Antiseptic Agents for Chronic Wounds

Subjects: Infectious Diseases

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Chronic wounds are wounds failing to proceed through the normal phases of healing in an orderly and timely manner. The definition of time without complete or partial healing differs across countries, ranging from 4 weeks to 3 months. In many parts of the world, antiseptic agents remain non-indicated in chronic wound care. In the current context of bacterial resistance to antibiotics and the development of new-generation antiseptic agents, wound antisepsis represents an asset for the prevention of wound infection.

Keywords: antiseptic agents ; efficiency ; iodine ; systematic review ; wound healing ; wound infection

1. Introduction

Chronic wounds are wounds failing to proceed through the normal phases of healing in an orderly and timely manner. The definition of time without complete or partial healing differs across countries, ranging from 4 weeks to 3 months [1]. The Wound Healing Society defines four types of chronic wounds: diabetic foot ulcers (DFU), vascular ulcers (containing venous and arterial ulcers), and pressure ulcers (PU) [2].

Infection is a common complication of chronic wounds. Historically, the research on wound infection control and improvement was focused on reducing the “pathogen burden”. However, quantitative consideration of microbial load is insufficient for assessing wound improvement or wound risk of infection [3][4]. Microorganisms in a chronic wound are co-aggregated together within a protective extracellular matrix, constituting a biofilm. This biofilm conformation induces a dramatically increased tolerance to host immune defences and a greater resistance to antimicrobials [5]. Biofilm delays wound healing by inducing an ineffective host inflammatory response and damaging host tissues [6]. For this reason, a management of the biofilm is more relevant for the treatment of chronic wound [7]. In 2011, Dissemond et al. classified wounds into four categories, depending on wound bed clinical and microbiological situation: (1) contaminated or colonised wounds without risk of infection; (2) colonised wounds at risk (WAR) or critically colonised wounds; (3) wounds with local infection; and (4) systemic infections and infected wounds. The authors suggested the use of antiseptic agents for wounds from the second category alongside other treatments [8].

Chronic wound care commences with wound bed preparation via (i) wound cleansing to create a wet or moist environment, favourable to healing. (ii) Wound debridement via removal of devitalised, contaminated tissue from within or adjacent to a wound, until surrounding healthy tissue is exposed [9][10]. Debridement can be mechanical (sharp debridement, surgical), enzymatical, or bio-surgical (e.g., maggot therapy) [11][12][13][14][15]. Negative pressure wound therapy has also been used for bacterial decontamination and wound bed preparation [16]. (iii) Application of a suitable dressing, according to the type of wound. (iv) Antibiotic treatment, exclusively for infected wounds. Other therapies are beneficial to specific wounds: compression therapy is required for venous leg ulcers (VLU) [17]; arterial revascularisation, offloading foot ulcers, and diabetes control are essential in DFU [18][19]; and skin assessment and care, offloading and pressure redistribution, dressings [19][20], and structured educational program are useful for all types of chronic wounds.

In some countries, tap water or saline remain the only recommended agents for wound cleansing. Antisepsis is a common, yet controversial, wound cleansing method. Some studies consider debridement alone insufficient to reduce the biofilm that delays wound healing and suggest antiseptics to delay biofilm reformation and reduce the risk of infection [7] [20]. Antiseptic agents may complement the debridement process and control infection.

The primary mode of action of antiseptics can be pharmacological, metabolic, and/or immunological [21]. Here, antiseptic agents are defined as medication that can prevent the growth or destroy microorganisms in or on a living tissue. Following this definition of medication, antiseptic agents must pass through a drug authorisation procedure with a medicine agency [22]. The main antiseptic agents used in chronic wound care are halogenated compounds, alcohol-based agents, biguanides (e.g., polyhexanide also called polyhexamethylenebiguanide or PHMB, chlorhexidine), and quaternary ammoniums (e.g., octenidine). Halogenated compounds include subfamilies such as the iodine/iodophor agents (e.g.,

povidone iodine, cadexomer iodine) and chlorous agents (hypochlorite, hypochlorous acid) [21][22]. Alternative therapeutics (e.g., honey, silver), while been antimicrobial agents are not antiseptic agents as they did not go through an authorisation procedure for this purpose [23]. They therefore are not part of the antiseptic agents' classification. International guidelines recommend against the routine use of topical antiseptics to manage infected chronic wounds [24][25][26][27].

2. Antiseptic Agents for Chronic Wounds

The researchers reviewed the RCT evidence for the use of antiseptic agents in chronic wound care in adult patients. Although saline is the main recommended product used in chronic wound cleansing, numerous clinical studies described the benefit of antiseptic agents in this situation [7][17][21][28][29][30]. A limited number of studies are available on the efficacy of antiseptic agents on chronic wound healing. More limited studies are available on the efficacy of antiseptics on pain. The trials are small, clinically heterogeneous, without clearly defined outcomes, and at high or unclear risk of bias. Of the 838 RCT identified, only 6 studies were included, representing a total of 725 patients.

The researchers review established a better wound healing with iodine compared to saline (2 RCT, 195 patients, RR 1.85 (1.27 to 2.69)), although the quality of the evidence was moderate. In contrast, no statistical efficacy of octenidine on healing rate (compared to saline) was seen with a high-quality evidence grade (1 RCT, 126 patients RR 1.03 (0.56 to 1.90)). Interestingly, none of the antiseptic agents influenced AE occurrence compared to saline. Notably, over half of the clinical trials have never been published. Most studies had unclear risk of bias, as previously described [31][32].

Of the 838 studies, most of them did not evaluate clinical signs of infection, and mainly focused on bacterial load reduction, a measure long deemed unsuitable [2][3][4]. Furthermore, the six included studies ignored the effect of biofilm in delaying the healing process. Of the two studies assessing microbiological impact on infection, none assessed biofilm reduction [33][34][35]. For future research, The researchers suggest the use of dynamic models mimicking the wound environment instead of the traditional quantitative microbial load in in vitro studies [36]. This includes non-static models and the consideration of multispecies biofilm reduction over a clinically relevant time (>1 month).

Although most guidelines recommend against the use of antiseptic agents [2][4][25][27], a recent consensus suggested using hypochlorite and polyhexanide in chronic wound care [21]. The researchers found no study demonstrating a significant effect of hypochlorite on the healing of chronic wounds. The researchers could not assess the efficacy of polyhexanide due to the heterogeneity of outcomes between studies. However, this consensus included other types of non-healing wounds such as post-surgical or burn wounds and made no distinction between WAR score categories (colonised and infected wounds). Finally, it also included non-randomised trials, which provide lower evidence than RCTs and different systematic bias are encountered [37]. The main limitation of this guideline is the extrapolation of recommendations from various studied wounds to specific chronic wound care. Another key problem is the attribution of effect to antiseptic agents when antibiotics were systematically used in case of infected wounds.

Following the diverse interpretations of study results in recommendations, future investigations in primary research must focus on value to patients and healthcare professionals, particularly treatment choice. The design of future trials should be driven by high-priority questions. Moreover, good practice guidelines must be followed at each step (e.g., design, implementation, reporting). Assessment of complete wound healing instead of wound healing rate would be more relevant, and time to complete wound healing should be reported as the main endpoint. Future research should be controlled at least against saline, and preferably with another or multiple other antiseptic agents. Another fruitful area of research would be the impact of antiseptic agents according to wound size. Two of the researchers included studies on two different antiseptic agents reported increased healing rate for wounds larger than 6 cm^2 versus smaller wounds [38][34]. Further good quality evidence studies may aid decision making about the use of topical antiseptics in the management of chronic wounds.

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