Renal Replacement Therapy

RESEARCH

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High-volume pre-dilution on-line hemodiafiltration is the adequate blood purification method from the viewpoint of amino acid nutrition

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Abstract

Background: We compared amino acid leakage among high-volume pre-dilution on-line hemodiafiltration (Pre O-HDF), hemodialysis (HD), and post-dilution on-line hemodiafiltration (Post O-HDF).

Subjects and methods: The subjects were 9 patients. For HD, the total dialysate flow rate was established as 500 mL/min. For high-volume Pre O-HDF, it was established as 600 mL/min, under a replacement fluid volume of 90 L. For Post O-HDF, it was established as 600 mL/min, under a replacement fluid volume of 10 L. In both procedures, the duration of treatment was 4 h, and the blood flow volume was 200 mL/min. We compared the leakages of total amino acid, non-essential amino acid, and essential amino acid, clear spaces (CSs), β_2-microglobulin (β_2-MG) reduction rate, Kt/V for urea, and albumin leakage among the three procedures.

Results: Amino acid leakages after high-volume Pre O-HDF were significantly lower than HD and Post O-HDF. The CSs after high-volume Pre O-HDF were significantly lower than Post O-HDF. The β_2-MG reduction rate after high-volume Pre O-HDF was significantly lower than Post O-HDF. The Kt/V for urea was not significantly different. Albumin leakages were below the detection limit (< 1 g) in the three procedures.

Conclusion: Under the treatment conditions we performed this time, high-volume Pre O-HDF reduces amino acid leakage in comparison with HD and Post O-HDF. High-volume Pre O-HDF is a therapeutic mode that suppresses amino acid leakage.

Keywords: Pre-dilution on-line hemodiafiltration, Amino acid, Nutrition, Frailty

Background

According to the 2018 Annual Dialysis Data Report by the Japanese Society for Dialysis Therapy, the mean age of hemodialysis patients as of the end of 2018 was 69.99 years. The mean age has been increasing each year, and the age-group accounting for the highest percentage of patients was 70–74 years for both men and women [1]. Prevention of sarcopenia and frailty in aging hemodialysis patients has become the most pressing challenge to tackle in order to preserve patients' quality of life and allow them to enjoy a rich life in their old age [2–4]. This challenge must be approached from the perspective of not only diet and exercise therapy but also blood purification therapy. In fact, patients on hemodialysis or peritoneal dialysis suffer a serious decline in nutritional status

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due to loss of amino acids and proteins through renal replacement therapy, as has been described in guidelines [5, 6].

To address this issue in blood purification therapy, we try to preserve nutrition by using high-volume predilution on-line hemodiafiltration (HDF) (high-volume Pre O-HDF), which uses a hemodiafilter that allows little albumin leakage and inhibits amino acid leakage by lowering the rate of diffusion of low molecular weight amino acids. Naturally, this method is also beneficial for elderly diabetic patients on hemodialysis because it stabilizes blood pressure during dialysis. However, the degree of amino acid (AA) (micromolecular substance) leakage remains to be clarified. In this study, we compared AA leakage among high-volume Pre O-HDF, hemodialysis (HD), and post-dilution on-line hemodiafiltration (Post O-HDF).

We sought to determine the optimal method to suppress amino acid losses during three types of dialysis (high-volume Pre O-HDF, HD, and Post O-HDF).

Methods

The subjects were 9 patients who had received maintenance dialysis in our hospital (7 males, including 4 diabetics, mean age 71.4 ± 2.5 years, mean duration of dialysis 9.3 ± 7.1 years) (Table 1). Table 2 shows the patient's general condition (serum albumin, pre-dialysis amino acid concentration, body weight) (Table 2). For HD, the total dialysate flow rate was established as 500 mL/min, and a dialyzer FX-220(Fresenius Medical Care GmbH, Bad Homburg, Germany) was used. For high-volume Pre O-HDF, it was established as 600 mL/min, and a hemodiafilter MFX-21Meco (Nipro Co., Osaka, Japan) was used under a displacing solution flow rate of 400 mL/min and displacing solution volume of 90 L. For Post O-HDF, it was established as 600 mL/min, and a hemodiafilter MFX-21Meco was used under a displacing solution flow rate of 44 mL/min and displacing solution volume of 10 L. According to the 2016 Annual Dialysis Data Report by the Japanese Society for Dialysis Therapy, the mean replacement fluid volume of Post O-HDF was 10.2L [7]. We set the replacement fluid volume with reference to the average. Filtration is started at 15 min after the start of dialysis to prevent excessive leakage of albumin. In both procedures, the duration of treatment was 4 h, and the blood flow volume was 200 mL/min (Table 3).

These dialysis conditions were changed only once, and data were collected at that time. The patients' original therapeutic mode and a sequential order of therapeutic modes in this study are different (Table 4).

We compared the leakages of total amino acid (TAA), non-essential amino acid (NEAA), and essential amino acid (EAA), clear spaces (CSs), β_2-microglobulin (β_2-MG) reduction rate, Kt/V urea, and albumin (Alb) leakage among the three procedures.

Twenty amino acids (aspartic acid, threonine, serine, asparagine, glutamic acid, glutamine, proline, glycine, alanine, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, histidine, tryptophan, lysine, and arginine) were measured by liquid chromatography–mass spectrometry.

Yamashita reported that loss of solutes with different pre-dialysis concentrations is better to be calculated as a ratio of the two and compared because the loss of solutes and pre-dialysis concentration are directly proportional

Table 1 Patients' characteristics

Number of patients	9
Gender; *N*	Male: 7, Female: 2
Age; years	71.4 ± 2.5
Dialysis vintage; years	9.3 ± 7.1
Diabetes; N	4

Table 2 The subjects' general condition

	High-volume Pre O-HDF	Post O-HDF	HD	*p* value		
				High-volume Pre O-HDF vs. Post O-HDF	High-volume Pre O-HDF vs. HD	Post O-HDF vs. HD
Body weight (kg)	58.4 ± 9.6	57.2 ± 10.0	58.2 ± 9.9	0.964		
Serum albumin (g/dL)	3.3 ± 0.3	3.7 ± 0.2	3.5 ± 0.3	0.055		
nPCR (g/kg/day)	0.80 ± 0.07	0.83 ± 0.12	0.86 ± 0.11	0.494		
GNRI	89.7 ± 5.3	91.9 ± 4.8	92.2 ± 6.4	0.627		
Total AA (nmol/ml)	2439 ± 333	2757 ± 341	2782 ± 331	0.095		
NEAA (nmol/ml)	1677 ± 284	1871 ± 295	1851 ± 312	0.372		
EAA (nmol/ml)	762 ± 96	885 ± 78	931 ± 92	0.027	0.002	0.567
BCAA (nmol/ml)	357 ± 56	387 ± 51	438 ± 65	0.574	0.029	0.212

Table 3 Dialysis prescription

	High-volume Pre O-HDF	Post O-HDF	HD
Hemodiafilter	MFX-21Meco		FX-220
Dialysate flow rate	600 ml/min		500 ml/min
Replacement flow rate	400 ml/min	44 ml/min	–
Replacement fluid volume	90L/session	10L/session	–
Treatment time	4 h		
Blood flow rate	200 ml/min		

Table 4 The patients' original therapeutic mode and a sequential order of therapeutic modes in this study

	Original treatment method			Sequential order of therapeutic modes in this study			
	Original mode	Replacement fluid volume	Hemodiafilter	Blood flow rate (ml/min)	1st	2nd	3rd
Patient 1	Pre O-HDF	60L	MFX-21Seco	250	HD	High-volume Pre O-HDF	Post O-HDF
Patient 2	Pre O-HDF	60L	NVF-21 M	250	HD	High-volume Pre O-HDF	Post O-HDF
Patient 3	Pre O-HDF	60L	MFX-21Meco	150	HD	High-volume Pre O-HDF	Post O-HDF
Patient 4	Pre O-HDF	60L	MFX-25Ueco	200	HD	High-volume Pre O-HDF	Post O-HDF
Patient 5	Pre O-HDF	60L	NVF-21 M	250	HD	High-volume Pre O-HDF	Post O-HDF
Patient 6	Pre O-HDF	60L	MFX-21Meco	250	High-volume Pre O-HDF	HD	Post O-HDF
Patient 7	Pre O-HDF	60L	GDF-21	250	High-volume Pre O-HDF	HD	Post O-HDF
Patient 8	Pre O-HDF	60L	GDF-21	300	High-volume Pre O-HDF	HD	Post O-HDF
Patient 9	Pre O-HDF	60L	MFX-25Ueco	250	High-volume Pre O-HDF	HD	Post O-HDF

[8]. CS denotes the volume at which the concentration of the solute of interest becomes zero. Clear space was calculated using the following equation:

$$CS = m/c_{pre}$$

Here, c_{pre} is the pre-dialysis concentration of amino acids and m is the leakage of amino acids.

Spent dialysate was also sampled continuously from the drain line at a flow rate of 2 L/h using a pump. Levels of 20 amino acids (aspartic acid, threonine, serine, asparagine, glutamic acid, glutamine, proline, glycine, alanine, valine, cystine, methionine, isoleucine, leucine, tyrosine, phenylalanine, histidine, tryptophan, lysine, arginine) were measured using liquid chromatography–mass spectrometry. Amino acids were categorized into TAAs, NEAAs (aspartic acid, serine, asparagine, glutamic acid, glutamine, proline, glycine, alanine, cystine, tyrosine, arginine), and EAAs (threonine, valine, methionine, isoleucine, leucine, phenylalanine, histidine, tryptophan, lysine).

Results are expressed as means ± SD. ANOVA were used for statistical analysis, and a p value of less than 0.05 was considered significant. All statistical analyses were carried out using StatView version 5.0

The study protocol was approved by the Institutional Ethical Committee of Kurata Hospital (Approval No. 2019–5).

Results

TAA leakages after high-volume Pre O-HDF, HD, and Post O-HDF were 4,511 ± 797 mg, 6,309 ± 1,072 mg, and 6,792 ± 876 mg, respectively. NEAA leakages were 2,892 ± 632 mg, 4,008 ± 772 mg, and 4,274 ± 679 mg, respectively. EAA leakages were 1,619 ± 286 mg, 2,301 ± 414 mg, and 2,517 ± 302 mg, respectively. The values after high-volume Pre O-HDF were significantly lower than Post O-HDF ($p < 0.01$ each). The values of TAA and EAA, after high-volume Pre O-HDF were significantly lower than HD ($p < 0.01$) (Fig. 1).

The CSs of TAA after high-volume Pre O-HDF, HD, and Post O-HDF were 14.6 ± 2.2 L, 17.7 ± 3.0 L, and 19.3 ± 2.1 L, respectively. Those of NEAA were 14.0 ± 2.2 L, 17.4 ± 3.0 L, and 18.5 ± 2.0 L, respectively. Those of EAA were 15.7 ± 2.2 L, 18.4 ± 3.1 L, and 21.1 ± 2.9 L, respectively. The values after high-volume Pre O-HDF were significantly lower than HD (TAA and NEAA: $p < 0.05$) and Post O-HDF ($p < 0.01$ each) (Fig. 2).

Table 5 shows the results of the β_2-MG reduction rates and Kt/V for urea among the three procedures. The

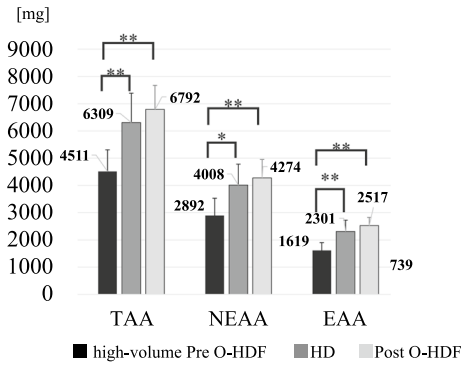

Fig. 1 Leakage of amino acids. The leaked amounts of TAA, NEAA, and EAA after high-volume Pre O-HDF were significantly lower than HD (TAA and EAA: $p < 0.01$, NEAA $p < 0.05$) and Post O-HDF ($p < 0.01$ each)

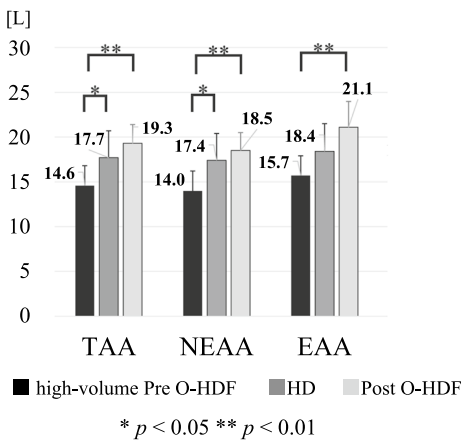

Fig. 2 Clear space of amino acids. The CSs of after high-volume Pre O-HDF were significantly lower than HD (TAA and NEAA: $p < 0.05$) and Post O-HDF ($p < 0.01$ each)

β2-MG reduction rates after high-volume Pre O-HDF were significantly lower than Post O-HDF ($p < 0.05$).

The Kt/V for urea were not significantly different.

Albumin leakages were below the detection limit (< 1 g) in the three procedures.

Discussion

Johansen et al. studied a cohort of 2275 adults who participated in the Dialysis Morbidity and Mortality Wave 2 study, of whom two-thirds met their definition of frailty. They revealed that frailty was independently associated with higher risk of death and with the combined outcome of death or hospitalization. Frailty is extremely common and is associated with adverse outcomes among incident dialysis patients. They concluded that given its prevalence and consequences, increased research efforts should focus on interventions aimed to prevent or attenuate frailty in the dialysis population [4].

In elderly patients, the muscle protein synthetic response to protein ingestion is reduced [9]. Furthermore, amino acids leak during dialytic therapy; therefore, to replenish a lack of the pooled plasma amino, decomposition of the skeletal muscle may progress [10]. Considering these, treatment conditions for reducing amino acid leakage are required to prevent flail sarcopenia, which has recently been emphasized, especially in elderly patients receiving dialysis.

According to the "Age and sex of HDF/HD patients 2017" published by the Japanese Society for Dialysis Therapy in 2017, the rate of HDF patients is higher than that of HD patients regardless of sex among those aged < 74 years, whereas the rate of HD patients is higher than that of HDF patients among those aged ≥ 75 years [11].

We previously reported that AA losses are lower during Pre O-HDF than HD of the same Kt/V for urea [12]. However, in clinical practice, Kt/V for urea of Pre O-HDF and HD or Post O-HDF is rarely the same. In most cases, Pre O-HDF will be lower than HD or Post O-HDF. For that reason, in this study, we examined three treatment modes under conditions that could be prescribed in actual clinical practice.

The reason for prescribing pre-HDF of 90L was that a higher replacement flow rate would reduce the flow rate of dialysate into the dialysis membrane and reduce the efficiency of removal of small molecular weight substances by diffusion, which would inhibit amino acid leakage. This is suggested by the fact that the Kt/V of Urea, which has almost the same molecular weight

Table 5 The β_2-MG reduction rates and Kt/V for urea among the three procedures

	High-volume Pre O-HDF	Post O-HDF	HD	*p* value		
				High-volume Pre O-HDF vs Post O-HDF	High-volume Pre O-HDF vs HD	Post O-HDF vs HD
β_2-MG reduction rate [%]	69.8 ± 5.0	75.9 ± 3.8	65.3 ± 5.0	0.036	0.150	< 0.01
Kt/V for urea	1.33 ± 0.17	1.48 ± 0.27	1.45 ± 0.23	0.381		

as amino acids, was significantly lower than that of other dialysis conditions. In this study, high-volume Pre O-HDF with a hemodiafilter, through which Alb leakage is slight, reduced AA leakage in comparison with HD and Post O-HDF, and also reduced CS in comparison with Post O-HDF. The Kt/V value was not significantly among the three procedures. However, a Kt/V value of 1.2 to be secured at minimum, which is recommended in the guidelines for maintenance hemodialysis: hemodialysis prescriptions established by the Japanese Society for Dialysis Therapy, could be maintained [13]. Amino acid leakage showed no significant difference between HD and Post O-HDF. Therefore, high-volume Pre O-HDF is the most advantageous blood purification method for elderly dialysis patients or those with malnutrition from the viewpoint of dietetics. It may also be useful for the prevention of sarcopenia and frail.

Our study has a limitation. It is because each of the three treatment modes was performed only once, so it is not clear whether these treatment modes contribute to the improvement in patients' nutritional status in the long term.

Conclusions

Under the treatment conditions we performed this time, high-volume Pre O-HDF reduces amino acid leakage in comparison with HD and Post O-HDF. High-volume Pre O-HDF is a therapeutic mode that suppresses amino acid leakage. The features of this method developed in Japan may be elicited through such a usage.

Abbreviations

HDF: Hemodiafiltration; Pre O-HDF: Pre-dilution on-line hemodiafiltration; HD: Hemodialysis; Post O-HDF: Post-dilution on-line hemodiafiltration; TAA: Total amino acid; NEAA: Non-essential amino acid; EAA: Essential amino acid; CS: Clear space; β_2-MG: β_2-Microglobulin; Alb: Albumin.

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Author contributions

MK and SU were involved in the study design and writing the manuscript. MK, SU, SH, AkK, MF, EH, and AsK participated in the study procedure implementation and data collection. NM, YK, and MH participated in the research design and substantially contributed to the study concept. KK and TH kindly reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Ethical Committee of Kurata Hospital (Approval No. 2019–5). All participants were provided with the opportunity to decline to participate in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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