

Dear editor and reviewers:

We thank you very much for your review and valuable suggestions. We are pleased to resubmit a revised version of our manuscript entitled “Hydrogen Gas Inhalation Promoted Recovery of a Patient in Persistent Vegetative State Caused by Intracerebral Hemorrhage: A Case Report (Manuscript ID:)” for consideration to publish in *World Journal of Clinical Cases*.

After carefully read and thoroughly discussion of all comments and recommendations, we have replied to all comments raised by our respectful reviewers, and we believe that all comments and recommendations are helpful and meaningful, and the necessary revision has helped us with making a significant improvement of this manuscript. Enclosed with this letter, please find our detailed responses to all comments as well as pages with modifications that we have made.

We sincerely thank you for your time and helping us with publishing a high standard manuscript. We humbly hope that our revision and careful responding to all comments related to our original submitted version has made the revised manuscript to be suitable for publication in *World Journal of Clinical Cases*.

Sincerely,

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Reviewer #1:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: *This report presents a successful treatment using high-dose hydrogen gas in a child who was diagnosed as persistent vegetative state for two months. The use of molecular hydrogen in the complementary treatment of neurological disorder has been proven by a large number of pre-clinical studies. The neuroprotective effects of molecular hydrogen are attributed to its anti-oxidative and anti-inflammatory property. A clinical trial further demonstrated its therapeutic effects in patients with SAH. However, the standard usage of gas hydrogen are limited to 1~4 % in concentration due to the explosive property of high-dose gas hydrogen. The authors hypothesized that high-dose hydrogen gas (66.7%) may be benefit to VGS patients. The idea may come from a study which indicated that higher dose of hydrogen gas (40%) showed therapeutic effects on ischemic stroke animal models. Nevertheless, this case is the first reported PVS case who responded to high-dose hydrogen gas treatment, thus, provides a clue for the connection between bench and bedside. Case reports with more cases or randomized control trials using the same strategy for the treatment of stroke patients who develop PVS lately may be a direction to provide the evidences of safety and efficacy in the future. The case presentation is comprehensive but the words are a little bit too lengthy for a case report.*

Answer: We agreed and appreciate all valuable comments, and we sincerely hope this clinic case report plus many related literatures can be helpful and meaningful for future clinical application of hydrogen gas in the treatment of PVS.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This is an interesting case report of hydrogen gas

inhalation promoting the recovery of an 11-year-old boy with persistent vegetative state. I have the following comments in no particular order:

1. *Please do not consider that the journal reviewers do not look at the uploaded files. CARE checklist has been filled in a manner as if to simply do away with a formality. Please re-upload with correctly filled checklist with page and line number.*

Answer: It's our negligence to upload a wrong file. We have re-upload with correctly filled checklist with page and line number.

2. *Please write imaging findings properly. Authors write 'X ray shadows on CT'. This is not technically correct.*

Answer: We appreciate and agreed reviewer's comment, and we re-worded "X ray shadows" to "low density of CT scan images" (Page 7, page 8, page 21).

3. *Please remove this line from the conclusion: "High-concentration of hydrogen gas inhalation may be an effective intervention for PVS and the recovery of other brain dysfunction caused by ICH" --> This case report does not allow us to make this conclusion. The main conclusion is: "Phase 1 Clinical trials are needed to explore the safety and efficacy of hydrogen gas inhalation in persistent vegetative state.*

Answer: We appreciate reviewer's recommendation. Therefore, we have changed conclusion (Page 15).

4. *Kindly make the corresponding change in both main text and abstract.*

Answer: We have made the corresponding change in abstract (Page 12) and main text (Page 14, Paragraph 3).

5. *Figure 2 the scale is incorrect. Some units are separated by one month and some units are separated by just 15 days (but have equal distance between them). Kindly redraw to scale.*

Answer: We have redrawn the scale in Figure 2 (Page 22).

6. *Wrong statement here: "In brief, these clinical observations suggested the potential effects of high concentration hydrogen gas inhalation on consciousness recovery, and muscle tone, locomotor function, and other health conditions were*

*significantly improved in this patient with ICH-induced PVS." Please change to:
"In brief, these clinical observations suggested a possible beneficial role of high
concentration hydrogen gas inhalation on consciousness recovery, and muscle
tone, locomotor function in this patient with ICH-induced PVS."*

Answer: We agreed and appreciated this recommendation and we have revised it
(Page 10, Paragraph 3).

Re-reviewer:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript has been revised but the same issue of overreach remains present. Authors continue to use over reaching statements in their manuscript When reviewer points to an issue of overreach and asks you to make one change in one place, then it is the authors' responsibility to make corresponding change at other places as well. This manuscript CANNOT HAVE ANY LANGUAGE that is taken to mean "hydrogen gas is effective for VGS treatment" This is a wrong conclusion and having this published will make authors and journal editors be seen as having insufficient quality control. This manuscript's language needs to be toned down at all places. Phrases like "suggests a possible role" " may have some effect which needs further investigation" "more evidence is needed" "no conclusive therapeutic evidence" should be used.

1. The first page of revised manuscript file below title section states: "Hydrogen Ameliorates Persistent Vegetative State" _ WRONG CONCLUSION.

Answer: We don't think it is a "WRONG CONCLUSION".

2. "Core tip: This case indicates that inhalation of hydrogen maybe may be an effective intervention candidate for patients with loss of consciousness." - please tone down further.

Answer: We don't think it is necessary to tone down further.

3. "Accumulated clinical and experimental biomedical evidence in a variety of models of different diseases HAS PROVEN that molecular hydrogen, administered either through gas inhalation or aqueous solution consumption, can act as a scavenger to selectively alleviate ROS and exert potent cellular protective effects." - Kindly change to "has suggested". These studies are in animals. No RCT exists.

Answer: We have changed "has proven" to "has suggested" in page 11, paragraph 1. We don't agree "These studies are in animals. No RCT exists." Please see Reference--Iida, A., Nosaka, N., Yumoto, T., Knaup, E., Naito, H., Nishiyama, C., . . . Nakao, A. (2016). The Clinical Application of Hydrogen as a Medical Treatment. *Acta Med Okayama*, 70(5), 331-337. doi:10.18926/AMO/54590