



Life Box: Inhaling Mixture of Hydrogen and Oxygen for Management Of COVID 19 Patient

INTRODUCTION

A mixture of Hydrogen (H_2) and Oxygen (O_2) gases is called oxyhydrogen in a ratio of 2: 1 was obtained from water electrolysis. However, in practice to avoid an oxidizing flame, a ratio 4: 1 or 5:1 may be used.¹ As a biological gas, hydrogen has the ability to diffuse freely across biological membranes, acting in various functional capacities.^{2,3} Hydrogen gas is also claimed to be used as an anti-inflammatory and antioxidant.⁴⁻⁷ A variety of approach has been invented to apply these effects in any diseases as well as wellness benefits by mixing it with Oxygen and commonly using Hydrogen/Oxygen generator or nebulizer.⁸

Life Box (or eBox) is claimed to have a mixture of Hydrogen and Oxygen generated from Water Fuel Apparatus (WFA) via electrolysis process that could help and cure COVID-19 patient. The box is a rectangular designed and can be easily installed and uninstalled. This technology mostly used in China and Taiwan using a variety of design. Hence, this rapid evidence review is conducted to provide brief information on the effectiveness and safety of inhaling mixture of Hydrogen and Oxygen based on request from the Director General of Health Malaysia following proposal by a company to introduce the technology to Ministry of Health Malaysia.

EVIDENCE on EFFECTIVENESS and SAFETY

There was no retrievable evidence from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines (Google Scholar) related to mixture of hydrogen-oxygen gas that could help and cure COVID-19 patient. However, there was one study related to hydrogen-oxygen mixture decreasing inspiratory effort in patients with tracheal stenosis while another two animal studies on improving cardiac dysfunction and myocardial pathological changes induced by intermittent hypoxia in rats and inhalation of hydrogen gas attenuates airway inflammation and oxidative stress in allergic asthmatic mice.⁹⁻¹¹

Zhang N et al. (2018) investigated the effect of inhalational mixture of hydrogen/oxygen gas (H_2/O_2 : 67%/33.3%) produced by the AMS-H-01 generator on the asthmatic mice model with ovalbumin (OVA)-induced allergic airway inflammation. The gas was administered for 60 minutes once a day for seven consecutive days. The results showed a reduction of lung resistance [3.53 ± 1.9 cm/ $H_2O/ml/s$ (pre); 2.052 ± 1.2 cm/ $H_2O/ml/s$ (post), $p < 0.05$], the accumulation of inflammatory cells [3.22 ± 0.67 (pre); 2.22 ± 0.67 (post), $p < 0.01$] and epithelial goblet cell hyperplasia [4.00 ± 0.81 (pre); 2.9 ± 0.73 (post), $p < 0.01$] which led to the reduction in mucus production. There was also significant reduction in inflammatory cytokines present in bronchoalveolar lavage fluid from asthmatic mice model. [IL-4 : 42.11 ± 24.31 (pre); 18.91 ± 10.66 pg/ml(post), $p < 0.05$], IL-13: 68.04 ± 35.26 pg/ml (pre); 32.57 ± 4.43 pg/ml (post), $p < 0.05$, TNF- α : 38.62 ± 14.12 pg/ml (pre); 26.12 ± 5.59 pg/ml (post), $p < 0.05$, CXCL15: 141.4 ± 40.75 pg/ml(pre); 106.3 ± 40.75 pg/ml(post), $p < 0.05$] A significant reduction was seen in the oxidative stress index measured by the levels of superoxide dismutase (SOD), malondialdehyde (MDA) and myeloperoxidase (MPO) [reduction in level of MDA (5.37nmol/mg to 1.82 nmol/mg, $p < 0.05$) and MPO (1.51 U/g to 1.11U/g, $p < 0.05$), increased in SOD activity (16.98 U/mg to 20.92U/mg)].¹¹

The China Treatment Guidelines for COVID-19 (7th Edition) suggested to add a hydrogen-oxygen gas mix (H₂/O₂: 66.6%/33.3%) aside from administering the effective oxygenation measures promptly, including nasal catheter, oxygen mask, and high flow nasal cannula among suitable patients (criteria not specified).¹²

There is one ongoing randomised clinical trial among 100 patients in China that compared conventional treatment plus Hydrogen/Oxygen inhaled with conventional treatment plus Oxygen inhaled.¹³ The trial that started on 15 February 2020 was targeted to complete in August 2020. It is related to the application of a Hydrogen-Oxygen generator with nebulizer in the improvement of symptoms in patients infected with COVID-19.¹³ The target primary outcome measure was the recovery time (the time from the patient's admission to the disease progression to critical type, up to two weeks).¹³

There was no retrievable evidence on the safety of inhaling mixture of Hydrogen and Oxygen gases among COVID-19 patients. However, a prospective self-control study to evaluate the efficacy and safety of breathing H₂-O₂ in 35 patients with severe acute tracheal stenosis reported no adverse reaction or no inhalation related discomfort occurred.⁹ The Hydrogen/Oxygen generator costs varies between products, ranging approximately from RM400 to RM30000.

CONCLUSION

There was no evidence retrieved from the scientific databases on the effectiveness and safety of hydrogen-oxygen gas mixture in COVID-19 patient. Further study (clinical trials) is required to ascertain its effectiveness.

REFERENCE

1. Shuai L, Zhong W, Kun JH, Lin C. Research on the Influence of Hydrogen and Oxygen Fuel Obtained from Water Electrolysis on Combustion Stability of Shale Gas Engines. International Journal of Automotive Technology. 2019 Feb 1;20(1):119-25.
2. Huang CS, Kawamura T, Toyoda Y et al. Recent advances in hydrogen research as a therapeutic medical gas. Free Radic Res. 2010;44(9):971-982.
3. Sano M, Suzuki M, Homma K et al. Promising novel therapy with hydrogen gas for emergency and critical care medicine. Acute Medicine and Surgery. 2018;5(2):113-118.
4. Kouhpayeh S, Shariati L, Boshtam M et al. The molecular story of COVID-19: NAD⁺ depletion addresses all questions in this infection. Preprints2020, 2020030346 (doi: 10.20944/preprints202003.0346.v1).
5. Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19) [Updated 2020 Mar 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK554776/>. Accessed on 9 April 2020.
6. Ge L, Yang M, Yang N-N et al. Molecular hydrogen: a preventive and therapeutic medical gas for various diseases. Oncotarget. 2017;8(60):102653-102673.
7. Perspective of the management of COVID-19 infection in China_HHO Gas Cures Used by Prof Dr. Nanshan Zhong, Director of National Clinical Research Centre for Respiratory Disease. Accessed on 7 April 2020. Available at https://www.youtube.com/watch?v=S2n_peRIHic&feature=youtu.be. Accessed on 9 April 2020.

8. Health-care hydrogen and oxygen supply equipment. CN202576577U. Available at <https://patents.google.com/patent/CN202576577U/en?oq=epoch+oxyhydrogen+generator+for+health>. Accessed on 8 April 2020.
9. Zhou ZQ, Zhong CH, Su ZQ, Li XY, Chen Y, Chen XB, Tang CL, Zhou LQ, Li SY. Breathing hydrogen-oxygen mixture decreases inspiratory effort in patients with tracheal stenosis. *Respiration*. 2019;97(1):42-51. Accessed on 8 April 2020.
10. Zhao YS, An JR, Yang S, Guan P, Yu FY, Li W, et al. (2019). Hydrogen and Oxygen Mixture to Improve Cardiac Dysfunction and Myocardial Pathological Changes Induced by Intermittent Hypoxia in Rats. *Oxidative medicine & cellular longevity*. 2019. <https://doi.org/10.1155/2019/7415212>, 10.1155/2019/7415212. Accessed on 8 April 2020.
11. Zhang N, Deng C, Zhang X et al. Inhalation of hydrogen gas attenuates airway inflammation and oxidative stress in allergic asthmatic mice. *Asthma Res Pract*. 2018;4:3-3.
12. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition). 2020. Available at: <https://www.chinalawtranslate.com/en/coronavirus-treatment-plan-7/>. Accessed on 8 April 2020.
13. US National Library of Medicine. Hydrogen-Oxygen Generator with Nebulizer in the Improvement of Symptoms in Patients Infected with COVID-19 (COVID-19). Available at <https://clinicaltrials.gov/ct2/show/NCT04336462>. Accessed on 9 April 2020.

Based on available evidence up to 9 April 2020

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Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

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