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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Beta-2 microglobulin removal with postdilution online hemodiafiltration – comparison of three different dialysis membranes

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SUMMARY

Introduction Accumulation of middle molecular weight uremic toxins causes various complications in chronic hemodialysis (HD) patients. Postdilution online hemodiafiltration (OL-HDF) efficiently removes these molecules.

This study aimed to assess the effectiveness of three different dialysis membranes in removing β_2-microglobulin (β_2m) within a single session of postdilution OL-HDF.

Method A prospective single-center study was carried out in 30 patients (23 males and seven females, average age 54.87 ± 11.66 years, time on dialysis 4.95 ± 5.4 years) on maintenance HD. Each patient was followed for three consecutive weeks on OL-HDF with three different dialyzers: DiacapPro 19H, FX CorDiax 800, and Elisio 21H, randomly switched weekly. The reduction ratios (RR) of β_2m and albumin were compared individually. The results were analyzed with the Kolmogorov–Smirnov test, ANOVA, and the Kruskal–Wallis test.

Results The average convective volume for all patients was 21.38 ± 2.97 L/session. β_2-m RR was 70.86 ± 6.87%, 74.69 ± 6.51%, and 70.04 ± 9.37% with Diacap Pro 19H, FX CorDiax 800 and Elisio 21H membrane, respectively (p = 0.054). Albumin RR was 6.20 ± 2.12% with Diacap Pro 19H membrane, 6.01 ± 2.97% with FX CorDiax 800 membrane, and 6.46 ± 2.91% with Elisio 21H membrane (p = 0.812). Albumin loss was < 4 g/dialysis treatment for all membranes.

Conclusion All investigated membranes effectively remove β_2-m in postdilution OL-HDF with a tolerable albumin loss. The highest β_2-m RR was determined for FX CorDiax 800 membrane, but with no statistically significant difference.

Keywords: uremic toxins; middle molecules; albumin; β_2-microglobulin; dialyzer; hemodiafiltration

INTRODUCTION

End-stage renal failure patients requiring maintenance hemodialysis (HD) exhibit significant retention of uremic toxins. Small, water-soluble molecules, weighing up to 500 Da and not bound to protein carriers are readily cleared with HD. However, larger and/or protein-bound uremic toxins are much more difficult to remove [1]. The "middle molecules," having a molecular weight 500–60,000 Da, include several cytokines, adipokines, growth factors, and signaling proteins, such as interleukin-1β, interleukin-6, interleukin-18, tumor necrosis factor α, β_2-microglobulin (β_2m), pentraxin-3, YKL-40, and leptin. They have diverse biological roles and are associated with chronic inflammation, cardiovascular disease, and other complications in HD patients [1]. Microinflammation, malnutrition, and oxidative stress are important non-traditional risk factors for the development of atherosclerosis and resistance to erythropoietin [1–5].

Conventional HD with high-flux membranes has very limited efficiency in removing larger middle molecules [1]. Modalities employing convective transport, such as online hemodiafiltration (OL-HDF), enable enhanced removal of large uremic toxins, thus achieving cardioprotective effect and improving outcomes for HD patients [6, 7, 8]. The efficiency of HDF in middle molecules removal depends on the overall convective volume (Vconv), which is related to vascular access blood flow (Qavf), effective blood flow (Qb), and membrane properties [6, 7, 8]. Contemporary HDF membranes have a high ultrafiltration coefficient (Kuf > 40 ml/h × mmHg), sieving coefficient for β_2m > 0.6, sieving coefficient for albumin < 0.01 to prevent albumin loss over 4 g / 4 hour session, internal capillary diameter > 200 μm and capillary density per surface area > 11,000 allowing for dialysate flow (Qd) of 400–500 mL/minute [6, 7, 8]. Vconv represents the sum of the substitution volume and the net ultrafiltration volume achieved to correct extracellular fluid overload. Vconv target should be ≥ 22L per dialysis session to achieve a convection dose target [6, 7, 8].

In clinical practice, the efficiency of HDF treatment in clearing middle molecules is assessed by determining serum β_2m levels before

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and after the procedure. β_2m is a water-soluble polypeptide, made of 99 amino-acid residues, with a molecular weight of 11,815 Da. Its plasma levels increase with age in healthy individuals related to the physiological decrease in glomerular filtration rate over 50 years of age. The substance was first discovered some 50 years ago after being isolated from the urine of patients with tubular proteinuria due to chronic cadmium poisoning [9]. Nevertheless, its significance in dialysis patients was only acknowledged 15 years later, when it was isolated as a major component of the amyloid substance in dialyzed individuals, predominantly targeting the cartilage of osteoarticular tissue [10]. The incidence of dialysis-related amyloidosis increases with patients' age and longer dialysis vintage. The Japanese Society for Dialysis Therapy recommends achieving maximum predialysis serum β_2m concentration < 30 mg/L, but preferably < 25 mg/L to attenuate the development of this condition [11]. Also, β_2m seems to be significantly associated with mortality in maintaining HD patients [12].

This study aimed to assess the effectiveness of three different dialysis membranes in removing the middle molecule uremic toxin, β_2m, with postdilution OL-HDF.

METHODS

This prospective, single-center study was carried out among 30 patients treated with maintenance postdilution OL-HDF at the Center for Nephrology and Dialysis, Kragujevac University Clinical Center. The study was conducted according to the Declaration of Helsinki and approved by the Ethics Committee of the Kragujevac University Clinical Center (Decision No 01-20-765). All the patients gave their informed consent for participation.

All the patients were receiving regular maintenance HDF program on Fresenius 5008S (Fresenius Medical Care, Bad Homburg, Germany), Gambro Artis (Baxter Gambro Dasco S.p.a., Medolla, Italy) and B. Braun Dialog+ (B. Braun Avitum AG, Melsungen, Germany) machines with controlled ultrafiltration, thrice weekly, with routine dialysis parameters: dialysis time four hours, dialysis buffer with bicarbonate, Qb range 257 ± 18.65 mL/minute and Qd of 500 mL/minute. Blood flow and Qd were not changed for any patient throughout the follow-up. The standard ultrapure dialysis fluid (bacterial count < 0.1 CFU/L and endotoxin content < 0.03 EU/mL) was used with dialysate temperature set at 37°C and sodium level of 140 mmol/L, potassium 2 mmol/L, magnesium 0.5 mmol/L, and calcium 1.25 mmol/L, 1.5 mmol/L or 1.75 mmol/L. The average Vconv was 21.38 ± 2.97 L per dialysis session (Table 1). All the patients were dialyzed through an arteriovenous fistula. The anticoagulation used was heparin sodium at an average dose of 4508.32 ± 541.92 IU per HDF session. Orders for anticoagulation type, dosage, and administration regimen (bolus injection and continuous infusion) remained unchanged. The patients received treatment with different erythropoiesis-stimulating agents (epoetin-α, epoetin-β, darbepoetin-α). All the patients were anuric with a diuresis of < 50 mL/day. Patients with an active infection, current bleeding issue, or on immunosuppressive therapy were not included in this investigation.

Table 1. Dialysis-related parameters in the investigated population

Variable	Mean ± SD
Qnuf (mL/min)	11.74 ± 3.9
Qsubs (mL/min)	80.64 ± 14.2
Qconv (mL/min)	92.37 ± 13.39
Vsubs (L)	18.58 ± 3.2
Vconv (L)	21.38 ± 2.97
FF (%)	36 ± 5
Qb (mL/min)	257 ± 18.65

Qnuf – net ultrafiltration rate; Qsubs – substitution flow rate; Qconv – convective flow rate; Vsubs – substitution volume; Vconv – overall convective volume; FF – filtration fraction; Qb – effective blood flow

Each patient was followed for three consecutive weeks during which three different dialyzers – DiacapPro 19H (B. Braun Avitum), FX CorDiax 800 (Fresenius Medical Care) and Elisio 21H (Nipro Corporation, Osaka, Japan) – were switched on a weekly basis. The technical characteristics of each membrane are presented in Table 2 [13, 14, 15]. Thus, each patient underwent three consecutive treatments with each dialyzer in a randomly assigned sequence. Dialyzer setup and preparation involving a pre-rinsing were done per the clinic's standard operating procedure. All the dialyzers were pre-rinsed in the same manner.

Blood was collected on mid-week dialysis before and after the treatment. Serum β_2m and albumin concentrations were determined by the turbidimetric method on the Beckman Coulter AU680 chemistry analyzer. The reference range for β_2m in healthy adults with this method is 0.97–1.84 mg/L and the optimum target predialysis β_2m

Table 2. Characteristics of investigated membranes

Characteristic	Diacap Pro 19H	FX CorDiax 800	Elisio 21H
Composition	a	Helixone plus	Polyethersulfone
Surface (m^2)	1.9	2	2.1
Kuf (mL/h/mmHg)	97	62	76
Capillary wall thickness (μm)	37	35	40
Internal capillary diameter (μm)	200	210	200
β_2-microglobulin SC	0.7	0.900	0.8
Albumin SC	<	0.001	0.002
Sterilization method	Gamma rays	Steam	Gamma rays
Manufacturer	B. Braun Avitum AG, Germany	Fresenius Medical Care, Germany	Nipro Corporation, Japan

Kuf – ultrafiltration coefficient, SC – sieving coefficient

serum level in dialyzed patients is < 25 mg/L. The serum albumin reference range is 35–57 g/L. β_2m reduction ratio (RR) was calculated from the following equation: $RR_{\beta 2m}$ (%) = [1 - (C_{post}/C_{pre})] × 100; where C_{pre} stands for β_2m level before and C_{post} for β_2m level after the predilution OL- HDF session [16]. Serum albumin concentration after OL-HDF session was calculated from the following formula: $Albumin_{post} = C_{alb}$ post/{1 + [(UF)/0.2 × (BW_{pre} – UF)]}, where C_{alb} is measured serum albumin concentration (g/L), UF is net ultrafiltration achieved during the particular dialysis session (L / 4 hours), and BW_{pre} is measured body weight before dialysis (kg) [16]. Albumin RR was determined from the equation: RR_{Alb} = [1 - (C_{post}/C_{pre})] × 100, where C_{pre} is serum albumin concentration before dialysis (g/L) and C_{post} is serum albumin concentration after dialysis (g(L) [16].

Ferritin and C-reactive protein (CRP) serum levels were determined on the Beckman Coulter AU680 apparatus. The reference range for ferritin in maintenance HD patients is 100–500 ng/mL. CRP was expressed as an average from two consecutive monthly measurements with a normal value being ≤ 5 mg/L and level > 5 mg/L signified the presence of microinflammation. Intact parathyroid hormone (iPTH) in serum was determined using the immunoradiometric assay on WALLAC WIZARD 1470 Gamma Counter (GMI, Ramsey, MN, USA). The normal range for iPTH is 11.8–64.5 pg/mL, and the upper limit for maintenance HD patients is 675 pg/mL [17]. Prealbumin and transferrin levels were determined with an immunoturbidimetric method on the Abbott Architect machine. The normal results for a prealbumin blood test in hemodialyzed adults are ≥ 0.3 g/L.

Normalized protein catabolic rate (nPCR) was calculated from the formula: nPCR = (PCR × 0.58)/Vd, where PCR is protein catabolic rate, Vd is body fluid volume. PCR was determined from the equation: PCR = [(9.35 × G) + (0.29 × Vd)], where G stands for an interdialytic rise in urea, which is established from the formula G = [(C1 - C2)/Id] × Vd, where C1 and C2 denote pre- and post-dialysis urea concentrations (mmol/L) and Id – the time between the two dialyzes (h). Body fluid volume is calculated as Vd = 0.58 × DW, where DW is dry body mass, i.e., patients' body mass after stable dialysis (kg) [18].

Interdialytic weight gain (IDWG) was calculated as the patients' weight at the beginning of each HD session minus the weight after the previous HD session, divided by the nephrologists' determined dry weight (%).

Dialysis adequacy was assessed based on the single pool Kt/V index calculated according to the Daugirdas' second-generation formula: Kt/Vsp = -ln(C_2/C_1 - 0.008 × T) + (4 - 3.5 × C_2/C_1) × UF/W, where C_1 and C_2 are pre-post dialysis urea levels (mmol/L), T is dialysis duration (h), UF – ultrafiltrate removed (L), and W body weight after HD (kg). According to the K/DOQI guidelines, the target Kt/Vsp is ≥ 1.2 [18].

The urea reduction ratio (URR) was calculated from the formula: URR = (1 - R) × 100%, where R is the difference between pre- and post-dialysis urea serum concentration. URR target range for adequate dialysis is 65–70% [18].

Arteriovenous fistula blood flow (Qavf) was measured with color Doppler ultrasound examination on a LOGIQ P5 machine (GE Healthcare, Chicago, IL, USA), with a 7.5 MHz probe. The reference range for adequate blood flow is 500–1000 mL/minute.

The data were analyzed by the Kolmogorov–Smirnov test, ANOVA, and Kruskal–Wallis test, using the SPSS Statistic for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) for statistical analysis.

RESULTS

The study population consisted of 23 males and seven females with an average age of 54.87 ± 11.66 years, an average time on dialysis of 4.95 ± 5.4 years, average body mass index of 23.49 ± 3.75 kg/m^2, and average dialysis adequacy index (spKt/V) of 1.41 ± 0.25 (Table 3). The etiology of end-stage renal disease was nephroangiosclerosis in 11 patients (36.66%), chronic glomerulonephritis in seven patients (23.32%), polycystic kidney disease in four patients (13.34%), and diabetic kidney disease, obstructive nephropathy, and unknown chronic nephropathy in one patient each. The comorbidities included hypertension (21 patients; 70%), hypertensive cardiomyopathy (seven patients; 23.32%), dilatative cardiomyopathy (one patient; 3.34%), and complications of diabetes mellitus (one patient; 3.34%). Mean serum indicators of anemia, iron status, microinflammation, malnutrition, and secondary hyperparathyroidism are presented in Table 4. The patients had well-controlled blood pressure and did not exceed the recommended values of IDWG.

Table 3. General patients' data

General patients' data	Mean ± SD
Number	30
Sex (M/F, %)	23/7 (76.66/23.34)
Age (years)	54.87 ± 11.66
Time on dialysis (years)	4.95 ± 5.4
Body mass index (kg/m^2)	23.49 ± 3.75
Systolic arterial blood pressure (mmHg)	128 ± 8.72
Diastolic arterial blood pressure (mmHg)	77.32 ± 5.12
Mean arterial blood pressure (mmHg)	94.22 ± 5.3
Dry body weight (kg)	71.82 ± 12.54
Interdialytic weight gain (kg)	2.35 ± 0.94
IDWG as a percentage of dry body weight (%)	3.44 ± 1.58
Ultrafiltration rate (mL/h)	587.5 ± 235.2
Ultrafiltration rate per body mass (mL/kg/h)	8.57 ± 3.92
Vascular access blood flow rate (ml/min)	936 ± 460.9
Single pool Kt/V	1.41 ± 0.25
Urea reduction ratio (%)	69.41 ± 7.06

IDWG – interdialytic weight gain

Twenty-one patients (70%) had predialysis serum β_2m level < 30 mg/L. Among them, 11 patients (36.67%) had predialysis serum β_2m level < 25 mg/L. The average RR of β_2m was 70.86 ± 6.87% with Diacap Pro 19H membrane, 74.69 ± 6.51%, with FX CorDiax 800 membrane, and 70.04 ± 9.37% with Elisio 21H membrane. No statistically

significant difference ($p > 0.05$) was observed between these values (Table 5).

Table 4. Laboratory parameters in the investigated population

Laboratory parameters	Mean ± SD
Hemoglobin (g/L)	101.2 ± 7.06
Hematocrit (%)	30.45 ± 1.78
Iron (m	11.2 ± 5.5
TSAT (%)	33.52 ± 15.2
Ferritin (ng/mL)	568.42 ± 267.85
Transferrin (g/L)	1.6 ± 0.4
iPTH (pg/mL)	220.22 ± 189.45
Total protein (g/L)	66.57 ± 3.02
Albumin (g/L)	39.77 ± 2.64
Prealbumin (g/L)	0.34 ± 0.09
Uric acid (m	368 ± 68.72
C-reactive protein (mg/L)	4.57 ± 5.48
nPCR (g/kg/24 hours)	2 ± 0.6

TSAT – transferrin saturation; nPCR – normalized protein catabolic rate; iPTH – intact parathyroid hormone

Table 5. β_2-microglobulin reduction rate, serum albumin decrease, and albumin reduction rate within a single post-dilution OL-HDF session

Variable	Membrane type			p
	Diacap Pro 19H	FX CorDiax 800	Elisio 21H	
RR-β_2M (%)	70.86 ± 6.87	74.69 ± 6.51	70.04 ± 9.37	0.054
Δ salbumin (g/L)	2.5 ± 0.92	2.4 ± 1.28	2.6 ± 1.2	0.746
RR-albumin (%)	6.2 ± 2.12	6.01 ± 2.97	6.46 ± 2.91	0.812

RR – reduction rate; Δ – difference between pre-and post-dialysis levels; s – serum

All the patients had post-dialysis serum albumin concentration > 35 g/L. The average decrease in serum albumin level after OL-HDF with Diacap Pro 19H, FX CorDiax 800, and Elisio 21H membranes was 2.5 ± 0.92 g/L, 2.4 ± 1.28 g/L, and 2.6 ± 1.2 g/L respectively. RR of albumin with the same membranes was 6.2 ± 2.12%, 6.01 ± 2.97%, and 6.46 ± 2.91%, respectively. No statistically significant difference ($p > 0.05$) was observed in neither of these parameters between different dialyzers (Table 5).

DISCUSSION

Cardiovascular diseases are the leading cause of death in patients on maintenance HD. Uremic toxins, altered endothelial function, chronic microinflammation, malnutrition, oxidative stress, resistance to erythropoietin, and anemia are the major non-traditional risk factors for the development of cardiovascular complications in this population [19, 20]. Early detection and optimal control of these issues seem to play a key role in preventing cardiovascular co-morbidity in HD patients [21]. In recent years, direct cardiotoxicity of uremic toxins has been increasingly demonstrated, while a reduction in middle molecule retention appears to be independently associated with decreased risk of mortality [22].

β_2m is a prototype of middle molecules, commonly used as a representative marker of this group of molecules retention and removal. Its concentration notably increases in end-stage renal failure and may cause the development of dialysis-related amyloidosis [23, 24]. The target β_2m predialysis level of < 30 mg/L was met in 70% of our study population, while 36.67% even had predialysis β^2m level < 25 ml/L [11, 23–26]. The highest β_2m removal rate in our study population was achieved with FX CorDiax 800 dialyzer, even though the difference was not statistically significant. This advantageous performance can be explained by the FX CorDiax membrane characteristics which have a higher sieving coefficient compared to the other investigated membranes.

Previous studies have demonstrated that the average β_2m removal rate ranges 50–60% with regular high-flux HD, to 70% with medium cut-off membranes, to 80–85% with high volume (Vconv > 22 L / dialysis session) post-dilution OL-HDF [23–26]. Somewhat lower β_2m RR achieved with post-dilution OL-HDF in our study population, ranging 70.04–74.69%, can be explained by lower than average Vconv and Qb in our study population (Table 1). High Vconv is the key factor for efficient removal of middle molecules with high volume online post-dilution and patients with Vconv < 22 L per dialysis session have significantly lower Qb and higher filtration fraction compared to patients with higher Vconv. Nevertheless, in clinical practice, Vconv ≥ 22 L per session is attainable in only around 75% of patients. In our study population, 50% of the patients achieved Vconv ≥ 22 L, while an overall of 66.67% had Vconv ≥ 20 L per dialysis session. Optimization of overall Vconv depends on patient-related factors, such as hematocrit and serum total protein level, as well as on dialysis-related determinants, including Qb, type of dialysis machine, and dialysis session length [27, 28]. The target Qb should be ≥ 350 mL/minute and it depends on Qavf and the diameter of dialysis needles. A mature fistula should have a blood flow rate greater than 600 mL/minute and some of the patients in our study group failed to fulfill this criterion due to poorly functioning fistulas, thus affecting the possibility to achieve target Qb [28]. High hematocrit and high total serum protein may increase filtration fraction and decrease the overall Vconv; however, this was not the case in our study population. In addition to these factors, achieving and maintaining target Vconv also requires continuous education and training of medical staff [28].

The lowest albumin loss during the HDF session in our study group was demonstrated with FX CorDiax 80 dialyzer. The advertised membrane characteristics for this dialyzer present a lower sieving coefficient for albumin compared to Elisio 21 dialyzer (Table 2). Nevertheless, all the patients in this study had albumin RR < 11%, accounting for a tolerable albumin loss of < 3.5 g per four-hour dialysis session. Furthermore, all the patients had post-dialysis serum albumin level > 35 g/L. Even though HDF provides better clearance of middle molecules than conventional dialysis, thus possibly improving survival, OL-HDF can lead to an increase in albumin loss across the dialyzer, especially with high permeability membrane and high Vconv, which can eventually lead to

malnutrition [29, 30]. It is therefore important to note that none of the patients in our study developed hypoalbuminemia.

CONCLUSION

All investigated membranes effectively remove middle-molecular-weight uremic toxins with acceptable albumin loss. The highest removal rate of β_2m and the lowest albumin loss was achieved with FX CorDiax 800 dialyzer.

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Уклањање бета-2 микроглобулина постдилуционом онлајн хемодијафилтрацијом – процена ефикасности три различите дијализне мембране

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САЖЕТАК

Увод/Циљ Накупљање уремијских токсина средње молекулске масе може узроковати бројне компликације код болесника лечених хроничним хемодијализама. Постдилуциона онлајн хемодијафилтрација (*OL-HDF*) успешно уклања ове молекуле.

Рад је имао за циљ да испита ефикасност три различите дијализне мембране у уклањању β_2-микроглобулина (β_2m) током појединачне сесије постдилуционе *OL-HDF*.

Методе Проспективном студијом је обухваћено 30 болесника (23 мушкараца и седам жена, просечне старости 54,87 ± 11,6 година, са дужином дијализног лечења 4,95 ± 5,4 године) који се лече постдилуционом *OL-HDF*-ом. Код свих испитаника је одређен индекс редукције β_2m и албумина током једног третмана постдилуционом *OL-HDF*-ом сукцесивном применом три дијализне мембране: *DiacapPro* 19*H*, *FX CorDiax* 800 и *Elisio* 21*H*. За статистичку анализу коришћени су Колмогоров–Смирновљев тест, *ANOVA* и Краскал–Волисов тест.

Резултати Просечан укупни конвективни волумен износио је 21,38 ± 2,97 литара по сесији. Индекс редукције β_2m износио је 70,86 ± 6,87% за мембрану *DiacapPro* 19*H*, 74,69 ± 6,51% за мембрану *FX CorDiax* 800, и 70,04 ± 9,37% за мембрану *Elisio* 21*H* (p = 0,054). Индекс редукције албумина је био 6,20 ± 2,12% за мембрану *DiacapPro* 19*H*, 6,01 ± 2,97% за мембрану *FX CorDiax* 800, и 6,46 ± 2,91% за мембрану *Elisio* 21*H* (p = 0,812). Губитак албумина у току појединачне дијализне сесије за све три дијализне мембране био је мањи од 4 *g* / 4 *h*.

Закључак Све испитане мембране ефикасно уклањају β_2m применом постдилуционе *OL-HDF* уз безбедан губитак протеина. Највећи индекс редукције β_2m уз најмањи губитак албумина остварен је применом мембране *FX CorDiax* 800.

Кључне речи: уремијски токсини; средњи молекули; албумин; β_2-микроглобулин; дијализатор; хемодијафилтрација