

Addressing the challenge of wound cleansing in the modern era

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Abstract

Over the past two decades a body of evidence has been generated to support the traditional use of water in cleansing wounds, with studies showing that the use of clean water does not increase the risk of infection or delay healing. However, recent advances in the understanding of wound management have encouraged reforms and led to the development of wound cleansing agents that have the potential to improve clinical outcomes. This article draws on in vitro and in vivo evidence including comparative studies of patients with acute and chronic wounds to consider the evidence supporting alternatives to water in wound cleansing.

Key words: ■ Antimicrobial ■ PHMB ■ Biofilm ■ Wound cleansing

Over the last 20 years, a body of evidence has been produced that supports the use of water as the wound cleanser of choice in the management of acute and chronic wounds. This research has generally focused on relative wound healing rates, and the comparative incidence of infection following wound cleansing with water or alternative cleansers. The comparative data produced in respect of post cleansing infection rates was produced following the diagnosis of infection using accepted Celcian clinical signs of infection, and/or in light of supportive laboratory culture of wound sampling. This work has been welcomed, and has broadly indicated that provided the water used in the cleansing process is at least of potable quality, wound healing will not be delayed. However, increasing insight over recent years as to how bacteria 'behave' when residing in and on soft tissue has indicated that although cleansing a wound with water may not be harmful, it may not play an active role in the promotion of healing, especially when managing chronic wounds where infection may be present without an associated host response. Is it now time to reconsider our approach to wound cleansing, and to contemplate an alternative to water as the cleansing agent of choice?

Why and when wounds require cleansing

It has been suggested that a wound may require cleansing when there is problematic excess exudate, the exudate

is obviously infected, foreign body contamination, gross contamination by dirt or bacteria, and when slough or necrotic tissue is present (Cutting, 1990). The value of water as a wound cleansing agent during the late 1980s and early 1990s should be viewed against the backdrop, at that time, of increasing in vitro evidence that the use of topical antiseptics was harmful to healing tissue (Brennan, Foster et al, 1986; Brennan and Leaper, 1985; Deas, Billings et al, 1986), and therefore caution in use was advised. Less clear, however, was the answer to the question of when in the history of a wound cleansing should take place, and the relevance of variations in practice in cleansing acute and chronic wounds. The advances made in our knowledge and understanding of wound care management in the last 20 years have encouraged reforms, and led to the introduction of wound cleansing agents that have the potential to improve clinical outcomes.

Background to wound infection

The human body contains an estimated 10^{14} cells, of which only 10% are mammalian (Teitelbaum and Walker 2002). The remainder are resident microbial flora, engendering an associated potential for disease that is always present despite the fact these microbiota have a role to play in maintaining individual health.

The potential for a wound to become infected is high as a wound surface is always heavily contaminated with a variety of bacterial species which may be aerobic and anaerobic (Bowler, Duerden et al, 2001). This, together with availability of fluid and nutrients found in wound exudate and the moist environment, contribute to an ideal setting for bacterial proliferation. Maintaining the wound bioburden at a level where the host remains in control is therefore an important aspect of management if avoiding the onset of wound infection with associated increase in patient morbidity is to be achieved.

In an immune-competent individual who is wounded, a cascade of cellular and biochemical activity is activated with the initial objective of cleansing the wound. This process includes the removal of micro-organisms and tissue debris from the wound bed and is associated with the generation of the Celcian signs of inflammation; redness, swelling, heat and pain. Temporal extension of the acute inflammatory response will be observed if infection intervenes. A range of factors increase the risk of supervening infection, including age, systemic disease, poor nutrition, down-regulation of the immune response and poor tissue perfusion of oxygen. In addition to the signs identified by Celsus, subtle indicators of infection have been categorized (Cutting and Harding, 1994; Cutting, White et al, 2005). The related accuracy of these subtle signs of infection has been tested (Cutting, 1998; Gardner, Frantz et al, 2001).

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Sub clinical infection (biofilms)

Accurate clinical assessment of a wound is a necessary and regularly repeated responsibility. Although acute wounds are easy to identify by virtue of their aetiology, chronic wounds may only be verified retrospectively. A corollary of this is the difficulty in determining the specific cause of the delay in healing. This has contributed to the generation of a classification system whereby wound features or characteristics are appraised. Such characteristics may include (among others) type and level of exudate, condition of the wound edge, wound bed tissue type, and 'infection'. Although the features of wound infection have been characterized (Cutting and Harding, 1994; Cutting, White et al, 2005), recent publications investigating wound biochemistry and cellularity (Armstrong and Jude 2002; Diegelmann 2003; Schultz, Mozingo et al, 2005; Smith, 2006; Yager, Kulina et al, 2007) indicate that chronic wounds are 'fixed' in a state of chronic inflammation, suggesting that a link exists between chronic wounds of different aetiologies. How can this chronic inflammatory state (which delays healing) exist without eliciting an obvious response from the host? A number of mechanisms have been proposed and three are referred to here. Allen et al (2005), have construed that pyocyanin (a virulence factor) expressed by *P. aeruginosa* is capable of suppressing the acute inflammatory response and is therefore able to immunoevade. Stephens et al (2003) have identified the importance of anaerobic organisms in chronic wounds and the related suppression of cellular wound healing responses. Wound biofilm provides a robust explanation for delayed healing. It has been reported that biofilms prevail in chronic wounds but are rare in acute wounds (James, Swogger et al, 2008). The view that biofilm is a significant barrier to healing (Bjarnsholt, Kirketerp-Møller et al, 2008) would be supported by replication studies, particularly in vivo, exploring the differences in healing between acute and chronic wounds.

Biofilms' role in delayed healing

Biofilms are complex microbial communities that are embedded in an extracellular matrix of proteins, nucleic acids and polysaccharides (slime) and are attached to a surface (Cooper and Okhiria 2006). Within the extracellular polymeric substance (EPS) a biological diversity may be found. The *raison d'être* of the biofilm is survival, and the EPS provides protection to the community from chemical and neutrophil attack. In addition to the maintenance of a chronic inflammatory state the sessile (attached) bacteria release proteases. The potential exists for these bacterial (exogenous) proteases to work in tandem with human (endogenous) proteases and degrade growth factors and tissue proteins that are integral to the healing process. It has also been proposed that effete neutrophils release proteases which inhibit the 'search and destroy' function of macrophages. The resulting tissue destruction and additional production of pro-inflammatory cytokines sustains the chronic inflammatory state (Wolcott, Rhoads et al, 2008).

Biofilm management

The concept of Biofilm Based Wound Care (BBWC) has been suggested as an effective method of managing biofilm infections (Wolcott, Rhoads et al, 2008). Integral to this concept is the

utility of debridement (Eldor, Raz et al, 2004; Williams, Enoch et al, 2005; Wolcott and Rhoads, 2008) in order to realise physical removal and suppression of biofilm. As a diagnostic tool for biofilm is currently not available, much debate exists around 'when to treat'. The significance of delayed healing as a result of biofilm presence is becoming recognised (Percival and Dowd, 2010; Schierle, De la Garza et al, 2009), and as such the relationship of delayed healing and the need for debridement is being acknowledged (Wolcott and Rhoads, 2008). Discussion continues over whether it is possible to 'see' a wound biofilm. As biofilm communities are microscopic it needs to be emphasised that it is not possible to visualise wound biofilm with the naked eye. However, it has been proposed that visual cues may be present that suggest biofilm presence. Cutting et al (2010) propose that the presence of slough in a chronic wound provides a visual indication of biofilm existence in a wound and that slough itself is a living bioburden conglomeration that necessitates debridement of the wound.

An additional component of BBWC is concurrent use of antimicrobials (Wolcott and Rhoads, 2008). Concern has been raised about a possible association between bacterial resistance and the widespread and sometimes indiscriminate use of antimicrobials (Russell, Tattawasart et al, 1998), (Tambe, Sampath et al, 2001). It has also been stated that through the implementation of appropriate policies, inappropriate antimicrobial use can be reduced (Jarvis, 1996). The focus of this paper was on improving clinician use of antimicrobials through the development and implementation of antimicrobial use committees. Extensive and acceptable use, in microbiological and clinical terms, of antimicrobials is vital. Antiseptics have been reported as having a positive contribution to make in the control of wound bioburden in wounds that are clearly infected or those that are at risk of infection (White, Cutting et al, 2006).

When deciding whether or not to use an antiseptic, it is important that wound chronicity as a result of biofilm presence is considered (Nelson, 2003).

Polyhexamethylene biguanide (PHMB)

Polyhexamethylene biguanide (PHMB) is also known as polyhexanide and polyaminopropyl biguanide. It is a commonly used antiseptic that is now incorporated into a number of dressings. PHMB compounds (polymeric biguanides) have a broad spectrum of biocidal activity and have a wide range of uses. They have been used as contact lens cleansers, in mouth washes and as an antiseptic including use in wounds (Fabry, Trampenau et al, 2007; Motta, Milne et al, 2004; Nascimento, Tanomaru et al, 2008; Salas Campos, Gómez Ferrero et al, 2006; Santodomingo-Rubido, 2007). PHMB is regarded as being safe to use following its inclusion as a preservative in cosmetics, where it has a low frequency of sensitization (Schnuch, Geier et al, 2007). PHMB binds to the cell envelope and causes disruption of the bacterial cell membrane, and the resulting increased permeability of the cell membrane allows leakage of ions (Broxton, Woodcock et al, 1983; Broxton, Woodcock et al, 1984a). Additional work from Ikeda et al (1983) showed that PHMB caused aggregation of the bacterial cell lipid membrane leading to increased fluidity and permeability. The subsequent liberation of lipopolysaccharides from the cell membrane and loss of potassium ions concludes in the demise of the microorganism (Yasuda, Ohmizo et al,

2003). PHMB is also known to be toxic to bacterial DNA (Allen, White et al, 2006). Peak activity occurs between pH5-6 (Broxton, Woodcock et al, 1984b). The author is unable to find any reports of bacteria acquiring resistance to PHMB.

Prontosan

Prontosan (B Braun) Wound Irrigation Solution and Prontosan Wound Gel are proprietary colourless, cleansing, decontamination and moisturising agents containing PHMB that are indicated for use in acute and chronic wounds. They may be used in conjunction with a range of dressing materials including occlusive dressings (Andriessen and Eberlein 2008). What differentiates Prontosan from other polymeric biguanides is the inclusion of betaine in the formulation. Betaine is an alkaloid surfactant that is found in sugar beet, other plants and in animals. *P. aeruginosa* is known to produce rhamnolipid (a virulence factor) that causes lysis of macrophages and polymorphonuclear leukocytes (PMNs) (Van Gennip, Christensen et al, 2009). Betaine has high water solubility and induces an osmotic stress effect on rhamnolipid. It also interferes with production of homoserine lactone (virulence factor) and the cell-cell signalling activity (quorum sensing) known to play a role in biofilm pathogenicity (Goldberg, Hancock et al, 2008; Pinzon-Gamez, 2009). The surface of many wounds is coated with denatured proteins (fibrin and collagen) lipoproteins and lipids from cell membranes and carbohydrates (hyaluronan). As these compounds denature they lose their solubility and coat the wound surface. Surfactants increase the solubility and thus enhance cleansing. The resulting low surface tension induced by the surfactant supports physical removal of debris and bacteria (Andriessen and Eberlein, 2008).

Evidence of Prontosan efficacy

In an in vitro study comparing efficacy of four sterile wound cleansing solutions (saline, Ringer's solution, Prontosan and Octenisept) on a wound coating model, Prontosan was the only solution that fragmented the test coatings and solubilised the denatured proteins (Kaehn 2009). The author concluded that this is an indispensable asset in order to achieve thorough yet gentle wound cleansing.

In an in vivo animal study Prontosan's activity on biofilms of methicillin resistant *Staphylococcus aureus* using a porcine partial thickness wound model was evaluated (Davis, Rivas et al, 2007). Mean counts of wound MRSA were recorded at 48 and 72 hours in four treatment groups; untreated control, sterile saline, Ringer's solution and Prontosan. A comparative reduction in MRSA at 48 and 72 hours was found in the Prontosan treated group. The reduction in the Prontosan group at 48 and 72 hours was found to be statistically significant compared to the other groups ($p < 0.05$). The study report records that the largest reduction of MRSA, following cleansing with Prontosan, was found from 48 to 72 hours signifying that extended irrigation may provide additional reduction in wound bioburden.

In a retrospective review of venous leg ulcer healing in 112 patients the clinical efficacy of wound cleansers was examined (Andriessen and Eberlein, 2008). At dressing change the study group received the wound rinsing solution Prontosan ($n=59$) and these were compared with the control group who received either Ringer's solution or saline ($n=53$). Inclusion/exclusion criteria were applied to both study and control groups and the

healing pattern of the ulcers was evaluated. The results show that more patients in the study group healed in the 6 month period when compared with the controls - 97% v. 89%. A shorter time to healing was also recorded in the study group when compared with the control group - 60% v. 28% within the first 3 months of treatment. Mean time to healing was 3.31 months (study group) compared to 4.42 months (control group) $p < 0.0001$. These findings sustain the results found in the Kaehn (2009) in vitro study.

Out-patients (571 women, 382 men) were recruited to a retrospective study examining efficacy of PHBM rinsing solution and PHMB-containing wound gel (Moller, Nolte et al, 2008). Wound types included diabetic foot - 62%, venous leg ulcers - 10%, pressure ulcers - 8%, post operative wound dehiscence - 16%, and radiotherapy wounds - 4%. At every dressing change the wound was cleansed with the PHMB irrigation solution and, depending on clinician decision, the PHMB gel or solution was used. The wounds were dressed with a foam dressing if lightly discharging or a fibrous dressing if more heavily exuding. On entry into the study 41% of patients (391) had a wound infection as determined by classical signs of inflammation (local infection) or systemic signs - raised CRP, ESR, leucocytosis, or fever. One hundred and five patients (11%) had heavily contaminated wounds. These patients received systemic antibiotics in addition to PHMB solution/gel. Following treatment the wound infection rate fell from 41% to 3% and antibiotic therapy was not required. Wound closure was achieved in 80% of wounds and 3% showed no improvement. Patient evaluation shows that PHMB solution/gel was painless in 99% of cases, and almost 66% reported an improvement in wound odour. The treatment was well tolerated with an improvement in patient quality of life.

Wound cleansing and infection with biofilm phenotype

A recent Cochrane Collaboration Review (Fernandez, Griffiths et al, 2010) reviewed randomised and quasi randomised controlled trials that compared water (cooled boiled water, distilled water and tap water) with the use of sterile saline and with another solution used for wound cleansing (*procaine spirit) in patients with acute and chronic wounds.

Their conclusions are not surprising, stating that there is no evidence that tap water increases infection when used to cleanse acute adult wounds and some evidence that it reduces it. The authors also added that there is not strong evidence that cleansing wounds per se increases healing or reduces infection. However, as with all systematic reviews the report needs to be read bearing in mind the associated confines that are imposed on this type of work. Cleansing was defined as 'the use of fluids to remove loosely adherent debris and necrotic tissue from the wound surface'. Yet, Rodeheaver and Ratliff (2007) offer a more detailed definition of wound cleansing as 'remove surface contaminants, bacteria and remnants of previous dressings from the wound surface and its surrounding skin'. As the Cochrane review included studies that compared wound healing outcomes/infection rates in wounds cleansed with the aforementioned agents it would seem that the latter definition would have been more appropriate.

*Procaine spirit is procaine HCL 2% with alcohol 70%. Anecdotal evidence suggests that it is commonly prescribed as a wound cleansing agent following surgery in Australia and Singapore.

In addition, the Cochrane review was unable to provide any insight into the impact of the cleansing modalities on wound biofilm. Recent attention has focussed on biofilms, (Cooper and Okhiria, 2006) – bacterial communities that reside on and possibly in the wound bed, and that exhibit resistance to traditional antimicrobial therapy (Percival, Cooper et al, 2010). Biofilms are becoming recognised as a major inhibitor to wound healing (Cutting et al, 2010), and as such their management in the wound environment needs to be addressed.

In respect of anti-biofilm efficacy of PHMB, some research is available. Clinical isolates of *E. coli* and *S. epidermidis* were exposed to five biocides at various concentrations and the biocidal activity was recorded. PHMB and peracetic acid were found to be the most active towards planktonic (free floating) cells and demonstrated a corresponding activity towards biofilm phenotype bacteria (Gilbert, Pemberton et al, 1990); Gilbert, Das et al, 2001).

In a clinical evaluation of 10 community patients with longstanding wounds (1–5 years; mean 2.6 years) Prontosan was used as the wound cleanser replacing normal saline that had been used for at least one month previously (Horrocks, 2006). Objectives of the evaluation included achieving a visible wound bed within 3 weeks of treatment, reducing wound size, ascertaining patient comfort with Prontosan, ease of application, and the recording of any adverse reactions. Achieving a visible wound bed was correlated with removal of wound biofilm in this cohort evaluation, and although this association cannot be conclusively confirmed this outcome does complement a number of the findings. These findings included an overall reduction in wound size (confirmed by photography and wound tracings); previous malodorous wounds were no longer odorous; and all patients reported considerable reduction or elimination of wound pain. Patients also reported considerable improvement in quality of life, and a reduction in community nurse visits. Horrocks (2006) concludes that Prontosan appears to offer a safe and cost-effective method of wound cleansing, being more efficient than normal saline.

Conclusions

Choice of cleansing solution should reflect the individual requirements of the wound and the patient and be underpinned by a sound knowledge/experience base. Numerous investigations have explored the merits of water or saline in wound cleansing, with the most profound conclusion being that wound cleansing with potable quality water appears to do no harm. The question that has yet to be answered is, which wound cleanser supports optimal healing so that patient morbidity is reduced, and expenditure in terms of both human and material resources is maintained at an economic level? If current thinking, that all chronic wounds are biofilm wounds (Wolcott and Rhoads, 2008), is sustained then we will need to rethink our approach to wound cleansing, as the studies examined above indicate that PHMB, in conjunction with a surfactant, is superior to isotonic solutions. In addition, there is evidence emerging that Prontosan is an effective wound cleanser in longstanding (chronic) wounds and has been found by patients to be pain-free, improve patient quality of life, effectively manage wound infection and to reduce the overall time to healing.

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