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Pilot Study of H_2 Therapy in Parkinson's Disease: A Randomized Double-Blind Placebo-Controlled Trial

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ABSTRACT

Background: Oxidative stress is involved in the progression of Parkinson's disease (PD). Recent studies have confirmed that molecular hydrogen (H_2) functions as a highly effective antioxidant in cultured cells and animal models. Drinking H_2-dissolved water (H_2-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 H_2-water in Japanese patients with levodopa-medicated PD. Participants drank 1,000 mL/day of H_2-water or pseudo water for 48 weeks.

Results: Total Unified Parkinson's Disease Rating Scale (UPDRS) scores in the H_2-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 H_2-water was safe and well tolerated, and a significant improvement in total UPDRS scores for patients in the H_2-water group was demonstrated.

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

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Relevant conflicts of interest/financial disclosures: Nothing to report. Full financial disclosures and author roles may be found in the online version of this article.

Received: 8 November 2012; **Revised:** 21 December 2012; **Accepted:** 26 December 2012

Published online 11 February 2013 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.25375

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 Hoen 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	
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	
Hoen 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	

[a]Mann–Whitney U test.
[b]Chi-square test.
[c]Significant 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.

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 (H_2) has recently been highlighted as a therapeutic and preventive antioxidant.[3,4] H_2-dissolved water (H_2-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 H_2-water reduces neurotoxic damage even after chronic toxic administration. In this study, we investigated whether H_2-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.

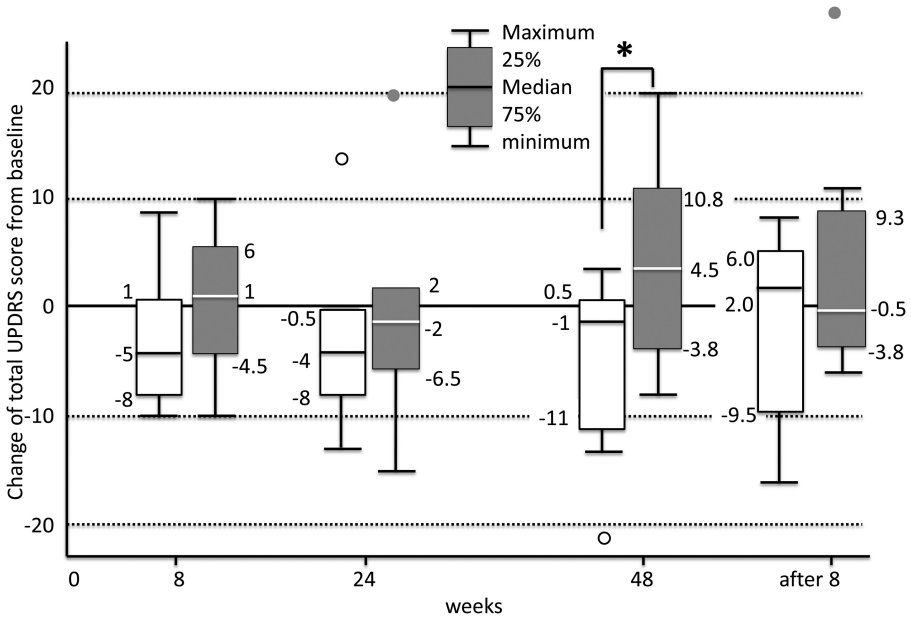

FIG. 1. Changes in total Unified Parkinson's Disease Rating Scale (UPDRS) scores from baseline are illustrated. The placebo group is indicated in gray, and the molecular hydrogen (H_2)-water group is indicated in white. Outliers are displayed as circles. In the placebo group, there were 9 samples at 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 H_2-water group, there were 9 samples across all time points.

Patients and Methods

Participants

This placebo-controlled, randomized, stratified, double-blind, parallel-group (1:1) clinical trial of H_2-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 PD[7] 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 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 H_2-water by dissolving 0.8 mM H_2 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.

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±standard deviation [SD], 62.7±9.4 years), including 11 women,

were randomized to H_2-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. H_2-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±SD) for the H_2-water group and 4.5 (median) and 4.1±9.2 (mean±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 H_2-water group. Additional analyses revealed no differences between groups (Table 1). Despite the small number of participants and the short duration of the study, H_2-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 H_2-water was placed into the stomach of a rat, H_2 was detected at a level of several μM in the blood.[8] After drinking H_2-water, approximately 40% of the H_2 ingested was consumed by the body[9]; however, no publication has reported the H_2 level in the human brain after drinking H_2-water. H_2 gas was detected in rat striatum only during inhalation. In addition, drinking H_2-water at 0.08 ppm did not lead to the detection of changes in H_2 concentration.[5] It is not known why even a low concentration of H_2-water was effective in the brain of model animals. Ohsawa et al. revealed that H_2 selectively reduced OH radicals, but not O_2^-, H_2O_2, 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 H_2 reduces oxidative stress in the brain after drinking H_2-water.

Six of 9 participants in our H_2-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 H_2-water in humans. The marked effect of H_2-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. ■

Acknowledgments: We thank Dr. K. Matsuoka of the Juntendo Clinical Research Center for advice on the statistical analysis. We also thank Ecomo International Company, Ltd. and Miz Company for rental of the Aquerablue and placebo machines.

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