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The rationale and clinical potential of on-line hemodiafiltration as renal replacement therapy

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Abstract

On-line hemodiafiltration (ol-HDF) was developed in the 1980s in response to the unmet medical needs observed with conventional low- and high-flux hemodialysis. Firstly, the limited overall efficacy of conventional HD treatment programs as compared to native kidney function has been consistently documented over the broad MW spectrum of uremic toxins as well as fluid volume and hemodynamic control. Secondly, the unphysiological profile of intermittent treatment leading to repetitive dialysis-induced hemodynamic stress is now a well-recognized component of cardiovascular disease and end organ damage. Thirdly, the bioincompatibility of patient-dialysis system leading to dialysis-induced biological reactions also identified as contributing to dialytic morbidity and mortality. To overcome these limitations and pitfalls, alternative convective-based therapies (hemofiltration and hemodiafiltration), using higher hemoincompatible membranes and ultrapure dialysis fluid, were proposed as a solution to enhance and enlarge MW spectrum of uremic compounds cleared and to reduce dialysis-patient biological interactions. In this context, online HDF appeared soon as the best viable and efficient renal replacement modality to cover these needs. Clinical development and implementation of ol-HDF showed also that dialytic convective dose matters with a threshold point (23 L/1.73 m^2 in post-dilution mode) to observe clinical benefits and outcomes improvements.

1 | INTRODUCTION

On-line hemodiafiltration (ol-HDF) was developed in the 1980s in response to the unmet medical needs observed with conventional low-flux hemodialysis.[1–3] At that time the standard of care, low-flux hemodialysis (HD) was associated with a significant intradialytic morbidity (i.e., symptomatic hypotensive episodes, cramps, and nausea), a relative high incidence of dialysis related disease (i.e., ß2M-amyloidosis, accelerated atherosclerosis, cardiac disease, and aging),[4,5] and poor long-term outcomes (i.e., mortality and poor quality of life).[6,7]

In this context, new treatment opportunities were explored focusing on increasing the spectrum of molecules cleared by HD (solute removal),[8,9] improvement of treatment tolerance (hemodynamic stability),[10–12] and reduction of patient-dialysis interaction (biocompatibility).[13]

2 | CLINICAL FACTS—UNMET MEDICAL NEEDS WITH CONVENTIONAL HEMODIALYSIS TREATMENT

Based on these facts, it was speculated that the blood purification method used was likely to be contributing to these outcomes through three main pathways: firstly, the relatively poor efficacy and/or the non-selectivity of uremic compounds cleared by low-flux membranes; secondly, dialysis-induced hemodynamic stress with reports of intradialytic morbidity; thirdly, dialysis-induced biologic reactions resulting from repetitive blood interaction with the dialyzer membrane and dialysis fluid contamination.

The limited efficacy of low flux HD treatment programs has been consistently documented. Casino et al. using the equivalent renal urea clearance (EKR) concept,[14] demonstrated that 4 h thrice weekly low flux HD provided only 10% to 12% of the equivalent renal urea

clearance. However, EKR does not account for the clearance of middle and larger molecular weight (MWt) uremic compounds. Urea retention is used as a marker of kidney disease and increases with a reduction in kidney function. Unfortunately, an increase in urea concentration does not necessarily reflect either the retention of other uremic compounds or uremic toxicity. As such, the clearance of urea does not necessarily equate to clearance of the other uremic toxins. This has led to increased interest in the accumulation of other uremic organic compounds including middle MWt (i.e., ß2M),[15] larger MWt (i.e., free light chains) and protein-bound uremic compounds (i.e., indoxyl sulfate (IS), p-cresyl sulfate (PCS), 3-carboxy-4-methyl-5-propyl-2-furanpropionate (CMPF),[16] and their potential role in in uremic toxicity (i.e., cardiovascular). Furthermore, several studies have shown that pharmacokinetic and pharmacodynamic (PK-PD) characteristics of these compounds have no relationship with urea.[17] Thus, urea clearance or urea nitrogen control per se was not found to be predictive of the retention level or toxicity risk associated with these various organic compounds.[18] As low-flux dialyzers did not clear larger MWt solutes, this brought about the middle molecule hypothesis that the retention of these compounds resulted in patient morbidity and mortality[19,20] and led to the development of more permeable membranes capable of removing higher MWt compounds and the introduction of high-flux HD. However, it was soon identified that the removal capacity of middle and large MWt compounds was dependent on convective clearance, which stimulated the generation of convective-based therapies (i.e., hemofiltration, hemodiafiltration, push-pull dialysis, and paired filtration dialysis). Over time, HDF has emerged as the most promising of these convective therapies.

Dialysis-induced hemodynamic stress is now a well-recognized component of cardiovascular disease and end organ damage mediated through repetitive ischemic insults.[21] Historically, intradialytic morbidity and hemodynamic instability were the main cause of dialysis intolerance, increasing disease burden and negatively affecting both patient and medical staff perception of HD. Several factors were suggested to cause this dialytic intolerance syndrome. Schematically, they included the nature of the dialyzer membrane (i.e., cellulosic and synthetic), dialysate buffer (i.e., acetate, lactate, and bicarbonate), dialysate water quality (i.e., bacterial or chemical contamination), dialysis modality (i.e., hemofiltration and hemodialysis), treatment time (i.e., short vs. long HD), and dialysis conditions (i.e., thermal balance, sodium, and ultrafiltration profiling). Interestingly, hemofiltration and other convective-based therapies emerged as capable of reducing hemodynamic instability and improving dialytic tolerance secondary to ultrafiltration and hypovolemia. Later, it was identified convective therapies increased peripheral vascular resistance and venous tone facilitating vascular refilling while preserving systemic arterial blood pressure. Several hypotheses were formulated to explain this paradoxical hemodynamic response to volume depletion between different dialysis modalities, including the infusion of a relative hypertonic solution and the removal of negative inotropic compounds, or vasodilating substances. However, it is now recognized that the hemodynamic stability associated with online HDF are due to the combination of a negative thermal balance, which increases the neuroendocrine response, and improved endothelial responses, so restoring the imbalance in peripheral vascular tone.

Dialysis-induced biological reactions, as part of the bio-incompatibility concept and blood-membrane interaction,[22] were also identified as contributing to intradialytic morbidity and long-term mortality.[23,24] Passage of blood through the extracorporeal circuit leads to cellular activation (leukocytes, monocytes-macrophages, platelets, and endothelial cells) and protein cascade activation (coagulation, complement, and kinin) with release of various mediators (cytokines and enzymes). Once activated, these pathways self-amplify, cross-react, and converge to trigger inflammation.[25,26] In addition, dialysis fluid contaminants (microbial byproducts, endotoxin, peptidoglycan, and muramyl dipeptides) can also activate inflammatory cells (monocytes-macrophages) and potentiate cytokine (IL1, IL6, and TNF-α) release.[27,28] This stimulated clinical research into the development of more hemocompatible membranes to reduce complement and contact phase activation and water quality to produce ultrapure dialysis fluid to prevent further induction of biological reactions due to microbial or byproduct contaminants.[29,30]

3 | ONLINE HEMODIAFILTRATION AS POTENTIAL AND EVOLUTIVE THERAPEUTIC SOLUTION

In order to overcome the limitations and pitfalls of conventional HD, alternative convective-based therapies (hemofiltration and hemodiafiltration) were proposed, incorporating less hemoincompatible membranes and ultrapure dialysis fluid.[26,31]

Lee Henderson and coworkers pioneered the introduction of hemofiltration, facilitated by availability of highly permeable synthetic membranes (Amicon, AN69, Polysulfone).[1,8] Initial clinical studies in the United States, Europe, and Japan confirmed the capacity of hemofiltration for removing middle MWt solutes and potential benefits on patient outcomes. However, practical and financial issues limited the uptake of hemofiltration, due to the longer session times required, need for sterile bags of replacement solution, accurate volumetric control, and increased costs.[32–35]

The use of sterile bags of replacement solution limited the amount of convective clearance achievable and increased costs. Thus the next major step in the development of convective therapies was the introduction of ultrapure quality online substitution fluid,[36] supported by a final cold in-line sterilization, using ultrafilters by the dialysis machine. Quality assurance was assured with the introduction of hygienic rules for the maintenance of dialysis machines and ultrafilters, combined with regular microbiologic monitoring of the complete water and dialysis fluid production.[37]

The next step was to combine diffusive and convective clearances in the same dialyzer module, originating the concept of HDF. HDF was introduced by Leber and coworkers relying on a complex gravimetric bag delivery system annexed to a standard dialysis machine to ensure fluid substitution.[38] Initial studies confirmed the clinical performances and potential high clearance of HDF, but identified limitations

with this bag method. Online HDF was proposed soon after this report in a pilot study by Canaud and coworkers as a potential, safe and viable alternative to the bag method.[39,40]

Interest in online HDF led to an increasing clinical implementation of online HDF in Western Europe.[41] Following pilot studies, further technical development and implementation of best practices have shown safety[42] and the high therapeutic potential of online HDF.[43,44] Currently, 98% of all HDF treatments are with online HDF, treating around 380,000 patients world-wide, confirming technique safety.[45]

In the era of evidence-based medicine, there are two ongoing multicenter clinical trials of online HDF (CONVINCE and H4RT) in Europe, designed to generate further evidences and whether online HDF should be the treatment of choice for dialysis patients.[46–48]

4 | EVIDENCE-BASED FACTS SUPPORTING CLINICAL BENEFITS OF ONLINE HDF

Over the last few decades, online HDF has been shown to be associated with several positive biological and clinical effects that may address unmet medical needs as described above.[49,50] In this section, we briefly summarized intermediary and most prominent clinical outcomes reported with online HDF therapy.

1. Safety of online production of substitution fluid is confirmed by the daily clinical use of online HDF treatments worldwide and specific microbiologic monitoring studies, provided best practices and hygienic rules are followed. All regulatory agencies (EMA, FDA, JSDT) and international notified bodies (AAMI, ISO 23500-1:2019) have agreed and approved the clinical use of online production of substitution fluid, and there have been no safety concerns associated with online HDF.
2. Superior removal capacity per unit time of online HDF across a large MWt spectrum has been proven by several studies. Using the solute reduction rate achieved per session, then online HDF increases small MWt removal (e.g., urea) by 10% to 15%, while middle MWt (e.g., Osteocalcin, Myoglobin, and ß2M) percent reduction[51] and mass removal per session are increased by almost 100% compared to high-flux HD.[15,52]
3. Greater hemodynamic stability and improved dialysis tolerance has been demonstrated in several studies, although not universal. Intradialytic hypotensive episodes are reduced on average by 50%[53] as well as intradialytic symptomatology (cramps, nausea, headache, fatigue) including children and elderly patients.[54,55] Post-dialysis recovery time does not seem to be significantly reduced by online HDF (average ≈ 120 min); however, it is interesting noting that in the same study 34% of HDF treated patients recovered almost instantaneously after HDF.[56]
4. Reduction in chronic subclinical inflammation has been confirmed in several studies including systematic reviews. Sensitive biomarkers of inflammation (CRP, IL1, IL6, and TNF-α) are significantly reduced with online HDF.[57] This benefit relies on the combined use of ultrapure dialysis fluid and reduction of the hemobiologic reactions due to membrane interactions.[58]
5. Versatility of online HDF is illustrated by its multipurpose use responding to individual needs (e.g., convective volumes 20 to 60 L) and the various HDF substitution modalities (i.e., post-, pre-, and mixed-dilution HDF).[59,60]
6. Cost-efficiency of online HDF production has been demonstrated in recent studies. Large volumes of substitution fluid can be produced and adjusted to individual patient needs at the cost of ultrapure dialysis fluid.[61] The extracost of online HDF is mainly represented by change of sterilizing ultrafilters, strict application of hygienic rules and tight microbiologic monitoring.[62]
7. Long-term clinical outcomes suggest that relative risk of all-cause and cardiovascular mortality is reduced by 20% to 25% in patients achieving high-volume online HDF. Threshold dialytic convective dose starts at 23 L/1.73 m^2 in postdilution HDF and increases almost linearly with higher total ultrafiltered volume administered. Today, the maximal convection dose remains unknown.[43,63,64] Mechanisms supporting clinical benefits of online HDF have been summarized in a recent review.[65]
8. Future perspectives may be envisaged with online modalities. Online production of dialysis water will potentially allow automated preparation and priming of the HD machine, bolus infusion during dialysis session to manage hypotension, feedback control of circulating volume and automated return of blood and rinsing back at the end of treatment. Automated procedures may facilitate patient care in-center or at home-based or self-care treatment.

5 | CONCLUSION

Today, online HDF reflects the state of the art and most advanced form of renal replacement therapy. Online HDF increases solute removal capacity of uremic compounds over an enlarged MWt spectrum, improves dialytic tolerance, reduces chronic inflammation and tends to reduce both morbidity and long-term mortality. Further studies are ongoing to generate further substantial evidences supporting the use of online HDF.

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