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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Nicoleta-Monica Popa-Fotea, MD, PhD, Assistant Professor, Department of Cardio-thoracic, University of Medicine and Pharmacy, Bucharest 050474, Romania. nicoleta.popa-fotea@drd.umfcd.ro

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CASE REPORT

Hydrogen inhalation promotes recovery of a patient in persistent vegetative state from intracerebral hemorrhage: A case report and literature review

Yan Huang, Feng-Ming Xiao, Wen-Jie Tang, Jing Qiao, Hai-Feng Wei, Yuan-Yun Xie, You-Zhen Wei

ORCID number: Yan Huang 0000-0003-0077-0358; Feng-Ming Xiao 0000-0001-6361-6775; Wen-Jie Tang 0000-0001-6394-3397; Jing Qiao 0000-0002-1130-0004; Hai-Feng Wei 0000-0001-8008-9276; Yuan-Yun Xie 0000-0002-1506-8388; You-Zhen Wei 0000-0002-5634-6073.

Author contributions: Wei YZ and Huang Y conceived the study design and carried out the study; Xiao FM, Wei YZ and Xie YY reviewed the literature; Xiao FM and Tang WJ contributed to manuscript drafting, acquisition of data, analysis and interpretation of data; Qiao J and Wei HF contributed to analysis and interpretation of data; Wei YZ and Xie YY performed critical revision of the manuscript for important intellectual content; Wei YZ performed final approval of the version of the article to be published.

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Yan Huang, Feng-Ming Xiao, Department of Rehabilitation, Qilu Children's Hospital of Shandong University, Jinan 250022, Shandong Province, China

Wen-Jie Tang, You-Zhen Wei, Research Center for Translational Medicine & Key Laboratory of Arrhythmias of the Ministry of Education of China, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, Shanghai Province, China

Jing Qiao, Department of Pediatrics, Shanghai East Hospital, Tongji University School of Medicine, Shanghai 200120, Shanghai Province, China

Hai-Feng Wei, Department of Clinical Imaging, The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan 250022, Shandong Province, China

Yuan-Yun Xie, National Clinic and Medicine Research Institute for Geriatric Diseases, Gannan Health Promotion and Translational Laboratory, The First Affiliated Hospital, Gannan University of Medical Sciences, Ganzhou 341000, Jiangxi Province, China

Corresponding author: You-Zhen Wei, MD, Professor, Research Center for Translational Medicine & Key Laboratory of Arrhythmias of the Ministry of Education of China, Shanghai East Hospital, Tongji University School of Medicine, No. 150 Jimo Road, Shanghai 200120, Shanghai Province, China. wei-youzhen@163.com

Abstract

BACKGROUND

Persistent vegetative state (PVS) is a devastating and long-lasting clinical condition with high morbidity and mortality; currently, there are no available effective interventions.

CASE SUMMARY

We report the case of an 11-year-old boy with PVS caused by severe intracerebral bleeding in the left hemisphere following anticoagulation treatment. The patient's PVS severity showed no notable improvement after 2-mo neuroprotective treatment and rehabilitation, including nerve growth factor and baclofen, hyperbaric oxygen, and comprehensive bedside rehabilitation therapies. Daily inhalation treatment (4-6 h) of high-concentration hydrogen (H_2) gas (66.6% H_2 + 33.3% O_2) was provided. Surprisingly, the patient's orientation, consciousness, ability to speak, facial expressions, and locomotor function were significantly

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restored, along with improvements in essential general health status, after H_2 gas inhalation treatment, which was consistent with stabilized neuropathology in the left hemisphere and increased Hounsfield unit values of computed tomography in the right hemisphere. The patient finally recovered to a near normal conscious state with a Coma Recovery Scale-Revised Score of 22 from his previous score of 3.

CONCLUSION

Phase 1 clinical trials are needed to explore the safety and efficacy of H_2 gas inhalation in patients with PVS.

Key Words: Hydrogen gas; Intracerebral hemorrhage; Consciousness recovery; Persistent vegetative state; Case report

Core Tip: We report a case in which hydrogen (H_2) gas inhalation promoted the recovery of an 11-year-old boy with persistent vegetative state (PVS) caused by severe intracerebral bleeding in the left hemisphere following anticoagulation treatment. The patient's PVS severity showed no notable improvement after a 2-mo routine neuroprotection treatment and rehabilitation. Surprisingly, the patient's orientation, consciousness, ability to speak, facial expressions, and locomotor function were significantly restored, after high-concentration H_2 gas inhalation treatment. This case indicates that inhalation of H_2 may be an effective intervention candidate for patients with loss of consciousness.

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INTRODUCTION

Urgent development of novel therapies for intracerebral hemorrhage (ICH) is required due to the high mortality of ICH and the lack of effective therapies[1]. Molecular hydrogen (H_2) is known to protect neurons against reactive oxygen species (ROS) induced by cerebral ischemia/reperfusion (I/R) injury[2,3]. Previous experimental studies have shown that H_2 gas can also alleviate inflammation and apoptosis[4], in addition to reducing neuronal damage in several rat models of diseases by suppressing the expression of S100 calcium-binding protein B, phosphorylation of c-Jun N-terminal kinase, and reactive astrogliosis[5-7]. H_2 gas inhalation selectively reduces hydroxyl radical and peroxynitrite levels *in vitro* and exerts an antioxidant effect, reflected by decreased brain concentrations of 4-hydroxynonenal (a specific marker for lipid peroxidation), and 8-hydroxyguanosine (a nucleic acid oxidation marker) in a rat middle cerebral artery occlusion model[2]. Clinical studies have also indicated the effectiveness of H_2 gas in the treatment of hepatic, renal, cardiac, and pulmonary diseases, including chronic obstructive pulmonary disease and coronavirus disease 2019[8-10]. H_2 gas inhalation or H_2-rich saline treatment has beneficial effects on early brain injury after subarachnoid hemorrhage[11,12], delayed brain injury in subarachnoid hemorrhage, and unilateral common carotid artery occlusion with the endovascular perforation method[13]. Here, we report the case of an 11-year-old boy treated by high-concentration H_2 gas inhalation that helped with the recovery from persistent vegetative state (PVS) caused by ICH, which is the first clinical report of high-dose H_2 gas therapy in a child in a PVS after ICH.

CASE PRESENTATION

Chief complaints

An 11-year-old boy treated with anticoagulation after aortic valve replacement surgery presented to the pediatric intensive care unit in our hospital following fever and abdominal pain for 2 d, and coma for 2 h on May 27, 2020.

History of present illness

An emergency brain surgical intervention was carried out immediately to relieve the intracranial pressure and, subsequently, reduce brain injury. Assisted by neuronavigation, both left ventricle and hematoma drains were established under general anesthesia. In addition, critical life support consisting of tracheostomy, intracranial pressure probe implantation, and mechanical ventilation was also established.

Approximately 6 wk (41 d) after surgery, the patient was still in a completely bedridden vegetative state (VS) with a Coma Recovery Scale-Revised (CRS-R) score [14] of 3 (auditory function: 0, visual function: 0, motor function: 1, verbal function: 0, communication: 0, and arousal: 2). Although his life support relied on nasal tube-feeding, the patient had normal heartbeat and breathing rates.

As the patient's VS status did not show signs of improvement for more than 4 wk after brain surgery, he was transferred to the rehabilitation department of the same hospital and was diagnosed with PVS, and neuroprotective treatments and rehabilitation training were initiated. The neuroprotective treatments included nasal administration of nerve growth factor, baclofen, and hyperbaric oxygen. The functional rehabilitation therapies included comprehensive bedside rehabilitation therapies, such as anticonvulsive treatment, range-of-motion maintenance, and swallowing and feeding training. Unfortunately, despite these therapeutic interventions for 4 more weeks, his PVS symptoms and severity showed no improvement. Therefore, it was necessary to explore a new and safe therapeutic intervention with potential effects on the patient who had been in a VS for over 2 mo.

History of past illness

At the age of 3 years, the patient underwent repair of an atrial septal defect and ventricular septal defect due to complex congenital heart disease. In October 2018, the patient underwent aortic valve replacement surgery. He received warfarin anticoagulant therapy for nearly 2 years after aortic valve replacement.

Personal and family history

The patient had no personal or family history.

Physical examination

The patient could occasionally open his eyes and yawn, but he had no response to pain stimulation, and could not distinguish between his family members and strangers. Moreover, he was unable to listen and follow instructions or speak. Furthermore, his body posture was abnormal, with bent elbows and ulnar deviation, wrist flexion, fists with high tonic metacarpophalangeal joints, and stiff, straightened lower limbs with inverted feet. His muscle tone was significantly high in the lower limbs with a modified Ashworth spasm scale score of 2. Additionally, the patient had no voluntary movement control and could not hold his head steady, sit down, stand alone, or walk. The patient, however, had normal reflexes, including biceps reflex +, triceps reflex +, cough reflex +, knee reflex +++, Achilles tendon reflex +++, and Babinski sign and ankle clonus +.

Laboratory examinations

Blood analysis revealed mild leukocytosis of 8.35 × 10^9/L, with predominant neutrophils (67%), and normal hematocrit and platelet count. Prothrombin and partial thromboplastin times were normal, and D-dimer was slightly increased at 1.08 mg/L. Blood biochemistry analyses and urine analysis were normal. Electrocardiogram showed a sinus rhythm, frequent atrial premature beats, abnormal left atrium, large left ventricle, and complete left bundle branch block.

Imaging examinations

A computed tomography (CT) scan of the patient showed irregularly shaped and low-density CT images of the left frontal, parietal, and basal ganglia regions, which covered most of the left hemisphere (Figures 1A, 1C, and 1E). Similar low-density CT

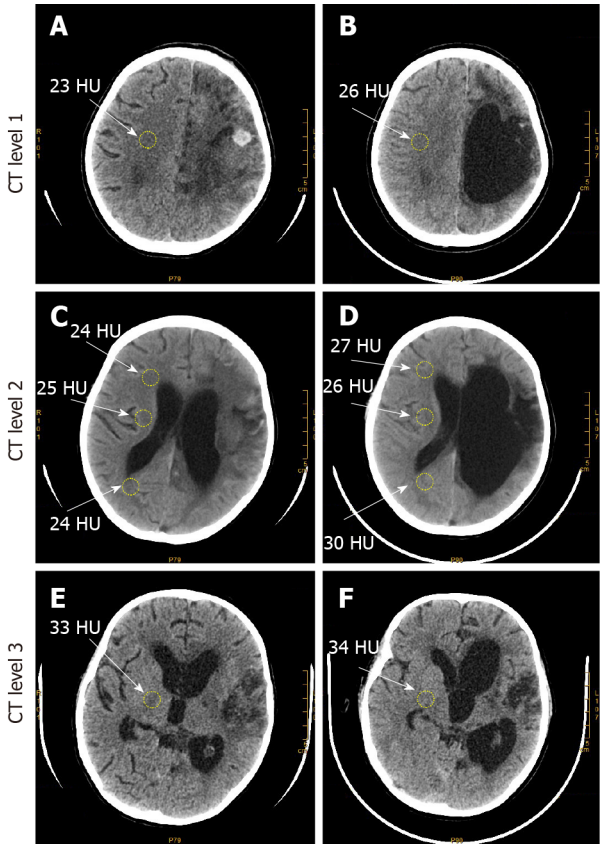

Figure 1 Effects of hydrogen therapy. A, C, and E: Severe and large-scale hemorrhage before treatment was observed in the left hemisphere, including significantly reduced computed tomography (CT) image density that covered the left prefrontal and parietal regions and the majority of the occipital gyrus; the left lateral ventricle was significantly enlarged compared to the right ventricle, and the midline brain structures also deviated from the normal position due to the hematoma and brain edema; B, D, and F: After treatment, the left hemisphere was significantly damaged by hemorrhage with a markedly enlarged left lateral ventricle and severe cerebral atrophy. However, significantly alleviated cerebral softening was observed in the right hemisphere, revealed by an increased CT number (Hounsfield units) in multiple brain regions (yellow circles), compared to those of similar brain regions (yellow circles) before treatment. The neuropathology stabilized in the left hemisphere and was alleviated in the right hemisphere after hydrogen gas inhalation treatment.

images were also observed in the posterior horn of the bilateral ventricles and the third and fourth ventricles near the sickle and sulci regions of the left brain. The left lateral ventricle was compressed and narrowed by the hematoma and cerebral edema compared to that of the right ventricle, and midline brain structures were also slightly shifted to the right.

FINAL DIAGNOSIS

PVS, coagulation dysfunction, ICH, brain hernia, and postsurgical syndrome after aortic valve replacement.

TREATMENT

H_2 has been used in the treatment of patients in critical situations such as traumatic brain injury and cerebral ischemia, and no side effects have been reported to date[15]. After a thorough discussion and explanation of the patient's status with his family and with their permission, high-concentration H_2 (66.6% H_2 and 33.3% O_2) inhalation treatment was administered. The treatment was given twice daily, for 2-3 h each time, for 5 mo. The initial H_2 gas inhalation treatment started 2 mo after the patient developed PVS.

OUTCOME AND FOLLOW-UP

To our surprise, the patient gradually began to show signs of improvement, such as spontaneous eye opening and occasional flexion/extension of his left lower limb shortly after treatment. A CT scan after treatment showed that the hematoma in the left hemisphere was replaced by an irregular cavity filled and surrounded by degenerated brain parenchyma indicated by shadows of low density on CT images after H_2 gas inhalation treatment, but the area with shadows of low density on CT images was reduced compared to that before treatment. The left lateral ventricle was markedly enlarged due to drainage of the left lateral ventricle and hematoma, as well as significant neuronal degeneration in the patient's left brain (Figures 1B, 1D, and 1F). These shadows of low density on CT images in the left hemisphere may have been caused by cerebral edema and ICH, and reduction of the shadows of low density on CT images indicated that the brain hemorrhage and edema were stabilized by H_2 gas inhalation treatment compared to that before treatment. Furthermore, the median CT number, *i.e.*, the X-ray attenuation coefficient, was 26 Hounsfield units (HU), 27 HU, 26 HU, 30 HU, and 34 HU in the precentral gyrus (Figure 1B), corpus callosum-forceps minor, internal capsule, corpus callosum-forceps-major (Figure 1C), and putamen in the patient's right hemisphere (Figure 1F), respectively, after H_2 gas inhalation treatment. These values were increased as compared to 23 HU, 24 HU, 25 HU, 24 HU, and 33 HU in the precentral gyrus (Figure 1A), corpus callosum-forceps minor, internal capsule, corpus callosum-forceps-major (Figure 1C), and putamen in the patient's right hemisphere (Figure 1E), respectively, before treatment. The increased CT numbers in the right hemisphere after treatment were possibly due to decreased cerebral edema and were critical to the recovery of brain function in the patient. Due to the significantly improved condition of the patient, the nasogastric tube was withdrawn, and he was switched from tube feeding to an oral liquid diet 1 mo after treatment.

In the 2 mo after the first administration of treatment, the patient's orientation and consciousness, visual pursuit, and localization to noxious stimulation also gradually recovered (Figure 2). The patient could follow simple instructions, open his mouth when his lips were touched with a spoon, chew soft food, and voluntarily bend and straighten his left lower limb. Moreover, the patient was making steady improvement with longer treatments of H_2 gas inhalation. Ninety days after the initiation of treatment, his motor function was significantly improved, and he was able to make reproducible movements following instructions and autonomously lift his left limbs. His ability to produce facial expressions was vastly improved compared to that before H_2 gas inhalation. He could briefly communicate with others and speak words and phrases. Five months after initiation of treatment with H_2 gas inhalation, the patient had recovered to a near normal state of consciousness with a CRS-R score of 22 (auditory function: 4, visual function: 5, motor function: 5, verbal function: 3, communication: 2, and arousal: 3) along with improved speech ability.

Furthermore, the patient had functional recovery (Table 1) and fine motor function improvements (Table 2) 6-7 mo after the initiation of treatment. The patient could understand simple instructions, identify items, and read numbers. He could make requests with a hand gesture, steadily hold his head straight, independently turn his body over to the right side, lift his hands up and reach his head, touch his eyes and nose with his hands, and make voluntary movements with his lower left limb.

In brief, these clinical observations suggested a possible beneficial role of high concentration H_2 gas inhalation in consciousness recovery, muscle tone, and locomotor function in this patient with ICH-induced PVS.

DISCUSSION

The brain of the PVS patient presented in this case report suffered mechanical damage due to abnormally high cerebral pressure, inflammation, oxidative stress, and other unknown injuries[16-19]. The patient failed to respond to neuroprotective treatment along with other methods of rehabilitation but steadily recovered after administration of high-concentration H_2 gas inhalation treatment. CT scans revealed that the patient's left hemisphere was severely damaged with an enlarged left lateral ventricle and significantly atrophied cerebral parenchyma. However, the CT numbers in the right hemisphere were notably increased after treatment. Other treatment effects included consciousness recovery, significantly alleviated motor and cognitive functional deficits, improved speech and facial expressions, and improvements in general health.

Table 1 Improvements in gross motor function in the patient following hydrogen inhalation treatment

	Baseline	1 mo	2 mo	3 mo	5 mo	8 mo
Lying & rolling	0	0	0	9.8	29.41	25.49
Sitting	0	0	0	0	0	8.33
Crawling & kneeling	0	0	0	0	0	0
Standing	0	0	0	0	0	0
Walking, running & jumping	0	0	0	0	0	0
Total score	0	0	0	1.96	5.68	6.76

Table 2 Improved fine motor function scores following treatment with hydrogen gas inhalation

	2020-11-08		2020-12-08		2021-03-08	
	Left	Right	Left	Right	Left	Right
Visual tracking	21	21	21	21	21	21
Upper limb joint activity	7	0	11	0	16	0
Grasping ability	9	0	15	0	20	0
Operation ability	12	0	17	0	16	0
Hand-eye coordination	17	0	28	0	27	0
Total score	51.64	29.36	59.38	29.36	61.70	29.36

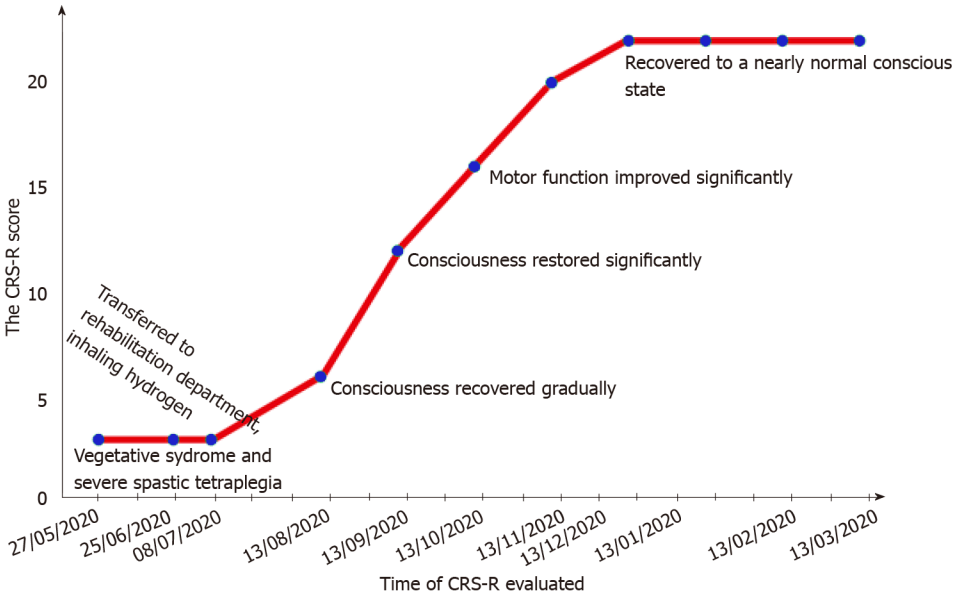

Figure 2 Schematic overview of the clinical progress in the improvement in Coma Recovery Scale-Revised scores and the recovery from persistent vegetative state in this patient. The patient failed to respond to brain surgery and brain protection and rehabilitation for nearly 2 mo. One month after hydrogen gas inhalation treatment, the Coma Recovery Scale-Revised (CRS-R) score of the patient increased from 3 to 6. After 2 more months of treatment, the patient's consciousness was significantly restored and showed greater subsequent improvements with significantly improved motor function, the ability to speak and express requests, and general health. By the end of the 5-mo treatment period with hydrogen gas inhalation, the patient had nearly recovered and stabilized to a normal consciousness state with a CRS-R score of 22. CRS-R: Coma Recovery Scale-Revised.

The possible underlying mechanisms of H_2 gas inhalation in this PVS patient may be closely related to its antioxidative and anti-inflammatory effects.

ICH is devastating and life-threatening, and is associated with severe disability and a high mortality rate, accounting for 10% to 15% of deaths caused by stroke[20]. The initial mechanisms of injury after ICH include mechanical destruction by accidental and abnormally increased intracerebral pressure, hematoma expansion, and/or

herniation caused by the hematoma itself[21]. Subsequent inflammation, oxidative stress, and impairment in blood flow around the hematoma contribute to edema formation, delayed cell death, and neurological deficits[17]. For example, excessive generation of ROS causes peroxidation of lipid-rich structures of the blood-brain barrier (BBB), resulting in life-threatening BBB disruption and vasogenic cerebral edema[22]. Increased oxidative stress-induced injury occurs in almost all types of brain cells (including neurons, astrocytes, and microglia) and is also closely related to ICH-induced inflammation[19,23]. Therefore, attenuation of early brain injury by targeting oxidative stress and inflammation is a feasible intervention strategy in ICH. Previous studies have also revealed that antioxidative and anti-inflammatory agents can reduce brain atrophy and recover striatal function and memory after ICH[16,24,25].

Since Ohsawa *et al*[2] reported that H_2 gas has antioxidant and anti-apoptotic properties that protect the brain against I/R injury and stroke by selectively neutralizing hydroxyl radicals, H_2 gas has reached the biomedical research forefront as a therapeutic medical gas. Accumulated clinical and experimental biomedical evidence in a variety of models of different diseases has suggested that molecular H_2, administered either through gas inhalation or aqueous solution consumption, can act as a scavenger to selectively alleviate ROS and exert potent cellular protective effects. Rat models of middle cerebral artery occlusion, rats with subarachnoid hemorrhage, and a mouse model of ICH have been used to explore the neuroprotective effects of H_2 gas [18,19]. These studies demonstrated that H_2 treatment could decrease oxidative stress, reduce cerebral infarction and hemorrhagic transformation, improve neurological functions, attenuate BBB disruption, and improve neurobehavioral function by ameliorating oxidative injury to lipids, proteins, and DNA. Therefore, oxidative stress relief may have been one of the underlying mechanisms of H_2 gas inhalation in this PVS patient regarding his recovery and other functional impro-vements.

Another mechanism underlying brain injury is its secondary inflammatory responses induced by ICH. Inflammation occurs immediately after ICH and includes astrocyte/microglia/macrophage activation and cytokine release [*e.g.*, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α)]. These factors are involved in the breakdown of the extracellular matrix, cellular integrity, and the BBB, in edema development, and in cell death processes[26-30]. Moreover, brain inflammatory responses develop into a chronic stage and result in further brain function damage, such as cognitive deficits[31]. Previous studies have shown that the anti-inflammatory properties of treatments may be effective in protecting the brain from secondary injuries caused by ICH; for example, melatonin can alleviate inflammatory responses and reduce DNA damage and mitochondrial injury after ICH[32].

H_2 can protect tissues and cells from a variety of diseases. For instance, H_2 gas inhalation can protect lung function by ameliorating airway inflammation in a murine allergic airway inflammation model[33]. Molecular H_2 can also protect the heart from cardiotoxicity and hepatotoxicity induced by doxorubicin by inhibiting inflammation and apoptosis[34]. H_2 also reduces inflammatory responses after exercise by decreasing inflammatory cytokines (TNF-α, IL-1β, and IL-6)[35]. Moreover, the anti-inflammatory effects of H_2 have been proven by its regulation of microglia in the nervous system after ischemic stroke[36]. Studies have also suggested that H_2 inhibits the degree of inflammation *via* inactivation of the NF-κB pathway and the NLRP3 inflammasome[24,37]. Therefore, anti-inflammation by H_2 gas inhalation might have also played a role in promoting this patient's recovery from PVS.

It is worth noting that not all PVS patients were responsive to molecular H_2 treatment in our clinical research. We tried high-concentration H_2 inhalation in patients with acute necrotizing encephalopathy, but there was no significant therapeutic effect regarding the recovery of consciousness in some patients after several weeks of high-concentration H_2 inhalation. Considering that the pathophysiological mechanisms of neural injury and recovery of consciousness in brain diseases are complicated, the effectiveness of H_2 gas treatment might be dependent on the severity of brain damage and the multiple underlying mechanisms of molecular H_2. Therefore, it may or may not be effective for all inflammation and oxidation-based diseases[38].

In summary, a patient with PVS caused by ICH did not respond to routine neuronal rehabilitation treatment but recovered consciousness and locomotor function and restored his speech and emotional expression abilities following the administration of high-concentration H_2 inhalation treatment for 5 mo. Although the exact underlying mechanisms remain unclear, molecular H_2 may protect the brain from ICH due to its antioxidative stress and anti-neuroinflammatory properties.

CONCLUSION

Phase 1 clinical trials are needed to determine the safety and efficacy of H_2 gas inhalation in PVS.

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