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Systematic Review

Inhalation of an Aerosol Solution of Hydrogen Peroxide and Sodium Bicarbonate for the Urgent Recanalization of the Respiratory Tract after Blockage by Mucus and Pus

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Abstract

Objective: To assess the effectiveness of inhalation of an aerosol solution of Hydrogen Peroxide and Sodium Bicarbonate for urgent recanalization of the respiratory after blockage by mucus and pus. Acute respiratory distress syndrome can lead to hypoxia secondary to respiratory obstruction caused by excessive accumulation of mucus and pus in the respiratory tract. In cases of severe hypoxia, artificial ventilation and extracorporeal membrane oxygenation are used to treat severe hypoxia in modern day medical practice. However, these treatment methods only take care of the hypoxia, but do not relieve obstruction of the respiratory tract.

Methods: A systematic review was carried out among the scientific literature and inventions using the online databases of the Federal Institute of Industrial Property of the Russian Federation and the Elibrary Library in accordance with the quality standards described in the AMSTAR measurement tool and the PRISMA 2009 checklist. A total of 428 inventions were discovered, 33 of which were evaluated for consideration.

Results: Known expectorants and mucolytics do not provide urgent and effective recanalization of the respiratory tract when it is obstructed by mucus, sputum and pus. It has been shown that an alkaline solution of hydrogen peroxide administered by inhalation in the form of an aerosol or with intra-pulmonary injection is able to provide urgent recanalization of the respiratory tract when it is obstructed by mucus, sputum, pus, blood and other colloidal fluids that contain the enzyme catalase. Therefore, inhalation of an alkaline solution of hydrogen peroxide has been proposed as a means to provide urgent recanalization of the respiratory tract. This drug is not only indicated in acute respiratory infections with COVID-19, but also in severe episodes of bronchial asthma, bronchiectasis, purulent obstructive bronchitis, cystic fibrosis, mechanical trauma, burns and allergic inflammation of the lungs and/or respiratory tract. The formulation, method of application, mechanism of local action, advantages and disadvantages of the specified solution are all described and explained.

Conclusion: A review of scientific literature and inventions has shown a real possibility of upgrading existing technologies for recanalization of the respiratory tract and blood oxygenation to inhalation of a warm alkaline solution of hydrogen peroxide. In Russia, it has been proven that the intrapulmonary use of an alkaline solution of hydrogen peroxide provides immediate recanalization of the respiratory tract and oxygenation of blood. It is hoped that the intrapulmonary use of an alkaline solution of hydrogen peroxide can become an alternative to extracorporeal membrane oxygenation.

Keywords: respiratory obstruction, COVID-19, mucolytic technology, expectorants, aerosol, solution, local action, pus solvents, recanalization

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1 INTRODUCTION

The current COVID-19 pandemic, caused by infection with a new strain of the coronavirus, continues to claim the lives of hundreds of thousands of patients worldwide. This is despite timely vaccination and treatment with a large arsenal of drugs[1-3]. New infections with the coronavirus have been found to be characterized by the development of atypical pneumonia, which in the critical stage of the disease is often complicated by acute respiratory distress syndrome (ARDS)[4-7]. ARDS is defined as respiratory failure that occurs within one week of a known clinical insult. It is characterized by bilateral opacity of lung fields on radiographic imaging that cannot be explained by atelectasis, fluid overload or heart failure, and by hypoxemia that is recalcitrant to conventional oxygen therapy. Therefore, the true threat to the lives of patients is not the virus itself or pneumonia, but a catastrophic decrease in the level of blood oxygenation below the level that is required for preservation of brain viability, i.e., a severe degree of hypoxia caused by ARDS.

It is no secret that severe hypoxia causes damage primarily to the brain cells, since it is the brain cells that have the most intense aerobic metabolism. It is reported that, hypoxic brain cell damage is the true cause of biological death in all patients with airway obstruction secondary to new infection with the coronavirus[8,9]. Despite the absence of oxygen, the brain cells do not stop their metabolism. However, in the absence of oxygen, this metabolism is severely disrupted and causes the death of brain cells. It has been shown that hypoxic brain cell damage is the true cause of death not only in patients with new coronavirus infections, but also those with obstructive bronchitis complicating severe bronchial asthma, drowning and meconium aspiration in neonates[10].

However, the standard of emergency therapy for severe ARDS-induced hypoxia secondary to COVID-19 has not yet been fully developed[11-13]. Moreover, no effective drug that can prevent death from hypoxic brain damage in case of catastrophic reduction of blood oxygenation levels has been developed[14]. Nevertheless, in these conditions, all patients with severe respiratory obstruction are admitted to the intensive care unit to inhale air that has a much higher percentage of oxygen[5,6,8]. For this purpose, an oxygen-enriched breathing mixture is used. It is reported that initially, this mixture is given using a breathing mask. If the effect is unsatisfactory, oxygen with the breathing mixture is given through an intubation tube using artificial mechanical lung ventilation[4,6,9,10,15-17].

However, increasing the pressure, volume and concentration of gaseous oxygen in the inhaled air does not always eliminate hypoxia in severe ARDS-induced hypoxia in patients with COVID-19[11]. Severe hypoxemia in COVID-19 is multifactorial[18]. It is very important to note that one of the causes of hypoxia in ARDS, which until now has received little attention from researchers, may be respiratory obstruction caused by accumulation of mucus, sputum, pus, serous fluid, fibrous fluid, plasma, blood and other types of colloidal biological fluid in the airway. There is no doubt that pus and other thick secretions can accumulate in the respiratory tract, especially in patients that have been superinfected with bacteria or fungi[14]. It has also been reported that accumulation of serous fluid in the airways can cause ARDS in tuberculosis. Accumulation of sputum, mucus, and pus in the airways has been shown to be a frequent cause of ARDS in bronchiectasis, mucoviscidosis, purulent obstructive bronchitis, paragonimus, pulmonary strongyloidiasis, legionnaires' disease and severe thoracic trauma[15]. That said, it is no secret that these lung diseases do not protect people from COVID-19. Therefore, in some cases, infection with COVID-19 can be coexist with these diseases, not just with bacterial and fungal superinfections. All this causes the airways of some patients to be filled with thick mucus and thick pus[8,14]. At the same time, generally accepted technologies of artificial ventilation are performed in ARDS-induced hypoxia without using drugs that can urgently dissolve sputum, mucus, pus, serous fluid and other colloidal fluids and remove them from the airways while replacing them with oxygen gas. Therefore, despite intensive artificial ventilation, the presence of sputum, mucus, pus, plasma, serous fluid and other colloidal fluids inside the airways does not allow increased airflow, gaseous exchange and blood oxygenation[15].

Nevertheless, treatment of patients with severe airway obstruction is still based on oxygen inhalation, injections of steroid and nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapeutic drugs, antihistamines and immunotropic drugs[19-22]. Intravenous and/or intramuscular injections of drugs are also recommended. Despite the fact that the drugs in question have failed to meet expectations and do not prevent death in the final stage of respiratory disease, the standard of care does not include expectorants capable of urgently dissolving mucus and pus and restoring patency of the airway[8,14,15]. At the same time, it has been repeatedly reported for approximately 100 years that injections of steroids, NSAIDs, antibiotics, antihistamines and anesthetic drugs can cause complications of varying severity. These complications can either be general or local. It has been reported that local complications in the form of local reversible or irreversible inflammation, necrosis and abscess formation may occur more frequently than general complications[23-25]. In particular, it has been reported that the most misunderstood and unpredictable complications arising after injection of these drugs are Nicolaou syndrome and Tachon's syndrome[26-28].

Under these conditions, the only effective and safe means of preserving the life and health of patients with severe respiratory obstruction secondary to infection with COVID-19 remains gaseous oxygen. The validity of the use of oxygen and its high efficiency in emergency medical care is proved by the successful preservation of life of patients with severe respiratory obstruction and severe hypoxia. However, for urgent effective oxygenation in COVID-19, there is often no alternative to extracorporeal membrane oxygenation (ECMO) because the technology of reliable intrapulmonary blood oxygenation has not yet been developed[29-31]. ECMO is not available to most patients, the technology itself is very dangerous and it is expensive[15,32].

However, the published relevant reviews are not comprehensive. They do not include discussions of all known and potential airway recanalization technologies that can increase intrapulmonary blood oxygenation during airway obstruction, particularly when the airway is filled with thick mucus and thick, sticky pus. Therefore, it is necessary to fill this gap in order to cover all potential technologies. This is necessary for the development of effective technologies for airway recanalization and blood oxygenation that can reduce mortality in SARS-CoV-2.

Thus, our current review aims to expand the list of airway recanalization technologies for use in cases of COVID-19 with airways obstructed by mucus and pus. Particular attention is paid to technologies of intrapulmonary administration of expectorants, mucolytic, pyolytic and hemolytic agents, all of which can urgently dissolve thick sputum, mucus, pus, serous fluid, fibrous fluid, plasma, blood and other colloidal fluids that may be obstructing the airway. Only with the help of such technologies is it going to be possible to urgently increase blood oxygenation levels in severe hypoxia caused by airway obstruction, and to keep patients alive in the final stage of atypical pneumonia complicated by ARDS in COVID-19.

2 METHODS

We conducted a thorough search using the online databases of the Federal Institute of Industrial Property of the Russian Federation and the Elibrary Library. We used the following keywords: "Coronavirus", "COVID-19", "SARS-COV-2", "treatment of atypical pneumonia", "airway obstruction", "obstructive bronchitis", "hypoxia", "oxygen", "resistance to hypoxia", "blood oxygenation", "mucolytics", "expectorants", "sputum", "mucus", "pus", "antiseptics", "disinfectants" and "hydrogen peroxide". The study was conducted without any restrictions on the year of publication. In addition, we studied the references and conducted a citation search. A systematic review was conducted in accordance with the quality standards described in the AMSTAR measurement tool and the PRISMA 2009 checklist[33,34]. Information about the essence of inventions written in Russian and English was included. The search strategy was based on the PICO model[35,36]. Two coauthors independently selected, evaluated and extracted the data. Any inconsistencies in the reviews were resolved by consensus. The flowchart for selecting articles was a spiral in which each spiral turn was an iteration[37,38]. The inclusion criteria in the study was limited to medicines, as well as devices and methods of their use, providing urgent dissolution of thick sputum, thick pus, rapid increase in pulmonary ventilation, elimination of respiratory obstruction, rapid increase in intrapulmonary blood oxygenation and local interaction factors. The exclusion criteria of the study included the absence of inventions designed for urgent dissolution, foaming of thick pus and sputum with streaks of blood and removal from the respiratory tract. The risk of individual bias in judgments was reduced by relying on the essence of the invention as a generally accepted criterion of novelty. A total of 428 inventions were found, 33 of which were evaluated for review.

3 RESULTS

3.1 Medical Care in Severe Coronavirus Infection

A review of the literature showed that the main hopes of researchers and physicians around the world for successfully treating patients with COVID-19 are still associated with the effectiveness of treatment of SARS syndrome[39]. It is reported that atypical pneumonia as a specific form of infectious disease was described in 2002-2003[40]. Atypical pneumonia has been found to be characteristic of an infectious disease caused by certain strains of coronavirus[40,41]. Known antiviral, chemotherapeutic, and anti-inflammatory medications have been used to treat patients with SARS from the very start[4,42-49]. However, clinical practice has exposed their low effectiveness in treating atypical pneumonia complicated by ARDS and severe hypoxia[50].

In parallel, various antiseptics and disinfectants have been widely used to prevent coronavirus infections. Experience in the use of these drugs has showed their high antiviral efficacy when applied locally. Solutions of these agents have a denaturing effect, and destroyed coronavirus upon interaction[51]. Therefore, antiseptics and disinfectants are well justified and firmly occupy the first place in the individual and community prevention of the COVID-19 pandemic[52-56]. Surprisingly, antiseptics and disinfectants are not included in the standard of medical care for COVID-19 patients, even those with severe respiratory obstruction. It is also paradoxical that in a situation where there are no effective drugs for the treatment of atypical pneumonia and urgent relief of hypoxia, researchers around the world continue to test antiviral, chemotherapeutic and immunomodulatory drugs, but not antiseptics and disinfectants[57]. Moreover, despite the lack of clear success in this direction, it is generally recognized that success in the treatment of COVID-19 will be achieved along the path of immune evasion of SARS-CoV-2 and the development of antiviral and immunomodulatory agents. The rationale for this very direction of drug discovery and development was the subject of a related review published recently[57].

However, the published relevant reviews are not comprehensive. They do not include technologies for airway recanalization of airways that are filled with thick mucus, pus, purulent exudate, blood and/or serous fluid. The reviews have not considered the potential role of expectorants, mucolytic drugs and drugs that dissolve thick pus, blood clots, caseous masses, fibrin filaments and colloidal fluids secreted by helminths for airway recanalization in tuberculosis, mucoviscidosis, bronchiectasis, closed and open lung trauma, thermal, chemical or physical-chemical burns of mucous membranes of the airways, allergic edema and/or idiopathic edema syndrome and helminthiasis in the respiratory system. In these lung diseases, the airways may be filled with the corresponding biological fluids, making it pulmonary ventilation very difficult. It has been reported that in pulmonary paragonimiasis, the airways are filled with large amounts of yellowish sputum[58-60]. In the case of strongyloidiasis, there are reports that the airways are filled with green sputum. The larvae of this worm also infiltrate the alveolar spaces and cause ARDS[61,62]. Legionellosis has been reported to cause severe pneumonia, which may be complicated by ARDS[63]. Traumatic lung injury is also complicated by filling of the airways with blood and hemoptysis[64-68]. It is well known that atypical pneumonia in COVID-19 can not only develop in healthy people, but also in patients with the above mentioned pulmonary diseases. In such cases, airway obstruction develops independently of coronavirus infection and SARS, and hypoxia develops largely due to the accumulation of mucus, pus, blood, serous, fibrinous fluid or even live helminths in the airways.

Modern expectorants and mucolytics are not classified as drugs for use in medical emergencies. These drugs are not in the treatment of patients with severe hypoxia caused by respiratory obstruction, including atypical pneumonia caused by infection with the new strain of coronavirus. Traditionally, expectorants and mucolytics are administered orally. After oral administration, the drugs only appear in the patient's blood 30 minutes after entering the stomach. Side effects such as nausea and vomiting may develop. These expectorants and mucolytics are used mainly to relieve thick and viscous sputum in chronic obstructive pulmonary disease (COPD), which is more often than not associated with cigarette smoking and is complicated by obstruction to expiratory airflow[69].

Oxygen therapy is widely used to combat hypoxia[2,11]. In pediatrics, nasal cannulas with heated humidified high-flow therapy are used for this purpose and forced pulmonary ventilation[10,13]. However, forced ventilation of the airways with respiratory gases does not always achieve the desired results. This is because obstruction of the airways with mucus, sputum, pus, blood and/or helminth larvae and products of their activity prevents the delivery of oxygen to the alveoli and absorption of oxygen into the blood. Therefore, despite sufficient oxygen content in the inhaled air, the oxygen saturation of patients with airway obstruction caused by lung trauma, worm infestation, cystic fibrosis, bronchiectasis, obstructive purulent bronchitis and other diseases often remains low. In this regard, forced ventilation of the airways with oxygen often becomes meaningless. Nevertheless, oxygen therapy remains the most accessible and safe technology of resuscitation in the daily practice of emergency medical care around the world. In our opinion, its only drawback can be eliminated if this method of oxygen therapy is supplemented with effective drugs capable of rapidly dissolving mucus, pus and blood with simultaneous release of oxygen gas in the airways and increased oxygen absorption into the blood.

Therefore, our current review aims to expand the arsenal of drugs and medical technologies that can be used for urgent recanalization of the airway in COVID-19 patients with airway obstruction caused by accumulation of mucus, pus, sputum and/or blood. In doing so, we focus on the technology of inhalation and/or intrapulmonary administration of expectorants, mucolytic, pyolytic and/

or hemolytic drugs, which in can dissolve these biological masses and improve the flow of air in the respiratory tract. Only such emergency medical technology can provide quick recanalization of the airways and increase blood oxygenation. Also, only such technology can compete with ECMO in reducing mortality in patients with severe atypical pneumonia complicated by respiratory obstruction in COVID-19. Finding an alternative to ECMO is a very worthy task, since ECMO is difficult to access, dangerous, and is expensive[32].

By definition, expectorants, mucolytic, pyolytic and hemolytic agents are agents that can dissolve thick mucus, pus and blood in the airways. This can optimize natural and artificial ventilation and increase intrapulmonary blood oxygenation in cases of severe airway obstruction[68-78]. Therefore, it is necessary to fill this gap in the relevant reviews and supplement them with the specified groups of drugs and potential technologies for effective recanalization of airways that are obstructed with mucus, pus and blood. This is necessary in order to identify their strengths and weaknesses as soon as possible, to develop generally available effective technologies for the personalized treatment of patients whose airway obstruction is caused by the accumulation of mucus, sputum, pus or blood accumulation in the airways. Research in this area is needed because drug-assisted airway recanalization with expectorants, mucolytic, pyolytic, and hemolytic agents may open a new pathway to blood oxygenation through the lungs, ultimately reducing mortality in patients infected with SARS-CoV-2[79].

3.2 How Hydrogen Peroxide can Turn Mucus, Sputum, Pus and Blood Into Oxygen Foam Inside the Respiratory Tract

It is reported that at the beginning of the 21st century, the resistance of infectious agents to traditional chemotherapeutic agents continues to increase. This is one of the reasons for their decreasing effectiveness of conventional drugs in the treatment of many infectious diseases, including COVID-19. Therefore, the course of infectious diseases is prolonged and often complicated by local purulent inflammatory processes[80] such as bacterial pneumonia, purulent bronchitis, pulmonary abscess and even purulent pleural empyema[81,82]. At the same time, the resistance of microorganisms to antiseptics and disinfectants remains relatively low. The effectiveness of antiseptics in the treatment of purulent diseases has long been unsatisfactory[83]. Studies have shown that the reason for the unsatisfactory effectiveness of antiseptics in the treatment of purulent diseases is that they do not have the ability to dissolve thick pus[84]. Traditionally, the treatment of purulent diseases was done using antiseptics and disinfectants. These had a deleterious effect on all forms of life, but did not have the ability to dissolve masses of thick pus and convert them into a soft oxygen foam[15]. However, it was shown that if their acidic properties were replaced by alkaline ones, antiseptics acquired new pharmacological activity when applied topically. Alkaline solutions of many salts, including sodium chloride solution, were now used to dissolve thick and sticky pus[15,70,75,85]. It turned out that the most potent agent for dissolving thick pus was warm alkaline hydrogen peroxide solution[15,78].

In this regard, our review is quite timely and justified. In recent years, there have been reports that warm aqueous solutions of well-known antiseptic drugs such as hydrogen peroxide and sodium hydrogen carbonate can not only sterilize, but can also quickly dissolve thick pus, mucus and blood, turning them into a soft white oxygenated foam upon local interaction[15,75-79]. More recently, drugs have been discovered that quickly dissolve thick pus and blood clots when applied topically. The first group of drugs is called the “pyolytic” drugs, pus dissolvers or pus-dissolving drugs. The second group of drugs is called skin bleach in the area of the bruise, bruise-bleaching (bruiser discolorers) drugs, or hemolytic drugs[86].

Parallel to these reports, there were reports confirming the promise held by these antiseptics in the treatment of COVID-19, especially hydrogen peroxide[51-56]. However, these reports lacked suggestions for airway recanalization in cases of respiratory obstruction caused by excessive mucus, sputum, pus, blood or helminth larvae. Additionally, several reports have appeared on the local effect of hydrogen peroxide solution on the viability of some biological tissues in the absence of dissolved oxygen. For example, hydrogen peroxide has been reported to protect fish’s brains from hypoxic damage and to keep fish alive in the absence of oxygen in the water in which the fish swim[87]. The report that hydrogen peroxide preserves the viability of bean seeds during their germination and swelling does not refute this ability of hydrogen peroxide[88]. However, there are 6 inventions in which the topical application of hydrogen peroxide is used to preserve the life of cells, tissues and/or the body in the absence of oxygen gas have been proposed for the first time. The essence of these inventions is presented in Table 1.

A review of the literature shows that over the past 10 years, there have been comprehensive studies on the dynamics of thick pus during local interaction with solutions of various antiseptics, disinfectants, plasma substitutes and other drugs considering their physical and chemical properties and/or physical and chemical factors of local interaction. It has been established that such physical and chemical properties of solutions as alkaline, oxidative, osmotic, temperature and gas-forming activity (ability to form cold boiling process within both solutions and purulent masses) turn solutions into pyolytic preparations[15,75,78,84]. Hydrogen peroxide and sodium bicarbonate solutions have the most potent pyolytic activity. It has been shown that the

Table 1. Inventions in Which the Use of Hydrogen Peroxide for Oxygenation of Blood and Increasing the Resistance of Body Tissues to Hypoxia is Proposed

	RU Patent No.	Title of the Invention	Composition of the Solution and Its Method of Use
1	2586292	Lympho-substitute for local maintenance and viability of organs and tissues in hypoxia and ischemia	0.01-0.02% Hydrogen peroxide 0.88% Sodium chloride 0.06-0.1% Glucose *Injection at the site of ischemia and/or hypoxia*
2	2538662	E.M.Soikher's hyper oxygenated agent for saturation of venous blood with oxygen	0.85% Sodium chloride 0.10% Sodium bicarbonate 0.05-0.29% Hydrogen peroxide *Injection into donor blood*
3	2604129	Agent for increasing resistance to hypoxia	0.3-0.5% Hydrogen peroxide Pressurized gaseous oxygen at 0.2 ATM *Enteral administration*
4	2563151	Method of maintenance of live fish during transportation and storage	6% Hydrogen peroxide *Injection into water with fish in a single dose of 0.2mL/kg of fish*
5	2639493	Energy drink	0.3-0.5% Hydrogen peroxide 7% Glucose 0.7% Ethyl alcohol Gas oxygen at an overpressure of 0.2 ATM *Enteral administration*
6	2634271	Means of increasing physical endurance	3% Hydrogen peroxide 7% Glucose Gas oxygen at an overpressure of 0.2 ATM *Enteral administration*

most effective solvent for dissolving thick pus is a solution heated to a temperature of +37°C, containing hydrogen peroxide at a concentration of up to 3% and sodium bicarbonate at a concentration of about 10% (saturated solution), and gases (carbon dioxide, oxygen or inert gases such as helium) at a pressure of 4 ATM. Several techniques have been developed for the local application of these solutions. The thick pus is not only dissolved, but is almost instantly transformed into a soft, white-colored oxygen foam. Hydrogen peroxide and sodium bicarbonate solutions are reported to dissolve, deodorize, decolorize and turn thick pus into a white oxygen foam due to the biochemical breakdown of hydrogen peroxide into water and oxygen gas by the enzyme catalase. This enzyme is always present in purulent masses. In our opinion, 10 inventions deserve special mention. The essence of these inventions is presented in Table 2.

A review of the literature showed that respiratory obstruction in children can occur not only because of excessive mucus secretion and pus accumulation, but also because the airways fill with blood, as occurs following chest trauma and pulmonary contusions. In addition, it has been shown that blood or traces of blood may be found in the sputum, mucus and pus in some forms of purulent bronchitis, pneumonia, lung infestation by worms, bronchiectasis and in some forms of allergic and idiopathic pulmonary edema. Therefore, it was very helpful to discover that hydrogen peroxide can dissolve not only pus, but also blood clots, mucus and sputum with traces of blood into oxygen foam. This is because all of these biological tissues contain the enzyme catalase[75,89]. The first patent for an invention related to the discoloration of bloodstains was issued in 2009. It was a "Method of express cleaning of blood stains from clothing" (RU Patent No. 2371532). The essence of the invention lies in the fact that to discolor blood stains, one must use warm alkaline solutions of hydrogen peroxide with a certain osmotic activity. 12 new drugs and medical technologies were later invented, designed for the rapid dissolution, discoloration and transformation of blood clots into foam, as well as skin discoloration in areas of bruises. The essence of these inventions is presented in Table 3.

Analysis of the proposed technologies shows that they are based on the local application of a warm, isotonic and slightly alkaline aqueous solutions of hydrogen peroxide. Local application of these solutions causes biochemical dissolution of viscous and dense tissues due to alkaline saponification of their protein-lipid complexes, physical destruction of their monolithic structure secondary to rapid release of oxygen gas bubbles and discoloration of

Table 2. Inventions in Which the Technology of Instantaneous Transformation of Thick Pus into Fluffy Oxygen Foam Using an Alkaline Solution of Hydrogen Peroxide was Proposed

	RU Patent No.	Title of the Invention	Composition of the Solution and Its Method of Use
1	2308894	Method for treating pleural empyema	2.4% Euphyllin pH 9.0 Local temperature +37 - +42°C *Injection into thick pus inside the pleural cavity with purulent empyema of the pleura*
2	2327471	Uterine lavage technique	0.9% Sodium chloride 3% Hydrogen peroxide Local temperature +42 - +45°C *Intrauterine injection for uterine bleeding*
3	2360685	Softening agent for thick and viscous pus	2.7-3.3% Hydrogen peroxide 5.0-10.0% Sodium bicarbonate Injection in thick pus
4	2331441	Hyper-gassed and hyper-osmotic antiseptic mixture	2.7-3.3% Hydrogen peroxide 2.0-10.0% Sodium chloride Gas Carbon dioxide an overpressure of 0.2 ATM *Injection into a mass of thick pus*
5	2468776	Method and means of removing sulfur plug	2.7-3.3% Hydrogen peroxide 2.0-10.0% Sodium chloride Gas Carbon dioxide an overpressure of 0.2 ATM *Injection into a mass of thick pus*
6	2452478	Multipurpose solution for epibulbar instillations	0.55-1.0% Hydrogen peroxide 1.0-1.5% Sodium bicarbonate 0.5-1.0% Lidocaine hydrochloride *Instillation into the conjunctival cavity*
7	2455010	Agent for fistula sanitation in infected pancreatic necrosis	0.9% Sodium chloride 0,142% Sodium hydrophosphate 0.120% Sodium dihydrophosphate pH 6.7-7.9 Osmotic activity 340-370 mosmol/L of water *Flushing of the fistula in infected pancreatic necrosis*
8	2659952	Bleaching cleanser of dentures	3.0±0.3% Hydrogen peroxide 2.0-10.0% Sodium bicarbonate Gas O_2 under excess pressure 0.2 ATM Local temperature +37 - +42°C *Baths for whitening dentures*
9	2723138	Method of using plaque removal solution with irrigation agent	2.0-10.0 % Sodium bicarbonate 2.7-3.3 % Hydrogen peroxide Gas Argon at equilibrium pressure of 3-4 ATM Temperature +43 - +65°C *Pour into the container of a dental irrigator, and then into the oral cavity*
10	2730451	Peeling agent for foot hyperkeratosis	0.5-20% Hydrogen peroxide 3.0-5.0% Potassium hydroxide Gas Oxygen an overpressure of 0.2 ATM pH 13.0-14.0 Osmotic activity 350-560 mosmol/L of water Local temperature +38 - +42°C *Irrigation of the feet with baths*

hemoglobin by oxidation[75,76]. In this case, hydrogen peroxide decomposes into water and oxygen gas under the action of the enzyme catalase, which is always present in blood stains.

In recent years, inhalation of a pus solvent aerosol has been recommended for the recanalization of the airway in patients with severe hypoxia caused by obstruction of the airway by

Table 3. Inventions in Which New Technologies Were Proposed for Instant Dissolution and Discoloration of Spots and Blood Clots by Local Application of a Warm Solution of Hydrogen Peroxide and Sodium Bicarbonate

	RU Patent No.	Title of the Invention	Composition of the Solution and Its Method of Use
1	2539380	Bruise bleacher	0.03-0.01% Hydrogen peroxide 1.8% Sodium bicarbonate 0.25% EDTA *Injection into the bruise area*
2	2589682	Bleaching agent	0.01-0.03% Hydrogen peroxide 1.7% Sodium bicarbonate 0.125-0.25% Lidocaine hydrochloride 0.25% EDTA *Injection into the bruise area*
3	2573382	Agent for whitening of intradermal bruises	0.01-0.03% Hydrogen peroxide 1.8% Sodium bicarbonate 0.001-0.05% Polysorbate *Injection into the bruise area*
4	2582215	Method for skin discoloration in areas with bruises	0.03% Hydrogen peroxide 1.8% Sodium bicarbonate 0.25% EDTA Local temperature +37 - +42°C *Injection into the bruise area*
5	2586278	Method for skin discoloration in areas with bruises	0.9% Sodium Chloride Local temperature +37 - +42°C *Intradermal injection into the bruise area*
6	2631593	Method for emergency bleaching and blood crust removal from skin in places of squeezed out acne	3% Hydrogen peroxide 10% Sodium bicarbonate *Application to the area affected with acne*
7	2639485	Means of intravital skin whitening near blue eyes	3±0.3% Hydrogen peroxide 2.0% Lidocaine Hydrochloride Sodium hydrochloride in an amount that ensures precipitation at a temperature of +45°C *Application to the skin in the bruise area*
8	2653465	Bleaching opener of dried blood for wrapping bandages adhered to a wound	0.75-1.0% Hydrogen peroxide 1.2% Sodium bicarbonate 0.5% Lidocaine hydrochloride *Wetting bandages stuck to the wound*
9	2647371	Discoloration of blood	3±0.3% Hydrogen peroxide ≥10% Sodium bicarbonate Local temperature +42°C Rehabilitation of wounds and cavities
10	2631592	Method for whitening of sores in the nailbed	3% Hydrogen peroxide 10% Sodium bicarbonate Local temperature +37 - +42°C *Injection into the hematoma in the nailbed*
11	2641386	Method for whitening of sores in the nailbed	0.03% Hydrogen peroxide 1.8% Sodium bicarbonate Local temperature +37 - +42°C *Injection into the hematoma cavity in the nailbed*
12	2679334	Method of emergency bleaching of skin hematomas under the eye	3% Hydrogen peroxide 10% Sodium bicarbonate Local temperature +37 - +42°C *Injection into the hematoma under the eye*

pus and mucus[90]. It has been shown that of suffocation caused by obstructive bronchitis can be eliminated by inhalation of the above aerosol almost immediately, and the positive therapeutic effect can be maintained by repeated inhalations of the drug. For this purpose, an aerosol prepared from a solution of 0.5% hydrogen peroxide and 1.2% sodium bicarbonate at pH 8.5, osmotic activity of 290 mosmol/L water and local temperature of +55°C was recommended. Inhalation of this aerosol is recommended in the treatment of acute suffocation (taken only once, on an as-required basis) and in the prevention of more suffocation episodes (taken 3 times a day). The duration of a single inhalation should not exceed 5min. It has been noted that the developed aerosol of pus solvent facilitates expectoration, breathing, dilates the bronchial lumen and increases the oxygen content in the airways without provoking bronchospasm. The effectiveness of the drug was confirmed by a positive bronchodilator test in patients with bronchial asthma following inhalation of Ventolin.

This technology of local intrapulmonary application of a warm aerosol of an alkaline solution of hydrogen peroxide by inhalation was invented for emergency treatment of purulent obstructive bronchitis (RU Patent No.2735502, 03.11.2020) and for recanalization of the respiratory tract in order to optimize artificial mechanical ventilation in patients with COVID-19 (RU Patent No.2742505, 08.02.2021).

In 2021, the first results of urgent airway recanalization using intrapulmonary injection of pus solvent solution were published[79]. These results were obtained from experiments on non-pedigreed rabbits, as well as on their isolated lungs under conditions of acute subtotal airway filling with artificial mucus. To simulate respiratory obstruction, 30mL of a special gel consisting of starch, gelatin and hemolyzed blood (RU Patent No.2748999, 02.06.2021) heated to a temperature of +37°C was injected into the trachea. Hemolyzed blood was used to enrich the gel with the enzyme catalase and to stain the gel red. The first series of experiments was performed on a model of respiratory obstruction of isolated rabbit lungs. To recanalize the airways, intrapulmonary injection of 1mL of pus solvent solution at +42°C was performed. A solution of 3% hydrogen peroxide and 1.8% sodium hydrogen carbonate was used as pus solvent. One second after the injection, white foam began to emerge from the open end of the trachea. A hissing sound was heard and splashing of foam was observed. At the same time, a change in the color of the lung tissue from scarlet to light scarlet was noted. The second series of experiments was carried out on a live rabbit weighing 1.7kg. 20mL of the developed gel was injected into its trachea. 3 minutes later, the value of blood oxygenation reached 40%. At this moment, intrapulmonary injection of 1mL of 3% hydrogen peroxide and 1.8% sodium hydrogen carbonate solution at +37°C was performed in the right half of the rabbit's chest. The blood oxygenation index was 46%, 50% and 79% after 1s, 3s and 8s respectively. Thereafter, the rabbit started breathing independently[91].

These results allowed the authors to conclude that intrapulmonary injection of warm alkaline hydrogen peroxide solution provides immediate dissolution and foaming of artificial sputum (gel) with the formation of oxygen gas, an increase in blood oxygenation and elimination of severe hypoxia. The developed method was named "Method of pulmonary oxygenation in COVID-19" (RU application No.2021102618, 04.02.2021) and "Method of emergency intrapulmonary blood oxygenation in COVID-19" (RU application No.2021114105, 20.05.2021).

4 DISCUSSION

Infection with the Coronavirus can develop both in healthy children and adults. People with such pulmonary diseases as purulent obstructive bronchitis, tuberculosis, bronchiectasis, cystic fibrosis, helminth infestation, mechanical injury, burns and edema of mucous membranes of the airways are particularly susceptible. The combination of these diseases increases the likelihood of the airways being filled with large amounts of thick mucus, sputum, pus, blood, lymph and products of worm larvae. This significantly worsens the biomechanics of breathing and causes hypoxia. Under these conditions, vaccines, serums, chemotherapeutic drugs, steroidal drugs, NSAIDs, antihistamines and immunotropic agents fail to achieve the desired results in emergency medical care. Modern expectorants and mucolytics are also unsuitable for emergency medical care of respiratory obstruction, regardless of the cause. Other drugs for emergency medical care in children and adults have not yet been developed[92,93].

It has been established that in respiratory obstruction, the true cause of death is not the coronavirus or another lung pathogen, but hypoxia. Because the airways are filled with thick, viscous and sticky biological fluids, much of the air introduced into the lungs from the upper respiratory tract does not reach the alveoli, and so the oxygen is not fully absorbed into the blood. The brain cells are the first to suffer the effects of the lack of oxygen in blood because they maintain a high degree of aerobic metabolism. Under conditions of oxygen deficiency, this eventually becomes the main cause of their death. Nevertheless, oxygen therapy remains the basis of emergency care in critical stages of the disease and in severe hypoxia. However, under conditions of accumulation of biological masses in the airways, artificial lung ventilation carried out by conventional technology does not always effectively increase blood oxygenation. It is believed that with such deterioration of respiratory biomechanics, blood oxygenation is possible only by ECMO. However, ECMO is usually not readily available at the emergency department. Also, it does not eliminate respiratory obstruction, nor does it increase pulmonary ventilation or normalize respiratory biomechanics and intrapulmonary blood oxygenation.

The main ingredients of the new drugs are the very ones that were used in old drugs, namely hydrogen peroxide, sodium bicarbonate and water. Despite this, they have a new mechanism of action. It is reported that a new ratio has been developed for the drugs to have enhanced pyolytic, mucolytic and hemolytic action, while giving them new physical and chemical properties. Moderate alkaline, hyperosmotic and hyperthermic activity has been shown to provide just the right action when used locally. It is very important to note that all the ingredients are safe to use. Water and "drinking soda" are food products, while hydrogen peroxide decomposes very quickly into water and oxygen gas. When acting locally in the upper respiratory tract, hydrogen peroxide has an antiviral effect, suppressing the survival and replication of many viruses, the coronavirus inclusive[94,95]. Hydrogen peroxide is an effective treatment for purulent diseases[70] and is available without prescription[96-98]. It is widely used in otorhinolaryngology and dentistry as a hygienic agent[99,100].

The review shows that a promising technology of airway recanalization after obstruction with biological colloidal fluids containing the catalase enzyme may be based on local application of warm alkaline hydrogen peroxide solution. To achieve this, the alkaline solution of hydrogen peroxide must be injected into the respiratory tract. This can be achieved by inhalation of an appropriate aerosol or by intrapulmonary injection.

The most well-known and safe technology for the introduction of a solution with pyolytic, mucolytic and hemolytic activity is inhalation using standard inhalers and nebulizers[14]. Despite these advantages, the speed and effectiveness of the action of pus solvent aerosol are reduced in cases of severe hypoxia, especially in subtotal and complete airway obstruction with pus and mucus. Aerosol inhalation is a gaseous form of dosing, and cannot deliver more than 1mL of pus solvent solution to the lungs. In bilateral subtotal and total airway obstruction by pus and mucus, urgent and effective recanalization of the airways can be achieved by administration of such a solution in a volume of about 1mL. Inhalation of pus solvent solution into the lungs from the upper airways does not provide immediate interaction of the drug with the peripheral parts of the airways and alveoli at a single inhalation. During the "upper" administration of the aerosol, it dissolves pus, mucus and sputum and blood streaks located at the beginning of the airway, not those in the peripheral parts of the bronchioles and alveoli. In addition, the aerosol penetrates only into the well ventilated, unobstructed parts of the airways and does not penetrate the completely obstructed areas, so it does not provide their immediate recanalization. In addition, the aerosol dissolves mucus, sputum and pus located in the trachea and large-medium bronchi. From here, the foam is propelled towards the mouth and nose and not the alveoli. This causes the peripheral parts of the airways to be clogged with mucus and pus. The latter phenomenon is characteristic of atypical pneumonia and is manifest on x-rays as hypo-inflation or collapse in the peripheral lung.

A completely new and previously unknown technology for the administration of alkaline hydrogen peroxide solution for recanalization of the airways is intrapulmonary injection. The review shows that intrapulmonary injection of alkaline hydrogen peroxide solution is a very promising method of emergency medical care for severe hypoxia caused by total and/or subtotal obstruction of the respiratory tract by biological fluids containing the enzyme catalase. However, no clinical studies on this method have been conducted.

Nevertheless, there is still hope that a way out of this stalemate will be found. There is hope that in the near future, new technology for intrapulmonary administration of alkaline hydrogen peroxide solution will be upgraded, perfected, clinically tested, and added to the arsenal of methods that can be used in the emergency treatment of severe hypoxia secondary to respiratory obstruction by biological fluids containing the enzyme catalase. Inhalation of aerosolized warm alkaline hydrogen peroxide solution in combination with artificial mechanical ventilation can constitute a worthy alternative to ECMO in severe hypoxia caused by respiratory obstruction in patients with COVID-19. This technology of local application of alkaline hydrogen peroxide solution can be used for personalization of emergency medical care for children and adults with a combination of coronavirus infections and bronchiectasis, purulent obstructive bronchitis, cystic fibrosis, trauma to pulmonary tissue, burns and edema of the airway mucosa.

In conclusion, it should be recalled that COVID-19 can not only cause irreversible hypoxic damage and brain cell death, but also acute and/or delayed brain ischemia, which can manifest as various neurological syndromes known as SAH[101]. Since brain cells have the least resistance to hypoxia and ischemia, urgent reoxygenation of the blood is required to keep the patient alive. That is why an immediate intrapulmonary application of alkaline hydrogen peroxide solution in the form of inhalation and/or injection is required in a critical (urgent) situation. It is impossible to realize this in everyday medical practice without the introduction of telemedicine[102].

5 CONCLUSION

A review of scientific literature and inventions showed a real possibility of upgrading existing technologies for recanalization of the respiratory tract and blood oxygenation by the intrapulmonary use of a warm alkaline solution of hydrogen peroxide. The introduction this drug into the respiratory tract can instantly clear the respiratory tract of mucus, sputum, pus and blood and increase pulmonary oxygenation. Inhalation of an aerosol of hydrogen peroxide and sodium bicarbonate increases the effectiveness of mucolytics and expectorants in airway obstruction caused by purulent obstructive bronchitis, and increases the effectiveness of artificial lung ventilation in COVID-19. Therefore, the technology of recanalization of the respiratory tract and blood oxygenation based on the introduction of a warm alkaline solution of hydrogen peroxide into the lumen of the respiratory tract deserves further careful research.

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Conflicts of Interest

The authors had no relevant conflicts of interests. Completed disclosure of interests form is available to view online as supporting information.

Author Contribution

Urakov A and Urakova N were responsible for conceptualization; Muhutdinov N and Yagudin I were responsible for methodology; Suntsova D was responsible for software; Shubina Z and Fisher E were responsible for validation; Fisher E was responsible for formal analysis; Urakov A and Urakova N were responsible for investigation; Svetova M was responsible for resources; Shubina Z was responsible for data curation; Urakova N and Muhutdinov N wrote and prepared the original draft; Urakov A and Fisher E wrote, reviewed and edited the manuscript; Urakov A was responsible for supervision. All authors contributed to draft the first manuscript, read, and approve the final manuscript.

Abbreviation List

ARDS, Acute respiratory distress syndrome
ECMO, Extracorporeal membrane oxygenation

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