

Why is on-line haemodiafiltration necessary as a renal replacement therapy option in chronic kidney disease patients?

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■ INTRODUCTION

It has been clearly shown over the last three decades that conventional haemodialysis (HD) is a very efficacious form of treatment which has increased the lifespan of more than one and half million chronic kidney disease stage 5 (CKD-5) patients worldwide. In contrast to this success story, the high morbidity and mortality rate still persisting in dialysis patients is, however, the upcoming renal replacement therapy (RRT) challenge. Further, it is frustrating for clinicians to note that despite major technical advances (among which are high-flux membranes, bicarbonate buffered dialysis fluid, ultrafiltration controlled machines, biocompatible material) and leading therapeutic achievements (correction of anaemia by erythropoietic stimulating agents (ESAs), correction of hyperlipidemia and so on) in RRT, there have been no significant progress in patient outcomes.

The increasing prevalence of dialysis-related pathology, including β_2 M-amyloidosis, accelerated atherosclerosis, left ventricular hypertrophy, ageing and malnutrition in long term treated patients, are other factors contributing to the partial failure of conventional RRT. While the precise causes of this dialysis-related pathology are not fully known, it can be speculated that several mechanisms contribute to the outcome.

To some extent, pathophysiologic mechanisms combine four main factors: limited clearance of mid-

dle solutes leading to the accumulation of middle and large uraemic toxins; poor biocompatibility of the dialysis system responsible for the periodic activation of cells and protein systems resulting in a microinflammation state; unphysiologic profile of intermittent treatment leading to alternate peaks and troughs and unfavourable correction of the *milieu interieur* composition, leaving metabolic disturbances such as permanent oxidative and carbonyl stress condition.

■ WHAT IS DIFFERENT ABOUT ON-LINE HAEMODIAFILTRATION?

Conventional diffusive-based dialysis modalities, including high-flux haemodialysis, are limited in their clearance of medium sized uraemic toxins. Convective methods which mimic the glomeruli filtration of native kidneys are required to enlarge the molecular weight spectrum of solutes removed during the dialysis session. On-line haemodiafiltration (ol-HDF) provides several advantages here. It combines diffusive and enhanced convective clearances, making it the most efficient modality for clearing small and medium uraemic toxins¹⁻³. Additionally, by using ultrapure dialysis fluid and high-flux synthetic membranes, it offers the most biocompatible dialysis system⁴⁻⁵. Moreover, as it

provides a virtually unlimited amount of sterile dialysis fluid by cold sterilisation filtration, it is an economical method for achieving high efficiency HDF (high fluid volume exchange) therapy with all substitution mode⁶⁻⁷ and as it maintains dialysis machine hardware options (fluid balancing system, thermal balance, blood volume monitoring, etc.), it retains the best technical options for optimising treatment efficacy and tolerance.

■ WHAT ARE THE TECHNICAL PREREQUISITES FOR STARTING OL-HDF?

ol-HDF methods require specific technical options and careful clinical monitoring to ensure safety and optimal performances. The summary below shows that this is not a big issue and can be easily provided in most dialysis facilities.

Patients should be equipped with a vascular access regularly providing an extracorporeal blood flow of 400ml/min. A high-flux dialyser is required to perform ol-HDF. Several dialysers made of synthetic polymers are available on the market. High flux dialysers share in common a dialysis membrane with high hydraulic permeability ($K_{UF} \geq 50$ ml/h/mmHg), high solute permeability (K_{0A} urea > 600 and β_2 -microglobulin > 60 ml/min) and large surface of exchange (1.50 to 2.10 m²).

Certified ol-HDF machines (blood monitoring and dialysate proportioning system) especially designed to safely achieve the dialysis session and to monitor treatment are needed. Bicarbonate-based dialysate solution and ultrafiltration controller have been generalised in dialysis machines, making dialysis sessions much smoother.

Ultrapure dialysate is a standard for ol-HDF machines. This is currently achieved by feeding dialysis machines with ultrapure water. The production of sterile and non-pyrogenic dialysis and substitution fluids is warranted by on-line cold sterilisation of the dialysate based on two sterilising ultrafilters interposed on the inlet dialysate line⁸. Sterility and microbial safety of the HDF machines is currently achieved by combining frequent heat and chemical disinfection procedures.

■ WHAT ARE THE CLINICAL BENEFICIAL EFFECTS OF OL-HDF?

Several reports have evidenced that the regular use of high efficiency HDF has beneficial effects on long-term dialysis patients.

Improvement of dialysis session tolerance is repeatedly reported with high efficiency HDF modalities⁹⁻¹⁰. Incidence of hypotensive episodes is reduced with HDF methods despite the significant weight loss¹¹. This is particularly important in hypotensive-prone and cardiac patients¹². This effect has been attributed to a positive vasomodulation effect involving several factors including a negative thermal balance, a high sodium concentration of the substitution fluid, the removal of vasodilating mediators and the absence of dialysate-derived contaminants^{13,14}. Post-dialysis fatigue is reduced with ol-HDF. This is particularly useful in elderly, diabetic, and other high risk patients¹⁵.

A better control of arterial pressure has been reported with high efficiency convective therapies¹¹. This beneficial effect is mainly due to the intradialytic haemodynamic stability that allows dry weight to be reached and to restore the sodium fluid balance more appropriately¹⁶. Length of sessions and compliance with a low sodium diet are also required to facilitate achievement of this primary objective. This positive effect is associated with a better anaemia correction and an adequate blood pressure control, suggesting that the effect may be linked to specific properties of ol-HDF^{17,18}.

High efficiency ol-HDF based on the regular use of ultrapure dialysate reduces the microinflammation of the HD patient. Based on sensitive markers of the acute phase reaction (CRP, IL1, IL6, IL1- and IL6-RA, albumin), several prospective studies have shown that the behaviour of these markers remains stable in the normal range over time in ol-HDF treated patients¹⁹. Preventing inflammation is a crucial target in order to reduce the incidence of dialysis-related complications in long-term dialysis patients²⁰.

Caloric and/or protein malnutrition is commonly observed in about one third of dialysis patients. Several recent studies have shown that the use of high flux membranes has a positive impact on the nutritional state as compared to low flux membranes²¹. Serum albumin as well as dietary protein intake tends to

increase when patients are treated with high flux membranes²². Indeed, one must recognise that this positive effect might stem from the combination of using high flux membranes with ultrapure dialysate and possibly by eliminating anorexia, and removing uraemic toxins via convective flux^{23,24}.

The regular use of high flux membranes with enhanced convective clearances has been shown to improve lipid profile^{25,26} and to reduce oxidative stress and AGEs in CKD-5 patients²⁷. While not fully understood, this beneficial effect may be partly due to the improved biocompatibility of the dialysis system associated with the combined use of synthetic membrane and ultrapure dialysate^{28,29}.

Neuropathy is a rare complication of RRT that is considered as a late marker of inadequate dialysis. It has been reported that intensification of treatment with high-efficiency convective methods can correct this neuropathy^{30,31}.

Renal anaemia, commonly observed in HD patients, requires EPO use in 80 to 100% of patients. Although controversial, it has been reported that high efficiency convective therapies were able to improve anaemia and to reduce EPO needs^{32,33}. This positive effect is particularly well illustrated when patients are switched from low-flux to high-efficiency HDF modalities or to HD using high-flux protein-leaking membranes. These observations suggest that high flux convective methods might remove protein-bound erythropoietic inhibitor substances³⁴.

Growth retardation is a major concern in CKD-5 children. This is a source of psychological difficulties during childhood. Conventional haemodialysis alone has not been able to reverse this development retardation. A recent study based on a daily ol-HDF schedule has been proved to correct growth in children with chronic kidney disease³⁵. This beneficial effect is achieved by combining a more efficacious treatment with an enhanced dietary and caloric intake and correction of *milieu interieur* disturbances (acidosis, calcium and phosphate control)³⁶. The combined use of growth hormone (GH), erythropoietic stimulating agents (ESA) and ol-HDF provides the opportunity to normalise growth rate in children with CKD^{37,38}.

Beta₂-microglobulin amyloidosis is a major disabling complication of long-term HD treated patients. Using carpal tunnel syndrome as crude and first manifesta-

tion of beta₂-microglobulin amyloidosis, it is commonly accepted that the incidence reaches 50% at 10 years and 100% at 20 years with conventional low-flux HD treatment. Several retrospective database studies indicate that regular use of high flux membranes in HD³⁹ and enhanced convective therapies such as ol-HDF may reduce its incidence by 50%^{40,41}. An interpretation of this beneficial effect is not easy due to the presence of several confounding factors. Enhanced removal of medium sized uraemic toxins and reduced inflammation appear, however, to be the most prominent protective factors⁴².

Morbidity and mortality are the most robust endpoints used to compare the efficacy of renal replacement therapy modalities. Here, the negative results of the HEMO-study reported recently with patients receiving either high dialysis dose or high flux membrane were relatively disappointing⁴³. It is, however, interesting to mention that the use of high flux membrane was associated with a reduced incidence of cardiovascular events. A recent reappraisal analysis of the HEMO-study has shown that high predialysis B₂M concentrations were strong and independent predictors of mortality in HD patients. This observation suggests that enhanced removal of medium sized uraemic toxins is beneficial for CKD patients. The European part of the DOPPS study has shown that high-efficiency HDF-treated patients had a better survival than regular HD treated patients in terms of age, sex, dialysis dose, comorbid conditions and country specificities⁴⁴. The relative risk of death was reduced by 35 percent in HDF treated patients compared to low flux HD patients. Independent investigators recently confirmed this positive finding when analysing a large European database (Euclid). The relative risk of death was reduced in this study by 36 percent in HDF treated patients⁴⁵. It has also been observed in a retrospective US study that high efficiency HDF based on two filters in series was able to reduce mortality in HDF by 65%⁴⁶.

■ WHAT IS NEEDED NOW?

High-efficiency ol-HDF currently offers the most effective and biocompatible renal replacement therapy modality in CKD-5 patients. Ol-HDF has several properties. It enlarges the spectrum of medium sized

uraemic toxins cleared, improves the haemocompatibility profile of the dialysis system and reduces the mortality risk in long-term haemodialysis patients.

Using either a daily treatment schedule or long slow nocturnal HDF programme, the weekly cumulative body solute clearance is enhanced by 80% while the *milieu interieur* composition change is reduced. Extended treatment time and/or frequency with the ol-HDF therapy provides an optimal, safe and effective form of renal replacement therapy for CKD patients⁴⁷.

What still remains to confirm the superiority of ol-HDF? Prospective randomised clinical trials comparing high flux HD to high efficiency ol-HDF are still lacking but this scientific evidence will certainly be provided by the prospective randomised trials currently ongoing in Europe^{48,49}.

Conflict of interest statement. None declared.

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