Experience in high-volume online hemodiafiltration. A longitudinal study of 47 months of follow-up in Ecuador.

Jorge Oswaldo Quinchuela Hidalgo 1, Gabriela Vanessa Tamayo Albán 1, Leonor Eugenia Briones Roca 2

1. Fresenius Medical Care Ecuador.

Abstract

Introduction: High-volume online hemodiafiltration (OL-HDF) offers clinical benefits concerning high-flux hemodialysis (HF-HD) in removing medium molecular weight solutes. The OL-HDF program in Fresenius clinics Medical Care del Ecuador (FMC-E) began in September 2018. This study aimed to determine the main epidemiological, clinical, and hospitalization parameters in the HDF-OL program and compare them with HD-AF patients.

Methods: The present longitudinal study was carried out in the statistics department of FMC-E. The study period was from September 3, 2018, to July 30, 2022. Patients receiving renal replacement therapy with >90 days in the hemodialysis program were included. Two groups were formed, the first with HD-AF patients and HDF-OL patients. The variables were: demographic, clinical, laboratory, and therapeutic. The source was the EuCLID computer system. The sample was nonprobabilistic. Noninferential and inferential statistics are used.

Results: 3653 patients in HD-AF and 1170 patients in HDF-OL were analyzed. The age of 53.1 years. 5.4 days of hospitalization/patient/year in the HD-AF group and 3.4 in the HDF-OL group (P<0.01). Hemoglobin 10.9 ± 1.6 gr/dl in HD-AF and 11.1 ± 1.7 gr/dl in HDF-OL (P<0.001), % transferrin saturation 32.6 ± 15.3% in HD-AF and 31.4 ± 13.5% in HDF-OL (P=0.02).

Conclusion: Patients undergoing OL-HDF have a better hematological profile with less anemia and less annual hospital requirement.

Keywords:
MESH: Renal Dialysis, Hemodialysis solutions, Hemodiafiltration, Intermittent Renal Replacement Therapy.
High volume online hemodiafiltration (OL-HDF) is a hemo-dialysis technique in which diffusion and especially convection mechanisms are used to achieve greater clearance of medium and high molecular weight solutes, implicated in multiple comorbidities and increased mortality, coming as close as possible to the physiological functioning of the glomerulus, where its elimination is carried out mainly by ultrafiltration [1]. Hemodiafiltration, by combining high-flow hemodialysis and hemofiltration, provides high purification efficiency for small, medium, and large molecules. In online hemodiafiltration, replacement fluid is produced simultaneously from the dialysis fluid itself; it can be infused before the filter (predilution), after the filter (postdilution), before and after the filter (mixed dilution) and in the middle part of the dialyzer (medium dilution). The postdia-
lution system is the most widely used and efficient, as it provides higher solute clearances with low convection volumes and is cost-effec-
tive. Predilution, medium and mixed hemodiafiltration are alter-
atives to the postdilution technique to increase the convective vol-
ume when there is insufficient blood flow or unfavorable hematologi-
cal conditions: high hematocrit, viscous blood, or high protein con-
centration.

There is ample scientific evidence of the multiple benefits of online hemodiafiltration (OL-HDF) in terms of decreased mortality from all causes, cardiovascular mortality, and among the cardiovas-
cular benefits: better hemodynamic stability and reduced episodes of arterial hypotension [2, 3].

Likewise, benefits are reported in the management of anemia with a decrease in the erythropoietin dose, improvement in phosphorus values, reduction in the incidence of amyloidosis due to beta 2 microglobulin deposits, and improvement in nutritional parameters [1].

In the Fresenius Medical Care Ecuador (FMC-E) clinics, the OL-HDF program began on September 3, 2018, with 72 patients, reaching 1,170 by July 30, 2022. This study aimed to determine the main epidemiological, clinical, and hospitalization parameters in the OL-HDF program and to compare some of them with patients on high-flow hemodialysis (PA-HD) in 21 FMC-E clinics.

Materials and methods

Study design
The present study is observational, descriptive, and longitudinal. The source is retrospective.

Scenery
The study was conducted in the statistics department of Fresenius Medical Care in Quito, Ecuador. The study period was from September 3, 2018, to July 30, 2022.

Participants

Patients with stage 5-d chronic kidney disease receiving renal function replacement therapy for >90 days in the hemodialysis program who had authorized and signed the data privacy notice document were included. Cases with incomplete data for analysis, incomplete medical records, or no follow-up after admission were eliminated. Two study groups were formed, the first with patients who received high-flow hemodialysis (HD-AF), and the second group was made up of patients assigned to the FMC-E group clinics that offer the online hemodiafiltration service (HDF-OL). The inclusion criteria to enter the OL-HDF program were pediatric patients with severe hemodynamic instability, diabetes, severe heart failure, ischemic heart disease, persistent difficulty controlling hyperphosphatemia, inflammatory states - malnutrition (MIA), secondary amyloidosis, myeloma, primary amy-
loidosis and light chain diseases, severe polynephropathy, pruritus or intractable insomnia, severe hypertension when dry weight is not reached due to hemodynamic instability, readmission to dialysis due to kidney transplant rejection and patients with a long life expectancy and low probability of transplantation.

Variables
The variables were age, type of vascular access, days of hospitalization, hemoglobin, transferrin saturation percentage, ferritin, erythro-
poietin dose, erythropoietin resistance index, iron dose, mean calcium, phosphorus, and intact PTH, dialysis treatment parameters, hydration status parameters, and body composition.

Data sources/measurements
The source was indirect; the EuCLID computer system was reviewed, which compiles the treatments and laboratory results of patients from twenty-one clinics of the FMC-E group. Body composition was per-
fomed with the BCM® bioimpedance monitor (Body Composition Monitor) at program entry and every 12 weeks.

Biases
To avoid possible interviewer, information, and memory biases, the principal investigator always kept the data with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Study size
The sample was nonprobabilistic, census type, where all possible cases of the study period were included.

Quantitative variables
Descriptivos y estadísticas inferenciales fueron utilizados. Los resultados se expresaron en una escala de promedios y desviación estándar. Los datos categóricos como el sexo son presentados en proporciones.

**Statistical analysis**
Noninferencial and inferential statistics are used. For the descriptive analysis, measures of central tendency and dispersion were calculated according to the measurement scale of each variable. Qualitative variables are presented as absolute numbers and percentages; quantitative variables are presented as medians and standard deviations.

Inferential analysis: Comparing values on the scale between the groups was carried out with Student’s t test; the importance and proportion were compared with the chi-square test. The statistical significance level was P < 0.05. The statistical package used was SPSS 28.0 (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp.).

**Results**

**Participants**
A total of 3,653 patients entered the HD-AF group, and 1,170 patients joined the HD-OL group.

**Characteristics of the treatments**
Patients underwent high-flow hemodialysis in 4008S machines (Fresenius Medical Care, Bad Homburg, Germany) and postdilution high-volume online hemodiafiltration in 5008/S volumetric machines (Fresenius Medical Care, Bad Homburg, Germany). The prescribed treatment duration for both modalities was 250 minutes, with a prescribed extracorporeal blood flow (QB) between 300-450 ml/min and dialysate flow (QD) of 500 ml/min. High-flow dialyzers were used: FX Classix for FA-HD and Fx Cordiax for OL-HDF. The composition of the dialysis fluid was the same in both modalities. In OL-HDF, ultrapure dialysate fluid was used with a bacterial count < 0.1 CFU/ml, and endotoxin count < 0.03 IU/ml.

**General characteristics of the sample**
The average age of the patients was 56.13 years; there was a more significant number of patients between the ages of 53 and 61 (277 patients) in OL-HDF (Figure 1).

**Figure 1.** Distribution by the age of patients on HDF-OL.

Concerning vascular access, 90.4% of patients on OL-HDF had arteriovenous fistula, 6.8% had a prosthesis, and 2.8% had a tunneled catheter, and patients with nontunneled catheters were not admitted to this modality. In the case of HD-AF patients, 68.8% had an arteriovenous fistula, 7% had a prosthesis, 18.30% had a tunneled catheter, and 5.90% had a nontunneled catheter (Figure 2).

**Figure 2.** Type of vascular access in the study groups.

**days of hospitalization**
A higher number of days of hospitalization per patient/year was observed in the FA-HD group than in the OL-HDF group (Figure 3).

**Figure 3.** Days of hospitalization per patient/year and modality.

**Hemoglobin, iron, and erythropoietin use**
Patients on OL-HDF had higher mean values of hemoglobin (11.05 mg/dl) compared with HD-AF (10.87 mg/dl) (P<0.01); they had lower average figures for percent transferrin saturation (HDF-OL 31.38% vs. HD-AF 32.60%) (P< 0.01). There was no significant difference between the difference in serum ferritin value in the prescription of erythropoietin and intravenous iron between both groups (Table 1).

Regarding calcium and phosphorus values, patients on HDF-OL had a higher percentage of compliance than patients on HD-AF (P<0.01). Higher iPTH values and a lower rate of compliance with
the matter were observed (HDF-OL: 56.5% vs. HD-AF 60.62%) \(P < 0.01\) (Table 1).

**Table 1. Variables were compared between the study groups.**

<table>
<thead>
<tr>
<th></th>
<th>HD group</th>
<th>HDF Group</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No.</strong></td>
<td>3653</td>
<td>1170</td>
<td></td>
</tr>
<tr>
<td><strong>Dialysis dose and treatment parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effective QB (ml/min)</td>
<td>364 ± 43</td>
<td>414 ± 36</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SBP pre (mmHg)</td>
<td>149 ± 21</td>
<td>150 ± 21</td>
<td>0.156</td>
</tr>
<tr>
<td>pre TAD (mmHg)</td>
<td>74 ± 12</td>
<td>78 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Kt/V) sp OCM</td>
<td>1.91 ± 0.4</td>
<td>2.00 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia and iron</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.9 ± 1.6</td>
<td>11.1 ± 1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% transferrin saturation</td>
<td>32.6 ± 15.3</td>
<td>31.4 ± 13.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Ferritin (mg/dL)</td>
<td>818 ± 469</td>
<td>806 ± 478</td>
<td>0.23</td>
</tr>
<tr>
<td>EPO dose/month</td>
<td>3089 ± 2376</td>
<td>3181 ± 2374</td>
<td>0.16</td>
</tr>
<tr>
<td>IRE (iu/wk/kg/gy)</td>
<td>2.4</td>
<td>2.2</td>
<td>DK</td>
</tr>
<tr>
<td>IV iron dose (Mg/month)</td>
<td>100 ± 0</td>
<td>100 ± 2.27</td>
<td>DK</td>
</tr>
</tbody>
</table>

**mineral metabolism**

<table>
<thead>
<tr>
<th></th>
<th>Calcium (mg/dl)</th>
<th>Phosphorus (mg/dl)</th>
<th>iPTH (pg/mL)</th>
<th>body composition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.6 ± 0.6</td>
<td>4.1 ± 1.3</td>
<td>390 ± 441</td>
<td>FTO (kg)</td>
</tr>
<tr>
<td></td>
<td>8.7 ± 0.7</td>
<td>4.3 ± 1.4</td>
<td>582 ± 647</td>
<td>13.9 ± 6.2</td>
</tr>
</tbody>
</table>

**Discussion**

For dialysis dose and treatment parameters, patients on OL-HDF had higher effective blood flow values \(P < 0.01\), achieved a convective volume >23 L/session, and had higher blood pressure figures than the patients on HD-AF \(P < 0.01\) (Table 1).

Regarding body composition, patients on OL-HDF had a better average lean tissue index and lower overhydration value and a lower percentage of relative overhydration compared to hemodialysis patients (LTI kg: 12.62 vs. 11.72) (OH liters 1.73 vs. 1.75) (RelOH: 10.39 vs. 10.93) \(P < 0.05\) (Table 1).

Online HDF improves the elimination of phosphorus, so it could be considered an option to enhance the treatment of hyperphosphatemia. In this sense, although some authors have shown that treatment with online HDF achieves better phosphorus clearance than conventional HD [18-20], others have not demonstrated differences in serum levels between high-flow HD and online HDF [21]. The present study found that patients in the OL-HDF arm had higher calcium and phosphorus values and a higher percentage of compliance within the target range compared with high-flow HD patients, in contrast to three large clinical trials such as the Turkish study, CONTRAST, and ESHOL, where they found no significant differences in these parameters between both study groups [7, 22], as well as with the study by Svára et al. (2016) [22], in which they reported that although the mean phosphorus levels were identical in the OL-HDF vs. high-flow HD group, they were significantly lower in the OL-HDF group [22]. Because it is not a randomized study, it is possible that the patients in the worst clinical condition and with the highest phosphorus levels were systematically included in the OL-HDF group; the initial and final PTH and phosphorus levels are not available. The most advisable thing in prospective studies would be to...
compare the delta value (initial minus final) in each group. Additionally, it must be taken into account that the P value in large samples is statistically significant despite the clinical significance being the same.

Higher diastolic blood pressure values were observed in the OL-HDF group, as in the study by Locatelli et al. (2010) [23], where an increase of 4.2 mmHg was reported in HDF patients compared to other groups, including the HD group. These results differ from those reported in the ESHOL and DOPPS study, in which there were no modifiable differences in systolic and diastolic pressures in both the high-flow HD and OL-HDF groups [2]; however, many studies report a better intradialytic hemodynamic stability even though the exact mechanism in HDF is not known, and there are many theories, such as vasodilation due to dialysis due to a thermal balance due to the infusion of cold fluid, elimination of substances that can cause vasodilation, better cardiac contractility, and slightly positive sodium balance due to hyponatremia in the ultrafiltrate secondary to the Gibbs-Donnan effect [2].

Unlike the study by Gallar et al. (2012) [21], in which the LTI values and percentage of overhydration were similar in both modalities (23), in the present study, better lean tissue and a lower rate of overhydration were observed in the OL-HDF group. We found a better dialysis dose in the OL-HDF group, confirming results from other studies [24].

This study constitutes the experience of OL-HDF in Ecuador since the FME Renal Units were among the first to implement high-volume online hemodiafiltration in the country. The limitations of this study are based on its retrospective, observational design, the data were obtained from the EuChID computer system, and there may be variability in the completion by health personnel. The strengths of the study lie in the sample size, multicenter, the previous training of the personnel before the start of the program, which allowed setting objectives as inclusion criteria to admit the patients to the program, and the objective convective volume > 23 L, which was achieved in most cases by accepting patients with functional vascular accesses that allow accurate, effective blood flows > 350 mL/min.

Conclusion

Patients on OL-HDF achieved adequate convective volumes (>23 L), increased Kt/V, better hemoglobin parameters, erythropoietin resistance index, calcium, phosphorus, LTI, and less overhydration. The other parameters evaluated did not show improvement compared to patients on FA-HD, such as transferrin saturation, erythropoietin dose, and iPTH. OL-HDF is a safe and effective modality for all patients. However, vascular access must ensure adequate blood flow (>350 mL/min) to achieve target convective volumes.

Abbreviations

HD-AF: High-flow hemodialysis.
OL-HDF: online hemodiafiltration.
iPTH: parathormone intact fraction.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

Author contributions

Jorge Oswaldo Quinchuela Hidalgo: Data curation, Formal analysis, Fundraising, Research, Methodology, Project management, Resources, Software, Writing – original draft.
Gabriela Vanessa Tamayo Albán: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition. Leonor Eugenia Briones Roca: Conceptualization, Supervision, Validation, Visualization, Writing: review and edition. All authors read and approved the final version of the manuscript.

Financing

Fresenius Medical Care provided the costs of the investigation. The studies, hemodiafiltration treatments, laboratory tests, and body composition measurements constituted the regular activity of the hemodialysis units and did not constitute a cost for the patients.

Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to the confidentiality of the participants.

Statements

Ethics committee approval and consent to participate

It does not apply to database studies.

Consent for publication

Not required for studies that do not publish patient photographs, CT scans, or X-ray studies.

Conflicts of interest

The authors are employees of Fresenius Medical Care.

Author Information

Jorge Oswaldo Quinchuela Hidalgo, Physician from the Central University of Ecuador (Quito, 2014). Medical specialist in Nephrology from the Pontificia Universidad Católica Argentina Santa María de los Buenos Aires (Buenos Aires, 2019). Attending physician of the nephrology service of the “Solón Espinosa Ayala” Cancer Hospital, Solca Núcleo de Quito. Part-time treating physician at Fresenius Medical Care Ecuador Clinics.
Leonor Eugenia Briones Roca, Doctor of Medicine and Surgery from the University of Guayaquil (Guayaquil, 2002). Specialist in Nephrology and Internal Environment from the University of Guayaquil (Guayaquil, 2012). Part-time attending physician at Fresenius Medical Care Ecuador Clinics (Manabí-Ecuador).

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