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PHMB- An Efficient Synthetic Polymer For Wound Healing

R.Sripriya*, S. S. Jayaraj
Department of Advanced Zoology and Biotechnology, Gurunanak College, Chennai
Corresponding author: R.Sripriya

Abstract : *Effectively managing and treating non-healing wounds or chronic wounds remains a challenge. Colonisation of bacteria is common in all types of wounds but when colonisation is associated with other contributing factors healing becomes a complicated process. An increase in the use of topical antimicrobial dressings for controlling colonisation and infection has been reported recently. Most of these dressings are designed to compensate a particular deficiency which is considered essential for wound to heal. Emergence of antimicrobial resistance has shifted focus to alternative antimicrobials of which polyhexamethylene biguanide (PHMB) deserves high attention in terms of bioburden management with broad-spectrum antimicrobial action and can easily be incorporated into recent wound infection treatment and prevention regimens. PHMB has been used for more than 60 years in a wide range of medical and non-medical applications and personal-care products. PHMB is structurally and functionally similar to AMPs in terms of its bactericidal action. PHMB impregnated wound dressings are recommended to be used for reducing infection and promoting healing in various disease conditions. It is available in various forms starting from cleansing solution to wound dressing material. The polymer PHMB has been banned to use in personal care products as it is suspected to be cancer-causing, it is environmentally detrimental and allergenic. Based on literature, PHMB is nontoxic to human cells, un- like some other antimicrobials, does not hinder the healing process and proved to be the only option to heal chronic wounds where other treatments failed.*

Keywords *- antiseptic, chronic, drug delivery, PHMB, polymer*

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I. INTRODUCTION

Wound healing is determined by the percentage of wound closure, remodelling and biochemical changes taking place in wound tissue. A complex series of events, namely hemostasis, inflammation, proliferation and maturation come into action when the skin is wounded [1]. Most wounds heal within the stipulated time frame but others fail or take a longer time to heal [2]. An epidemiological study reported that prevalence of chronic wounds in the Indian population is 4.5/1000 [3]. The three principles of wound management are: understand the aetiology, identify and control the factors affecting healing and select the appropriate drug/dressing/system to enhance the healing process. Bacterial burden and biofilm have been recognized as key factors contributing to persistent inflammation, tissue destruction, delayed wound healing and other serious complications, especially in individuals who are frail and immune-compromised [4]. Reducing the risk of infection through effective management of wound bioburden is an essential aspect of wound care [5] World Union of Wound Healing Societies (WUWHS) [6] while early diagnosis can reduce the risk of complications and treatment costs [7]. Wound infection causes serious delays in healing as microbes consume nutrients and oxygen, which are essential for healing from the wound bed [8,9]. Effectively managing and treating wound infection is still challenging, although a wide range of products and pharmaceutical interventions are available to clinicians. Recent years have seen an increased use of topical antimicrobial dressings for controlling colonisation and infection.

II. CHRONIC WOUNDS

Chronic wounds are wounds that failed to proceed through the orderly events of healing to produce anatomic and functional integrity within a stipulated timeframe of 4 to 6 weeks [10]. Non-healing wounds include venous, diabetic and pressure ulcers. Colonisation of bacteria is common in all types of wounds but when colonisation is associated with other factors such as poor vascular supply and host immune system, hypoxia, or metabolic disorders, pathology of the wound bed and virulence of the bacteria present in the wound bed, all these factors can contribute to complicate and delay the healing process [11-16]. Systemic antibiotics are prescribed to treat infection for duration of 7-14 days, after which the wound is reviewed and treatment should be stopped if the therapy was successful [17]. Only patients with uncomplicated chronic wounds respond to the therapy. Prolonged and frequent use of systemic antibiotics leads to undesirable adverse effects and development of antibacterial resistance [18]. Consequently, it is necessary to restrict their use as a first-line

treatment in local wound bioburden management, particularly in chronic wounds. Bacterial burden is determined by calculating the colony-forming units in wound tissue biopsies and the ultimate outcome is based on patient's comfort, which includes less pain and malodour, no adverse events and improved quality of life. An alternative to systemic delivery is topical application of drugs to treat infection, which requires lesser amounts of drug and provides onsite action. Topical antimicrobials should be used only in patients where signs and symptoms of bacterial bioburden interfere in the healing process [19]. The decision about which topical antimicrobial is to be used should be made on the basis of wound aetiology, knowledge about factors hindering healing, as well as the drug's antimicrobial efficacy, wound toxicity, systemic absorption and potential for bacterial resistance development [20], together with considering product availability.

Wound dressing

In recent years there has been an increase in the use of topical antimicrobial dressings to control colonisation and infection [19]. An ideal antimicrobial dressing should be easy to handle, absorbs excessive wound exudate, non-traumatic and cost-effective. The selection of dressing should be based on the type of wound and depth, level of exudates, the dressing's ability to provide moist wound environment, enhance epidermal cell migration, promote angiogenesis and connective tissue synthesis, allow gaseous exchange, maintain appropriate wound tissue temperature to improve the blood flow to the wound bed and enhance epidermal migration, provide protection against bacterial contamination/ infection, all while being non-adherent to the wound and easy to remove after healing. The dressing must provide debridement action to enhance leucocytes migration and support the accumulation of enzyme and must be sterile, non-toxic and non-allergic. Most dressings are designed and applied to the wound to compensate for a particular deficiency that is considered essential for wound to heal and must control the factors that hinder healing. The types of dressing include gauze, film, foams, composites and interactive dressings. Most interactive dressings insulate the wound surface from excessive heat loss, which is thought to inhibit fibroblast activity. Interactive dressings include dressings made of alginates, collagen, hyaluronic acid products, hydrocolloids and hydrogels [21]. To facilitate healing, dressings will protect the wound from contamination and keep the wound surface moist to maintain the integrity of the cells present in the wound site. A moist wound bed is essential for the migration of dividing cells [22].

Drugs used in topical application

Drugs commonly used to control infection includes chlorhexidine, povidone iodine, triclosan, silver sulfadiazine [23], Polymyxin B sulphate, Bacitracin, Mupirocin, Fusidic acid [24]. Due to emergence of antimicrobial resistance, focus has shifted toward alternative antimicrobials, of which polyhexamethylene biguanide (PHMB), also known as polyhexanide, offers an alternative approach in terms of bioburden management and can easily be incorporated into recent wound infection treatment and prevention regimens. In a comparative analysis of topical antimicrobials, PHMB was reported as effective in terms of biocompatibility, antimicrobial activity and cytotoxicity [25].

PHMB is a synthetic polymer with broad-spectrum antimicrobial action that has been used for more than 60 years in a wide range of medical and non-medical applications [26,27]. PHMB, is also found in many personal-care products, "including skin care, cosmetics, eye-care solutions, surgery care, wound care dressings, contact lens cleaning solutions, perioperative cleansing products, swimming pool cleaners and wound care products. Reported evidence has shown that PHMB, due to its specific modes of action, is able to manage bioburden by either preventing the ingress of bacteria into the wound, or delivering a potent antiseptic/antimicrobial agent to the wound bed. It is effective against a broad spectrum of microbes, including both Gram-positive and Gram-negative bacteria [28], and selected fungi [29] as well as methicillin-resistant Staphylococcus aureus (MRSA) [30], vancomycin-resistant enterococcus (VRE). PHMB has also been reported effective against bacterial biofilms in-vitro [31,32], and has proved superior to silver nitrate in terms of its effects on fibrin accumulation. PHMB has the ability to inhibit the formation of reactive oxygen species *in vitro*, which may underlie its anti-inflammatory effects *in vivo*. Moreover, clinically relevant concentrations of PHMB enhanced the *in vitro* proliferation of normal human keratinocytes [33].

Structure of PHMB

PHMB has a chemical structure very similar to antimicrobial peptides (AMPs) that occur naturally in keratinocytes and neutrophils. Naturally occurring AMPs are produced during immune responses and have antibacterial, antiviral and anti-fungal effects [34]. The basic molecular chain of PHMB can be repeated 2–30 times, with increasing polymer chain length correlating with increasing antimicrobial efficacy.

Mode of action of PHMB

PHMB is also functionally similar to AMPs in terms of its bactericidal action [35]. PHMB enters the bacterial cell membrane and adheres to it causing cellular disruption by leakage of potassium ions and other cytosolic components [36-39], which leads to bacterial cell death. There is also evidence that PHMB penetrates the target cell, binds to DNA and other nucleic acids [40] and causes damage to or inactivates bacterial DNA. Because of its multi-modal action, acquired resistance to PHMB is unlikely [41] and has not been reported yet.

Existing evidence on use of PHMB

In leg and foot ulcers

In a study of the healing pattern in 5 case reports of leg and foot ulcers, PHMB impregnated wound dressings recorded greater wound reduction (80%) within 3 weeks and in the case of patients with diabetic ulcers complete healing occurred within 5 to 6 weeks without frequent dressing change [42]. In an assessment of wound cleansing solutions for the treatment of problem wounds (n=59) the use of PHMB solution in venous ulcers led to a significantly reduced healing time ($p<0.0001$) when compared to the control group treated with Ringer's solution or saline [43]. PHMB-treated wounds healed faster and in cases with a lower risk of secondary infection. Sibbald et al., 2017 [44] reported that 5.3% of leg and foot ulcers treated with PHMB foam at week four displayed polymicrobial organisms in contrast to 33% of the ulcers treated with the non-PHMB foam dressing ($p=0.04$). PHMB dressing was a significant predictor in reducing superficial bacterial burden ($p=0.016$). Ability of an antimicrobial agent to eradicate multi-drug resistant bacteria is increasingly important. Pressure ulcers colonised with MRSA were randomly treated with a PHMB impregnated dressing or a PHMB swab at dressing change. MRSA was not detectable in wounds treated with PHMB dressing versus 13% in wounds treated with PHMB swab ($p<0.05$) [45]. Brantley J, et.al., [46] used collagen matrix with PHMB and reported that complete wound closure was achieved in 4 of 5 wounds after an average of 6.8 weeks following the first dressing application. Similarly Dimitrios Lintzeris et.al., [47] studied the effect collagen matrix with PHMB on chronic wounds which had failed to respond to previous conventional or adjuvant therapy. A total of 8 patients with 9 wounds and wound aetiologies included 3 pressure ulcers, 1 diabetic foot ulcer, 1 venous leg ulcer, 2 postsurgical wound dehiscences, 1 ulcer secondary to calciphylaxis, and 1traumatic wound secondary to hematoma. Six of 9 wounds in this study were reported as healed with an average time to closure of 10 weeks from the first application of dressing.

In infection control

The effect of PHMB agents on bacterial burden in chronic wounds of various aetiologies was examined using semi- quantitative [45,48,49] and quantitative bacteriology. PHMB dressings achieved a faster, more substantial reduction in bacterial count and reduction in the number of polymicrobial organisms [50,51]. PHMB was well-tolerated in dialysis patients treated for infections, and only 2 cases out of 106 patients were reported with transient local skin erythema [52].

i) In the form of wound dressing

PHMB impregnated wound dressings are recommended to be used for reducing infection and promoting healing in persistent wounds without heavy exudates. Based on in-vivo and in-vitro results of studies on PHMB, Dissemond et al., [53] recommended its use as a primary topical antimicrobial in the treatment of critically colonised or locally infected acute and chronic wounds. PHMB impregnated wound dressings have been reported to achieve faster and sustained reduction in bacterial count in bioburden of chronic wounds [54]. Even in pressure ulcers, PHMB impregnated dressings were able to eradicate MRSA completely. These dressing were found to achieve earlier elimination (within 3 days) of MRSA and other three pathogens, namely P. aeruginosa, E. Cloaca and,S. aureus in tracheostomy sites, compared to non-antimicrobial gauze (11 days). Wright and colleagues [55] compared the effectiveness of a silver dressing to a dry gauze dressing containing PHMB (Kerlix AMD) that showed reduction in bioburden with both dressings when tested in an *in vitro* bactericidal assay. Alternatively, Motta and associates [51] demonstrated a good response in decreasing the number of organisms present in the wound using Kerlix AMD compared to gauze where packing the dressing into the wound was required. In a double-blind test comparing the effect of gauze compresses soaked in 0.2% PHMB (n=45) and Ringer's lactate solution (n=35), the PHMB group had better wound healing and faster reduction of Gram-positive infections. Better tissue compatibility was also observed with PHMB compared to the control group [56].

Roth et al., [57] made a comparative study on postoperative infections with PHMB, povidone iodine, Ringer's solution and hydrogen peroxide. The lowest frequency of postoperative wound infection was observed in wounds treated with PHMB after wound debridement. The efficacy of polyhexanide (0.04%) soaked dressings observed following surgery in patients with chronic venous ulcers where, after 3 days of antiseptic therapy, 72 ulcers (30.7%) were bacteriologically negative; after 7 days, 139 (60.1%). At the time of follow-up, 203 patients (87.8%) were free of recurrence. PHMB foam dressing was found to be a significant predictor of

reduced wound size and lower superficial bacterial burden (P=0.016) with significant reduction in pain at week 2 (P=0.0006) and at week 4 (P=0.02) when compared to the non-antimicrobial foam dressing [50].

ii) In the form of gel

Valenzuela and Perucho NS [54] compared the efficacy of 0.1% PHMB gel with standard of care to control bacterial burden in chronic wounds. After 2 weeks, PHMB reduced bacterial bioburden, decreased wound area, slough in wound bed, pain and exudate and increased granulation tissue compared with standard care treatments.

iii) In the form of wound cleansing solution

Romanelli et al., [58] evaluated the efficacy and tolerability of a wound cleansing solution containing PHMB to control bacterial burden in chronic wounds. The group receiving PHMB-containing wound cleansing solution reported better pain control at the end of treatment ($p<0.05$) than the control group. PHMB was found to be well- tolerated, with better control of wound odour and significantly control of wound bioburden.

In pain reduction

Pain is a common factor experienced by chronic wound patients. Sibbald et al., [50] noted that PHMB dressings can achieve significant pain reduction as early as two weeks after application when compared with non-antimicrobial foam dressing ($p<0.001$). In a comparative study of PHMB biocellulose dressing versus silver dressing in critically colonised and painful wounds, the patients treated with PHMB dressing reported significant lower pain ($p<0.001$). Treatment- related adverse effects due to the use of PHMB dressings have not been reported so far [59]. Eberlein et.al.,[49] also compared PHMB-containing biocellulose dressing with silver wound dressing in critically colonised or locally infected wounds and found that both dressing regimens exerted a positive antimicrobial effect but the PHMB product was significantly more effective in reducing the pain after the dressing change compared to silver.

In burn wounds

In a randomised controlled trial (RCT) (n=60) of second degree burns treated with a 0.3% PHMB-impregnated wound dressing, healing occurred within 10 days. Although this was not different from a silver dressing, the wounds treated with the PHMB dressing healed significantly faster ($p<0.001$). Daeschlein et al., [60] compared the efficacy of PHMB (versus silver nitrate and povidone iodine in the treatment of second-degree burns (n=14) and poorly healing pressure ulcers with mesh grafts (n=4). They found that PHMB was superior to povidone-iodine and silver nitrate in terms of regeneration of the epithelium, with reduction in wound pain and improved patient comfort. They also observed a reduction in fibrin formation in the PHMB group compared to the silver nitrate- treated group.

In peri-wound skin redness

In one randomised controlled trial (RCT) (n=42 wounds), 0.3% PHMB-impregnated dressing was found to be not more effective than a silver dressing in promoting wound healing; however, there was a significantly ($p<0.006$) more rapid reduction in peri-wound skin redness associated with the 0.3% PHMB-impregnated wound dressing [49].

In skin contusions and lacerations

In one uncontrolled trial involving paediatric patients (n=20, mean age 5.6 years) with skin contusions and lacerations of the heel (mean baseline wound size 8.60cm^2) showed 100% healing within 14 days (12.95±7.69 days) when treated with a biocellular matrix dressing impregnated with 0.3% PHMB [61].

Clinical safety of using PHMB

Reported evidence states that PHMB has good clinical safety [62-64], targeted action on bacterial cells (specific mechanism of action with regard to acidic lipids of bacterial membranes, with only minor effects on neutral lipids of human cellular membranes) [65,66], with a biocompatibility index >1 [67], PHMB showed no known toxic risks [35], risks of resorption [68] and low risk of contact sensitisation [69,70] with sustainability in delivery of the active pharmaceutical ingredient [71]. Müller G and Kramer A. [67] showed that PHMB is nontoxic to human cells unlike some other antimicrobials and does not hinder the healing process.

PHBM products currently available on the market

PHMB-based products have been proven to have broad antimicrobial spectrum and good biocompatibility. A number of PHMB wound care formats are available in the form of a topical solution (often used in eye care), irrigation fluid, gauze and foam-impregnated dressings.

i) Wound rinsing solution

The wound rinsing solution Prontosan® (B Braun Medical Ltd, Sheffield, UK) is not considered to be an antiseptic/ antimicrobial agent, but a medical device with PHMB added as a preservative, i.e. the company product claims are based on a purely physical cleansing effect.

ii) **Wound dressings**

The wound dressings currently available commercially include ActivHeal® PHMB Foam dressings marketed by Advanced Medical Solutions Ltd., UK. It is a sterile antimicrobial wound dressings, consisting of a hydrophilic polyurethane foam that is designed to absorb exudates. This is laminated to a pink, low-friction, waterproof polyurethane film, which provides a bacterial barrier to the wound.

Suprasorb® X+PHMB (Activa Healthcare, an L&R Company) is a biosynthetic cellulose fibre dressing impregnated with PHMB. According to the manufacturer this product is able to donate PHMB at the wound surface and into the wound fluid, making it an effective treatment for infected and colonised wounds. Suprasorb X+PHMB is currently listed in the UK Drug Tariff as an antimicrobial dressing.

CelluDress-PHMB (Medicareplus International Ltd, UK) is a sterile moist wound dressing impregnated with a special PHMB antimicrobial complex. The dressing has a three-layer structure. The two outer layers are nonadherent to minimise adherence to the wound and improve patient comfort. The middle biocellulose layer is designed to function as a reservoir for the antimicrobial solution as well as an absorption layer for wound pathogens. The dressing protects against the development of wound infection by absorbing and binding to the negatively-charged micro-organisms, decreasing the bacterial load in the dressing and preventing bacterial growth in the wound [72].

Wound care products containing PHMB include Kerlix AMD™, Excilon AMD™, and Telfa AMD™ (Tyco HealthCare, Mansfield, Mass) and XCell® Cellulose Wound Dressing Antimicrobial (Xylos Corp, Langhorne, Pa).The products Telfa® AMD and Telfa AMD Island (Covidien UK Commercial Ltd, Hampshire, UK) are constructed as low absorbency perforated plastic film-faced wound dressings impregnated with PHMB, and are marketed as a barrier to bacterial colonisation. Kendall AMD, Kendall AMD Plus (Covidien UK Commercial Ltd, Hampshire, UK) are constructed as a foam-based dressing containing PHMB. It is claimed that these products can act as an effective antimicrobial barrier and can reduce bacterial load within wound exudates. All of these products are currently listed on the UK Drug Tariff as antimicrobial dressings.

Cases where PHMB must be avoided

PHMB is not recommended to be used for peritoneal lavage and antiseptic joint lavage (cartilage toxicity), in any part of the central nervous system (CNS), including the meninges and intralumbal applications, in applications involving the middle or inner ear and intraocular applications [73]. It is contraindicated during the first 4 months of pregnancy but may be used in later stages after risk assessment it should not be used in patients allergic to PHMB.

III. CONCLUSION

The use of polymer PHMB as a preservative in cosmetic products at concentrations higher than 0.3% has been banned, since January 2015. The use PHMB in personal-care products is legal in the USA, and there are still many debates on the safety profile of the ingredient with some companies insisting that the ingredient is safe. The Scientific Committee on Consumer Safety (SCCS) [74] has conducted an oral PHMB chronic toxicity/carcinogenicity assay using a rat model and observed an increased incidence of haemangiosarcomas (statistically not significant) at the highest dose of 2000 ppm PHMB. In some related studies in mice, PHMB increased the incidence of vascular tumors, mainly in the liver and that of haemangiosarcomas in females when applied on skin at the highest dose (750 mg/kg bw/d; considered to exceed MTD) tested. Based on the outcome of the above studies the polymer is classified as Carc 2 H351 (suspected of causing cancer). Moreover, the substance is suspected to be detrimental to the environment and it is allergenic. It has also been proposed that evidence from the chronic rat study is not sufficient to demonstrate a clear treatment-related effect [75]. In 2016, the SCCS [76] issued a preliminary revised opinion stating that the use of polyaminopropyl biguanide as a preservative is safe in all cosmetic products at concentrations up to 0.1%. PHMB has also been described as 'practically non-toxic' in concentrations up to 0.3% [25], with good cell and tissue tolerability and a very low risk of sensitisation [27]. Based on medical surveillance information, obtained between 2004 and 2007, no cases of skin sensitization were reported from employees who came in contact with PHMB HCl in the workplaces [76]. The prophylactic use of PHMB-impregnated dressings has reduced the incidence of surgical site infection rates, which can be expensive to treat. Indeed, preliminary trials suggest it may be highly cost effective in this regard. PHMB impregnated dressings appear to be cost effective when compared to standard wound dressings. Cost reductions were related to reduced requirement for dressing changes that could save both equipment and staff costs.

The existing evidence shows that topical PHMB may promote healing of chronic stalled wounds, reduce bacterial burden, eliminate MRSA, and alleviate wound-related pain. However, small study sizes, inconsistent measurements, methodological flaws, and short follow-up period make it difficult to formulate definitive clinical recommendations. Additional randomised controlled trials are needed to demonstrate the effectiveness of PHMB on different wound types and advantages over other existing topical antimicrobial agents. Currently there are more than 3000 types of wound dressings available on the market to aid physicians in addressing all aspects of wound management [21]. However there is still a pressing need for a superior product that heals chronic wounds such as venous leg ulcers, diabetic wound and pressure ulcers which often fail to achieve complete healing. Hence, developing a dressing material that addresses the major factors that interfere with the normal healing process will tremendously help patients and wound care practitioners. Outcome measurements should include the use of tools that have proved valid, reliable, sensitive to change, and effective in assessing wound size, bacterial burden, and patient-oriented outcomes such as pain and quality of life. Finally, future PHMB trials should include financial breakdowns of the cost of treatment. No patients in the trials or case reports experienced adverse effects associated with a PHMB-impregnated wound dressing. In the selected studies, the use of wound healing, measured objectively by estimating changes in wound surface areas as a primary endpoint remains contentious. Most of the studies reporting on the healing aspect have not considered complete wound closure as the bench-mark to measure effectiveness of PHMB dressings: moreover, the healing rates of the longest follow-up periods reported were too short. Considering the complexity of the healing process and the volatility of the bacterial balance within a chronic wound environment, the study durations were likely too short to demonstrate sustained and ongoing improvement.

Further studies are needed for a thorough analysis of the effectiveness of PHMB and the assessment of relative efficiencies across the range of available products in different contexts. The outcome may inform on the appropriate methods for drug incorporation, optimal concentration of drug to be incorporated, mode of delivery to utilise only its beneficial effects in chronic wound healing.

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