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Local Warm Alkaline Hydrogen Peroxide Solutions and Targeted Temperature Management Improve the Treatment of Chronic Wounds

Aleksandr Urakov[1,*], Natalya Urakova[2], Aleksey Reshetnikov[3] and Roman Rozov[4]
[1]Department of General and Clinical Pharmacology, Izhevsk State Medical Academy, Izhevsk, Russia.
[2]Department of Obstetrics and Gynecology, Izhevsk State Medical Academy, Izhevsk, Russia.
[3]Department of Surgical Dentistry, ReSto Dental Clinic, Izhevsk, Russia.
[4]Department of Orthopedic Dentistry and Materials Science with a Course in Orthodontics, First St. Petersburg State Medical University named after Academician I.P. Pavlov, Saint-Petersburg, Russia.

Corresponding author: Aleksandr Urakov (e-mail: urakoval@live.ru).

Abstract: **Introduction:** To date, there is no systematic review of the effect of local hypo-, normo- and hyperthermia on the processes of local interaction of antiseptics with dense biological masses covering the surface of chronic wounds. Accelerated and reliable cleansing of the wound surface from purulent masses still remains an unsolved problem of surgery. **Methods:** 6 inventions were found from beginning to 1986 in databases such as EAPATIS, BYPATENTS, DWPI, DEPATISnet, PATENTSCOPE, Espacenet, RUPTO, USPTO, CIPO, CNIPA, KIPRIS, PatSearch, J-PlatPat, Google Patents and TPO. Due to the small number of inventions, methodological heterogeneity, and differences in the content of their claims, a quantitative meta-analysis could not be performed. **Results:** The prospects of innovative proposals on the influence of local hypothermia and local hyperthermia on the process of local interaction of antiseptic drug solutions with purulent masses and blood on the surface of chronic wounds have been analyzed. The results of the included studies were presented only qualitatively (descriptively). **Conclusion:** The first review of inventions presents formulations of invented drugs created by physicochemical repurposing of hydrogen peroxide from antiseptic to pyolytics, mucolytics, hemolytics, expectorants and oxygen-releasing antihypoxants. Warm alkaline hydrogen peroxide solutions (WAHPSs) have been shown to rapidly and reliably dissolve thick purulent masses, blood clots and dried blood spots, turning them into a lush oxygenating foam. Temperature regimes that optimize the sanitizing and washing action of WAHPSs in the treatment of chronic wounds and accelerate hemostasis in parenchymatous bleeding are specified.

Key Words: pus, blood, pyolytic, hemolytic, hemostatic, sanitation, wound dressings, temperature

I. INTRODUCTION

In some cases, wound healing is delayed for more than 8 weeks, and the wound surface becomes infected and covered with purulent masses. In such cases, chronic wounds are considered to be formed [1]–[4]. The most well-known chronic wounds are venous ulcers of the lower leg due to thrombophlebitis and pressure ulcers (bedsores) due to excessive prolonged ischemia due to mechanical compression of the lower body blood vessels by the body weight of bedridden, infirm, weak and emaciated patients, including children with cerebral palsy [5]–[7]. Unfortunately, there are still no effective drugs and ways of their application for effective treatment of chronic wounds. At the same time, the costs of treating patients are enormous and amount to billions of dollars for countries and individuals [8]–[11]. One of the unsolved problems in the treatment of chronic wounds is their cleansing from purulent masses [7], [12]–[14]. Therefore, it is purulent masses in chronic wounds that are becoming an independent problem in the treatment of people with purulent wounds [15]–[18].

Thus, there is an urgent need to develop an innovative solution for accelerated purulent clearance of chronic wounds [7], [12]–[20]. In our opinion, this solution can be found in the relevant inventions. It is likely that the invented new drugs and methods of their application for dissolving and liquefying dense purulent masses may be particularly promising among them [7], [12], [20]–[22].

II. METHODS

The study was conducted in all period of data bases to 31.01.2024. In addition, we studied the references and conducted a citation search. The protocol of this investigation was not retrospectively recorded in the International Prospective Register of Systematic Reviews (PROSPERO). Additionally, ethical approval was not warranted as this investigation used only published literature (articles and inventions). The methodology of the study was built on the search and analysis of existing inventions and articles. Inventions were searched in electronic databases BYPATENTS, EAPATIS, DEPATISnet, PATENTSCOPE, DWPI, Espacenet, USPTO, CIPO, RUPTO, KIPRIS, CNIPA, TPO, PatSearch, J-PlatPat and Google Patents. Articles were searched in electronic databases SCOPUS, PudMed, Web of Science, Crossref, Google and E-Library.

The criteria for inclusion in the study were drugs and methods (medical technologies) that provide dissolution of thick purulent masses, cleansing of the wound surface from pus, acceleration of healing of chronic wounds due to chemical, biochemical, physicochemical and/or mechanical factors of local interaction. The exclusion criterion for the study was the absence of inventions providing urgent dissolution of thick pus and cleansing of the wound from it. The risk of individual judgment bias was reduced by using the nature of the invention as a generally accepted novelty criterion. A total of 27 inventions were identified, of which 6 were evaluated for consideration.

III. RESULT

Currently, the established treatment regimen for chronic wounds consists of daily renewal of wound dressings and short-term irrigation of the wound surface with antiseptic solutions during the period between the removal of the old dressing and the application of a new dressing [7], [23]. In recent years, the low efficacy of standard antiseptics, saline isotonic and hypertonic solutions has been attributed to the fact that they are used at room temperature. In addition, the solutions of most of them were found to have pH less than 7.0. In other words, it was found that the solutions of antiseptics are acidic. It was concluded that it is because of the cold and acidic properties of modern detergent and antiseptic solutions that they are not conducive to the dissolution of thick pus and the healing of chronic wounds. This conclusion was confirmed by the fact that the use of the same solutions heated to a temperature of +37 - +45 °C and alkaline (with a pH value greater than 7.0) increases the ability of solutions to dissolve dense purulent masses. Therefore, the use of alkaline solutions of antiseptics accelerates the cleansing and healing of chronic wounds [7], [21]–[24]. A few years later, it was found that the most effective pyolitics can be very quickly and cheaply obtained by physicochemical repurposing of hydrogen peroxide solution by heating, giving the solution the "right" osmotic, alkaline activity, and gas saturation under overpressure [7], [20], [22].

The beginning of this new direction in the treatment of chronic wounds was initiated by the invention of "The way of treating long-term non-healing wounds" [25]. The fact is that it was in this invention that the combination of targeted temperature management (TTM) with antiseptic and pyolitic in the form of continuous drug-thermal course therapy of chronic wounds was proposed for the first time:

- Each time during daily sanitizing treatment of a chronic wound, cleaning the wound with a solution of 3% hydrogen peroxide at +37°C was suggested immediately after removal of the wound dressing;
- The open wound surface should be heated for 15 minutes with infrared radiation until the development of persistent thermal hyperemia in it, but not above a temperature of +42°C;
- After that, the wound should be covered with a new wound dressing moistened with a solution of 2-4% sodium chloride at a temperature of +42°C and a warming element should be placed on the dressing, with the help of which the temperature in the wound should be maintained within +37°C during the whole period until the next sanation (hygiene) of the wound.

It should be noted that the therapeutic effect obtained by the authors as a result of using this method of treatment of chronic wounds was very good. It was reported that in 2 days after the beginning of the application of this method in patients with pressure sores (compression ulcers) in chronic wounds began rapid formation of granulation tissue. Daily renewal of wound dressings and irrigation of the open wound surface of chronic wounds with a warm solution of 3% hydrogen peroxide completely cleared the wound surface of purulent masses and ensured healing of chronic wounds in 7-14 days [7], [25].

Subsequently, the possibility of potentiation of local cleansing effect of warm hydrogen peroxide solution on dense purulent masses was discovered by replacing acid activity in hydrogen peroxide solution with alkaline activity. At the same time, in order to exclude alkaline burn, it was proposed to limit the alkaline activity of hydrogen peroxide solution within pH 8.4. For this purpose, it was suggested to use sodium bicarbonate [12], [20]–[24]. Then another discovery was made. It was found that additional dissolution of gases (carbon dioxide gas, oxygen gas, or inert gases) in WAHPSs under overpressure increased the efficiency of the pyolytic activity of WAHPss [20], [26]–[29]. Very soon, antiseptics with pyolytic activity were called "pyolytics" [19], and warm alkaline hydrogen peroxide solutions (WAHPSs) were proposed as a reference representative of this group [30], [31].

The above discoveries were first described in such inventions as "Softening agent for thick and viscous pus" and "Bleaching cleanser of dentures" [32], [33]. In particular, a solution of 2.0-10.0 % sodium bicarbonate and 3±0.3 % hydrogen peroxide heated to a temperature of 37-42 °C, which was enriched with oxygen gas due to an overpressure of 0.2 atm, was proposed as a bleaching cleanser of dentures. This solution was shown to have pyolytic, hemolytic,

deodorizing, bleaching and disinfectant effects when applied topically. It was reported that such local action is achieved due to hyperthermic softening of dense purulent masses (and other colloidal biological masses), alkaline saponification of lipid and protein-lipid complexes that form the basis of pus, cavitation loosening of dense masses, their dissolution and oxidative discoloration.

By now it has been established that warm hydrogen peroxide solution "explodes" and decolorizes not only purulent masses, but also blood, clots and dry blood spots, sputum, mucus and serous fluid of the respiratory tract, dental plaque and meconium [7], [18]–[22]. The fact is that the mechanism of local explosive and discoloring action of WAHPSs on the above biological masses is provided by the transformation of hydrogen peroxide into oxygen and water due to the presence of the enzyme catalase. It has been shown that irrigation of various surfaces with warm hydrogen peroxide solutions heats purulent masses (or other colloidal liquids) from +25 °C to +37 °C, which softens them due to relative local hyperthermia. Due to the fact that purulent masses (and many other colloidal biological masses) contain the enzyme catalase, the interaction of warm hydrogen peroxide solution with them promotes intensive metabolism of the drug and its rapid transformation into water and oxygen gas. Moreover, this process is very intense and resembles a "cold boiling". The very intensive release of oxygen, which forms the process of cold boiling, "explodes" the purulent masses and turns them into oxygen foam [25]–[28], [30], [31].

At the same time, the released oxygen gas has antiseptic, antihypoxic, deodorizing effect on the wound surface and stimulating effect on aerobic metabolism of granulation tissue [7], [27]. The process of oxygen extraction from hydrogen peroxide is so effective that hydrogen peroxide has been proposed to relieve bronchial asthma attack and acute respiratory syndrome (ARDS) in COVID-19 by inhalation and intrapulmonary injection of WAHPs. Such a proposal first formed the basis of inventions such as "Aerosol for inhalations in obstructive bronchitis", "Aerosol for invasive mechanical ventilation in COVID-19" and "Warm alkaline solution of hydrogen peroxide for intrapulmonary injection" [34]–[36].

IV. DISCUSSION

Initially, there were only a few reports that local warming therapy (LWT) could help treat chronic wounds such as pressure sores, venous ulcers, arterial ulcers, and diabetic foot ulcers [37]–[39]. However, for a long time, there was no convincing evidence for the correctness of this assumption. This study aimed to find evidence for the feasibility of LWT in the treatment of chronic wounds. From the review of inventions and scientific articles, it is evident that one of the important factors in the long-term healing of chronic wounds is the local temperature of the wound bed, purulent masses covering the wound surface, and solutions of standard washing and antiseptic drugs [7], [27], [40].

The fact that the wound bed, pus, and medications usually have a temperature below +37 °C has been known for a long time. However, it was previously thought that a wound bed temperature between +31 and +33 °C was normal [41]–[43]. Therefore, the magnitude of the local temperature in the wound was not considered to be a factor in wound healing [44].

Nevertheless, in 2002, a method of treating chronic wounds was invented based on maintaining local hyperthermia in the wound bed continuously for several days by artificially heating the wound and using warm antiseptic solutions: hydrogen peroxide and hypertonic sodium chloride solution [25]. It has been reported that infrared heating of an open wound to +42 °C stimulates metabolism according to Arrhenius' law and accelerates the healing process. Moreover, the proposed level of local hyperthermia is completely safe, as it excludes thermal burn of granulation tissue. In addition, the authors showed that the additional use of hypertonic solution of 2-4% sodium chloride at a temperature of +42 °C for irrigation of the wound and wound dressing, as well as the warming of the wetted dressing with a coolant up to +37 °C until the next regular wound sanitation turns the wound dressing into a warm moisturizing compress [7].

It was shown that such a warm moisturizing compress with hypertonic sodium chloride solution creates a local "greenhouse" effect in the wound, which preserves moisture and a safe level of local hyperthermia in the wound, as well as provides antiseptic action. All this increases the effectiveness of the fight against infectious agents and accelerates the healing of chronic wounds [7]. Moreover, it is very convenient to use infrared thermography with a thermal imager to control the dynamics of local hyperthermia [45]–[49].

A few years later, the possibility of repurposing antiseptics into pyolytics by changing their physicochemical properties was discovered [7], [20]–[23]. Warm alkaline hydrogen peroxide solutions (WAHPSs) have been shown to be leaders in dissolving thick purulent masses [19], [26]–[31]. However, the search for other options for rapid dissolution of thick purulent masses using hydrogen peroxide antiseptic did not stop there. To increase the efficiency of removing thick purulent masses with WAHPSs from various surfaces, including the wound surface, it has been proposed to saturate WAHPSs solutions with pressurized gases [20], [21], [31]. Studies have shown that due to moderate hyperthermia, alkaline activity and hypergassing, WAHPSs acquire a unique physicochemical activity that gives them leadership in dissolving thick purulent masses [27]. Therefore, in 2023, it was first proposed to complement the treatment of chronic wounds with pyolytics and warm wound dressings. In this case, solutions of 3% hydrogen peroxide and 2-10% sodium bicarbonate, heated to a temperature of +37 - +45 °C and enriched with dissolved carbon dioxide or oxygen due to excess pressure of 0.2 atm, were proposed as pyolytics.

V. CONCLUSION

Due to purposeful physicochemical repurposing of hydrogen peroxide in the beginning of the 21st century in Russia,

a new group of medicines was developed - warm alkaline hydrogen peroxide solutions (WAHPSs). It was found that heating solutions of 3% hydrogen peroxide and 2 – 10% sodium bicarbonate to the temperature of +37 - +45 °C, alkalizing them to pH 8.4 - 8.5 and increasing the content of dissolved carbon dioxide gas or oxygen gas in them due to excess pressure gives them a unique physical and chemical activity. Due to this nonspecific physicochemical activity, WAHPSs have a unique local action on purulent masses (and other biological masses containing the enzyme catalase): pyolytic, bleaching, deodorizing, antihypoxic, oxygen-releasing, disinfecting, detergent and foaming action [50]–[53]. The results of laboratory and experimental studies have shown that irrigation of chronic wounds with WAHPSs and application of prolonged local hyperthermia in wounds shortens the removal of purulent masses from the wound surface and healing of chronic wounds. However, for a definitive conclusion, further research needs to be continued to better understand this topic.

ETHICAL STATEMENT

The present article no study with human participants or animals performed by any of the authors.

AUTHORS CONTRIBUTION

AU and NU data collection and writing, AR and RR data collection & idea of research and proof reading, NU and AU analysed and interpreted data. All authors have read and approved the final manuscript.

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CONFLICTS OF INTEREST

No conflicts of interest have been declared by the authors.

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