Searching for the Holy Grail: A review of current evidence for the advantage of haemodiafiltration as a treatment for ESRD over conventional haemodialysis

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Abstract

Most patients with end stage renal disease (ESRD) are supported with maintenance haemodialysis (HD) and this has been the case for many years. Recent improvements in water quality have led to the increased use of high-flux HD and more recently of online-haemodiafiltration (HDF). HDF has been promoted by some clinicians and by renal industry as potentially offering improved clinical and quality of life outcomes for patients over conventional HD. However, despite such benefits making theoretical sense very few studies of the use of HDF as compared to HD (especially high-flux HD) have been able to demonstrate any significant benefit for the therapy. This article reviews the most recent research that has compared HDF and HD and has identified that the evidence for the benefit of HDF remains elusive. This article, therefore, concludes that there is currently still not sufficient evidence from the research to support the contention that HDF confers benefits to patients over conventional HD and thereby no compelling evidence to justify its widespread use as a preferred form of treatment.

Introduction

Most patients in the United Kingdom (UK) and Europe who are treated for end stage renal disease (ESRD) are treated with haemodialysis (HD) (ERA-EDTA Registry 2010). In recent years, as more and more dialysis centres have improved the quality of their water supplies and manufacturers have improved and reduced the cost of larger pore dialysers this treatment has increasingly been high flux HD with the aim of removing greater proportions of middle-sized molecules such as phosphate. There is now a drive led by some clinicians and to a certain extent manufacturers of dialysis equipment to go one stage further and instead treat patients with haemodiafiltration (HDF), with the expectation that patient clinical outcomes, especially in respect of clinical outcomes, but also for quality of life indicators will be improved. However, despite enthusiasm for HDF in some circles the Holy Grail of reliable evidence from clinical trials supporting its increased use remains elusive. This article will describe the mechanism of HDF and review some of the more recent research within the field of HDF and thereby discuss the current evidence for the wide scale adoption of the therapy. Conclusions will be drawn as to the current state of evidence for or against the promotion of HDF as a standard therapy for ESRD in light of the research evidence presented.

Background

Standard maintenance HD relies mainly on diffusion across a semi-permeable membrane in order to clear solutes from the patient's blood. Small amounts of solute are also cleared through convective processes as dissolved material in the ultrafiltrate, but this is limited due to relatively low ultrafiltration (UF) volumes. HDF it is proposed improves solute clearance, especially for middle-molecule solutes such as phosphate, by greatly increasing the convective component of the procedure. To achieve this increased convective flow HDF works to artificially increase UF rates by infusing a replacement fluid into the extracorporeal circuit. The replacement (or substitution) fluid may be infused immediately prior to the dialyser (predilution HDF) or after the dialyser (postdilution

HDF). In order to facilitate the large convective volumes and increased removal of middle-molecule solutes it is necessary to use high-flux dialysers with increased pore sizes. Because modern on-line HDF systems generate the replacement fluid using the dialysis water supply the system requires very high levels of water purification to minimise the risk of toxins or infective agents from the water supply entering the patient's bloodstream (Mahon et al 2013). The process of HDF is summarised graphically in figure 1.

The prevalence of HDF as a therapy varies widely, ranging between 0.3 and 232 per million of population within Europe (ERA-EDTA Registry 2010) with similar variation reported in other jurisdictions (ANZDATA 2012). In many areas it remains unavailable to any patients, some centres utilise a combination of HD and HDF, often based upon locally determined patient criteria or trial and error as to what suits patients best. Some centres have adopted HDF as their standard treatment. Nephrologists according to Locatelli et al (2017) have cited dialysis-related amyloidosis, polyneuropathy, haemodynamic instability and longer life-expectancy as 'strong indicators' for prescribing HDF rather than HD.

In HDF the addition of the replacement or substitution fluid results in dilution of the blood in the dialyser (especially predilution HDF) which in turn reduces the concentration gradient between the blood and dialysate compartments thereby reducing the effectiveness of diffusion somewhat. This is generally more than compensated for, however, by maximising the levels of replacement fluid and therefore rates of convective transport (Thomas 2014). The interaction between convection and diffusion in HDF does not, therefore, produce a simple additive effect and there is often a trade-off between the higher rate of removal of larger molecules sought and a reduced diffusion rate of often smaller molecules.

The claimed rationale for HDF is that its use will not only improve solute clearance in patients, especially of phosphate and other middle molecules but also that it will help to reduce the severity of longer-term side-effects of HD such as hyperphosphataemia, hypertension and cardio-vascular disease (CVD)(Davenport et al 2010). It is also postulated that HDF will help with the problem of residual syndrome whereby the accumulation of dialyzable solutes has been shown to cause increased morbidity and mortality in long-term HD patients (Nagaoka et al 2011).

A key limiting factor to the effective use of HDF therapies derives from the high levels of trans-membrane pressure (TMP) generated by the infusion of the replacement fluid. For example in post-dilution HDF the recommended replacement fluid flow of upto 25% of the overall blood flow can create problems with high TMP, even with appropriate high-flux dialysers (Thomas 2014). Switching to predilution HDF can help solve this problem, but adding the fluid before the dialyser significantly reduces the solute concentration of the blood in the dialyser thereby reducing diffusion rates even further. Attempts are made to counter this by achieving higher rates of convection, but this tends to mean the predilution HDF requires approximately double the rate of replacement fluid (Thomas 2014).

A further limiting factor on patient suitability for HDF is the need that the therapy, to be effective, requires dialysis blood flows of around 350ml/min or above. This makes the therapy less suitable for patients with sub-optimal vascular access or cardio-vascular complications that preclude high blood flow rates (Thomas 2014).

Post-dilution haemodiafiltration offers the most effective removal of middle molecular solutes but highest efficiencies are often limited by increased blood viscosity and associated clotting. For this reason patients' anticoagulation doses will often need to be increased if they are switched to HDF, this may also preclude the therapy as a viable option for some patient groups (Thomas 2014). Clotting in the dialyser and associated rises in protein concentration can result in further increasing TMP and increasingly impaired removal of solutes. Predilution HDF partially overcomes this

problem, but at the price of affecting the overall efficiency of this method as a consequence of diminished solute concentrations (Nagaoka et al 2011).

By joining both modalities in what is termed mixed HDF, it is claimed that higher therapeutic benefit can be achieved with reduced levels of intradialytic complications (Susantitaphong et al 2012). In mixed HDF, a feedback system automatically maintains constant haemodynamic conditions adjusted to the characteristics of modern high-flux dialysers. It is claimed that by better preserving the hydraulic characteristics of the dialyser, it is possible to achieve greater substitution volumes and thus higher ultrafiltration. This results in significantly higher convective removal of small and middle molecule uremic toxins while minimising albumin loss that could compromise the nutritional status of patients (Pedrini et al 2006). The online feedback system automatically adjusts and controls the infusion rate between pre-dilution and post-dilution treatment and the total infusion volume as a sum of both. The system also takes into account flow conditions, internal pressures, such as Arterial and Venous pressure changes and the permeability of the dialyser (TMP) during the treatment. Mixed HDF is, therefore, considered by some as an innovation that improves patient outcomes by providing a high fluid exchange enhancing the removal of small and middle molecular uraemic toxins and claims are made for improved patients' quality of life and reduced morbidity associated with hyperphosphataemia and CVD (Susantitaphong et al 2012).

HDF Evidence Base

Despite considerable theory underpinning the rationale, evidence for the increased effectiveness of HDF over high-flux or even standard HD in removing larger molecule solutes has been limited and evidence for overall patient benefits is patchy at best. European Best Practice Guidelines on Haemodialysis (Tattersall et al 2007) suggest consideration of HDF as a means of delaying long-term complications of dialysis and also recommend keeping replacement fluid volumes as high as possible.

The largest single study into HDF was the ESHOL Study (Maduel et al 2013). This study involved over 900 patients in 27 Catalonian dialysis units and the researchers randomised patients to either HD or on-line HDF, dialysis time did not differ between the two groups but blood and dialysate flow rates were higher in the HDF group. Most of the HD patients were treated using high-flux dialysers. Patients were followed up for an average of 2 years. The study reported a 30% reduction in all-cause mortality for HDF compared to HD, especially with respect of risk of stroke or infectious mortality. The authors cite the small number of patients receiving low-flux HD as a potential weakness of the study, but seem to make no comment as to the possible effect on the findings of the higher blood and dialysate flow rates of the patients randomised to the HDF group. The ESHOL Study concluded that HDF reduced all-cause mortality when compared to conventional HD treatment.

Nistor et al (2015) undertook a Cochrane review of twenty separate HDF studies (randomised control trials (RCTs) and quasi-RCTs) comprising a total of nearly 3500 patients. The ESHOL Study cited above was included in the review. The review followed up an earlier one (Rabindranath et al 2006) which was funded by the National Kidney Research Fund (UK) which concluded there was insufficient evidence to recommend HDF therapies as opposed to conventional HD. The studies reviewed by Nistor et al were very heterogeneous and prone to selection bias arising out of patient suitability issues. Differences also arose on the basis of whether patients randomised to HDF were compared to patients receiving high-flux or low-flux HD – some papers failed to specify. Bias was identified as a problem in a significant number of the studies reviewed arising out of incomplete outcome data, selective reporting and in a number of cases commercial sponsorship on authorship, data management or both.

The Nistor et al (2015) review found that HDF did result in a significant reduction in death from cardiovascular causes when compared to HD, which they quantified in terms of HDF potentially

preventing 25 cardiovascular deaths for every 1000 patients treated when compared to HD. However, when the reviewers looked at all-cause mortality they found no significant advantage for HDF over HD therapy. In terms of morbidity Nistor et al also found no significant advantage to HDF over HD in terms of non-fatal cardiovascular events or hospitalisation rates, though analysis of this was hampered by the ten year spread of the papers reviewed which could have biased some hospitalisation rates. Nistor et al found no significant differences across the studies in systolic blood pressure rates either pre/post treatment or intradialytic, though there have been studies that have claimed this as a positive outcome of HDF. Only a minority (8) of the studies reviewed by Nistor et al undertook any analysis of patient quality of life (QoL) measures and their findings based on this limited data were that there was no significant evidence of any QoL advantage for HDF over conventional HD therapies. Finally, the Nistor review did find some evidence for increased urea clearance in patients receiving HDF evidenced by increased Kt/V scores but there was no real evidence to link this to overall improvements in patient outcomes.

More recent analysis of DOPPS data by Locatelli et al (2017) has also concluded that HDF could not demonstrate improved patient survival over conventional HD therapy. This was a cohort study of patients aged 18 or over and receiving in-centre HD or HDF. Patients were randomly sampled from 20 HD facilities in each of seven European countries. 23% of the patients in the cohort were receiving HDF. Importantly, in their review of the literature Locatelli et al (2017) also acknowledge that little reliable data exists to confer any significant benefit in terms of mortality or morbidity to HDF over conventional HD.

Many individual studies, however, do cite evidence the HDF patients are generally healthier overall then HD patients. Generally, these data, however, often lose significance once selection bias of patients chosen for HDF therapy are removed (Locatelli et al 2017). There is evidence from a number of individual studies that HDF can be beneficial for individual patients (Davenport et al 2010, Oates et al 2011, Maduell et al 2013, Dey et al 2015, Hill et al 2017) and for this reason many units have made the therapy available to increasing numbers of HD patients in recent years. Most commonly reported benefits of HDF in these studies include; improved haemodynamic stability during treatment, improved blood pressure control, improved dialysis clearance (Kt/V), improved phosphate control (sometime with ability to reduce dose of phosphate binders) and often qualitative indications of improved quality of life. Susantitaphong et al (2012) claim that mixed HDF yields increased patient longevity with improved quality of life as well as reduced rates of CVD and hypertension. Cost savings are also claimed on the basis that fewer dialysers and dialysis circuits need replacing due to clotting episodes. It must be stated, however, that this study was conducted on only twelve patients in one centre. They state in their paper that more, larger scale, research is needed into the method but as yet no independent studies have been published to this effect. Certainly it is the author's experience that HDF has been beneficial for individual patients, but this is of course merely anecdotal evidence and no attempt can be made to ascribe cause and effect.

Conclusion

Despite the theoretical basis for expecting improved patient outcomes from HDF over conventional HD the actual evidence for this from the quite considerable number of trials undertaken that compare the two therapies have thus far failed to demonstrate any real patient benefit in terms of all-cause mortality, morbidity or quality of life. The Cochrane Review undertaken by Nistor et al (2015) supports this conclusion and could only find statistically significant evidence for patient improvement with respect to reduced mortality from CVD for patients receiving HDF. These findings have been replicated in the more recent large scale cohort study of DOPPS data completed by Locatelli et al (2017).

HDF does however continue to be promoted as a therapy improvement over HD by some clinicians and, significantly, manufacturers of dialysis equipment. In many cases the enthusiasm evinced by

clinicians involved in dialysis relates to personal and often anecdotal evidence that it is claimed shows the advantage of the therapy for certain individuals. It is the conclusion of this review that, whilst it may be very reasonable to transfer individual patients onto HDF if there is a clinical benefit to the individual there is, as yet, no convincing case for large scale migration of patients, or indeed whole units over to HDF. In many cases the cost differential between HDF and HD has declined in recent years and the provision of ultrapure water supplies is much more general than in the past and so it could be argued that a mixed provision of HDF and HD within units is the most appropriate approach in order to facilitate selection of patients to one or the other on the basis on individual patient circumstance.

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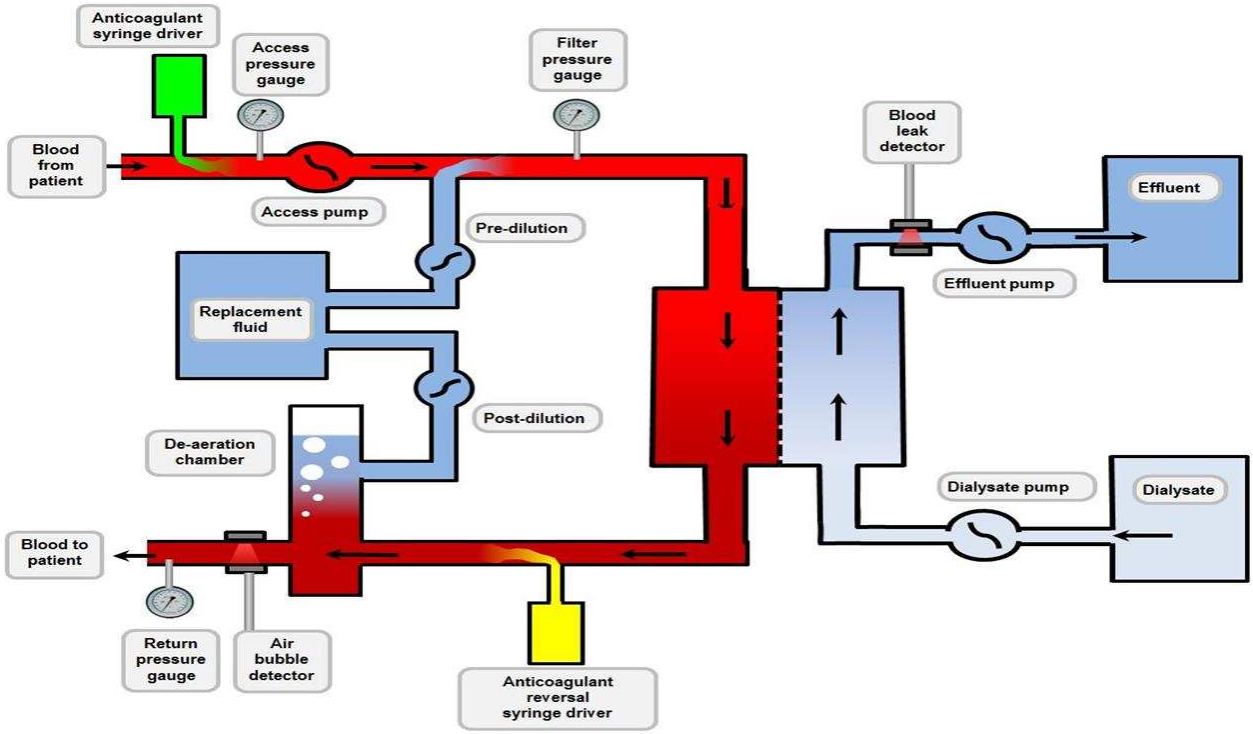

Figure 1. HDF Process