International Journal of Gerontology 14 (2020) 149–150
https://doi.org/10.6890/IJGE.202005_14(2).0013

International Journal of Gerontology

journal homepage: http://www.sgecm.org.tw/ijge/

Brief Communication

Short-Term H_2 Inhalation Improves Cognitive Function in Older Women: A Pilot Study

Darinka Korovljev, Tatjana Trivic, Valdemar Štajer, Patrik Drid, Bunpei Sato, Sergej Ostojic *

Faculty of Sport and Physical Education, University of Novi Sad, Lovcenska 16, Novi Sad, Serbia

ARTICLE INFO

Accepted 2 October 2018

Keywords:
molecular hydrogen,
cognitive health,
older women

SUMMARY

We analyzed the effects of 4-week H_2 inhalation on cognitive performance in women aged 65 and above. The participants (n = 13) were community-dwelling older women (age 68.0 ± 3.0 years; weight 66.9 ± 10.3 kg; height 161.1 ± 5.8 cm) who volunteered to participate in this open-label pilot trial (ClinicalTrials.gov, NCT02830854). The participants received H_2 by inhalation for 15 min once per day for 4 weeks. The cognitive function was assessed using the Mini Mental State Exam (MMSE) and Alzheimer disease assessment scale cognitive subscale (ADAS-Cog) at baseline and at follow up. H_2 intervention significantly increased total MMSE scores (for 14.2% on average; $p < 0.01$), thereby improving cognitive function from mild dementia at baseline (a score of 25.6 out of 30) to normal cognition at follow up (above a cut score of 27). In addition, ADAS-Cog scores were significantly improved by H_2 inhalation, with better performance for word recall test ($p < 0.01$), and improved word recognition ($p = 0.01$) at post-administration, respectively. This pilot trial seems to corroborate previous animal studies, suggesting that gaseous H_2 might be considered as a beneficial agent for age-related cognitive health.

1. Introduction

A decline in cognitive function accompanies aging as one of the most distinctive and hard-to-manage features of the process of growing old. Many different pharmacological and non-pharmacological procedures have been used to tackle age-related cognitive impairment in clinical environment with mixed results.[1] Molecular hydrogen (H_2) is a novel biomedical gas with polyvalent therapeutic properties.[2] H_2 has recently been reported to alleviate cognitive impairment and neurodegeneration in several animal models,[3–5] yet no studies so far evaluated its effectiveness in human trials. In this open-label pilot study, we analyzed the effects of 4-week H_2 inhalation on cognitive performance in women aged 65 and above.

2. Methods

The participants (n = 13) were community-dwelling older women (age 68.0 ± 3.0 years; weight 66.9 ± 10.3 kg; height 161.1 ± 5.8 cm) who volunteered to participate in this open-label pilot trial (registered at ClinicalTrials.gov, NCT02830854). Exclusion criteria included the presence of serious disease or psychiatric comorbidity. The study was conducted according to the guidelines of the Declaration of Helsinki, with local institutional review board approved the study protocol. All participants gave their informed consent, and were asked to maintain their usual lifestyle and dietary intake during the study. The participants received H_2 by inhalation for 15 min once per day for 4 weeks. Gaseous H_2 (4%) was provided by biological gas supplying apparatus (MIZ Company Ltd, Kanagawa, Japan), with day-to-day H_2 inhalation supervised by study investigators throughout the trial. The primary endpoint of treatment efficacy was the change in the Mini Mental State Exam (MMSE) score from baseline to week 4. Additionally, assessment of other cognition markers and side-effects evaluation were performed at baseline and after 4 weeks after study commence. The cognitive function of participants was assessed using the MMSE and Alzheimer disease assessment scale cognitive subscale (ADAS-Cog). MMSE is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment in elderly.[6] ADAS-Cog is a cognitive testing instrument that consists of 11 tasks measuring the disturbances of memory, language, praxis, attention and other cognitive abilities in the assessment of dementia.[6] In addition to above tests, participants were instructed to report any adverse events of H_2 intervention through an open-ended questionnaire for self-assessment of side effects (e.g. nausea, headache) during the study. Wilcoxon signed rank test was used to establish if any significant differences existed between participants' responses over time of intervention (baseline vs. post-administration). Significance level was set at $p \leq 0.05$.

3. Results

All participants completed the follow-up measures, with no participants were excluded from the study due to adverse events, or reported any side effect of H_2 intervention. The compliance with the regimen was 95.8%. Changes in cognitive function outcomes during the study (baseline vs. 4-week follow up) are presented in Table.

H_2 intervention significantly increased total MMSE scores (for 14.2% on average; $p < 0.01$), thereby improving cognitive function from mild dementia at baseline (a score of 25.6 out of 30) to normal

* Corresponding author.
E-mail address: sergej.ostojic@chess.edu.rs (S. Ostojic)

Table
Changes in cognitive performance after H_2 inhalation in older women (n = 13). Values are mean ± SD.

	Baseline	At 4 weeks	% Change (95% CI)	p
MMSE				
Total score	25.6 ± 1.6	29.1 ± 1.1	14.2 (8.6 to 19.8)	< 0.001
ADAS-Cog				
Word recall task	3.6 ± 1.0	8.1 ± 1.2	140.0 (94.4 to 185.6)	< 0.001
Word recognition*	4.2 ± 3.2	1.1 ± 1.0	-40.1 (-93.3 to 13.1)	0.01

Abbreviations. MMSE, Mini Mental State Examination; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; CI, confidence interval.
* Lower score means better word recognition.

cognition at follow up (above a cut score of 27). In addition, ADAS-Cog scores were significantly improved by H_2 inhalation, with better performance for word recall test (p < 0.01), and improved word recognition (p = 0.01) at post-administration, respectively. Other nine domains of ADAS-Cog scores (naming task, commands, constructional praxis, ideational praxis, orientation, spoken language ability, remembering test instructions, word-finding difficulty, and comprehension) were performed correctly (e.g. score = 0) at both assessment periods (not presented).

4. Discussion

In this first-in-human, open-label trial of H_2 efficacy for cognitive performance in elderly, a daily inhalation of 15 min of gaseous H_2 for four weeks improved selected markers of cognition in a cohort of apparently healthy women aged 65 and above. Twelve women (out of 13) displayed higher MMSE scores at post-administration, while enhanced word-sensitive cognition was reported in ADAS-Cog test after H_2 intervention. In addition, inhaling H_2 appeared to have acceptable safety profiles, with no evidence of subjectively reported side effects. This pilot trial seems to corroborate previous animal studies, suggesting that gaseous H_2 might be considered as a beneficial agent for age-related cognitive health. Cognitive impairment appears to be closely related to oxidative stress in elderly.[7] Since exogenous H_2 acts as a selective antioxidant,[2] it might help to maintain or retrieve redox balance within the central nervous system, and promote cognitive longevity. Nagata and co-workers reported that consumption of H_2 reduces oxidative stress in the brain, and prevents oxidative stress-induced decline in hippocampus-dependent learning and memory tasks in mice.[3] Besides antioxidant effect, H_2 is also reported having an anti-inflammatory and anti-apoptosis effect, an anti-allergic action, a lipid metabolism-improving effect, a neuroprotective effect, and an intracellular signaling regulatory effect.[8] These diverse effects would also contribute to the improvement of cognitive impairment, and the accurate mechanism of H_2 to affect cognition requires future research. However, several limitations must be considered when study findings are interpreted. The study population included only female participants; it remains unknown whether gaseous H_2 affects cognitive performance in older men and if gender-based differences occur in response to H_2 inhalation. Other limitations include relatively small sample size and no control or placebo-control group. Finally, a 4-week study is perhaps too short to exam the lasting effect of cognitive benefit and to avoid the possibility of practice effect when repeated during serial cognitive tests. Hence, randomized controlled trials are highly warranted to substantiate this cognition-boosting power of gaseous H_2 in humans, with other markers of cognitive function (e.g. functional neuroimaging, cerebrospinal fluid and blood-based biomarkers) monitored during the intervention, as well as further validation in larger samples. If proven effective and safe in well-designed human trials, gaseous H_2 might be considered as an innovative therapeutic agent for other cognitive disorders, including amnesia, Alzheimer's disease or vascular dementia in the future.

Funding

This work was supported by the Serbian Ministry of Education, Science and Technological Development (Grant # 175037), and the Provincial Secretariat for Science and Technological Development (Grant # 114-451-710/2016-03). The funders had no role in study design, data collection, analysis, and interpretation, decision to publish, or preparation of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

1. Shatenstein B, Barberger-Gateau P, Mecocci P. Prevention of age-related cognitive decline: Which strategies, when, and for whom? *J Alzheimers Dis.* 2015;48:35–53.
2. Ostojic SM. Molecular hydrogen: An inert gas turns clinically effective. *Ann Med.* 2015;47:301–304.
3. Nagata K, Nakashima-Kamimura N, Mikami T, et al. 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.
4. 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.
5. Li J, Wang C, Zhang JH, et al. Hydrogen-rich saline improves memory function in a rat model of amyloid-beta-induced Alzheimer's disease by reduction of oxidative stress. *Brain Res*. 2010;1328:152–161.
6. Lin JS, O'Connor E, Rossom RC, et al. *Screening for cognitive impairment in older adults: An evidence update for the U.S. Preventive Services Task Force*. Rockville, MD: Agency for Healthcare Research and Quality; 2013 (Evidence Report No. 107. AHRQ Publication No. 14-05198-EF-1).
7. Berr C. Oxidative stress and cognitive impairment in the elderly. *J Nutr Health Aging.* 2002;6:261–266.
8. Ohta S. Molecular hydrogen as a preventive and therapeutic medical gas: Initiation, development and potential of hydrogen medicine. *Pharmacol Ther.* 2014;144:1–11.