Clinical use of 0.1% polyhexanide and propylbetaine on acute and hard-to-heal wounds: a literature review

Objective: To summarise the findings on the effect of the clinical use of 0.1% polyhexanide–propylbetaine (PHMB/betaine) solution/gel on acute and hard-to-heal (chronic) wound healing.
Method: A literature search was conducted in MEDLINE, CINAHL, Embase, Scopus and the CENTRAL Trials Registry of the Cochrane Collaboration. Paired reviewers conducted title and abstract screening and full-text screening to identify experimental, quasi-experimental and observational studies. Study quality and risk of bias were not formally evaluated.
Results: A total of 17 studies met the eligibility criteria. The findings from 12 studies indicated that the use of 0.1% PHMB/betaine solution/gel had: a low risk of contact sensitivity; could help debridement during wound cleansing; aided effective wound bed preparation; reduced wound size, odour and exudate; improved pain control; reduced microbial load; and enhanced wound healing. The results of three studies indicated that both 0.1% PHMB and saline solution were effective in reducing bacterial load, while another showed that adding 0.1% PHMB to tie-over dressings had no effect on reducing bacterial loads in wounds. Another study concluded that disinfection and granulation of pressure ulcers with hydrobalance dressing with 0.3% PHMB was faster and more effective than using 0.1% PHMB/betaine.
Conclusion: The findings of this literature review showed that 0.1% PHMB/betaine solution/gel appeared to be useful and safe for wound cleansing, was effective in removing soft debris and slough from the wound bed, and created a wound environment optimal for healing. Although these actions cannot be attributed solely to this treatment modality, these results do highlight the unique action of this combined product. However, more robust studies are needed to confirm these results.
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chronic wound • debridement • hard-to-heal wound • infection • injury • pain management • wound • wound care • wound cleansing • wound dressing • wound healing

Wounds may require several years to heal and impose an immense financial burden on society, not only through an economic burden on the healthcare system but also through a reduction in economic productivity.[1–5] Affected patients can experience severe pain, emotional and physical distress, reduced mobility and social isolation.[6,7]

Wound healing occurs as a result of a series of complex biochemical and cellular processes that includes cell proliferation, migration, differentiation and remodelling.[8,9] When cells and the wound environment are compromised by local or systemic conditions, healing is hindered and the wound may become hard-to-heal (chronic). A hard-to-heal wound is one that has not progressed normally through the stages of wound healing, has become fixed in the inflammatory phase and failed to progress or respond to treatment over the expected healing timeframe.[4,10,11]

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Wound bed preparation has been recognised globally as a vital step in the healing process; it should not be viewed in isolation from holistic wound assessment, which considers underlying and associated aetiologies, such as concomitant diseases, nutritional status and lifestyle choices,[10,12,13] as well as the patient's psychosocial needs.

It is well known that hard-to-heal wounds are rarely affected by a single factor, and that systemic and local factors should be addressed in order to support wound healing; local barriers to healing, such as maintaining moisture balance in the wound bed, management of the bioburden, and presence of necrosis and slough, must be identified and removed before attempting wound closure.[13,14]

Microbial load is a factor to consider when wounds fail to heal. The presence of microorganisms contributes to the triggering of the inflammatory phase of wound healing. This phase is the host's effort to regain control over risk of bacterial invasion. When the immune response is less than adequate to achieve this goal, microorganisms can establish themselves in the supportive wound environment. Factors associated with increased risk of wound infection include:[11]

- Characteristics of the individual (e.g., poorly controlled diabetes, radiation therapy or chemotherapy, conditions associated with hypoxia and/or poor tissue perfusion, immune system disorders, inappropriate

antibiotic prophylaxis, protein–energy malnutrition, alcohol, smoking and drug misuse)
- Characteristics of the wound(s) (e.g., contaminated or dirty wounds, pre-existing infection or sepsis, degree of chronicity/duration of the wound, large wound area)
- Characteristics of the environment (e.g., hospitalisation, inadequate management of moisture and exudate, inadequate pressure offloading, inappropriate dressing removal technique).

Reviews have also reported evidence supporting the presence of biofilms in hard-to-heal wounds.[15,16] Biofilms are complex microbial communities living within a three-dimensional extracellular polysaccharide matrix embedded in a thick slimy blanket of sugar and proteins; this matrix acts as a barrier, protecting the microorganisms from cellular and chemical attack.[12–14,17]

The identification of biofilm in a wound via visual indicators has been an area of debate.[18] Some commentary has suggested that foreign material (e.g., fibrin, necrotic tissue, slough, slimy surface substance) on a wound surface may represent biofilm,[19,20] but the visible appearance of some wounds is not a conclusive indicator for its identification. Many wounds that appear to be healthy to the naked eye are shown via laboratory investigation to have biofilm present that contributes to stalling healing. Biofilm can form deep in wound tissue where it is impossible to identify visually.[21,22]

Currently, there is no specific clinical manifestation for the diagnosis of biofilm. Previous studies have shown that the clinical symptoms of bacterial biofilm that colonise wounds are similar to those of hard-to-heal infected wounds, such as pale wound bed, yellow exudate, necrotic tissue and clear tissue fluid.[23] In 2012, a World Biofilm Seminar summarised the clinical diagnostic criteria of a biofilm infection.[24] These criteria were updated in 2017 by a Global Wound Biofilm Expert Panel and included:[25,26]
- Recalcitrance to appropriate antimicrobial treatment
- Failure of appropriate antibiotic treatment
- Delayed healing
- Cycles of recurrent infection/exacerbation
- Increased exudate/moisture
- Low-level chronic inflammation
- Low-level erythema.

Clinical assessment must be supplemented with microbiological investigation (swabbing, needle aspiration, tissue biopsy) and other types of diagnostic techniques to improve the accuracy of the clinical diagnosis of biofilm infection, such as the use of scanning electron microscopy (SEM) and confocal laser scanning microscopy (CLSM), that can identify biofilms in wounds that do not show any evidence of acute infection.[27]

Wound cleansing may affect and improve biofilm prevention and treatment. This practice is an intrinsic element of wound bed preparation and involves the application of a non-toxic fluid to remove debris, excess exudate and metabolic wastes from the wound bed and surrounding skin, thus establishing an optimal wound healing environment.[28–33]

Wound cleansing comprises three elements: technique; equipment; and solution.[34,35] The optimal method of wound cleansing and the ideal cleansing agent have not been established conclusively.[11]

Wound cleansing methods have changed over time; swabbing wounds was the preferred method of choice until it was suggested that this may damage the newly formed granulating tissue.[34] Current practice favours wound irrigation, as this is less likely to damage healthy tissue even though achieving the right level of pressure can be difficult. A force of 15 PSI has been shown to remove bacteria more effectively than 10 PSI. As a general rule, lower pressures are adequate for cleansing clean granulating wounds, with higher pressures reserved for those wounds requiring deeper cleansing.[36] It is important to warm the irrigant to 37°C/98.6°F to minimise temperature changes to the wound bed. Radical change to wound temperature can impede wound healing because it delays mitotic cell division and leukocytic activity.[37]

The equipment needed for wound cleansing will depend on the technique chosen, for example a needle and syringe for irrigation, or a bucket or a shower for bathing.[34,38]

Wound cleansing solutions commonly used in wound management include sterile normal saline (NS), sterile water, potable tap water and liquid antiseptics. NS is the favoured cleansing solution because it does not interfere with the normal healing process, damage tissue, cause sensitisation or allergies or alter the normal bacterial flora of the skin.[39–42] Tap water is also recommended and there is no evidence that using it to cleanse acute wounds in adults or children increases or reduces infection. The decision to use tap water should take into account the water quality, nature of the wound and the patient's general condition, including the presence of comorbidities.[43,44] NS, sterile water and potable tap water are non-antiseptic solutions and have no effect on biofilm. Biofilm adhesion is strong and highly resistant to cleansing by irrigation with isotonic solution; due to their size and hydrophobic surface, most proteins and other substances either present in or forming wound coatings are not water soluble.[45]

When wound healing does not progress normally or infection is suspected, a solution with a surfactant, antiseptic or antimicrobial agent is recommended.[9] Therapeutic wound cleansing should have the potential to disrupt biofilm and kill planktonic bacteria and other microorganisms, promote safety of the wound and the individual, and maintain and protect the periwound from maceration. Some commonly used antiseptic solutions are: polyhexanide (polyhexamethylene biguanide, PHMB); PHMB with betaine (a surfactant); povidone–iodine; octenidine with ethylhexylglycerin (a surfactant); hypochlorous acid (HOCl); and sodium hypochlorite (NaOCl).[11] Clinicians should be aware of the cytotoxicity of each solution, appropriate concentrations and the individual wound requirements when choosing the most appropriate solution.[46]

Current consensus on wound antisepsis[11,47] discourages the use of antiseptic solutions such as: chlorhexidine digluconate (risk of anaphylactic reactions, cytotoxicity, development of resistant microbes); topical silver sulfadiazine (cytotoxicity, risk for absorptive side effects); chinolinole and nitrofural (toxic risks); dyes; organic mercury compounds; hydrogen peroxide; and topical antibiotics.

The use of a wound cleansing solution containing the surfactant component betaine and the antimicrobial PHMB was advocated in a 2004 consensus paper.[48] On a molecular level, betaine has a hydrophilic 'head' that is attracted to water molecules, and a hydrophobic 'tail' that repels water, and attracts dirt and debris. The hydrophilic head remains in the solution, pulling the dirt and debris away from the wound base and causing it to become suspended in the irrigating fluid, enabling it to be flushed away and preventing recontamination.[49,50]

Propyl betaine also interferes with the production of N-acyl homoserine lactone, a signalling molecule used in the cell-to-cell communication of biofilms, which plays a role in biofilm pathogenicity. The ability of betaine to disrupt biofilms is particularly beneficial as biofilms are resistant to cleansing with normal saline, which simply glides over the biofilm without removing it.[51]

PHMB is a highly effective broad spectrum antimicrobial that has been found to reduce bioburden and promote healing, with low risk of contact sensitisation and good clinical safety.[52] PHMB interacts with acidic, negatively charged phospholipid compositions in the bacterial membrane, which leads to increased fluidity, permeability and loss of integrity, followed by the death of the organisms.[49–51,53–56]

Worldwide, there are a large number of PHMB-containing products on the market. In clinical practice, the usually applied concentrations of PHMB solutions for wound antisepsis are 20.0%, 0.02% and 0.04% (wound irrigation solutions/wound cleansers: 0.04%, 0.02% and 0.1%; hydrogels containing PHMB for wound cleansing: 0.04% and 0.1%; and PHMB-containing dressings show concentrations of 0.2–0.5% or 0.3% if PHMB is an auxiliary pharmaceutical ingredient).[53]

A number of authors have investigated the clinical efficacy of PHMB in these different concentrations and preparations,[57–64] reporting: complete re-epithelialisation of wounds; faster removal of critical bacteria load from the colonised wounds; good tolerability; reduced chronic pain caused by the wound and bacterial burden. In vitro studies have also shown: a broad antimicrobial action; a prolonged duration of post-antiseptic effect; additional anti-inflammatory properties; reduction of biofilm and fibrin; a good biocompatibility index; and no known risk of resorption.[53,65]

Aim

Although there is an increasing number of papers on the activity of PHMB in different concentrations, there are no reviews summarising the available knowledge on the use of a wound cleansing product containing the surfactant component betaine and the antimicrobial PHMB. The aim of this literature review was to summarise the findings of the effect of the clinical use of 0.1% PHMB/betaine wound irrigation solution or gel on the healing of acute and hard-to-heal wounds. More specifically, the objective was to review the current literature to determine its effectiveness in wound healing, bacterial burden, and patient- or clinician-related outcomes.

Methods

An electronic literature search was conducted in August 2019 by searching the databases MEDLINE, CINAHL, Embase, Scopus and the CENTRAL Trials Registry of the Cochrane Collaboration. Individual search strategies were developed for each index, adopting the controlled vocabularies. Search terms used were: "polihexanide"; "biguanides"; "local anti-infective agents"; "betaine"; "surface-active agents"; "gels"; "solutions"; "cleaning compounds"; "therapeutic irrigation"; "biofilms"; "debridement"; "wound healing"; "wound infection"; "chronic wound"; "wound care"; "skin ulcer"; "wound and injuries"; "pain management".

The search was limited to English, French, Spanish, and Italian language studies. The search period covered was 2000–2019 and included studies involving patients of any age, sex, and in any care setting, with acute or hard-to-heal wounds. Studies were considered eligible if they:

- Involved experimental, quasi-experimental or observational study design
- Evaluated 0.1% PHMB/betaine solution/gel compared with any other options (e.g., NS, Ringer's solution, etc.), or with/without any cointerventions (e.g., negative pressure wound therapy (NPWT), etc.)
- Reported on outcomes as follows: wound healing; bacterial burden; patient- and clinician-oriented outcomes.

Exclusion criteria were as follows:

- Case reports, editorials, letters or discursive papers
- Studies evaluating different concentrations from 0.1%
- Studies analysing maintenance preventive care or general care of exit-sites (e.g., peritoneal dialysis catheter, etc.) in order to prevent exit-site infection
- Animal or in vitro studies.

Titles and abstracts were screened based on the a priori eligibility criteria by two reviewers independently. Disagreements between reviewers were resolved by consensus with a third reviewer. Full-text articles for potentially eligible titles and abstracts were then retrieved and screened for eligibility independently by the two reviewers using the same a priori criteria, with consensus established via discussion with a third reviewer. To ensure completeness of the search, additional relevant articles were identified by handsearching the references of included studies.

The following data were extracted from all eligible articles: author and year of publication; study design; aim; participant characteristics; intervention; outcomes; and main results. Data extraction was conducted by two

reviewers independently, with consensus established via discussion with a third reviewer. Study quality and risk of bias were not formally evaluated.

Results

A total of 1137 articles were identified in the literature search. After removing duplicates and excluding remaining records via title and abstract assessment, 60 studies were deemed potentially eligible, and were retrieved as full-text articles; 43 were excluded for not fulfilling the inclusion criteria. Finally, 17 studies met the inclusion criteria. Of these eligible studies: seven were randomised controlled trials;[66–72] one was a prospective randomised effectiveness study;[73] and nine were observational studies.[74–82]

Sample sizes ranged from 2267–28,970 participants. The timeframe for the included studies was 2006–2018. Of the studies: four were conducted in the US;[73,77–79] four in Italy;[67,70,76,81] one each in Spain;[66] Austria;[68] Sweden;[69] Brazil;[72] Thailand;[71] the Netherlands;[74] two in Germany;[75,80] and one in five European countries.[82] Of the included studies, five were multicentre studies.[66,70,76,80,82]

The studies compared 0.1% PHMB/betaine with: NS;[66,67,70,72,73] sterile water;[69] NS or Ringer's solution;[74,75] hydrobalance dressing with 0.3% polyhexanide;[68] and silver sulfadiazine.[71] Instillation of 0.1% PHMB/betaine solution in association with NPWT with instillation and a dwell time (NPWTi-d) (devices: V.A.C. Ulta System with VeraFlo, Acelity, US/V.A.C. VeraFlo Therapy, KCI, US) was evaluated in three studies. [73,77,78]

Reported outcomes included: change in wound size; improvement in wound characteristics; time to complete wound healing; proportion of wounds healed; antiseptic efficacy; systemic or local adverse events; pain; patient and staff satisfaction; resource use; and cost.

Change in wound size

Valenzuela and Perucho[66] reported change in absolute ulcer size after two weeks of treatment. The absolute reduction in ulcer size was 19.71cm^2 (95% confidence interval (CI): 3.79–24.31cm^2) for the 0.1% PHMB/betaine gel group versus 5.65cm^2 (95% CI: –0.17–11.47cm^2) in the NS group. Data analysis showed statistically significant differences for the PHMB/betaine group for wound size reduction (p=0.013).

Romanelli et al.[67] reported that wound size was not statistically different in the NS or 0.1% PHMB/betaine solution groups from baseline to the end of the study, and the authors stated that this was mainly due to the short period of observation (four weeks). No data were available to support this observation.

Durante et al.[76] observed a significant reduction in the mean values for all parameters examined (maximum length, minimum length and area of the wound) from baseline to the final visit (control after 60 days of treatment with 0.1% PHMB/betaine gel), equal to –17.5±21.4cm, –15.5±21.1cm and –8.3±16.7cm^2, respectively. The change was statistically significant for all parameters (p<0.0001 for maximum length and width, p=0.0001 for the area of the wound).

Bellingeri et al.[70] assessed the wound size using the Bates–Jensen Wound Assessment Tool[83] (BWAT) on day 0 (T0), day 7 (T1), day 14 (T2), day 21 (T3) and day 28 (T4). Data analysis showed statistically significant differences for the 0.1% PHMB/betaine solution group compared with the NS group between T0 and T4 for wound size reduction BWAT scores (p=0.049).

Moore et al.[79] reported changes in absolute wound area in patients treated with 0.1% PHMB/betaine gel and/or solution, with diabetic ulcers having the largest changed median area of 461mm^2 and venous ulcers having the smallest changed median area of 65mm^2. The largest healed wound was a surgical incision of the lower abdomen affecting 18,850mm^2.

Improvement in wound characteristics

Valenzuela and Perucho[66] reported improvements in the 0.1% PHMB/betaine gel group compared with the NS group: in the percentage of granulation tissue (p=0.013), and slough in the wound bed (p=0.002); in the presence of wound exudate (p=0.008), and purulent exudate (p=0.005); in oedema and erythema of periwound skin (p=0.000; p=0.004, respectively); and in control of wound odour (p=0.029).

Wild et al.[68] found that in patients treated with a PHMB-containing hydrobalance dressing, the formation of granulation tissue after two weeks was better and faster than in the 0.1% PHMB/betaine solution group; however, the data for the between-group difference was not reported.

At the final visit, Durante et al.[76] observed that the majority of patients treated with 0.1% PHMB/betaine gel (about 75%) had intact periwound skin or wound edges, compared with 18% and 28%, respectively, of patients with undamaged skin at the baseline visit. A reduction in the level of exudate was also observed, with 74% of patients having no exudate at the final visit, compared with 15% of patients with non-exudative wounds at the baseline. The percentage of patients with evidence of biofilm decreased from 23.4% (baseline) to 1.6% (final visit), with granulating wound bed increasing from 5% (baseline) to 59% (final visit), and with a re-epithelialising wound bed, from 0.8% (baseline) to 26.6% (baseline).

Bellingeri et al.[70] reported statistically significant differences between T0 and T4 (28 days) in BWAT score for inflammatory items (p=0.03), and an improvement in the granulation tissue (p=0.043) in favour of the 0.1% PHMB/betaine solution group compared with the NS group.

Ricci[81] found that 0.1% PHMB/betaine solution efficacy depended on time of application. The author used the Wound Bed Preparation Score[84] (WBP) to determine prognosis and changes in management of wounds. In patients treated with gauze soaked with 0.1% PHMB/betaine solution applied to the wound for 10 minutes at daily dressing changes for 14 days, an

improvement in tissues was observed. At the time of the enrolment, 16 cases were classified as B; at day 14, 12 had evolved to A, three remained unchanged and one worsened to C. Of the 14 cases classified as C at enrolment, two evolved to A, nine to B, and three remained unchanged. The exudate score did not change but there was a minimal reduction in the level of exudate. Improvement in periwound skin was observed in 29 out of 30 cases.

The course of clinical assessment of re-epithelialisation in the study population reported by Kiefer et al.,[80] showed that on postoperative day 5 (after one administration of 0.1% PHMB/0.14% betaine gel), complete graft take and re-epithelialisation were observed in 14 patients (27.5%). Only five patients showed a re-epithelialisation of <100% on postoperative day 7 (after two treatments) and none on day 9 (after three treatments).

Time to complete wound healing

Andriessen and Eberlein[74] found that the wounds of the patients treated with 0.1% PHMB/betaine solution compared with those treated with Ringer's solution or saline, healed in more cases during the study's six-month period (97% versus 89%, respectively) and in a shorter time, within the first three months of treatment (60% versus 28%, respectively). There was a statistically significant difference between treatment groups (p=0.0001) in time to healing. The mean time to healing for the 0.1% PHMB/betaine group was 3.31 (standard error (SE)=0.17) months compared with 4.42 (SE=0.19) months for the Ringer's solution or saline group.

Kaehn and Eberlein[75] revealed that the mean time to healing in the 0.1% PHMB/betaine rinsing solution group was superior to the physiological saline solution (0.9% NaCl)/Ringer's solution group, with a healing delay of >1 month in the latter group, (4.42±1.41 months versus 3.31±1.32 months, respectively; p<0.001).

Gabriel et al.[77] reported that patients who received NPWT with instillation of 0.1% PHMB/betaine solution or NS and a dwell time (reticulated open-cell foam dressing designed for use with NPWTi-d placed on the wound; solutions instilled to fill the foam with a set soaking time ranging from 1–60 seconds, followed by NPWT of –125mmHg for 1–2 hours) showed a shorter mean time to wound closure, compared with patients treated with traditional NPWT (black or silver foam placed in the wound with –125mmHg continuous pressure) (4.1 days versus 20.9 days, respectively; p=0.0001).

Moore et al.[79] found that in patients treated with 0.1% PHMB/betaine gel and/or solution, days to wound closure varied on aetiology, with venous ulcers healing in the shortest period of time (median time of 20 days), while diabetic ulcers tended to take the longest to heal (median time of 92 days).

Wattanaploy et al.[71] showed no significant difference in healing time of partial-thickness burns between a 0.1% PHMB/betaine gel-treated group compared with a silver sulfadiazine-treated group (17.8±2.2 days versus 18.8±2.1 days, respectively; p=0.13).

Kiefer et al.[80] reported that the median time to complete re-epithelialisation in patients with deep-, partial-, and full-thickness burns treated with 0.1% PHMB/0.14% betaine gel after split-thickness skin grafting was seven days (mean: 7.1±0.2 days, 95% CI: 5–9 days).

Proportion of wounds healed

Andriessen and Eberlein[74] showed that during the study's six-month observation period, 47 of 53 (89%) wounds in the Ringer's solution or NS group healed completely, and 57 of 59 (97%) wounds healed completely in the 0.1% PHMB/betaine solution group.

Kaehn and Eberlein[75] reported that after three months of treatment with 0.1% PHMB/0.14% betaine rinsing solution 60% (n=35) of wounds had healed compared with 28% (n=15) in the 0.9% NaCl or Ringer's solution group. After the end of the observation period of six months the healing rates in both groups were satisfactory (PHMB/betaine 97% versus saline/Ringer's solution 89%).

Kim et al.[78] observed that the percentage of wounds closed before discharge was significantly higher in the six-minutes NPWTi-d therapy group with instillation of 0.1% PHMB/betaine solution compared with the traditional NPWT group (p=0.0004).

Kim et al.[73] reported no statistically significant difference between the NS (n=39, 92.9%) and 0.1% PHMB/betaine solution (n=39, 95.1%) groups for NPWT instillation cohorts for the proportion of wounds that remained closed at the 30-day follow-up.

Antiseptic efficacy

The Valenzuela and Perucho trial[66] reported statistically significant differences in microbiological cultures between 0.1% PHMB/betaine gel and NS groups (p=0.004) after two weeks of treatment.

Kaehn and Eberlein[75] observed that, during the period of wound treatment, infection rates were 3% (n=29) in the 0.1% PHMB/betaine group compared with 13% (n=7) in the 0.9% NaCl/Ringer's solution group (p=0.056).

Wild et al.[68] reported that in the 0.1% PHMB/betaine solution group after one week of treatment, six of 15 (40.00%) patients had meticillin-resistant *Staphylococcus aureus* (MRSA) eradicated from their pressure ulcers (PUs), and after two weeks, this was 10 of 15 (66.67%) patients. In the hydrobalance dressing with 0.3% polyhexanide group, after one week of treatment, 13 of 15 (86.67%) patients had MRSA eradicated from their PUs, and after two weeks, this was 15 of 15 (100%; p<0.05).

Durante et al.[76] reported that the presence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* was observed after 60 days of treatment with 0.1% PHMB/betaine gel on four and one patients, respectively, compared with several pathogens isolated on 11 patients at baseline.

Kim et al.[78] observed that the overall wound culture improvement was not different between the NPWT

group and the 6- or 20-minute NPWTi-d with 0.1% PHMB/betaine solution groups; however, when Gram-negative bacteria, *Corynebacterium*, and yeast were excluded from analysis, there was a significantly greater improvement in the 6-minute NPWTi-d group than in the NPWT group (p=0.0001).

Andriessen and Eberlein[74] observed that during the course of treatment infection occurred in seven (13%) cases in the group (n=53) treated with Ringer's solution or NS, and that infection was noted in two (3%) cases in the 0.1% PHMB/betaine solution group (n=59).

Moore et al.[79] reported that antimicrobial therapy was initiated based on signs and symptoms of clinical infection in five of the 49 patients treated with 0.1% PHMB/betaine gel and solution. The percentage of patients requiring antimicrobial therapy was 10.2%, and this was limited to surgical and traumatic wounds.

Saleh et al.[69] investigated whether a 0.1% PHMB-based antiseptic solution (n=20) added to tie-over dressings used in facial full-thickness skin grafting compared with sterile water (n=20) could reduce the bacterial load of wounds. Quantitative and qualitative bacterial analysis performed on wounds before surgery, at the end of surgery, and seven days postoperatively, showed no statistically significant difference in bacterial reductions between the groups. The surgical site infection rates were higher in the PHMB group (8/20) than in the control group (2/20) (p=0.028). All patients with infection had a significantly higher bacterial load measured postoperatively after one week. Coagulase-negative *Staphylococci* and *Staphylococcus aureus* were the predominant species, and four of 10 infected wounds contained *Staphylococcus aureus*. Statistical analyses showed that patient characteristics, including wound location, did not correlate to infection rates.

Wattanaploy et al.[71] reported that none of the patients had burn wound infection and there were no significant differences in bacterial colonisation rates in patients treated with 0.1% PHMB/betaine gel compared with those in the silver sulfadiazine treatment group; six (26.1%) patients in both groups had positive surface swab culture, but there were no signs of infection, and routine swab cultures in the following week were negative.

Borges et al.[72] reported that 0.1% PHMB solution (n=8) exhibited the same efficacy as 0.9% saline solution (n=19) in reducing bacterial load in venous leg ulcers during the cleansing process. Only wound area (cm^2) and bacterial count (colony forming units/g) showed a significant relationship (p=0.0070) after cleansing the wound. Neither cleansing solution eliminated biofilm in the wound tissue, as revealed by transmission electron microscopy.

Ricci[81] observed a change in the Cutting and Harding infection score[85] at the end of the two-week treatment, with application of 0.1% PHMB/betaine solution for 10 minutes, with one case having two positive signs (odour and increased exudate) while in five cases only one sign was reported (odour=3; bleeding=1, worsening of granulation tissue=1).

Kiefer et al.[80] reported that none of the patients treated with 0.1% PHMB/0.14% betaine gel after split-thickness skin grafting had burn wound infection.

Systemic or local adverse events

The tolerability of the treatment and the absence of any local or systemic side-effects were reported by three studies.[67,70,76]

The retrospective data review conducted by Ciprandi et al.[82] on newborns, infants and children with burns reported adverse events in five children (n=198), including: itching (n=3); rash (n=1) and hypergranulating tissue (n=1). No event was severe and all but the latter case (moderate with treatment withdrawal) were mild. For these patients, no serious health worsening could be determined to be caused by the 0.1% PHMB/betaine solution/gel. Clinical signs of infection due to *Staphylococcus aureus* during treatment developed in 11 patients and antibiotics were given to eight of these; the use of 0.1% PHMB/betaine solution/gel was continued.

In one study,[79] it was reported that two of the 49 enrolled patients had wound-related adverse events after the application of 0.1% PHMB/betaine gel and solution. This included one patient who had periwound inflammation 29 days after the initial administration, and another patient who had periwound itchiness, likely due to the adhesive tape, 71 days after initial administration. Both events resolved without sequelae.

Kiefer et al.[80] reported that mild-to-moderate pruritus at skin graft sites occurred in two patients and that these adverse events were possibly caused by the 0.1% PHMB/0.14% betaine gel.

Pain

Valenzuela and Perucho[66] reported an improvement in pain control (p=0.049) in the 0.1% PHMB/betaine gel group compared with the NS group.

Romanelli et al.[67] found that pain control was achieved during and at the end of the treatment in the 0.1% PHMB/betaine solution group compared with the NS group (p<0.05).

Wild et al.[68] reported a marked pain reduction in patients treated with a hydrobalance dressing with 0.3% polyhexanide compared with the 0.1% PHMB/betaine solution group (at day 0, mean visual analogue scale (VAS) score: 7.4±0.47 versus 6.8±0.53, respectively; at day 14, mean VAS: 1.3±0.36 versus 3.22±1.2, respectively).

Durante et al.[76] reported that the average pain score decreased significantly from baseline to the final visit (VAS p<0.0001; Face, Legs, Activity, Cry, Consolability scale p<0.00005).

Bellingeri et al.[70] found similar pain scores in patients treated with NS or 0.1% PHMB/betaine solution (average VAS score 3.0), and no statistically significant difference in pain associated to the wounds, to dressing changes or in the pain experienced between dressing changes.

Wattanaploy et al.[71] showed that the Numeric Pain Rating Scale (NRS)-11 pain score of the 0.1%

PHMB/betaine gel group was significantly less than that of the silver sulfadiazine group at 4–9 days after treatment (p<0.001).

Ricci[81] reported an average reduction of VAS pain score of 47% in patients treated with 0.1% PHMB/betaine solution.

Kiefer et al.[80] reported that the changes in pain at the grafted site treated with 0.1% PHMB/0.14% betaine gel from day 0, directly after split-thickness skin grafting on day 5, and every other day until day 29 or until complete graft take occurred, were not significant in two trial centres, but significant in one (p=0.01).

Patients and staff satisfaction

Wattanaploy et al.[71] assessed the satisfaction level in experienced surgeons, nurses and patients. Staff reported that the 0.1% PHMB/betaine gel was easier with regard to dressing changes than silver sulfadiazine, and the wound dressing with 0.1% PHMB/betaine gel was easier to evaluate than the dressing with silver sulfadiazine. The patients were also satisfied with the PHMB/betaine gel when compared with silver sulfadiazine. The satisfaction with stickiness, clean wound bed, pain upon and after application was assessed as 'average' to 'very good' for the 0.1% PHMB/betaine gel, while satisfaction with silver sulfadiazine was assessed as 'very poor' to 'average'.

Ciprandi et al.[82] reported that all physicians were satisfied with the treatment, and considered it 'good' or 'very good' (16.2% and 10.5%, respectively) on a scale of 1–5 (1='unsatisfied', 2='satisfied', 3='good', 4='very good', 5='excellent'). There were no negative feedback.

Resource use and cost

At the final visit, Durante et al.[76] reported a reduction in frequency of dressing changes (every 1.4±2.3 days) compared with the original prescription at the baseline visit, with a consequent reduction in overall treatment costs. The authors did not report any details of variation around these estimates.

The study by Gabriel et al.[77] showed patients who received NPWTi-d with NS or 0.1% PHMB/betaine solution: required fewer operative debridements compared with patients treated with NPWT (2.0 versus 4.4, respectively; p<0.0001); experienced a shorter average length of hospital stay (8.1 versus 27.4 days, respectively; p<0.0001); and length of therapy (4.1 versus 20.9 days, respectively; p<0.0001). The hypothetical economic model developed by the authors to estimate the average overall costs of treatments, showed an average reduction of $8143 USD for operative debridements costs with NPWTi-d and a $1418 difference in average therapy costs between NPWTi-d and NPWT patients.

Kim et al.[78] reported that hospital stay was shorter for the NPWTi-d with 0.1% PHMB/betaine solution group compared with the NPWT with no instillation group (p=0.034); number of operative visits was lower for the NPWTi-d group compared with the NPWT with no instillation group (p≤0.05).

Kim et al.[73] found no statistically significant difference between the NS and 0.1% PHMB/betaine solution NPWTi-d cohorts for the number of operating room visits, and length of hospital stay for both the intention-to-treat and per-protocol analyses (p=0.19, p=0.68, respectively; p=0.19, p=0.08, respectively).

Wattanaploy et al.[71] found no significant difference in treatment cost in patients with partial-thickness burns treated with 0.1% PHMB/betaine gel or silver sulfadiazine (p=0.057).

Discussion

The findings from most of the studies included in this literature review suggested that 0.1% PHMB/betaine solution/gel contributed to: optimisation of the local wound environment; wound improvement and evolution; a decrease in pain intensity without systemic or local side-effects; controlling surface bioburden, since this wound cleanser reduces surface tension; and may support physical removal of debris and bacteria.[48,65]

However, some studies showed controversial findings[68,71–73] reporting no significant differences in infection rates and bacterial load in patients treated with 0.1% PHMB/betaine compared with NS, sterile water or silver sulfadiazine, and more effective disinfection and faster granulation in patients treated with hydrobalance dressing with 0.3% PHMB than 0.1% PHMB/betaine solution. In one trial, addition of 0.1% PHMB solution to a tie-over dressing had no effect on reducing bacterial loads in wounds and resulted in an increased surgical site infection rate in full-thickness skin grafting.[69]

Referring to this significantly higher risk of infections (χ^2: 4.8; p=0.028), it is acknowledged that the local reduction and/or elimination of isolated bacterial species may not be useful and even counterproductive, as an existing wound bacteria balance may be disturbed.[86,87] This can cause an overgrowth of other species that might be harmful, and it is possible that PHMB, by reducing the commensal flora, could give rise to an increased colonisation of *Staphylococcus aureus* or other pathogens.[69]

It is widely acknowledged that it is more than the presence of bacteria that leads to adverse events in wounds. In 2016 the International Wound Infection Institute updated the wound infection continuum to reflect that microbes other than bacteria are associated with wound infection, and microbial virulence, as well as the number and the number of different species of bacteria or microbes present, contributes to the development of wound infection. The stages in the continuum describe the gradual increase in the microbial burden and the activities of the microorganisms, together with the response they invoke in the host.[11] In 10 of the studies selected for inclusion in the review, bacterial burden was determined by clinical evaluation,[74,79,81] bacteriology[66,68,69,72,76,78] or both,[71] and qualitative and semi-quantitative methods were used to analyse swabs.

Identifying the responsible pathogen is required in order to select optimum antimicrobial therapy for infected wounds, but debate exists regarding the best sampling technique to obtain a specimen for microbiological analysis. Despite being minimally invasive, easier to perform and widely employed in practice, wound swabs capture microorganisms from the surface rather than microorganisms that have invaded the tissue, and may not distinguish between colonisation and wound infection. Unequal distribution of pathogens in wounds has been demonstrated,[21] and this can influence the effectiveness of a wound swab in obtaining a microbial specimen. Although the optimum method of sample collection has not yet been determined, the Levine technique is superior to the Z-swab technique.[88] Needle aspiration samples a limited portion and may enter uninfected tissue. Wound biopsies are rarely performed on a routine basis due to cost, invasiveness and discomfort to the individual, but are more sensitive for antibiotic-resistant wounds than Levine swabs, provide qualitative/quantitative information about the bacterial load, and are preferred to monitor the response to treatment.[88]

Since many microorganisms are difficult to culture by standard techniques, strategies to characterise genetic markers of microbial species using molecular techniques[89,90]—some of which are used to identify biofilm in a wound—have been developed.[91,92] In addition, use of DNA sequencing techniques that can more precisely identify species of microbes in a wound specimen is rapidly advancing, including microbes not identified by culture-based techniques.[11,93]

Sterile rules, planimetry, gridded transparent acetate sheets, photographic images,[66,67,70,76] software for the analysis of the digital photographs,[68] and photo-planimetric analysing software[80] were used to measure wound size. In two studies,[70,81] evaluation of wound healing was completed by using standardised tools, such as BWAT[83] and WBP Score.[84]

Nevertheless, the descriptions of how the authors measured healing progress were not always clear in all studies. Furthermore, some studies did not report initial wound size data or reported only descriptions of the size of the wound, without complete information about the characteristics of the wound itself, or reported a reduction in the percentage of patients showing the presence of biofilms in wound bed without details about the method used to diagnose its presence. An accurate and thorough wound assessment is an essential component of the treatment programme. Biofilms are not visible to the naked eye and cannot be detected by routine swabbing,[85] since they are often <100µm and have no macroscopically distinguishable features.[94]

Although sloughing and a shiny wound surface have been proposed as clinical signs of biofilm formation, there is little evidence to support an association between these features and the presence of a biofilm.[16] Guidelines for the identification and treatment of biofilms in hard-to-heal wounds[25,27] stated that approaches, such as the use of SEM and CLSM, are the most reliable types of diagnostic techniques, but are highly specialised and not practical in a typical clinical setting.[95]

Wound healing is an intricate process. In general terms, the factors that influence repair can be categorised into intrinsic, extrinsic and iatrogenic factors. These factors are related, and the systemic factors act through the local effects affecting wound healing.[96,97]

It is claimed that due to the complexity of factors influencing a hard-to-heal wound, no single therapeutic intervention will have any significant impact on improving the wound.[98] Although the studies considered in this review suggest that 0.1% PHMB/betaine may be effective, it is difficult to determine whether there is any additional benefit from its use or whether the superior results are because of the effectiveness of associated treatments, such as NPWT, secondary dressings, compression or bandages, and it is likely that this association enhances the effectiveness of all these treatment modalities. In relation to this issue, Kim et al.[73] suggested that the choice of solution may not be critical to the success or failure of NPWT, and that a possible contribution to the positive clinical results may be related to the intermittent negative pressure which creates a more ideal environment for wound healing.

Wound healing is a multifactorial process and is not exclusively defined by the wound dressing materials and the creation of optimal local wound bed conditions, even though local wound management measures have been shown to play an important role.[4,99]

In the event of infection, a wound fails to heal, the patient experiences increased trauma, treatment costs rise, and general wound management practices become more demanding on resources. Using 0.1% PHMB/betaine to prevent increased bioburden may help to improve a patient's quality of life by reducing pain, odour, and factors that affect mobility, sleep and social interaction.[100,101] This may also lead to a reduction in the number of nursing visits required.[102]

With regard to economic burden, one study[71] found no significant difference in treatment cost in patients treated with 0.1% PHMB/betaine gel or silver sulfadiazine, while another[76] reported a reduction of dressing change frequency, with a consequent reduction of the overall treatment costs. The length of hospital stay was evaluated by three studies,[73,77,78] although this outcome can be heavily influenced by factors unrelated to the wound.

In five studies,[66,67,71,76,81] 0.1% PHMB/betaine solution/gel was shown to reduce pain. A treatment that can contribute to pain-free dressing changes can help to reduce patient anxiety and the level of pain experienced.[103,104] Removal of encrusted dressing causes pain to patients and by moisturising wound dressings with 0.1% PHMB/betaine solution they can be released without causing trauma to the wound surface. The wound can be irrigated with the solution to loosen surface debris, covered with soaked gauze pads, and afterwards wiped with solution-soaked gauze to

facilitate removal of surface debris and contaminants, biofilm and devitalised tissue. The 0.1% PHMB/betaine gel allows wound cleansing to continue, maintains a moist wound healing environment until the next dressing change and is easy to remove.[49] These characteristics reduce mechanical stimuli at the wound, and the perception of pain is decreased. Following irrigation, the gel may be directly applied to the wound, filled into wound cavities, or dressings can be moistened with the gel prior to application. The intention is to coat the wound copiously with the gel, although this may require review if the wound or surrounding skin becomes overly wet or macerated. A secondary dressing should then be applied over the gel. The gel may be used in conjunction with many types of secondary dressings including non-adherent dressings/gauzes, absorptive fibrous dressings, foams and adhesive dressings. When used with absorptive products, an increased amount of gel may be required to keep the wound bed moist as some will be absorbed into the secondary dressing.[49] There is no magic 'one-size-fits-all' dressing; the selection of the most appropriate dressing will depend on the goal of treatment, phase of healing, wound type, position and level of exudate, and frequency of dressing changes, and cannot be made in isolation from the clinical situation (the needs and risk factors of the patient, patient choice, lifestyle, comfort and cost-effectiveness).[9,12]

The tolerability of the treatment and the absence of any local or systemic side-effects on the most fragile skins, such as in older people and children, was reported by five of the studies retrieved,[66,67,70,76,82] confirming that PHMB and PHMB/betaine are uncommon contact allergens in terms of irritant and/or allergic contact dermatitis, and are safe and effective biocides, as endorsed by an interdisciplinary expert panel.[53]

In detail, Ciprandi et al.[82] reported that the use of PHMB/betaine-containing products, as a part of burns treatment, is safe and well tolerated for use in newborns, infants and children, complementing the studies already conducted in adults. In this study, there were 11 (5.6%) reports of burn infection, with eight children requiring antibiotics. These infections resolved rapidly and study treatment with 0.1% PHMB/betaine was continued. The risk of infection in paediatric burns is well known, and Ciprandi et al.[82] noted that the rate was therefore low compared with general reports in the literature.

Periwound inflammation and itchiness after the initial administration of 0.1% PHMB/betaine that resolved without sequelae was reported in one study.[79] Mild-to-moderate pruritus at skin graft sites, with a possible relationship to PHMB/betaine gel, was reported in another study.[80] Bervoets and Aerts[102] published a case report which illustrated the situation of a 59-year-old non-atopic female patient with a long history of bilateral leg ulcers and multiple contact allergies (iodine, cetyl alcohol, limonene and linalool hydroperoxides); the patient presented with acute worsening of her wounds, accompanied by perilesional eczema and mild hand dermatitis after cleaning the leg wounds herself daily with a liquid wound cleanser containing 0.1% PHMB/betaine and applying a wound gel with the same pharmaceutical ingredient concentration. This case and others reporting severe anaphylaxis caused by PHMB in different concentrations, such as 20.0%,[105,106] 0.3% and 0.02%,[107] or by 0.1% PHMB/betaine[107] reinforce the importance of thorough allergy assessment; patients presenting with a history of allergic and/or anaphylactic symptoms should be screened by taking a thorough medical history as well as adequate allergy testing, such as patch testing with 2.5% and/or 5% PHMB in water.[108]

Limitations

The findings of this review have to be viewed in light of some limitations. This was a narrative style literature review[109,110] that summarised the findings of the effect of the clinical use of 0.1% PHMB/betaine on acute and hard-to-heal wounds by incorporating multiple study types rather than focusing on a single study design.

The first limitation of this study is related to the quality assessment of eligible studies adopted for this review, since quality and risk of bias were not formally appraised with standardised critical appraisal tools. Additional limitations include the retrospective and monocentric design of some studies, the limited number of patients enrolled in some studies, the potential selection and information bias, the lack of control groups and blinding, the heterogeneous data collection, and the too-short observation periods to determine differences in wound closure rates, as reported by the authors of included studies. In this review, we included articles published in English, French, Spanish and Italian. Articles published in other languages could also have been important in this review and this is another limitation.

Although these weaknesses limit the results of this review, to the best of our knowledge, the current study is the first review the effect of the clinical use of 0.1% PHMB/betaine with a comprehensive literature search and a complete overview on this topic.

Conclusions

The findings from this review showed that the use of 0.1% PHMB/betaine solution/gel can help debridement during wound cleansing, aids effective wound bed preparation, reduces the microbial load of a critically colonised or infected hard-to-heal wound, reduces inflammatory signs, and enhances wound healing. Although these actions cannot be attributed solely to this treatment modality, the results of this review do highlight the unique action of this combination product. However, although most of the studies included in this literature review support this treatment, further carefully designed, prospective, long-term studies with larger samples across multiple study sites, are needed to confirm these results. **JWC**

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Reflective questions

- In what way does the use of 0.1% polyhexanide-propylbetaine for cleansing, rinsing and moistening acute and hard-to-heal wounds improve the wound bed condition?
- What is its clinical effectiveness with regards to wound healing and infection reduction?
- What are its benefits to patients with regards to wound pain, dressing changes and patient quality of life?
- What might the cost benefits be to using this treatment?

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