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REVIEW ARTICLE

A CLINICAL APPLICATION FOR HINDENBURG'S BLIMP; HYDROGEN IN THE TREATMENT OF BRAIN INJURY

APLIKACJA KLINICZNA DLA STEROWCA HINDENBURGA; WODÓR W LECZENIU URAZÓW MÓZGU

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ABSTRACT

Introduction

Brain injury (BI) is well-known as a potential cause of irreversible brain damage in humans, often leading to devastating consequences. Currently, there exists no effective treatment in the reversal of BI. However, experimental studies on using hydrogen-rich saline or gas inhalation in animal models has revealed neuroprotective effects; in the setting of BI, hydrogen serves as an antioxidant, anti-inflammatory, and a cytoprotective agent, ultimately aiding in the reversal of cellular damage. The aim of this manuscript is to review existing studies where hydrogen-infused saline was applied in the setting of BI in order to determine whether it should be further studied; if positive, we hope to bring further attention to potential treatments that could serve revolutionary in BI.

Methods

A literature review of current studies was performed, utilizing the Pubmed database. Any studies which focused on the treatment of BI using hydrogen-rich saline were included; relevant keywords searched were: hydrogen-rich saline; brain injury; molecular hydrogen; hydrogen therapy; animal study. A total of 17 studies were included in this review.

Results

In reviewing the 17 studies found, one study observed the effect of hydrogen gas inhalation while the other 15 utilized hydrogen-rich saline infusion; each of the 16 studies illustrated that the therapeutic application of hydrogen alleviated BI.

Conclusions

In conclusion, though there have not yet been any clinical trials in human subjects, preliminary studies on animal models show promise in the treatment of various brain injury (BI) by means of therapeutic hydrogen in saline or gaseous forms.

Keywords: trauma, brain injury, neurology, hydrogen, hydrogen-infused

STRESZCZENIE

Wstęp

Uszkodzenie mózgu (UM) jest dobrze znane jako potencjalna przyczyna nieodwracalnych urazów mózgu u ludzi, często prowadzących do niszczycielskie konsekwencje. Obecnie nie ma

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skutecznej metody odwrócenia UM. Jednak badania eksperymentalne dotyczące stosowania bogatej w wodór soli fizjologicznej lub wdychania gazów w modelach zwierzęcych ujawniły działanie neuroprotekcyjne; w przypadku UM wodór służy jako przeciwutleniacz, środek przeciwzapalny i cytoochronny, ostatecznie pomagając w odwróceniu uszkodzeń komórkowych. Celem tego manuskryptu jest przegląd istniejących badań, w których roztwór soli fizjologicznej z infuzją wodoru został zastosowany w warunkach UM, w celu ustalenia, czy należy go dalej badać; jeśli pozytywne, mamy nadzieję, że zwrócimy większą uwagę na potencjalne metody leczenia, które mogą być rewolucyjne w UM.

Metody
Przegląd piśmiennictwa aktualnych badań przeprowadzono z wykorzystaniem bazy danych Pubmed. Uwzględniono wszelkie badania, które skupiały się na leczeniu UM przy użyciu soli fizjologicznej bogatej w wodór; wyszukiwane słowa kluczowe to: sól fizjologiczna bogata w wodór; uraz mózgu; wodór cząsteczkowy; terapia wodorowa; badania na zwierzętach. W tym przeglądzie uwzględniono łącznie 17 badań.

Wyniki
Przeglądając 17 znalezionych badań, w jednym badaniu zaobserwowano efekt inhalacji gazowego wodoru, podczas gdy w pozostałych 15 wykorzystano wlew soli fizjologicznej bogatej w wodór; każde z 16 badań pokazało, że terapeutyczne zastosowanie wodoru łagodzi UM.

Wnioski
Podsumowując, chociaż nie przeprowadzono jeszcze żadnych prób klinicznych na ludziach, wstępne badania na modelach zwierzęcych są obiecujące w leczeniu różnych uszkodzeń mózgu (UM) za pomocą terapeutycznego wodoru w postaci soli fizjologicznej lub w postaci gazowej.

Słowa kluczowe: neurologia, wodór, uraz, uszkodzenie mózgu, infuzja wodoru

Introduction
Brain injury (BI) is well-known as a potential cause of irreversible brain damage in humans, often leading to impairment of bodily functions, paralysis, or even death. The etiology of BI may be linked to many factors including trauma, ischemic and hemorrhagic stroke, ischemia-reperfusion injury, and even intentional deep hypothermic circulatory arrest (DHCA) as part of surgical preparation (Figure 1). Traumatic injury may result from concuss ons, hematomas, fractures of the skull, edema, or diffuse axonal injury. Conversely, non-traumatic reasons can be categorized into hypoxic/anoxic injury from a respiratory cause, ischemic/hemorrhagic stroke from a hematogenous anomaly, and even cardiac arrest (Figure 2).

Depending on the severity of the damage and its cause, the prognosis for this diagnosis can vary greatly; damage may be self-resolving or poor, even fatal in some circumstances. Currently, the treatment of BI, regardless of its cause, is focused heavily on the management and resolution of downstream, associated symptoms. In regards to the reversal or treatment of BI itself, there presently exists no "gold standard" or effective treatment (Figure 1).

However, experimental studies on using hydrogen-rich saline or gas inhalation in animal models have revealed neuroprotective effects; (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.*, 2017; Ke *et al.*, 2020; Gao *et al.,* 2017; Li *et al.,* 2017;

Brain injury (BI)

Etiology: trauma, ischemic/hemorrhagic stroke, ischemia-reperfusion injury, intentional deep hypothermic circulatory arrest (DHCA)

Prognosis: Ranges depending on severity, can be self-resolving or extremely poor, even fatal

Current Treatment: symptom-focused, no specific "gold standard" or indicated treatment

Figure 1. Etiology, prognosis, and current treatment of BI

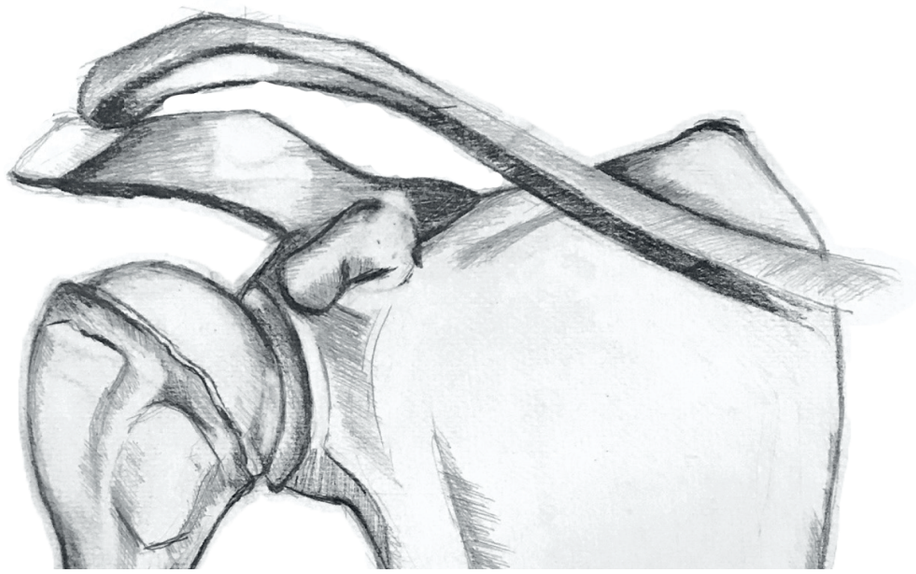

Figure 2. Traumatic vs. non-traumatic BI

Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,*2012; Ji *et al.,* 2011; Shen *et al.,* 2011) in the setting of BI, hydrogen serves as an antioxidant, anti-inflammatory, and a cytoprotective agent, ultimately aiding in the reversal of cellular damage (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.,* 2017; Ke *et al.,* 2020; Gao *et al.,*2017; Li *et al.,* 2017; Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,* 2012; Ji *et al.,* 2011; Shen *et al.,* 2011).

To better understand the mechanism of how hydrogen-infused treatments may combat the physiological effects of BI, we must reflect on the pathophysiology of BI itself and address its cellular and microvascular consequences (Sekhon *et al.,* 2017; Albert-Weissenberger *et al.,* 2019). In hypoxic/anoxic conditions of BI, decreased oxygen concentration at oxygen-dependent complex IV of the

electron transport chain leads to decreased adenosine triphosphate (ATP) production (Sekhon *et al.,* 2017). This decrease in ATP leads to a buildup of intracellular calcium which ultimately may cause mitochondrial membrane damage and dysfunction. Most notably, in the case of reperfusion injury following ischemic events or impaired microcellular conditions, there may be an increased production of reactive oxygen species (ROS) which can directly cause mitochondrial leakage; increased ROS also promotes the activity of xanthine oxidase, which further promotes the positive feedback mechanism of ROS production (Sekhon *et al.,* 2017; Di Meo *et al.,* 2016).

Meanwhile, microvascular consequences may be observed as well, since ROS may lead to a loss of nitric oxide bioactivity within blood vessels, impairing endothelial vasodilation, and potentially resulting in endothelial damage (Sekhon *et al.,* 2017; Di Meo *et al.,* 2016). This damage may lead to both the formation of microthrombi as well as increased porousness of the blood-brain barrier; this may lead to cerebral edema as well as the formation of microthrombi which can limit blood flow in affected vessels and further exacerbate ischemic conditions. Regardless of the mechanism, increased ROS may eventually cause damage to cellular DNA which promotes apoptosis of affected cells. In the case of neurons, a stable tissue that is incapable of regeneration or replication, this effect may have devastating downstream consequences (Sekhon *et al.,* 2017; Albert-Weissenberger *et al.,* 2019; Di Meo *et al.,* 2016) (Figure 3).

In response to this elevated production of ROS, hydrogen, a small and highly diffusible molecule may be extremely effective in the treatment and neutralization of these oxygen species into more benign molecules (Khatri *et al.,* 2018). When hydrogen molecules are introduced into this environment, the resultant reduction of oxidative stress may help to minimize tissue damage; given its small size, high diffusibility, and antioxidant properties, hydrogen may serve as a perfect treatment in these conditions (Ohta 2012) (Figure 4).

The aim of this manuscript is to compile and review existing studies where hydrogen-infused saline was applied in the setting of BI in order to determine whether it should be further studied; if the outlook is positive, we hope to bring further attention to potential treatments that could serve revolutionary in the realm of a condition with scarce treatment options at present.

Material and methods

A literature review of current studies was performed, utilizing the Pubmed database. Any studies which focused on the treatment of BI using hydrogen-rich saline or hydrogen gas administration were included and their results were compared. Relevant keywords utilized in this search were: hydrogen-rich saline; brain injury; molecular hydrogen; hydrogen therapy; animal study (Figure 5). After compiling all applicable studies, a total of 17 studies were included in this review; out of the 17 studies found, one study observed the effect of hydrogen gas inhalation via nebulizer, while the other 16 utilized hydrogen-rich saline infusion intraperitoneally – all of the studies analyzed were animal studies (Figure 6).

Results

When analyzing the 17 studies, 5 of them focused on subarachnoid hemorrhage, 7 on ischemic reperfusion, 2 on traumatic injury, 1 after cardiopulmonary bypass injury, 1 after cardiac arrest, and 1 resulting from intentional deep hypothermic circulatory arrest (DHCA) (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.,* 2017; Ke *et al.,* 2020; Gao *et al.,*2017; Li *et al.,* 2017; Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,*2012; Ji *et al.,* 2011; Shen *et al.,* 2011). In each of the 17 studies, regardless of underlying etiology or administration style, results illustrated

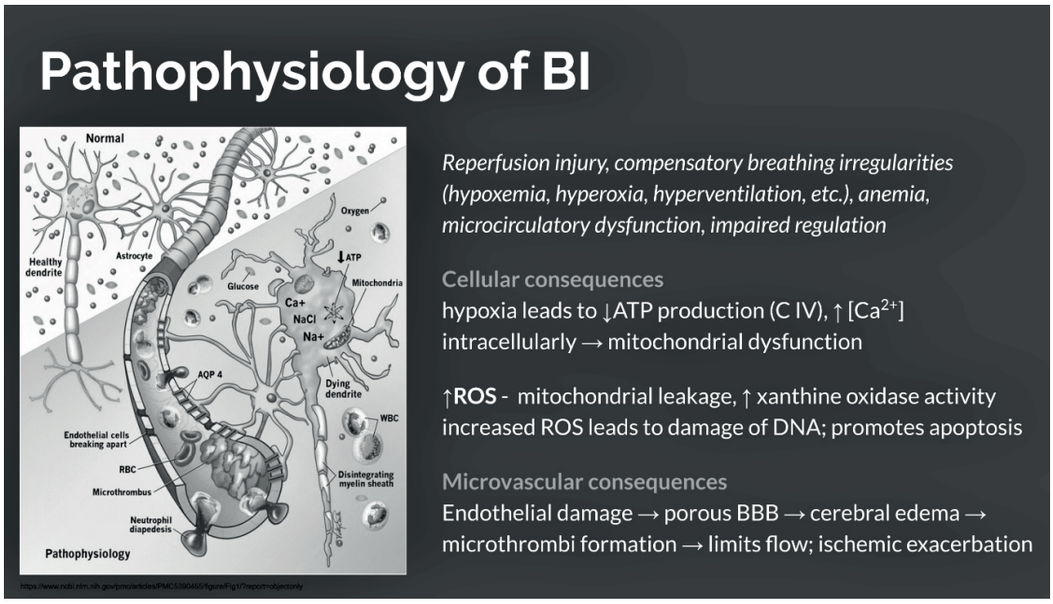

Figure 3. Pathophysiology of BI from cellular and microvascular perspectives

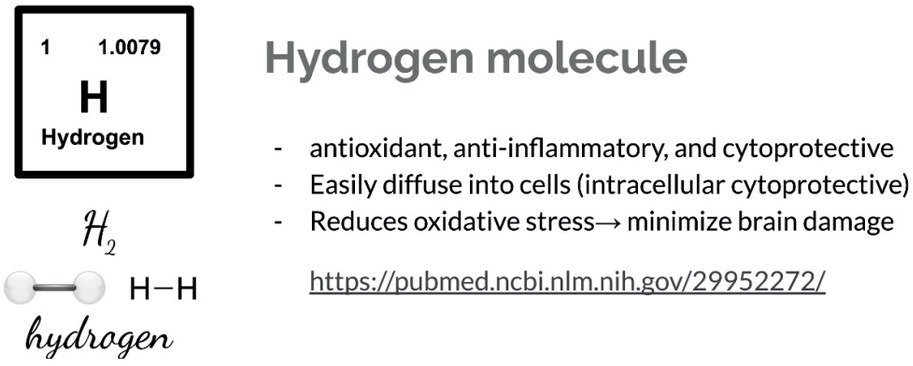

Figure 4. Clinical effects and molecular properties of hydrogen

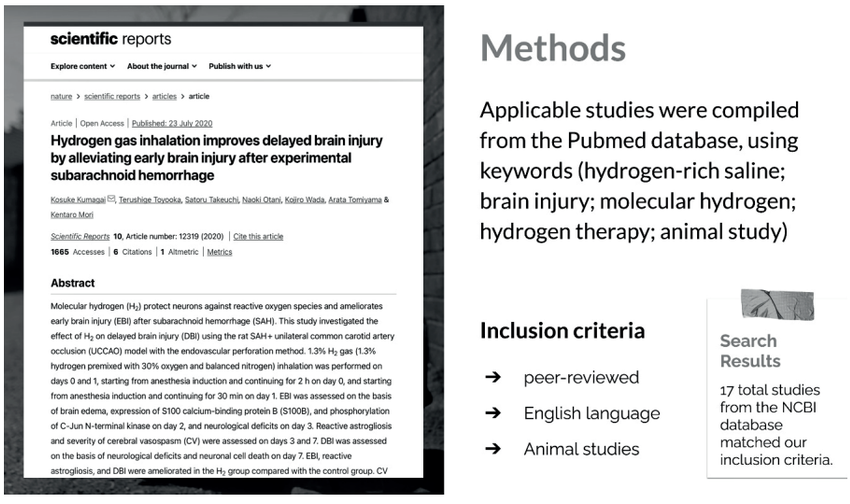

Figure 5. Methods and inclusion criteria of the study

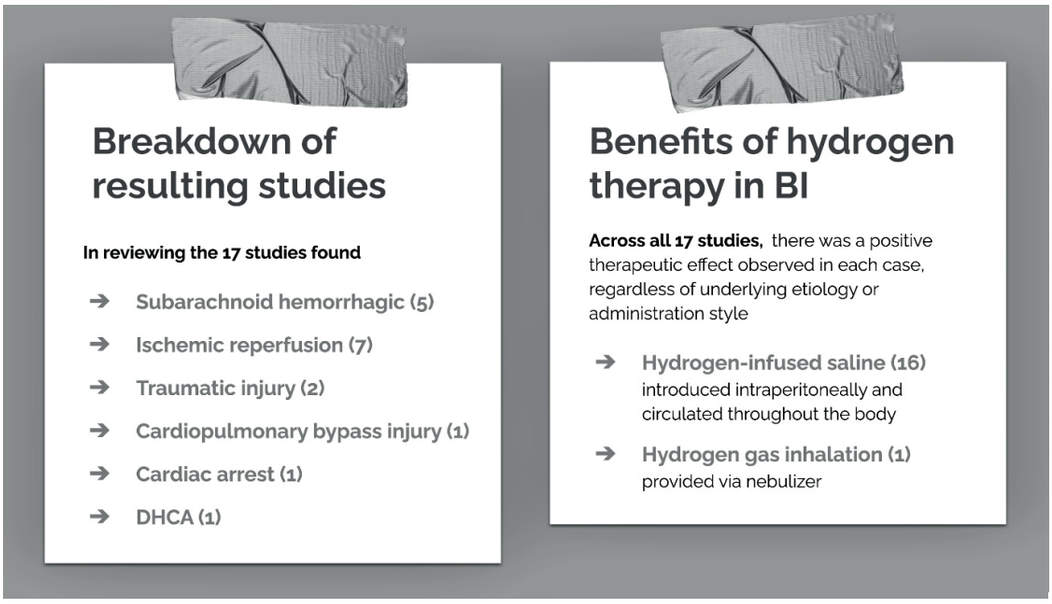

Figure 6. Categorization of studies analyzed

that the therapeutic application of hydrogen alleviated BI and its downstream repercussions (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.,* 2017; Ke *et al.,* 2020; Gao *et al.,*2017; Li *et al.,* 2017; Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,* 2012; Ji *et al.,* 2011; Shen *et al.,* 2011). Hydrogen-infused saline exerted cardioprotective effects through the involvement of ATP-dependent potassium channels and permeability of mitochondrial pores. Meanwhile, hydrogen gas inhalation perioperatively diminished the extent and prevalence of neurologic injury, revealed through increased neural activity and decreased activity of neural repair enzymes. Regardless of the application, hydrogen led to a significant reduction in oxidative stress, minimizing damage and improving prognosis in patients with BI, whether traumatic or not (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.,* 2017; Ke *et al.,* 2020; Gao *et al.,*2017; Li *et al.,* 2017; Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,*2012; Ji *et al.,* 2011; Shen *et al.,* 2011) (Figure 5).

Discussion

The neuroprotective, anti-inflammatory, and cytoprotective properties of hydrogen may already be observed on a molecular level as it may specifically reduce hydroxide species while modifying critical gene expression and signal transduction pathways which maintain redox homeostasis and modulate cellular stress response(s) (Kumagai *et al.* 2020; Hu *et al.,* 2022; Jiang *et al.,* 2021; Chen *et al.,* 2017; Ke *et al.,* 2020; Gao *et al.,* 2017; Li *et al.,* 2017; Bai *et al.,* 2016 Shao *et al.,* 2016; Zhao *et al.,* 2015; Ciu *et al.,* 2014; Huo *et al.,* 2014; Hong *et al.,* 2014; Zhuang *et al.,* 2013; Ji *et al.,*2012; Ji *et al.,* 2011; Shen *et al.,* 2011; Slezak *et al.,* 2021). In neutralizing ROS, hydrogen may logically aid in the reversal of cellular damage. Additionally, the impact of hydrogen molecules on enzymes, kinases, and signals within apoptotic and autophagic processes may illustrate the added therapeutic benefit in antiaging and regenerative potential in more than just BI alone (Fu *et al.,* 2022). In conclusion, though there have not yet been any clinical trials in human subjects, preliminary studies on animal models show promise in the treatment of various brain injuries by means of therapeutic hydrogen in saline or gaseous forms. Hydrogen-rich

saline could be applied in patients after brain trauma, stroke, or cardiopulmonary resuscitation in order to treat BI and minimize the negative consequences of these events (Figure 7). When observing limitations, it must be acknowledged that there could be some discrepancy when applying results from animals to humans; therefore, clinical trials must be performed in order to assess the safety and ultimate effect of treatment with hydrogen-infused saline or gas (Figure 8). Additionally, the administration of hydrogen gas could prove toxic in high concentrations, leading to the precipitation of symptoms like headache, nausea – or in extreme conditions – death. Conversely, peritoneal administration of hydrogen-infused saline does not present with intoxication risk in the same way, as long as the fluid volume administered remains within an appropriate range. Considering the extremely limited risk, preliminary results from these animal studies are extremely promising in the setting of BI, where patients are currently left without any type of "gold standard" care. The clinical application of hydrogen-infused saline could help to treat BI, mitigate resultant damage, and preserve critical brain function in patients affected (Figure 8).

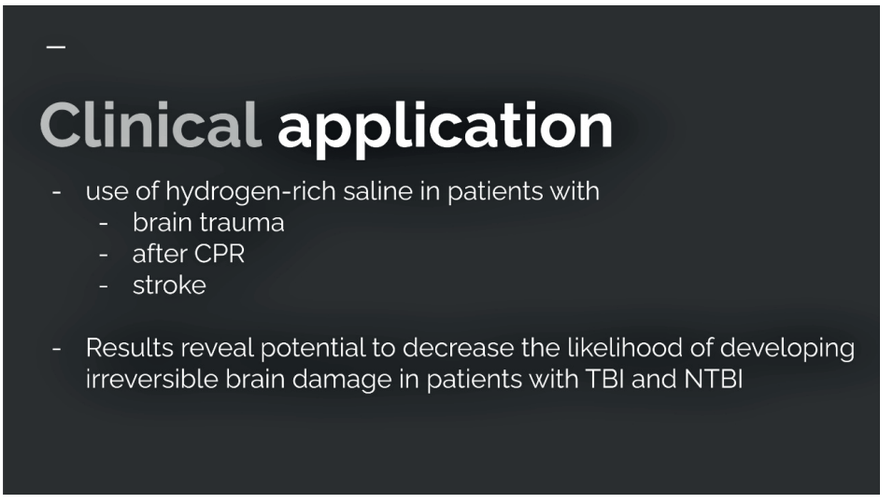

Figure 7. Clinical applications of hydrogen-rich saline

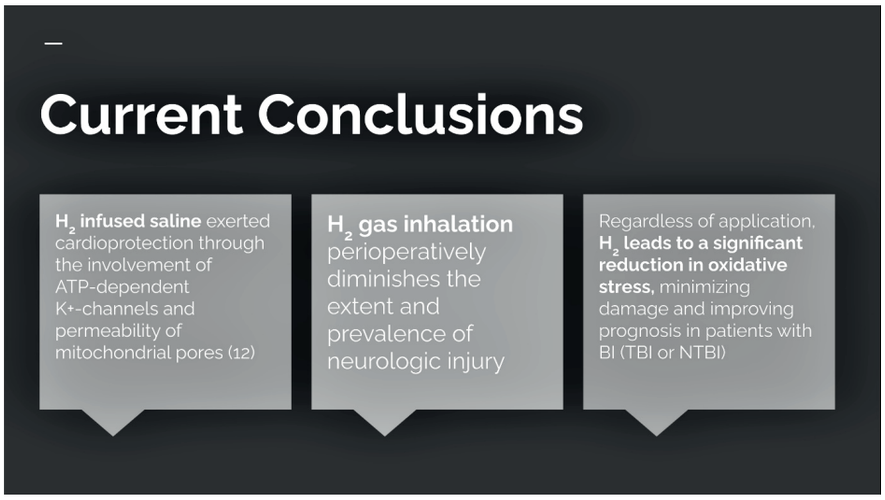

Figure 8. Conclusions regarding the clinical application of hydrogen-rich saline

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