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Hypothesis

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Hydrogen therapy may be an effective and specific novel treatment for aplastic anemia

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B Data Collection
C Statistical Analysis
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F Literature Search
G Funds Collection

Summary

Aplastic anemia (AA) is a rare bone marrow failure disorder with high mortality rate, which is characterized by pancytopenia and an associated increase in the risk of hemorrhage, infection, organ dysfunction and death. The oxidation phenomenon and/or the formation of free radicals have been suggested to be causally related to various hematological disorders, including aplastic anemia. TNF-α, IL-6, and IL-2 also play important roles in the pathogenesis of AA. Recent studies have provided evidence that hydrogen inhalation can selectively reduce cytotoxic oxygen radicals and exert antioxidant effects. It was also reported that hydrogen could suppress the levels of TNF-α and IL-6. Based on these findings, we hypothesize that hydrogen therapy may be an effective, simple, economic and novel strategy in the treatment of aplastic anemia.

key words: **hydrogen • aplastic anemia • antioxidant**

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Background

In 2007, Ohsawa et al. [1] discovered that hydrogen gas has antioxidant and antiapoptotic properties that protect the brain against ischemia-reperfusion injury and stroke by selectively neutralizing hydroxyl and peroxynitrite radicals. Since then, hydrogen gas has come to the forefront of therapeutic medical gas research. Recent basic and clinical research has revealed that hydrogen is an important physiological regulatory factor, with antioxidant, anti-inflammatory and anti-apoptotic protective effects on cells and organs. We have proposed and demonstrated that hydrogen has radioprotective effects in cultured cells and mice [2–5]. Other researchers have shown that hydrogen can improve myocardial and hepatic ischemia-reperfusion injury, neonatal hypoxia-ischemia, and Parkinson's disease [6–10]. Recent studies also proved that by down-regulation of cytokines, such as IL-6, tumour necrosis factor-α (TNF-α), IFN-γ, hydrogen could inhibit oxidative stress-induced inflammatory tissue injury [11–13]. Cardinal et al. found that orally administered hydrogen water can prevent chronic allograft nephropathy and improve survival in a model of rodent renal transplantation. They found fewer graft-infiltrating T cells in allografts obtained from hydrogen water-treated recipients compared to those obtained from regular water-treated controls [13]. In addition, as the most abundant chemical element in the universe, hydrogen may have a huge potential as a safe and potent therapeutic medical gas. Hydrogen is highly diffusible and could potentially reach subcellular compartments, such as mitochondria and nuclei, which are the primary site of reactive oxygen species (ROS) generation and DNA damage [1]. Hydrogen selectively reduces detrimental hydroxyl radicals and peroxynitrite, but does not decrease the steady-state levels of nitric oxide (NO) and did not eliminate O_2^-or H_2O_2 when tested *in vitro* [1]. Endogenous NO signalling pathways modulate pulmonary vascular tone and endothelial interactions [14]. O_2^- and H_2O_2 have important functions in neutrophils and macrophages, which must generate ROS in order to kill some types of bacteria engulfed by phagocytosis [1]. Hydrogen is continuously produced by colonic bacteria in the body and normally circulates in the blood [15]; breathing 49% hydrogen has been demonstrated to be safe during very deep technical diving [16]. Recently, Saitoh et al. [17. tried to detect possible adverse effects of hydrogen-enriched water therapy, including mutagenicity, genotoxicity and subchronic oral toxicity. They found hydrogen could decrease aspartate aminotransferase and alanine aminotransferase in male rats; these differences were within normal clinical ranges and occurred only in male rats, so the changes were not considered to be biologically significant. In a human study, Nakao et al. hypothesized that loose stools, increased bowel movement, heartburn and headache may be related to hydrogen exposure [18], but these reported adverse events were not confirmed to be related with hydrogen. All the investigators thought it was safe to use hydrogen in human studies [19].

Although hydrogen has been demonstrated to be effective in various disease models, no study has been conducted to investigate the effects of hydrogen in the treatment of aplastic anemia (AA), in which ROS, IL-6, tumour necrosis factor-α (TNF-α) and IFN-γ play pivotal roles [20–22].

The Hypothesis

Aplastic anemia is a rare bone marrow failure disorder with high mortality rate, and is often of unknown etiology [23,24]. The evidence of myelotoxicity of several drugs, infectious agents, solvents, and other chemical agents is circumstantial. No tests are available that could confirm their cause-effect relationship. Thus, most cases are classified as idiopathic [18]. Aplastic anemia has been suggested to be related to the oxidation phenomena and/or the formation of free radicals [20,25]. Ahamed [26] evaluated the status of oxidative stress in the blood of children with aplastic anemia. Under aplastic anemia condition, higher production of ROS leads to increased membrane lipid peroxidation with a concomitant decrease in antioxidants like glutathione (GSH) and activity of antioxidant enzymes such as erythrocyte catalase (CAT) also increases ability to scavenge these free radicals. The key cellular events in the development of aplastic anemia (AA) are the activation and expansion of T cells, which leads to an autoimmune response and hypersecretion of inflammatory cytokines such as IFN-γ and TNF-α (1). The autoimmune response results in destruction of hematopoietic stem and progenitor cells in the BM by cytotoxic lymphocytes. The hypersecretion of inflammatory cytokines lead to suppression of stem cells [27]. Many studies have suggested that abnormalities of TNF-α and IL-6 may play important roles in the pathogenesis of AA [21,22,28]. The production of TNF-α and IL-6 have been found to be significantly elevated in AA patients. Elevated TNF-α levels may also contribute to bone marrow failure by upregulating the Fas receptors on progenitor cells, which leads to apoptosis of target hematopoietic precursors [29,30] and by enhancing production of reactive oxygen free radicals, which are detrimental to progenitors [21]. IL-6 also has been reported to be related with the development of AA [27].

Numerous strategies have been applied in the treatment of AA, including immunosuppression and hematopoietic stem-cell transplantation treatment. In the treatment of immunosuppression, most specialists use an antithymocyte globulins (ATG)-based regimen in combination with cyclosporine, based on the outcomes of relatively large studies performed in the 1990s [31].There are also some alternatives to the treatment of ATG plus cyclosporine by using Cyclophosphamide, Androgen [32,33], growth factors such as Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Granulocyte Colony Stimulating Factor (G-CSF) [34,35], and some other immunosuppressive drugs. Treating AA by allogeneic transplantation from a matched sibling donor could also cure the great majority of patients [36]. Hematopoietic and immune system cells are replaced by stem-cell transplantation. Although these treatments could alleviate the disease, more attention should be paid to the adverse effects and some problems of immunosuppression and hematopoietic stem-cell transplantation therapy. For immunosuppression, the drugs used for treatment have many adverse effects. For example, ATG could cause anaphylaxis, fever, chills, and hives and Cyclosporine could cause severe allergic reactions,chest pain, diarrhea, fast or irregular heartbeat, flushing of the face, etc. Many drugs have yet to be tested in aplastic anemia. Again, the costs of intensification need to be balanced against the benefits of higher hematologic response rates and lower rates of relapse and evolution. For transplantation, the immediate challenge is

the extension of stem-cell replacement to all patients with a histocompatible sibling, and to others who lack a family donor using alternative stem-cell sources. In addition, it is difficult to avoid complications, particularly second malignancies, even with conditioning regimens.

Various researchers have attempted to identify novel, nontoxic, effective, and convenient drugs to cure or alleviate aplastic anemia [32–35].

Our hypothesis is that hydrogen gas may have a therapeutic effect on aplastic anemia. Our theory is original and probably of great importance, because therapeutic medical gases has never been used for aplastic anemia previously.

Our hypothesis is based on the theory that hydrogen can selectively reduce hydroxyl and peroxynitrite radicals and down-regulate cytokines such as IL-6 and tumour necrosis factor-α (TNF-α). Free radicals have been suggested to play an important role in aplastic anemia [20,25]. The production of TNF-α and IL-6 have been found significantly higher in AA patients. Elevated TNF-α and IL-6 levels may contribute to bone marrow failure [21,22,27].Thus, hydrogen may exert a therapeutic effect on aplastic anemia.

Evaluation of the Hypothesis

For testing the hypothesis, hydrogen gas could be administered by 2 ways. First, it may be administered to patients via inhalation as room air at safe concentrations (<4.6% in air by volume). Second, we can dissolve hydrogen gas into water, delivering it as drinking water. This may be more practical in daily life and more suitable for daily consumption for therapeutic use. Hydrogen-rich drinking water can be generated by several methods including dissolving electrolyzed hydrogen into pure water, dissolving hydrogen into water under high pressure, and utilizing electrochemical reaction of magnesium with water. We propose the experimental study by detecting complete blood counts (CBC), total BM cells from tibiae and femurs, spleen colony-forming units in an AA model as described by Jichun Chen et al. [37]. We also propose to detect the levels of TNF-α and IL6, which have been demonstrated to play important roles in the pathogenesis of AA. Plasma malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-OHdG), and endogenous antioxidants such as SOD and GSH will also be detected *in vivo*. To discover potential mechanisms of the therapeutic effects of hydrogen on the AA model, we will examine gene-expression profiles, such as expression of Caspase, JNK and FAS as described by Omokaro et al. We propose that our study on treating aplastic anemia with hydrogen gas will start as soon as possible [38].

Implications of the Hypothesis

In view of the high lethality rate of aplastic anemia, hydrogen gas may give us increased hope for greater survival with few adverse effects. This study will open a new therapeutic avenue, combining the fields of therapeutic medical gases and aplastic anemia.

Conflicts of interest statement

None declared.

Abbreviations

AA – aplastic anemia; **TNF-α –** Tumor necrosis factor-alpha; **IL-6 –** Interleukin 6; **ROS –** reactive oxygen species; **MDA –** malondialdehyde; **8-OHdG –** 8-hydroxydeoxyguanosine; **SOD –** Superoxide Dismutase; **GSH –** Glutathione.

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