Emerging Clinical Evidence on Online Hemodiafiltration: Does Volume of Ultrafiltration Matter?

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Key Words

End-stage chronic kidney disease · Renal replacement therapy · Hemodiafiltration · Convective volume · Patient outcome

Abstract

Online hemodiafiltration (OL-HDF), first described in 1985, is today a widely prescribed treatment modality for end-stage chronic kidney disease (CKD) patients. Other than in the United States, prescription of the treatment modality is widespread with a steady increase since its inception. Indeed, in Western Europe, more CKD patients receive OL-HDF than peritoneal dialysis, hitherto the second most prescribed therapy after conventional hemodialysis. The rise and success of OL-HDF can be attributed to diverse clinical advantages that have been documented over the last two decades. Numerous publications attest to the beneficial effects of OL-HDF in terms of removal of a broad spectrum of uremic toxin, anemia control, phosphate reduction, increased hemodynamic stability and blood pressure control and less dialysis-related amyloidosis, to mention just a few. Significantly, the improvement in these conditions is considered to contribute to improved patient outcomes. Despite the extended worldwide clinical experience, elaborate scientific validation of the principles of the therapy and technical innovations that facilitate its prescription, a point of contention is whether OL-HDF leads to a reduction of mortality rates. A number

of observational and retrospective analyses have indicated a survival benefit, while prospective investigations involving small numbers of patients but nevertheless specifically addressing survival have further supplied evidence of improved survival with OL-HDF. The quest for large-scale, multicenter prospective randomized controlled trials examining patient survival led to the CONTRAST and the Turkish OL-HDF trials. Both trials have been concluded and published recently. In this chapter, we document and assess the key investigations that have examined the impact of OL-HDF on patient outcome and survival. Based on the findings of previous analyses and of the two recently concluded trials, it appears that the volume of convection appears to be decisive towards the survival benefit accredited to OL-HDF. We consider the implications of this new evidence.

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Introduction

Online hemodiafiltration (OL-HDF) has gained increasing clinical acceptance over the last two decades, being recognized as a safe, comfortable and more efficient alternative to conventional hemodialysis [1]. The cold sterilization filtration process of dialysis fluids (dialysate and infusate) enabled by online sterilizing filters offers a safe and affordable way of producing large amounts of substitution fluid for HDF modalities [2, 3]. OL-HDF ma-

chines have the advantages of being certified by European-notified bodies and recognized by EBPG [4–6]. The versatility of online production of dialysis fluids permits to cover adequately all individual patient needs in terms of volume of substitution (metabolic needs), site of substitution as post-, pre- or mixed-dilution (hemorrhologic characteristics) and blood flow limitations [7, 8]. Automation and technical improvements of OL-HDF machines have considerably simplified their handling and provide the same user confidence and comfort as for standard HD machines. Cost-effectiveness of OL-HDF, which varies from one country to another, depends upon the costs of disposable filters, additional microbiological monitoring and specific hygienic rules requested by individual health authorities to warrant absolute safety of the method [9].

The scientific nephrology community has also underlined that the OL-HDF option offers the best platform for developing renal replacement therapies of the future. By enhancing solute removal capacities and giving unlimited access to quasi-sterile and non-pyrogenic intravenous quality fluid, OL-HDF offers new ways for moving to total automation (e.g. priming, rinsing and feedback volume-controlled systems) and therapy cost-saving [10].

From a clinician's perspective and considering the potential benefits of chronic kidney disease (CKD) patient outcomes, it seems puzzling not to offer OL-HDF as a first-line renal replacement therapy in end-stage CKD [9, 11]. In this chapter, we assess all the investigations that have examined the impact of OL-HDF on patient survival. Based on the findings of previous analyses and of the two recently randomized concluded trials, we consider the implications of this new evidence for the supporting role of OL-HDF in the renal replacement therapy armamentarium.

Substitution of Fluid in Online Hemodiafiltration

The essence of HDF is the controlled replacement of large volumes of ultrafiltered plasma water by infusion of substitution fluid into the blood of the patient while maintaining a constant dialysate flow [12, 13]. The ultrafiltration volume is the sum of the infused fluid volume and the volume of fluid that needs to be removed due to weight gain between dialysis treatment sessions. The addition of substitution fluid and its subsequent removal from diluted blood has been shown to be a more efficient means of reducing the levels of various uremic toxins that accumulate in CKD.

Uremia is attributed to the build-up of a large number of solutes of various sizes. There is general consensus that both small and large uremic retention solutes, commonly referred to as uremic toxins, need to be removed during renal replacement therapy to enhance patient well-being [14]. A number of treatment strategies have been developed to achieve this objective. A fundamental approach to enable the removal of larger uremic solutes was the development of high-flux dialysis membranes having sufficiently high mean pore sizes to allow large solutes to pass through yet restrict the leakage of useful substances beyond a certain size range [15]. By adding and removing substitution fluid in conjunction with the use of high-flux membranes, a more efficient means of removing a broad spectrum of uremic toxins is achieved. This approach incorporates the convective transport (passage of solutes following fluid flow by ultrafiltration across high-permeability membranes, also known as 'solvent drag') component, in addition to the diffusive transport (based on the difference in concentration between the blood and dialysis fluid compartments) mechanism for the removal of solutes [16, 17]. Dialysis machines with highly reliable volumetric control and balancing systems ensure risk-free fluid balance and management of simultaneous fluid reinfusion and ultrafiltration.

Although the essentials of conventional HDF (involving infusion of defined volumes of sterile substitution fluid from bags) have been validated since the 1970s, the availability of unlimited quantities of cheap, high-purity (microbiologically) replacement fluids initially restricted the application of the therapy to a wider patient population [18, 19]. The advent in 1985 of 'online' preparation of non-pyrogenic substitution fluid from dialysis fluid fulfilled these limitations, paving the way to an entirely new era of more efficient blood detoxification [20, 21]. New technologies and concepts have evolved since this landmark to facilitate the delivery of large volumes of highly pure substitution fluids during OL-HDF.

There are two main variants of OL-HDF, depending on the site of administration of substitution fluid in the extracorporeal circuit. When substitution fluid enters the circuit before the dialyzer in predilution HDF, blood is diluted before solute transfer mechanisms occur across the semipermeable membrane. When substitution fluid is administered after the dialyzer (postdilution OL-HDF), ultrafiltered fluid volume is essentially replaced. The choice between pre- or postdilution depends mainly on considerations of blood rheology and filtration fraction of individual patients.

Clinical Experience with Online Hemodiafiltration: Focus on Patient Survival

Since 1985, the number of CKD patients treated with OL-HDF has risen steadily. At the end of 2011, worldwide 4.9% of the HD patients were treated with the OL-HDF modality, taking into account that no OL-HDF is in use in the USA which constitutes around 20% of the world's HD population. In Western Europe, 18% of the HD population is treated with OL-HDF, with countries such as Switzerland, Slovenia and Slovakia having over 60% of their patients on OL-HDF [1].

The growth in the prescription of OL-HDF is attributed to a number of clinical benefits as perceived by both patients and nephrologists. Among the main documented conditions and pathways positively affected by the therapy are: (a) enhanced removal of larger uremic toxins; numerous studies have verified significant reduction of β_2 -microglobulin (β_2 -MG), a recognized surrogate of the middle molecules and also involved in diverse pathological conditions [22–24]; (b) better control of anemia, with a reduction of erythropoietin dosage [25–28]; (c) a more effective removal of phosphate and control of hyperphosphatemia [29–31]; (d) improved lipid profiles [32, 33]; (e) reduced inflammation and oxidative stress [34–37]; (f) lower incidence of side effects, hypotensive episodes and hospitalization [38, 39], and (g) better patient well-being and quality of life: recovery of nutritional status, increased appetite and feeling of being more energetic [40, 41].

The essential facts and figures regarding the study type, design and objectives of the main clinical studies on OL-HDF examining patient outcomes are summarized in table 1. The investigations include retrospective analyses, prospective observational as well as prospective small-scale (e.g. single-center) assessment of patient mortality rates with OL-HDF. The key findings and conclusions (outcomes) of each of these studies are also listed in table 1. Varying objectives, study design or methodology (parameters assessed and statistics) make this body of evidence highly heterogeneous but nevertheless represents a highly valuable indicator of the clinical efficiency and efficacy of OL-HDF. Detailed assessment of the value as well as limitations of these investigations have been reviewed and published [41].

Thus, the extensive clinical experience acquired over almost three decades has established OL-HDF as an advanced and beneficial renal replacement therapy modality in routine practice. Significantly, no clinical incidences or studies indicating any detrimental aspects of the OL-HDF therapy option have been published.

The CONTRAST and Turkish OL-HDF Studies: Large-Scale Prospective Randomized Controlled Trials Examining the Impact of OL-HDF on Patient Survival

Despite the acknowledged clinical advantages accredited to OL-HDF, a wider prescription of the modality has been held back by the call for more conclusive evidence in the form of large-scale, prospective randomized clinical trials to demonstrate a survival benefit for OL-HDF [42]. As indicated in table 1, the issue of patient survival has been already been addressed for some time with a number of studies suggesting reduced patient mortality when patients are treated with OL-HDF. However, as this evidence indicating a survival benefit with OL-HDF has been derived from observational or retrospective analyses from a small patient population, the need for larger, multicenter clinical trials has been frequently emphasized to strengthen the case for OL-HDF. Consequently, two such trials, the CONTRAST and the Turkish OL-HDF studies, were undertaken and their results published recently. Table 2 summarizes the salient features of the two studies.

The Turkish HDF Study (table 2) that compared OL-HDF with high-flux hemodialysis (HF-HD) in terms of mortality and morbidity likewise found no differences between the two groups with respect to the primary endpoint (composite of all-cause mortality and non-fatal cardiovascular event rate) [43]. In the post hoc analysis, treatment with substitution volumes over the median of 17.4 l/session (high-efficiency OL-HDF) was associated with a significant risk reduction of both overall and cardiovascular mortality.

The CONTRAST Study (table 2), comparing survival rates between low-flux dialysis and postdilution OL-HDF, did not reveal differences between the two treatment modes in terms of the primary endpoint, namely all-cause mortality [44]. Further, there were no significant differences between the two groups in the frequency and incidence of fatal and non-fatal cardiovascular events. However, post hoc analyses again showed a significant inverse relationship between delivered convection volume and mortality risk. After correction for potential confounding factors, the hazard ratio for all-cause mortality was considerably lower in the group of patients treated with the highest delivered convective volumes (>21.95 liters).

Despite the fact that the CONTRAST and the Turkish OL-HDF studies were randomized controlled trials, both studies present some significant pitfalls that contribute to reduce strength of the evidence. As partially addressed by

Table 1. Clinical trials and studies on OL-HDF

Locatelli et al. [39]	Open-label RCT/LF-HD vs. predilution OL-HDF vs. predilution OL-HDF/27 centers (Italy); 146 patients/2-year follow-up. Endpoint: intradialytic hypotension. – Unlike conventional HD, convective therapies (HDF and HF) reduce ISH (primary endpoint) in long-term dialysis patients.
Schiff [56]	Unblinded, prospective cross-over RCT/ultrapure HF-HD vs. OL-HDF/1 center (Germany); 76 patients/4-year follow-up. Endpoint: mortality, diverse biochemical indices, quality of life. – OL-HDF is a safe, effective and well-tolerated therapy for end-stage renal disease patients even in the long run. – Both HF-HD and OL-HDF were associated with sustained reductions of pretreatment β_2 -MG levels, the decrease being greater with OL-HDF.
Wizeman et al. [49]	Prospective RCT/LF-HD vs. OL-HDF/1 center (Germany); 44 patients/2-year follow-up. Endpoint: morbidity, mortality, β_2 -MG as marker of uremic toxicity, hypotension, anemia. – No difference for morbidity, mortality, blood pressure, hypotensive episodes, hematocrit and EPO dose. – OL-HDF ensures an excellent dialysis quality which apparently takes time to translate into measurable clinical sequelae.
Locatelli et al. [57]	High-efficiency LF-HD vs. HF-HD vs. HDF/71 centers (Italy); 380 patients/24-month follow-up. Endpoint: polysulfone vs. cuprophane, HF-HD vs. HDF. – Significant decrease in predialysis β_2 -MG in HF-HD and HDF could have a clinical impact considering that its accumulation and amyloidosis are important long-term dialysis-related complications.
Tiranathanagul et al. [51]	Prospective, observational, non-randomized/HF-HD vs. predilution OL-HDF/1 center (Thailand); 22 patients/3-year follow-up. Endpoint: adequacy, biochemical parameters. – For OL-HDF, decreased incidence of hypotension, improved nutritional status and patient well-being, well-controlled lipid profile, normal C-reactive protein maintained, elevated removal of (β_2 -MG).
Vliar et al. [58]	Retrospective observational comparative analysis/HF-HD vs. OL-HDF/1 center (UK); 858 patients/18-year period. Endpoint: survival, anemia management, nutrition, blood pressure. – Improved mortality with OL-HDF compared with HF-HD: treatment solely with HDF had a hazard for death of 0.66 compared with patients treated solely with HF-HD. – No benefits of HDF over HF-HD with respect to anemia management, nutrition, mineral bone metabolism or blood pressure control.
Panichi et al. [59]	Prospective, observational/LF-HD vs. HF-HD vs. HDF/15 centers (Italy); 757 patients/30-month follow-up. Endpoint: all-cause and cardiovascular mortality, inflammation markers. – HDF was associated with an improved cumulative survival independent of the dialysis dose. – Synergic effect of CRP and proinflammatory cytokines as the strong predictors of all-cause and cardiovascular mortality.
Vinhas et al. [60]	Prospective, observational/HF-HD vs. OL-HDF/1 center (Portugal); 329 patients/3-year follow-up. Endpoint: all-cause mortality, hospitalization relative risk, biochemical parameters. – Annual crude mortality rate decreased from 19.9 deaths/100 patient-years (HF-HD) to 8.9 deaths/100 patient-years (HDF period); survival attributed to reduction of cardiovascular mortality. – Relative risk for hospitalization was not significantly reduced for patients on HDF compared to those on HD.
Canaud et al. [61]	Observational/LF-HD vs. HF-HD vs. low- and high-efficiency OL-HDF/multicenter (France, Germany, Italy, Spain, UK); 2,165 patients/ $\sim$ 3-year follow-up. Endpoint: mortality rates. – Patients on high-efficiency HDF had a significant 35% lower mortality risk than those on LF-HD. – Patients on HDF had a higher likelihood of having albumin >4 g/dl and a lower likelihood of ferritin >800 ng/dl than LF-HD.
Jirka et al. [62]	Prospective, epidemiological, observational/HD vs. HDF/multicenter (Czech Republic, Hungary, Italy, UK); 2,564 patients/1-year follow-up. Endpoint: mortality risk. – After adjustment for age, gender, comorbidities and time on renal replacement therapies, mortality risk reduction was 35.5% with HDF compared to HD.
Bosch et al. [63]	Prospective, observational/high-efficiency LF-HD vs. HF-HD vs. HDF/1 center (USA); 183 patients/6-year study. Endpoint: survival. – Kaplan-Meier survival curves of all patients (i.e. including all 3 modalities) were compared with those from USRDS data. – Standardized mortality data (SMR), derived for each high-efficiency treatment modality, showed significance only for HDF (relative to USRDS data), indicating better survival for this modality.
Locatelli et al. [64]	Historical, prospective/HD vs. HDF vs. hemofiltration/44 centers; 6,444 patients/follow-up till $\sim$ 30 months. Endpoint: mortality and amyloid-related amyloidosis. – Trend towards better survival: the relative risk for mortality adjusted for age, gender and comorbidities was 10% lower in patients treated with HDF and hemofiltration. – Adjusting for age and diabetic status, the relative risk for carpal tunnel syndrome surgery was 42% lower in patients treated with HDF and hemofiltration (compared to standard HD).

Table 2. The Turkish OL-HDF and CONTRAST studies

Study details	The Turkish OL-HDF Study (2012) [43]	The CONTRAST Study (2012) [44]
Title	Comparison of postdilution OL-HDF and HD (Turkish HDF Study)	Convective Transport Study (CONTRAST)
Type	Open-label, prospective randomized trial	Randomized controlled trial
Design	HF-HD vs. postdilution OL-HDF	Low-flux HD vs. OL-HDF
Number of centers/ country	10/South-East Turkey	29 (26 = the Netherlands; 2 = Canada; 1 = Norway)
Number of patients	782	714 (358 to postdilution HDF; 356 to HF-HD)
Endpoints	<i>Primary:</i> composite of all-cause mortality and non-fatal cardiovascular events <i>Secondary:</i> cardiovascular mortality	<i>Primary:</i> all-cause mortality <i>Secondary:</i> fatal and non-fatal cardiovascular events
Duration	2 years; follow-up reached maximum of 39 months due to slow recruitment	Mean follow-up period of 3 years (range 0.4–6.6 years)
Results	(1) No difference between HF-HD and OL-HDF in terms of primary endpoint (2) In post hoc analysis, OL-HDF with >17.4 liters substitution volume associated with better cardiovascular and overall survival	(1) No differences between low-flux dialysis and OL-HDF in terms of primary endpoint (2) In post hoc analysis, OL-HDF-treated group with highest convection volume (>21.95 liters) showed considerably lower mortality than patients on low-flux dialysis

Kuhlmann [45] in the editorial accompanying the CONTRAST Study, ultrafiltration volume targeted in the pre-specified study protocol (5–6 liters/h) was achieved only in one-third of the dialysis patients. In addition, large variations of ultrafiltration volumes were noted from center to center (range 13–22 liters/session) underlining the gap between prescription and treatment delivery. Factors impeding the capacity of achieving the prescribed ultrafiltration volume have been clearly identified by Penne et al. [46]. For a fixed treatment duration time, they rely on a poor blood flow, high albumin concentration and high hematocrit [46]. As a matter of fact, one can argue that targeted ultrafiltration volume was not adequately achieved in the majority of patients, a situation of protocol violation that may invalidate primary objectives of both studies.

Interestingly, the findings of both the CONTRAST and the Turkish HDF studies are consistent with the DOPPS data which first suggested the link between convection dose and favorable patient outcomes [47]. Although the DOPPS results were based on observational analysis, the findings were based on the study of a large patient population in four different countries, thereby taking into account differences between therapy practices. A survival benefit was described for high-efficiency

OL-HDF (>15 liters/session substitution volume, excluding net ultrafiltration for weight loss).

Three separate studies thus suggest that the volume of convection imparts a survival benefit for dialysis patients in terms of reducing mortality rates. Two of the studies reach this conclusion based on subgroup analyses and one on observational data. Despite such limitations, each study involved a large patient population and was carried out independently in different countries. The emerging trend that the exchange volume is possibly a decisive criterion of patient survival with OL-HDF is consistent with both the current understanding of uremic toxicity and the mechanisms involved in the detoxification of blood with dialysis therapies.

Convective Volume – A New Paradigm of High-Efficiency Therapies?

In order to judge the efficacy and the potential clinical benefits of OL-HDF, it is essential to use a quantifying indicator of the convective clearance. Following the recommendations of the EUDIAL group, it has been proposed to use the total volume of ultrafiltration achieved per HDF session adjusted to postdilution mode for the

various dilution modalities (pre-, mixed- or mid-HDF). This is an easy and clinically relevant surrogate indicator of the convective component. Alternatively, it is proposed to assess more precisely the biological effect by dosing biomarkers to reflect the convective action of the HDF. Among uremic toxins, β_2 -MG, a 12-kDa peptide, seems to be one of the most representative and clinically relevant representatives of the middle molecule uremic toxins and strongly implicated in both morbidity and mortality of CKD patients. Although it may be too early to set some predialysis (or time-average concentration) target values for circulating β_2 -MG concentration, it is interesting to note that in a post hoc analysis of the HEMO study, Cheung et al. [48] have identified that predialysis serum β_2 -MG concentrations >27.5 mg/l were associated with an increased risk of death in a dose-dependent manner. Indeed, the HEMO study has established that the relative risk of death accounting for confounding factors was 11% higher per each 10-mg/l increase of predialysis β_2 -MG concentrations based on the threshold value of 27.5 mg/l in HD patients. From a clinical perspective, until more precise data are provided, the threshold value of 27.5 mg/l concentration of β_2 -MG could be taken as a risk reference indicator for HD patients [48]. In this perspective, it is worth noting that studies analyzing predialysis β_2 -MG concentrations in OL-HDF-treated patients are highly concordant, reporting values comprised between 22 and 25 mg/l [23, 49–52].

It is attractive to suggest that the application of high exchange volumes are the sum of diverse clinical practices applied over the last two decades to refine and enhance convective therapies. From a recent per-protocol analysis of the CONTRAST Study, it has been shown that the volume of substitution that can be achieved is a summation of patient-related factors, medical prescription components, nursing practices and technically related factors. Among components that condition the success of delivering the optimal therapy in HDF, it is interesting noting that four groups of factors interact in unison and condition deliverability of the suitable convective dose: (a) some are related to the patient characteristics including the vascular access flow deliverable, the total protein concentration (protocrit) and the hematocrit; (b) some depend on the OL-HDF prescription and in this case the duration of session is determinant; (c) some are conditioned by facility nursing practices including anticoagulation regimen and protocol as well as quality care of achieving best blood flow and OL-HDF targets, and (d) some are dependent on technical features of the OL-HDF machine and fluid management, setting the priority ei-

ther on the ultrafiltration flow or the transmembrane pressure limits. It is not our intent to detail the ways of ensuring the optimal volume of ultrafiltration here, but simply to underline the fact that findings of the aforementioned OL-HDF studies cannot be interpreted without some form that is adjusted to the volume of ultrafiltration achieved per session (or per week) for each individual patient [53].

The recent findings of the two large-scale randomized controlled trials (CONTRAST and Turkish OL-HDF studies) have reinforced the concept of convective dose originated by the cohort DOPPS study [47]. Based on recent clinical findings, it is now tempting to speculate that the threshold total convective volume to bring a significant beneficial effect to CKD patient outcome should be in the range of 19–22 liters/session in postdilution HDF mode. To satisfy more closely patient metabolic needs, the convective volume may be tailored and expressed as liters per kilogram body weight (70–80 ml/kg/h) or body surface area (2,000–2,500 ml/m²/h). When different HDF modalities are used (e.g. predilution or mixed dilution) to facilitate the application of HDF in problematic patients (e.g. poor blood flow, hemorheologic difficulties), an appropriate dilution factor should additionally be accounted for in calculating the effective convective volume delivered to the patient.

Conclusion

Based on the findings of previous cohort studies and of the two recently reported randomized controlled trials (CONTRAST and Turkish OL-HDF), one can conclude that the volume of convection matters. It may represent a decisive component of the survival benefit for OL-HDF-treated patients. From a statistical viewpoint, the two recent interventional trials will be registered as negative studies not achieving their primary objective of reducing all-cause and cardiovascular mortality in dialysis patients. Again, from a methodological viewpoint, one should note that a targeted convective volume was achieved in a minority of patients (one third) and interestingly only these patients had significant survival benefits. From a purely clinical perspective, it would be unfortunate to deprive end-stage CKD patients from deriving advantages from a superior renal replacement therapy due simply to suboptimal care practices and methodological considerations [54, 55].

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