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Haemodiafiltration: Present time technical, clinical, and financial issues

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ABSTRACT

Online haemodiafiltration (HDF) is not a generic term that covers all convection-based renal replacement modalities – an optimal convection dose must be delivered to improve outcomes of end-stage kidney disease patients. In this brief article, we review current facts on HDF technical features, clinical/biological effects, and financial issues. In summary, HDF today offers highly efficient solute removal over the to-date widest known uraemic toxin molecular weight spectrum. Both safety and efficacy have been demonstrated in several short- and medium-term clinical studies. Recent randomized controled clinical trials and systematic reviews accredited the superiority of online HDF over standard haemodialysis (HD) when adequate convection dose is delivered. Additional clinical trials are needed to establish the optimal convection dose for different clinical settings (e.g. different patient characteristics and/or ethnicities, different substitution fluid delivery modalities) and to establish the cost-effectiveness of HDF compared to standard HD.

Key-Words: Chronic kidney disease; convective dose; end-stage kidney disease; patient outcomes; renal replacement therapy.

INTRODUCTION

In the early 1980s, the development of haemodiafiltration (HDF) was initially conceived as an attempt to cover unmet needs and shortfalls observed with the use of short conventional haemodialysis (HD) therapy. HDF was postulated to be beneficial both for the short-term, by improving efficacy (i.e. enhancing clearance of low and middle molecular weight uraemic toxins) and tolerability (i.e. increasing cardiovascular stability), and for the long-term, being putatively capable of reducing dialysis-related pathology (e.g. amyloidosis, ageing, accelerated atherosclerosis)[1].

TECHNICAL AND SAFETY FEATURES

After the pioneering work of Leber *et al.* describing HDF using bags of substitution fluid[2], it soon

became clear from both a technical and economical viewpoint that on-line preparation of substitution fluid was the only viable method to implement HDF as a sustainable renal replacement therapy option in chronic kidney disease patients[3,4].

Microbial safety of online HDF methods

Several clinical studies have confirmed the safety of the online HDF (ol-HDF) provided that appropriate CE marked and certified HDF machines are used and best clinical practices are applied[5,6]. The CONTRAST study confirmed the reliability and safety of the method in over 20,000 HDF sessions[7]. In addition, using sensitive biomarkers of the acute-phase reaction (C-reactive protein, various interleukins), several prospective studies have shown reduced stimulation of these markers compare to HD[8].

Flexibility of online HDF machines

The online HDF approach affords access to virtually unlimited volumes of substitution fluid as well as to various HDF options. This unique aspect facilitates not only achievement of an optimal targeted convection volume per patient (defined as the sum of the substitution volume and the volume removed for weight loss), but also allows one to select the most appropriate substitution fluid delivery modality (i.e. post-dilution, pre-dilution, mixed-dilution) according to the patient's individual profile[9].

Accuracy and reliability of online HDF machines

Today, the technical features of HDF machines ensure delivery of an optimal convection-based treatment for all patients with incredible accuracy. Irrespective of the convection volume targeted, fluid balance (including ultrafiltration required for weight loss) is achieved with a precision of ±100g with modern HDF machines. Ultrafiltration flow is optimized during HDF sessions by means of automated ultrafiltration control systems (e.g., AutoSub plus) ensuring a maximal tolerable filtration fraction and achievement of targeted convection volume[10].

BIOLOGICAL AND CLINICAL EFFECTS

Enhanced solute removal and clinical benefits of HDF

Several controlled studies have confirmed enhanced clearance and mass removal of β2-microglobulin with HDF (30 to 40% higher than high-flux HD) accompanied by a 10 to 20% decline in circulating blood β2-microglobulin concentrations[11,12]. Phosphate mass removal could be enhanced by 15 to 20%[13] and pre-dialysis serum phosphate levels were reduced by 6% while the percentage of patients reaching target pre-treatment serum phosphorus levels increased from 64 to 74% in the CONTRAST study[14]. Higher clearances of a number of other uraemic compounds have also been documented with HDF, including complement factor D (a pro-inflammatory mediator), leptin (16 kDa, involved in loss of appetite), FGF23 (30kDa, implicated in metabolic bone disorders and vascular calcification) and various cytokines, and circulating advanced glycosylation end products (AGEs) and AGE precursors[15,16]. ESA dose could be reduced in several clinical studies, the benefit being attributed to the combined effects of the higher solute removal of middle-sized toxins (erythropoietic inhibitor substances) and the use of higher quality water and dialysis fluid (reducing inflammation)[17]. This effect was not confirmed in a recent meta-analysis[18]. Several large cohort studies indicate that the extended use of high-flux membranes and convective therapies have a beneficial impact on the development of β2-microglobulin amyloidosis, reducing the incidence of carpal tunnel syndrome. This beneficial effect probably results from the regular use of ultrapure water and biocompatible materials, preventing inflammation, combined with convective modalities that enhance β2-microglobulin removal[19].

Better dialysis session tolerance

A significant reduction in episodes of intradialytic hypotension was observed in HDF compared to conventional HD[20]. This has been ascribed to negative thermal balance (due to infusion of relatively cool replacement fluid), a high sodium concentration of the substitution fluid, and/or removal of vasodilating mediators[21].

Patient outcome

The ultimate benefits of HDF therapy for ESKD patients are survival improvement and hospitalization

reduction. Several retrospective cohort studies that suggested that HDF had beneficial effects on patient outcomes have been confirmed by recent prospective randomized controlled trials[22,23]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) first suggested that patients being treated with high-efficiency HDF (substitution volume of 15 – 25 L/session) had a 35% lower mortality than those treated with low-flux HD; however, comparison with high-flux HD and low-efficiency HDF (‹15 L/session), did not yield statistically significant results[24].

Two recent prospective randomized trials (CONTRAST and Turkish HDF studies) failed to show beneficial effects on mortality (all-cause or cardiovascular mortality) as primary endpoint. Interestingly, both studies showed beneficial effects in post-hoc analyses restricted to patients with high convection volumes (› 20 L/session)[25,26]. The fact that 50 to 66% of patients enrolled did not achieve the targeted convection volume underlines the importance of best clinical practices and some weakness of these studies[27].

The most recent randomized controlled trial, the Catalonian ESHOL study, complying with best clinical practices and achieving targeted convection volume in 90% of patients, proved that mortality was reduced by 30% (all-cause and cardiovascular cause) in patients treated with high-volume HDF. In addition, this study found a reduction in hypotensive episodes (28%), stroke (61%) and infection (55%) for the high-volume HDF patients compared to the HD patients[28]. The remaining question today concerns the magnitude of the effective convection volume that should, optimally, be delivered, i.e., the sum of the substitution volume and the volume ultrafiltered to compensate for weight gain[29,30]. The CONTRAST study was the first RCT study that aimed to answer this question. It was designed to target delivery of 24L of convection volume per treatment, but only achieved an average of 20.7 L[27,31]. *Post hoc* analysis showed that survival was significantly higher in the tertile of patients treated with the highest convection volume, ›21.95 L[25]. A similar study was conducted in parallel in Turkey. Here online HDF was compared with high-flux HD, a substitution volume of at least 15 L was targeted, and a median substitution volume of 17.4 L was achieved[26]. The result was similar to CONTRAST in that no difference in survival could be shown for the global population, but again a *post hoc* analysis of HDF patients treated with convection volumes of › 19.9 L (17.4 L substitution volume ± 2.5 L weight loss), revealed significantly improved survival for this subgroup. The secondary result from these two large, randomized, controlled studies was confirmed by the ESHOL study, which in its primary analysis showed that all patients treated with HDF with convection volumes exceeding 23.1 L per session had significantly improved survival compared to patients treated with high-flux HD[28]. A summary of the different substitution and convection volumes reported in association with improved patient survival in the different studies mentioned above is presented in Table 1.

Several meta-analyses and/or systematic reviews addressing benefits of HDF compared to standard HD have reported conflicting results[18,32]. Unfortunately, these meta-analyses aggregated several different convection-based methods under the umbrella of "convective therapies" (i.e. haemofiltration, acetate-free biofiltration, low volume haemodiafiltration). Failure to account for the effective convection volume achieved presents a major shortcoming in their

Table 1

Summary of the different substitution and convection volumes reported in association with improved patient survival in key studies (conversion between substitution and convection volumes assume 2.5 L fluid removal to compensate for interdialytic weight gain).

Study	Volume type targeted in the study	Substitution Volume *to improve outcome*	Convection Volume *to improve outcome*
DOPPS Canaud *et al.*	Substitution volume	≥ 15 L/session	≥ 17.5 L/session
CONTRAST Grooteman *et al.*	Convection volume	› 19.45 L/session	› 21.95 L/session
Turkish OL-HDF Ok *et al.*	Substitution volume	› 17.4 L/session	› 19.9 L/session
ESHOL Maduell *et al.*	Convection volume	› 20.6 L/session	› 23.1 L/session

findings. The EUDIAL group, an official ERA-EDTA working group, clearly identified improved outcomes in patients receiving adequately dosed haemodiafiltration[33]. The remaining and burning question for the nephrology community is now to identify the threshold and/or optimal convection dose for improving outcomes of ESKD patients.

Online haemodiafiltration can no longer be considered an experimental treatment, but has matured to a renal replacement therapy that is used daily to sustain life in more than 70,000 ESKD patients in Europe[34].

FINANCIAL ISSUES

Cost of HDF treatment relies on the cost of the three main components: 1. The online HDF machine and technical features; 2. Disposable tubing sets and ultrafilters for substitution fluid sterility; 3. Microbiological monitoring of water and substitution/dialysis fluid quality. If one accepts that HDF is an optional technical feature of most available HD machines in Europe, and ultrapure water and dialysis fluid are anyway required for high-flux HD (backtransport of dialysis fluid), then the extra cost of HDF is only bound to the cost of the disposable tubing set (blood and substitution lines) and is not significantly different from high-flux HD[35]. A recent comparison of the costs of different HDF machines in a non-profit French organization revealed that the extra cost per treatment is between +0.17 and +0.23 Euros, but varies between -1.29 and +4.58 Euros, according to the type of HDF machines. This difference was mainly due to the disposable tubing set including (or not) a final sterilizing ultrafilter in the substitution line[36].

Reimbursement policy differs from country to country and sometimes even within countries, from region to region. In the majority of European countries, HDF is reimbursed at the same tariff as high-flux HD, meaning that no extra reimbursement is provided for this method. Cost-saving effects of HDF have not yet been extensively analysed; nevertheless, one can postulate some savings due to an improvement in the inflammation profile, less ESA consumption, and a reduction in the use of phosphate binders. A recent sub-analysis of the CONTRAST study focusing on cost-utility of HDF (QALY) did not show favourable results compared to regular HD, but also suffered the shortcoming of not taking the role of convection volume into consideration[37].

CONCLUSION

Online HDF offers efficient solute removal over a wide spectrum of uraemic toxin molecular weights. Both safety and efficacy have been proven in several short- and medium-term clinical studies. Recent randomized controled clinical trials tend to support the superiority of online HDF compare to standard HD when a high convection dose (or convection volume) is delivered.

Further clinical trials are needed to establish the optimal convection dose in different clinical settings (e.g. patient characteristics and/or ethnicities, substitution modalities) and to establish the cost-effectiveness of HDF compared to standard HD.

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