Renal Replacement Therapy

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Impact of hemodialysis solutions containing different levels of molecular hydrogen (H2) on the patient-reported outcome of fatigue

Susumu Uemura[1], Yoshitaka Kegasa[2], Keigo Tada[1], Taichi Tsukahara[1], Shigeru Kabayama[3], Tae Yamamoto[3], Mariko Miyazaki[3], Joji Takada[4] and Masaaki Nakayama[3,5*]

Abstract

Background: Reportedly, dialysis solutions containing molecular hydrogen (H2) might ameliorate patient-reported fatigue in hemodialysis (HD) patients. However, it is unknown whether its impact might differ with different H2 levels.

Method: This single-arm, prospective observational study examined 105 patients on chronic HD (62 males; mean age, 66 years; mean HD duration, 117 months). All patients were originally treated with an HD solution with 47 ppb (mean) H2 for more than 12 months, followed by an HD solution with 154 ppb (mean) H2 for 8 weeks. Baseline and changes in subjective fatigue status rated on a numerical rating scale (NRS) were assessed before the start of the study (baseline) and 8th week of the study.

Results: Patients were classified into three groups according to the presence of subjective fatigue at baseline: Group A (15.2%), presence of fatigue on both HD and HD-free days; Group B (28.6%), fatigue only on HD days; and Group C (56.2%), freedom from fatigue. In Group A, NRS scores during the 8-week period were significantly decreased as compared with 0 week, at the 4th and 8th week on HD days, and at the 8th week on HD-free day, respectively. While no consistent changes were found in other groups. At the 8th week, 64 patients (61%) presented absence of or decrease in the NRS score of fatigue, while the rest of patients did not present the decrease in NRS (the non-improved: 39%). Regarding the factors related to the non-improved, prescription of antihypertensive agents was a significant independent risk factor by multivariate analysis, indicating the possible involvement of excess fall in blood pressure (BP) in those patients.

Conclusion: Amelioration of the patient-reported outcome of fatigue might be influenced by H2 levels in the HD solution, and the optimal H2 level in the dialysate needs to be elucidated in consideration of clinical type of fatigue and BP control status.

Keywords: Electrolyzed water, Dialysate, Fatigue, Molecular hydrogen

Introduction

Fatigue is one of the most common symptoms in patients on chronic dialysis. Fatigue in these patients is closely related to a low quality of life [1–3] and constitutes an independent risk factor for patient survival [4–6]. Amelioration of fatigue in dialysis patients is thus a crucial issue. Among the various contributing factors, bio-incompatibility of the dialysis system might

*Correspondence: nakayama@luke.ac.jp

[3] Research Division of Chronic Kidney Disease and Dialysis Treatment, Tohoku University Hospital, Sendai, Japan
Full list of author information is available at the end of the article

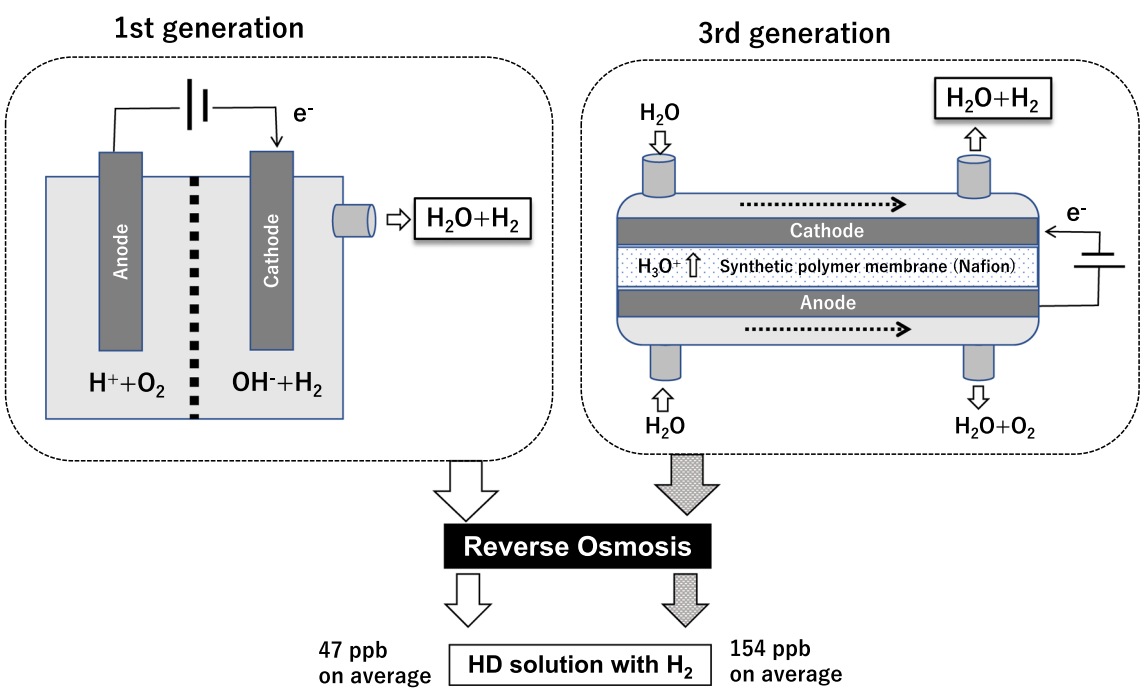

Fig. 1 Outlines of the two types of hemodialysis systems using the technology of electrolysis of water to deliver dialysis solutions containing hydrogen molecules: **a** the first-generation system, **b** the third-generation system

be involved in the development of hemodialysis (HD)-related fatigue, through enhanced oxidative stress during HD [7, 8].

Molecular hydrogen (H2), an inert gas, has been shown to be a bioactive molecule that can suppress oxidative stress and inflammation and thereby might protect against cellular and organ damage in various disease models [9]. Hence, an HD system employing electrolyzed water containing H2 (E-HD) has been developed to improve the biocompatibility of the HD fluid [10–14]. In the original electrolyzed water system (first-generation system), H2-containing water was processed by direct electrolysis of water using a platinum (Pb)-coating electrode (Fig. 1a), which could generate an HD solution with H2 levels in the vicinity of 20–100 ppb at maximum. Owing to technological innovations, the current system (third-generation system) can provide HD solutions with H2 levels of up to 200 ppb by water electrolysis using a semisynthetic membrane Nafion (Fig. 1b).

Reportedly, with the first-generation system, a single HD session results in an increase in the reduced/oxidized serum albumin ratio [15, 16], and decreases in serum monocyte chemotactic protein 1 and myeloperoxidase (MPO) are observed with a 6-month HD course [13], and a significant reduction in composite clinical events (mortality, cardiovascular, and leg amputation) is seen over a 5-year observation period [14]. With the third-generation system, on the other hand, a significant reduction in oxidative markers (malondialdehyde-protein) and preservation of antioxidant (thioredoxin) levels were reported with a single HD session [17]. Amelioration of fatigue has been suggested by both systems [17–19]. However, it is unknown whether the impact of these two systems on fatigue differs due to their different H2 levels.

To clarify the issue, the patients who had been treated by the first-generation system (H2 level of HD solution: 47 ppb on average) at Higashi-Muroran Clinic were subjected to studying the changes of patient-reported outcome of fatigue, just after the system replacement to the third generation (153 ppb on average).

Materials and methods

Patients

Participants in this prospective observational study comprised patients on regular dialysis therapy who were treated at Higashi-Muroran clinic (Muroran, Japan) between January and March 2021. All patients had been receiving E-HD using the first-generation system ($n=105$, male 59.0%, age 66 ± 11 years, HD duration 117 ± 109 months) regularly three times a week for 4–5 h/sessions, using a high-performance membrane dialyzer, for more than 12 months. All patients

were recruited in the study before switching to the high H2 dialysate using the third-generation system. All the recruited patients subsequently receive the high H2 dialysate. There were no any contraindications to switching to the higher H2 levels, and there was no any change in the dialysis protocol after the change in dialysate.

Informed consent was obtained from all participants, and the study protocol was fully approved by the Ethics Review Committee of St. Luke's International Hospital (Tokyo, Japan) (approval date: June/19/2019; approval number: 18-RZ013). All methods were performed in accordance with the relevant guidelines and regulations.

Assessments of fatigue

Patient fatigue was evaluated using both a numerical rating scale (NRS) and our own original fatigue scale (Additional file 1: S2) [18, 20]. All questionnaires were provided in written format. The NRS is a unidimensional scale with the left end anchored to "no tiredness at all (0)" and the right end to "complete exhaustion [10]." Our original fatigue scale is a four-grade self-evaluation by the patient: Grade 1, no fatigue, patient acts in the ordinary way without any sense of fatigue; Grade 2, mild fatigue, patient acts in the ordinary way but feels tired; Grade 3, moderate fatigue, patient feels tired even with light work; and Grade 4, intense fatigue, patient feels very tired and falls asleep. The original scale, which is a patient-reported evaluation, was employed in the present study, in order to set the cutoff level of fatigue NRS which is equivalent to the patient-reported outcome of fatigue.

Assessments of fatigue were performed by all patients at four time points using questionnaire asking "How did you feel tired in the previous HD day, and the next day of HD?": the period within 2 weeks before commencement of the third-generation system (baseline), and at the 2nd week, 4th week, and 8th week after commencement of use of the third-generation system. Assessments of fatigue were made on a randomly chosen HD day during the particular week in each phase. The cutoff value of NRS score ≧4 for the presence of substantial fatigue was determined by analysis of the receiver operating characteristic (ROC) curve, in which original fatigue scale Grade 3 or 4 on HD day was defined as presenting with fatigue in the study (NRS = 3.5: sensitivity 0.918, specificity 0.789; NRS = 4.5: sensitivity 0.935, specificity 0.855).

Patients grouping

Three types of fatigue presentation: According to the definition of an NRS score of more than 4 at baseline indicating the presence of fatigue, patients were classified into the following three groups: Group A defined as having chronic-type fatigue (presence of fatigue on both HD and HD-free days), Group B as having HD-responsive-type fatigue (presence of fatigue on HD day and absence of fatigue on HD-free day), and Group C as fatigue-free (absence of fatigue on both HD and HD-free days).

Clinical outcomes by the third-generation system: Furthermore, patients were classified into two groups according to the change of NRS on the HD day between baseline and 8th week: those patients who reported an improvement in fatigue (Improved group) and those who reported persistence and/or worsening of fatigue (Non-improved group). The respective groups were defined as follows: Improved group: $\Delta NRS = < -1$ in Groups A and B, $\Delta NRS < = \pm 0$ in Group C; and Non-improved group: $\Delta NRS > = \pm 0$ in Groups A and B, $\Delta NRS > = +1$ in Group C, where $\Delta NRS =$ (NRS at 8 w minus NRS at 0 w) on the HD day.

Measurements

Blood samples were obtained from all patients at baseline period and the 8th week, before and after a session of HD. Blood samples were centrifuged with ethylenediaminetetraacetic acid, and all samples were stored at −80 °C until needed for measurements. Plasma MPO was measured by an ELISA kit (Human Myeloperoxidase Quantikine ELISA Kit; R&D Systems, Minneapolis, MN, USA). The amount of H2 dissolved in the HD solution was measured using a DH Meter (DH-35A; DKK-TOA, Tokyo, Japan).

Overview of the E-HD system

Briefly, E-HD solutions were prepared as follows: Tap water was supplied to an electrolyzed water hemodialysis system (Trim Medical Institute Co., Osaka, Japan), where water was processed using activated charcoal filtration and water softening and then electrolyzed by a water electrolysis system (Fig. 1a,b). Water on the anode side was drained, and water from the cathode side (electrolyzed water) was collected to supply the reverse osmosis module. The intensity of electrolysis was adjusted to obtain the target H2 concentration. Reverse osmosis water containing H2 produced by the electrolyzed water hemodialysis system was supplied to prepare the HD solution. The composition of the final E-HD solution for clinical use was the same as that of the standard HD solution, with the exception of the presence of dissolved H2 in the E-HD, with no differences in terms of electrolyte levels or pH [12, 13, 15, 17, 19]. The H2 levels of HD solution generated by the two systems were as follows (mean ± SD): 47 ± 13 ppb, 24–85 ppb (36 measurements) in the first-generation system, and 154 ± 31 ppb, 71–228 ppb (30 measurements) in the third-generation system, respectively.

Analysis

Variables are expressed as mean ± standard deviation (SD) or percentage (%), as appropriate. Statistical significance was set at the level of $P < 0.05$. Comparisons between groups were made using the paired t test, non-parametric Wilcoxon signed-rank test, and chi-square test. Time courses were analyzed using repeated-measures analysis of variance and the Bonferroni procedure for multiple comparisons. All statistical analyses were performed using SPSS version 22.0 (IBM Corp. in Armonk, NY, USA).

Results

Regarding the types of fatigue presentation at baseline, 16 patients (15.2%, Group A) were defined as having chronic-type fatigue, 30 patients (28.6%, Group B) as having HD-responsive-type fatigue, and 59 patients (56.2%, Group C) as fatigue-free. No significant differences in patient profiles were seen among the three groups (Table 1).

During the 8-week observation period, significant decreases in NRS scores were seen in Group A on HD day at the 4th week ($p < 0.038$) and 8th week ($p < 0.035$) as compared to baseline (6.43 ± 1.59 at baseline, 5.75 ± 2.43 at the 2nd week, 5.37 ± 2.39 at the 4th week, 5.00 ± 2.63 at the 8th week, respectively), and there was a significant decrease on HD-free day at the 8th week ($p < 0.002$) as compared to baseline (5.20 ± 1.26 at baseline, 4.60 ± 1.84 at the 2nd week, 4.80 ± 2.17 at the 4th week, and 3.73 ± 1.75 at the 8th week), while in Groups B and C, no significant changes in fatigue scores were seen on both HD day (Group B: 5.90 ± 1.29 at baseline, 5.20 ± 2.26 at the 2nd week, 5.00 ± 2.39 at the 4th week, and 5.03 ± 2.42 at the 8th week; Group C: 1.62 ± 1.11 at baseline, 2.26 ± 2.31 at the 2nd week, 2.09 ± 2.07 at the 4th week, and 2.31 ± 2.18 at the 8th week, respectively) and HD-free day (Group B: 1.93 ± 1.18 at baseline, 2.54 ± 1.68 at the 2nd week, 2.77 ± 2.57 at the 4th week, and 2.25 ± 2.25 at the 8th week; Group C: 0.90 ± 1.07 at baseline, 1.54 ± 2.07 at the 2nd week, 1.03 ± 1.13 at the 4th week, and 1.55 ± 1.50 at the 8th week, respectively) (Fig. 2a, b).

As to the outcome of NRS at the 8th week, a total of 64 cases (61.0%) were classified as the Improved group (10 cases in Group A, 62.5%; 18 in Group B, 60.0%; 36 in Group C, 61.0%, respectively), and the rest of 41 cases (39.0%) were classified as the Non-improved group. In terms of the profiles of the two groups at baseline, although no differences were found in patient demographics, higher dry weight and cardiothoracic ratio (CTR) were noted in the Improved group as compared to the Non-improved group, despite equivalent BP levels before and after the HD session in the two groups. At the 8th week, systolic BP before HD was lower in

Table 1 Patient demographics

	Group A Chronic type	Group B HD-responsive type	Group C Fatigue-free type	*p value*
N	16 (15.2%)	30 (28.6%)	59 (56.2%)	(100.0%)
Age (years)	66.2 ± 14.7	67.7 ± 11.4	66.0 ± 10.8	*0.08*
Male (%)	7 (43.8%)	18 (60.0%)	37 (62.7%)	*0.55*
HD vintage (months)	145 ± 133	140 ± 129	95 ± 86	*0.09*
Presence of DM	8 (50.0%)	18 (60.0%)	33 (55.9%)	*0.94*
History of CVD	6 (37.5%)	11 (36.7%)	17 (28.8%)	*0.85*
Prescription of antihypertensive agent	8 (50.0%)	20 (66.7%)	34 (57.6%)	*0.71*
Dry weight (kg)	58.2 ± 14.8	56.5 + 13.8	60.9 + 15.6	*0.41*
CTR (%)	49.3 ± 4.5	47.7 ± 4.8	47.3 ± 4.8	*0.34*
Pre-SBP	161 ± 18	158 ± 26	157 ± 26	*0.81*
Pre-DBP (mmHg)	86 [1] 12	S0 ± 11	81 + 14	*0.30*
Post-SBP	134 ± 20	125 ± 16	134 ± 18	*0.07*
Post-DBP (mmHg)	75 ± 16	65 ± 10	72 ± 12	*0.01*
UF volume (kg)	2.8 ± 0.5	2.7 ± 0.7	2.8 ± 0.7	*0.66*
Creatinine (mg/dL)	10.0 ± 2.9	9.2 ± 1.9	9.4 ± 2.5	*0.52*
Hemoglobin (g/dL)	11.2 ± 1.8	10.8 ± 0.8	11.1 ± 0.9	*0.21*

HD, hemodialysis; DM, diabetes mellitus; CVD, cardiovascular diseases; CTR, cardiothoracic ratio; Pre, pre-HD; Post, post-HD; SBP, systolic blood pressure; DBP, diastolic blood pressure; UF, ultrafiltration.

Group A: patients who reported fatigue on both HD and HD-free days at baseline; Group B: patients who reported fatigue on HD days, but not on HD-free days; Group C: patients who did not report fatigue on both HD and HD-free days

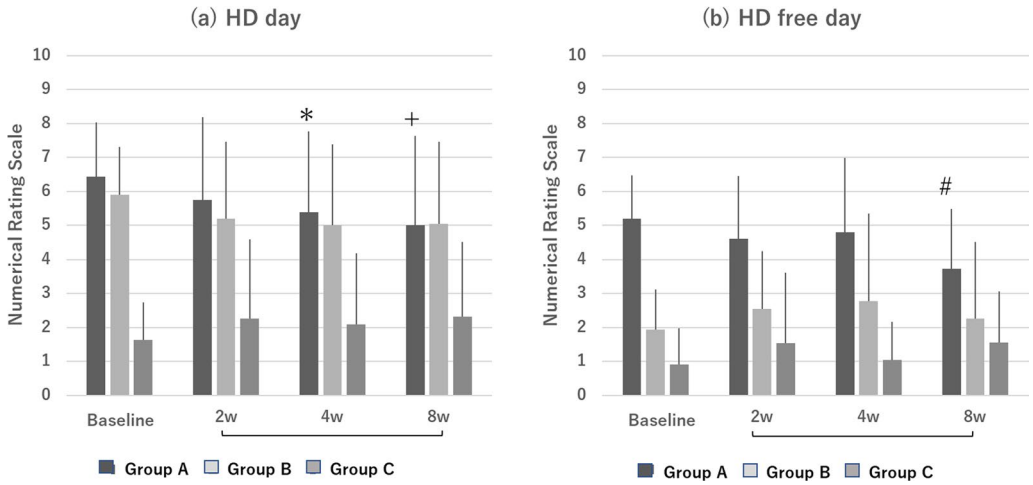

Fig. 2 Serial changes in numerical rating scale (NRS) scores for fatigue on the hemodialysis (HD) day (**a**) and the HD-free day (**b**). *$p = 0.038$ vs. baseline, +:$p = 0.035$ versus baseline, #: $p = 0.002$ versus baseline. NRS (mean ± SD). Baseline: within 2 weeks before the start of study. Group A ($n = 16$): patients who reported fatigue on both HD and HD-free days at baseline; Group B ($n = 30$): patients who reported fatigue on HD days, but not on HD-free days; Group C ($n = 59$): patients who did not report fatigue on both HD and HD-free days

the Non-improved group as compared to the Improved group, despite that antihypertensive agents were not changed in the Non-improved group (Table 2). Antihypertensive agents were identified as an independent risk factor for the Non-improved group by multiple logistic analysis (Table 3).

Differences in MPO levels, as a surrogate marker of oxidative stress, in the entire patient cohort between the

Table 2 Comparison of patients who presented absence of or a decrease in the level of fatigue on HD day (Improved group) with those who did not present decrease in the level of fatigue (Non-improved group) at baseline as compared to 8th week

	Improved group (I)	**($n = 64$)**		**Non-improved group (*M*)**	**($n = 41$)**		***Group I versus N***
	Ow	**8w**	***p value***	**Ow**	**8w**	***p value***	
NRS on HD day	3.51 ± 2.66	2.09 ± 1.98	0.00	3.75 ± 2.35	5.65 ± 2.12	*0.00*	*Ow: 0.62, 8w: 0.00*
NRS on HD-free day	1.65 ± 1.87	1.23 ± 1.46	0.03	2.12 ± 1.74	3.41 ± 1.80	*0.00*	*Ow: 0.19, 8w: 0.00*
Age (years)	65.3 ± 11.9			68.4 ± 10.7			*0.18*
HD vintage (months)	103 ± 99			136 ± 121			*0.12*
Male (%)	39 (60.9%)			22 (53.7%)			*0.59*
DM	38 (59.4%)			21 (51.2%)			*0.53*
CVD	21(32.8%)			13 (31.7%)			*0.99*
AHA	33 (51.6%)	30 (46.9%)	0.72	28 (68.3%|	28 (68.3%)	*1.00*	*Ow: 0.13, 8w: 0.05*
UF(L)	2.8 ± 0.7	2.8 ± 0.6	*0.65*	2.6 ± 0.7	2.6 ± 0.6	*0.82*	*Ow.0.12*
Dry weight (kg)	61.7 ± 15.0	61.8 ± 14.9	*0.32*	55.0 ± 14.2	56.5 ± 12.2	*0.37*	*Ow: 0.02*
CTR (%)	48.5 ± 5.1	47.9 ± 4.8	*0.04*	46.4 ± 3.8	46.5 ± 5.1	*0.80*	*Ow: 0.03*
Pre-SBP (mmHg)	160 ± 27	155 ± 26	*0.06*	154 ± 20	146 ± 18	*0.01*	*Ow: 0.25, 8w: 0.05*
DBP	82 ± 13	79 ± 12	*0.01*	78 ± 12	75 ± 10	*0.05*	*Ow: 0.12, 8w: 0.08*
Post-SBP (mmHg)	133 ± 17	127 ± 20	*0.01*	128 ± 20	125 ± 15	*0.17*	*Ow: 0.21, 8w: 0.51*
DBP	70 ± 11	67 ± 13	*0.02*	70 ± 14	67 ± 13	*0.06*	*0w:0.81,* 8 W.*0.79*
Hb (g/dL)	10.8 ± 0.9	10.8 ± 0.9	*0.96*	11.2 ± 0.9	10.7 ± 1.0	*0.01*	*Ow: 0.05*
Pre-MPO (pg/mL)	74.8 ± 58.5	74.2 ± 63.0	*0.84*	71.0 ± 46.7	68.5 ± 64.1	*0.48*	*0w:0.72, 8w: 0.65*
Post-MPO (pg/mL)	307.7 ± 244.7	277.8 ± 217.1	*0.28*	244.8 ± 151.8	262.3 ± 229.6	*0.34*	*0w:0.14, 8w: 0.73*

NRS, Numerical rating scale (0 to 10); HD, hemodialysis; DM, diabetes mellitus; CVD, cardiovascular diseases; AHA, antihypertensive agents; UF, ultrafiltration volume; CTR, cardiothoracic ratio; pre, pre-HD; post, post-HD; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; MPO, myeloperoxidase.

Table 3 Multiple logistic analysis for patients with Non-improved group

	OR	95% CI	*p* value
Male	1.16	(0.41–3.27)	*0.77*
Age (years\)	0.95	(0.90–1.01)	*0.08*
CVD history	0.89	(0.30–2.59)	*0.07*
HD vintage (months)	0.99	(0.99–1.00)	*0.07*
UF (kg)	1.26	(0.53–3.00)	*0.59*
Dry weight (kg)	1.00	(0.98–1.03)	*0.76*
CTR (%)	1.10	(0.98–1.22)	*0.08*
Pre-SBP (mmHg)	1.01	(0.98–1.04)	*0.08*
Change in SBP (mmHg)	0.99	(0.96–1.02)	*0.55*
Hb (g/dL)	1.32	(0.73–2.37)	*0.34*
Antihypertensive agents	3.56	(1.28–9.90)	*0.01*
Change in post-MPO (%)	0.98	(0.97–1.00)	*0.06*

Multivariate logistic regression was used to calculate ORs and 95% confidence intervals (95% CI) after simultaneously controlling for multiple potential confounders

OR, odds ratio; HD, hemodialysis; CVD, cardiovascular diseases; UF, ultrafiltration volume; CTR, cardiothoracic ratio; Pre-SBP, pre-HD systolic blood pressure; Change in SBP, pre-HD SBP – post-HD SBP; , hemoglobin; Change in MPO, % change of post-HD serum MPO level.

Data at 8 w were used for UF, dry weight, CTR, pre-SBP, change in SBP, and antihypertensive agents

baseline and the 8th week are shown in Table 4. There was a significant difference in post-HD LN(MPO) levels between baseline and 8th week, but no consistent changes were found in the three respective groups. In addition, no significant differences were found in MPO levels between the Improved group and the Non-improved group (Table 2).

Discussion

The present study aimed to examine the clinical impact of HD solutions with higher H2 levels on the patient-reported outcome of fatigue. In this prospective single-arm study, we observed serial changes in patient-reported outcomes of fatigue over the 8-week period after changing from HD with a solution containing an average of 47 ppb H2 to a solution with 154 ppb H2 on average. The findings can be summarized as follows: Overall, significant decreases in NRS scores were confirmed with the use of HD solution containing higher H2 levels, on HD and HD-free days in patients who presented chronic fatigue on both HD and HD-free days at baseline (Additional file 1: S1), while no significant changes were found in others, including patients who presented fatigue on HD day but not on HD-free day.

In previous studies, fatigue in HD patients was reportedly ameliorated by H2-containing HD solutions, both in the first-generation system with 47 ppb H2 and in the third-generation system with 154 ppb H2 on average. However, in the present study, we did not find consistent trend in improving fatigue levels in those patients with fatigue on HD day after replacement of the system used,

Table 4 Changes of plasma myeloperoxidase levels

	All	Group A	Group B	Group C	*p value (among groups)*
Pre-HD: MPO pg/mL					
Baseline	73.3 ± 54.1	94 1 ± 93.9	73.5 ± 44.6	67.5 ± 42.4	*0.22*
8th week	72.0 + 63.1	93.7 ± 105.3	77.0 ± 76.4	63.5 ± 33.2	*0.21*
p value	*0.79*	*0.98*	*0.75*	*0.98*	
Post-HD: MPO pg/mL					
Baseline	283.5 ± 215.2	370.6 ± 293.3	229.9 ± 165.8	287.2 ± 208.3	*0.10*
8th week	271.8 ± 221.0	317.1 ± 222.4	195.0 ± 54.9	299.1 ± 242.1	*0.07*
p value	*0.47*	*0.51*	*0.002*	*0.53*	
Pre-HD: LN(MPO pg/mL)					
Baseline	4.11 ± 0.58	4.26 ± 0.69	4.12 ± 0.61	4.06 ± 0.53	*0.46*
8th week	4.07 ± 0.58	4.17 ± 0.76	4.08 ± 0.67	4.03 ± 0.47	*0.68*
p value	*0.39*	*0.54*	*0.67*	*0.54*	
Post-HD: LN(MPO pg/mL)					
Baseline	5.41 ± 0.70	5.66 ± 0.73	5.18 ± 0.76	5.46 ± 0.64	*0.06*
8th week	5.32 ± 0.77	5.55 ± 0.64	4.98 ± 0.78	5.43 ± 0.74	*0.01*
p value	*0.02*	*0.52*	*0.002*	*0.52*	

MPO, myeloperoxidase; *LN*, natural logarithm

Group A ($n = 16$): patients who reported fatigue on both HD and HD-free days at baseline; Group B ($n = 30$): patients who reported fatigue on HD days, but not on HD-free days; Group C ($n = 59$): patients who did not report fatigue on both HD and HD-free days

i.e., 61% of patients presented improved level of fatigue on HD day (Improved group), while the rest 39% of patients did not (Non-improved group) at the 8th week as compared to baseline. These conflicting results might indicate the possible benefit of higher H2 solutions in some patients, but possible demerit in others.

Regarding the clinical backgrounds of the two groups, the Non-improved group was characterized by a lower CTR and dry weight at baseline and significantly lower BP before HD at the 8th week as compared to the Improved group. No episode of abrupt fall in BP during HD was noted during the study periods in both groups. However, in the Non-improved group, 70% of the patients received antihypertensive agents, and their BP before HD was significantly reduced at the 8th week, despite their increased dry weight at the 8th week (Table 3). We previously reported the antihypertensive effect of E-HD [14, 18], resulting in a decreased dose requirement of antihypertensive agents after the start of E-HD. This effect might have been due to H2, as was recently verified in an animal model [21]. Thus, we speculate that a greater decrease in BP after the introduction of higher H2-containing HD solutions might have canceled the mitigating effect on fatigue in the Non-improved group. The result that the prescription of antihypertensive agents was identified as an independent contributing factor for the non-improvement by higher H2 (Table 3) may well support the notion.

In analogy with the speculation on the Non-improved group, the fact that patients of Group A benefited higher H2 solution, whereas those of Group B did not, might be, at least partly, explained in terms of the lower BP after HD in Group B (Table 1), i.e., the pre-HD basal mean BP; 111 ± 13 mmHg in Group A and 106 ± 14 mmHg in Group B ($p = 0.252$, unpaired-t), the post-HD basal mean BP; 94 ± 15 mmHg in Group A and 85 ± 10 mmHg in Group B ($p = 0.025$), respectively. We think the possibility cannot be excluded that the excess fall in BP during the study period might have canceled the mitigating effect on fatigue by higher H2 in Group B.

Fatigue is closely related to nutritional and physical state. However, there were not significant changes in body mass index, serum albumin, and blood urea nitrogen levels during the 8-week periods (data not shown), although the fatigue scores were changed at least 4 weeks after the introduction of the third-generation system in Group A. Accordingly, it seems that the mitigating effect on fatigue by H2 may be direct, at least partly, and be independent of the nutritional changes.

As to the decreased fatigue on HD-free day by higher H2 in patients with chronic fatigue (Group A), the reason is not clear. However, we suppose several factors may be involved with the mechanism, i.e., progressive improvement in blood redox status as reflected by increased ratio of reduced-type serum albumin [16], possible elevation of antioxidant, thioredoxin along with its less consumption during HD [17]. The exact mechanism needs to be elucidated.

Regarding the surrogate marker of oxidative stress—MPO, we previously reported that a change in MPO levels during HD might be connected with the induction of fatigue by HD [17]. In our study, pre-HD MPO levels were not different between the baseline and the 8th week, although post-HD LN (MPO) levels were marginally but significantly lower at the 8th week, indicating the possibility of better biocompatibility of higher H2 solutions. However, no differences in MPO levels were found between the Improved and the Non-improved groups (Table 2). Therefore, taken together, the above results suggest that fine adjustments of dry weight and antihypertensive doses might help ameliorate symptoms of fatigue in patients with Non-improved group. This speculation needs to be verified in clinical practice in the future.

Several limitations to the present study need to be kept in mind. First, the study was an observational study with a single arm, was non-blinded, and lacked a control group. In order to derive concrete conclusions, future randomized controlled blinded studies are required. Second, the questionnaire did not clearly define the timing of assessment of fatigue, e.g., before HD or after HD. This is critically important especially in Group B. Third, the available BP data only included pre- and post-HD measurements, and no home BP data were obtained. Therefore, the discussions about the excess fall in BP and its influence on fatigue levels are all speculative, and precise data of BP changes are necessary for obtaining precise insights. Fourth, the present study did not prove the benefit of higher H2 solutions, because the effect of H2 levels above 154 ppb (mean) remains unclear. Additionally, achievement of higher H2 levels cannot necessarily be ensured because of limitations of the technology of current systems. Fifth, we defined the fatigue criteria by more than Grade 3 (our original scale), which profoundly decreased ADL in their everyday life. However, we cannot exclude those type of patients with Grade 2, the presence of fatigue with little impact on ADL, from fatigue criteria. Finally, the observation period of the study might not have been long enough to examine the influence of the higher dialysate H2 content on fatigue. The observed trends toward a decrease in NRS scores on the HD day over the 8-week observation period in Groups A and B indicate the need for longer observation periods to reach a conclusion.

Conclusion

Amelioration of the patient-reported outcome of fatigue might be influenced by H2 levels in the HD solution and the control of blood pressure using antihypertensive agents. Optimal levels of H2 in the dialysate need to be elucidated in consideration of clinical type of fatigue and blood pressure control status.

Abbreviations

HD: Hemodialysis; H2: Molecular hydrogen; E-HD: Hemodialysis using electrolyzed water containing H2; NRS: Numerical rating scale; MPO: Myeloperoxidase.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41100-022-00422-7.

Additional file 1. S1. Changes of NRS in Group A during the study. **S2.** Questionnaires to patients.

Acknowledgements

We sincerely thank all the participating patients. We also thank the staff of Higashi-Muroran clinic for collecting patient data.

Author contributions

SU and MN designed the study and analyzed the data. MN drafted the manuscript. SU, KT, and TT collected and entered data. SU, YK, JT, and MN contributed to data acquisition and interpretation. SU, SK, TY, MM, and JT reviewed the draft, and all authors read and approved the final manuscript.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was fully approved by the Ethics Review Committee of St Luke's International Hospital (Tokyo, Japan) (Approval date: June/19/2019; Approval number: 18-RZ013) and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants.

Consent for publication

Not applicable.

Competing interests

SK is an employee of Nihon Trim Co., Ltd., and SK, TY, MM, and MN belong to the Research Division of Tohoku University (Cooperative Research Division with Nihon Trim Co., Ltd.).

Author details

[1]Division of Clinical Engineering, Nikko Memorial Hospital, Muroran, Japan. [2]Clinical Engineering, Higashi-Muroran Clinic, Muroran, Japan. [3]Research Division of Chronic Kidney Disease and Dialysis Treatment, Tohoku University Hospital, Sendai, Japan. [4]Higashi-Muroran Clinic, Muroran, Japan. [5]Division of Nephrology, St. Luke's International Hospital, 9-1 Akashicho, Chuo-ku, Tokyo, Japan.

Received: 28 March 2022 Accepted: 12 July 2022
Published online: 25 July 2022

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