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Contribution of Topical Agents to Wound Healing

Tadej Voljč and Danijela Semenič

Abstract

The process of wound healing is often accompanied by bacterial infection or critical colonization, which leads to an extension of the inflammatory response phase and delayed epithelization. In the review of scientific articles, we found the description and mode of action of topical antiseptic agents, including silver and sodium hypochlorite solution, to control the spread of microorganisms. The value of hyaluronic acid for wound healing is described. Furthermore, a novel treatment option with microspheres is mentioned. Attachment of cells to microspheres establishes a local cytokine response that acts anti-inflammatory, cell attachment results also in morphological and functional cell changes that reactivate healing.

Keywords: chronic wounds, wound infections, antisepsis, silver, microspheres, polystyrene microspheres, hyaluronic acid, sodium hypochlorite

1. Introduction

Chronic wounds represent a serious problem for both the patient and the physician.

As chronic wounds are considered venous ulcers, wounds due to peripheral arterial occlusive disease, diabetic neuropathic, diabetic ischemic, diabetic neuroischemic wounds, pressure sores and atypic chronic wounds.

Atypical chronic wounds comprise less than 5% of all chronic wounds [1, 2]. They may present with a clinical picture the clinician has not previously encountered, therefore raising a diagnostic dilemma and challenge. A full range of pathogenic categories, including vascular, autoimmune, inflammatory, infectious, neoplastic, genetic, and drug-related processes, can cause an atypical ulcer [1–3].

Also, every acute wound has a certain potential to become chronic, usually with co-infection or when associated diseases are present.

For the successful treatment of chronic wounds, it is necessary to know and treat the underlying cause and provide the wound appropriate method to optimize wound healing.

2. Silver active compounds

Metallic silver has been used in the treatment of infections from at least the 18th century [4]. More recently products containing silver have been developed for the topical treatment of chronic wounds due to its antiseptic and anti-inflammatory activity [5, 6].

While metallic silver is chemically largely inert, it readily releases an electron in contact with moisture, becoming more reactive and gaining significant biocidal properties. In its ionized form (Ag^+) silver can interfere with thiol ($-\text{SH}$) groups, promote the production of reactive oxygen species (ROS) and bind to bacterial DNA and RNA. Through these mechanisms it causes structural changes to the bacterial cell wall, intracellular and nuclear membranes, disrupts the production of ATP and inhibits replication, ultimately leading to the loss of function and cell death [4–8]. Silver ion-release products are effective against various bacteria, including methicillin-resistant *S. aureus* (MRSA) and vancomycin resistant enterococcus (VRE) [4], fungi and viral pathogens [9]. Silver containing wound dressings are able to reduce the number of viable bacteria in a matter of minutes [10]. Silver ions were shown to destabilize the biofilm produced by *S. epidermidis* [11]. As such it presents a good adjuvant treatment option to combine with surgical debridement for dealing with bacterial biofilm.

Bacterial resistance to silver has rarely been reported, likely due to its multiple mechanisms of bactericidal action [12]. However, most reported cases of bacterial resistance to silver stem from burn units, where large amounts of silver salts were used as wound antiseptics. Among the described silver resistant strains were *E. coli*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Salmonella typhimurium* and *Pseudomonas stutzeri*. The outbreak of a silver resistant strain of *Salmonella* even caused the closure of a burn unit at the Massachusetts General Hospital after three patients have died of septicemia in 1973 [13, 14].

While ionic silver has the highest therapeutic capacity, it is also rapidly inactivated after being applied to a wound due to its high nonspecific reactivity [7]. Instead, nanoparticles of silver have been used in modern wound dressings, combining a large active surface area and a degree of control over the rate of Ag^+ release into the wound [7, 8]. Silver wound dressings have been developed in several ways, some binding nanocrystalline silver to carbon fibers, attaching it to polyurethane foam, attaching it to hydrocellular foam and coating it over polyethylene. Silver can either be presented at the surface of the product facing the wound, diffusing and acting on the wound itself, or be bound inside a foam or mesh acting on the pathogens absorbed into the material [15, 16]. In a favorable environment silver cations can be released into the wound for several days from a single dressing [17], avoiding frequent dressing changes and unnecessary wound manipulation. After an initial lag the rate of Ag^+ release can be constant [7].

The majority of review articles noted the poor quality of the published data on the use of silver in wound care. Many studies in this area are funded or performed by manufacturers of silver-containing wound dressings [12], adding to the risk of bias.

The therapeutic range of Ag^+ concentration is 30–60 ppm, above which a toxic effect on skin keratinocytes becomes increasingly likely. The goal is thus to have a silver wound dressing that can exert a concentration of silver cations in the wound within the therapeutic range (30–60 ppm) for a prolonged period of time (several days) [12, 13].

Traditional preparations of silver in wound care, silver nitrate and silver sulfadiazine, are as such of limited suitability, providing an initial Ag^+ concentration very much above the therapeutic range (3176 ppm and 3025 ppm respectively), with little residual activity [13].

Nanocrystalline silver incorporating wound dressings are able to provide a Ag^+ concentration of 50–100 ppm in a constant manner [12, 18]. As such they are more suited in the treatment of infected wounds compared to traditional silver preparations, albeit still providing a wound silver ion concentration above the target range. The effect of silver ions has been shown to have a synergistic effect with negative

pressure wound therapy, with silver-coated polyurethane foam providing better results than the use of a polyurethane sponge alone [12]. In this way wound Ag⁺ concentration of 20–40 ppm can be achieved, falling in the optimal range. A similar effect can be observed by adding a layer of silver-coated nylon between a polyurethane sponge and the wound [19].

Despite their broad spectrum of antimicrobial action and low incidence of bacterial resistance silver-containing products do not come without limitations. The use of silver sulfadiazine, a once very popular preparation of silver, especially in the treatment of burn wounds, is nowadays widely discouraged due to the comparatively high risk of negative effects on the viable wound tissue and little to no advantages when compared to nanocrystalline silver preparations [12, 13, 20]. Not only traditional preparations of silver but nanocrystalline silver, too, has been shown to have an inhibitory effect on epithelization, albeit to a lower extent [20, 21]. Considering this and other possible side effects of silver-releasing products they are thus not recommended for treating non-infected, clean wounds or closed surgical incisions [12].

Silver-releasing products have been shown to reduce the viability, induce oxidative stress and DNA damage in porcine ex vivo skin cells, as well as promote the production of pro-inflammatory IL-6 by monocytes and reducing the oxidative burst and viability of neutrophils in a dose-dependent manner [20]. It should thus come as no surprise that though an important tool in the fight against wound infections they should be used cautiously. The current state of research suggests they should be used on infected wounds for up to 2 weeks, after which the wound should be evaluated. If there is clear improvement with persistent signs of infection the use can be continued until a total of 4 weeks of silver-assisted therapy is reached. If there is no sign of improvement after two weeks the use should be discontinued immediately. Silver-releasing products should not be used for over 4 weeks without a good clinical rationale [22].

Topical application of silver in a nonadhesive wound dressing can be used not only for the treatment of typical chronic wounds, but also for un-usual wounds for example for the treatment of pyoderma gangrenosum ulcers [23]. Pyoderma gangrenosum (PG) is often associated with autoimmune disease and is a neutrophilic dermatosis, characterized by a wide range of clinical presentations, among which recurrent cutaneous ulcerations are the most characteristic [24]. Ulcers are very painful [23]. In addition to systemic immunosuppressant therapy, topical or intralesional drugs can be used [25].

3. Hyaluronic acid

Hyaluronic acid (HA) is a linear glycosaminoglycan (GAG) molecule composed of disaccharide units of GlcNAc and D-glucuronic acid linked together with β -1,4 and β -1,3 glycosidic bonds. The sequence can be repeated over 20,000 times [26]. Hyaluronic acid was first discovered in the vitreous humor in 1934 by Karl Meyer and John Palmer. They proposed the name “hyaluronic acid” lending from the Greek hyaloid (vitreous) and uronic acid, one of the two repeating monosaccharide units [26].

Most human cells have the ability to synthesize HA at some point in their cell cycle, leading to the presence of HA as a component of the extracellular matrix (ECM) in many tissues throughout the human body [27, 28]. The hygroscopic and viscoelastic properties of HA and its derivatives provide a lubricating environment for cells [29]. Its derivatives are an important role in HA's function. It is involved in various processes, from fertilization and development to cancer [26]. Hyaluronic

acid and its signaling receptors play a role in initiating an inflammatory response, maintaining structural cell integrity, and promoting recovery from tissue injury [30]. Interestingly, high molecular weight HA displays an anti-inflammatory effect whereas low molecular weight HA acts immunostimulatory and pro-inflammatory [31–33]. High molecular weight HA has been shown to exhibit a cytoprotective effect [34].

HA stimulates the development of fibrin, phagocytic activity, neutrophil and macrophage mobility, assists in cellular infiltration and in the mobilization of proinflammatory cytokines [29, 35]. Hyaluronic acid plays a role in all stages of wound healing [35]. In the early granulation stage HA, abundant in the ECM, facilitates cell proliferation and migration into the temporary wound matrix, and helps with the organization of the granulation tissue matrix. At a later stage HA helps to stabilize the matrix by scavenging free radicals. In the proliferation stage HA plays a role in supporting and regulating basal keratinocytes [35]. A lower HA content has been observed in hypertrophic scars and in the keloid compared to ordinary scars [32].

Due to its many regulatory functions hyaluronic acid has seen significant use as a topical agent in wound treatment. Without yet a clear literature consensus on its efficacy there does seem to be an overall positive effect of HA on the healing of chronic wound ulcers of various etiologies, burns and epithelial surgical wounds no matter the form in which HA is applied (e.g., pad, cream or substrate) [36]. However, the low number of high-quality studies in this area limits any systematic review trying to determine HA's effects in clinical use. To illustrate, a marked increase in the healing rate of diabetic foot ulcers was described in a paper, even when compared to other forms of ulcers among chronic wounds [36, 37], while another systematic review found no advantage whatsoever in the HA group when compared to paraffin gauze [29]. Both systematic reviews were only able to include two papers studying the topic.

3.1 Combination of different active substances (Ag^+ , chlorhexidine, hyaluronic acid)

Modern wound healing products combine different active substances in a single product, better adjusting the finished product to the clinical requirements of a certain wound type. An example is a combination of Ag^+ and chlorhexidine, both

Figure 1.
Chronic wound before treatment with a combination of Ag^+ , chlorhexidine and hyaluronic acid in a spray.

Figure 2.
The result of treatment with spray that contains Ag⁺, chlorhexidine and hyaluronic acid after 6 weeks.

antiseptic agents bound to silicon dioxide, with added hyaluronic acid to promote the healing process.

Figure 1 shows an example of a chronic wound treated in our institution. Written consent for publication by the patient was obtained.

Presented is a 73-year-old male patient, with diabetes, venous insufficiency, peripheral arterial disease, and heart failure, with consequent bilateral lower leg edema. The treatment was carried out with a combination of Ag⁺, chlorhexidine and hyaluronic acid in a spray, every 2 days, covered by a non-adhesive modern dressing. The result of treatment is visible after 6 weeks (**Figure 2**).

Promising results for this combination have also been reported regarding the incontinence associated dermatitis related wound regression rate, moisture control and pain reduction in a study [38].

4. Sodium hypochlorite

Sodium hypochlorite is a strong oxidizing agent and was first discovered in 1787 in Paris by Berthollet. During World War I it was used by Alexis Carrel and Henry D. Dakin as an effective antiseptic agent for combat wounds, sparking its popularity as a wound antiseptic between the two world wars. The popularity of such use later declined with the rise of antibiotics, but it remained a popular household product – sodium hypochlorite is the active ingredient in bleach [39].

With an increasing awareness of the limitations of antibiotic drugs it is again being investigated as a viable option for the prevention and treatment of wound infections. Today a 0.5% sodium hypochlorite solution or more diluted preparations are used. Dakin's solution has been known to have a bactericidal effect against *S. aureus* (MRSA and non methicillin-resistant), *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*, *Serratia marcescens*, *Enterobacter cloacae*, group D enterococci, *Bacteroides fragilis*, *Streptococcus mitis*, *Staphylococcus epidermidis*, and a fungicidal effect on *Candida albicans* among others [39].

However, as a strong oxidizing agent it is certainly able to exert an important cytotoxic effect on healthy human cells, too. While lower concentrations of sodium hypochlorite have been shown to retain their bactericidal effect, it seems that the cytotoxic effect on human cells sees a stronger reduction with dilution [39]. This area is notably lacking in detailed research.

While sodium hypochlorite is currently not widely used as a wound antiseptic some institutions are reporting positive results with its use. It has been reported to be effective in the treatment of infected and open wounds [39]. In patients undergoing coronary artery bypass surgery it has been shown to be more effective as an irrigator for the prevention of post-sternotomy wound infections when compared to povidone-iodine [40]. It has also been investigated as an irrigator for drain tubes after breast and axillary operations, helping provide much lower rates of positive drain bulb cultures and a lower bacterial load when combined with a chlorhexidine disc at the drain exit site and compared to the standard of drain care (cleansing with alcohol swabs) [41].

5. Polystyrene microspheres

The microspheres are round in shape, located in a suspension of sterile water-soluble solution at a concentration of 0.025%, consist of polystyrene and have a diameter of 5 micrometers.

They are intended for topical application on the wound bed, applied in the form of drops (1–2 drops/cm² of the wound bed). The mechanism of action is explained by both preclinical in vitro and in vivo studies [42], where the presence of microspheres shows increased cell proliferation, increased cell migration and also increased activity of membrane-bound enzyme proteolytic complexes on cells [43].

The property of the size and surface of the microspheres offers a supportive microenvironment on the surface of the chronic wound, as it serves as an additional surface to which epithelial, endothelial, and even inflammatory cells can attach and migrate [44, 45]. Microspheres have a negative charge on their surface, which accelerates the secretion of growth factors such as growth factor beta-1 [45], and an excess of proteolytic enzymes, which inhibit normal healing, metalloproteinases and human neutrophil elastase, also bind to their surface [42].

The purpose of treatment with microspheres is, in a way, to “de-chronicize” a chronic wound into an acute wound condition, by inducing changes in the microenvironment that would allow the best possible conditions for healing [46].

In a study where microspheres were administered to 54 patients with chronic wounds of various etiologies over a period of 4.5 weeks [42], an effective reduction in wound size and area was described. 39% of the wounds completely healed, and in the remaining cases, effective growth of granulation tissue of the wound bed was observed, which covered up to 75% of the surface of the wound bottom [42].

Accelerated growth of granulation tissue is an indicator that the wound is in the proliferative phase of healing. Granulation tissue is the basis for later re-epithelialization or surgical closure of the wound with suturing, skin graft or flap [47], and the healing indicator is a reduction in wound size, which means that epithelialization began from the edges of the wound [42]. Wounds where bone or tendon are exposed in depth are less responsive to healing [48, 49], but according to the results described in the literature, such wounds may also respond effectively to microsphere treatment [42].

From the possible side effects in the literature, pain and itching are the most common symptoms [42].

In a multicenter randomized double-blind study treating 66 patients with a chronic wound of various etiologies, complete wound healing was found in 20% of patients, in 80% of patients the wound bed was 3/4 covered with granulations after 12 weeks of treatment [46].

Treatment with the application of microspheres potentially accelerates the growth of granulation tissue and epithelialization. We also notice that after the

Figure 3.
Chronic wound before treatment with polystyrene microspheres.

Figure 4.
Effective epithelization and scar formation after 12 weeks of treatment with polystyrene microspheres.

application of microspheres, fibrin plaques are easier to remove from the surface of the wound bottom. Microsphere therapy is suitable for the treatment of both inpatient and outpatient patients, and application by the community health service

is also possible. The secondary coating covering the microspheres must be non-adhesive and as non-absorbent as possible.

An example where the effective treatment with microspheres is presented is a 44-year-old male patient with a chronic wound on the skin of the abdominal wall after a hepatectomy, after hernioplasty and subsequent resection of the infected hernia mesh. Drops with microspheres were applied on the wound bed every 2 days, over which a non-adhesive modern wound dressing with a silicone contact layer and polyurethane foam was applied. The condition of the wound before treatment (**Figure 3**) and the condition after 12 weeks of treatment (**Figure 4**) with effective epithelization and scar formation [50].

6. Activated charcoal

With its biocompatibility and large surface area, activated charcoal acts as a useful adsorbent of fatty molecules. The most important raw materials for its production are rice, coconut shell and different types of wood. Activated charcoal is obtained by heating the material to around 1000°C in an oxygen-free environment and the subsequent breakdown of carbon-rich compounds. Through this process the material becomes porous, greatly increasing its surface area and its adsorbent capacity [51].

Commercial activated charcoal containing wound dressings contain between 85 and 98% active carbon, with the main difference being the material used to cover the charcoal cloth. Such materials include viscose rayon, alginate, polyethylene, polyamide and nylon [52]. *E.coli* was among the first cultures whose adherence to activated charcoal has been studied [53]. Gram-negative bacteria have been found to adhere stronger and wash out less easily from activated charcoal than Gram-positive bacteria [54].

7. Polyhexanide

Polyhexanide, also known as polyhexamethylene biguanide (PHMB), is a synthetic compound with a broad antimicrobial spectrum, including various types of Gram-positive and Gram-negative bacteria and some fungi (*Candida* spp., *Aspergillus* spp.). It acts as a strong base, binding to negatively charged phospholipid molecules in cell membranes of microorganisms, disturbing their integrity and leading to loss of viability. Its effect on neutral phospholipids of human cells is supposed to be negligible [55].

Betaine, with its amphoteric properties, acts as a surfactant and can be used in the cleaning of wounds. Often polyhexanide and betaine are used together in order to reduce the microbial burden and promote wound healing. As a combination they are available in a number of commercial products and were shown to be effective in reducing the number of viable bacteria in a formed biofilm produced by MRSA [55, 56]. Products containing both polyhexanide and betaine are currently often used in the management of pressure ulcers, venous ulcers and other chronic wounds, while further indications are under investigation [55].

8. Povidone iodine

Povidone iodine's broad spectrum of activity, ability to penetrate biofilms, lack of associated resistance, anti-inflammatory properties, low cytotoxicity and good

tolerability have been cited as important factors, and no negative effect on wound healing has been observed in clinical practice [57].

The efficacy of povidone iodine on wound healing in the presence of biofilms has been reviewed [57, 58]. Studies have confirmed the *in vitro* efficacy of povidone iodine against *S. epidermidis* and *S. aureus* growth, as well as the inhibition of staphylococcal biofilm formation at sub-inhibitory concentrations [57–59].

9. Other topical agents

Different clinical practices are used according to different medical institutions in the world. However, several other compounds are also part of a wound-care specialist's daily routine. According to the conclusion of infectious disease specialists and surgical infection specialist at the University Medical Center Ljubljana, antibiotic ointments for chronic wounds are not recommended, with purpose, to prevent possible acquired microbial resistance. Topical antibiotic ointment is occasionally used only for impetiginous skin lesions and dermatological indications, not for the treatment of chronic wounds.

The use of topical antibiotics should be discouraged if appropriate antiseptics are available [57, 60].

While the general principles of action remain similar across different substances, a chapter on topical wound healing agents would not be complete without a brief overview of other important agents.

9.1 Mafenide acetate

Mafenidine acetate has been developed as a topical Sulphonamide in 1966. It is effective in reducing the wound bacterial load through the inhibition of nucleoside synthesis and became especially popular in the treatment of burn wounds. First marketed as a 10% cream formulation it did not come without important side effects – both local (neoeschar formation, pain) and systemic (metabolic acidosis) [61, 62]. Its concentration has later been reduced to 5%, with a reduction in the incidence of side effects, but even with preparations used today inhibitory effects on skin DNA and protein synthesis remain a concern [61–63]. This and the high cost of mafenide therapy led to recent research interests on whether the mafenide concentration could further be reduced. While the 5% mafenide acetate cream remains an important agent in burn treatment, novel research indicates that a 2.5% mafenide cream could be equally efficacious as its 5% counterpart [61, 62].

9.2 Bacitracin

Bacitracin is derived from *Bacillus Subtilis* and the *licheniformis* group of bacteria and is one of the most widely used topical antibiotics. Its bactericidal activity spans against several Gram-positive and Gram-negative organisms [64]. Bacitracin can provide a 90% reduction of bacterial viability in 1 hour after application and an important reduction of bacterial adherence, without important systemic effects being associated with topical use [65]. There is some evidence to support its use in the prevention of surgical wound infections, however, the use of bacitracin for superficial clean wounds is discouraged [66–69]. While having important antibiotic properties it has also been reported to cause allergic contact dermatitis in a range from 7.7 to 9.2% in a patch-test. As with many antibiotic agents topical products have been associated with an increase in microbial antibiotic resistance. The recommended alternative to bacitracin and other topical

antibiotics for the treatment of superficial clean wounds is white petrolatum, with comparable wound infection and wound healing rates [68, 69].

9.3 Neomycin

With a largely similar profile of side effects to bacitracin, is another highly popular topical antibiotic agent [68]. It is classified as an aminoglycoside and inhibits bacterial protein synthesis by binding to ribosomal RNA. It is effective against Gram-negative bacteria, with the exception of *Pseudomonas aeruginosa*, against some Gram-positive bacteria, including staphylococci, but not against streptococci and anaerobes. Its use extends across the spectrum of the prevention and treatment of chronic and non-chronic wound infections, superinfections and burns [64]. The incidence of allergic contact dermatitis is higher compared to bacitracin (7–13% in a patch-test) [69]. Plasmid-mediated resistance to neomycin has been reported in several bacterial strains, including staphylococci, *E. coli*, *Klebsiella spp.* and *Proteus spp.* [64].

10. Conclusions

Hyaluronic acid, activated charcoal, chlorhexidine, sodium hypochlorite, polyhexanide and polystyrene microspheres serve as good examples of different already well established and potential up-and-coming topical treatment solutions. The advantage of these active ingredients is that no acquired microbial resistance, has been known so far.

By ensuring the optimal microenvironment of the wound, the transition from the inflammatory phase to the proliferative phase of healing is enabled.

The choice of treatment method must be both clinically and cost-effectively.

A short review chapter discusses the possibilities for managing the bacterial load in the wound bed, the advantages and disadvantages of different topical agents and their mode of action.

As with many already established formulations, new topical agents should be put through testing in the form of blinded randomized controlled trials, in order to provide valid support for the formulation's efficacy and safety. Only through this process can we achieve important and much needed evidence-based advances in regard to the treatment of wounds with novel and ever developing topical agents.

Conflict of interest

The authors declare no conflict of interest.

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