

Pilot Study of H₂ Therapy in Parkinson's Disease: A Randomized Double-Blind Placebo-Controlled Trial

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Background: Oxidative stress is involved in the progression of Parkinson's disease (PD). Recent studies have confirmed that molecular hydrogen (H₂) functions as a highly effective antioxidant in cultured cells and animal models. Drinking H₂-dissolved water (H₂-water) reduced oxidative stress and improved Parkinson's features in model animals.

Methods: In this a placebo-controlled, randomized, double-blind, parallel-group clinical pilot study, the authors assessed the efficacy of H₂-water in Japanese patients with levodopa-medicated PD. Participants drank 1,000 mL/day of H₂-water or pseudo water for 48 weeks.

Results: Total Unified Parkinson's Disease Rating Scale (UPDRS) scores in the H₂-water group (n=9) improved (median, -1.0; mean±standard deviation, -5.7±8.4), whereas UPDRS scores in the placebo group (n=8) worsened (median, 4.5; mean±standard deviation, 4.1±9.2). Despite the minimal number of patients and the short duration of the trial, the difference was significant (*P*<0.05).

Conclusions: The results indicated that drinking H₂-water was safe and well tolerated, and a significant improvement in total UPDRS scores for patients in the

H₂-water group was demonstrated. © 2013 Movement Disorder Society

Key Words: hydrogen; Parkinson's disease; randomized double-blind placebo-controlled trial; oxidative stress

The increase in iron and lipid peroxidation and the decrease in reduced glutathione levels observed in the substantia nigra of patients with Parkinson's disease (PD)^{1,2} suggest that oxidative stress may play a role in the pathogenesis of PD. Molecular hydrogen (H₂) has recently been highlighted as a therapeutic and preventive antioxidant.^{3,4} H₂-dissolved water (H₂-water) reduces dopaminergic neuronal cell loss and down-regulates 4-hydroxy-2-nonenal, which is an oxidative stress marker, in dopaminergic neurons in the substantia nigra of PD animal models compared with normal water,^{5,6} indicating that the intake of H₂-water reduces neurotoxic damage even after chronic toxic administration. In this study, we investigated whether H₂-water could modify the progression of PD as assessed by changes in total scores on the Unified Parkinson's Disease Rating Scale (UPDRS) from baseline to scores at 48 weeks.

Patients and Methods

Participants

This placebo-controlled, randomized, stratified, double-blind, parallel-group (1:1) clinical trial of H₂-water for the treatment of PD was organized in our hospital according to Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study was approved by the ethics committee of our institution. Written informed consent was obtained. All patients diagnosed with PD⁷ were medicated with levodopa (L-dopa) and had an on-phase modified Hoehn and Yahr staging score between 1 and 4. Exclusion criteria included the presence of parkinsonism other than PD and the presence of other serious disease, malignant tumor, or adverse events caused by drugs. Antiparkinsonian drugs had not been changed during the 8 weeks before the baseline assessment.

Procedures

Participants were assigned using a minimization method based on age, sex, modified Hoehn and Yahr

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TABLE 1. Baseline characteristics of the study patients and changes in Unified Parkinson's Disease Rating Scale scores from baseline

Characteristic	Placebo water group	Molecular hydrogen water group	P ^a
Women: No. (%)	6 (66.7)	5 (55.6)	0.35 ^b
Age, y			
Mean±SD	60.1±10.6	65.2±8.5	0.436
Median	61.0	63.0	
Severity of disease			
Modified Hoehn and Yahr stage			
Mean±SD	2.1±0.2	2.1±0.2	0.73
Median	2.0	2.0	
Total UPDRS			
Mean±SD	18.7±4.3	15.3±2.7	0.65
Median	19.0	16.0	
UPDRS-II			
Mean±SD	4.1±1.5	1.8±0.5	0.34
Median	2.0	1.0	
UPDRS-III			
Mean±SD	13.2±3.1	12.6±2.6	1.00
Median	10.0	12.0	
Disease duration, y			
Mean±SD	7.2±2.1	6.5±1.2	0.666
Median	4.0	6.0	
Treatment, y			
Mean±SD	3.7±1.8	4.5±1.0	0.161
Median	1.0	4.0	
Levodopa daily dose, mg			
Mean±SD	400±62	364±47	0.73
Median	350	300	
Other medication, no. of patients			
Dopamine agonist	7	5	
Anticholinergic agents	2	2	
Selegiline	1	4	
Entacapone	2	0	
Amantidine	1	1	
Zonisamide	1	5	
Change scores from baseline			
Total UPDRS			
Week 8			
Mean±SD	0.4±6.3	-3.1±6.2	0.19
Median	1.0	-5.0	
Week 24			
Mean±SD	-1.1±9.6	-2.4±7.9	0.65
Median	-2.0	-4.0	
Week 48			
Mean±SD	4.1±9.2	-5.7±8.4	0.046 ^c
Median	4.5	-1.0	
After week 8			
Mean±SD	3.9±11.9	-1.3±8.7	0.61
Median	-0.5	2.0	
UPDRS-II			
Week 8			
Mean±SD	-0.7±2.6	0.1±1.8	0.93
Median	0.0	0.0	
Week 24			
Mean±SD	-0.3±2.7	1.2±3.5	0.34
Median	0.0	1.0	
Week 48			
Mean±SD	1.4±3.0	0.4±2.6	0.48
Median	1.0	0.0	
After week 8			
Mean±SD	1.3±3.8	1.4±3.0	0.89
Median	2.5	1.0	

TABLE 1. Continued

Characteristic	Placebo water group	Molecular hydrogen water group	P ^a
UPDRS-III			
Week 8			
Mean±SD	1.1±5.2	-2.4±5.7	0.16
Median	0.0	-3.0	
Week 24			
Mean±SD	-0.3±8.3	-3.2±5.7	0.55
Median	-1.0	-2.0	
Week 48			
Mean±SD	2.3±8.5	-5.8±7.2	0.074
Median	0.0	-4.0	
After week 8			
Mean±SD	2.5±11.6	-2.4±8.0	0.67
Median	0.0	1.0	
Hoehn and Yahr stage			
Week 8			
Mean±SD	0.6±0.3	-0.1±0.2	0.34
Median	0.0	0.0	
Week 24			
Mean±SD	0.2±0.3	-0.2±0.5	0.09
Median	0.0	0.0	
Week 48			
Mean±SD	0.2±0.4	-0.2±0.6	0.17
Median	0.0	0.0	
After week 8			
Mean±SD	0.1±0.7	-0.1±0.5	0.82
Median	0.0	0.0	

^aMann-Whitney U test.

^bChi-square test.

^cSignificant difference between the 2 groups (P<0.05).

Abbreviations: SD, standard deviation; UPDRS-II, United Parkinson's Disease Rating Scale part II, self-evaluation of the activities of daily life; UPDRS-III, United Parkinson's Disease Rating Scale part III, clinician-scored motor evaluation.

stage, and disease duration. Assignments were made sequentially by 1 author (M.H.) who dispensed therapy but was not otherwise involved in the study.

The participants prepared saturated H₂-water by dissolving 0.8 mM H₂ using Aquerablue (Ecomo International Company, Ltd., Fukuoka, Japan) and drank 1000 mL of it daily for 48 weeks. Placebo water was prepared using a placebo machine.

The changes in total score on the UPDRS (parts I–IV) from baseline to week 8, week 24, and week 48 and after week 8 were evaluated. The primary endpoint of treatment efficacy in individuals with PD was the change in the total score on the UPDRS from baseline to week 48. Changes in scores for UPDRS part II (self-evaluation of the activities of daily life) and part III (clinician-scored motor evaluation) and in the Hoehn and Yahr stage at the same time points and the suspension of the protocol because of the addition of L-dopa or disease progression also were analyzed. Assessment of adverse events and screening laboratory studies were performed at the same time.

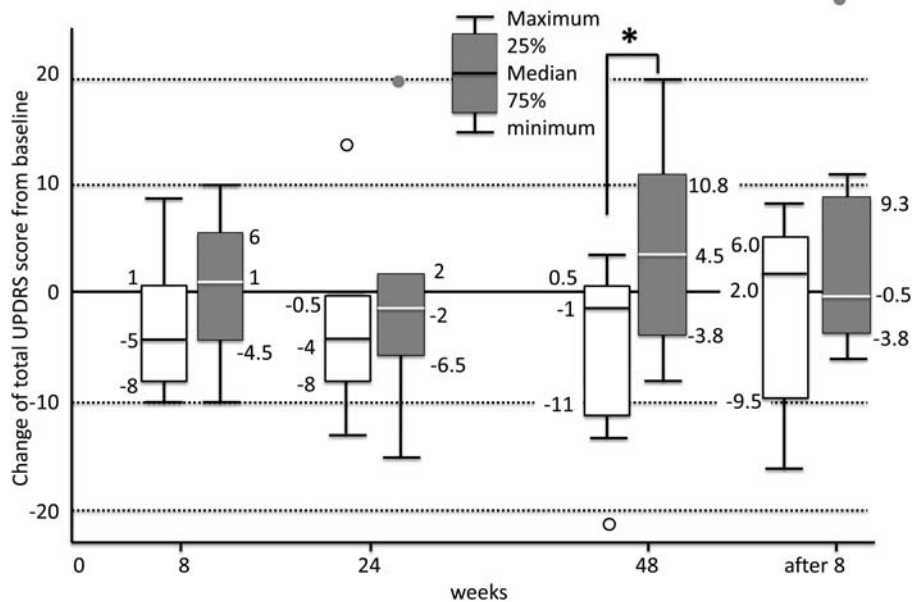


FIG. 1. Changes in total Unified Parkinson's Disease Rating Scale (UPDRS) scores from baseline are illustrated. The placebo group is indicated in gray, and the molecular hydrogen (H₂-water) group is indicated in white. Outliers are displayed as circles. In the placebo group, there were 9 samples at baseline, 9 samples at week 8, 9 samples at week 24, 8 samples at week 48, and 8 samples after the week-8 visit. In the H₂-water group, there were 9 samples across all time points.

Statistical Analyses

We calculated that the enrollment of a minimum of 8 participants would be required to detect a 5% difference in the change of UPDRS scores between the 2 groups, with a standard deviation of the mean difference of 3.5% at a 2-sided α level of 0.05 and 80%. Assuming 1 dropout, a total of 9 patients was required.

Variations in the endpoints between baseline and treatment were compared between groups using the Mann-Whitney *U* test. Statistical tests were 2-sided at a significance level of 0.05. Analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL).

Results

Eighteen participants with PD (mean age \pm standard deviation [SD], 62.7 \pm 9.4 years), including 11 women, were randomized to H₂-water or placebo treatment (Table 1) between January 2010 and March 2011. One patient in the placebo group could not continue the study because of pollakiuria. None of the patients altered the L-dopa treatment or their antiparkinsonian drugs during the drinking period. H₂-water was well tolerated, and participants exhibited no adverse effects. The variation in the total UPDRS score from the baseline to week 48 (which was the primary endpoint of the study) was -1.0 (median) and -5.7 ± 8.4 (mean \pm SD) for the H₂-water group and 4.5 (median) and 4.1 ± 9.2 (mean \pm SD) for the placebo group ($P < 0.05$) (Fig. 1, Table 1). Six of 9 participants exhibited improvement, and 1 of 9 showed no changes in

the H₂-water group. Additional analyses revealed no differences between groups (Table 1). Despite the small number of participants and the short duration of the study, H₂-water led to a significant improvement in PD.

Discussion

The current results in patients with PD agree with previous findings obtained in PD animal models.^{5,6} When H₂-water was placed into the stomach of a rat, H₂ was detected at a level of several μ M in the blood.⁸ After drinking H₂-water, approximately 40% of the H₂ ingested was consumed by the body⁹; however, no publication has reported the H₂ level in the human brain after drinking H₂-water. H₂ gas was detected in rat striatum only during inhalation. In addition, drinking H₂-water at 0.08 ppm did not lead to the detection of changes in H₂ concentration.⁵ It is not known why even a low concentration of H₂-water was effective in the brain of model animals. Ohsawa et al. revealed that H₂ selectively reduced OH radicals, but not O₂⁻, H₂O₂, or NO, in a cell-free system.³ The effects of hydrogen have been attributed not only to scavenging oxidative radicals, but also to alterations of gene expression and signal-modulating activities.¹⁰ However, it remains unknown how H₂ reduces oxidative stress in the brain after drinking H₂-water.

Six of 9 participants in our H₂-water group exhibited improvement, with a total UPDRS score improvement of approximately 5 points over 48 weeks. Despite the short duration of the current study and the minimal number participants, a significant

improvement in the total UPDRS score for patients with PD was demonstrated. This was almost equal to the best scores obtained in nonergot dopamine agonist studies, in which the total scores on UPDRS parts II and III exhibited an improvement >5 points.¹¹

To our knowledge, this study is the first randomized double-blind, placebo-controlled, parallel-group trial of H₂-water in humans. The marked effect of H₂-water in PD should be confirmed in longer and larger trials that include patients who are not medicated with L-dopa or de novo patients. ■

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References

- Dexter DT, Wells FR, Agid F, Agid Y, Lees AJ, Jenner P, Marsden CD. Increased nigral iron content in postmortem Parkinsonian brain. *Lancet* 1987;8569:1219–1220.
- Yoritaka A, Hattori N, Uchida K, Tanaka M, Stadtman ER, Mizuno Y. Immunohistochemical detection of 4-hydroxynonenal protein adducts in Parkinson disease. *Proc Natl Acad Sci U S A* 1996;93:2696–2701.
- Ohsawa I, Ishikawa M, Takahashi K, et al. Hydrogen acts as a therapeutic antioxidant by selectively reducing cytotoxic oxygen radicals. *Nat Med* 2007;13:688–694.
- Ohta S. Molecular hydrogen is a novel antioxidant to efficiently reduce oxidative stress with potential for the improvement of mitochondrial diseases. *Biochim Biophys Acta* 2012;1820:586–594.
- Fujita K, Seike T, Yutsudo N, et al. Hydrogen in drinking water reduces dopaminergic neuronal loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease [serial online]. *PLoS One* 2009;30:e7247.
- Fu Y, Ito M, Fujita Y, et al. Molecular hydrogen is protective against 6-hydroxydopamine-induced nigrostriatal degeneration in a rat model of Parkinson's disease. *Neurosci Lett* 2009;453:81–85.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry* 1992;55:181–184.
- Nagata K, Nakashima-Kamimura N, Mikami T, Ohsawa I, Ohta S. Consumption of molecular hydrogen prevents the stress-induced impairments in hippocampus-dependent learning tasks during chronic physical restraint in mice. *Neuropsychopharmacology* 2009;34:501–508.
- Shimouchi A, Nose K, Shirai M, Kondo T. Estimation of molecular hydrogen consumption in the human whole body after the ingestion of hydrogen-rich water. *Adv Exp Med Biol* 2012;737:245–250.
- Ohno K, Ito M, Ichihara M, Ito M. Molecular hydrogen as an emerging therapeutic medical gas for neurodegenerative and other disease [serial online]. *Oxid Med Cell Longev* 2012;2012:353152.
- Fox SH, Katzenschlager R, Lim SY, et al. The Movement Disorder Society Evidence-Based Medicine Review Update: treatments for the motor symptoms of Parkinson's disease. *Mov Disord* 2011;26:S2–S41.