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Review Article

Pyolytics as a product of the physical–chemical repurposing of antiseptics and an alternative to larval therapy for chronic wounds

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ABSTRACT

The traditional treatment of chronic wounds involves daily cleansing of the wound surface from purulent necrotic masses using mechanical and medicinal methods, accompanied by regular replacement of wound dressing. In this case, medicinal wound cleansing lasts 10–15 mins from the time of replacement of the old wound dressing with the new one. According to established practice, medicinal sanitation of infected and purulent wounds during dressing involves irrigation of the wound surface with cleansing solutions, antiseptics, and/or antibiotics. In severe cases, the above therapy is supplemented with live larvae of the necrophage fly, which are injected into purulent necrotic masses and left in them under wound dressing until wounds are completely cleansed from pus. Nevertheless, the generally accepted course of treatment of chronic wounds remains ineffective. The use of pyolytics and their supplementation with wound dressings in the form of warm wet compresses, which create a local greenhouse effect in wounds, was reported to accelerate the healing of chronic wounds. Pyolytics are a group of antiseptics developed in Russia. They are warm alkaline solutions of hydrogen peroxide; when they interact with purulent necrotic masses, these solutions dissolve very quickly and foam them. Because of the interaction with pyolytics, thick purulent masses immediately turn into fluffy oxygenated foam. Pyolytics have been developed because of the physicochemical repurposing of aqueous solutions of sodium hydrogen carbonate and hydrogen peroxide. To accelerate the healing of chronic wounds, a recommendation was to irrigate the surface of chronic wounds with 3% hydrogen peroxide and 2–10% sodium bicarbonate solutions, heated to 37–45°C, which have alkaline activity at pH 8.4–8.5 and are enriched with dissolved carbon dioxide or oxygen (due to excess pressure of 0.2 atm). This study presented the importance of treating chronic wounds using politics and treatment outcomes using pyolytics along with warm moist dressing compresses, demonstrating a wound-healing effect. Consequently, physical and chemical reprofiling of antiseptics may make them effective pyolytics, and the combination of pyolytics with warm wound dressings such as warm moist compresses, which create a local greenhouse effect on wounds, accelerates the healing of chronic wounds.

Keywords: physical–chemical repurposing; antiseptics; wound dressings; purulent masses; chronic wounds; wound healing; localized hyperthermia.

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Обзорная статья

Пиолитики как продукты физико-химического перепрофилирования антисептиков и альтернатива терапии личинками мясной мухи хронических ран

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АННОТАЦИЯ

Традиционное лечение пациентов с хроническими ранами представляет собой курс ежедневных однократных процедур очищения поверхности ран от гнойно-некротических масс механическими и лекарственными методами, сопровождаемыми регулярным обновлением раневых повязок. При этом процедуры лекарственного очищения ран длятся 10–15 мин в промежутках между заменой «старых» раневых повязок на «новые». По сложившейся практике лекарственное санирование инфицированных и гнойных ран во время перевязок заключается в орошении раневой поверхности очищающими растворами, растворами антисептиков и/или антибиотиков. В тяжелых случаях указанная терапия дополняется живыми личинками мухи-некрофага, которых вводят в гнойно-некротические массы и оставляют под раневыми повязками вплоть до полного очищения ран от гноя. Тем не менее эффективность общепринятого курсового лечения хронических ран остается недостаточно высокой. Ускорить заживление хронических ран позволяет применение пиолитиков и дополнение их раневыми повязками, выполненными в виде теплых влажных компрессов, создающих в ранах местный парниковый эффект. Пиолитики — это разработанная в России группа антисептиков, представляющих собой теплые щелочные растворы перекиси водорода, которые при взаимодействии с гнойно-некротическими массами очень быстро растворяют и вспенивают их. В результате взаимодействия с пиолитиками густые гнойные массы тут же превращаются в пушистую кислородную пену. Показано, что пиолитики были разработаны благодаря физико-химическому перепрофилированию водных растворов гидрокарбоната натрия и перекиси водорода. Для ускорения заживления хронических ран было предложено орошать поверхность хронических ран 3 % раствором перекиси водорода и 2–10 % раствором бикарбоната натрия, нагретым до температуры 37–45 °C, обладающим щелочной активностью при pH 8,4–8,5 и обогащенным растворенным углекислым газом или кислородом (за счет избыточного давления 0,2 атм). Указана сущность изобретенной технологии лечения хронических ран с использованием пиолитиков и приведены результаты лечения хронических ран пиолитиками в комбинации с теплыми влажными повязками-компрессами, которые подтверждают наличие ранозаживляющего эффекта. Следовательно, физико-химическое перепрофилирование антисептиков позволяет превращать их в эффективные пиолитики, а комбинация пиолитиков с теплыми раневыми повязками, выполненными в виде теплых влажных компрессов, создающими в ранах местный парниковый эффект, ускоряет заживление хронических ран.

Ключевые слова: физико-химическое перепрофилирование; антисептики; пиолитики; раневые повязки; гнойные массы; хронические раны; заживление ран; локальная гипертермия.

Как цитировать

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INTRODUCTION

Chronic wounds are an ongoing medical issue that has yet to be addressed. Poor circulation, diabetes mellitus, a weakened immune system, or advanced age are common causes of delayed wound healing [1–4]. Most wounds heal within a week, but some may take several weeks or longer. A wound is considered chronic if it has not healed within 8 weeks [5]. Chronic wounds, particularly venous ulcers in the lower extremities [6], require treatment. Therapeutic treatment involves regular cleansing of purulent necrotic masses and wound closure with dressings and bandages.

Unfortunately, no definitive drugs or treatments for chronic wounds have yet been developed [7]. Treating chronic wound patients is expensive [7–9]. Diabetic foot ulcers are particularly challenging to treat. Diabetic foot ulcers affect an estimated 19 million people worldwide each year. In about 80% of cases, individuals diagnosed with diabetes mellitus are treated with lower limb amputation, which increases the risk of patient mortality [10, 11].

Chronic wound treatment must address the unsolved issue of infection and suppuration [12]. The presence of purulent necrotic masses on the wound surface often complicates and delays patient care [13, 14]. The presence of purulent masses in chronic wounds and the lack of effective pyolytic drugs in normal medical care contribute to low treatment efficiency and high financial costs [16].

TRADITIONAL TREATMENT OF CHRONIC WOUNDS

Infection-induced purulent masses are essential in developing chronic wounds [17]. Cleaning solutions, topical antiseptics, and antibiotics are necessary to sanitize chronic wounds due to the infectious contamination that causes purulent masses [18, 19]. These therapeutic solutions irrigate chronic wounds without regulating the local temperature or alkaline and osmotic activity. Under these conditions, treatment with detergents, antiseptics, and chemotherapeutic drugs is unsuccessful [18–20]. However, efforts to increase the efficacy of antimicrobial drugs continue using various methods.

Previously, new antibiotics were associated with increased chances of wound treatment success. However, in recent years, wound dressings have been actively updated to optimize medicine administration to the wound [21–23]. Antibiotic resistance has emerged among infectious agents. Nevertheless, regular dressing changes remain among the most important success factors in treating chronic wounds [24]. In this case, the surface of the chronic wound is usually treated mechanically and medically while the soiled wound dressing is changed for a clean one. An open wound is generally treated for 10–15 min before a new dressing is placed on the chronic wound [25]. Therefore, wound dressings must be used and replaced regularly to treat chronic wounds successfully.

Dressings that keep moisture in the wound bed are designed to improve sanitation and speed up the healing process of chronic wounds [24–27]. However, insufficient data support the assertion that modernized dressings are more effective in expediting the healing of chronic wounds than conventional gauze with a sodium chloride (food salt) solution [28–31]. Conventional wound dressings are ineffective in promoting healing in chronic wounds with a high exudation rate. Therefore, there is a need to develop innovative dressings. To address these issues, researchers have developed various low-cost and innovative wound dressings [32]. However, achieving significant success in treating chronic wounds using these new dressings remains challenging. Furthermore, in some cases, dressings might lead to wound suppuration [33, 34]. Covering the surface of chronic wounds with biofilm dressings might worsen wound sanitation.

For decades, necrophagous meat fly larvae have been used to clean purulent necrotic wounds and speed up the healing process of chronic wounds [35–37]. Larvae facilitate the healing of purulent wounds by promoting the sanitation of purulent necrotic tissues. The use of larvae for therapeutic purposes gained popularity in the early ninth century but declined in the 1940s with the advent of antiseptic wound treatment and antibiotics. However, because of the recent emergence of microbial resistance to chemotherapeutic drugs, larvae have regained popularity for treating complex wounds. Larvae perform wound sanitation by mechanically disrupting dense purulent masses by continuous movement, secreting proteolytic enzymes and antibacterial substances, and ingesting and digesting bacteria and necrotic tissue [38–41]. In addition, the larvae affect the epidermal growth factor and interleukin 6. Wound sanitation using necrophagous fly larvae was shown to be helpful in 85% of patients with chronic wounds. Therefore, larval therapy has been proposed as a potentially effective treatment for certain chronic wounds.

Purulent necrotic masses often interfere with the healing process of chronic wounds. Pyolytics are not included in regular medical care, and traditional methods of treating chronic wounds with sanitizing agents, chemotherapeutic drugs, and wound dressings fail to loosen and dissolve these dense masses. However, the larvae of the necrophagous meat fly are more efficacious [42–44]. Consequently, the complexity of drug treatment for chronic wounds, which necessitates the use of larval therapy, stems from a lack of alternative drugs. Pyolytics are currently not a viable option.

ANTISEPTIC PYOLYTICS AS AN ALTERNATIVE TO MEAT FLY LARVAE

The conventional technique for treating chronic wounds involves covering the wound surface with a wound dressing for approximately 1 day. After this, the soiled dressing is removed, and the wound is opened for 10–15 min. During this time, the wound is treated with detergents, antiseptics, and/or chemotherapeutic drugs. Finally, a fresh, clean wound dressing is used [25]. Wound dressings are typically changed every day, and the open wound surface is irrigated with boiling water, 0.9% sodium chloride solution (saline), conventional detergents, topical antiseptics, and/or chemotherapeutic drugs [27]. However, the primary objective of drug sanitation for chronic wounds is typically disinfection rather than the removal of purulent necrotic masses [45]. Antiseptics, rather than pyolytics, are currently used to treat chronic wounds. Furthermore, solutions with a high concentration of antiseptics thicken rather than liquefy purulent masses [45–47]. Therefore, in cases where liquefaction of thick purulent necrotic masses in chronic wounds is complex, meat fly larvae are still nurtured in the wounds [48].

According to several authors, the local effect of drugs on biological tissues, including purulent masses, is determined by their nonspecific physicochemical activity rather than their particular pharmacological activity [47, 49–54]. According to this proposal, it is recommended to consider both the specific activity of drugs contained in finished pharmaceutical preparations (e.g., tablets, solutions, and aerosols) and their nonspecific activity caused by physicochemical properties, such as temperature, osmotic pressure, acidity (or alkalinity), and carbonation [55]. Until recently, the mechanism of action of drug solutions was purely determined by their particular activity, with no respect for their physicochemical properties and relevant local interaction factors with biological tissues. This approach is incomplete. This representation accurately depicts the mechanism of action of drugs on the whole organism following absorption into the blood. However, it does not fully explain how drugs function locally when interacting with biological tissues. The mechanical and physicochemical properties of drugs in certain dosage forms can help identify the mechanism of local action on purulent masses and wound surfaces in chronic wounds. Cold cleansing solutions at 24 °C and acid activity at pH <7.0 do not dissolve dense pus. However, following heating to 37°C–45°C and switching from acid to alkaline activity at a pH of 8.4–8.5, the same solutions dissolve dense purulent masses [45, 47, 55]. The results indicate that local hyperthermia and alkalinization of drug solutions might improve the interaction of antiseptics with dense and solid biological masses, particularly purulent ones, resulting in quicker and more effective liquefaction and dissolution. This has resulted in developing a new approach to drug research known as "physicochemical repurposing of drugs" [51, 52, 54].

This concept is not new; instead, it is a rediscovery of an old practice [16, 47]. Warm alkaline water and hot water steam have been used since ancient times to rapidly remove thick purulent masses from the surface of chronic wounds and mucous membranes of the respiratory tract in cases of purulent inflammation of the nose, nasopharynx, larynx, trachea, and bronchi. Traditionally, people used ash to alkalize water and warm stones and warmers to treat wounds [56, 57]. They were then replaced by specially developed physiotherapy and balneotherapy treatments [58–60].

However, researchers neglected warm alkaline solutions and hot vapors (aerosols) at the start of the 21st century. The revival of traditional chronic wound treatments began with the discovery of a method for treating long-term nonhealing wounds (Russian Federation patent no. 2187287, dated August 20, 2002) [16, 47]. This innovation recommends using local physiotherapy, such as local hyperthermia and warm local antiseptics, rather than local chemotherapeutic drugs and steroids to treat chronic wounds. After removing the soiled wound dressing, clean the wound surface with a warm 3% hydrogen peroxide solution at 37°C. Then, apply infrared radiation to the open wound surface for 15 min until persistent thermal hyperemia develops but does not exceed 42°C. The wound should be treated with a new dressing soaked with a warm 2%–4% sodium chloride solution at 42°C. Then, apply a warming element to the dressing to keep the local temperature in the wound at 37°C until the wound sanitation dressing procedure is completed. Patients with pressure sores (compression ulcers) in chronic wounds showed rapid granulation tissue development 2–3 days after initiating this treatment. Chronic wounds healed after 1–2 weeks after using this method on a continuous application.

In addition, the description of the present invention shows that daily wound dressing renewal and irrigation of open wound surfaces in chronic wounds with a warm 3% hydrogen peroxide solution at 37°C can remove purulent masses from the wound surface. This is due to the hyperthermia and humidity softening the dense, purulent masses. The enzyme catalase in the wound activates a cold boiling process, which destroys dense purulent masses and mechanically removes them from the wound. This is due to the decomposition of hydrogen peroxide into water and oxygen under catalase. The released oxygen generates gas bubbles that form pathological masses, resulting in fluffy white oxygen foam. Oxygen gas possesses pyolytic, disinfecting, deodorizing, bleaching, and antihypoxic effects. Furthermore, the antihypoxic effect of oxygen gas promotes aerobic metabolism in granulation tissue cells, accelerating wound healing.

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According to the technique description, administering infrared heat to an open wound at 42°C for 15 min increases the metabolism of granulation tissue in line with the Arrhenius law, which speeds up the healing process. Importantly, this method should not be used on tissues susceptible to heat burns. Using a 2%–4% hypertonic sodium chloride solution at 42°C to irrigate the wound and apply a fresh dressing, as well as warming the soaked dressing with a heating medium up to 37°C until the wound is sanitized, transforms the dressing into a warm, moisturizing compress. A warm, moisturizing compress containing hypertonic sodium chloride solution might provide a local greenhouse effect in the wound. This preserves moisture and ensures a safe level of local hyperthermia while disinfecting [16]. The physicochemical properties of antiseptics and their local interaction with purulent necrotic masses can effectively combat infectious agents and speed up the healing of chronic wounds.

In subsequent years, increasing the pyolytic effect of warm hydrogen peroxide solution on thick pus masses was possible by making the solution alkaline (pH 8.4) with sodium bicarbonate and dissolving carbon dioxide or oxygen gas under high pressure. These concepts were initially achieved in the innovations “means for liquefying thick and sticky pus” (RF patent no. 2360685, dated July 10, 2009) and “bleaching denture cleaner” (RF patent No. 2659952, dated July 4, 2018). A denture bleaching cleaner was presented using a 2.0%–10.0% sodium bicarbonate solution heated to 37°C–42°C and a 3.0% ± 0.3% hydrogen peroxide solution enriched with oxygen by an overpressure of 0.2 atm. When administered locally, this solution exhibited pyolytic, hemolytic, deodorizing, bleaching, and disinfecting properties. Local action is achieved by hyperthermic softening of dense purulent masses, alkaline saponification of lipid and protein–lipid complexes, cavitation loosening of dense masses, dissolution, and oxidative discoloration [61, 62]. In Russia, a group of hygienic agents with physicochemical pyolytic activity was found and termed “pus solvents.” In recent years, this group has been renamed “pyolytics.” Pyolytics are primarily a group of repurposed antiseptics, which are warm alkaline hydrogen peroxide solutions [49, 63]. To date, it has been demonstrated that the most effective and safe pus solvents are warm solutions containing 2%–4% sodium hydrogen carbonate solution and 0.5%–3.0% hydrogen peroxide solution, heated to 42°C–45°C [45, 53, 54].

Other studies have found that a warm alkaline hydrogen peroxide solution has pyolytic, mucolytic, and hemolytic effects on purulent masses, mucus, sputum, and blood. This effect has been found not only in laboratory conditions (*in vitro*) but also in experimental conditions in isolated lungs and live rabbits, as well as in clinical settings in patients with bronchial asthma during acute respiratory obstruction induced by natural pus and/or artificial sputum. Warm alkaline hydrogen peroxide solution applied, inhaled, and/or injected (including intrapulmonary injection) can transform thick and viscous sputum, mucus, pus, and blood clots into fluffy oxygen foam within 8–11 s of local contact [50, 64–66]. These findings indicate that warm alkaline hydrogen peroxide solutions might be used to hasten the sanitization of chronic wounds. In addition, laboratory, experimental, and clinical studies have shown that sanitizing treatment for chronic wounds may be achieved by combining warm alkaline hydrogen peroxide solutions with moist wound dressing compresses. This treatment can be considered an alternative to traditional drug disinfection and larval dissolution of purulent necrotic masses in chronic wounds, as it can be used for immediate cleansing and acceleration of the healing process.

CONCLUSIONS

Thus, in the early 21st century, Russia had completed the physicochemical conversion of antiseptic solutions, including hydrogen peroxide and sodium bicarbonate, into antiseptic pyolytics. According to research, a simple process can transform antiseptic solutions into effective pyolytics, such as 0.5%–3% hydrogen peroxide and 2%–10% sodium bicarbonate. It is heating the solution to 37°C–45°C, alkalinizing it to pH 8.4–8.5, and increasing the concentration of dissolved carbon dioxide or oxygen gas (due to 0.2 atm of overpressure). The development of antiseptic pyolytics resulted in a new drug group. This group is unique because all developed pyolytics are warm alkaline hydrogen peroxide solutions that may include dissolved gases under high pressure, resulting in hypergasse. One distinctive feature of the pyolytics above is their nonspecific (physicochemical) activity. This activity interacts locally with purulent masses, enabling them to rapidly transform into fluffy oxygen foam. Furthermore, it has been recommended to modernize the wound dressing into a warm, moist wound dressing compress that creates a greenhouse effect in the wound.

The initial results of using the developed antiseptic pyolytics and warm, moist wound dressing compress to treat chronic wounds show disinfecting, pyolytic, bleaching, deodorizing, antihypoxic, and wound healing effects. Warm alkaline hydrogen peroxide solutions and warm, moist wound dressing compresses can be used instead of traditional drug treatment and laser therapy to sanitize chronic wounds. These results show that pyolytics, derived from the physicochemical repurposing of aqueous hydrogen peroxide and sodium bicarbonate solutions, can be considered a new group of drugs. Pyolytics are hygienic (sanitizing) antiseptic drugs that may be used to treat chronic wounds. Much research is needed to determine the advantages and disadvantages of warm alkaline hydrogen peroxide solutions combined with warm wound dressings for treating various types of chronic wounds.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: N.A. Urakova, A.P. Reshetnikov, Yi Wang, V.P. Bodduluri, A.V. Samorodov, R.A. Rozov, A.A. Shchemeleva, V.E. Novikov, E.V. Pozhilova — manuscript drafting, writing and pilot data analyses; A.L. Urakov, P.D. Shabanov — editing of the article, development of the general concept.

Competing interests. The authors declare that they have no competing interests.

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