studies, many randomised controlled trials which will provide more robust data are already underway. This review aims to provide a concise update of the recent and novel trends in haemodialysis.

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Key words: Haemodiafiltration, High flux dialysis, Home haemodialysis, Nocturnal haemodialysis, Short daily haemodialysis

Introduction

Despite advances in haemodialysis technology over the past 40 years and rapid proliferation of clinical guidelines over the last decade promoting evidence-based practices, the mortality of end-stage renal failure patients on conventional thrice-weekly in-centre haemodialysis remains remarkably high. Morbidity remains prevalent with frequent problems of hypertension, fluid overload and the attendant cardiac sequelae, anaemia, mineral and bone disorders, inflammation, poor nutritional status, poor functional status and psychological disorders. These imply that the delivery of haemodialysis in its current format is sub-optimal. There have been increasing reports on the use of alternative dialysis regimens including longer and/or more frequent haemodialysis especially in a home setting, haemodiafiltration and high flux dialysers in an attempt to improve these vexing outcomes. Although observational studies have reported encouraging results with these newer therapies, we need evidence from randomised controlled trials (RCT) to better delineate the benefits, risks and costs of these therapies and to determine if certain groups of patients will benefit more from one therapy than another. Whilst better survival is the key to popularisation of a newer therapy in place of conventional thrice weekly in-centre haemodialysis, other factors would include patient's acceptance of the new therapy, and importantly cost considerations to the patient and organisations paying for dialysis. This paper aims to provide an overview of the alternative dialysis regimens that are currently available (Table 1).

Home Haemodialysis

Home haemodialysis (HHD) is seeing a resurgence in popularity after being in the shadow of centre-based dialysis over the last 20 years. HHD was a popular modality of dialysis in the early era of haemodialysis but was largely replaced by centre-based haemodialysis in the pursuing years mainly as a consequence of reimbursement issues and unfamiliarity of new medical staff with the concept of HHD. With numerous reports of improved survival and quality of life with longer and/or more frequent haemodialysis which is best performed at home and the introduction of newer, more user-friendly dialysis machines, we are seeing

Table 1. Recent Advances in Chronic Haemodialysis

1. Home haemodialysis
2. Nocturnal haemodialysis
3. Short daily haemodialysis
4. Haemodiafiltration
5. High flux dialysers

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a revival of HHD. Australia and New Zealand currently have the highest percentage of dialysis patients on HHD.[1]

Benefits of Home Dialysis

One of the main selling points of home dialysis is the flexibility of therapy. Patients have the freedom to adjust the dialysis schedule to suit their lifestyle needs with the proviso that they are compliant with therapy. They are empowered to direct the dialysis therapies, giving them a sense of control over their lives which is an important motivation for patients to continue treatment for a chronic illness. Treatment regimens for the home patient include but are not limited to, conventional thrice-weekly 4-hour dialysis, short daily haemodialysis and nocturnal haemodialysis of various frequencies.

HHD patients report improved quality of life compared with centre-based patients, close to that of successful kidney transplant patients.[2,3] Apart from the flexibility, home dialysis allows better reintegration with society and enables patients to return to employment (especially with overnight dialysis). The inconvenience and time wasted on travelling and the costs of transportation are also eliminated with HHD.

Patients on HHD have reported better survival than patients dialysing in-centre.[4,5] For patients who maintain a similar haemodialysis regimen at home as those who are dialysed in-centre, the reasons why HHD is associated with improved survival are not entirely well understood although earlier studies have suggested a selection bias as home patients tended to be younger with less comorbidities. However, a retrospective nested case cohort study by Saner et al[6] and data from USRDS[4] seem to suggest a survival advantage for HHD patients compared with in-centre patients (both groups doing conventional hours of haemodialysis), even after adjustments for differences in demographics and comorbidities. The impressive observational results of short daily haemodialysis and nocturnal haemodialysis, both of which are best performed at home, will be described in a later section.

Economics of Home Dialysis

HHD appears to be economically more viable and sustainable than centre-based dialysis as minimal infrastructural maintenance and manpower costs are incurred for HHD compared to caring for the same patient in a dialysis centre.[5,7] In times of spiraling manpower costs, nursing shortages, lack of physical space for expansion and financial pressures on dialysis providers and payors, HHD is certainly worth a re-look.

Home Dialysis for Every Patient?

Not everyone is suitable for HHD though; underlining the importance of careful psychosocial and medical evaluation. Some patients do not want to 'hospitalise' or 'institutionalise' their homes and prefer to leave therapy to medical staff in a dialysis centre. Others are reluctant to leave a centre-based facility as they take solace in the company of other patients and the comfort of knowing that medical attention is readily available. The necessity to needle the vascular access and worry of life-threatening haemorrhage from needle dislodgement or leaking dialysers while dialysing at night can be a source of constant worry for the patient. This said, HHD has been shown to be a safe modality of dialysis.[8] Suitability of the home for dialysis setup and space for storage of supplies need to be taken into consideration. A considerable period of time (usually 4 to 6 weeks) needs to be set aside for training of the home patient, which can be a challenge for those in employment. Patient 'burnout' is a real issue which can lead to non-compliance with dialysis. The long-term effects of HHD on the carer and family also need further evaluation. Some reports have raised concerns of a higher incidence of access related infections and sepsis in nocturnal patients[9] especially, although the reports are not consistent and require further validation.

A successful home programme must emphasise the importance of aseptic cannulation techniques and reinforce patient safety measures to prevent serious haemorrhage from needle dislodgement, as well as equipping patients with machine maintenance and trouble shooting skills. There must be readily available nursing and technical support round the clock, with home visits to assess the patient's competence and coping mechanisms and to provide technical maintenance support. Respite centre dialysis should be readily available whenever required. As industry innovations continue to produce more user-friendly machines that are compact, transportable, water-source independent (available in USA)[10] and more affordable, the stage is set for more patients to take up HHD. HHD can certainly be performed successfully by many more patients than at present. There is no place like home and it is a very rare home patient that will voluntarily return to centre-based dialysis once initiated on HHD.

Longer and/or More Frequent Dialysis

The randomised HEMO[11] study could not show further improvement in mortality rates for higher dose conventional in-centre haemodialysis compared with standard dose using Kt/V_{urea} as a marker of dialysis adequacy. This outlines limitations of current in-centre thrice-weekly haemodialysis therapy which was shaped largely as a compromise between patient acceptance, facility and manpower constraints, financial considerations and reimbursement issues. Although the HEMO study did not demonstrate a survival benefit, it does not necessarily rule out benefits of more intensive therapies. The HEMO study looked at urea kinetics; however, removal of other molecules (e.g.

phosphate) and middle molecular weight substances [e.g. beta 2-microglobulin (β2M)] could be equally important. The removal of these molecules is often time-dependent and longer dialysis could be the key to improving survival.

Longer and/or frequent dialysis makes sense physiologically. Increasing the frequency of dialysis reduces the inter-dialytic fluid gains, thereby reducing the incidence of intra-dialytic hypotension. Inter-dialytic increases in urea and other solutes are dissipated more frequently, resulting in decreased time averaged solute concentrations and enhances the efficiency of dialysis. Longer dialysis improves haemodynamic stability as ultrafiltration occurs over a longer period of time. There is also increased removal of solutes that are cleared in a time-dependent fashion, e.g. phosphate and β2M.

Nocturnal Haemodialysis

Daily nocturnal haemodialysis (NHD) consists of 5 to 7 overnight treatments per week, 6 to 8 hours per session. Nocturnal haemodialysis can also be performed on alternate nights, a common practice in certain states of Australia. NHD is performed at home, although in-centre nocturnal haemodialysis is potentially feasible for less frequent treatment schedules.

Benefits of NHD

Available literature on NHD has reported consistent benefits including improved blood pressure control,[12,13] regression of left ventricular hypertrophy,[12,14] improvement in cardiac function[15] and better phosphate control with elimination of phosphate binders in most patients.[8,16] In fact, patients enjoy a more liberal diet with no phosphate restrictions and may even require phosphate supplementation in the dialysate. Less consistent findings include improvement in endothelial function and vascular compliance,[17] improved quality of life[13,18] and cognitive function,[19] improved nutrition[20] and correction of anaemia[13] and sleep apnoea.[21] Most of these studies have, however, been cohort and case-control studies. The advantages of dialysing at home have been discussed previously. NHD also relieves the dialysis patient of fluid and dietary restrictions, which can translate into better quality of life. Patients on NHD have reported reduced dialysis-associated adverse effects which are encountered commonly with conventional haemodialysis, due to rapid solute and fluid removal rates. Observational studies have also shown reduced mortality,[22,23] decreased hospitalisations[9,23] and healthcare-related cost savings with NHD.[24]

The first RCT of NHD was by Culleton et al in 2007.[14] Fifty-two subjects were randomised to either begin NHD or remain on conventional thrice-weekly haemodialysis. Left ventricular mass measured by magnetic resonance imaging (MRI) decreased with NHD and increased with conventional dialysis [mean between-group difference -15.3g; 95% confidence interval (CI), -1.0 to -29.6 g; P = 0.04]. Systolic blood pressure, serum phosphate, calcium-phosphate product and parathyroid hormone level decreased only with NHD. More NHD patients discontinued anti-hypertensives and phosphate binders. No differences in anaemia control, vascular access complications or rate of hospitalisation were detected. Although NHD did not improve overall measures of quality of life, it was associated with significant improvements in selected kidney-specific quality of life domains.[14,25] The main limitations include the relatively small numbers and short follow-up.

Concerns with NHD

Concerns have been raised about the potential for longer and/or more frequent haemodialysis therapies to result in an increase in vascular access complications, e.g. technical failure or infection.[9] However, most studies have not reported an increase in vascular access complications with nocturnal haemodialysis.[26,27] Sleeping on dialysis can be difficult, especially in the initial period as patients require some time to build up their confidence in the concept of nocturnal dialysis and to overcome the fear of needle dislodgement. Temporary use of a sedative at night is helpful in these cases. Remote monitoring of patients is not a universal practice and patients have been known to dialyse alone overnight. NHD is safe and there have only been very few reports of serious blood loss with needle dislodgements. Careful taping and anchoring of the needles, with the use of blood/moisture sensors to detect blood and dialysate leaks are essential for patient safety.

Short Daily Haemodialysis

Short daily haemodialysis (SDHD) consists of 1.5- to 3-hour daytime treatments either in-centre or more conveniently at home, 5 to 6 days per week.

Benefits of SDHD

Observational studies have reported improved blood pressure control with decreased use of anti-hypertensives, reduction in cardiac hypertrophy parameters, reduction in erythropoietin doses, improved nutritional status and phosphate control and better quality of life in patients on SDHD.[28,29] Some of the reported benefits, however, were not entirely consistent among the studies due to several methodological limitations including non-randomised study designs, small sample sizes, selection biases, non-uniformity of the definition of SDHD and short follow-up periods.

Recent interim results of the ongoing FREEDOM study, which is a prospective observational cohort study with matched control group looking at the clinical and economic benefits of SDHD compared with conventional haemodialysis, show that the significant reduction in

depressive symptoms experienced by patients after 4 months of home SDHD therapy with the NxStage System One™ continues to be sustained after 12 months (29th Annual Dialysis Conference, Houston).

Kjellstrand et al[30] reported better survival of patients on SDHD than that of matched historical controls on thrice-weekly haemodialysis, which was similar to that of age-matched deceased donor kidney transplant recipients. Data on hospitalisation and length of stays in SDHD were inconsistent in a systematic review by Punal et al.[29] There was no increase in vascular access complications when comparing SDHD with conventional haemodialysis.[28,29]

Despite the encouraging reports of longer and/or more frequent dialysis, there is a dearth of RCTs looking at the effects of these therapies on the hard outcome of survival. Most studies have been non-randomised, small in numbers and largely looking at surrogate outcome measures.

Frequent Haemodialysis Network Trials

The Frequent Haemodialysis Network (FHN) is conducting 2 multi-centre RCTs in daily (6 times per week) dialysis.[31] In the daily study, 250 patients will be randomised to receive in-centre haemodialysis either 6 times per week or 3 times per week. The daily arm will receive dialysis for 1.5 to 2.75 hours (median 2.4 hours) per session with a target eKt/V of 0.9 (median weekly stdKt/V of 3.8). The conventional arm will receive dialysis for more than 2.5 hours per session (median 3.5 hours) with a target eKt/V of more than 1.1 (median weekly stdKt/V of 2.5). In the nocturnal study, 250 patients will be randomised to receive either 6 times per week nocturnal haemodialysis at home or 3 times per week conventional hours HHD. The nocturnal arm will receive dialysis for a minimum of 6 hours per session (median 7 hours) with a minimum weekly stdKt/V of 4 (median 5.6). Both trials will produce substantially greater separation than in the HEMO study where differences in median weekly treatment time and stdKt/V between the 3-times weekly high and standard dose groups were 18% and 17%, respectively.[32] Unfortunately, the small sample sizes preclude the ability to detect differences in mortality as an independent primary outcome measure. As such, the 2 co-primary outcomes are a composite of mortality with the change over 12 months in left ventricular mass as measured by cardiac MRI and a composite of mortality with the change over 12 months in the 36-item Short Form RAND physical health composite score. Regression of left ventricular hypertrophy has been considered a reasonable surrogate marker of mortality in renal patients[33] and has been included as one of the co-primary outcomes.

Mortality data from well conducted, adequately powered RCTs in this setting will be hard to obtain in view of logistic difficulties and financial considerations with such big trials. Nonetheless, results from the FHN trials will augment available data on more frequent dialysis and provide more robust information than what observational studies can offer. Data on patient outcomes from dialysis registries, such as the International Quotidian Dialysis Registry and national dialysis registries, will further complement data on these therapies.

Despite the reported benefits, other factors that would need consideration before embarking on NHD or SDHD include patient acceptance of longer and/or more frequent dialysis, higher perceived burden of disease, increased cost of transportation if dialysis is done in-centre and increased cost of consumable items.

The cost of providing more frequent dialysis varies, depending on reimbursement policies. Increased consumable items, electricity and water bills, staffing, training and facility costs, as well as capital expenses related to home dialysis setup will need to be considered. However, with vastly improved intermediate outcomes and lower morbidities expected with such therapies in observational studies, the reduction in healthcare-related costs from reduced medications and less frequent hospitalisations could sway the tide in favour of more frequent dialysis from an economic point of view.[24,34] The FHN trials will also attempt to estimate the costs of providing frequent haemodialysis.[31]

Haemodiafiltration

Haemodiafiltration (HDF) is an extracorporeal therapy that combines diffusive and convective transport for solute removal using a highly permeable membrane. Ultrafiltration exceeds the desired fluid loss and sterile replacement fluid must be infused to achieve the target fluid balance. Haemodialysis using high flux membranes can be considered a form of 'low efficiency' HDF. Internal filtration which occurs with high flux haemodialysis can be considerable (8-10 L per treatment). Ultrafiltration in this case exceeds the target weight loss and is compensated by back filtration. Unfortunately, the exact volume of ultrafiltration in high flux haemodialysis is unpredictable and not measurable on a routine basis. In contrast, ultrafiltration can be much larger and can be controlled in HDF. The replacement fluid can be infused pre-dilution, mid-dilution, post-dilution or in combination (Fig. 1). In pre-dilution mode, less solute clearance is obtained for a given filtration volume as diffusion is less effective in view of the dilution effect of replacement fluid infused before the dialyser. Post-dilution HDF can result in a higher incidence of dialyser clotting, especially when the total ultrafiltration rate exceeds 30% of the blood flow rate. HDF was previously performed with commercially-produced replacement fluid in bags. This has limited its use in view of the logistical difficulties and higher cost. On-line production of replacement fluid

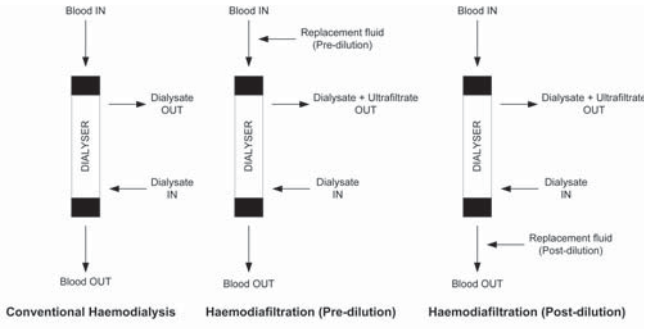

Fig. 1. Comparison of haemodialysis and haemodiafiltration.

is now available and has made HDF easier to perform. Water quality is important in HDF as a substantial amount of on-line produced replacement fluid is infused into the patient. Ultrapure dialysate is produced on-line, from which replacement fluid is continuously obtained by an extra step of ultrafiltration.

Benefits of HDF

HDF results in improved small solute clearances although the increase is modest as the removal of these substances is far more dependent on diffusive rather than convective transport.[35] More importantly, studies have demonstrated a 20% to 30% greater clearance of β2M with HDF[36,37] compared with high flux haemodialysis, resulting in lower pre-dialysis serum β2M levels and a decreased incidence of dialysis-related amyloidosis.[38] Although there is currently no causal relationship between β2M level and mortality, pre-dialysis β2M level was associated with all-cause mortality [Relative Risk (RR) 1.11 per 10 mg/L increase in β2M level; CI 1.05 to 1.19; $P = 0.001$], even after adjusting for residual renal clearance and number of pre-study years on dialysis in the HEMO study,[39] with similar findings in a Japanese study.[40] Higher β2M levels were associated with an increased risk of infectious death.[41] HDF is also capable of clearing other middle and larger molecular weight solutes including p-cresol, homocysteine, advanced glycation end products, and inflammatory mediators.[38] A measurable reduction of these middle and larger molecules suspected to be clinically relevant uremic toxins is seen in HDF and not in low flux haemodialysis. Superior clearance of phosphate during HDF has also been documented in most[38] but not all studies.[42] There have also been reports of decreased erythropoietin resistance,[43,44] reduced inflammation[45] and improved nutrition with HDF.[44] The results have not been entirely consistent as most studies were small in numbers with methodological limitations. Quality of life was improved in one study although the authors did not use a validated scoring tool.[46] Other studies have not been able to demonstrate conclusive improvements in quality of life.[37,44]

There have been many reports of improved intra-dialytic haemodynamic stability with HDF. However, this beneficial effect has been postulated to be due to the cooling of blood via enhanced thermal losses within the extracorporeal system in HDF as no difference in haemodynamic stability was demonstrated between HDF and temperature-controlled haemodialysis.[47]

Observational studies have reported a 10% to 60% reduction in mortality[45,48,49] with HDF although 2 early randomised studies did not reveal a survival benefit as they were underpowered.[42,50] In the European Dialysis Outcomes and Practice Patterns Study,[48] high efficiency HDF (defined as convection volume >15L per session) was associated with a 35% reduction in the risk of mortality when compared with low flux haemodialysis (RR, 0.65; $P = 0.01$), even after correcting for confounding factors. There was no significant reduction in mortality risk with low efficiency HDF in the study.

Randomised Controlled Trials in HDF

Although observational data have suggested tantalising beneficial effects of HDF, there is a paucity of results from RCTs. Three such studies are currently underway.[51] The Dutch Convective Transport Study aims to involve 700 patients comparing HDF (target replacement volume of 6 L/h in a post-dilution mode) with standard low flux haemodialysis, looking at all-cause mortality and cardiovascular morbidity and mortality over a follow-up period of 3 years. A French trial is comparing HDF with high flux haemodialysis in 600 patients, with the primary end-point of intra-dialytic morbidity and secondary end-points of all-cause and cardiovascular mortality and other laboratory markers over a follow-up period of 2 years. An Italian study which has been completed (results awaited), aimed at randomising 250 patients to either a convective therapy (predilution HDF or haemofiltration) or low flux haemodialysis, with the primary end-points of haemodynamic stability and blood pressure control and secondary end-points of morbidity relating to intradialytic symptoms, all-cause and cardiovascular mortality over a follow-up period of 2 years. Unfortunately, 2 of the 3 RCTs used low flux dialysers as the comparator group instead of high flux dialysers which would have been more appropriate in contemporary dialysis.

HDF has potential advantages over high flux haemodialysis which may improve the quality of therapy and survival of patients within the treatment frequency and duration that are currently considered as conventional. HDF with online production of replacement fluid is now easily available, safe and modest in terms of cost increment[52] over high flux haemodialysis. Whilst we await definitive data from RCTs, we can perhaps consider utilising this modality

more frequently in selected patients undergoing centre-based dialysis where resources limit the ability to increase frequency and duration of dialysis.

High Flux Dialysers

The use of high flux dialysers has increased tremendously over the past decade although there have been no guidelines recommending universal use of these dialysers except in cases of haemofiltration or haemodiafiltration.

Rationale for High Flux Dialysers

Early observational studies have suggested an association between the use of high flux dialysers and reduced mortality. However, patients randomised to the high flux arm (β2M clearance of >20 mL/min) of the HEMO[11] study had a mortality rate that was no different from that of patients randomised to the low flux arm (β2M clearance <10 mL/min), (RR, 0.92; CI, 0.81 to 1.05; $P = 0.23$). Although the high flux group could not demonstrate a beneficial effect on the primary outcome of all-cause mortality, there were significant risk reductions in death from cardiac causes and in the combined outcome of first hospitalisation for cardiac causes or death from cardiac causes in the high flux group. Post-hoc analysis suggests a survival benefit of high flux membranes for patients on haemodialysis for more than 3.7 years.[53] Additional post-hoc analyses suggested a decreased risk of death from cerebrovascular disease for patients on high flux haemodialysis without baseline evidence of cerebrovascular disease or with a duration of dialysis therapy longer than 3.7 years.[54] A post-hoc analysis of the 4D study, which was originally designed to analyse the effect of atorvastatin in diabetic chronic haemodialysis patients on the composite endpoint of cardiovascular mortality and morbidity, showed a superior survival in patients treated with high flux compared with low flux membranes.[55] Despite some positive results with high flux dialysis, caution must be advised with interpretation of these results as they were obtained from post-hoc analyses.

Membrane Permeability Outcome Study

The MPO study[56] is a multi-centre European RCT which was originally designed to study the outcome of high flux membranes on patient survival in haemodialysis patients with serum albumin ≤4 g/dL. However, the study was amended underway due to slow enrolment, such that the study protocol was opened to patients with serum albumin >4 g/dL. Seven hundred and thirty-eight incident haemodialysis patients were enrolled with a follow-up of 3 to 7.5 years. In the overall group (consisting of serum albumin ≤4 g/dL and serum albumin >4 g/dL), no survival advantage for high flux vs low flux membranes was observed. However, patients with serum albumin ≤4 g/dL had significantly higher survival rates in the high flux group compared with the low flux group (RR of mortality 0.63; CI, 0.45 to 0.90; $P = 0.01$). Diabetic patients showed a survival advantage for high flux haemodialysis, both in the overall group and subgroup with serum albumin ≤4 g/dL, albeit in a secondary analysis. The MPO study differed from the HEMO study in that only incident patients were included, reuse of dialysers was not allowed and there was likely to be higher β2M clearance in the high flux arm of the MPO study compared with the high flux arm of the HEMO study.

In the light of these studies, selected subgroups such as diabetics, hypoalbuminaemic patients or patients who have been on haemodialysis for a long period of time may benefit from dialysis with high flux membranes.

Conclusion

Whilst we are unsure which of the alternative dialysis regimens offers the best survival outcomes and quality of life, we do know that conventional thrice-weekly in-centre haemodialysis is certainly not optimal. As more robust data from RCTs become available in the near future, it is perhaps reasonable and prudent to start exploring these alternative dialysis regimens in selected patient groups who are at risk of poorer outcomes with conventional haemodialysis or in enthusiastic patients who are ready to embark on these newer therapies.

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