Efficiency of a novel dialysate reduction system in which hydrogen gas is dissolved in an acid concentrate

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【Original Article】

Efficiency of a novel dialysate reduction system in which hydrogen gas is dissolved in an acid concentrate
透析液Ａ原液水素還元装置の効果

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Abstract

〔Objective〕 In hemodialysis patients, oxidative stress can be exacerbated by the dialysis procedure itself, bio-incompatibilities with the dialysis apparatus, or by the loss of antioxidants during dialysis. Here, we report the development of a novel dialysate reduction system and estimate its effect on oxidative stress. 〔Methods〕 A total of 14 patients receiving maintenance hemodialysis were enrolled in this study. We performed hemodialysis for 4 weeks using a system to dissolve hydrogen gas in an acid concentrate. We then estimated the changes in the oxidation reduction potential (ORP) and biochemical data. 〔Results〕 In the conventional dialysis system, the ORP of the blood had increased by 68.1 ± 30.5 mV at the exit of the dialyzer, compared with the value at the entrance, whereas the use of the reduction device suppressed the increase to 29.3 ± 20.5 mV (P = 0.012). The ferritin level also decreased from 91.9 ± 77.0 ng/mL to 63.0 ± 46.7 ng/mL (P = 0.035). 〔Conclusion〕 A novel dialysate reduction system suppressed elevations in the ORP of blood. The ferritin level, which is an indicator of chronic inflammation, was also reduced. This system might be useful for reducing oxidative stress in hemodialysis patients.

Key words : Dialysate reduction, Hemodialysis, Molecular hydrogen, Oxidation reduction potential, Oxidative stress

Ⅰ. Introduction

Accumulating evidence indicates that oxidative stress, which is caused by an imbalance between oxidants and antioxidants, is elevated in subjects with uremia; furthermore, enhanced oxidative stress appears to play a central role in the development of comorbidities, such as cardiovascular disease[1, 2]. In chronic hemodialysis patients, oxidative stress can be exacerbated by the dialysis procedure itself, by bio-incompatibilities with the dialysis apparatus, or by the loss of antioxidants during dialysis [1, 3, 4]. Moreover, the oxidation reduction potential (ORP), which is used to estimate oxidative stress, is much higher in dialysate than in human blood. Recently, the hydrogen molecule (H_2) has been shown to possess a unique biological capacity enabling it to act as an anti-oxidative and anti-inflammatory substance[5]. H_2 administration has been shown to ameliorate organ damage in various models of ischemia and inflammation[6]. Here, we report the development of a novel dialysate reduction system in which hydrogen gas is dissolved in an acid concentrate, and we estimate the effect of this system on oxidative stress.

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Ⅱ. Materials and Methods

A total of 14 patients receiving maintenance hemodialysis were enrolled in this study. The system for dissolving hydrogen gas in an acid concentrate is shown in Figure 1. Briefly, using a personal dialysis apparatus, acid concentrate is supplied to the new apparatus, and endotoxin and bubbles are removed through the separator. H_2 is supplied by a solid polymer electrolyte membrane hydrogen generator and adds to the acid concentrate through the H_2 gas addition apparatus. The acid concentrate, which is reduced by the H_2 gas, moves to the dialysis fluid supply equipment. The dialysate reduction system is shown in Figure 2.

We performed hemodialysis using this system for 4 weeks. The ORP is a relatively new integrated measure of the balance between total oxidants (reactive oxygen species) and reductants (antioxidants) that reflects oxidative stress in a biological system. When the oxidant activity exceeds the reductant activity, the biological sample is under a state of oxidative stress and higher ORP levels reflect a higher state of oxidative stress[7, 8]. We measured the ORP levels in blood and dialysate using a portable ORP RM-30P (TOA DKK, Tokyo, Japan). We then estimated the changes in ORP for both the dialysate and the blood, and we compared this novel dialysate reduction system with conventional hemodialysis therapy. We also estimated the change in the blood cell count, biochemistry data, and fatigue after hemodialysis using a visual analog scale (VAS: 0 [none] to 10 [maximum]) before and after 4 weeks of treatment with this novel system. The VAS consisted of a 10-cm horizontal line with written descriptions at each end; subjects were asked to mark the point on the line that they felt best represented their perceptions of their current states.[9] The possible scores ranged from 0 to 10 and were measured in centimeters on a 10-cm vertical line using a pen. The score was obtained by measuring the line from "No Fatigue" to the point indicated by the subject that represented their fatigue level, with a higher VAS score reflecting a higher level of fatigue.

This study was permitted by the research ethics committee of Sangenjaya Hospital (Approved No. H2604). Written informed consent was obtained from all patients. The data were expressed as the means ± S.D. Paired t-tests were used to examine the changes in variables. All the statistical calculations were performed using JMP 5.1 software. P values less than 0.05 were considered statistically significant.

（3頁 Figure 2. Appearance of dialysate reduction systemを参照）

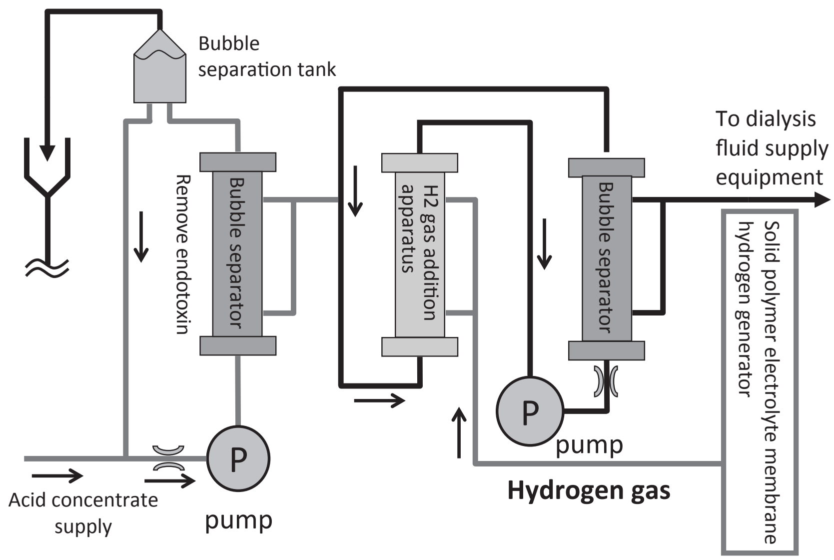

Figure 1.
System for dissolving hydrogen gas to acid concentrate

Ⅲ. Results

The background characteristics of the study participants are shown in Table 1. The mean patient age was 61.9 ± 13.9 years, and the mean duration of hemodialysis therapy was 9.6 ± 9.2 years. All the patients underwent hemodialysis 3 times a week. The mean hemodialysis time was 3.9 ± 0.4 hours, and the mean blood flow was 244 ± 45 mL/min. The quantity of dialysate was 500 mL/min, and high-performance membranes were used for all the patients (Table 2). The ORP of the dialysate using this dialysis system was 174 ± 70 mV lower than that of the conventional dialysis system. The dialysate pH and bicarbonate level were similar between the conventional system and the new dialysis reduction system. In the conventional dialysis system, the ORP of the blood had increased by 68.1 ± 30.5 mV at the exit of the dialyzer, compared with the value at the entrance, whereas the use of the reduction device suppressed the increase to 29.3 ± 20.5 mV (P = 0.012). On the other hand, in the conventional dialysis system, the ORP of the dialysate had decreased by 126 ± 35 mV at the exit of the dialyzer, compared with the value at the entrance, whereas the use of the reduction device suppressed the decrease to 74 ± 31 mV (P < 0.0001, Table 3). The blood cell count did not change significantly (Table 4). For the biochemistry data, the ferritin level decreased from 91.9 ± 77.0 ng/mL to 63.0 ± 46.7 (P = 0.035), while all other investigated parameters did not show any significant changes (Table 4). However, in two patients whose malondialdehyde-modified low-density lipoprotein (MDA-LDL) levels were above the normal range, the MDA-LDL values were reduced to within the normal range (from 147 U/L to 110 U/L, and from 123 U/L to 74 U/L). After 4 weeks of treatment using the novel system, the MDA-LDL values were within the normal range in all the patients. The VAS score for fatigue after hemodialysis also decreased from 2.9 ± 2.7 to 2.0 ± 2.5 (P = 0.015).

Table 1.
Background characteristics of the study participants

	Quantity
Gender (M/F)	11 / 3
Age (year)	61.9 ± 13.9
Duration of HD (year)	9.6 ± 9.2
Primary Cause of ESKD, n	
Chronic glomerulonephritis	6
Diabetic Nephropathy	4
Nephrosclerosis	2
Unknown and others	2

means ± S.D.

Table 2.
Hemodialysis data

	Quantity
Treatment time (hr)	3.9 ± 0.4
Quantity of blood flow (ml/min)	244 ± 45
Dialyzer	
NV-13S	2
NV-15S	1
APS-18SA	2
APS-21SA	7
PN-220S	2

means ± S.D.

Ⅳ. Discussion

We have developed a novel dialysate reduction system in which hydrogen gas is dissolved in an acid concentrate. Our new dialysis system enables a reduction in the ORP of dialysate. During dialysis treatment using this device, a significant decrease in the change in the ORP of blood was also observed. The ferritin level, which is an indicator of chronic inflammation, and the VAS score for fatigue were also decreased.

Ohsawa et al. studied the antioxidant properties of molecular H_2 and reported that it selectively reduces hydroxyl radical and peroxynitrite[5]. H_2 is an inert gas with no known adverse effects.

Recent studies have shown that the administration of H_2 dissolved in water can suppress oxidative or inflammatory injury to organs in animal models, such as ischemic reperfusion in the brain[5] and liver[8], stress-induced oxidative injury in the hippocampus[10], and inflammatory reactions in the colon induced by dextran sodium sulphate[11]. Furthermore, H_2 inhalation mitigates small intestine inflammation arising from transplantation[12]. Diatomic hydrogen has been reported to be a selective antioxidant with the following characteristics: 1) it can easily diffuse across the cellular membrane to reach sub-cellular compartments, 2) it does not influence physiological parameters in the blood (temperature, blood pressure, pH, pO_2), 3) it does not disturb metabolic oxidation-reduction reactions and cell signaling, 4). it can be well tolerated at high concentrations with few systemic side –effects, 5) it is inexpensive, and 6) it has multiple mechanisms of action (antioxidant effect, anti-inflammatory effect, inhibition of apoptosis, and anti-allergic effect)[13].

In the field of hemodialysis, Nakayama et al. found that adding H_2 to hemodialysis solutions using water electrolysis after a 1-month run-in period ameliorated inflammatory reactions, decreased plasma oxidative markers and improved

Table 3.
Change of ORP
Blood: V side – A side
Dialysate: Out – In

	Conventional system	Dialysate reduction system	P value
Change of ORP			
Blood (mV)	+68 ± 31	+29 ± 21	0.012
Dialysate (mV)	-126 ± 35	-74 ± 31	<0.0001

means ± S.D.
OPR: oxidation reduction potential

Table 4.
Change of laboratory examination

	Pre	Post	P value
White blood cell (/μL)	6050 ± 1957	5964 ± 1615	NS
Hemoglobin (g/dL)	10.7 ± 1.0	10.9 ± 0.8	NS
Platelet (x104/μL)	17.8 ± 5.5	19.5 ± 7.9	NS
Albumin (g/dL)	4.0 ± 0.2	4.0 ± 0.2	NS
Creatinine (mg/dL)	11.0 ± 2.5	18.3 ± 27.4	NS
Sodium (mEq/L)	139 ± 4	140 ± 3	NS
Potassium (mEq/L)	4.7 ± 0.5	4.8 ± 0.6	NS
Chlorine (mEq/L)	100 ± 4	101 ± 4	NS
LDL-cholesterol (mg/dL)	78 ± 26	78 ± 25	NS
MDA-LDL (U/L)	77 ± 30	78 ± 20	NS
MDA-LDL / LDL	1.0 ± 0.3	1.0 ± 0.2	NS
Iron (mg/dL)	54 ± 25	57 ± 21	NS
Total iron-binding capacity (mg/dL)	254 ± 34	269 ± 33	NS
Ferritin (ng/mL)	91.9 ± 77.0	63.0 ± 46.7	0.035
Transferrin saturation (%)	21.0 ± 9.3	21.9 ± 9.1	NS
c-reactive protein (mg/dL)	0.83 ± 1.9	0.26 ± 0.4	NS

means ± S.D.
LDL: low-density lipoprotein
MDA- LDL: malondialdehyde-modified low-density lipoprotein

blood pressure control during a 6-month trial[14]. The reduced/oxidized albumin ratio can be increased by a single HD session using electrolyzed water[15]. Another study using the same method for electrolyzed water hemodialysis showed an improvement in the fraction of reduced albumin after 6 months of treatment[16]. These findings indicate that the use of an H_2-enriched solution may prove to be a novel approach to ameliorating dialysis-related complications[17].

Using the above-mentioned system, water was electrolyzed by the supply of a direct current to the anode and cathode electrode plates. The water on the anode side was drained, and the water from the cathode side (which contains highly dissolved H_2) was collected to supply the reverse osmosis equipment. Electrolyzed water is characterized by alkalinity and the presence of dissolved hydrogen molecules (H_2)[17]. Unlike their dialysate, our novel system directly adds H_2 using a solid polymer electrolyte membrane hydrogen generator. As a result, our system does not affect the pH of the dialysate. Our new dialysis system reduced the ORP of the dialysate. During dialysis treatment using this device, a significant decrease in the change in the ORP of the blood was also observed. The change in the ORP was much larger in the dialysate than in the blood, but the reason for this difference was unclear. The difference between the dialysate flow rate and the blood flow rate may have affected the change in the ORP.

We observed a reduction in ferritin and the VAS score for fatigue after hemodialysis. This therapy may change the trivalent iron in ferritin to bivalent iron. When trivalent iron is changed to bivalent iron, it loses its ability to bind with ferritin. This change may promote the translocation of ferritin from an extracellular location to an intracellular location. Methemoglobin, which contains trivalent iron, is unable to deliver oxygen. Using this apparatus, methemoglobin might also be reduced to normal hemoglobin, which can transport oxygen. Such changes may partly explain the improvement in the VAS score for fatigue. We examined the MDA-LDL values as an oxidant stress marker. In two patients whose MDA-LDL values were above the normal range, the MDA-LDL values decreased to within the normal range. After 4 weeks of treatment using this novel system, the MDA-LDL values were within the normal range in all the patients after.

The present study had several limitations. The number of participants was relatively small, and the observation period was relatively short. Furthermore, other oxidant stress markers, such as reduced albumin, were not evaluated. A larger study population and a longer observation period are needed.

In conclusion, a novel dialysate reduction system in which hydrogen gas is dissolved in an acid concentrate enabled a reduction in the ORP of the dialysate. In dialysis treatment using this device, a significant decrease in the change in the ORP of blood was also observed. The ferritin level, which is an indicator of chronic inflammation, and the VAS score for fatigue were also reduced. This system might be useful for reducing oxidative stress in hemodialysis patients.

The authors state that they have no Conflict of Interest (COI).

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References

1) Morena M, Delbosc S, Dupuy AM, et al. Overproduction of reactive oxygen species in end-stage renal disease patients: a potential component of hemodialysis-associated infl ammation. Hemodial Int 9:37-46, 2005.

2) Kaysen GA. The microinflammatory state in uremia: causes and potential consequences. J Am Soc Nephrol 12:1549-1557, 2001.

3) Wratten ML, Tetta C, Ursini F, et al. Oxidant stress in hemodialysis: prevention and treatment strategies. Kidney Int Suppl 58:S126-132, 2000.

4) Himmelfarb J, Lazarus JM, Hakim R. Reactive oxygen species production by monocytes and polymorphonuclear leukocytes during dialysis. Am J Kidney Dis 17:271-276, 1991.

5) Ohsawa I, Ishikawa M, Takahashi K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. Nat Med 13:688-694, 2007.

6) Ohta S. Recent progress toward hydrogen medicine: Potential of molecular hydrogen for preventive and therapeutic applications. Curr Pharm Des 17:2241-2252, 2011.

7) Milić S, Bogdanović Pristov J, Mutavdžić D, et al. The relationship of physicochemical properties to the antioxidative activity of free amino acids in Fenton system. Environ Sci Technol 49:4245-4254, 2015.

8) Fukuda K, Asoh S, Ishikawa M, et al. Inhalation of hydrogen gas suppresses hepatic injury caused by ischemia/reperfusion through reducing oxidative stress. Biochem Biophys Res Commun 361:670-674, 2007.

9) Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. Research in Nursing & Health 13:227-236, 1990.

10) Nagata K, Nakashima-Kamimura N, Mikami T, et al. Consumption of molecular hydrogen prevents the stress-induced ImpaI/Rments in hippocampus-dependent learning tasks during chronic physical restraint in mice. Neuropsychopharmacology 34:501-508, 2009.

11) Kajiya M, Silva MJ, Sato K, et al. Hydrogen mediates suppression of colon inflammation induced by dextran sodium sulfate. Biochem Biophys Res Commun 386:11-15, 2009.

12) Buchholz BM, Kaczorowski DJ, Sugimoto R, et al. Hydrogen inhalation ameliorates oxidative stress in transplantation induced intestinal graft injury. Am J

Transplant 8:2015-2024, 2008.
13) Hong Y, Chen S, Zhang JM. Hydrogen as a Selective Antioxidant: Hydrogen as a selective antioxidant: a review of clinical and experimental studies. J Int Med Res 38:1893-1903, 2010.
14) Nakayama M, Nakano H, Hamada H, et al. A novel bioactive haemodialysis system using dissolved dihydrogen (H2) produced by water electrolysis: a clinical trial. Nephrol Dial Transplant 25:3026-3033, 2010.
15) Terawaki H, Zhu WJ, Matsuyama Y, et al. Effect of a hydrogen (H2)-enriched solution on the albumin redox of hemodialysis patients. Hemodial Int 18:459-466, 2014.
16) Maeda K, Yoshizaki S, Iida T, et al. Improvement of the fraction of human mercaptalbumin on hemodialysis treatment using hydrogen-dissolved hemodialysis fluid: a prospective observational study. Renal Replacement Therapy 2:42, 2016.
17) Nakayama M, Kabayama S, Ito S. The hydrogen molecule as antioxidant therapy: clinical application in hemodialysis and perspectives. Renal Replacement Therapy 2:23, 2016.

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【原著】

透析液 A 原液水素還元装置の効果

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要　旨

【目的】血液透析患者は血液の透析膜との接触や透析液の曝露，透析液中に抗酸化物質が喪失すること等により酸化ストレスにさらされている．そこで，新規の透析液原液水素還元装置の酸化ストレスに対する効果を調べた．【方法】維持透析患者 14 名を対象に 4 週間，透析液 A 原液を水素にて還元した装置を使用し，透析液ならびに血液の酸化還元電位 oxidation reduction potential（ORP），生化学，血算値を評価した．【結果】従来の透析では血液の ORP はダイアライザーの前後で 68.1 ± 30.5 mV 上昇したのに対し，この装置ではその上昇が 29.3 ± 20.5 mV に抑えられた（P = 0.012）．フェリチン値は 4 週間の治療で 91.9 ± 77.0 ng/mL から 63.0 ± 46.7 ng/mL へと減少した（P = 0.035）．【結論】新規の還元装置によって血液の ORP の上昇を抑えることができた．フェリチンは炎症の指標でもあるが，この装置によって低下が認められた．この装置は透析患者の酸化ストレスを改善させる可能性がある．

キーワード：透析液還元，血液透析，水素分子，酸化還元電位，酸化ストレス