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Using Medium Cut-Off Membranes in Online Hemodiafiltration: Results and Considerations

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Abstract

Aim: Medium cut-off membranes are not used in hemodiafiltration methods because they are considered to lose large amounts of albumin and there is a potential risk to patients. This study was designed to determine whether the use of medium cut-off membranes in online hemodiafiltration (post- and pre-dilution) was safe, and to what extent do patients benefit when using online hemodiafiltration with these filters in terms of medium molecular weight toxins. **Patients Methods:** Fifteen patients (7F, 8M), median age 71 years, who had been on dialysis for 17 - 486 months, were randomly enrolled. They were scheduled to undergo predilution online hemodiafiltration (Group A), post-dilution (Group B), and expanded hemodialysis (Group C) sessions with the same medium cut-off dialyzer and a session conventional hemodialysis with a low flux filter of the same surface area (Group D). **Results:** The Kt/V and urea reduction ratio of the Groups A and B were better than Groups C and D (but not in all comparisons). Specifically, Kt/V was better in Group B in comparison with Groups C and D. Also, urea reduction ratio of Group A was better than in Group D, and Group B was marginally better than Group D ($p < 0.06$). The removal of β_2-microglobulin (in mg/session) and prolactin (% differences) in online hemodiafiltration (pre- or post-dilution) were better in comparison with other methods of dialysis assessed in this study (expanded or conventional hemodialysis). Only the comparison of removed amount of β_2-microglobulin in postdilution online hemodiafiltration (Group B) and in expanded hemodialysis (Group C) shows a marginal significance of p value ($p = 0.055$). The amount of albumin lost (in g/session) (Table 3) was significantly higher with online hemodiafiltration (pre- or post-dilution) compared to both expanded hemodialysis and conventional hemodialysis. The largest albumin loss observed was 130.3 g/session in postdilution online hemodiafiltration. Also, in predilution online hemodiafiltration, 3 patients had zero albumin loss, while in postdilution, 2 had 0 albumin loss, in comparison to the expanded hemodialysis group of whom 7 losses ranged from 23.0 to 80.0 g/session. No clinical side effects (*i.e.* episodes of hypotension) were recorded in our patients during the study with any of the methods used. **Conclusion:** From the study it is concluded that the application of medium cut-off dialyzers provided higher clearance of toxins (small and medium molecular weight) with a toleration of albumin loss in postdilution online hemodiafiltration in comparison to the expanded hemodialysis. In relation to removing medium molecular weight toxins when cannot be applied postdilution online hemodiafiltration using the predilution hemodiafiltration, is a better choice than expanded hemodialysis for the best possible clearance provided, without side effects.

Keywords

Medium Cut-Off, Hemodiafiltration, Predilution, Postdilution, Expanded Hemodialysis, Conventional Hemodialysis, Kt/V, URR, β_2-Microglobulin, Prolactin

1. Introduction

The accumulation of medium molecular weight (MW) uremic toxins, which are poorly removed by conventional hemodialysis, may play an important role in the occurrence of cardiovascular events in hemodialyzed patients [1]. However, high flux hemodialysis did not provide clinical improvement with better clearance of these molecules [2], while online hemodiafiltration (HDF) with its better clearance of MW toxins improved survival (CONVINCE study) [3]. Of course, online HDF has limited use: a) because it may not be possible to apply it to all patients, due to technical reasons (low blood supply from the fistula or central venous catheter), as is the case in Japan, b) it is not widely available in many countries, nor is its uncontrollable use allowed to those who need it due to financial reasons (there is a limitation on the percentage of patients allowed to use it in most countries in the world) [4] [5], and c) due to the inability of the dialysis machine (artificial kidney) to provide sufficient and ultrapure dialysate during a dialysis session [6].

In particular, in Japan, where online HDF cannot be applied due to the inability of vascular access to provide a sufficient amount of blood to enable a large substitution volume in postdilution, ultimately, with medium cut-off dialyzers (MCO) and the application of expanded hemodialysis (HDx), improved survival was achieved, with 90% of patients being cleared with this method [7]. This is conventional hemodialysis with the new type of filters (super high flux, as they are called in Japan) or medium cut-off (MCO, as they are called in Europe) [8] [9], which have a larger pore size in the capillaries than classic high flux filters and a smaller internal diameter, which allows high rates of both internal filtration and backfiltration and can improve the removal of medium and large MW toxins [10] [11]. Thus, while the intact membrane of the MCO dialyzer allows the passage of MW molecules above 70,000 Da to some extent, the sieving coefficient (SC) of these membranes shifts towards lower MW during the dialysis session. In particular, the pores of the capillaries of the MCO membranes before contact with the blood are slightly larger and within the first 40 min of the session, a natural protein layer is created on their surface [12] which reduces their radius to 3.0 - 3.5 nm, which affects the removal of dissolved toxins. Because this does not allow the loss of significant amounts of albumin, which has a radius of 3.51 nm [12] [13]. However, since the duration of the hemodialysis session is approximately 4 hours, this means that in the remaining time, *i.e.* 83% of the duration of the treatment, blood purification is achieved by a membrane, the performance of which is affected by this protein coating. Ultimately, MCO membranes aim to improve the removal of toxins with medium MW by selectively not allowing the removal of proteins, thus limiting albumin loss below 5 g/session, as highlighted by previous study [7].

MCO membrane hemodialysis has been called HDx because of the wider range of dissolved toxins and molecules that it can remove by diffusion and convention [14]. As these dialyzers have larger pores, they could remove molecules of various sizes, from small to large, including those categorized as large-medium. The term HDx was therefore proposed to define a process where diffusion and convention are easily combined within an MCO capillary dialyzer [15]. This is due to the cut-off of the membrane pores with an increased size and the sufficient internal diameter of the filter capillaries, events that favor internal (within the dialyzer) reverse filtration (backfiltration), combined with an architectural structure, which allows MCO membranes to achieve good removal of medium and large MW toxins, compared to conventional hemodialysis [13]. Backfiltration, although it is an invisible mechanism, allows a significant volume of ultrafiltrate to be moved by convention into the dialyzer capillaries from the dialysate (blood space), where precisely in the dialyzer the filtration occurs in its proximal part and the backfiltration compensates for the excessive filtration rate in its distal part [16]. The ultraviolet radiation control system present in the hemodialysis machine regulates the process and provides the exact amount of pure filtration required for the patient's planned weight loss.

The question that arises with the emergence of HDx and its advantages is its indications, determining who should be included and who is expected to benefit from it. It must be determined whether HDx should be used as a rescue therapy for patients with complications related to uremic toxin (erythropoietin-resistant anemia, malnutrition-inflammatory syndrome, bone and cardiovascular disorders) or as an optional therapy for patients who develop severe complications. HDx could perhaps be an ideal therapy for patients who are transitioning from peritoneal dialysis to hemodialysis and are awaiting renal graft for transplantation. The answer to these questions may come from personal experience and studies, as has happened for previous innovative therapies, such as bicarbonate hemodialysis and HDF.

The present study was designed to investigate whether MCO dialyzers can be used in online HDF methods (with pre- or post-dilution), how much patients could benefit, and what risks such use entails (if any and to what extent).

2. Patients and Methods

2.1. Patients

This prospective, interventional study was performed in «Dimokrition» Renal Unit (one center), Komotini, Greece, from March 2025 to December 2025. The study examined the effectiveness and side effects of using an MCO dialyzer in two online HDF methods (pre- and post-dilution), compared to its classic use of the same filter in the HDx. At the same time, the effectiveness of an equal surface filter in conventional hemodialysis (low flux) was also comparatively assessed.

The study included patients who were at least 6 months in dialysis, who were on a program 3 times a week, of at least 4 hours/session. All patients were stabilized. Excluded from the study patients who were <18 years old, pregnant women, those with malnutrition, those with arrhythmias or a major cardiac event 3 months before the beginning of the study and those who had frequent hypotensive episodes during dialysis session or were hemodynamically unstable. Patients with chronic inflammatory diseases and severe dysfunction of liver, heart and lungs were also excluded. All patients had the ability to provide blood from their vascular access of 400 ml/min (both from internal arteriovenous anastomosis and from a jugular permanent hemodialysis catheter).

2.2. Methods

Each patient underwent with the same dialyzer one session of predilution online HDF (Group A), one with postdilution online HDF (Group B) and another one with HDx with the same filter (Group C). We also have done one session of conventional hemodialysis with low flux dialyzer of the same composition and surface area (Group D) to compare effectiveness with the previously mentioned dialysis methods. All sessions were done on Wednesday or Thursday and the distance between them was one week. The order in which the dialysis sessions with the MCO dialyzer were performed in each patient was first the predilution online HDF, then one week the postdilution online HDF and another week latter the HDx. Finally, one week later the session with the low flux dialyzer (conventional hemodialysis) was performed. All patients underwent dialysis sessions with Nikkiso DBB EXA machines.

The filters used were polyethersulfone (Elisio 21 HX, Nipro [Super High Flux]) for online HDF and HDx, with a surface area of 2.1 m^2, and Elisio 21L (low flux dialyzer) for conventional hemodialysis with surface area also of 2.1 m^2. All patients were dialyzed with the same dialysate in terms of sodium (140 mmol/L), potassium (3.0 mmol/L), calcium (1.5 mmol/L), bicarbonates (33 mmol/L), glucose (5.6 mmol/L), acetate 3 mmol/L, and magnesium (0.5 mmol/L). All patients used vemiparin (2500 - 3500 IU/session) as an anticoagulant for dialysis needs. The blood pump (blood supply) was 400 ml/min, while the dialysate supply was 500 ml/min for all. The substitution volume for the postdilution online HDF was the 25% of blood pump (*i.e.* 100 ml/min) and for predilution online HDF the 50% of blood pump (*i.e.* 200 ml/min). The duration of each dialysis session was 4 hours.

Blood sample was taken from the arterial fistula (or from arterial catheter line) before the start of dialysis and at the end (2 minutes after reducing the blood pump to 50 ml/min), for analysis of serum urea, creatinine, albumin, β_2-microglobulin and prolactin.

The ultrafiltrate was collected in a specially made volumetric barrel, where its volume was determined. After the end of the session and after thoroughly stirring the ultrafiltrate with an electric stirrer for 10 minutes, a sample was taken to determine the urea, creatinine, albumin and β_2-microglobulin concentration (prolactin could not be determined in the total ultrafiltrate because of its very low concentration therein). The reduction ratio (RR) has been calculated by the following equation: RR = (Substance$_{Pre}$ − Substance$_{Post}$: Substance$_{Pre}$) × 100 (where the substance was urea, prolactin or β_2-microglobulin). The Daugirdas II formula [17] was used to evaluate the effectiveness of hemodialysis (Kt/V). The % change in serum prolactin was determined before and after the end of the session, as well as the amount of albumin removed in the ultrafiltrate in each patient and during each dialysis method. The primary outcomes of the study were the integration of online HDF methods with the MCO dialyzer, and their effectiveness and safety compared to extended hemodialysis and the tolerance of these methods, with recording of hypotensive episodes that any patient would likely experience due to albumin loss during the application of online HDF methods.

The Abbott Alinity C analyzer was used to determine the parameters studied. Serum urea was determined by an enzymatic method, creatinine with kinetics, while albumin was determined by a colorimetric method. Serum prolactin determined photometrically (which determines the total molecule of prolactin and not only the monomer) and β_2-microglobulin immunoturbidometrically.

2.3. Statistical Analysis

Data was analyzed using SPSS for Windows (edition 22.0, IBM SPSS Statistics. IBM Corp., Armonk, New York, USA). Quantitative data are presented as mean and standard deviation (mean ± SD). Comparison of quantitative data between groups was made using t-test for dependent samples. Statistically significant changes were considered with a significance level of $p < 0.05$.

2.4. Ethical Committee

This prospective study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects and was approved by the Scientific Council of the General Hospital of Komotini, Greece (03/02/2025, registration number 1/2025). The patients included in the study agreed to sign their consent to participate, after being thoroughly informed about the protocol.

3. Results

A total of 15 patients were included in the study (7F, 8M), median age 71 years (range 54 to 85), who had been on dialysis for 17 - 486 months (mean ± SD = 134.5 ± 140.8 months). The primary renal diseases were glomerulonephritis (4), diabetic nephropathy (1), polycystic kidney disease (3), hypertensive nephrosclerosis (2), lupus nephropathy (1), lithium nephropathy (1), nephrolithiasis (1), and unknown cause (2). Only three patients had residual diuresis (about 1000 ml/24h each), with GFR < 2 ml/min. Eleven of the 15 patients had arterio-venous fistula, one arteriovenous graft and 3 central permanent hemodialysis vein catheters.

No patient had to reduce the delivered convection rate (delivered convection volume) due to an alarm in any of the online HDF methods used. The patients' transmembrane pressure (TMP) in the last hour of the session was in Group A 189 ± 48.4 (range 117 - 279), in Group B 91.7 ± 20.3 (range 73 - 153), and in Group C 7.0 ± 5.5 (range 0 - 18). A statistically significant difference was noted between Groups A and B ($p < 0.001$), Groups A and C ($p < 0.001$) and Groups B and C ($p < 0.001$). It is underlined that the substitution volume was achieved in all patients in each method online HDF (50% of blood pump which was 400 ml/min in predilution και 25% of blood pump which was also 400 ml/min in postdilution). The mean±SD of ultrafiltrate during predilution online HDF was 1633 ± 505 ml, during postdilution HDF 1593 ± 399 ml and during HDx 1553 ± 576 ml (no statistical differences were noted between them, p = NS in all comparisons).

Kt/V and urea reduction ratio (URR) show that Groups in A and B were better than Groups C and D (but not in all comparisons) (**Table 1**). Specifically, Kt/V was better in Group B in comparison with Groups C and D and was marginally better in comparison with Group B ($p = 0.054$). Also, URR of Group A was better than in Group D, and Group B was marginally better than Group D ($p < 0.06$). That means URR in predilution online HDF was better and postdilution online HDF was a little bit better in comparison with conventional hemodialysis.

Table 1. It contains the Kt/V and URR of patients in each group and their statistical analysis (Group A = predilution online HDF, Group B = postdilution online HDF, Group C = HDx hemodialysis, Group D = conventional hemodialysis).

Patients	Kt/V				URR (%)			
	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D
1	1.91	1.93	1.89	1.87	79.8	80.4	79.8	79.5
2	2.05	2.12	1.96	2.07	83.4	83.9	80.6	82.5
3	1.72	1.86	1.64	2.20	77.0	79.4	75.4	77.2
4	2.31	2.23	2.32	2.11	85.8	85.3	86.5	83.6
5	1.89	1.94	1.77	1.77	80.1	80.8	77.8	78.1
6	1.57	1.48	1.47	1.50	74.5	72.5	72.0	73.4

Continued

7	1.90	2.08	1.90	1.82	80.7	83.3	81.1	79.0
8	2.10	2.45	2.08	2.15	83.5	86.8	82.2	83.2
9	2.38	2.58	2.38	2.42	86.7	88.3	86.7	87.3
10	1.68	1.75	1.70	1.42	76.7	78.5	77.4	71.0
11	2.37	2.51	2.58	2.00	86.3	88.0	88.3	88.6
12	1.93	2.07	1.92	1.88	81.5	73.6	82.1	80.0
13	2.45	2.53	2.29	2.19	87.4	87.9	85.6	84.2
14	2.18	1.99	1.83	1.69	84.3	82.2	80.1	76.6
15	1.87	1.87	1.97	1.97	80.7	81.4	82.4	82.4
Mean ± SD (range) median	2.02 ± 0.28 (1.57 - 2.45) 1.93	2.09 ± 0.31 (1.48 - 2.58) 2.07	1.98 ± 0.29 (1.47 - 2.58) 1.92	1.94 ± 0.26 (1.42 - 2.42) 1.97	81.8 ± 4.0 (74.5 - 87.4) 81.4	82.2 ± 4.7 (72.5 - 88.3) 82.2	81.2 ± 4.3 (72 - 88.3) 81.1	80.4 ± 4.7 (71 - 88.6) 80.0
p	A-B = 0.054 A-C = NS A-D = NS B-C < 0.006 B-D < 0.02 C-D = NS				A-B = NS A-C = NS A-D < 0.05 B-C = NS B-D < 0.06 C-D = NS			

Table 2 shows the better removal of β_2-microglobulin (in mg/session) and prolactin (% differences) in online HDF (pre- or post-dilution) in comparison with the other methods of dialysis assessed in this study (HDx or conventional hemodialysis). Only the comparison of removed amount of β_2-microglobulin in post-dilution online HDF and in HDx shows a marginal significance of p value ($p = 0.055$). That means patients with online HDF using MCO dialyzer succeeds better clearance of medium MW toxins.

Table 2. It shows the amount of β_2-microglobulin removed (in mg/session), as well as in the % change of serum prolactin/session. Statistically it appears that the amount of β_2-microglobulin removed was clearly better with predilution online HDF, compared to HDx. Also, the change (%) in prolactin (decrease) seems to be greater with online HDF (better with postdilution) compared to HDx.

Patients	Removed amount of β_2-microglobulin (mg/session)				Change (%) of serum prolactin during one session			
	Group A	Group B	Group C	Group D	Group A	Group B	Group C	Group D
1	34.3	29.28	24.6	30.6	65.4	77.0	50.3	+4.7
2	42.0	21.97	24.2	18.1	53.0	16.1	43.7	+4,6
3	34.0	36.55	24.6	24.5	54.9	68.5	33.0	-7.1
4	25.7	29.10	18.18	24.4	72.9	80.1	64.7	-5.4
5	42.6	36.6	18.7	24.4	57.4	77.1	50.2	+4.4
6	34.0	29.34	24.2	24.4	49.6	58.9	36.9	-3.4
7	34.3	36.5	31.3	24.3	60.3	72.1	51.8	-17.2
8	25.7	29.3	31.2	24.5	57.8	81.4	55.3	-29
9	33.8	21.87	24.7	30.75	61.8	80.1	61.8	+3.2
10	42.5	30.22	31.2	24.42	65.9	75.5	51.8	+6.6

Continued

11	25.5	21.75	30.4	24.3	73.8	83.7	69.5	71.7
12	34.2	29.28	24.5	27.7	67.0	76.8	54.8	+8.0
13	25.5	29.28	18.37	24.3	75.5	87.4	66.3	+1.5
14	34.0	36.45	39.3	24.4	53.9	73.5	54.2	-7.5
15	33.76	36.2	30.5	30.5	62.7	56.6	66.8	-66.8
Mean ± SD (range) median	33.4 ± 6.1 (25.5 - 42.6) 34	30.2 ± 5.2 (21.75 - 36.6) 29.3	26.4 ± 5.7 (18.2 - 39.3) 24.6	25.4 ± 3.2 (18.1 - 30.8) 24.4	62.7 ± 7.9 (49.6 - 75.5) 61.8	71.0 ± 16.8 (16.1 - 87.4) 76.8	54.1 ± 10.4 (33 - 69.5) 54.2	(noted increase in 8, Mean ± SD = 13.1 ± 22.2) (noted decrease in 7, Mean ± SD = 19.5 ± 21.0)
p	A-B = NS A-C < 0.005 A-D < 0.001 B-C = 0.055 B-D < 0.008 C-D = NS				A-B < 0.04 A-C < 0.001 B-C < 0.001			

Table 3 shows the amount of albumin lost (in g/session), which was significantly greater with online HDF (pre- or post-dilution) compared to both HDx and conventional hemodialysis. The largest albumin loss observed was 130.4 g/session (in postdilution HDF). As can be seen from **Table 3**, in predilution online HDF 3 of the patients had zero albumin loss, while in postdilution 2 had 0 loss albumin, when with the same filter in HDx group 7 losses ranged from 23.03 to 79.95 g/session, but 5 had 0 loss.

Table 3. The amount of albumin lost (in g/session) was significantly greater with online HDF (pre- and post-dilution) compared to both HDx and conventional hemodialysis. It is worth emphasizing that 11 patients in Group A (predilution), 10 patients in Group B (postdilution), and 7 patients in Group C (HDx) had albumin loss > 20 g/session.

	Group A		Group B		Group C		Removed amount of albumin (g/session)			
Patients	Serum albumin (g/dL)						Group A	Group B	Group C	Group D
	pre	post	pre	post	pre	post				
1	4.3	4.4	4.2	4.7	3.9	4.3	37.7	95.2	33.2	1.0
2	3.8	3.9	3.7	3.7	4.1	3.8	0	4.4	0	0.4
3	3.9	4.1	3.8	4.0	4.0	4.2	59.5	16.1	80.0	0.3
4	4.0	4.2	4.1	3.8	4.0	3.9	124.8	23.3	23.0	0.1
5	3.9	4.2	3.9	4.2	3.8	4.3	102.2	20.5	69.8	0
6	3.9	4.0	4.0	4.0	3.8	3.9	0	0	0	0
7	3.7	3.7	3.8	3.8	3.8	3.9	60.0	67.1	1.2	0
8	3.9	4.2	3.8	4.3	3.8	4.6	24.0	0	6.1	0

Continued

9	3.8	4.0	3.8	3.3	3.8	4.0	0	16.0	29.1	0
10	4.0	4.5	4.1	4.4	3.9	4.2	73.1	79.1	0	0.3
11	3.8	4.1	3.9	3.9	4.0	4.2	45.8	55.1	0	0.3
12	4.0	4.5	4.2	4.6	4.1	4.7	18.8	123.0	40.4	0
13	4.0	4.4	3.9	4.8	3.9	4.3	86.7	130.3	69.3	0.8
14	4.0	4.1	3.7	3.7	3.9	3.7	35.7	129.8	0	0.1
15	3.9	4.0	3.7	3.8	3.7	3.7	35.4	86.9	13.3	0.1
Mean ± SD	3.9 ± 0.1	**4.1 ± 0.2**	3.9 ± 0.2	**4.1 ± 0.4**	3.9 ± 0.1	**4.1 ± 0.3**	46.9 ± 36.5 (0 - 124.8) Median 37.7 (3 had 0)	56.5 ± 47.0 (0 - 130.3) Median 55.1 (2 had 0)	24.4 ± 27.7 (0 - 80) Median 13.3 (5 had 0)	0.23 ± 0.30 (0 - 1.0) Median 0.10
p (serum pre-post)	<0.0001		<0.01		<0.02					
p (serum levels at the end)	No statistically significant difference was found in serum albumin levels at the end of each dialysis session between groups (bold numbers)									
p (removed albumin amount)							A-B = NS A-C < 0.04 A-D < 0.001 B-C < 0.05 B-D < 0.001 C-D < 0.01			

In addition, the serum albumin concentration was determined before (pre) and after the end (post) of the session (A, B and C) and a significant difference was found between pre- and post-session in each group. However, no difference was noted in the serum albumin levels after the end of the session (post) when comparing the levels between groups A, B and C (**Table 3**).

No clinical side effects (hypotension episodes) were recorded in our patients during the study with any of the methods used. No one complained about anything during the session and thereafter.

4. Discussion

Because urea accumulation determines the need for dialysis and its removal indicates its effectiveness, the urea Kt/V index is appropriate for patients undergoing conventional hemodialysis. Both K/DOQI and JSDT (Japan) recommend a dialysis dose with a Kt/V of 1.4 per session and a minimum Kt/V of 1.2 [18] [19], however, both in this study and in our regular controls, we achieved a much higher Kt/V. However, it has been found that patients on dialysis with MCO dialyzer have a better prognosis, even with the same Kt/V [20].

No difference was found in the reduction rate of small MW toxins (urea, creatinine, phosphorus) in online HDF compared to HDx [21] [22], however, in this study we found a better Kt/V delivered in postdilution online HDF, compared to HDx ($p < 0.006$) and conventional hemodialysis ($p < 0.02$), results with which others also agree when comparing online HDF with HDx (1.80 ± 0.30 vs. 1.5 ± 0.2, p = 0.0002) [23]. Of course, our Kt/V in postdilution online HDF was on average higher in comparison with HDx and conventional hemodialysis (2.09 ± 0.31 in postdilution vs 1.98 ± 0.29 in HDx and vs 1.94 + 0.28 in conventional hemodialysis), while it was marginally larger compared to the predilution online HDF (2.09 ± 0.31 in postdilution vs 2.02 ± 0.28 in predilution) (**Table 1**).

Hemodialysis with MCO dialyzers in HDx seems attractive, given their better permeability, selective retention of dissolved molecules (albumin) and better backfiltration resulting from the combined diffusion and convention within the same filter, without substitution fluid (which is necessary in online HDF). Thus, based on the existing data, one can claim that MCO dialyzers have at least the same efficiency as online HDF dialyzers in removing medium MW uremic toxins, such as β_2-microglobulin (MW 11,800 Da). These dialyzers present special characteristics, which include not only a higher ultrafiltration coefficient, but also a higher clearance rate of β_2-microglobulin [24]. The latter is a uremic toxin, the prototype of medium MW molecules.

Initially, it should be mentioned that HDx provides better toxin clearance compared to conventional hemodialysis, as researchers found, who with MCO dialyzers in HDx found a greater reduction in medium and larger MW toxins, compared to high flux hemodialysis (β_2-microglobulin RR 74.7% vs. 69.7%) [21].

In the literature, of course, there have been conflicting results regarding the removal of β_2-microglobulin with HDx, compared to postdilution online HDF, regardless of the substitution volume [21] [25]-[28]. In 9 patients with high-volume postdilution online HDF or HDx (4-week treatments with each dialyzer), researchers found no difference in the reduction rate of β_2-microglobulin levels (67.9 ± 11.7% vs 71.6 ± 5.7, p = 0.26) [11], as many others have found [25] [26] [29] [30]. Recently, however, a meta-analysis of 18 studies with 853 patients found that HDx is less effective than online HDF in removing β_2-microglobulin, but better for larger MW toxins [31]. Others in 39 hemodialyzed patients found better β_2-microglobulin removal with HDx compared to conventional hemodialysis (β_2-microglobulin reduction by 71.5% - 72.0% in a 4-hour dialysis session), which was however better with postdilution online HDF (78.5% vs 80.6%) [32], as we also found by determining the amount of β_2-microglobulin removed, which was greater in predilution online HDF compared to HDx using the same dialyzer (Group A-C < 0.005), but also marginally significantly greater in postdilution online HDF compared to HDx (p = 0.055) (**Table 2**).

Studies have compared the removal of uremic toxins between HDx and online HDF based on the reduction ratio (RR%) for various uremic toxins of medium MW. It is known that the effectiveness of online HDF depends mainly on the convention volume, which is influenced by the vascular access supply [15], the filtration fraction (ultrafiltration rate) and the ultrafiltration coefficient of the dialyzer. One study showed that the minimum convention volume in predilution online HDF, required to overcome the effectiveness of HDx, was 17.6 L/session, with a blood flow of 400 ml/min and 19.2 L/session with a flow of 350 ml/min [33]. Another study showed that online HDF with a large convention volume (mean ± SD = 28 ± 8 L/session) had a higher RR for medium MW uremic toxins compared to the HDx group [21]. We found statistically significant differences in the amount of β_2-microglobulin removed with a 400 ml/min blood pump and 4-hour sessions (**Table 2**).

It also appears that the removal of the medium MW uremic toxins depends not only on the dialyzer and the method of dialysis, but also on factors such as the duration of dialysis session and the volume of the ultrafiltrate. That is, high-volume predilution online HDF showed better removal of various medium MW toxins (β_2-microglobulin). In a study, it was found that the RR of prolactin with online HDF was 45% and 61% with HDx ($p < 0.001$). In fact, the RR of prolactin with MCO dialyzer was 60.0 ± 8.20% and with online HDF 69.2% ± 9.13%, a difference that was significant ($p < 0.001$), when the blood supply to the filter was 450 ± 80 ml/min [21]. However, we found better prolactin clearance with online HDF (both predilution [62.7% ± 7.9%] and postdilution [71.0% ± 16.8%]), compared to HDx [54.1% ± 10.4%], with better postdilution online HDF) (**Table 2**). Maduell *et al.* who studied HDx in 18 patients with various dialyzers, with a mean session duration of 285 ± 19 min, blood flow of 444 ± 16 ml/min and dialysate flow of 400 ml/min, found a RR of prolactin of 65.1% ± 6.0% with Elisio HX 19 and 64.7% ± 8.5% with Theranova 400 HDx [34].

Potential disadvantages of MCO dialyzer include a) loss of albumin in dialysate and b) reverse transport of toxins from the dialysate into the blood (backfiltration), although some of them adsorb toxins and thus inhibit their reverse transport.

MCO filters were designed to be able to remove toxins of medium and large MW (above the size that the high flux filter can remove and up to the MW of albumin, without losing the latter to the dialysate), so that they are suitable for use in conventional hemodialysis programs and treatment methods, *i.e.* 4-hour sessions, 3 times a week. These present special characteristics, which include not only a higher ultrafiltration coefficient, but with small loss of albumin [26] [35]. It is noted that the loss of albumin to the dialysate, with low flux filters is less than 1 g/session (and in high flux it was found <1 g/session), while with HDx and online HDF it ranges from 1.5 and 2.5 g/session [22] [34]. In Europe, large volume (16 - 26 L) postdilution online is used, with membranes of low permeability for albumin and with limited albumin loss, not exceeding 3.4 g/session [36] or 5 g/session at a convention volume of 23 L/session [13] [37], without of course being able to calculate the albumin adsorbed on the walls of the filter capillaries. The loss of albumin through MCO dialyzers (although theoretically tolerable), is what does not allow these filters to be used in other dialysis methods, such as e.g. in online HDF, to avoid its increased losses of albumin, which could obviously lead to a progressive decrease in its serum levels [38].

The safety of HDx is therefore ensured by reducing the pore size of the filters to limit albumin losses below 5 g/session [13] [37]. In this regard, most published studies report that MCO membranes lead to a greater loss of albumin than conventional hemodialysis, while presenting unstable results compared to online HDF. Thus, in the study by Maduell *et al.*, Elisio HX filters in HDx showed an average loss of albumin in the dialysate of 1.6 g/session, higher than that removed with conventional hemodialysis [34]. Also, in a study with a blood flow of 300-350 ml/min and dialyzer with a surface area of 2.0 and 2.1 m^2, they achieved Kt/V of 1.13 to 1.91, with minimal albumin loss (257.14 ± 303.35 mg/session, with Elisio-HX dialyzer) [39], much smaller quantity than what we found in our study (**Table 3**). In our study, the greater amount of albumin noted to be lost in the online methods with the MCO dialyzer could be attributed to the higher TMP recorded in the online methods, compared to the HDx.

Although MCO membranes lead to a greater loss of albumin than conventional hemodialysis, the findings are not comparable with online HDF [10] [26]. A recent systematic review found no significant difference in albumin loss between HDx and online HDF [31], while in the study by Lukkanalikitkul *et al.*, minimal % change in albumin was observed with MCO filters (9.73% ± 7.70% in online HDF and 5.15% ± 6.67% in HDx, p = 0.051), while its serum levels at the end of the study did not differ between the two groups (4.02 ± 0.24 vs. 4.00 ± 0.23 g/dl, p = 0.74) [23]. Garcıa-Prieto *et al.* found that albumin losses were 0.03 g/session with MCO dialyzers and 3.1 g/session with online HDF (p = 0.001) [21]. Although it seems that the safety of MCO dialyzers is maintained by regulating the size of their capillary pores, thus limiting albumin loss to below 5 g/session [7], as shown by several studies, we, with the dialysis conditions we applied (blood pump 400 ml/min, dialysate flow rate 500 ml/min and session duration 4 hours), we found higher albumin lose in online HDF using MCO dialyzers in comparison to HDx (**Table 3**).

Albumin is the most abundant circulating plasma protein (serum range levels 3.5 - 5.0 g/dl in healthy individuals), while hepatocytes synthesize 10 - 15 g of it daily. It has even been suggested that a small and controlled loss of albumin can stimulate its synthesis, which is important, since its levels are associated with better general health and survival. This amount is apparently sufficient to prevent significant hypoalbuminemia in cases of large albumin loss from a dialyzer. Thus, from the comparison of the serum albumin levels in each group after the end of the session, it seems that there were no differences between them (p = NS in all comparisons, **Table 3**), when the ultrafiltrate removed/session was similar within the groups. If we also consider the enormous capacity of albumin production by the liver in normal conditions and in the presence of sufficient structural elements (proteins-amino acids) [40], it becomes clear that the problem of hypoalbuminemia does not arise perhaps in most patients, regardless of the dialysis method used (with MCO dialyzer).

As mentioned above, there are two main causes of hypoalbuminemia, the one due to its reduced production, due to an inflammatory or infectious cause (known as protein-energy wasting syndrome) and the other due to albumin losses (as occurs, for example, in peritoneal dialysis, where its weekly losses range from 21 - 42 g/1.73 m^2, which are well tolerated and not associated with poor outcome) [41] or in other forms of dialysis (e.g. online HDF, HDx). In the first case, in inflammatory or infectious conditions there is suppression of the gene responsible for albumin production by the liver (due to stimulation of acute phase response) and of course there is a situation where the possible inflammatory process also determines survival [42]. In the second case, there is simply a loss of albumin, which the liver can replace by increasing its production, when this works normally. Indeed, there is a possibility of increased hepatic synthesis of albumin [37], perhaps by 3 - 4 times [40], in which case the problem is resolved, while a better method of removing toxins is offered by various methods (e.g. with online HDF with MCO dialyzers or even with HDx), as we found in this study.

Furthermore, if we take into account the fact that high-flux hemodialysis has been shown to have better removal of toxins, despite greater albumin loss and serum albumin levels < 4 g/dl, compared to those on a conventional hemodialysis program, it is suggested that in addition to the serum albumin level, mortality is affected by β_2-microglobulin clearance and the albumin sieving coefficient of the dialyzer. Indeed, one study found that high albumin leakage and the occurrence of hypoalbuminemia do not worsen survival in hemodialysis patients with dialyzers achieving β_2-microglobulin clearance ≥ 50 ml/min or in patients undergoing online HDF [43].

Also, in hemodialyzed patients without inflammation, mortality was not found to be significantly different between those with hypoalbuminemia and those with normoalbuminemia [44]. Thus, it has been suggested that mild hypoalbuminemia due to high albumin leakage is not an independent predictor of mortality in the absence of protein-energy-wasting syndrome or inflammation. Furthermore, survival was found to be better in HDx hemodialysis with high albumin leakage compared to online HDF with low albumin leakage, suggesting that polyethersulfone (PES) was the cause of this difference, in which was attributed the better survival [45].

The degree of purity of the dialysate also plays a role in better survival with MCO dialyzers, which was also shown in the CONVINCE study [3]. Thus, in addition to the better clearance of medium and large MW toxins, HDx has a much better survival due to the excellent water quality (ultrapure substitution fluid), which improves the prognosis of hemodialyzed patients in Japan, and which contributed to the lower levels of C-reactive protein, as shown in one study. According to the researchers, this may be due to the purer dialysate they achieved there, on the basis that the backfiltration in HDx is greater and it would be necessary for the dialysate to be as pure as possible [20].

Furthermore, in Europe, in postdilution online HDF of large volumes, albumin leakage when it does not exceed 3.4 g/session [36] or 5 g/session with a substitution volume of 23 L/session, does not seem to be of particular concern. Accordingly, in Japan, where predilution online HDF is performed, moderate to large substitution volume and using low to high-permeability membranes, or in post-dilution online HDF of low to moderate substitution volume, with low to high-permeability membranes, safe albumin leakage has been defined as less than 5 g/session [46] [47]. This loss is not associated with reduced survival [43]. The disadvantages of hypoalbuminemia are edema, hypotension caused during the dialysis session (intradialytic) because of hypovolemia, and increases in serum levels of fibrinogen and lipoprotein-α.

In our study, both from the fact that albumin losses were about twice as much with online HDF with MCO dialyzers in comparison with HDx there were at least 7 patients with albumin loss in first one similar to that of these in HDx who could perhaps benefit from the implementation of online HDF with MCO filters which is better in the removal of small and medium MW toxins and when this cannot be applied with predilution online HDF with se same dialyzer, is also preferable for the best clearance provided.

Thoughts and Proposal: In predilution online HDF (Group A) 3 patients had zero albumin loss, but 11 had loss of albumin more than 20 g/session, when in patients of Group B (postdilution) 2 patients had 0 loss of albumin, but 10 had loss more than 20 g/session, in comparison with HDx where 5 patients had 0 albumin loss but 7 patients had loss of albumin more than 20 g/session. With these results, why not allow the use of MPO dialyzers for online HDF, when HDx also has a significant loss of albumin? On the other hand, looking at the clearance provided, it seems that postdilution online HDF with MCO dialyzers was probably better for small MW toxins than HDx, while the clearance of β_2-microglobulin in predilution was better than in HDx, but also postdilution online HDF was marginally better than HDx. Regarding the % clearance of prolactin, postdilution and predilution online HDF were better than HDx. With these data and the knowledge that the liver can produce a much larger amount of albumin than is lost most of dialyzed patients by any method (as shown in this study), it would be advisable to try online HDF (pre- or post-dilution) with MCO dialyzer in all patients and to use these methods in those who lose smaller amounts of albumin, which certainly perform better than HDx and of course offer better survival. Perhaps the cost of MCO dialyzers should also be considered here!

Limitations of the study: These include the small sample size, the fact that the estimates were based on a single session with each method, and the fact that we were unable to determine the levels of prolactin lost in the ultrafiltrate. We also did not include in our study measurements of other toxins with a higher MW than that of prolactin and lower than that of albumin, to show the contribution of HDx in the removal of larger toxins. However, the fact that we measured the total amount of toxins removed in the ultrafiltrate (except for prolactin, whose amounts in the ultrafiltrate were very small and difficult to determine), gives value to our study, compared to others who checked the percentage change in the serum levels of toxins and which apparently continues to be produced during the dialysis session. However, our results are positive and strong, especially for those who cannot be in a high volume online HDF method.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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