



Evaluation of low-volume post-dilution online hemodiafiltration with Japanese high-performance hemodiafilters

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Received: 16 October 2019 / Accepted: 23 March 2020 / Published online: 7 April 2020
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Abstract

Purpose To assess the removal performance of low-volume post-hemodiafiltration (HDF) with Japanese hemodiafilters and the removal performance with 20 % reduction in the total dialysate flow rate (Q_d total).

Methods Subjects were 8 patients undergoing pre-HDF. Study 1: Post-HDF was performed at a blood flow rate (Q_b) of 250 mL/min and a total volume of substitution fluid (Vs) of 12 L/session(s) for 4 hrs using Fineflux-210Seco (FIX), ABH-21PA (ABH), and NVF-21H (NVF). We assessed removal efficiency of small molecular solutes, low-molecular-weight-proteins and the amount of albumin loss. Study 2: Post-HDF was performed at Vs of 12 L/s under G-1, Q_d total of 500 and Q_b of 250 mL/min; G-2, Q_d total of 400 and Q_b of 250 mL/min; and G-3, Q_d total of 400 and Q_b of 300 mL/min. Removal efficiency was compared and analyzed between these conditions.

Results Study 1: The results using FIX, ABH and NVF are shown in order. The Kt/V were 1.8, 1.9 and 1.8. The β_2 -Microglobulin (MG) removal rate (RR) (%) were 81.2, 83.1 and 82.8, and the α_1 -MG RR were 37.4, 40.2 and 38.5, respectively. Study 2: The results in G-1, 2 and 3 are shown in order. The Kt/V and the RR of small solutes, were significantly higher in G-3. The β_2 -MG RR (%) were 81.2, 80.1 and 81.0, and the α_1 -MG RR were 37.4, 37.5 and 38.0, respectively.

Conclusions Low-volume post-HDF performed at Q_b of 250 mL/min with Japanese high-performance hemodiafilters exhibited favorable removal efficiency for all solutes. Even with 20 % reduction in Q_d total, the removal performance was also favorable.

Keywords Post-dilution online hemodiafiltration · High-volume post-dilution online hemodiafiltration · Low-volume post-dilution online hemodiafiltration · Japanese hemodiafilter · α_1 -Microglobulin

Introduction

At the end of 2017, in Japan, there were 334,505 dialysis patients, 21.1 % of whom were receiving online (OL) hemodiafiltration (HDF). In Japan, the pre-dilution OL-HDF (pre-HDF) is used in 84.4 % of patients on OL-HDF. Kikuchi et al. reported that pre-HDF with a volume of substitution fluid (Vs) of 40 L or more favorably affects patient prognosis

compared to pre-HDF with Vs of 40 L or less and hemodialysis (HD) [1]. Conversely, in Europe, OL-HDF has been performed in the post-dilution OL-HDF (post-HDF). High-volume post-HDF with a high blood flow rate (Q_b) has been reported to improve patient prognosis, and its effect has been reported to be enhanced with increased Vs [2–4].

In Japan, post-HDF has not been widely accepted, mainly because albumin (Alb) loss was difficult to control in post-HDF and because hemodialysis with high Q_b was not preferable. We previously reported that pre-HDF was superior to post-HDF in terms of biocompatibility [5]. Later, we reported that post-HDF using recent high-performance hemodiafilter efficiently removed low-molecular-weight protein (LMWP), caused only mild Alb loss, and was comparable with pre-HDF in terms of biocompatibility [6]. Our study showed that high-efficiency post-HDF could be achieved

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without high Q_b and high V_s by selecting an appropriate hemodiafilter.

In Study 1 of the present study, post-HDF was performed with 3 types of Japanese high-performance hemodiafilters at V_s of 12 L/session (s) and Q_b of 250 mL/min, and the removal performance was assessed. Then, we examined whether this low-volume post-HDF with moderate Q_b exhibited removal efficiency adequate for HDF. In Study 2, removal performance of post-HDF with fixed V_s of 12 L/s and 20 % reduction in the total dialysate flow rate (Q_d total) was assessed to examine whether the dialysate volume could be reduced.

Patients and methods

Ethical approval

All subjects enrolled in this research have given their informed consent. The study has been approved by our institutional committee on human and/or animal research, and this protocol has been found acceptable by them (approved number: 2019-05).

Study design and population

This prospective, single-center study included 8 stable dialysis patients undergoing maintenance dialysis by pre-HDF in our clinic (Table 1). Each patient had received pre-HDF 3 times per week (i.e., on Monday, Wednesday, and Friday or on Tuesday, Thursday, and Saturday) for 6 months or longer (Fig. 1).

Study 1 In the patients, pre-HDF was switched to post-HDF on Friday or Saturday, and post-HDF was performed 3 times under the same conditions. In the third session (on the middle day of the week), samples were collected. According to this dialysis schedule, post-HDF was repeated using 3 types of hemodiafilters for 3 weeks. The hemodiafilters used were Fineflux-210Seco (FIX) (asymmetric triacetate [ATA] membrane, Nipro Co., Osaka, Japan) in the first week, ABH-21PA (ABH) (polysulfone [PS] membrane, Asahi Kasei Medical Co., Ltd. Tokyo, Japan) in the second week, and NVF-21H (NVF) (PS membrane, Toray Medical Co., Ltd., Tokyo, Japan) in the third week (Table 2). Post-HDF was performed at Q_b of 250 mL/min and V_s of 12 L/s for 4 hrs (Table 3).

Table 1 Patient background characteristics

Patient number	Sex	Age (year)	Dialysis vintage (months)	Cause of ESRD	Dry weight (kg)
1	M	44	305	VUR	53.4
2	M	75	81	PCK	58.5
3	M	37	36	DMN	64.3
4	M	70	72	DMN	60.5
5	F	44	13	DMN	58.5
6	F	74	163	CGN	41.9
7	F	63	13	Unknown	54.2
8	F	60	238	CGN	44.4
Average		58.4 ± 14.9	115.1 ± 109.3		54.5 ± 7.8

M male, *F* female, *ESRD* end-stage renal disease, *VUR* vesicoureteral reflux, *PCK* polycystic kidney disease, *DMN* diabetic nephropathy, *CGN* chronic glomerulonephritis

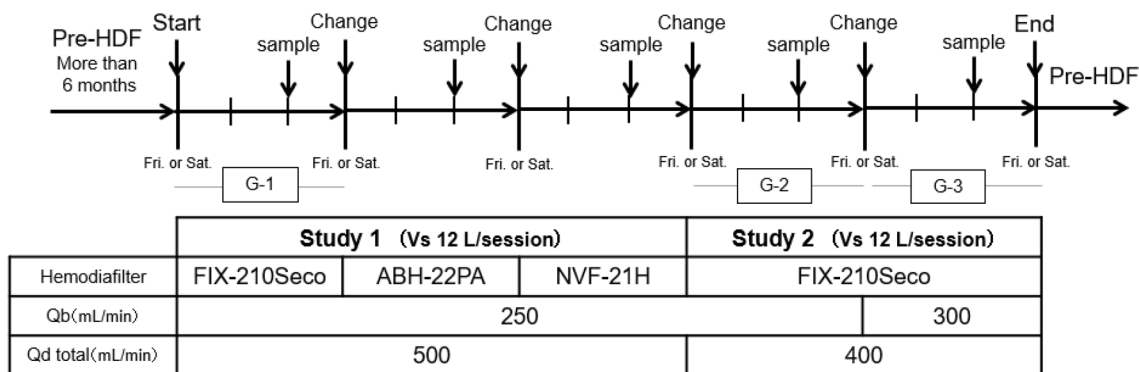


Fig. 1 Design of study 1 and study 2

Table 2 Hemodiafilter specifications

	FIX-210S	ABH-22PA	NVF-21H
Membrane material	ATA	PS	PS
Sieving coefficient β_2 -microglobulin	0.93	0.78	–
Sieving coefficient albumin	0.01	0.01↓	0.009
Membrane surface area (m ²)	2.1	2.2	2.1

ATA asymmetric triacetate, PS polysulfone

Table 3 Treatment modes in study 1

	FIX-210S	ABH-22PA	NVF-21H
Q_b (mL/min)	250		
Q_d (mL/min)	500		
Treatment time (h)	4		
Substitution fluid (L/session)	12		
(mL/min)	50		
Net dialysate flow rate (mL/min)	450		
$Q_S + Q_F$ (mL/min)	63.3 ± 5.6	62.6 ± 4.8	62.2 ± 5.0
Filtration fraction (%)			
Blood flow	25.3 ± 2.2	25.0 ± 1.9	24.9 ± 2.0
Plasma flow	41.3 ± 3.6	40.8 ± 1.9	41.9 ± 3.9

Q_b blood flow rate, Q_d dialysate flow rate

Study 2 The patients who participated in Study 2 were the same as those who participated in Study 1. Post-HDF using FIX was performed at a fixed Vs of 12 L/s, Q_d reduced to 400 mL/min, and Q_b of 250 mL/min in Group 2 (G-2) or 300 mL/min in Group 3 (G-3). The removal efficiency in these groups was compared with that of post-HDF performed at total Q_d ($Q_{d\text{total}}$) of 500 mL/min and Q_b of 250 mL/min in Group 1 (G-1: this was done in the first term of study 1). In Study 2, post-HDF was also performed 3 times under the same conditions, and samples were collected in the third session (Table 4).

Data collection

To assess removal performance, we measured the standardized dialysis dose (Kt/V); the removal rates and amounts of urea [molecular weight (MW): 60 Da], creatinine (MW: 113 Da), phosphorus (MW: 30.97 Da), β_2 -microglobulin (MG) (MW: 11.8 kDa), and α_1 -MG (MW: 33 kDa); and the removal rate of prolactin (MW: 22 kDa). To measure the removal amount of each solute and the amount of Alb loss, spent dialysate was pooled at 2 L/h. At the end of a post-HDF session, the pooled fluid was thoroughly stirred, and then samples were collected.

Table 4 Treatment modes in study 2

	G-1	G-2	G-3
Q_b (mL/min)	250	250	300
Q_d (mL/min)	500	400	400
Treatment time (h)		4	
Substitution fluid (L/session)		12	
(mL/min)		50	
Net dialysate flow rate (mL/min)	450	350	350
$Q_S + Q_F$ (mL/min)	63.3 ± 5.6	63.3 ± 5.1	62.9 ± 5.0
Filtration fraction (%)			
Blood flow	25.3 ± 2.2	25.3 ± 2.0	21.0 ± 1.7 ^{#,++}
Plasma Flow	41.3 ± 3.6	42.9 ± 4.2	35.3 ± 3.2 ^{#,++}

Q_b blood flow rate, Q_d dialysate flow rate, vs. versus, G-1 group 1, G-2 group 2, G-3 group 3

Friedman test, [#] $p < 0.05$ vs. G-1, ⁺⁺ $p < 0.01$ vs. G-2

Filtration fractions for post-HDF with blood flow and plasma flow were calculated with the equations presented as follows [7]:

$$\text{Filtration fraction}_{(\text{Blood flow})} = \frac{Q_S + Q_F}{Q_B} \times 100, \quad (1)$$

$$Q_p = \left(1 - \frac{Ht}{100}\right) \times (1 - 0.0107 \times TP) \times Q_b, \quad (2)$$

$$\text{Filtration fraction}_{(\text{Plasma flow})} = \frac{Q_S + Q_F}{Q_p} \times 100. \quad (3)$$

Of the laboratory data, those affected by concentration due to ultrafiltration after dialysis were corrected for the hematocrit values.

Statistical analysis

All results are expressed as a mean and standard deviation. The Friedman test was performed to analyze all parameters using StatMate III for Windows (ATMS Corp., Tokyo, Japan). A p value less than 5 % was considered as the significance level.

Results

Study 1 The respective results are presented in the order of FIX, ABH, and NVF. Kt/V values were 1.82 ± 0.29 , 1.89 ± 0.32 , and 1.83 ± 0.31 . There were significant differences between FIX and ABH, and between ABH and NVF in Kt/V. The removal rates of urea (%) were 76.9 ± 4.8 ,

78.3 ± 4.9, and 77.3 ± 5.1, with a significant difference between ABH and NVF. Removal rates of β_2 -MG (%) were 81.2 ± 2.6, 83.1 ± 4.3, and 82.8 ± 3.7. Removal rates of prolactin (%) were 80.2 ± 3.2, 78.0 ± 9.9 and 77.9 ± 7.3, and removal rates of α_1 -MG (%) were 37.4 ± 3.9, 40.2 ± 8.2 and 38.5 ± 7.0, respectively. Amounts of Alb loss (g/s) were 3.4 ± 0.7, 5.4 ± 2.1, and 5.4 ± 2.8, but no significant difference was observed. Ratios of α_1 -MG/Alb (mg/g) were 44.4 ± 9.3, 33.0 ± 9.7, and 36.9 ± 10.5. For 1 g of Alb loss, the removal amount of α_1 -MG was higher for FIX, but it did not significantly differ between the hemodiafilters (Table 5). During post-HDF, the increase in transmembrane pressure (TMP) was mild for all hemodiafilters, and it remained at 100 mmHg or lower until the end of each session.

Study 2 The respective results are presented in the order of G-1, G-2, and G-3. Kt/V values were 1.82 ± 0.29, 1.77 ± 0.28, and 2.02 ± 0.36. As with the removal rates of urea and creatinine, Kt/V was significantly highest in G-3. Removal rates of β_2 -MG (%) were 81.2 ± 2.6, 80.1 ± 4.2, and 81.0 ± 3.6; the rate in G-1 was significantly higher than that in G-2 ($p < 0.05$). Removal rates of prolactin (%) were 80.2 ± 3.2, 79.6 ± 5.1, and 80.5 ± 5.0. Removal rates of α_1 -MG (%) were 37.4 ± 3.9, 37.5 ± 6.5, and 38.0 ± 5.8. Amounts of Alb loss (g/s) were 3.4 ± 0.7, 3.8 ± 1.1, and 4.0 ± 0.8, showing no significant difference. Removal amounts of β_2 -MG (g) were 0.222 ± 0.03, 0.199 ± 0.03, and 0.198 ± 0.03; the amount was significantly highest in G-1. Removal amounts of α_1 -MG (g) were 0.146 ± 0.033, 0.163 ± 0.03, and 0.180 ± 0.005; the amount was significantly highest in G-3.

In addition, ratios of α_1 -MG/Alb were 44.4 ± 9.3, 40.2 ± 9.6, and 42.0 ± 8.2 (Table 6).

Discussion

The FIX series consists of 4 types of products (i.e., FIX-U, -S, -E, and -M), and the NVF series consists of 3 types of products (i.e., NVF-P, -H, and -M). The membranes of the FIX-U and NVF-P have the largest pore size among the respective series. From these products, we selected and used the FIX-S and NVF-H, with which post-HDF was assumed to yield adequate removal performance for LMWP and to keep Alb loss within the adequate range. As for ABH-PA, which is the only available type of the product, there was no alternative.

In the present study, because post-HDF was performed at Q_d total of 500 mL/min and V_s of 12 L/s, the net Q_d was 450 mL/min. Under this condition, the efficiency in removing small molecular solutes by diffusion was expressed as Kt/V of 1.8 or higher and removal rates of 75 % or higher for urea and 70 % for creatinine, which were favorable. We previously reported that HDF should be set with target removal rates of 80 % for β_2 -MG and 35 % for α_1 -MG when dialysis patients with various complications are treated [8, 9]. Post-HDF performed under the conditions set in the present study was a therapeutic strategy demonstrating the original features of HDF (i.e., efficient removal of middle- to large-molecular-weight solutes), because the removal rates were 80 % or higher for β_2 -MG and 35 % or higher for α_1 -MG.

Table 5 Results of study 1

	FIX-210S	ABH-22PA	NVF-21H
Kt/V	1.82 ± 0.29	1.89 ± 0.32	1.83 ± 0.31 ⁺
Removal rate (%)			
Urea	76.9 ± 4.8	78.3 ± 4.9**	77.3 ± 5.1
Creatinine	70.9 ± 5.3	71.9 ± 4.8	71.3 ± 5.5
Phosphorus	62.3 ± 5.3	66.2 ± 4.7	63.3 ± 7.4
β_2 -microglobulin	81.2 ± 2.6	83.1 ± 4.3	82.8 ± 3.7
Prolactin	80.2 ± 3.2	78.0 ± 9.9	77.9 ± 7.3
α_1 -microglobulin	37.4 ± 3.9	40.2 ± 8.2	38.5 ± 7.0
Removal amount (g)			
Urea	14.2 ± 4.2	12.0 ± 3.5	11.6 ± 2.8
Creatinine	1.9 ± 0.4	1.8 ± 0.4	1.8 ± 0.4
Phosphorus	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2
β_2 -microglobulin	0.222 ± 0.026	0.199 ± 0.025**	0.198 ± 0.027 [#]
α_1 -microglobulin	0.146 ± 0.030	0.163 ± 0.026	0.180 ± 0.054
Loss of albumin in dialysate (g)	3.4 ± 0.7	5.4 ± 2.1	5.4 ± 2.8
Serum Albumin level (g/dL)	3.73 ± 0.14	3.64 ± 0.11	3.66 ± 0.18
α_1 -microglobulin/albumin	44.4 ± 9.3	33.0 ± 9.7	36.9 ± 10.5

Vs. versus

Friedman test, ** $p < 0.01$ vs. FIX-210S, # $p < 0.05$ vs. FIX-210S, + $p < 0.05$ vs. ABH-22PA

Table 6 Results of study 2

	G-1	G-2	G-3
Kt/V	1.82 ± 0.29	1.77 ± 0.28	2.02 ± 0.36 ^{#,++}
Removal rate (%)			
Urea	76.9 ± 4.8	76.1 ± 4.8	80.2 ± 5.0 ^{#,++}
Creatinine	70.9 ± 5.3	69.8 ± 4.7	74.6 ± 5.2 ^{#,++}
Phosphorus	62.3 ± 5.3	60.9 ± 11.9	66.5 ± 7.7
β ₂ -microglobulin	81.2 ± 2.6	80.1 ± 4.2*	81.0 ± 3.6
Prolactin	80.2 ± 3.2	79.6 ± 5.1	80.5 ± 5.0
α ₁ -microglobulin	37.4 ± 3.9	37.5 ± 6.5	38.0 ± 5.8
Removal amount (g)			
Urea	14.2 ± 4.2	11.8 ± 3.0	12.9 ± 2.9
Creatinine	1.9 ± 0.4	1.8 ± 0.4	1.9 ± 0.4
Phosphorus	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.1
β ₂ -microglobulin	0.222 ± 0.026	0.202 ± 0.024*	0.202 ± 0.023 ^{##}
α ₁ -microglobulin	0.146 ± 0.030	0.145 ± 0.032	0.162 ± 0.026 ^{##,+}
Loss of albumin in dialysate (g)	3.4 ± 0.7	3.8 ± 1.1	4.0 ± 0.8
Serum Albumin level (g/dL)	3.73 ± 0.14	3.69 ± 0.25	3.61 ± 0.20
α ₁ -microglobulin/albumin	44.4 ± 9.3	40.2 ± 9.6	42.0 ± 8.2

Vs. versus, G-1 group 1, G-2 group 2, G-3 group 3

Friedman test, * $p < 0.05$ vs. G-1, # $p < 0.05$ vs. G-1, ## $p < 0.01$ vs. G-1, + $p < 0.05$ vs. G-2, ++ $p < 0.01$ vs. G-2

The European style of post-HDF requires a high V_s (15–30 L/s) to improve efficiency in removing solutes by convection [10]. High V_s inevitably leads to high Q_b to prevent hemoconcentration. For example, in the ESHOL study, Q_b and V_s were reported to be 384–392 mL/min and 20.8–21.8 L/s, respectively [3]. There is no other way but to state that high V_s and high Q_b are required, because the removal performance of hemodiafilters used for HDF in Europe is unsatisfactory for substances in the LMWP range.

The European style of post-HDF at high Q_b is associated with 2 disadvantages. The first disadvantage is the risk of excessive loss of amino acids. Because amino acids are small molecular solutes, their loss increases with higher Q_b . Excessive loss of amino acids obviously has an adverse effect on the nutritional status of patients. The second disadvantage is the increased risk of the development of micro air-bubbles in the blood tube circuit. Stegmayr et al. reported that when Q_b is 300 mL/min or higher, micro air-bubbles always develop in the blood tube circuit, enter the body via a dialysis membrane, and adversely affect the body [11–13]. With Q_b of 250 mL/min, at which post-HDF was performed in the present study, the risk of the development of micro air-bubbles is low. Based on these 2 disadvantages, the Japanese style of post-HDF, characterized by low-volume of substitution fluid and moderate Q_b using Japanese high-performance hemodiafilters, clearly appears to be superior to the European style of post-HDF. Furthermore, the former may also be superior in biocompatibility, because the increase in TMP during post-HDF is mild [14].

Among the 3 types of hemodiafilters used in the present study, Kt/V, removal rate of urea, removal rate and amount of β₂-MG showed significant differences in several comparisons. However, it is unlikely that these differences could result in a problem in clinical practice. There was no significant difference in the amount of Alb loss. When using FIX, however, even though the serum level of Alb was high, the amount of Alb loss was low and its standard deviation was also small. The ratio of α₁-MG/Alb was also at its highest when FIX was used (Table 5). These results indicate that FIX is capable of suppressing Alb loss and efficiently removing α₁-MG to some extent. These findings imply that the radii of pores on the FIX vary within a small range, and that there are none or only a few shunt pores (i.e., non-standard, large pores). Because the problem with conventional post-HDF is the difficulty in controlling Alb loss, under the present circumstances, the FIX appears to be the most appropriate hemodiafilter for post-HDF among those 3 types of hemodiafilters.

When post-HDF was performed at V_s of 12 L/s for 4 hrs with 20 % reduction in $Q_{d\text{total}}$ (i.e., $Q_{d\text{total}}$ of 400 mL/min), the net Q_d was 350 mL/min, and the removal efficiency for small molecular solutes was only slightly decreased. Furthermore, because V_s remained the same, it is not surprising that the removal efficiency for LMWP was unchanged. When Q_b was 300 mL/min, the removal efficiency for small molecular solutes was significantly improved. However, it should be kept in mind that the loss of amino acids and the risk of development of micro-air-bubbles increase with higher Q_b .

Conclusions

Low-volume post-HDF with moderate Q_b using Japanese high-performance hemodiafilters can efficiently remove small-, middle-, and large-molecular-weight solutes. In addition, even when $Q_{d,total}$ is reduced by 20 %, favorable removal performance is achieved for all solutes. Thus, post-HDF will be presumably performed more often, and the European style of high-volume post-HDF is considered unnecessary in Japan.

Acknowledgements This study received no external funding and was self-funded by Kenji Sakurai.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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