On-line haemodiafiltration after the ESHOL study

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To the great technical advances in haemodialysis (HD), such as HD monitors with ultrafiltration control, bicarbonate and ultrapure dialysate and dialysers with high permeability membranes, we must now add on-line haemodiafiltration (OL-HDF).[1] Its recognition is the result of many previous studies, but its ultimate accolade is the ESHOL study, which is discussed below.[2,3] Haemodiafiltration (HDF), in its various forms, is a technique with a long history in the treatment of stage 5D chronic kidney disease patients.[4,5] HDF techniques that use comercial solutions as replacement fluid have some disadvantages: the complexity of the technique, which requires a dialysis monitor capable of adapting the replacement infusion to ultrafiltration, the cost of serum and, therefore, of the technique, and lastly, limitation of the amount of convective transport, for example, between 8 and 9l in 4-hour acetate-free biofiltration (AFB).[6] All of these disadvantages have limited its use. By contrast OL-HDF, in which dialysate itself is used as replacement fluid, has managed to avoid many disadvantages, supplanting the other HDF techniques. The introduction of monitors that allow OL-HDF to be carried out very safely has resulted in its gradual implementation in clinical practice. The advantages of OL-HDF are: its cost, which is not much greater than that of high-flux HD (HF-HD), OL-HDF is currently considered to be cost-effective[7] and the possibility of achieving high convective transport volumes during OL-HDF sessions.[4,5,8]

Since its implementation in clinical practice, we have observed various clinical advantages in OL-HDF over HD: improved haemodynamic stability, an improved response to erythropoiesis-stimulating agents, greater elimination of phosphates and β2-microglobulin, a decrease in the incidence of dialysis-related amyloidosis, a decrease in markers-mediators of chronic inflammation, better preservation of nutritional condition, better response to the growth hormone in children on dialysis, good response of hepatic encephalopathy and better preservation of residual renal function (RRF).[9-22] In observational studies, better patient survival has been demonstrated using this technique with respect to conventional HD.[23-26]

The number of dialysis patients treated using OL-HDF has been steadily increasing in most countries. In some regions, for example in Catalonia in 2007, its use has even been encouraged. This has allowed its use to increase rapidly and has opened the way for a study such as ESHOL to be carried out.[2] The initiative of Catalan nephrologists coordinated by Dr F. Maduell and the support from Catalonian health authorities have made this study possible and through it, this technique has received its ultimate accolade. It is very important to bear the foregoing in mind, because without the initiative of nephrologists and the encouragement and interest from the health administration, progress cannot be made in clinical medicine. In a survey carried out in 2010 by the Spanish Society of Nephrology to all of Spain, 22.5% of HD patients were on OL-HDF. However, this growth has not been uniform. In 2010, according to a survey carried out by the Madrid Society of Nephrology, in the Community of Madrid, there were only 154 prevalent OL-HDF patients in a population of 6,445,499 inhabitants. While, in Catalonia, 948 patients received dialysis using this technique in a population of 7,504,881 inhabitants.[2] In the Communities of Madrid and Andalusia, the percentage of OL-HDF dialysis patients continues to be very low, increasing gradually only due to the initiative of nephrologists and, occasionally, with the opposition of health administrations.

WHAT DID WE KNOW ABOUT ON-LINE HAEMODIAFILTRATION BEFORE THE ESHOL STUDY?

OL-HDF is a dialysis technique that combines diffusive transport of conventional or low-flow HD (LF-HD) with a significant amount of convective transport. As such, it is capable of eliminating a higher amount of medium-sized and large molecules than LF-HD, in which diffusive transport

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is predominant.[8] It is well known that the retention of these uraemic molecules has been associated with various chronic complications in HD patients.[5,12,13,15,16,27]

This difference is minor with regard to HF-HD. Ultrafiltration and backfiltration, which occurs inside the high permeability dialyser, function like real OL-HDF. HF-HD should be considered as a low effective form of OL-HDF (5-7l per session). As such, the difference between the two techniques would be marked by the total ultrafiltrate volume, which in the case of OL-HDF, should be greater than 20l per session.

In addition to the partial clinical benefits already mentioned, the consolidation of a treatment, in this case a dialysis technique, is based on demonstrating its contribution to improved morbidity, mortality or quality of life. In this regard, we have large observational studies (DOPPS, EuCliD, RISCAVID), which indicate better survival in OL-HDF patients compared HD patients.[23-26] By contrast, two randomised studies have recently been published that do not show significant differences in the two year mortality rate between OL-HDF and HD patients in one LF[28] and one HF-HD case.[29] However, in subsequent subanalyses, when patients with ultrafiltration and convective transport above 22 or 20l/session were separated, an improvement in survival of 39% and 46%, respectively, were demonstrated.

WHAT DOES THE ESHOL STUDY TEACH US?

The ESHOL study[3] is the first controlled randomised trial that has shown a 30% reduction in overall mortality of OL-HDF patients, with respect to those on HF-HDF, with this parameter being the study's main objective. Annual mortality in the OL-HDF group was 9.8% and in the HD group, it was 14.1%. The latter percentage is similar to that of mortality in HD in the Spanish Registry of Renal Patients. In a recent mortality study on 7316 Spanish HD patients, the mean annual mortality rate was 12%, half way between these two figures. 23.2% of these patients were on OL-HDF.[30] In the ESHOL study, the difference in mortality, favouring OL-HDF patients with respect to HF-HD patients, was already evident after 18 months of follow-up.

Causes of mortality that contribute to this decrease in overall mortality in the OL-HDF group include acute stroke (AS) and infection. A potential explanation of a decrease in fatal AS in the OL-HDF group would be the greater haemodynamic stability of patients on this technique, with hypotension being avoided as a source of disease. This had been demonstrated previously with other HDF techniques, such as AFB.[6] As for infections, a decrease in the chronic inflammatory condition of these patients and an improved immunological response could play a key role. The elimination of molecules that mediate inflammation and a greater elimination of molecules that inhibit the immunological response could explain this result.[17] In relation to the foregoing, an improvement in OL-HDF patient morbidity was also observed, which was evaluated based on a 22% decrease in hospital admissions due to any reason.

All of these results were consistent and maintained when corrected for age, sex, diabetes, comorbidity (Charlson) and type of vascular access, variables that were different to those of the randomised study, which also influenced mortality. Given the study design and taking into account that at baseline, these parameters were similar in HF-HD and OL-HDF patients, the power of this technique as an independent factor for predicting a reduction in mortality is demonstrated.

In the ESHOL study, no differences were observed in blood pressure (BP), anaemia or serum phosphorus levels of OL-HDF patients with respect to those of HF-HD patients. By contrast, in some non-randomised studies there have been improvements in these aspects in OL-HDF. Factors other than the technique itself probably have an influence, for example, BP, dialysate sodium concentration and its balance, interdialytic weight gain and achieving the dry weight.[31]

HOW SHOULD WE CONTROL PATIENTS ON ON-LINE HAEMODIAFILTRATION?

In HD, to control the dialysis dose administered, Kt/V or Kt are used. For both these parameters, there are minimum levels below which mortality increases in HD patients. Are these parameters useful as mortality markers in OL-HDF? This aspect needs to be clarified. They probably are but they should not be the only parameters to be measured. In the absence of further evidence, OL-HDF patients should have, as those on HD, an eKtV >1.2 or a minimum Kt of 40-45l for females and 45-50l for males.[32]

Kt/V usually increases 10% when transferring from HD to postdilution OL-HDF. In a subanalysis of the RISCAVID study, we observed a 13.6% increase in Kt/V after six months of treatment with OL-HDF, with respect to its baseline value in HD.[33] This increase in Kt/V in postdilution OL-HDF may help achieve optimal Kt levels >45l in females and >50l in males. In this regard, in the study by Molina Núñez et al.[34], the parameters that were changed in HD to achieve the recommended Kt in all patients were: increased blood flow and effective session time, a greater dialyser area and the transfer to OL-HDF.

In OL-HDF, another parameter to control is the total ultrafiltrate volume, corresponding to the infusion and negative balance necessary to maintain dry weight. This volume should be greater than 20l per postdilution OL-HDF session. According to data of the ESHOL study, the optimal value would be somewhat higher: >24l per session. In the ESHOL study, the reduction in the risk of death was 40% and 45% in OL-HDF

subgroups with 23-25l and >25l per session, respectively. This convective transport volume must be associated with a dialyser sieving coefficient for β2-microglobulin ≥0.7 (0.6 for the Eudial Group),[35] which ensures good elimination of medium-sized molecules in the ultrafiltrate volume.

A more controversial aspect is whether β2-microglobulin should be controlled in OL-HDF.[16,35,36] In clinical practice, it does not seem reasonable to control either its clearance or reduction rate but it may be desirable for the OL-HDF patient to have pre-HD serum β2-microglobulin levels <25mg/l.

β2-microglobulin is a medium-sized molecule that is related to complications in HD patients, such as dialysis amyloidosis. Its clearance is significantly higher in techniques with high convective transport, such as OL-HDF.[16,36] Moreover, it has been shown to be a death risk marker in the HD patient population.[37] In a subanalysis of the HEMO study,[38] it was concluded that high levels of β2-microglobulin are associated with an increased risk of death. In the subgroup of patients with more than 3.7 years on dialysis, higher clearance or Kt/V of β2-microglobulin was associated with lower mortality. In a preliminary analysis of the CONTRAST study,[39] we observed that OL-HDF patients had lower β2-microglobulin levels than HD patients. Along with clearance, the other factor that has a fundamental impact on β2-microglobulin levels is FRR, which we should always attempt to preserve in HD patients. Moreover, serum β2-microglobulin levels do not only depend on its elimination, dialysis and FRR, but also on its formation/production, which is occasionally very high. This aspect must be borne in mind when interpreting serum levels in specific cases.

HOW CAN WE ACHIEVE MORE THAN 20-24L CONVECTIVE TRANSPORT PER SESSION?

The haemoconcentration created by postdilution OL-HDF in the dialyser does not usually cause complications if the filtration fraction (FF) is lower than 25% (relationship between ultrafiltrate and blood flow). This means that, to achieve 24l in 4 hours, we require 100ml/min of ultrafiltrate and therefore, 400ml/min of blood flow.

In patients with limited blood flow, such as those with catheters, this maximum rate may compromise the 20-24l ultrafiltration per session target. Various methods of achieving greater ultrafiltration in postdilution OL-HDF have been reported. One of these methods was reported by Maduell et al.[40] and applies to FMC® 4008S and 5008 monitors. It consists of prescribing infusion flow automatically and adding an increase of 20ml/min and modifying protein and/or haematocrit concentration in the autoregulation. As such, there is better performance without a significant increase in the alarms (14%). Another method of improving FF is achieved with the Gambro® Ultracontrol system. Our group has achieved a mean FF of 30%. This gave us total ultrafiltration volumes of 30l for 4 hour sessions.[41] The type of dialyser used is key in this technique.[42] The FMC® Cordiax-Autosub system can also achieve high FF without complications, although there is still a lack of published evidence.

WHAT ON-LINE HAEMODIAFILTRATION METHOD ARE WE REFERING TO? WHAT IS THE EQUIVALENCE BETWEEN THE DIFFERENT FORMS?

What we described above is valid for postdilution OL-HDF. The predilution method usually does not achieve a higher elimination of small molecules, such as urea, than its HD equivalent. To achieve an elimination of medium-sized molecules that is equivalent to postdilution elimination, it is necessary to use ultrafiltration/infusion volumes that are two to three times higher.[35,43] It does not have problems caused by haemoconcentration, but its clearance is also dependent on blood flow.

There are two types of OL-HDF that combine pre and postdilution infusion: *mid-dilution and mix-dilution OL-HDF*.[44-46] It is yet to be established what pre and postdilutions are equivalent to postdilution infusions. It is recently conducted a study comparing the mix with posdilution and observed that it had a similar clearance capacity.[47] It is unknown whether with low blood flow there can be better prevention of postdilution OL-HDF complications.

Calculating the dilution factor (DF) is a mathematical approach to determining equivalence of predilution infusion volumes with respect to postdilution volumes.[35] When in HDF part of the replacement fluid is infused before the dialyser (predilution), the ultrafiltrate volume must be corrected by this DF, which assesses the decrease in clearance of substances caused by dilution. The FD formula is = blood flow (BF) x (1 – haematocrit [Ht] x 0.93 / (BF x (1 – Ht) x 0.93) + predilution infusion flow (preIF). For example, for a BF of 300ml/min, Ht of 40% (0.4) and a preIF of 200ml/min, we have a DF of 0.46. With a preIF of 200ml/min in these circumstances and a DF = 0.46, we would have an equivalent postdilution flow (preIF x 0.46) of 92ml/min. the interaction between convective and diffusive transport means that this calculation is only approximate and can vary in accordance with factors such as the dialyser.

WHICH PATIENTS BENEFIT MOST FROM THIS TECHNIQUE AND THEREFORE SHOULD BE THE FIRST TO BE INCLUDED?

Classically, in Spain at least, we have tended to include young, male patients with a large body size and type 1 diabetes in OL-HDF programmes. In Japan they have also preferred young patients with few comorbidities and a long time on

dialysis.[48] It does not seem that this should be the case. The ESHOL study shows us that the type of patients who benefit most from OL-HDF are those who are older, non-diabetic, those who receive dialysis via an arteriovenous fistula (AVF) and those who have higher comorbidity.

OL-HDF is beneficial for most patients with a sufficient real BF of 250ml/min? but, if we have limited resources, we should begin with older patients, who have fewer possibilities of transplantation.[49]

WHAT LIMITATIONS OR SPECIFIC CARE DOES ON-LINE HAEMODIAFILTRATION REQUIRE?

OL-HDF eliminates more non-protein-bound uraemic toxins of a medium molecular weight than HF-HD, while it also may eliminate a higher amount of amino acids, peptides, proteins, vitamins and drugs. In patients with normal intake and an nPCR (normalised protein catabolic rate) >1g/kg/day, there is no reason why this should be a problem.

We are always asking ourselves the question whether it is necessary to supplement certain vitamins in HD patients, in general and specifically in certain techniques such as OL-HDF. P ascorbate would be reduced both in LF-HD and in OL-HDF patients,[50] but neither S-cobalamin (vitamin B12) or S-folate would be reduced in the blood of OL-HDF patients. It seems reasonable to measure them once a year in order to avoid deficiencies or whenever there are symptoms consistent with their deficiency. Some studies demonstrate better behaviour for vitamin D in OL-HDF patients.[51,52]

A significant amount of albumin can be lost in OL-HDF. High transmembrane pressure typical of this technique increases albumin loss in membranes with a cut-off point that would allow the passage of small amounts of albumin. In a study carried out in France,[53] 11 types of dialysers with different membranes were tested in OL-HDF, in one patient group. They assessed the infusion litres achieved, the β2-microglobulin reduction rate and the loss of albumin in the sessions. Although the convective transport volume was related to the β2-microglobulin reduction rate, there were dissociations, for example, higher elimination of β2-microglobulin with Fx1000® than with Fx100®, with the first being a dialyser specially designed for OL-HDF. With respect to albumin loss, FDY210® and REXEED 21® were notable. In a recent study,[47] our group observed minimum albumin elimination with helixone dialysers both in postdilution OL-HDF and in the mix. Loss is always higher in the first half hour and as such, it is desirable for transmembrane pressure to increase gradually over this period.

Lastly, some drugs, especially certain antibiotics, should be taken as a supplement after the OL-HDF session. Molecules with a molecular weight greater than 500 daltons and a low protein-binding proportion are eliminated significantly in OL-HDF. A study has been published on the pharmacodynamics of piperacillin in OL-HDF patients.[54] Other antibiotics such as vancomycin and tazobactam with similar pharmacokinetics should be taken as supplements after each session.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the contents of this article.

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