



OPINION ARTICLE

Should hydrogen therapy be included in a musculoskeletal medicine routine? [version 1; referees: 2 approved]

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Abstract

Molecular hydrogen (H₂) has recently been recognized as a potential novel therapeutic agent in biomedicine. Initially proposed to be a possible treatment for certain types of neuromuscular disorders, cardio-metabolic diseases and cancer, H₂ improved clinical end-points and surrogate markers in several clinical trials, mainly acting as an anti-inflammatory agent and powerful antioxidant. In this paper, the medicinal properties of H₂ in musculoskeletal medicine are discussed with the aim to provide an updated and practical overview for health professionals working in this field.

Open Peer Review

Referee Status:

	Invited Referees	
	1	2
version 1 published 10 Nov 2016	 report	 report
1 Xiaoli Sun , Second Military Medical University China, Ning Zhang , Second Military Medical University China		
2 Steven R. Brenner , Saint Louis University School of Medicine USA		

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Background

As the oldest and the most abundant molecule in the universe, molecular hydrogen (H_2) has been traditionally recognized as a biologically inert gas. However, several trials in the past 10 years reported beneficial effects of H_2 in the clinical environment, revealing its possible role as a novel therapeutic agent in medicine¹⁻⁵. Usually administered orally or via inhalation, H_2 improves both patient- and clinician-reported outcomes, and biomarkers of different pathologies and disorders, from metabolic diseases to chronic systemic inflammatory disorders to cancer [for detailed review see Ref. 6]. Its clinical relevance seems to be particularly notable in the musculoskeletal medicine, with several small-scale short-term studies⁷⁻⁹ reporting that H_2 was able to restore the health and functional abilities of patients after acute injuries or chronic illnesses affecting the muscles and bones. Since musculoskeletal conditions account for a large proportion of a general practitioner's workload¹⁰, one might consider H_2 as a promising medication or adjuvant that could alleviate these prevalent conditions. In this opinion paper, the medicinal properties of H_2 in musculoskeletal medicine are discussed to provide an updated and practical overview for health professionals working in this field.

Promising results from preliminary studies

Being prompted by the prominent effects of H_2 on disuse muscle atrophy, cartilage trauma, and osteopenia in animal studies¹¹⁻¹³, a number of clinical investigators from 2010 onwards evaluated the effectiveness of H_2 in patients suffering from different muscle and bone ailments – from sprains and strains to chronic joint disorders to myopathies⁷⁻⁹. Typically, these studies were designed as single-blind pilot trials, with small sample sizes (< 40 participants) and of short duration (≤ 12 weeks). Although limited in size and scope, those studies can provide early support for specific therapeutic claims about H_2 in musculoskeletal medicine. In a first trial, a combination of oral and topical H_2 resulted in a faster return to normal joint flexibility in 36 young men who had suffered sports-related soft tissue injuries, when administered for 14 days as a complementary treatment to a traditional medical protocol for soft tissue injuries⁷. H_2 intervention (hydrogen-rich packs 6 times per day for 20 min and 2 g of oral H_2 daily) was found to augment plasma viscosity decrease after an injury, while other biomarkers of inflammation (C-reactive protein, interleukin-6) and clinical outcomes (pain scores at rest and at walking, degree of limb swelling) were not affected by the intervention⁷. Another study in Japan reported that drinking 530 ml of a liquid containing 4 to 5 ppm of H_2 every day for 4 weeks significantly reduced disease activity in 20 patients with rheumatoid arthritis, as evaluated by changes in the degree of tenderness and swelling in 28 joints and C-reactive protein levels⁸. H_2 was administered as an adjuvant to regular disease-modifying anti-rheumatic drugs and biological drugs, with the efficacy of H_2 found to be not inferior comparing to abatacept, methotrexate or a combination of two. In total, 47.4% of patients went into remission, with anti-citrullinated protein antibody (ACPA)-positive patients (ACPA levels above 300 U/mL; patients with worse prognosis and higher rates of erosive damage) responding best to the treatment. Finally, the consumption of water containing a high concentration of H_2 (31% saturation) for up to 12 weeks improved surrogate markers of muscle pain and fatigability in 22 patients with inherited and acquired myopathies treated with low-dose prednisone⁹. Taken

together, the above studies seem to pave the way for a future use of H_2 therapy in musculoskeletal medicine.

Take it with a grain of salt

Compared with conventional treatment protocols in musculoskeletal medicine, based on drugs and methods that are well-described with respect to efficacy and safety^{14,15}, H_2 still has a long journey ahead before it can be recognized as a common remedy in this medical discipline. At the moment, H_2 therapy is not adequately described in terms of approval, labeling, side effects, and pharmacovigilance information in musculoskeletal medicine. There are no dose escalation studies yet, and the optimal and safest dose range for H_2 remains unknown; furthermore, no federal agency or industrial entity provides appropriate patient counseling information about H_2 . The US Food and Drug Administration (FDA) recently issued a notice (GRAS Notice No. 520)¹⁶ of a claim that the use of H_2 solubilized in water (up to a concentration of 2.14%) is generally recognized as safe (GRAS) when it is added to beverages and beverage containers in order to prevent oxidation. Based on the information provided by the H_2 gas-manufacturing company, as well as other information available to the FDA, the agency had no questions about the conclusion that hydrogen gas is GRAS under the intended conditions of use. However, the FDA has not made its own determination regarding the GRAS status of the subject use of H_2 gas¹⁶. This seems to be the only formal information currently available concerning the use of H_2 in food or medicine! Despite this lack of formal approval, there are many formulations and devices widely available in the market that claim to supply H_2 for the use in musculoskeletal disorders, from gas-producing machines to dietary supplements and beverages, with H_2 amount varying greatly across the different products. Consequently, consumers might be exposed to easy-to-acquire but questionable products containing H_2 .

Among other important medical issues that need to be addressed, including long-term safety or pharmacokinetics, the main question remains whether H_2 should be considered as a dietary supplement or a medicine, since the FDA declares that a product intended for inhalation (such as H_2) is not a dietary supplement¹⁷. Therefore, considering H_2 , or at least some H_2 forms, for much stricter assessment and regulation by formally recognizing it as a drug in the future, might be more appropriate for this promising bioactive gas. So, it will take many more studies and tighter regulation before H_2 therapy can be endorsed as a routine protocol (or adjuvant to standard treatment) in musculoskeletal medicine. In the meantime, H_2 should be regarded as an experimental agent and not recommended to treat muscle or bone conditions in the general population.

Competing interests

No competing interests were disclosed.

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Referee Report 08 December 2016

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Steven R. Brenner

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The title is appropriate with reference to the content of the article.

The article is a review of the literature with reference to utilizing molecular hydrogen to enhance sports related injuries.

After a detailed review of the literature, the conclusion is there is not enough information to make any solid recommendation concerning utilizing molecular hydrogen to treat sports related injuries, so the implication is probably molecular hydrogen doesn't improve recovery from sports related injuries enough to make any difference.

This appears to be a good review of the related literature.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Referee Report 08 December 2016

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This opinion paper provides an undated and practical overview on the properties of molecular hydrogen in musculoskeletal medicine. The paper focuses on the preliminary studies of H₂ on musculoskeletal medicine, and the concerns over the general use of products containing H₂. I sympathize the author's prudent attitudes, which toward the hydrogen should be regarded as an experimental agent and not recommended to general use provisionally. However, I think this paper should also mention the long-term diving practices which high pressure hydrogen inhalation involved to prove the possible safe use of H₂ gas.

We have read this submission. We believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.

Author Response 08 Dec 2016

Sergej Ostojic, University of Novi Sad, Serbia

This comment is well taken. Several preliminary studies indeed reported a relative safety of H₂ inhalation in humans. The mixture of hydrogen, helium and oxygen (Hydra 10) was safely used in the deepest recorded diving (701 m) in an on-shore hyperbaric chamber (Lafay et al. Undersea Hyperb Med 1995;22:51–60). Another study reported no physiological disturbances in patients with cerebral ischemia after exposed to inhalational H₂ (Ono et al. Med Gas Res. 2012;2:21). Our group demonstrated no side effects of gaseous H₂ in women with age-related cognitive decline (Ostojic et al. 2016, unpublished data). Nevertheless, more studies are needed to confirm the long-term safety of H₂ gas in clinical environment, including musculoskeletal medicine.

Competing Interests: No competing interests to decline.