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Review article

Hydrogen peroxide formulations and methods of their use for blood oxygen saturation

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ABSTRACT

The antiseptic hydrogen peroxide is widely used in the treatment of various septic wounds and abrasions and injuries at home. In addition, in recent years there have been reports on the possibility of using hydrogen peroxide as an antihypoxant.Analysis of the results showed that unique formulations of hydrogen peroxide solutions and antihypoxic technologies of their use for pharmacological and cold support of organ and tissue function under hypoxic conditions without the use of gaseous oxygen were developed.The innovative technology is based on the local cooling of a selected area of the body while injecting a hydrogen peroxide solution of the "right" formulation.A hydrogen peroxide solution of the "right" formulation has been shown to be an alternative to arterial blood for oxygen-deficient tissues because hydrogen peroxide increases the oxygen content of tissues, including venous blood, which it converts to arterial blood because it forms oxyhemoglobin.

Keywords: Hydrogen Peroxide, Oxygen, Blood Oxygenation, Hypoxia, Ischaemia, Temperature.

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INTRODUCTION

Hydrogen peroxide is an over-the-counter antiseptic used topically for the aseptic treatment of purulent wounds [1-3]. This antiseptic is the only drug that is degraded by the enzyme catalase into water and molecular oxygen [4-7]. Due to its oxidising effect, molecular oxygen is able to have a deodorizing and inactivating effect on blood, pus and other biological fluids, as well as having a detrimental effect on pathological microflora [8-10]. Hydrogen peroxide is also us an oxidising agent in general-purpose disinfectants, chlorine-free bleaches, fabric stain removers, contact lens disinfectants and hair dye, as well as in some teeth whitening products [11,12]. It was also used as a detergent and bleach when washing ceramics [13-15]. According to established medical practice, a 3-6% hydrogen peroxide solution was considered to be the most effective and safe drug for external topical application for medical purposes [16]. Acidic hydrogen peroxide solutions have been found to be more stable during storage than alkaline solutions. Therefore, for about 100 years hydrogen peroxide solutions, which involve transport and/or storage, have been produced with acidic properties [17]. For long term storage of the hydrogen peroxide solution it is recommended to add a stabilizer to this solution (US Patent No 3383174, May 14, 1968), namely a small amount of pyrophosphoric acid, or to stabilise the acidity of the solution in another way in the pH range of 1 to 7 (US Patent No 6327963, January 14, 1936).However, at the beginning of the 21st century, Russian researchers have shown that when used topically, all drugs can have not only a specific effect related to the pharmacological activity of the main ingredients, but also a non-specific effect due to the physical-chemical properties of the pharmaceutical forms (solid, liquid, gaseous) [18-26] . It has been shown that by targeting a dosage form with a drug with a "desired" physical-chemical property, this property can independently provide the drug with the "desired" mechanism of action when applied topically [27-30]. It has been reported that acid (alkaline), osmotic, thermal and gaseous activity of drugs plays a major role in their local action [31,32]. However, the dependence of the local action of hydrogen peroxide solution on such its physico-chemical quality indicators as temperature, pH, osmotic activity and the presence of dissolved gases remains insufficiently studied so far. Currently, hydrogen peroxide solution is used only with regard to its approximate concentration in solution. Specific physicochemical properties of solutions of different series numbers and drug manufacturers are not taken into account. Under these conditions, Russia was the first in the world to suggest that hydrogen peroxide solutions with different concentrations of the main ingredient, temperature, pH, osmotic activity, and different content of dissolved gases may have different mechanisms of action when applied topically [23,26]. That is why the study of the spectrum of

physico-chemical modernization of the quality of hydrogen peroxide solutions has already begun.

The purpose of this paper is to review articles and inventions devoted to the use of hydrogen peroxide to develop new antihypoxic drugs and technologies to protect organs and tissues from hypoxic damage.

New formulation of hydrogen peroxide solution providing it with oxygen-releasing and antihypoxic effects

The history of discovery and medical application of hydrogen peroxide solution convincingly proves effectiveness and safety of external application of 3-6% hydrogen peroxide solution for disinfecting and washing effect. Over 100 years of clinical use, the formulation of a 3-6% hydrogen peroxide solution and the technology of its use did not undergo significant changes until Russian researchers took it up [33,34].The most significant success in modernizing the hydrogen peroxide solution formulation was the additional introduction of sodium bicarbonate, gaseous oxygen under increased pressure, and heating to body temperature [11,29,35,36] .

The fact is ~~that~~ replacing the acidic activity in the hydrogen peroxide solution with alkaline activity reduces the local irritant action, because blood and most human body tissues have alkaline activity within pH 7.4. At the same time, sodium bicarbonate is a natural alkaline buffer in the human body and has buffering properties that allow the hydrogen peroxide solution to remain within pH 8.4-8.5 [11,13,35]. In turn, it has been shown that saturation of hydrogen peroxide solution with gas (carbon dioxide, oxygen, or inert gases) multiplies the rate of onset, intensity, and duration of cold boiling when the drug interacts with biological tissues regardless of the content of catalase enzyme in them [13,15,25,26]. In addition, heating an alkaline and carbonated hydrogen peroxide solution to human body temperature also reduces the local irritant effect of the drug when applied locally [29].

It was shown that hydrogen peroxide and sodium bicarbonate solution, when heated to body temperature and replacing the acidic activity with alkaline activity within pH 8.5, acquires the ability to cold boil with foam formation during local interaction with biological tissues containing the enzyme catalase. It was found that when used locally warm alkaline hydrogen peroxide solutions (WAHPS) quickly dissolve and foam dense pus masses, thick mucus, thick sputum, blood clots, releasing oxygen gas, as well as bleach blood stains. This mechanism of local action of WAHPS for recanalization and antihypoxic action has been recommended [11,35,37].

Specifically, WAHPS containing 0.1-3% hydrogen peroxide, has been recommended for airway sanitation for airway obstruction caused by purulent obstructive bronchitis and/or nonspecific pneumonia in COVID-19 [36,37]. The fact is that when airways are filled with mucus, sputum, pus and/or blood, traditional mucolytics and expectorants and their application technologies do not provide urgent airway recanalization and urgent intrapulmonary blood oxygenation [35]. At the same time, unique results were obtained in Russia that convincingly prove the clinical efficacy of inhaled application of aerosolized WAHPS as an intrapulmonary pyolytic, mucolytic, expectorant and oxygen-releasing agent, which provides urgent recanalization of the airways during respiratory obstruction caused by purulent obstructive bronchitis [39].

Additionally, it is reported that the introduction of a WAHPS into the lungs provides a rapid and effective dissolution of thick sputum, mucus and pus inside the respiratory tract. This has been shown to release molecular oxygen, which can be absorbed into the blood through the alveoli, increasing blood oxygen saturation [37,39]. This evidence was obtained under in vitro conditions using isolated portions of pus, mucus, sputum, and patient blood, under experimental conditions using isolated rabbit lungs, and under in vivo conditions on awake rabbits. In both series of experiments, the airways were filled with artificial sputum. In both series of experiments, the airways were filled with artificial sputum [37] . Under the aforementioned conditions, it has been proven that WAHPS turns pus, blood, thick sputum and mucus into oxygen foam a few seconds after local interaction begins and increases blood oxygen saturation to normal levels [39,40]. It is concluded that a WAHPS during intrapulmonary injection, as well as when inhaled in the form of an aerosol, has the following local effect: direct mucolytic, pyolytic, expectorant, hemolytic, discoloring and oxygen-releasing action [37,38] .The oxygen releasing effect of hydrogen peroxide was first shown in experiments with aquarium fish that swam in water inside hermetically sealed containers without oxygen gas access (RU Patent No. 2563151, 20.09.2015) [41] . Experimental results showed that the introduction of hydrogen peroxide in a calculated dose inside the fish's stomach using a stomach probe, or in the water in which the fish swam, or by injecting the drug inside the fish dorsal muscle, increased the duration of fish survival in hermetically sealed containers. The oxygen-releasing activity of the hydrogen peroxide solution and its ability to increase tissue oxygen content was also shown on a portion of isolated venous blood in vitro condition (RU Patent No. 2538662, 10.01.2015). The results of laboratory studies have shown that injection of hydrogen peroxide solution into a portion of preserved donor blood provides urgent oxygen enrichment of red blood cells and conversion of venous blood into arterial blood. It is reported that hydrogen peroxide is easily broken down into water and oxygen gas due to the fact that the blood contains sufficient amounts of the enzyme catalase, and the red blood cells immediately assimilate molecular oxygen through hemoglobin oxygenation. In

turn, hemoglobin oxygenation and oxygenation of the blood eliminates hypoxia. Therefore, injectable and enteral administration of hydrogen peroxide solutions with appropriate formulation and physical-chemical properties is recommended as a promising direction in the development of drugs and technologies for their use for extrapulmonary oxygenation of blood and/or other tissues in the future.

Due to the discovery of this mechanism of action, WAHPS has been proposed as an aerosol for inhalation use during a severe attack of bronchial asthma and obstructive bronchitis for immediate and reliable expectorant, oxygen-releasing and antihypoxic action inside the airways during acute hypoxia [38-40]. The authors suggest that intrapulmonary introduction of WAHPS can be an alternative to extracorporeal membrane oxygenation (ECMO) to urgently increase blood oxygen saturation in severe hypoxia caused by COVID-19. The fact is that it is hypoxic brain cell damage that is the true cause of biological death of patients with severe SARS [42].

In recent years, Russia has issued several patents for inventions based on the use of hydrogen peroxide solution and intended for extra-pulmonary blood oxygenation: RU Patent No. 2604129, 10. 12.2016; RU Patent No. 2586292, 10.06.2016; RU Patent No. 2639493, 21.12.2018; RU Patent No. 2634271, 24.10.2017.

A drug designed to increase resistance to hypoxia (RU Patent No. 2604129).

This invention intended for oral administration. Agent represents 0.3-0.5 % solution of hydrogen peroxide, oxygen at excess pressure of 0.2 ATM at +8 °C and drinking water. The drug is absorbed into the blood through the stomach wall and increases blood saturation.

Arterial blood substitute drug (RU Patent No. 2586292).

This drug is a solution of 0.01-0.02% hydrogen peroxide with isotonic and iso-alkaline activity, designed for local injection delivery of oxygen to tissues in hypoxia or ischemia. The fact is that the solution has an optimal content of hydrogen peroxide, which is able to release oxygen similarly to arterial blood, but excludes the formation of gas bubbles and therefore does not cause gas embolism.

Life-giving drink (RU Patent No. 2639493).

The invented new drug, intended for enteral nutrition of children, contains glucose, ethanol and 0.3-0.5% hydrogen peroxide, as well as oxygen gas under excessive pressure, similar to a conventional carbonated drink. Such a drink provides rapid absorption of glucose, ethyl alcohol, oxygen gas and hydrogen peroxide into the blood. These ingredients provide the basic vital metabolic processes in the child's body in a critical situation.

Doping (RU Patent No. 2634271).

This drink includes glucose, hydrogen peroxide and oxygen gas at overpressure. Therefore, the enteral use of such a drink ensures the intake of water, oxygen and glucose into it, increases physical endurance when the adaptation reserves are depleted.

CONCLUSION

Hydrogen peroxide is very widely used in medicine as an antiseptic. The drug is traditionally used externally for the antiseptic treatment of purulent wounds. This article summarizes the first scientific articles and inventions devoted to proving the possibility of using a WAHPS to ensure the delivery of oxygen to organs and tissues instead of gaseous oxygen. The articles and inventions considered indicate the possibility of using a WAHPS instead of arterial blood in critical situations, since hydrogen peroxide is rapidly decomposed by the enzyme catalase into water and oxygen. It follows that hydrogen peroxide can temporarily replace oxyhemoglobin, and a hydrogen peroxide solution with the appropriate formulation and physical and chemical properties can replace arterial blood in desperate situations to preserve oxygen exchange in tissues.

The above-mentioned proposals are extremely important because they indicate new indications for the medical use of hydrogen peroxide solutions with various physical-chemical properties and indicate the possibility of using hydrogen peroxide for the development of arterial blood substitutes.

Conflict of interest

The authors declare no conflicts of interest for this study.

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