Review

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Clinical Expectation of Online Hemodiafiltration: A Japanese Perspective

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Key Words

Online hemodiafiltration · Predilution mode · Postdilution mode · Japan

Abstract

Many pieces of evidence of online hemodiafiltration (HDF) have been reported, and the clinical advantage of postdilution online HDF with sufficient substitution is now established. After the approval of online HDF in 2012, the number of online HDF patients has been dramatically increasing in Japan and reached 10% of the total dialysis population at the end of 2013. One of the marked characteristics of Japanese online HDF is a widespread use of predilution treatment and, in 2013, 90.8% of online HDFs were carried out with the predilution mode. The main reason for the wide use of predilution online HDF results from the low blood flow rate in Japan, by which it is difficult to substitute a sufficient volume during the limited treatment time. Other reasons to choose the predilution mode include the reduction of albumin loss and the suppression of membrane fouling during treatment. Contrary to postdilution treatment, adequate clinical evidence has not been reported for predilution online HDF to provide a better outcome of the patients. A further clinical trial is expected to elucidate the clinical advantages over conventional hemodialysis for predilution online HDF.

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Current Status of Online Hemodiafiltration in Japan

Online hemodiafiltration (HDF) was officially approved for the treatment of end-stage renal disease (ESRD) patients and for reimbursement by the Japanese health insurance system in April 2012. This occurred after both strict quality control criteria for the purified dialysate and the substitution fluid had been established, and had been approved for health insurance reimbursement in 2010.

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Table 1. Change in number of HDF patients in the years 2009–2013

Dialysis method	2009	2010	2011	2012	2013
Facility HD	253,807	262,973	270,072	268,275	264,211
HDF					
Offline HDF	9,299	9,421	8,573	7,157	7,149
Online HDF	6,852	4,829	4,890	14,069	23,536
PP-HDF	237	159	145	109	263
AFBF	465	458	507	390	423
Subtotal	16,853	14,867	14,115	21,725	31,471
Total	270,660	277,840	284,187	290,000	295,582

PP-HDF = Push-and-pull HDF; AFBF = acetate-free biofiltration.

Number of HDF Patients

Since the approval of online HDF, the number of HDF patients has been dramatically increasing (table 1). Although the total number of HDF patients temporarily decreased between 2009 and 2011, it increased in both 2012 and 2013 due to the increased number of online HDF cases which now represent 10% of the total dialysis population in Japan (315,000 cases) [1, 2].

There were 4,890 patients using online HDF in 2011 which accounted for 34.6% of the total HDF population. The number of cases increased about fivefold to 23,536 in 2013, which accounted for 75.0% of the entire HDF population. In contrast, the absolute number of patients who were treated by HDF other than online has been constant or decreasing. These findings suggest that many patients changed their treatment modality from hemodialysis (HD) to online HDF during this time due to the approval and reimbursement of online HDF.

Pre- or Postdilution and Substitution Volume

Postdilution was the major dilution treatment in Japan until 2011 since over 90% of HDF patients did not use online HDF. However, with the widespread use of online HDF after 2012, predilution treatment increased significantly. In 2013, among the 21,197 patients using online HDF, 19,244 (90.8%) underwent predilution and only 1,439 (6.8%) postdilution treatment, respectively. For offline HDF patients, 580 (9.9%) among the 5,846 patients underwent predilution and 5,214 (89.2%) postdilution HDF, respectively. The main reason for the use of the predilution mode for online HDF patients results from the low blood flow rate (average 200–220 ml/min) in Japanese patients (table 2). With this average blood flow rate, it is difficult to substitute an adequate volume during the limited (average 4 h) treatment time. The greater prevalence of predilution treatment for online HDF in Japan is clearly different from that in European countries with the volume of substitution fluid also being different between Europe and Japan. In the case of offline HDF patients, the mean substitution volumes were 7.9 and 9.4 liters for the post- and predilution treatments in 2013, respectively. For online HDF patients, the mean volumes were 9.2 and 40.6 liters for the post- and predilution treatments, respectively [2]. The mean volume of 9.2 liters for postdilution online HDF patients is clearly lower than that of European countries and the reported level that is necessary to provide a better outcome for the online HDF patients [3–5].

A positive relationship was observed between the substitution fluid volume and postdialysis body weight for patients who underwent postdilution HDF. However, for patients who underwent predilution online HDF, no relation was observed between the two parameters, and a substitution volume in the range of 20–50 liters was most commonly used for all the body weight groups. These findings suggest that the substitution volume seems to be determined without precise consideration of the patient body size in Japanese predilution HDF patients.

Comparison of Parameters between the Patients Treated with HD and Online HDF

The patient background, urea kinetics, and nutrition and inflammation markers were compared among (1) patients on HD at facilities (facility HD patients), (2) pa-

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Table 2. Comparison between patients receiving HD and patients receiving online HDF

	Facility HD	Online HDF	
		postdilution	predilution
Basic background			
Patients, n	182,721	1,244	16,358
Males, n	114,549	760	10,153
Males, %	62.7	61.1	62.1
Diabetics, %	36.9	26.4	28.3
Age, years	67.4±12.2	64.4±12.3	63.6±12.2
Dialysis duration, years	8.8±6.9	12.4±9.1	11.4±8.6
Postdialysis body weight (male), kg	59.2±11.9	61.0±11.9	61.2±12.1
Postdialysis body weight (female), kg	47.8±10.3	48.0±10.3	48.9±9.9
Urea kinetics			
Dialysis time, min	241.2±30.0	244.1±30.9	250.5±30.5
Blood flow rate, ml/min	206.8±34.1	221.5±39.1	230.8±42.9
Kt/V (male)	1.39±0.25	1.43±0.28	1.46±0.28
Kt/V (female)	1.61±0.31	1.69±0.31	1.72±0.33
Normalized protein catabolic rate (male)	0.86±0.17	0.86±0.18	0.88±0.17
Normalized protein catabolic rate (female)	0.89±0.19	0.91±0.19	0.92±0.18
Other			
Serum albumin, g/dl	3.62±0.42	3.59±0.40	3.66±0.36
C-reactive protein, mg/dl	0.63±1.88	0.51±1.37	0.50±1.59

Data are from patients treated 3 times a week for more than 2 years. Figures represent mean ± SD unless otherwise indicated.

tients using online postdilution HDF (postdilution online HDF patients) and (3) patients who underwent predilution online HDF (predilution online HDF patients), who had undergone one of the three dialysis treatments 3 times a week for more than 2 years (table 2) [1, 2]. Facility HD patients had the highest mean age and prevalence rate of diabetes, the shortest dialysis treatment duration, the lowest posttreatment body weight, the shortest treatment time, and the lowest blood flow rate and spKt/V. However, no remarkable difference was observed in normalized protein catabolic rate, serum albumin and C-reactive protein levels. Also no difference was observed in serum creatinine before treatment, creatinine generation rate, serum calcium, phosphorus, intact parathyroid hormone, total cholesterol, hemoglobin levels and mean erythropoiesis-stimulating agent dose (data not shown).

These findings suggest that online HDF is given to relatively young patients, without diabetes and with a longer duration of dialysis, and is not given to specific patients on regular dialysis treatment in Japan. The prescription of dose or condition for HDF is determined by the clinicians at each facility and varies considerably.

Rationale to Start Online HDF

Based on a questionnaire survey of 16,305 patients, online HDF was started to (1) prevent dialysis complications, such as dialysis-related amyloidosis in 30.8% of the patients, (2) increase the efficiency of dialysis for uremic accumulates, including middle- to large-molecular-weight substances, such as α_1-microglobulin in 18.0% of the patients, (3) treat dialysis-related hypotension in 17.2% of the patients, (4) treat dialysis-related amyloidosis in 14.4% of the patients and for (5) intractable pruritus in 7.1% of the patients, (6) restless leg syndrome in 3.3% of the patients and (7) arthralgia not related to dialysis-related amyloidosis in 2.3% of the patients [2].

Expectation for Online HDF from the Japanese Perspective

It is very important to establish evidence to support the clinical effect of predilution online HDF. Many clinical effects for online HDF have been reported. These include the reduction of dialysis-related hypotension [6], improvement of anemia with sparing erythropoiesis-stimulating agent dosage [7–9], prevention of the deterioration of dialysis-related amyloidosis, improvement of the nutritional status by reducing inflammatory stress [10], cardiovascular protection by preserving vascular endothelial cell function [11, 12], relief of both peripheral neuropathy and insomnia [13, 14], preservation of residual renal function [15] and ultimately a survival benefit [3]. These effects are due to the better quality of dialysis fluid, the greater efficiency of removing uremic accumulates and the better hemodynamic stability during treatment resulting in prevention of dialysis-related hypotension. In particular, the greater ability to remove middle- to large-molecular-weight substances that could not be effectively removed by HD is essential for achieving excellent clinical effects.

Many of the clinical effects listed above were the result of postdilution online HDF with a high substitution volume. The removal efficiency of postdilution online HDF for middle- to large-molecular-weight substances around the size of β_2-microglobulin is high and increases with the volume of the substitution fluid. However, eliminating substances around the size of α_1-microglobulin results in the removal of a greater amount of albumin by high-volume postdilution online HDF because the molecular cutoff point of hemodiafilters available in Japan is higher than that of hemodiafilters available in European countries. This is the major reason why predilution online HDF is frequently used in Japan. Uremic accumulates close in size to albumin can be safely and effectively removed by predilution online HDF. The low blood flow rate in Japanese patients that makes it difficult to achieve a high-substitution-volume postdilution online HDF within the limited treatment time is another reason for the high prevalence of predilution online HDF in Japan. At this time, however, the evidence to support the clinical effect of predilution online HDF is not as strong as that of postdilution HDF.

The preventive effects of predilution online HDF on both dialysis-related hypotension and disequilibrium syndrome have been reported by an Italian group [6]. Although the patient number is small in a Japanese study, predilution online HDF also resulted in better hemodynamic stability, reduction of pain-associated dialysis-related amyloidosis and improvement of nutritional status based on both the geriatric nutritional risk index and increased muscular volume [16]. However, it is essential for Japanese physicians to establish strong evidence that supports at least the similar beneficial effect of predilution online HDF to that of postdilution high-volume online HDF. A large-scale multicenter clinical study to compare the intradialytic hemodynamic stability between predilution and postdilution online HDF is now being conducted by the Japanese Society for Hemodiafiltration. We expect the results will objectively clarify the therapeutic value of predilution online HDF.

Clinical Effect of Online HDF: Further Expectations

Another mechanism responsible for the beneficial clinical effect of online HDF is the increased elimination of protein-bound uremic substances, including indoxyl sulfate and paracresyl sulfate, which have strong toxic effects on kidney tissues and on the vascular system [17]. In addition, for the disorder of mineral metabolism, it was reported that there was a reduction in fibroblast growth factor-23 by online HDF, which is a representative biomarker of poor outcome for both chronic kidney disease and ESRD patients [18]. Increased phosphate removal, which was not found by the Italian group [19], is also expected to affect the serum calcification propensity and levels of calcified protein particles which are strongly related to the ectopic vascular calcification in ESRD patients. In addition, hepcidin removal is an important mechanism for the better management of anemia [9].

Elevated free light chain removal is a target research area not only for the treatment of myeloma kidney and free light chain disease, but also for the improvement of survival of CKD patients [20]. For a better understanding of the mechanism of change in the inflammation process, research on the elimination of apoptosis markers (tumor necrosis factor receptors I and II, death receptor-5), DNA methylation and circulating mitochondrial DNA is required [21, 22].

For the better understanding of the effect of online HDF, the subgroups for whom online HDF is especially effective and those for whom it is not effective should be further clarified. In particular, this is very important due to the increasing number of elderly or diabetic patients. Predilution online HDF may have a favorable influence on the prognosis and clinical symptoms of elderly patients due to its low albumin leakage characteristics and hemodynamic stability during treatment. A positive effect on both pediatric and pregnant cases is also expected.

Online HDF is widely used in the intensive care unit. A previous clinical trial did not support the beneficial effect on critically ill patients with acute kidney injury [23], but further study is needed. The use for both acute liver support and drug toxicity should be further examined.

Need for Socioeconomic Analysis of Online HDF

Recently, the effect of different dialysis treatments, such as frequent treatment and/or long-time HD, has been reported. Online HDF is regarded as most effective as a 4- to 5-hour and 3 times a week treatment, and is considered as a better treatment option than conventional HD. However, the effect of frequent treatment and/or long-time use of online HDF has not been examined. Whether these treatment options further improve the patient outcome or not should be clarified not only from the perspective of the clinical outcome, but also from that of the socioeconomic impact.

Disclosure Statement

Tadao Akizawa is an advisor of Nipro, Kyowa Kirin, JT, Bayer and Astellas and received lecture fees from Bayer, Chugai and Kyowa Kirin.

Fumihiko Koiwa is an advisor of Kissei and received lecture fees from Kyowa Kirin.

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