ABSTRACT

A wound offers an ideal environment for the growth and proliferation of a variety of microorganisms which in some cases may lead to localised or even systemic infections that can be catastrophic for the patient - the development of biofilms exacerbates these infections. Over the past few decades, there has been a progressive development of antimicrobial resistance (AMR) in microorganisms across the board in healthcare sectors. Such resistant microorganisms have arisen primarily due to the abuse and overuse of antimicrobial treatments and the subsequent ability of microorganisms to rapidly change and mutate as a defence mechanism against treatment (e.g., antibiotics). These resistant microorganisms are now at such a level that they are of grave concern to the World Health Organisation (WHO) and are one of the leading causes of illness and mortality in the 21st Century. Treatment of such infections becomes imperative but presents a significant challenge for the clinician in that treatment must be effective but not add to the development of new microbes with AMR.

The strategy of antimicrobial stewardship has stemmed from the need to counteract these resistant microorganisms and requires that current antimicrobial treatments be used wisely to prevent amplification of AMR. It also requires new, improved, or alternative methods of treatment that will not worsen the situation. Thus, any antimicrobial treatment should be effective whilst not causing further development of resistance. Some antiseptics fall into this category and particularly polyhexamethylene hydrochloride biguanide (PHMB) has certain characteristics that make it an ideal solution to this problem of AMR, specifically within wound care applications. PHMB is a broad-spectrum antimicrobial that kills bacteria, fungi, parasites, and certain viruses with a high therapeutic index that is widely used in clinics, homes, and industry. It has been used for many years and has not been shown to cause the development of resistance and is safe (non-cytotoxic) not causing damage to newly growing wound tissue. Importantly there is substantial evidence for its effective use in wound care applications providing a sound basis for evidence-based practice.

This review presents the evidence for the use of PHMB treatments in wound care and its alignment with antimicrobial stewardship for the prevention and treatment of wound infection.

Keywords: polyhexamethylene hydrochloride biguanide (PHMB); infection; wound care; antimicrobial resistance

INTRODUCTION

Various levels of microorganism can be present in wounds. These levels range from wound colonisation, which is characterised by the presence of replicating bacteria in the wound but without causing any detrimental effects on the wound or tissue,[1] to wound infection which is typified by the

presence of high levels of proliferating bacteria that causes local tissue damage and delayed healing.[2] Wound infection involves the presence of more than one species of microorganism and, for wounds, *Staphylococcus* and *Pseudomonas* spp. are the most common.[3,4]

However, wound infection can be exacerbated by the development of a biofilm: a community of microbial cells organised within a slimy extracellular matrix that is adherent to a surface (e.g., a wound surface).[5] The presence of antimicrobial-resistant (AMR) microorganisms and the increased resistance to antimicrobial agents offered by a biofilm[6] means that the removal of AMR microbes and biofilm are key to promoting wound healing.[7] For infected wounds, the inclusion of antimicrobials is a requirement of the treatment regimen, and the use of topical antimicrobial agents can be an important component for infection control in wound care.[8]

Topical antimicrobials can be divided into three main groups:

- Disinfectants which are chemical substances or compounds used to inactivate or destroy microorganisms on inert surfaces (e.g., sodium hypochlorite).
- Antiseptics which are substances that destroy or inhibit the growth or action of microorganisms (as bacteria) especially in or on living tissue (e.g., polyhexamethylene hydrochloride biguanide (polyhexanide, PHMB), chlorhexidine, iodine, silver, hydrogen peroxide).
- Antibiotics which are substances that can inhibit or kill microorganisms (e.g., bacitracin, mupirocin, neomycin).

Disinfectants in the health-care setting are applied to inanimate objects and materials such as instruments and surfaces to control and prevent infection. Disinfectants are not used on wounds but are used to reduce microbial numbers on objects such as hospital trolleys and surgical instruments.[9] Antiseptics and antibiotics are used to treat wound infections however there are advantages and disadvantages. For example, in contrast to antibiotics that specifically target a particular pathogen, antiseptics can target multiple microorganisms and therefore have a broader spectrum of activity. Antiseptic solutions are applied topically and help to reduce wound bioburden which is critical in promoting wound healing.[8,10] Previously, antiseptics were not recommended for routine use in wound care,[11] their rise in popularity is driven in part by the current drive to reduce the prescribing of antibiotics due to concerns about drug resistance.[8,12]

PHMB is a molecule composed of repeating basic biguanidine units connected by hexamethylene hydrocarbon chains leading to a cationic and amphipathic structure (Figure 1).[13-15] PHMB is a mixture of polymers and is a synthetic compound structurally similar to naturally occurring antimicrobial

peptides (AMPs). The basic molecular chain of PHMB can be repeated from two to 30 times, with increasing polymer chain length correlating with increasing antiseptic/antimicrobial efficacy.[16] PHMB was first synthesized in the 1950s.[17] PHMB has been reviewed by the US Environmental Protection Agency (EPA) and noted, with the exception of occupational users, as having a very low aggregate risk of adverse health effects to the public or environment.[17-19] It has been shown to have a limited effect on mammalian cells.[18] There is evidence that there is a wide safety margin when used in cosmetic[20] and clinical applications,[21] including wound care treatments.[22] It has low absorption via the epidermis and therefore a low probability of occurrence of allergic reactions.[17]

Several mechanisms of action (MoA) have been proposed. Previous studies on the MoA of PHMB have focused on its ability to interact with microbial membranes in preference to mammalian membranes.[23-25] As previously stated, PHMB is structurally similar to AMPs and these AMPs have a broad spectrum of activity against bacteria, viruses, and fungi.[26] They are positively charged molecules that bind to bacterial cell membranes and induce cell lysis by destroying membrane integrity (Figure 2). PHMB binds to the negatively charged phosphate head groups of phospholipids at the bacteria cell wall, causing increased rigidity, sinking non-polar segments into hydrophobic domains, disrupting the membrane with subsequent cytoplasmic shedding culminating in cell death.[27,28] The destabilisation of the bacterial membranes causes leakage of a number of important ions resulting in cell death.[29] At high concentrations of PHMB – concentrations used under antiseptic conditions – the bactericidal effect is very rapid but even at low concentrations the release of cellular constituents occurs. Other studies have suggested an alternate mechanism of action for PHMB. PHMB is able to enter bacterial cells, arrest cell division, and condense chromosomes.[18] PHMB initiates the formation of a complex between PHMB and bacterial nucleic acid which results in the precipitation of DNA and its inactivation.[30-32] The binding of PHMB to DNA potentially blocks DNA replication or DNA repair pathways with subsequent cell division arrest and chromosome condensation (Figure 3).[15,18]

PHMB is a broad-spectrum antimicrobial that kills bacteria, fungi, parasites and certain viruses with a high therapeutic index that is widely used in clinics, homes and industry.[33] It is a chemical antiseptic that is used as an active ingredient in a variety of personal care wet wipes and wound management products, wound irrigation solutions, sterile dressings and disinfectants.[27] A systematic review of the effectiveness of PHMB for the treatment of chronic wounds supports the use of this antiseptic in chronic wounds.[34] PHMB wound solutions have demonstrated experimentally anti-biofilm efficacy against wound pathogens such as *Pseudomonas aeruginosa*, *Staphylococcus aureus* and the multispecies biofilm,[35] biofilms,[35-37] and AMR microorganisms.[38] There are numerous types of dressings, both commercially available and under development, that contain PHMB as an antimicrobial component used to reduce or eradicate bacterial infections. PHMB gauze and foam

dressings do not release the PHMB into the wound; the bacteria are killed in the dressing above the wound.[39]

The bactericidal properties of PHMB have been demonstrated against a wide range of species[14] with the killing activity being shown to be rapid (within one hour of application).[18] Also, the comparatively lower level of killing activity against mammalian cells (e.g., human cells) compared with microorganisms contributes to its high therapeutic index.[40]

AIM

The aim of this review is to provide an overview of the clinical evidence exploring the antimicrobial role of polyhexamethylene biguanide (PHMB) on wound healing.

METHODS

In this narrative review, we searched the PubMed database using the following keywords and keyword search strings: (phmb OR "polyhexamethylene biguanide" OR polyhexanide), antimicrobial, and (wound OR ulcer). Published papers from Jan-1995 to Sept-2022 were included (Table 1).

In addition, a manual search for papers in wound care journals not indexed in PubMed (e.g., Wounds UK, Wounds International) and related to the use of clinical use of PHMB in wounds was also carried out. Papers identified as relevant from reference lists, but which were not identified in the other searches carried out were also included in this narrative review.

RESULTS

Seventy-two records were identified from the search of the PubMed database using the search strategy summarised in the Methods and Table 1. A further 11 papers were identified from wound care journals not indexed in the PubMed database, an additional 14 papers were included as relevant and identified from reviews and paper reference lists. A total of 97 papers were identified for appraisal.

After an initial appraisal of the titles and abstracts 41 papers were excluded using the exclusion criteria detailed in Table 1. Papers assessed as not being relevant to the aim of the narrative review were also excluded. One paper was excluded at this stage as a duplicate reference. Once concluded, 55 papers were included as the basis for this narrative review (Figure 4).

DISCUSSION

The experimental evidence demonstrates antimicrobial activity for PHMB against a wide variety of microorganisms including both gram-negative and gram-positive bacteria, pathogenic fungi, viruses, and unicellular protozoa (Table 2).

The antimicrobial activity of PHMB in clinical wound healing

PHMB and the treatment of wound infection

There is a significant body of evidence for the use of PHMB (as a solution or having been incorporated into a dressing matrix) against a variety of microorganisms (Table 3).

PHMB solutions

Clinically, as part of routine wound treatment, fluid irrigation is used to dislodge foreign debris, loosely attached bacteria and devitalised tissue from the wound surface.[41] The goal of wound irrigation is to remove foreign material, decrease bacterial contamination of the wound, and to remove cellular debris or exudate from the surface of the wound.[42] Normal saline or Ringer's solution are most frequently used to irrigate both acute and chronic wounds.[43] These solutions are isotonic, minimally toxic to exposed tissue and do not impede healing progression whilst being relatively cost effective.[42] In addition, there are specialised wound cleansers that contain antimicrobials that are effective in the treatment of wounds where a reduction of wound bioburden to host-manageable levels is required.[44] These antimicrobials include sodium hypochlorite,[35,45] hypochlorous acid,[46-48] povidone-iodine,[49] and PHMB/polyhexanide.[50-52]

There are several clinical studies documenting the effect of PHMB solutions on wound bioburden in a variety of wound types (Table 4). Chronic wounds such as venous leg ulcers,[50,51,53,54] diabetic foot ulcers,[53,56,57] pressure ulcers,[53,58] and malignant wounds[59] have all benefitted from treatment including the use of PHMB solutions. Burn wounds[60] and acute wounds such as surgical wounds,[61-63] skin graft donor site wounds,[64] and traumatic wounds[65] have also shown positive results for PHMB solution irrigation in terms of reducing wound bioburden. Irrigation of wounds with PHMB solution as part of negative pressure wound therapy (NPWT) is an example of PHMB solutions being used as an adjunct with medical devices to treat contaminated and/or infected wounds[57,66] including orthopaedic patients with problematic wounds.[67,68]

Several studies indicated that treatment with PHMB solutions led to an improvement in wound condition[69] and improved healing response.[26,51,58,60,70] In the studies where level of bioburden or risk of infection was a wound parameter under study several indicated reductions in levels of microorganisms[50,53,61,62] and a decrease in the likelihood of infection developing.[61,63,65,67,68] Few studies

indicated that the use of PHMB solutions had no effect on bacterial loads in wounds,[57,64] and one study indicated that biofilm remained after treatment with PHMB solution application.[50]

PHMB wound dressings

A Cochrane Review concluded that there was little evidence to suggest that one wound dressing (advanced (e.g., films, hydrocolloid) or otherwise) was any better at reducing the risk of surgical site infections, or that covering a wound with any dressing reduced the risk of infection.[71] Most evidence presented is of relatively low quality.[71] Table 5 summarises the clinical evidence available (including randomised controlled trials) for the use of PHMB-incorporated dressings in the treatment of acute and chronic wounds.

PHMB has been incorporated into a number of different dressing types including gauze,[72-76] gel,[56,69,70,77-82] foam dressings,[83-85] collagen matrix dressings,[86-89] bio-cellulose dressings,[90-97] and hydro-active dressings.[98] PHMB-incorporated wound dressings have been used to treat a variety of acute wounds[84] including surgical wounds,[75,96,99] skin graft donor sites,[74,78,95] paediatric heel lacerations,[92] and burn wounds,[76,80,82,97] as well as a number of different difficult-to-heal wounds[70,72,77,85,86,89,94,98,100] including venous leg ulcers,[69] diabetic foot ulcers,[56,79] pressure ulcers,[101] and other complex wounds.[81]

Several studies indicated that treatment with PHMB-impregnated dressings led to an improvement in wound condition[69,77,88,90,95,98] and improved healing response.[56,70,72,74,83,87-90,92,94,97] In the studies where the level of bioburden or risk of infection was a wound parameter under study several indicated reductions in levels of microorganisms[72,73,83-86,91,93,94,98,100-102] and a decrease in the likelihood of infection developing.[70,74-76,84,99,100,102]

PHMB and the prevention of wound infection

Several studies identified in this review provide an insight into the potential use of PHMB in the prevention of wound infection. In the case of some wounds, treatment with PHMB resulted in no wound infections developing over the course of the studies; a finding true for both studies with acute[61,63,65,75,76,84] and chronic wounds.[70,100,102] For example, in one study several patients with venous leg ulcers remained infection free in wounds that were at high risk of reinfection,[102] and in a group of patients with non-healing wounds the use of PHMB reduced the requirement for further antimicrobial treatment.[70] However, in one study, soaking of tie-over dressings with PHMB solution (where sutures are placed around the skin graft which are then tied over a bolster made of PHMB-soaked gauze) in full-thickness skin grafting had no effect on post-operative bacterial loads and increased the risk of surgical site infection development.[64]

Anti-biofilm activity of PHMB

Biofilms are ubiquitous in wounds and are a major cause of delayed healing.[35,103] Their management presents a significant challenge to clinicians treating infected wounds, and a variety of antimicrobials (e.g., iodine, silver, polyhexamethylene biguanide, octenidine, hypochlorous acid, benzalkonium chloride, and a surfactant-based topical containing poloxamer 188) have been used and tested for effectiveness.[104] The effectiveness of PHMB against biofilms has been demonstrated in a number of experimental studies.[35,38]

Several studies have demonstrated a reduction in the presence of biofilm in chronic wounds when these wounds are treated with PHMB-impregnated dressings.[88,94] In one study, treatment with a polyhexanide and propyl betaine-based gel resulted in improvement in wound appearance and reduction in wound area. There was also a decrease in the percentage of patients with wounds with devitalised tissue and/or with biofilm.[77] The precise contribution of PHMB to this anti-biofilm activity is unclear as betaine is a surfactant able to disrupt biofilm.[105] In a further study, although a PHMB solution was effective at reducing bacterial load in venous leg ulcers the authors reported that wound biofilm was still present after wound cleansing with PHMB solutions.[50]

PHMB and its effect on antimicrobial-resistant microorganisms

The effectiveness of PHMB's antiseptic activity against microorganisms extends to a number of antimicrobial-resistant bacteria in laboratory studies,[106] including bacteria identified by the WHO as "priority resistant pathogens".[37,107] Clinical evidence for a significant antimicrobial effect of PHMB is currently sparse with no specific clinical studies investigating this important subject having been carried out. However, there are some studies that give an insight into the potential impact of PHMB on antibiotic-resistant bacteria. Several studies report reductions in the level of MRSA in wounds as a result of treatment with PHMB.[75,83,101] Chai et al[56] report the healing of a diabetic foot ulcer with a multi-drug resistant *Pseudomonas* infection after treatment with PHMB.

Aligning the use of PHMB wound treatments with antimicrobial stewardship

Biofilm plays a significant role in the development of antimicrobial resistant bacteria by encouraging the transfer of antibiotic resistant genes between bacterial species.[108] The World Health Organisation (WHO) has declared "that AMR is one of the top 10 global public health threats facing humanity" (Ghosh et al,[109] p. 555). It is noteworthy, that PHMB is effective against antimicrobial resistant bacteria, and in particular some of those microorganisms identified by the WHO as priority resistant pathogens (Figure 5). Additionally, with the resistance of microbes specifically to antibiotics, there is the emergence of multidrug-resistant nosocomial infections.[110] The ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas*

aeruginosa, *Enterobacter* spp.) are the leading cause of nosocomial infections across the world, with many ESKAPE bacteria becoming drug resistant.[111] Several studies have investigated the effectiveness of PHMB against such antimicrobial-resistant microorganisms, and results suggest that PHMB is effective against all ESKAPE pathogens.[50,112]

In an age of increasing resistance, antiseptics are emerging as an alternative (to antibiotics) for infection control because of their much lower risk (or absence) of bacterial resistance.[113] This is particularly important as resistance to PHMB has not been reported despite being used for decades.[15,114] A study reported a reduced susceptibility of MRSA with prolonged exposure to low levels of PHMB.[115]

The development of AMR has diminished the effectiveness of many antimicrobials used to prevent/treat wound infections. AMR is a growing public health challenge worldwide that has been identified as one of the top 10 threats to global health by the WHO.[116] To help address AMR, Antimicrobial Stewardship (AMS) programmes have been developed, designed to educate healthcare workers and control the prescribing and targeting of antibiotics and hence reduce the likelihood of AMR. The topical use of antiseptics for wound care has a role in antimicrobial stewardship strategy.[117-119] The inclusion of PHMB in wound treatments supports AMS in that it is an effective antimicrobial treatment whilst not causing microbial resistance.

Conclusion

The aim of this narrative review was to provide an overview of clinical evidence exploring the antimicrobial role of polyhexamethylene biguanide (PHMB) on wound healing. This was undertaken through searching the PubMed database and undertaking a manual search for appropriate papers based on identified key words relevant to the primary research question. The resulting papers identified were interrogated for those that aligned with the primary research question. Analysis of these papers showed that the experimental evidence demonstrates significant antimicrobial activity for PHMB against a wide variety of microorganisms including both gram-negative, gram-positive bacteria, as well as biofilms and antimicrobial resistant bacteria. Additionally, PHMB was demonstrated to be effective against pathogenic fungi, viruses and unicellular protozoa.

The mechanism of action of PHMB as an antimicrobial was defined in terms of a two-stage process:

1. attachment and integration into the bacteria cell wall, inducing pores in this structure resulting in leakage of bacterial intracellular components.
2. transition of PHMB through the bacterial cell wall and then interaction of PHMB with nuclear components resulting in condensation of proteins and inactivation of the bacteria.

The review identified evidence that supports a key role for PHMB in the prevention and treatment of wound infection against many different microorganisms and across a wide variety of different wound types. Included papers highlighted alignment with the use of PHMB in supporting an AMS role in that it is not only a highly effective antimicrobial, specifically against biofilms and resistant microorganisms, but that importantly it does not induce such antimicrobial resistance.

Reflective Questions:

1. What microbials is PHMB effective against?
2. What are the two MOA of PHMB against bacteria?
3. Is PHMB effective against biofilms and/or antimicrobial resistant organisms eg MRSA?
4. Is there evidence to show that PHMB can cause antimicrobial resistance?
5. Can PHMB supports and antimicrobial stewardship strategy in preventing developing of AMR, if so why?

WORD COUNT – approx. 2890

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