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Antiseptic pyolytics and warming wet compresses improve the prospect of healing chronic wounds

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Abstract

Infection and suppuration of chronic wounds reduce the effectiveness of their treatment with a course of antibiotics and antiseptics combined with frequently renewed dressings. Therefore, daily short-term procedures of cleaning wounds from purulent-necrotic masses by mechanical methods, including the use of cleansing solutions and necrophage fly larvae, are also part of the general practice of chronic wound treatment. But even they do not always provide rapid healing of chronic wounds. In this connection, it is suggested to supplement the treatment of chronic wounds with preparations dissolving dense pus and wound dressings made in the form of warm moist compresses creating a local greenhouse effect in the wounds. Solutions of 3% hydrogen peroxide and 2–10% sodium bicarbonate heated to a temperature of 37°–45°C, possessing alkaline activity at pH 8.4–8.5 and enriched with dissolved carbon dioxide or oxygen gas (due to overpressure of 0.2 atm were suggested as pyolytic drugs. The first results of the use of pyolytics and warm moist dressings-compresses in the treatment of chronic wounds demonstrate a wound-healing effect. It is suggested to consider sanitizing therapy with pyolytics and warm moist wound dressings-compresses as an alternative to the use of modern cleansing solutions and artificial introduction of larvae of the necrophage fly into the purulent masses of chronic wounds to dissolve dense pus and accelerate the healing process.

Keywords

Chronic wounds, growth factors, wound infection, wound healing, local hyperthermia, antiseptics, wound dressings

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Introduction

Usually, acute, surgical wounds heal on their own in 7–10 days in healthy people and do not require the use of special wound-healing medications. However, sometimes wound healing is delayed and the wound surface becomes infected and covered with purulent masses. When wounds do not heal for more than 8–12 weeks, it is considered that chronic wounds have formed [1].

To date, the following causes of delayed wound healing have been identified: poor circulation (ischemia or venous stasis), infection, elevated blood sugar levels in diabetes, and immune suppression [1, 2]. The best-known chronic wounds are pressure ulcers (PUs) and venous ulcers of the lower leg. Typically, venous ulcers of the lower leg arise due to venous stasis from thrombophlebitis, and PUs arise from excessively prolonged ischemia due to mechanical compression of the blood vessels of the lower body by the body weight of bedridden, infirm, frail, and exhausted patients, including children with cerebral palsy [3–5].

Unfortunately, chronic wounds are still a global problem because effective treatments for them have not been conclusively developed, and the cost of treating sick people is enormous and includes billions of dollars for countries and individuals. In particular, PUs and diabetic foot ulcers make up the most significant portion of these hard-to-heal wounds [6]. At the same time, PUs increase mortality by 2–6 times [3, 7, 8].

Traditions of chronic wound care have relied on the use of natural materials. Current advanced technologies in the treatment of chronic wounds involve the use of nanofiber wound dressings that accelerate the healing process. It is reported that these dressings can promote tissue regeneration, wound fluid transport, and air elasticity for cell proliferation and regeneration [9].

One of the unresolved problems in the treatment of chronic wounds is their infection because it causes pus masses to appear in the wounds, which makes it difficult to heal. Because of this, it is often the purulent masses in chronic wounds that become an independent treatment problem for people with purulent wounds [10].

Wound infection and wound dressings

There is no doubt that an important role in the formation of chronic wounds is played by the infectious process and the purulent masses born by it [10]. That is why two main strategies are used for the prevention and treatment of chronic wounds: systemic antibiotics and antiseptics. However, in recent years, the systemic use of antibiotics in chronic wounds worldwide has been alarming [11]. However, the effectiveness of antimicrobial drugs in treating chronic wounds is still not high enough. In this case, great hopes are pinned on eliminating the resistance of infection to known antibiotics [11–15]. However, the search for effective antimicrobial agents and improvements in their use for the successful treatment of chronic wounds continues [16]. In recent years, several new approaches have been proposed for the treatment of chronic wounds. One of these innovations is the improvement of methods of drug delivery to the wound [6, 9, 12, 14–16]. There is little evidence of resistance to new antimicrobial agents such: as modern antiseptics, silver, honey, iodine, and xylitol. Topical antibiotics are effective for a short period of time, are inactivated by debris can select out resistant strains of bacteria, and are prohibited in modern wound treatment. It has been reported that modern antiseptics such as octenidine dichloride, polyhexamethyl biguanide (PHMB), and povidone-iodine are noncytotoxic solutions, reduce the bacterial burden and remove surface contaminants and debris while minimizing trauma. Even in very difficult wounds e.g., neoplastic ulceration efficacy of modern antiseptics and therapies can be effective especially when assessing clinical and microbiological aspects [17, 18]. In turn, topical or systemic infection of the chronic wound should be treated by systemic antibiotic therapy—oral or parenteral.

At the same time the usefulness of wound dressings, which have been traditionally used in chronic wound treatment since long ago, is not questioned [19–21]. For the healing of chronic wounds, various wound dressings are used, which can be made on the basis of hydrogels, silver-coated membranes, and allogeneic skin plates. In particular, special wound dressings made of polyurethane foam, non-adhesive gel-forming dressings, so-called antimicrobial dressings, wound dressings with activated carbon or metronidazole gel, etc. are used for the treatment of chronic wounds [22]. The fact is that treatment of chronic wounds traditionally starts exactly with regular mechanical cleansing of them from purulent and necrotic masses and wound surface closure with wound dressings, bandages, and/or biofilms [1]. Therefore, dressing acute and chronic wounds is one of the main activities of every practitioner. It has been shown that different dressings are used for this purpose: from classic types of moisture-retaining dressings to silver-coated varieties and biological dressings that serve as skin substitutes. It has also been shown that proper use of these dressings can help keep the wound bed moist, which promotes epithelial migration, angiogenesis, growth factor preservation, and autolytic sanitation [9, 23–25].

However, a network meta-analysis (NMA) of data from 39 studies (21 dressings and topical agents for PUs treatment were evaluated) did not accurately determine which dressings or topical agents were most likely to heal PUs, and it was generally unclear whether the treatments considered were more effective than gauze with physiological (saline) solution [24]. It has been shown that, on the one hand, wound infection can colonize wound dressings and biofilms and contribute to wound infection, and on the other hand, wound dressings can adsorb microbial toxins and reduce wound toxicity [24–26]. In parallel, other researchers came to the conclusion that the closure of chronic wounds by bacterial biofilms can be an obstacle to their healing, and the artificial introduction of larvae of the necrophage fly into the purulent masses of chronic wounds dissolves dense pus and accelerates the healing process [27]. The fact is that infection of chronic wounds causes their suppuration, and the appearance of purulent masses slows down healing [28]. Therefore, the dissolution of purulent masses using larval therapy accelerates the healing of chronic wounds.

Consequently, successful treatment of chronic wounds is impossible without complete removal of purulent masses from their surface. However, no chemotherapeutic drugs and wound dressings effective in dissolving dense pus in purulent wounds have been developed so far [23].

On the other hand, there is an opinion that steroidal anti-inflammatory drugs can play a positive role in wound healing [29]. However, in recent years, injectable dexamethasone has been shown to inhibit wound healing in mouse experiments [30, 31]. Therefore, the role of steroidal anti-inflammatory drugs in chronic wound healing remains unclear.

Pyolytics

Treatment of chronic wounds usually includes wound irrigation, debridement, and using modern wound dressing changed every few days. More than 30 years ago, treatment of chronic wounds included daily renewal of dressings in combination with wound sanitation by irrigation with physiological (saline) solution, 2–10% hypertonic sodium chloride solution, and/or 3–6% hydrogen peroxide solution [32]. But since the end of the 20th century, irrigation with 2–10% hypertonic NaCl and 3–6% H_2O_2 is prohibited as they have a toxic effect on cells essential to healing and do not kill bacteria and destroy biofilm [33]. However, until now there is no clarity in understanding what is the mechanism of local action of cleansing solutions and wound dressings on pus masses and the healing process of chronic wounds [1].

In this connection, it is encouraging to consider not only the specific activity of the drugs in their composition but also the non-specific activity of the drug solutions due to their physical and chemical properties such as the value of temperature, osmotic activity, acid (alkaline) activity, degree of carbonation, etc. [34]. The following paradox has been reported: the generally accepted mechanism of action of drug solutions takes into account the specific activity of the drugs included in the solutions but does not take into account the nonspecific activity of the drug's solutions [34–36]. It has been shown that the generally accepted representation is sufficient to explain the mechanism of general action of drugs on the whole body (i.e., after absorption of drugs into the blood), but it is insufficient to explain the mechanism of local action of drug solutions on purulent masses during local interaction. In turn, expanding the information on the mechanism of action of drug solutions through the information on their physicochemical properties explains well the mechanism of their local action on purulent masses and wound surfaces of chronic wounds. In particular, it was reported that cleansing solutions having room temperature within 24°C and acidic activity at pH less than 7.0 do not contribute to the dissolution of thick pus and the healing of chronic wounds. At the same time the same solutions, when heated to a temperature of 37°–45°C and when the acid activity changes to alkaline activity at pH 8.4–8.5, contribute to the dissolution of thick pus masses and the cleansing of chronic wounds [35, 36].

Analysis of this suggestion showed that it is not so much new as it is well-forgotten old [36]. It has been shown that the mentioned physical-chemical factors of local interaction (heating to body temperature or higher, as well as alkalizing) were used by mankind since ancient times to treat chronic wounds and/or to quickly remove thick pus masses from the surface of chronic wounds and mucous membranes of airways in purulent inflammation of the nose, nasopharynx, larynx, trachea, and bronchi. Initially, people used hot water steam, warm solution, ashes (or ash infusion), and hot-water bottles (or their substitutes) for this purpose [32]. Then they were replaced by specially developed physiotherapy and balneotherapy. In recent years, the treatment strategy for chronic wounds has relied on oxygen enrichment of dressings, which aims to prevent hypoxia in the wound. New wound models and treatments are being developed [37, 38].

At the same time, until the beginning of the 21st century, researchers did not pay close attention to warm alkaline solutions and vapors (aerosols). A return to the forgotten tradition of chronic wound care began with the invention of "A way of treating long-term non-healing wounds" (RU Patent No. 2187287, 20.08.2002) [35, 36]. In this invention, it was proposed to rely not on local chemotherapeutics and steroids for wound healing in the course treatment of chronic wounds, but on local physiotherapy including local hyperthermia and local antiseptics. In this invention, after removing the wound dressing, it was proposed to clean the wound with a 3% hydrogen peroxide solution at a temperature of 37°C, and then to warm the open wound surface for 15 minutes using infrared radiation until persistent thermal hyperemia, but not higher than a temperature of 42°C. Then it was suggested to cover the wound with a new wound dressing, moisten it with a solution of 2–4% sodium chloride at a temperature of 42°C and then apply a warming element on the dressing with which to maintain the temperature in the wound within 37°C during the whole period until the next sanitation (hygiene) of the wound. In the description of this invention, examples of the effectiveness of the treatment of chronic wounds using the invented method were reported. In these examples, the following advantages of the new method were shown: in patients with bedsores (compression ulcers) in the complete absence of granulation tissue in chronic wounds, the use of the new method promoted the appearance of granulation in 2–3 days and accelerated the healing of chronic wounds.

By now the mechanism of action of this complex of physiotherapy has been almost completely clarified [35]. It has been shown that daily renewal of the wound dressing and short-term irrigation of the open wound surface of chronic wounds with a 3% hydrogen peroxide solution at 37°C clears the wound surface of pus masses. The point is that irrigation of a wound with a warm solution excludes cooling of pus in an open wound and its hardening with temperature decrease. On the other hand, pus masses contain catalase, which splits hydrogen peroxide into oxygen gas and water, which provides "explosive" destruction of thick pus masses and their mechanical removal through a cold boiling process. At the same time, the released oxygen gas has an antiseptic, antihypoxic, deodorizing effect on the wound surface and stimulating effect on granulation tissue aerobic metabolism.

Infrared heating of an open wound to 42°C for 15 minutes was found to stimulate metabolism according to the Arrhenius law and accelerate the healing process, but exclude thermal burns of granulation tissue. Subsequent use of a hypertonic solution of 2–4% sodium chloride at 42°C for irrigation of the wound and a new wound dressing, as well as warming the moistened dressing with a heat carrier to 37°C until the next wound sanitation turns the wound dressing into a warm humidifying compress. In turn, such a warm humidifying compress with hypertonic sodium chloride solution creates a local "greenhouse" effect in the wound, which preserves moisture in the wound and a safe level of local hyperthermia, and also provides antiseptic action, which allows successful fighting of infectious agents, accelerating the appearance of granulation tissue and the healing of chronic wounds (RU Patent No. 2187287, 20.08.2002) [35, 36].

In addition, the possibility of potentiating the local cleansing effect of a warm hydrogen peroxide solution on thick pus masses by providing the solution with alkaline activity within pH 8.4 using sodium bicarbonate and additional dissolution of carbon dioxide gas or oxygen gas under excessive pressure has been shown. These suggestions were first specified in the invention "Softening agent for thick and viscous pus" (Ru Patent No. 2360685, 10.07.2009) and "Bleaching cleanser of dentures" (RU Patent No. 2659952, 04.07.2018). 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 and enriched with oxygen gas due to excess pressure of 0.2 atm was proposed as a bleaching denture cleanser. When applied topically, this solution has been shown to have pyolytic, hemolytic, deodorizing, bleaching, and disinfecting effects. It has been reported that this local action is achieved through hyperthermal softening of dense pus 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.

Thus, due to moderate hyperthermia, alkaline activity, and hypergasity, warm alkaline hydrogen peroxide solution (WAHPS) acquires a unique physical-chemical activity, which ensures its leadership in dissolving thick pus masses [35]. Therefore, WAHPSs were first called "Pus Dissolvers" and then "Pyolytics" [39]. In this regard, sanitizing therapy of chronic wounds with WAHPSs can be considered as an alternative to the artificial injection of necrophage fly larvae into purulent masses of chronic wounds to dissolve dense pus and accelerate the healing process [27]. The described features of the local action of antiseptic pyolytics and warming wet compresses do not contradict the objectives of chronic wound therapy. Moreover, WAHPSs and warming wet compresses have some advantages over the known chemotherapy drugs, since it is reported that specialists are not aware of any chemotherapy drug that has properties that promote wound healing [40, 41].

Conclusion

At the beginning of the 21st century, the repurposing of hydrogen peroxide and sodium bicarbonate antiseptics into antiseptic pyolytics was completed. The success of the development of new drugs was ensured by a targeted change in the physicochemical properties of the solutions of these drugs. It has been shown that by heating to 37°–45°C, by alkalizing to pH 8.4–8.5, and by increasing the content of dissolved carbon dioxide gas or oxygen gas (due to overpressure of 0.2 atm) the solutions of 3% hydrogen peroxide and 2–10% sodium bicarbonate acquire unique physico-chemical activity. Due to this nonspecific activity, WAHPSs in local interaction with purulent masses have the following local effects: pyolytic, bleaching, deodorizing, antihypoxic, and disinfecting effects. In parallel, it was proposed to upgrade the wound dressing into a warm moist wound dressing compress. It is reported that the first results of the application of the developed antiseptic pyolytics and warm moist wound dressings-compresses during the course treatment of chronic wounds showed the possibility of optimizing the development of granulation tissue in them, which, in turn, can accelerate the healing of chronic wounds. In the future, we will have to conduct many different studies that are necessary to clarify the advantages and disadvantages of proposed warm alkaline solutions of hydrogen peroxide containing certain gases. In the future, it is necessary not only to clarify the advantages and disadvantages of antiseptic pyolytics, but also to develop details of medical technologies for their use in the treatment of various types of chronic wounds. Nevertheless, the given preliminary data give hope that the latest achievements obtained in the field of physico-chemical pharmacology of antiseptics can be used in the future for the search and development of new drugs and methods of their application to optimize the treatment of chronic wounds.

Abbreviations

PUs: pressure ulcers

WAHPS: warm alkaline hydrogen peroxide solution

Declarations

Author contributions

AU: Conceptualization, Investigation & Writing-original draft, Supervision. NU: Writing—original draft. EF: Investigation, Validation. A Shchemeleva: Writing—original draft. A Stolyarenko: Writing—review & editing. VM: Investigation, Validation. MZ: Writing—original draft. All authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

The datasets for this manuscript are not publicly available due to trade secrets, as the data belong to the Institute of Thermology. The fact is that the Institute of Thermology is a private. Requests for accessing the data sets should be directed to Aleksandr Urakov, urakoval@live.ru.

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