LITERATURE REVIEW

Hyperbaric Oxygen Therapy as an Adjuvant Treatment in Hydrochloric Acid Poisoning: A Literature Review

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ABSTRACT

Background: Suicide is the second most common cause of death and is a major public health problem in many countries globally. Chemical poisoning, such as hydrochloric acid (HCl), accounted for 18.8% of the total suicide cases in Indonesia. Through ingestion, this acid chemical contributes as the most common cause of swallowing injuries that can adversely affect the gastrointestinal mucosal through various pathological processes, primarily through an excessive inflammatory process. On the other hand, hyperbaric oxygen therapy (HBOT) has been widely used as a non-pharmacological therapy in many diseases, although its mechanism for reducing inflammation in HCl poisoning has remained unclear. **Objective:** This study aimed to provide a better understanding on hyperbaric oxygen's biomolecular mechanism as a potential adjuvant therapy in HCl poisoning. **Discussion:** HCl poisoning causes an excessive inflammatory process, leading to tissue hypoxia indicated by increased expression of Hypoxia Inducible Factor 1 (HIF-1). Hyperbaric oxygen therapy decreases the expression of HIF-1 through activation of the HIF-1 hydroxylation pathway via prolyl hydroxylase (PDH) in the proline pathway and HIF inhibiting factor (FIH) in the asparagine pathway. Reactivating both pathways will decrease HIF-1 activity, eventually reducing the ongoing inflammatory process. In addition, HBOT also plays a role in wound healing by stimulating angiogenesis growth factors. **Conclusion:** Hyperbaric oxygen therapy has the potential to be used as adjuvant therapy in HCl poisoning due to its beneficial effects on reducing inflammatory mediators and wound healing.

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Highlights

1. In Indonesia, 18.8% of all suicides were the result of chemical poisoning, such as using hydrochloric acid (HCl).
2. Hyperbaric Oxygen Therapy (HBOT) can be used as an emergency therapy for acute pathology or as a supplementary treatment for chronic illness.

BACKGROUND

Hydrochloric acid (HCl) is the main ingredient of Porstex, a plaque or scale-cleaning solution commonly used in households (Caroline, et al., 2021). Hydrochloric acid is a chemical that often causes swallowing injuries, about 2% are stricture incidences (Arnold & Numanoglu, 2017; Marsella, et al., 2017). In the United States (U.S), as many as 5,000 cases per year are reported due to ingestion of caustic substances, one of which is hydrochloric acid. Injuries resulting from these actions cause various damages in young children with an incidence rate of about 80%, while the rest occur in adults with suicidal ideation. (Arnold & Numanoglu, 2017; Marsella, et al., 2017). There are 5–518 cases of pediatric caustic consumption per 100,000 population per year (Arnold & Numanoglu, 2017). Chemical poisoning such as hydrochloric acid (HCl) also accounted for 18.8% of the total suicide cases in Indonesia (Arnold & Numanoglu, 2017). Acid poisoning causes serious injuries such as esophageal stricture and dysphagia to death (Marsella, et al., 2017). The primary mechanism of acid poisoning is inflammation. Hydrochloric acid causes the pH in the local tissue to drop when hydrogen ions are released. Then, coagulation necrosis and tissue ulceration ensue, leading to connective tissue consolidation and intramural vascular thrombosis, ulceration, fibrosis, and hemolysis. The central management in cases of hydrochloric acid poisoning is by performing the ABC stabilization to avoid airway edema and vomiting in patients, as well as to prevent further organ damage and supplemental oxygen in patients with respiratory symptoms (Arnold & Numanoglu, 2017; Marsella et al., 2017).

Hyperbaric Oxygen Therapy (HBOT) can be used as an urgent treatment for acute pathology or as an adjunct support for chronic disease. The main principle of HBOT is to provide pure oxygen concentration (100%) under high pressure in a room with a minimum size of 2 ATA (Ortega et al., 2021). de Wolde, et al., (2021) conducted a research which showed that hyperbaric oxygen therapy induced hyperoxia and oxidative stress. However, it is uncertain whether this induction can significantly reduce inflammation (de Wolde, et al., 2021). It is possible that hyperbaric oxygen therapy reduces inflammation and can be used as adjuvant therapy in hydrochloric acid poisoning. However, the mechanism of hyperbaric oxygen therapy implementation to hydrochloric acid poisoning is still much to be studied and has remained unknown (de Wolde, et al., 2021).

OBJECTIVE

The purpose of the study was to provide a better understanding on hyperbaric oxygen's biomolecular mechanism as a potential adjuvant therapy in HCl poisoning.

DISCUSSION

HCl poisoning

Hydrochloric acid (HCl) is a strong and corrosive acid solution (Handaya & Sunardi, 2017). In everyday life, hydrochloric acid is often used in chemicals for pools, porcelain cleaners, and bathroom cleaners (National Center for Biotechnology Information, 2021). HCl has been widely abused as a means of suicide and is one of the most commonly treated causes of chemical burns (Manjhi, et al., 2015). In the United States, injuries from ingestion of caustic substances (such as sulfuric acid, oxalic acid, hydrochloric acid, phosphoric acid) are rare, and only 5,000 cases are reported annually. The frequency of cases is bimodal, with the peak cases being children and adults. Children account for 80% of poisoning cases globally, mostly as a result of inadvertent consumptions. Adult cases, on the other hand, are more commonly associated with suicide intent and are frequently life-threatening (Marsella et al., 2017). Chemicals poisoning such as hydrochloric acid (HCl) also accounted for 18.8% of the total suicide cases in Indonesia (Ministry of Health of the Republic of Indonesia, 2019).

The pathophysiology of HCl poisoning begins with a local change in pH accompanied by a protein denaturation process that reduces the number of amide bonds (Williams & Lee, 2018). It can lead to edema, ulceration, and tissue necrosis leading to intramural vascular thrombosis, fibrosis, and hemolysis. The occurrence of coagulation necrosis is characterized by shallow ulcers accompanied by the formation of eschar, which is brown or black dead tissue with crusts on the wound detached from healthy skin due to burns (Williams & Lee, 2018). The acute toxicity of HCl causes an increase in the concentration of chloride ions in the blood, which leads to an acid-base imbalance, namely metabolic

acidosis. HCL toxicity can cause abdominal pain, swallowing difficulty, nausea, and vomiting in the gastrointestinal system. Ingestion of HCL can also cause severe corrosive sores on the lips, mouth, throat, esophagus, and stomach accompanied by bleeding, perforation, scar tissue formation, peritonitis, and stricture formation sequelae (Williams & Lee, 2018). HCl toxicity can also cause liver damage and ischemia, kidney failure and nephritis, decreased blood pressure due to gastrointestinal bleeding, fluid deficiency (hypovolemic shock), and circulatory collapse. The long-term side effects of consuming HCL can cause discoloration and tooth enamel erosion (National Center for Biotechnology Information, 2021).

Hyperbaric Oxygen Therapy

Hyperbaric Oxygen Therapy gives pure oxygen concentration (100%) under high pressure in a chamber. The minimum pressure for HBOT is 2 ATA (Ortega et al., 2021). The high-pressure chamber used in the HBOT has two types: monoplace chamber and multiple chambers. Monoplace chamber is used for one person, while multiple chambers can handle up to 20 people at a time. The duration of HBOT sessions varies from 1.5 to 2 hours and can be done 1 to 3 times a day for 20-60 times the therapeutic dose depending on the patient's condition (Kirby, et al., 2019). The therapeutic principle of HBOT is a consequence of increased pressure and oxygen concentration. It increases oxygen diffusion to the tissues, an increase in the concentration of oxygen in the blood, and a decrease in the size of gas bubbles in the blood. The process follows Henry and Boyle-Mariotte's law (Ortega, et al., 2021).

The major properties of HBOT include angiogenesis, vasoconstriction, fibroblast proliferation, leukocyte oxidative death, toxin inhibition, antibacterial, and antibiotic synergy. HBOT generates quick and severe vasoconstriction in tissues due to hyperoxia. In ischemic tissue, this process is accompanied by compensation in the form of enhanced plasma oxygen transport and microvascular blood flow, which HBOT increases. Such vasoconstriction reduces post-traumatic tissue edema, which contributes to treating wounds, compartment syndrome, and burns (Choudhury, 2018). HBOT also lowers lactate buildup in ischemic tissue and prevents the postischemic drop in ATP generation. The effects of HBOT on immunity, oxygen transport, and hemodynamics are complex. Hypoxia and edema are reduced as a result of the good therapeutic effect, allowing the body to respond appropriately to infection and ischemia. As an antimicrobial, hyperbaric oxygen can cause the creation of oxygen free radicals, which can oxidize proteins and lipid membranes, damage DNA, and prevent bacteria from performing their metabolic functions. HBOT is also efficient against anaerobic germs and helps leukocytes kill bacteria via their oxygen-dependent peroxidase system. In addition, it is known that hyperbaric oxygen also triggers oxygen-dependent transport of various antibiotics across the bacterial cell wall (Choudhury, 2018).

From a biomolecular standpoint, HBOT can impact cytokines, prostaglandins (PGs), and nitric oxide (NO). HBOT inhibits the generation of TNF-α (tumor necrosis factor-alpha) and reduces the production of proinf lammatory cytokines generated by stimuli (TNF-α and endothelin). In addition, HBOT can also decrease PGE2 and COX-2 mRNA levels. HBOT significantly increases VEGF, PDGF, and FGF levels via nitric oxide modulation. Capillary development and wound granulation are stimulated by the growth factors VEGF and PDGF, while FGF plays the same role in angiogenesis and induces neurodevelopment, keratinocyte organization, and proliferation (Gottfried et al., 2021).

There are several indications for HBOT, most of which are grouped into three main effects (a) accelerated wound healing and increased angiogenesis, (b) enhanced antimicrobial effects, and (c) medical emergency (Ortega, et al., 2021). Indications for HBOT include carbon monoxide poisoning, arterial gas embolism, decompression syndrome, crush injury, increased wound healing, exceptional anemia due to blood loss, intracranial abscess, and refractory osteomyelitis (Gottfried et al., 2021). There are two types of contraindications for HBOT: absolute and relative. The sole, absolute contraindication is an untreated pneumothorax (Kirby, et al., 2019). Chronic obstructive lung illness, high fever, epilepsy, pregnancy, inability to maneuver, Eustachian tube dysfunction, claustrophobia, respiratory tract infections, and a history of surgery are all relative contraindications. HBOT complications include barotrauma, the inability to equalize the pressure of the air-containing area and the surrounding environment causes harm. Ear barotrauma is the most prevalent condition, which can impact the middle ear, sinuses/paranasal, teeth, or lungs (Gottfried et al., 2021). Chest tightness, coughing, exhaustion, headache, vomiting, and a burning feeling in the chest are other HBOT adverse effects. One of the most significant effects is oxygen poisoning, which can include neurological (e.g.,

seizures) and pulmonary (e.g., pulmonary edema and respiratory failure) symptoms (Gottfried et al., 2021).

Effect of Hyperbaric Oxygen Therapy in hydrochloric acid poisoning

Hyperbaric Oxygen therapy (HBOT) has been widely used as a non-pharmacological therapy for several diseases through various mechanisms. Nowadays, several indications exist for HBOT application, especially its beneficial effect on wound healing caused by diabetes, pressure sores, burns, and radiation injuries (Kirby, et al., 2019). On the other hand, the hydrochloric acid (HCl) contained in most porcelain cleansers is often misused as a way to commit suicide (Marsella, et al., 2017). Compared to the other routes, HCl poisoning through oral ingestion is the most common way to commit suicide (Agency for Toxic Substances and Disease Registry, 2016). However, the application of HBOT in the case of HCl poisoning has not been carried out and studied further.

HCl consumption can adversely affect the body through various pathological processes (Williams & Lee, 2018). This process starts with a change in local pH that becomes more acidic, followed by increased protein denaturation, thereby reducing the number of amide bonds (Williams & Lee, 2018). These conditions cause burns injury, edema, ulceration, and necrosis of the gastrointestinal mucosal tissue that will eventually lead to intramural vascular thrombosis, fibrosis, and hemolysis (Williams & Lee, 2018). This pathological process gives rise to four primary symptoms: esophageal mucosal burns, laryngeal edema, ulceration, and necrosis of intestinal tissue (Williams & Lee, 2018). These symptoms are known to be stimulated by various proinflammatory mediators, including TNF-α, IL-1β, and IL-6 which are responsible for mucosal burns, C1 inhibitor deficiency, and Bradykinin that are responsible in laryngeal edema, as well as IL-6, IL-7, IL-10, IL-15, IL-21, IL-22, and IFN-γ that are responsible in ulceration and necrosis of intestinal tissue (Huang, et al., 2018). Thus, it can be concluded that there is an excessive inflammatory process that plays a role in HCl poisoning.

The excessive inflammatory process often causes tissue hypoxia through increased metabolic demands and decreased metabolite substrate. Thus, depriving oxygen levels in injured cells stimulating oxygen-dependent gene expression, namely, Hypoxia Inducible Factor 1 (HIF-1) (Sunkari, et al., 2015). HIF-1 is a heterodimeric transcription factor composed of alpha and beta subunits released as adaptive responses of cells to hypoxia (Sunkari et al., 2015). HIF-1 activity is regulated through hydroxylation of its alpha subunit by prolyl hydroxylases (PHDs) in normoxia, followed by binding of von Hippel-Lindau tumor suppressor protein (pVHL) that further leads to degradation of the alpha subunit. In contrast, under hypoxic conditions, including inflammation, HIF-1 alpha, and beta availability are stabilized against degradation (Sunkari, et al., 2015). However, HIF-1 is a proinflammatory mediator that induces inflammation and cell apoptosis (Novak, et al., 2016). In other words, the role of HIF-1 in HC1 poisoning only exacerbates the already existing inflammatory process. Therefore, in addition to primary therapy, an adjuvant therapy is also needed to reduce the inflammatory process. In this case, hyperbaric oxygen therapy (HBOT) can play an essential role as the adjuvant therapy (Novak, et al., 2016).

Hyperbaric oxygen will decrease the expression of HIF-1, which eventually reduces the inflammatory process. The primary mechanism of HBOT in reducing inflammation is through inhalation of pure oxygen concentration (100%), accompanied by an increase in air pressure of about two to three times higher than normal air pressure. It will increase the tissue oxygen concentration with oxygen-rich plasma, especially in inflamed tissues (de Wolde et al., 2021). It leads to activation of the HIF-1 hydroxylation pathway via prolyl hydroxylase (PDH) in the proline pathway and HIF inhibiting factor (FIH) in the asparagine pathway. Ultimately, reactivation of both of these pathways will lead to a decrease in HIF-1 expression. In addition, hyperbaric oxygen therapy also reduces other inflammatory mediators, such as IL-1β, IL-6, IL-8, IFN-γ, NF-B, and TNF-α. Moreover, hyperbaric oxygen therapy also plays a role in wound healing by stimulating angiogenesis growth factors such as EGF, PGF, and VEGF (de Wolde, et al., 2021).

On the other hand, studies that specifically discuss the effect of hyperbaric oxygen on HCl levels have not been carried out. However, analyzing the possible chemical reactions between HCl and oxygen shows that continuous oxygen administration will reduce the level of HCl by converting it into water and chlorine gas (Abdollahi & Nikfar, 2014). Meanwhile, chlorine gas is classified as a lung irritant that can cause acute damage to the upper and lower respiratory tract (Abdollahi &Nikfar, 2014). Therefore, the application of hyperbaric oxygen therapy in HCl poisoning requires a precise dose

calculation to minimize the side effects of chlorine gas.

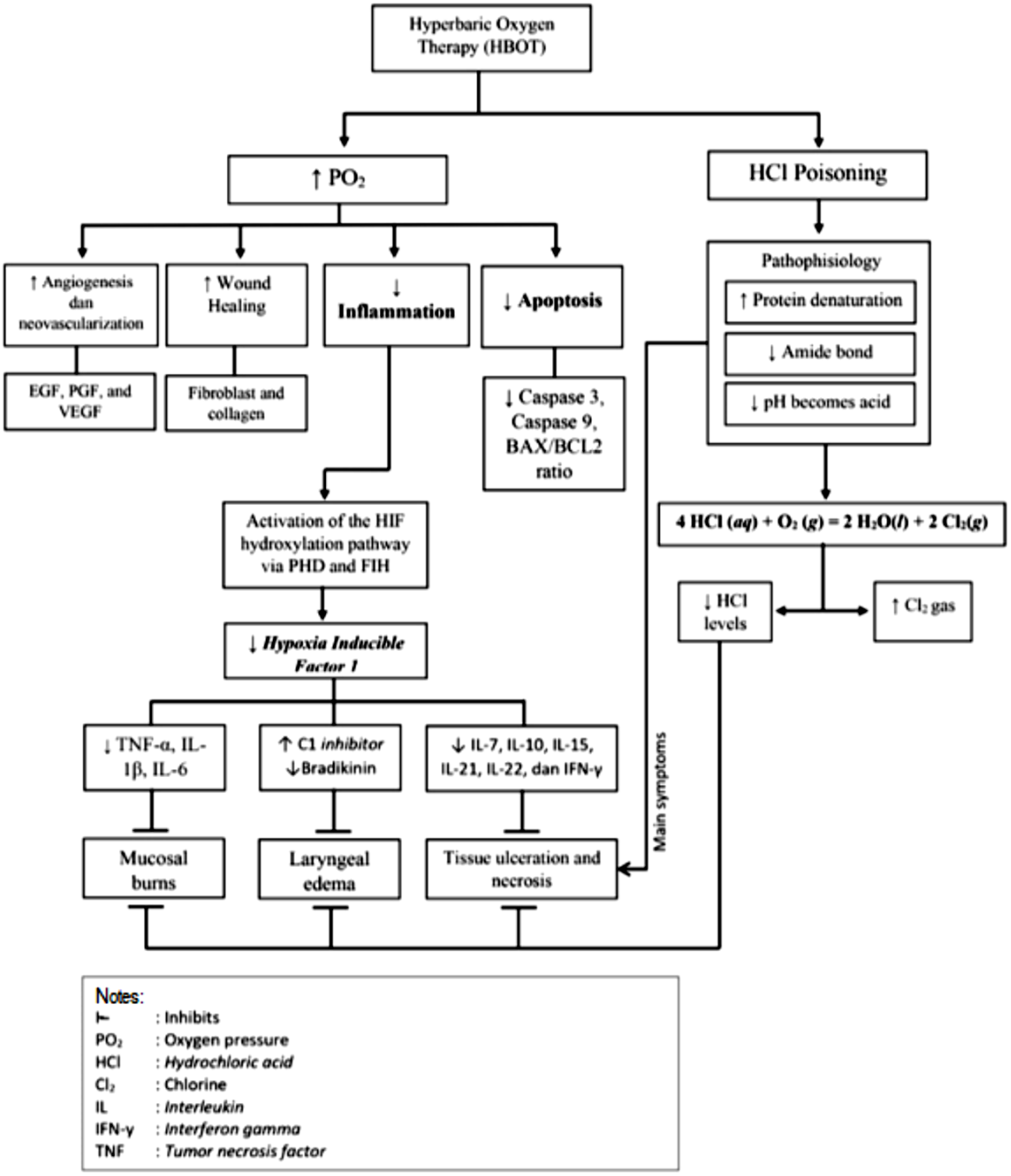

Figure 1. The mechanisms of hyperbaric oxygen therapy for HCl poisoning treatment.

Strength and limitations

No research have been conducted that explicitly examine the impact of hyperbaric oxygen on HCl levels. The use of hyperbaric oxygen treatment in HCl poisoning requires a precise dosage estimate to avoid chlorine gas adverse effects.

CONCLUSION

Hyperbaric oxygen therapy has the potential to be used as an adjuvant therapy in the treatment of HCl poisoning due to its ability to reduce inflammatory mediators and aid wound healing. However, further research is needed to determine how the chlorine gas produced from the chemical reaction between hydrochloric acid solution and oxygen can be appropriately anticipated by giving the right dose of HBOT so that the therapy can achieve excellent and maximum results, because chlorine gas is a dangerous substance that is toxic and has irritant properties for the respiratory tract.

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Author Contribution
All authors have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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